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SELECTED LECTURES IN OBSTETRICS

A manual

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S45

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The textbook presents the main lectures on physiological and pathological obstetrics at the modern scientific level. The main attention is paid to the problems of pregnancy and preterm birth, gestosis, obstetric hemorrhage, and fetal distress. Clinical guidelines of the European and American communities were used in the preparation of the material.

The textbook corresponds to the midwifery curricula and can be recommended as an additional source for the training of 5th and 6th year students.

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ЗМІСТ

LIST OF ABBREVIATIONS

AFI — amniotic fluid index
AFP — alpha-fetoprotein
BV — bacterial vaginosis
CRL — crown rump length
CTG — cardiotocogram
EDD — expected date of delivery
EFW — estimated fetal weight
FGR — fetal growth restriction
FHR — fetal heart rate
GFR — glomerular filtration rate
hCG — human chorionic gonadotropin
HPL — human placental lactogen
LMP — last normal menstrual period
LOA — left occipitoanterior
LOP — left occipitoposterior
MRI — Magnetic Resonance Imaging
ms — milliseconds
NICU — neonatal intensive care unit;
PAPP-A — pregnancy-associated plasma Protein-A
PI — pulsatility index
PlGF — placental growth factor
ROA — right occipitoanterior
SFH — symphysis fundal height
sFlt-1 — soluble fms-like tyrosine kinase
STV — short-term variation
WCC — white cell count
CRL — crown-rump length

Lecture 1

PHYSIOLOGY OF PREGNANCY. METHODS OF EXAMINATION OF PREGNANT WOMEN. PERINATAL CARE

Topic Relevance

During pregnancy, progressive anatomical, physiological and biochemical changes occur in all body systems. It is a phenomenon of maternal adaptation to the needs of the growing fetus. Without proper understanding, these physiologic adaptations of normal pregnancy may be misinterpreted as pathologic.

Systematic examination and counselling of the woman during pregnancy is called prenatal care. Examination should be regular and periodic, according to the needs of the individual. Essentially, prenatal care begins before pregnancy and ends during labor and the postpartum period. Prenatal care consists of careful history taking, examinations (general and obstetric) and counselling.

Educational Materials

PHYSIOLOGICAL CHANGES DURING PREGNANCY. GENITAL TRACT CHANGES

Uterus

The effect of the hormonal stimulation is the greatest on the tissues of the genital tract, and uterine muscle fibers during pregnancy increase 15 times of their length before pregnancy, the uterine weight increases from 50 g to 1000 g correspondingly. At early terms of pregnancy, the growth occurs by hyperplasia, and more particularly by hypertrophy of the muscle fibers, as a result the uterus becomes a thick-walled spherical organ. From the 20th week growth almost ceases and the uterus expands by distension, the stretching of the muscle fibers takes place due to the mechanical effect

of the growing fetus. With distension the wall of the uterus becomes thinner and the shape cylindrical. The uterine blood vessels also undergo hypertrophy and become increasingly tortuous in the first half of pregnancy, but after this no further growth occurs, and the additional length necessary to accommodate the continued stretching of the uterus is achieved by unfolding of the vessels.

The uterus is derived from the two Müllerian ducts and the myometrium is made up of a thin external, largely longitudinal, layer; a thin inner, largely circular layer; and a thick, intricately interlaced middle layer, which comprises two spiral systems of interdigitating muscles derived from the two Müllerian ducts through which the blood vessels run. Apposition of two double curve muscle fibers gives a "8" shape figure. So, when the muscles contract, they occlude the blood vessels running through the fibers and hence called living ligature. The proportion of muscle to connective tissue is the greatest in the fundal area and diminishes as the lower segment of the uterus and cervix is approached, the lower half of the cervix having no more than 10% of muscle tissue.

The effect of the uterine distension is to stretch both interdigitating spiral systems and to increase the angle of crossing of the fibers, in the thinner lower segment area where the fibers cross at an angle of about 160° and are less stretched. Incision of the myometrium in this zone is anatomically more suitable, and experience of the lower segment cesarean section confirms that healing is better.

Contractions (Braxton–Hicks). Uterine contractions during pregnancy were named after Braxton Hicks, who first described their occurrence during pregnancy. From the first weeks of pregnancy, the uterus undergoes spontaneous contractions. This can be felt during bimanual palpation in early pregnancy or by feeling the abdomen, where the uterus becomes hard at one moment and soft at another. The contractions are irregular, infrequent, spasmodic and painless, and do not affect cervical dilation. The patient does not feel the contractions. Later on, the contractions become more frequent and intense, which causes the patient some discomfort.

The lower uterine segment is that part of the lower uterus and upper cervix lying between the line of attachment of the peritoneum

of the uterovesical pouch superiorly and the histological internal os inferiorly. It is that part of the uterus where the proportion of muscle diminishes, this muscle being replaced increasingly by connective tissue (75%), which forms 90% of the cervical tissues (mainly collagen fibers). Because of this the lower uterine segment becomes stretched in late pregnancy as the thickly muscled fundus draws it up from the relatively fixed cervix.

Cervix

The cervix becomes softer and swollen in pregnancy, with the result that the columnar epithelium lining the cervical canal becomes exposed to the vaginal secretions. This change in the cervix is due to estradiol, which increases the hygroscopic properties of the cervical connective tissue and loosens the acid mucopolysaccharides (glycosaminoglycans) of the collagen-binding ground substance.

Prostaglandins effect on the collagen fibers, especially in the last weeks of pregnancy. At the same time, collagenase is secreted from leukocytes, which also aids in the breakdown of collagen. The cervix becomes softer and more easily dilatable — the so-called ripening of the cervix. In this way the cervix is more easily able to dilate in labor.

Vagina

The vaginal mucosa becomes thicker, the vaginal muscle hypertrophies, and there is an alteration in the composition of the surrounding connective tissue, with the result that the vagina dilates more easily to accommodate the fetus during parturition. Estrogen-initiated changes occur early in pregnancy, and there is increased desquamation of superficial vaginal mucosal cells with increased vaginal discharge during pregnancy. If pathogens — bacterial, fungal (e.g. candida) or parasitic (e.g. trichomonads) — enter the vagina, it is easier for them to gain a foothold and therefore vaginitis is more common in pregnancy.

Cardiovascular System

The plasma volume increases to fill the additional intravascular space created by the placenta and the blood vessels. The red cell

mass increases to meet the increased demand for oxygen. Because the increase in red blood cell mass is proportionately less than the increase in plasma volume, the concentration of red blood cells in the blood falls as the hemoglobin concentration falls. Although the hemoglobin concentration falls to about 120 g/L at the 32nd week, total hemoglobin is higher than in the absence of pregnancy. At the same time, the number of white blood cells increases (to about 10,500/mL), as well as the number of platelets (Fig. 1.1).

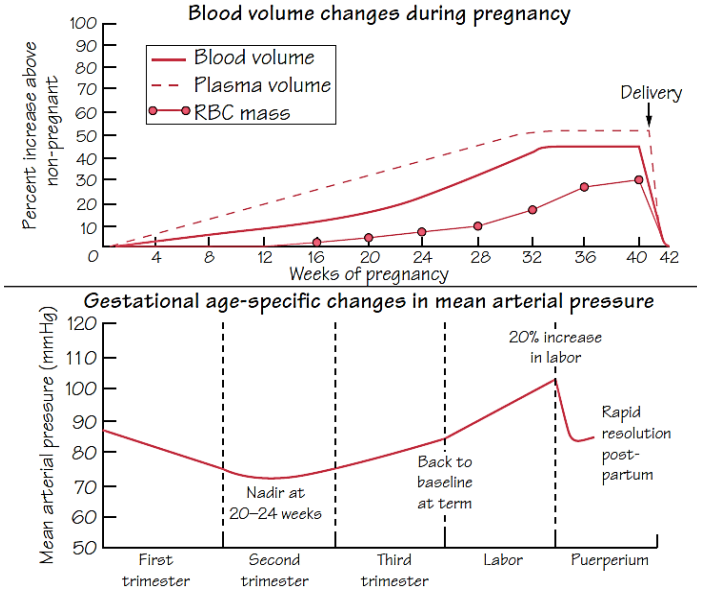


Fig. 1.1.

Source: Obstetrics and Gynecology at a Glance, 4th Edition Errol R. Norwitz, John O. Schorge

Cardiovascular dynamics. To cope with the increased blood volume and extra oxygen demand of pregnancy, cardiac output increases by 30–50%. Most of the increased cardiac output is due to an increase in stroke volume, but the heart rate increases by about 15%. The increase in cardiac output is counterbalanced by a decrease in peripheral resistance. For these reasons, blood

pressure decreases in early pregnancy, returning to pre-pregnancy levels by the third trimester.

Like other blood vessels, veins in the legs become dilated. Leg veins are affected especially in late pregnancy due to obstruction of venous return caused by increased pressure of venous blood returning from the uterus and mechanical pressure of the uterus on the vena cava. This may lead to varicose leg veins (and sometimes the vulvar veins) in susceptible women.

Regional distribution of the blood. The uterus receives most of the blood flow required for normal placental perfusion, which reaches 500 ml/min by the end of pregnancy. Renal blood flow and plasma flow increase to 400 mL/min compared to non-pregnant values by week 16 of gestation, and remain at this high level to the end of pregnancy. Blood flow through the capillaries of the skin and mucous membranes increases, reaching a maximum of 300–400 mL/min by week 36. The increased skin blood flow is associated with peripheral vasodilatation. This is the reason why pregnant women "feel the heat", sweat easily and often profusely, and may complain of nasal congestion.

Respiratory System

Respiratory adaptations during pregnancy aim to optimize maternal and fetal oxygenation and to facilitate the transfer of waste CO_2 from fetus to mother.

Many pregnant women report a subjective perception of shortness of breath (dyspnea) in the absence of pathology. Its reason is unclear (Fig. 1.2, p. 10).

The mechanics of respiration change with pregnancy. The ribs bulge outward and the level of the diaphragm rises by 4 cm.

During pregnancy, tidal volume increases by 200 mL (40%), resulting in a 100–200 mL (5%) increase in vital capacity and a 200 mL (20%) decrease in the residual volume, thereby leaving less air in the lungs at the end of expiration. The respiratory rate does not change. This effect is thought to be due to increased secretion of progesterone. The end result is an increase in minute ventilation and a decrease in arterial PCO_2. Arterial PO_2 slightly raises.

A compensatory decrease in bicarbonate enables the pH to remain unchanged. Thus, pregnancy represents a state of compensated respiratory alkalosis (Fig. 1.3, p. 11).

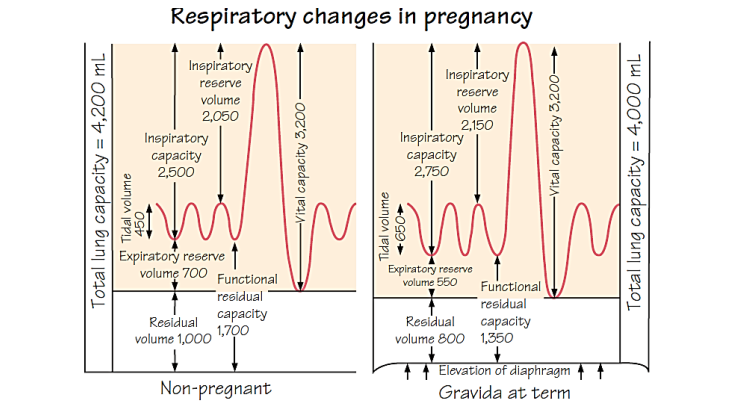
Alimentary System

Nausea ("morning sickness") occurs in >70% of pregnancies. Symptoms usually go away by 17 weeks.

Progesterone causes relaxation of gastrointestinal smooth muscle, resulting in delayed gastric emptying and increased reflux.

Pregnancy predisposes to cholelithiasis (gallstones). Most gallstones in pregnancy are cholesterol stones.

Pregnancy is a "diabetogenic state" with evidence of insulin resistance and reduced peripheral uptake of glucose (due to increased levels of placental anti-insulin hormones, primarily human chorionic



Effect of pregnancy on pulmonary-function testing

- Forced expiratory volume in one second (FEV_1)…no change in pregnancy (80–85% of vital capacity)
- Forced vital capacity (FVC)…….....no change (~ 3.5 L)
- FEV_1/FVC ratio…….....no change (>85%)
- Peak expiratory flow rate…….....no change (~ 450 L/min)

Fig. 1.2.

Source: Obstetrics and Gynecology at a Glance, 4th Edition Errol R. Norwitz, John O. Schorge

somatolactotropin or placental lactogen). These mechanisms are designed to provide a continuous supply of glucose to the fetus.

Renal System

Glomerular filtration rate (GFR) increases by 50% early in pregnancy, leading to an increase in creatinine clearance and a 25% decrease in serum creatinine and urea level.

Increased GFR results in an increase in filtered sodium. Aldosterone levels increase two-threefold to reabsorb this sodium.

Increased GFR also results in decreased glucose resorption. Therefore, 15% of normal pregnant women have glycosuria.

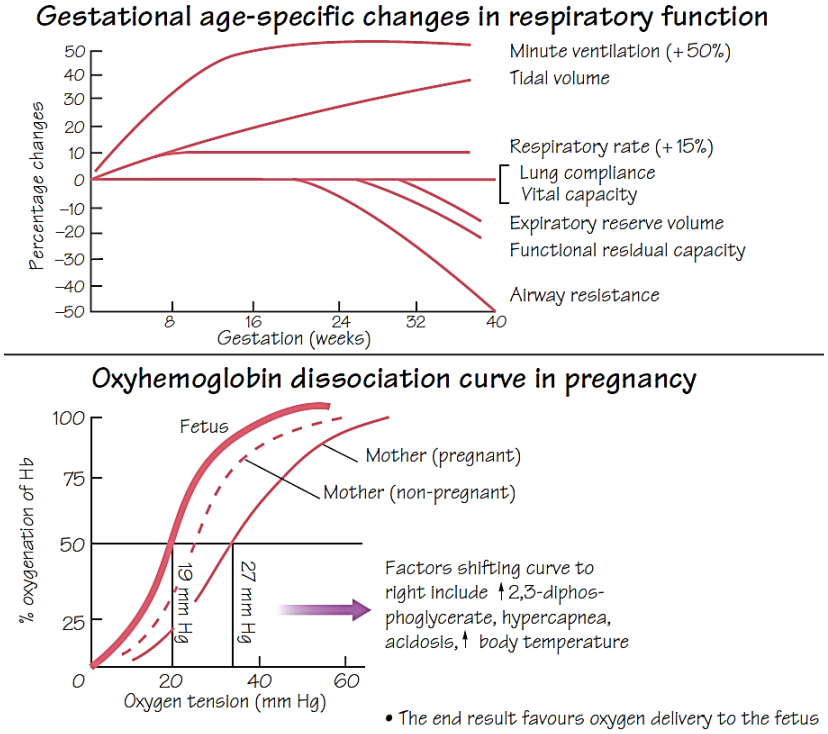


Fig. 1.3.

Source: Obstetrics and Gynecology at a Glance, 4th Edition Errol R. Norwitz, John O. Schorge

Moderate hydronephrosis and hydroureter are common sonographic findings that are due to high progesterone levels and partial obstruction from the fetal uterus.

Five percent of pregnant women have bacteria in their urine. Pregnancy does not increase the incidence of asymptomatic bacteriuria, but these women are more likely to develop pyelonephritis (20–30%).

Hematologic System

Increased intravascular volume results in dilutional anemia. Elevated erythropoietin levels lead to a compensatory increase in total red cell mass, but never fully correct the anemia.

A modest increase in white blood cell count (leukocytosis) can be seen during pregnancy, but the differential count should not change.

Mild thrombocytopenia (<150,000 platelets/mL) is seen in 10% of pregnant women. It's rarely clinically significant.

Pregnancy represents a hypercoagulable state with increased circulating levels of factors II (fibrinogen), VII, IX, and X. These changes protect the mother from excessive blood loss at delivery, but also predispose to thromboembolism.

Immune System

Human chorionic gonadotropin can reduce the immune response of pregnant women. In addition, serum levels of IgG, IgA and IgM decrease from the 10th week of pregnancy, reaching their lowest level by the 30th week and remaining at this level.

Weight Gain in Pregnancy

The better absorption of nutrients from the gut, the reduction of muscle tone and thyroid activity produce a decrease in the maternal metabolism. The body adapts to preserve and nourish the growing fetus. During pregnancy a woman inevitably gains weight. A healthy person may expect to gain 12.5 kg (range 9–15 kg) in pregnancy, of which 9 kg is gained during the last 20 weeks. The "ideal" weight gain is only a guide, and has individual variations. However, a woman whose prepregnancy weight is in the normal range (body mass index (BMI) 19–24.9) or who

is overweight (BMI 25–29.9) should avoid excessive weight gain (more than 15 kg), as it may be difficult for a woman to regain her pre-pregnancy weight after giving birth. This is a concern for many women who want to make sure they regain their pre-pregnancy figure and weight as soon as possible after having a baby.

After childbirth, weight loss varies greatly. Six weeks after giving birth, the average woman weighs 3 kg more than she did before pregnancy. Six months after childbirth, she will weigh about 1 kg more than before pregnancy.

The situation is different for obese and underweight women, both during pregnancy and after childbirth. An obese woman (BMI>30) should be encouraged to limit her weight gain during pregnancy, as she has an increased risk that pre-eclampsia may occur and that she will have a large baby. She should have a glucose tolerance test performed to exclude gestational diabetes mellitus, and she should be advised to eat a healthy but not a very low-energy diet.

Underweight women (BMI<18) should avoid pregnancy until they have gained weight, as there is a 20% chance of having a low birth weight baby.

Weight gain in pregnancy is caused by several factors:

- The products of conception — the fetus, placenta and amniotic fluid.
- The maternal factors — the uterus and breasts, the increased blood volume, the increased stores of fat, water retention.

Fetus, placenta and amniotic fluid. During the first 20 weeks of pregnancy fetal weight gain is slow; during the second 20 weeks it increases more rapidly. The increase in placental weight is opposite to the increase in fetal weight. The volume of amniotic fluid increases rapidly from 10 weeks, amounting to 300 mL at 20 weeks, 600 mL at 30 weeks and reaching 1000 mL at 35 weeks. After this a small decline in the total quantity of amniotic fluid occurs.

Maternal factors. The weight of the uterus increases throughout pregnancy. This happens faster during the first 20 weeks, when myohyperplasia occurs, than during the second 20 weeks, when most of the increase is due to stretching of muscle

fibers. The breasts increase in weight throughout pregnancy due to fat deposition, increased fluid retention, and the growth of glandular elements. Blood volume also increases during pregnancy. The amount of fat stored in adipose tissue depends on the amount of fat and carbohydrates in the diet. Typically, a baby gains 2.5–3.0 kg of fat, of which 90% is stored during the first 30 weeks. Fat contains 90–105 MJ of energy, which can be released after birth for various activities, including breastfeeding. In a normal pregnancy, the total amount of fluid in the body increases by 6–8 liters, of which 2–4 liters are extracellular. Most of the fluid is retained until the 30th week, but a pregnant woman who does not have clinical edema retains 2–3 liters of extracellular fluid in the last 10 weeks of pregnancy.

Energy

The resting metabolic rate (RMR) in pregnancy is 10–15% higher than in non-pregnant women. The extra energy required in the 40 weeks of pregnancy for the increased RMR, the growth of the fetus and placenta, the increase in size of the uterus and breasts, and the extra fat is about 250 MJ. This amounts to about 0.9 MJ (about 215 kcal) per day, the amount provided by two slices of bread and 100 ml of milk. A pregnant woman does not need to eat for two!

Endocrine Glands

The endocrine glands play a very important role in the physiology of reproduction. At 6–8 weeks, the functions of the corpus luteum are transferred to the placenta, which temporarily acts as a new endocrine organ or hormone production center.

The placenta produces a variety of hormones, among which protein and steroid hormones are important.

Human chorionic gonadotropin (hCG). Human chorionic gonadotropin is a glycoprotein. Human chorionic gonadotropin is chemically and functionally similar to pituitary luteinizing hormone. This subunit is biochemically similar to LH, FSH and TSH, while the beta subunit is relatively unique to hCG. Its molecular weight is 36,000–40,000 daltons. Placental GnRH can control the formation of hCG.

Functions:

(1) Stimulates progesterone secretion by the corpus luteum during pregnancy. Preservation and maintenance of the corpus luteum until 6 weeks of pregnancy is the main biological function of hCG.

(2) Human chorionic gonadotropin stimulates testosterone production by fetal male Leydig cells in association with fetal pituitary gonadotropins. It is indirectly involved in the development of male external genitalia.

(3) Possesses immunosuppressive activity that may suppress immune rejection of the fetus as a homograft in the mother.

(4) Stimulates steroidogenesis in the adrenal glands and placenta.

(5) Stimulates the maternal thyroid gland through its thyroid-stimulating activity.

(6) Promotes the secretion of relaxin by the corpus luteum.

Human chorionic gonadotropin levels in the different phases of pregnancy: hCG is produced by the syncytiotrophoblast of the placenta and released into the bloodstream of the mother and fetus. The half-life of hCG in plasma is around 36 hours. Using a radioimmunoassay, it can be detected in maternal serum or urine as early as 8–9 days after fertilization. In early pregnancy, the doubling time of the hCG concentration in plasma is 1.4–2 days. The maximum values in blood and urine reach 100 and 200 IU/ml between 60–70 days of pregnancy. The concentrations fall slowly and reach a low value of 10–20 IU/ml between 100 and 130 days. High hCG concentrations can be detected in: (a) multiple pregnancies, (b) hydatidiform mole or choriocarcinoma and relatively high concentrations in: (c) pregnancies with fetal 21-trisomy (Down syndrome). Lower plasma levels are observed in ectopic pregnancies and spontaneous abortions. Human chorionic gonadotropin disappears from the circulation within 2 weeks after delivery.

Human placental lactogen (HPL). It is also known as human chorionic somatomammotropin. The hormone is synthesized by the syncytiotrophoblast of the placenta. The hormone is chemically and immunologically similar to pituitary growth hormone and prolactin. Human placental lactogen is first detected in maternal serum in the 3rd week. The level rises progressively

from 5 to 25 μg/ml by the 36th week. The plasma concentration of HPL is proportional to the placental mass.

Functions: Human placental lactogen counteracts the effect of insulin. A high level of maternal insulin promotes protein synthesis. Human placental lactogen causes maternal lipolysis and promotes the transfer of glucose and amino acids to the fetus. As a strong angiogenic hormone, it contributes to the development of the fetal vascular system. It promotes the growth of the breasts for lactation.

Pregnancy-associated plasma protein A (PAPP-A) is secreted by the syncytiotrophoblast. It acts as an immunosuppressant during pregnancy.

Estrogen. In late pregnancy, estriol is the most important among three major estrogens. It produces in the syncytiotrophoblast. The placenta is an incomplete endocrine organ as it has no capability of independent steroidogenesis like that of the ovary. For steroidogenesis, it depends much on the precursors derived mainly from the fetal and partly from the maternal sources. The fetal adrenal gland and the placenta contain the complementary enzyme system.

Estriol is first detected at 9 weeks (0.05 ng/ml) and gradually increases to 30 ng/ml by the end of pregnancy. Fetal death, fetal anomalies (adrenal atrophy, anencephaly, Down's syndrome), hydatidiform mole, placental sulphatase or aromatase deficiency are associated with low estriol levels.

Progesterone. Up to 6 weeks of pregnancy, the corpus luteum secretes 17-hydroxyprogesterone. Then progesterone is produced by trophoblast and excreted in greater amount by the placenta. The daily rate of progesterone production at the end of pregnancy is around 250 mg. Low progesterone levels are observed in cases of ectopic pregnancy and abortion. High levels are observed in cases of hydatidiform moles and rhesus immunization. Plasma progesterone level falls rapidly and is undetectable after 24 hours after delivery.

Functions of steroid hormones (estrogen and progesterone)

- Together they play an important role in maintaining pregnancy. Estrogen causes hypertrophy and hyperplasia of the uterine myometrium, thereby increasing uterine accommodation and blood flow. Progesterone in combination with estrogen stimulates uterine growth, induces decidual endometrial changes necessary for implantation, and inhibits myometrial contraction.
- Mammary gland development and hypertrophy during pregnancy is enabled by a number of hormones. Ductal hypertrophy and proliferation occur under the action of estrogen, and the lobulo-alveolar system under the combined action of estrogen and progesterone.
- Both steroids are necessary for the maternal organs to adapt to the ever-increasing needs of the growing fetus.
- Progesterone keeps the uterus at rest by stabilizing lysosomal membranes and inhibiting the synthesis of prostaglandins. During labor, progesterone and estrogens act antagonistically.
- Estrogens sensitize the myometrium to oxytocin and prostaglandins.
- Estrogens play an important role in cervical maturation.
- Progesterone, together with hCG and decidual cortisol, suppresses T-lymphocyte-mediated tissue rejection and protects the conceptus.
- Together they inhibit the cyclic oscillatory activity of the gonadotropin-gonadal axis, thereby preserving the function of the gonads.

Relaxin. This is a peptide hormone that is structurally related to insulin. The main source of production is the corpus luteum of the ovary, but a certain amount of the hormone can also be produced by the placenta and the decidual membrane. It is believed that this hormone relaxes the myometrium, symphysis and sacroiliac joints during pregnancy and promotes cervical ripening through its biochemical action.

DIAGNOSIS OF PREGNANCY

The length of pregnancy is traditionally calculated by doctors in 10 lunar months or 9 calendar months and 7 days, or 280 days or 40 weeks, calculated from the first day of the last menstrual period.

This is called menstrual or gestational age. However, fertilization usually occurs 14 days before the expected absence of menstruation, and in the case of a normal 28-day cycle, approximately 14 days after the first day of menstruation. Thus, the true gestational age is calculated by subtracting 14 days from 280 days, i.e. 266 days. This figure is known as the age of fertilization or ovulation and is often used by embryologists.

Symptoms of pregnancy can be divided into three groups: presumptive, probable and definitive.

Presumptive symptoms and signs: It includes the features mainly appreciated by the women. (1) Amenorrhea. (2) Frequency of micturition. (3) Morning sickness. (4) Fatigue. (5) Breast changes. (6) Skin changes. (7) Quickening.

Probable signs: (1) Abdominal enlargement. (2) Braxton Hicks contractions. (3) External ballottement. (4) Outlining the fetus. (5) Changes in the size, shape and consistency of the uterus. (6) Jacquemier's sign. (7) Softening of the cervix. (8) Osiander's sign. (9) Internal ballottement. (10) Immunological test.

Definitive or absolute signs: (1) Palpation of fetal parts and perception of active fetal movements by the examiner at about 20th week. (2) Auscultation of fetal heart sounds. (3) Ultrasound evidence of embryo as early as 6th week and later on the fetus.

The following are the presumptive symptoms and signs (unrelated to uterus and fetus) of pregnancy:

Amenorrhea during the reproductive period in an otherwise healthy individual with normal previous menstruation is most likely due to pregnancy unless proven otherwise. However, cyclic bleeding may be observed up to 12 weeks of gestation until the decidual space disappears as a result of fusion of the *decidua vera* with the *decidua capsularis*. Such bleeding is usually scanty, lasts less than usual, and roughly corresponds to the date of the expected menstruation. This is called the placental sign. This type of bleeding should not be confused with the frequently occurring pathologic bleeding, i.e., threatened abortion. Pregnancy can, however, occur in women who have previously suffered from amenorrhea — during lactation and puberty.

Fatigue is a frequent symptom which may occur early in pregnancy.

Morning sickness occurs in about 50% of cases, and is more common in the first pregnancy than in subsequent pregnancies. It usually occurs shortly after the absence of menstruation and rarely lasts longer than the first trimester. The intensity of nausea varies from nausea when getting up to loss of appetite and vomiting. However, it usually does not affect the health of the mother.

Frequent urination is a rather unpleasant symptom in the 8th–12th week of pregnancy. Frequent urination is a rather unpleasant symptom in the 8th–12th week of pregnancy due to (1) pressure of the bulky uterus on the bottom of the bladder due to excessive prolapse of the uterus, (2) stagnation of the bladder mucosa, and (3) changes in the mother's osmoregulation, which lead to increased thirst and polyuria. When the uterus becomes erect again after the 12th week, the symptom disappears.

Breast discomfort in the form of a feeling of fullness and "tingling" occurs as early as the 6th–8th week, especially in first-time mothers.

Changes in the mammary glands can be observed between 6 and 8 weeks. Increase in size with vascular congestion, which is noticeable through the thin veins under the skin. The nipple and areola (primary) become more pigmented, especially in dark-skinned women. The secondary areola, which is especially pronounced in first-time mothers, usually appears around the 20th week.

Notable changes: (1) A linear pigmented area (linea nigra) extending from the symphysis pubis to the pubic cartilage is seen as early as 20 weeks. (2) Streaks (both pink and white) are seen to varying degrees in the lower abdomen, more on the sides. (3) Chloasma: pigmentation on the forehead and cheeks may appear around 24 weeks.

The "kick" (sensation of life) means the woman's perception of active fetal movements. It is usually felt around the 20th week, about 2 weeks earlier in multiple pregnancies. Its occurrence is a useful indicator for calculating the expected date of delivery with sufficient accuracy.

The following are likely signs of pregnancy (related to the uterus and how the mother feels):

Enlargement of the lower abdomen due to the growth of the uterus.

Changes in the pelvic area: Changes in the pelvic area are varied and occur at different times. Taken together, they can be informative in diagnosing pregnancy.

Jacquemie's sign or Chadwick's sign: This is a dark discoloration of the vaginal vestibule and the front wall, which becomes noticeable at the 8th week of pregnancy. The discoloration is associated with local vascular occlusion.

Vaginal signs: (A) In addition to cyanotic discoloration of the vaginal anterior wall. (B) The walls become soft and. (C) Abundant, non-irritating mucoid discharge appears in the 6th week. (D) In the 8th week of pregnancy.

Signs of the cervix: (A) The cervix softens as early as the 6th week (Goodell's sign), slightly earlier in women with many children. The pregnant cervix feels like the lips of the mouth, while in non-pregnant women it resembles the tip of the nose. (B) When examined with a mirror, the cervix is bluish in color. This is due to increased vascularity.

Uterine signs

- Size, shape and consistency — the uterus is enlarged to the size of hen's egg at 6th week, size of a goose egg at 8th week and size of a fetal head by 12th week. The pyriform shape of the non-pregnant uterus becomes globular by 12 weeks.
- There may be asymmetrical enlargement of the uterus if there is lateral implantation. This is called Piskacek's sign where one half is firmer than the other half. As pregnancy advances, symmetry is restored. The pregnant uterus feels soft and elastic.
- *Hegar's sign:* It is present in two-thirds of cases. It can be demonstrated between 6–10 weeks, a little earlier in multiparous women. This sign is based on the fact that: (1) the upper part of the body of the uterus is enlarged by the growing fetus, (2) the lower part of the body is empty and extremely soft and (3) the cervix is comparatively firm. Because of variation in consistency, on bimanual examination (two fingers in the anterior fornix and the abdominal fingers behind the uterus), the abdominal and vaginal fingers seem to oppose below the body of the uterus. Examination must be gentle to avoid the risk of abortion.
- *Palmer's sign:* Regular and rhythmic uterine contraction can be elicited during bimanual examination as early as 4–8 weeks. Palmer in 1949, first described it and it is a valuable sign when elicited. To elicit the test, the uterus is cupped between the internal fingers and the external fingers for about 2–3 minutes. During contraction, the uterus becomes firm and well defined but during relaxation, becomes soft and ill defined. While the contraction phase lasts for about 30 seconds, with increasing duration of pregnancy, the relaxation phase increases. After the 10th week, the relaxation phase is so much increased that the test is difficult to perform.

Fundal height is increased with progressive enlargement of the uterus. Approximate duration of pregnancy can be ascertained by noting the height of the uterus in relation to different levels in the abdomen.

The following formula is a useful guide for the purpose. The uterus remains a pelvic organ until the 12th week; it may just be palpable in the abdomen as a suprapubic bulge. The height of the uterus is at the midpoint of the distance between the pubic symphysis and the umbilicus at 16 weeks; at the level of the umbilicus at 24 weeks; and at the junction of the lower third and upper two-thirds of the distance between the umbilicus and the ensiform cartilage at 28 weeks.

The distance between the umbilicus and the ensiform cartilage is divided into three equal parts. The fundal height corresponds to the junction of the upper and middle third at 32 weeks, up to the level of ensiform cartilage at 36th week and it comes down to a 32-week level at 40th week because of engagement of the presenting part. To determine whether the height of the uterus corresponds to 32 weeks or 40 weeks, you need to check the attachment of the head. If the head is floating, it corresponds to 32 weeks of pregnancy, and if the head is engaged, it corresponds to 40 weeks of pregnancy (Fig. 1.4, p. 22).

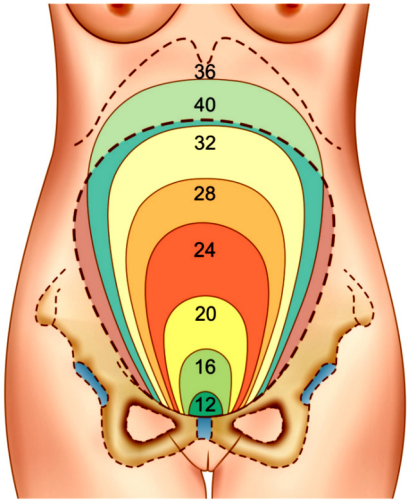


Fig. 1.4. The level of the fundus uteri at different weeks.
Note the change of the uterine shape

Source: Antenatal care.pptx

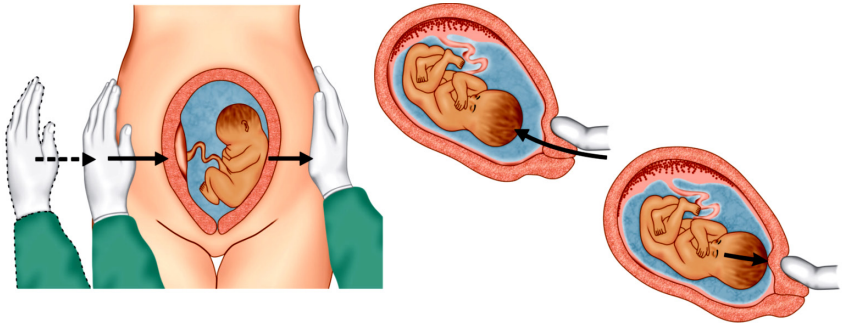
External ballottement is usually elicited as early as 20th week when the fetus is relatively smaller than the volume of the amniotic fluid. It is difficult to elicit in obese patients and in cases with scanty *liquor amnii*. It is best elicited in breech presentation with the head at the fundus.

Internal ballottement can be elicited between 16th–28th week. The fetus is too small before 16th week and too large to displace after 28th week. However, the test may not be elicited in cases with scanty *liquor amnii*, or when the fetus is transversely placed (Fig. 1.5).

Immunological test. Principle: Pregnancy tests are based on the detection of an antigen (hCG) present in the mother's urine or serum using commercially available polyclonal or monoclonal antibodies. Timing: Diagnosis of pregnancy by detection of hCG in maternal serum or urine can be made on days 8–11 after conception. The test is not reliable after 12 weeks.

Other uses of pregnancy tests. In addition to diagnosing uterine pregnancy, the tests are used to diagnose ectopic pregnancy,

to monitor pregnancy after in vitro fertilization and embryo transfer, and to monitor cases of hydatidiform mole and choriocarcinoma. The accuracy of the test ranges from 98.6–99.0%. In the non-pregnant state, the level is below 1 mIU/ml. Definitive or absolute signs are related to the fetus.



A B C

Fig. 1.5. (A) External ballottement; (B and C) steps showing how to elicit internal ballottement

Source: Diagnosis of pregnancy garbha nidana

Palpation of fetal parts and perception of active fetal movements by the examiner: Active fetal movements can be felt at intervals by placing the hand over the uterus as early as 20th week. It not only gives positive evidence of pregnancy but of a live fetus. The intensity varies from a faint flutter in early months to stronger movements in later months.

Auscultation: Fetal heart sound (FHS) is the most conclusive clinical sign of pregnancy. With an ordinary stethoscope it can be detected between 18–20 weeks. The sounds resemble the tick of a watch under a pillow. Its location varies with the position of the fetus. The rate varies from 110–160 beats per minute.

Ultrasonic

The intradecidual gestational sac (GS) is identified as early as 29–35 days of pregnancy. Fetal obstruction and gestational age are determined by detecting the following structures using transvaginal ultrasound: gestational and yolk sac at 5th menstrual week; fetal pole

and cardiac activity — 6 weeks; embryonic movements at 7 weeks. Fetal gestational age is best determined by measuring crown-rump length (CRL) between 7 and 12 weeks (variation ±5 days). The Doppler effect of ultrasound can reliably detect fetal heart rate up to 10 weeks.

Routine ultrasonography at 18–20 weeks allows a detailed study of fetal anatomy, placental location and cervical canal integrity. Gestational age is determined by measuring biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femoral length (FL). The most accurate measurement is made between 12 and 20 weeks (variation ±8 days). BPD is a measurement of the diameter of a developing baby's skull, from one parietal bone to the other. The anatomy of the fetal organs is examined to determine any malformations. The viability of the fetus is determined by a real-time ultrasound. The absence of a fetal heartbeat confirms fetal death.

Estimation of gestational age using BPD, HC, AC and FL in the third trimester is less accurate (variation ±3 weeks). Fetal AC at the level of the umbilical vein is used to assess gestational age and fetal growth profile (IUGR or macrosomia). Fetal weight estimation can be done using tables. Amniotic fluid volume determination is performed to detect oligohydramnios (AFI<5) or polyhydramnios (AFI>25). Placental anatomy: location (fundus or previa), thickness (placentomegaly in diabetes) or other abnormalities are noted. Fetal life, fetal number, presentation and organ anatomy are re-evaluated as in the first and second trimesters.

Magnetic resonance imaging (MRI) can be used to examine fetal anatomy, perform biometrics, and evaluate complex malformations. Radiographic evidence of a fetal skeletal shadow may be visible as early as 16 weeks.

Chronological occurrence of specific symptoms and signs of pregnancy

After 6–8 weeks: Symptoms — amenorrhea, morning sickness, frequent urination, fatigue, breast discomfort. Signs: breast enlargement, visible, engorged veins under the skin; nipples and

areola more pigmented. Internal examination shows: positive Jacquemier's sign, softening of the cervix, bluish discoloration of the cervix and Osiander's sign; positive Hegar and Palmer's signs. Enlargement of the uterus varies from the size of a hen's egg to a medium-sized orange. Immunological tests are positive. Sonographic confirmation of a pregnancy ring.

At 16 weeks: Symptoms — except amenorrhea, all previous symptoms disappear. Signs: Breast changes — pigmentation of the primary areola and prominence of Montgomery's tubercles, colostrum. Uterus halfway between pubis and umbilicus, Braxton Hicks contractions, uterine souffle, fetal ballottement. Sonographic diagnosis.

At 20 weeks: Symptoms — amenorrhea, quickening (18 weeks). Signs: appearance of a secondary areola (20 weeks), linea nigra (20 weeks), uterus at the level of the umbilicus at 24 weeks, Braxton Hicks contractions, external ballottement (20 weeks), fetal parts (20 weeks), fetal movements (20 weeks), FHS (20 weeks), internal ballottement (16–28 weeks). Sonographic diagnosis.

Signs of a previous birth

The following signs should be considered when diagnosing early labor.

- Breasts become flabbier; nipples are prominent in those who breastfed their child; a primary areola pigmentation remains, as do the white striae.
- The abdominal wall is laxer and looser. Silvery-white streaks and linea alba may be present.
- The uterine wall is less rigid and the contour of the uterus is broad and round rather than ovoid.
- The perineum is lax and evidence of old scars from previous perineal tears or episiotomies may be found.
- The introitus is gaping and carunculae myrtiformes are present.
- Vagina is more spacious.
- Cervix in nulliparous is conical with a round external os. In parous women, it becomes cylindrical and the external os is a transverse patulous slit that can admit the fingertip. However, with surgical manipulation, a nulliparous cervix can also be torn and resembles a multiparous cervix.

ESTIMATION OF GESTATIONAL AGE AND PREDICTION OF EXPECTED DELIVERY DATE

Gestational age is approximately 280 days, calculated from the first day of the last normal menstrual period (LMP). The accurate LMP is the most reliable parameter for estimating gestational age. But in a significant number of cases (20–30%), patients either cannot remember the LMP or report it inaccurately. The matter becomes more complicated when conception occurs during lactational amenorrhea or shortly after stopping birth control pills (ovulation may be delayed by 4–6 weeks), or in case of bleeding in early pregnancy. The following parameters are useful either individually or in combination to predict gestational age with a reasonable degree of accuracy.

Patient statement

- Date of fertile coitus: If the patient can remember with certainty the date of each fertile coitus, it is quite reliable to predict the expected date of delivery with an accuracy of 50% within 7 days on either side. To calculate the expected date, add 266 days to the date of each fertile coitus.
- Naegele's formula: Provided that the periods are regular, it is a very useful and commonly practiced means of calculating the expected date. Its range of prediction is about 50%, with 7 days on either side of the EDD (estimated delivery date). If the interval of the cycles is longer, the extra days must be added, and if the interval is shorter, the lesser days must be subtracted to get the EDD.

Calculation of the estimated delivery date

This is done according to Naegele's formula (1812) by adding 9 calendar months and 7 days to the first day of the last normal period (28-day cycle). Alternatively, one can count back three calendar months from the first day of the last period and then add seven days to get the estimated delivery date; usually the first method is used.

Example: The woman had her first day of her last menstrual period on January, 1. By adding 9 calendar months you get October, 1 and then adds 7 days, i.e. October, 8, which becomes the expected delivery date. In IVF pregnancies, the LMP date is 14 days before the embryo transfer date (266 days).

A probable date of birth can be calculated by adding 20 weeks in primigravidae and 22 weeks in multiparous women to the date of acceleration.

Previous records: You must add the required weeks to get 40 weeks.

- The size of the uterus before the 12th week corresponds to the period of amenorrhea.
- Height of the uterus above the pubic symphysis in relation to the landmarks of the abdominal wall.
- Auscultation of the FHR at least after 18–20 weeks with an ordinary stethoscope and after 10 weeks with Doppler ultrasound. Palpation of fetal parts at the 20th week.
- Registration of a positive immunological pregnancy test at the time of the first missed menstruation, not earlier.
- Ultrasound findings are at the earliest: (a) gestational sac — at 5 weeks; (b) measurement of CRL determined at 7 weeks is about 10 mm; in 10 weeks — 34 mm (CRL in cm + 6.5 = week of pregnancy). CRL is the most accurate (variation ±5 days). The second trimester by BPD, HC, AC and FL measurement. The most accurate values are between 12 and 20 weeks (variation ±8 days). The third trimester — less reliable, variation ±16 days.

Estimation of fetal weight

- The height of the uterus above the pubic symphysis in centimeters multiplied by the abdominal circumference measured at the level of the umbilicus gives the weight of the fetus in grams. *Example*: Height of the uterus above the pubic symphysis = 34 cm and abdominal circumference = 95 cm. The weight of the fetus is 34×95=3230 g. However, the approximate size of the fetus is modified by the amount of amniotic fluid and the thickness of the abdominal wall.
- Sonography: Fetal weight is estimated by combining a number of biometric data, such as BPD, HC, AC and FL. The tables (Hadlock, Shepard) are currently used (computer software). The estimated weight of the fetus is likely to be within 10 percent of the actual weight.

FETUS-IN-UTERO

The fetus lies in the uterus in a closed sac filled with amniotic fluid. It has enough freedom of movement until it becomes relatively fixed in the later months of pregnancy. Until then, the fetus should be examined regularly, noting its position, presentation, location and attitude. An idea of the size of the fetus or the amount of amniotic fluid can be obtained.

Lie: Lie is a relationship of the long axis of the fetus to the long axis of the centralized uterus or maternal spine. The most common lie is longitudinal (99.5%). The lie can be transverse or oblique. Sometimes the lie is unstable until the onset of labor, then it becomes either longitudinal or transverse.

Presentation: The part of the fetus that occupies the lower pole of the uterus (pelvic brim) is called the presentation of the fetus. Accordingly, the presentation can be cephalic (96.5%), podalic (3%), scapular and other (0.5%). When more than one part of the fetus presents, it is called a compound presentation.

Presenting part: The presenting part is defined as the part of the presentation that lies above the internal os and is palpated by the examining finger through the cervical opening. In the cephalic presentation, the presenting part can be the vertex (most common), the brow or face, depending on the degree of flexion of the head.

Similarly, fetal legs may be flexed (complete breech presentation), extended (patent breech presentation), or a foot may be present (foot presentation) in a breech presentation. However, the terms "presentation" and "presenting part" are often used interchangeably and are more commonly used in clinical practice according to the latter definition.

Attitude: The relationship of the different parts of the fetus to each other is called the fetal attitude. The universal attitude is the flexion attitude. In the later months, the head, trunk and limbs of the fetus maintain a flexed position of all joints, forming an ovoid mass roughly corresponding to the shape of the ovoid uterus. The characteristic flexible posture may be modified by the amount of amniotic fluid. There may be exceptions to this universal posture and there may be extension of the head (deflexion of the vertex, forehead or face,

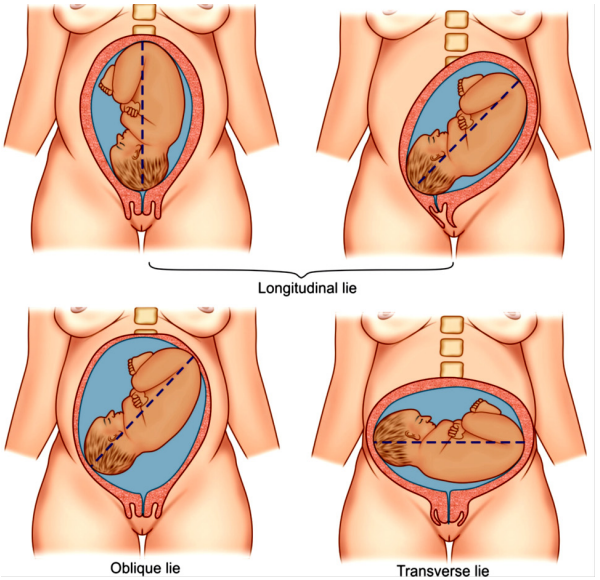


Fig. 1.6. Variations of the fetal lie

Source: BOOK TITLE: DC Dutta's Textbook of Obstetrics

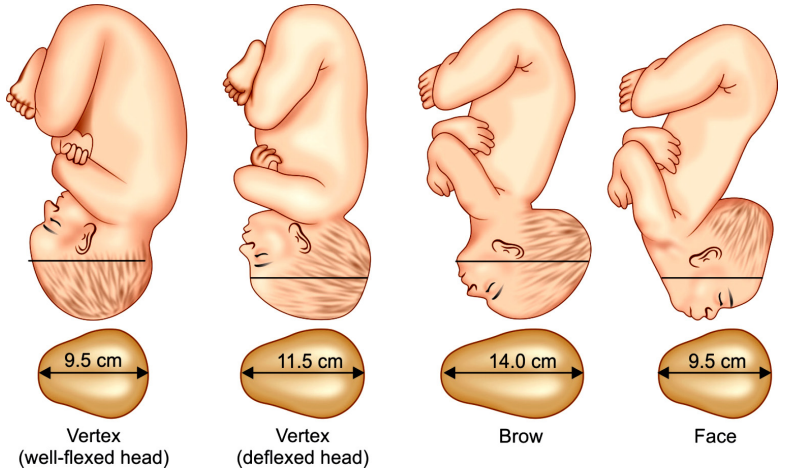


Fig. 1.7. Variations of head presentation in different postures

Source: Book title: DC Dutta's Textbook of Obstetrics

depending on the degree of extension) or the legs may be extended in the breech presentation. The course of labor may be modified accordingly under such circumstances (Fig. 1.6, 1.7, p. 29).

Denominator: It is an arbitrary bony fixed point on the presenting part that relates to the different quadrants of the maternal pelvis. The following are the denominators of the different presentations: occiput in the vertex, mentum (chin) in the face, anterior eminence in the forehead, sacrum in the coccyx and acromion in the shoulder.

Position: It is the relationship of the denominator to the different quadrants of the pelvis. To describe it, the pelvis is divided into equal segments of 45° to place the denominator in each segment. So, theoretically there are 8 positions for each presenting part.

The anterior, posterior, right or left position refers to the maternal pelvis with the mother in the upright position. However, some have retained the conventional description of the four vertex positions. The vertex occupying the left anterior quadrant of the pelvis is the most common and is called the left occipitoanterior (LOA). This is the first vertex position. Similarly, the right occipitoanterior (ROA) is the second vertex; the right occipitoposterior (ROP) is the third vertex, and the left occipitoposterior (LOP) is the fourth vertex position (Fig. 1.8, p. 31).

In the flexed position, the fetus takes the shape of an egg, the long vertical podalic axis of which measures about 25 cm at the time of birth. The fetus comfortably adapts to the longitudinal axis of the ovoid shape of the uterine cavity at the time of birth. Therefore, the longitudinal lie predominates.

The head presentation, which represents the absolute majority in longitudinal lies, can be explained by the following: (1) gravitation — the heavier head sinks downwards; (2) accommodation — the smallest circumference of the flexed head is about 27.5 cm and the circumference of the pelvis with both thighs flexed is about 32.5 cm. The head and podalic poles can be comfortably accommodated in the narrow lower pole and the wider fundal area of the uterus, respectively.

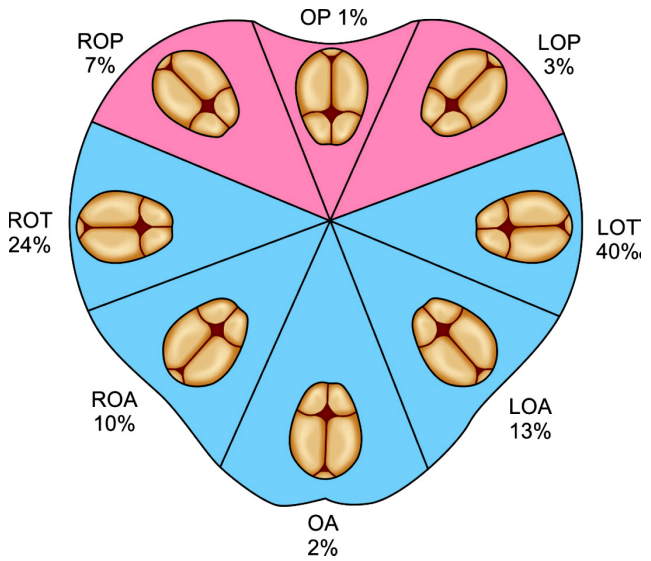


Fig. 1.8. The position and relative frequency of the vertex at the onset of labor

Source: Book title: DC Dutta's Textbook of Obstetrics

METHODS OF OBSTETRIC EXAMINATION

Abdominal examination

A thorough and systematic examination of the abdomen beyond 28 weeks of pregnancy can usefully diagnose the lie, position, presentation and attitude of the fetus. It is possible that the lie and presentation of the fetus will change, especially due to excess amniotic fluid, so regular check-ups are necessary.

Preparations: Verbal consent for the examination is obtained. The patient is asked to empty the bladder. She is placed in a supine position with the thighs slightly flexed. The abdomen is completely exposed. The examiner stands on the right side of the patient (Fig. 1.9, p. 32).

Inspection: Determine (1) whether the ovoid uterine is longitudinal, transverse or oblique, (2) contour of the uterus — fundal notch, convex

or flattened anterior wall, cylindrical or spherical shape, (3) excessive enlargement of the uterus, (4) skin condition of the abdomen for signs of ringworm or scabies and (5) any incision scars on the abdomen.

Palpation: Symphysis fundal height (SFH): In case of deviation, the uterus must be centralized. The upper border of the fundus is located on the ulnar border of the left hand and this point is marked. The distance between the upper border of the pubic symphysis and the marked point is measured in centimeters with a tape measure. At 24 weeks, the SFH measured in centimeters corresponds to the number of weeks up to 36 weeks. A deviation of ±2 cm is accepted as normal (Fig. 1.10).

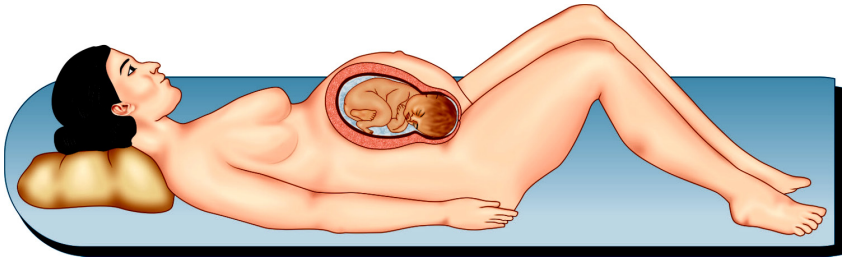


Fig. 1.9. Position of the woman during the obstetric examination

Source: Chapter 07 Pregnancy Diagnosis

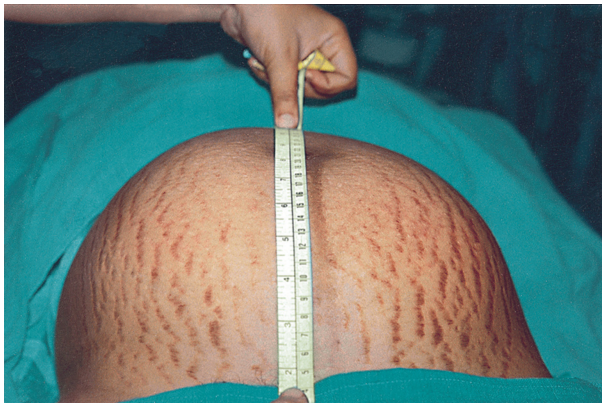


Fig. 1.10. Symphysis fundal height

Source: Chapter 07 Pregnancy diagnosis

There are situations where the height of the uterus may not correspond to the period of amenorrhea. The conditions in which the height of the uterus is greater than the period of amenorrhea are the following: (1) wrong date of the last menstrual period, (2) twins, (3) polyhydramnios, (4) large baby, (5) pelvic tumors — ovarian or myoma, (6) hydatidiform mole and (7) concealed accidental bleeding. The conditions in which the height of the uterus is less than the period of amenorrhea are the following: (1) wrong date of the last menstrual period, (2) scanty amniotic fluid supply, (3) fetal growth retardation and (4) intrauterine fetal death.

Obstetric maneuvers (Leopold maneuvers)

Palpation should be performed with extreme gentleness. Clumsy and pointless palpation is not only uninformative, but can also lead to excessive irritation of the uterus. Palpation should be stopped during Braxton–Hicks contraction or uterine contraction during labor.

Fundal grip (First Leopold maneuver): Palpation is performed looking at the patient's face. The entire fundal area is palpated with both hands placed flat on it to determine which pole of the fetus is located in the fundus: (a) broad, soft and irregular mass, suggestive of breech, or (b) smooth, hard and spherical mass, suggestive of a head. In the transverse position, neither of the fetal poles can be palpated in the fundal area.

Lateral or umbilical grip (Second Leopold maneuver): Palpation is done looking at the patient's face. The hands must be placed flat on both sides of the umbilicus to palpate the sides and front of the uterus in turn to find out the position of the back, limbs and anterior shoulder. The back is characterized by a gently curved and resistant feel. The "limb side" is comparatively empty and has small, knob-like, irregular parts. After identifying the back, it is important to note its position, whether it is placed forward or towards the flank or transversely. Likewise, the arrangement of the small parts must be noted, whether they are placed laterally or in front, occupying both sides. The location of the anterior shoulder should be sought. It forms a well-marked prominence in the lower part of the uterus above the head. It can be placed near the midline or far from the midline.

Pawlik's grip (Third Leopold maneuver): The examination is performed looking at the patient's face. The overstreched thumb and four fingers of the right hand are placed over the lower pole of the uterus, holding the ulnar edge of the palm at the upper border of the pubic symphysis. As the fingers and thumb approach, the presenting part is clearly grasped (if not locked) and mobility from side to side is also tested. In the transverse position, Pawlik's grip is empty.

Pelvic grip (Fourth Leopold maneuver): The examination is performed facing the patient's feet. Four fingers of both hands are placed on either side of the midline in the lower pole of the uterus and parallel to the inguinal ligament. The fingers are pressed downward and backward in a sort of approximation to the fingertips to palpate the part that occupies the lower pole of the uterus (presentation). If it is the head, the following features should be noted: (1) precise area of presentation, (2) attitude and (3) engagement.

To determine the presenting part, the greater mass of the head (cephalic prominence) is carefully palpated and its relationship to the limbs and back noted. The attitude of the head can be determined from the relative position of the sincipital and occipital poles. Engagement is determined by noting the presence or absence of the sincipital and occipital poles or whether there is convergence or divergence of the fingertips on palpation. This pelvic grip with both hands is preferred as it is most comfortable for the woman and provides the most information (Fig. 1.11, p. 35).

Auscultation. Auscultation of clear fetal heart sounds (FHS) not only helps in diagnosing a live baby, but the localization of maximum intensity can also resolve doubts about fetal presentation. Fetal heart sounds are best heard through the back (left scapular region) in vertex and breech presentation, where the convex part of the back is in contact with the uterine wall. However, in facial presentation, heart sounds are heard through the fetal chest.

Typically, the maximum intensity of the FHS is below the umbilicus in cephalic presentation and around the umbilicus in breech presentation. In different positions of the vertex, the location of the FHS depends on the position of the back and the degree

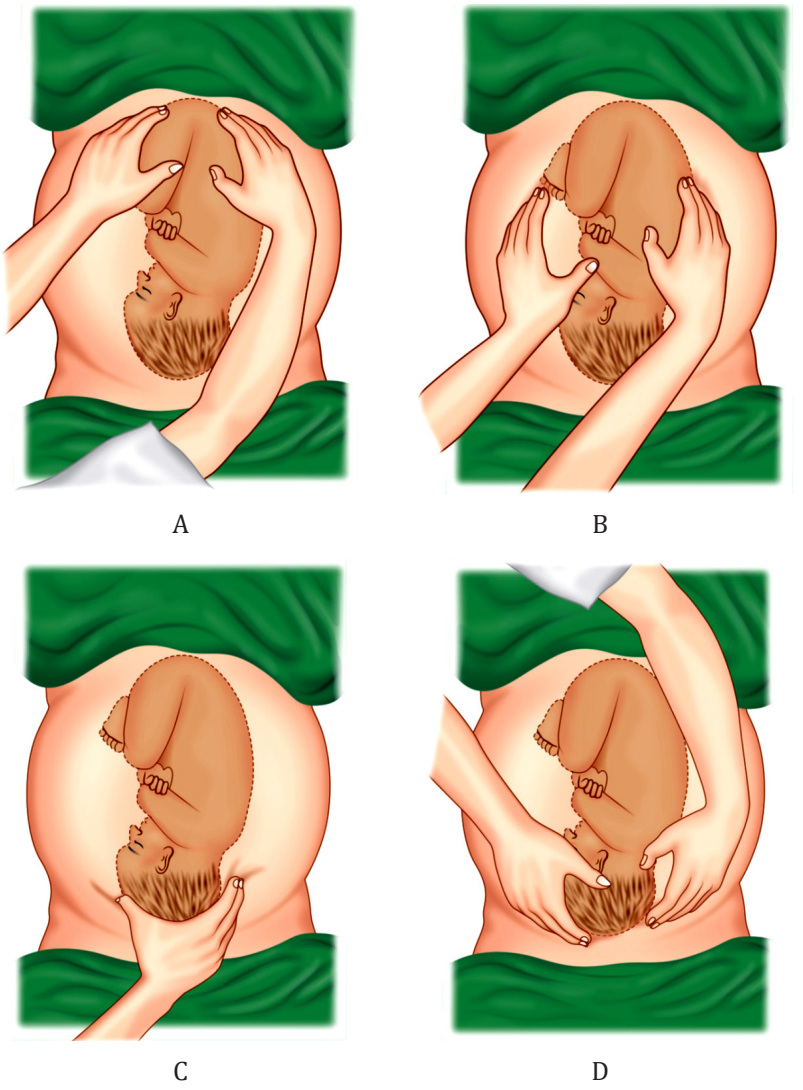


Fig. 1.11. Obstetric maneuvers (Leopold maneuver):
(A) Fundal grip (first Leopold); (B) Lateral grip (second Leopold);
(C) Pawlik's grip (third Leopold); (D) Pelvic grip (fourth Leopold)

Source: Chapter-07 Pregnancy diagnosis

of head depression. In the occipitoanterior position, the FHS is located in the middle of the spinoumbilical line on the same side. In the occipitolateral position, it is heard more laterally and in the occipitolateral position it is heard far back towards the mother's flank on the same side.

Internal examination. Diagnosis of fetal presentation and position may not be accurate during internal examination during pregnancy when the cervix remains closed. However, during labor, accurate information can be obtained by palpating the sagittal suture and fontanelles through the open cervix. There is no need to emphasize the importance of strict aseptic precautions in vaginal examination.

Ultrasound. Diagnosis of the lie, presentation and position can be difficult in cases of severe obesity, irritated uterus, excessive amniotic fluid and deeply engaged head, especially in primigravidae. Ultrasound can be used to localize the head and body.

ENGAGEMENT

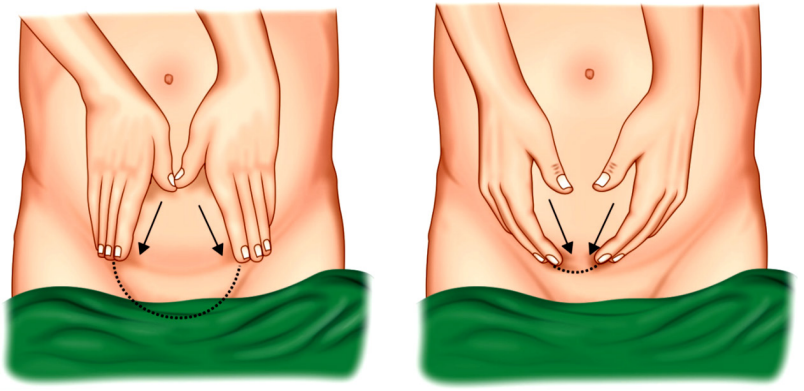
When the greatest horizontal plane, the biparietal, has passed the plane of the pelvic brim, the head is said to be engaged.

Diagnosis

First pelvic grip: (1) Both the poles (sinciput and occiput) are not felt per abdomen. However, the sincipital pole can be felt with difficulty even though the head is engaged. (2) Divergence of the examining fingers of both hands while trying to push downwards on the lower abdomen. Convergence of the fingers while palpating the lateral aspects of the fetal head indicates that the head is not yet engaged (Fig. 1.12, 1.13, p. 37).

Vaginal examination: Lower pole of the unmolded head is usually at or below the level of the ischial spines.

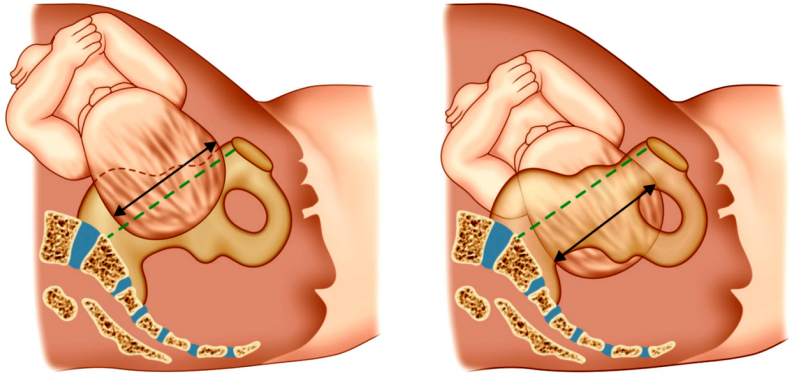
Significance: Engagement of the head always excludes disproportion at the brim, as the head is the best pelvimeter. The traditional concept that in primigravidae, the engagement occurs by 38 weeks is not corroborative in clinical practice. In majority, the engagement occurs between 38–42 weeks or even during the first stage of labor. In multigravidae, however, the engagement occurs



A B

Fig. 1.12. Abdominal palpation to determine engagement of the head: (A) Divergence of fingers — engaged head, (B) Convergence fingers — not engaged

Source: Chapter-08 The Fetus-in-Utero BOOK TITLE: DC Dutta's Textbook of Obstetrics



A B

Fig. 1.13. The relationship of the biparietal diameter to the pelvic brim and that of lower pole of the head to the ischial spines in: (A) Non-engaged head; (B) Engaged head

Source: Chapter-08 The Fetus-in-Utero BOOK TITLE: DC Dutta's Textbook of Obstetrics

late in the first stage of labor after the rupture of the membranes. However, if the head fails to engage in primigravidae even at 38th week, the causes are to be sought for. Common causes are: (1) Deflexed head placing the larger diameter to engage, (2) Cephalopelvic disproportion or big head or a combination of both, (3) Polyhydramnios, (4) Poor formation or yielding of lower uterine segment — preventing the head to sink into the pelvis, (5) Hydrocephalus, (6) Placenta previa, (7) Pelvic tumors — ovarian or myoma, (8) High pelvic inclination, (9) Functional — when no cause can be detected (20%).

Fixed head: The word "fixed" should not be used to designate an engaged head. Whereas, an engaged head is fixed but conversely, the fixed head is not necessarily engaged. When an egg is placed on the egg cup, it remains fixed yet the maximum diameter does not pass through the rim. Similarly, the head may be fixed to the brim but that does not mean that the maximum diameter of the head (biparietal) will pass through the brim.

VAGINAL EXAMINATION

Time: Vaginal examination is performed in the antenatal clinic when the patient first visits the clinic before 12 weeks. This is done (1) to diagnose pregnancy, (2) to confirm the size of the uterus with the period of amenorrhea and (3) to exclude any pelvic pathology. However, internal examination is omitted if there is a history of abortion and occasional vaginal bleeding in the current pregnancy. Ultrasound examination has replaced routine internal examination. It is more informative and without known side effects.

Procedure: The vaginal examination is performed in the antenatal clinic. The woman must empty her bladder before the examination and be placed in a supine position with the thighs flexed and the buttocks at the foot of the table. The hands are washed with soap and a sterile glove is placed on the examining hand (usually the right).

Steps

Inspection: By separating the labia — with the two left fingers (thumb and index finger) — the type of vaginal discharge (if any)

is determined. A cystocele, uterine prolapse or rectocele must be diagnosed.

Speculum examination: This should be done before the bimanual examination, especially if the vaginal smear is to be taken for exfoliative cytology. A bivalve speculum is used. The cervix and the fornix of the vagina are examined with the help of a good light source placed behind it. If there is discharge, a cervical smear for exfoliative cytology or a vaginal smear from the upper vagina can be taken.

Bimanual: Two fingers (index and middle) of the right hand are inserted deep into the vagina while the left hand separates the labia. The left hand is now placed suprapubic. A gentle and systematic examination should be performed to determine:

(1) Cervix: consistency, direction and possible pathologies.

(2) Uterus: size, shape, position and consistency. Early pregnancy is the best time to accurately determine the size of the uterus and the duration of pregnancy.

(3) Adnexae: Any mass palpable through the fornix. If the introitus is narrow, a finger may be inserted for examination. No attempt should be made to assess the pelvis at this stage.

Lecture 2

PRETERM LABOR. MISCARRIAGE

Topic Relevance

Preterm birth is the single most important factor affecting perinatal outcomes in terms of morbidity and mortality. Preterm labor is defined by WHO as the onset of regular uterine contractions, between viability and 37 weeks' gestation, associated with cervical effacement and dilatation. Current guidelines from many progressive countries describe a "threshold of viability" between 22 and 26 weeks; thus, preterm birth occurs between 22–26 weeks and 37 weeks' gestation. Up to 30–40% of cases preterm birth are iatrogenic due to deliberate induction of labor or pre-labor cesarean section for conditions causing maternal or fetal compromise. In other cases, preterm labor occurs as a result of spontaneous preterm labor, with or without rupture of the diaphragm, and the factors causing these births are the subject of much scientific interest and discussion.

Educational Materials

EPIDEMIOLOGY DEFINITIONS

Preterm birth is defined as delivery of a baby before 37 completed weeks of pregnancy. Legally, in the UK, the 1992 Amendment to the Infant Life Preservation Act defined the limit of viability at 24 weeks. However, a small number of infants born at 23 weeks survive. Mortality in preterm babies born after 32 weeks' gestation is similar to that of babies born at term. The risk of neonatal mortality or survival with disability becomes significant in very preterm infants (defined as those born between 28 and 32 weeks) but is most significant in extremely preterm infants (defined as those born before 28 weeks). In modern obstetric practice, the estimation of gestational age is based mainly on fetal biometry measured by ultrasound

in the first or second trimester, rather than on the date of the last menstruation. However, in the past, assessment of gestational age was not always accurate and pediatric statistics were based on birth weight rather than gestational age data. Low birth weight is defined as less than 2.25 kg, very low birth weight as less than 1.5 kg and extremely low birth weight as less than 1 kg. Using these definitions to describe outcome data leads to blurring of the distinction between preterm babies and small-for-gestational-age babies, particularly in the low birth weight category, and also fails to differentiate the normally grown preterm neonate from the neonate who is both preterm and small for gestational age.

Incidence

Each year, about 15 million babies are born prematurely worldwide. The incidence of preterm birth varies considerably around the world. In most developed nations the rate of preterm birth is below 10%, the UK rate is around 7% and in the USA the rate fluctuates between 9% and 12% with huge geographical or interstate variation. Countries with preterm birth rates exceeding 15% include Malawi, Congo, Comoros, Zimbabwe, Equatorial Guinea, Mozambique, Gabon, Pakistan, Indonesia, Mauritania and Botswana. The greatest numbers of preterm births occur in India, China, Nigeria, Pakistan, Indonesia and the USA. Preterm birth rates are increasing in almost all countries for which reliable data are available. Especially in the developed world, this is associated with assisted reproduction increasing the rates of multiple pregnancy and an increased tendency to obstetric intervention. US strategies to encourage obstetricians to resort less to elective preterm births to treat conditions such as growth restriction and pre-eclampsia have resulted in a significant localized decrease in the incidence of preterm birth, although this applies mainly to late preterm births. The proportion of preterm births at each gestational age or age week increases almost exponentially from about 32 weeks onwards. This means that the great majority of preterm births occur at later gestations. In England about 15% of all preterm births occur before 32 weeks, whilst 70% occur between 35 and 37 weeks (Fig. 2.1, p. 42). The UK rate of preterm birth before 32 weeks has remained relatively stable

at 1–2%. About a quarter of preterm births are planned deliveries, usually for pre-eclampsia, intrauterine growth restriction or maternal illness. The remaining births are caused by preterm labor and delivery.

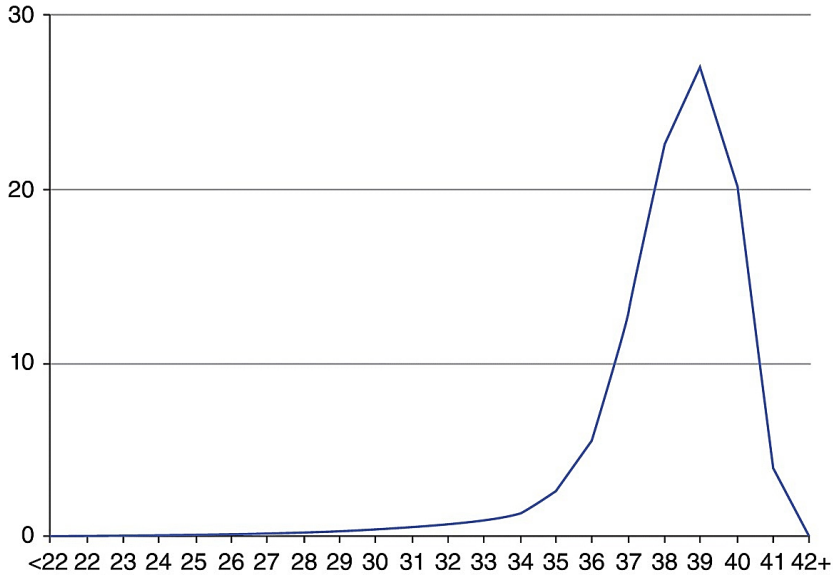


Fig. 2.1. Live birth percentages by gestation, 2011 birth cohort, England and Wales

Source: UK Office for National Statistics

The incidence of spontaneous preterm labor is lowest in women in their 20s. The risk is increased in teenagers and over 30 years old. There is a higher incidence of preterm labor in first pregnancies. The risk gradually decreases with each subsequent term of labor. Marital status, cigarette smoking, environmental stress, poor nutrition and use of alcohol, coffee and street drugs (especially cocaine) are associated with an increased risk of preterm birth. However, many of these factors are interconnected and all the factors are associated with social disadvantage. There is a connection between race and risk of preterm delivery. In studies of populations where black and white women have similar lifestyles, levels of income and access to medical

care (e.g. in US Army personnel), preterm delivery rates show a less marked ethnic variation. However, the identification of specific genetic polymorphisms that increase the risk of preterm labor does suggest that genetic and environmental factors may be involved, which explains the increased risk of preterm labor in certain ethnic populations. The studies have shown that prenatal smoking cessation programs reduce the risk of preterm birth, although there is currently no evidence that other interventions, such as increased frequency of prenatal care, dietary advice, or increased social support, reduce the risk of preterm birth.

Neonatal outcomes after preterm birth

As of 2014, preterm births became the main cause of death of children under the age of 5 throughout the world. Of the 6.3 million children who died before the age of 5 years in 2013, 52% died from infection and 44% died in the neonatal period. The three leading causes of death were complications of preterm birth (15.4%), pneumonia (14.9%) and complications of labor and delivery (10.5%). Previously infection had been the main cause of death in this age group but global improvements in the management of pneumonia, diarrhea and measles since the turn of the century has significantly reduced the impact of these diseases on childhood mortality. Survival rates of preterm infants differ dramatically by place of birth. Over 90% of extremely preterm babies (<28 weeks) born in low-income countries die within the first few days of life, while less than 10% of babies born at this gestation die in high-income settings, a 10:90 survival gap. The risk of a neonatal death due to complications of preterm birth is more than 12-fold higher in Africa than in Europe. In developed countries, particularly in the UK, survival rates of preterm infants have steadily improved over the past three decades, mainly due to the introduction of surfactant therapy, improved neonatal respiratory therapy, and increased use of prenatal steroids (Fig. 2.2, p. 44). The Epicure study, which examined extremely preterm infants born in 1995, reported mortality rates of 100%, 90% and 80% for preterm infants admitted to neonatal units at 21, 22 and 23 weeks of gestation respectively. A subsequent Epicure II study repeated this exercise in a similar cohort born in 2006 and found that although

survival rates for babies born between 22 and 25 weeks' gestation had increased since 1995, the pattern of major neonatal morbidity and survival rates had remained unchanged. Therefore, improved survival for very preterm infants has been associated with an increase in the proportion of children with cerebral palsy who were born preterm. Neonatal mortality rises gradually between 32 and 28 weeks, from 2 to 8%, and then more dramatically and exponentially to 80% at 23 weeks.

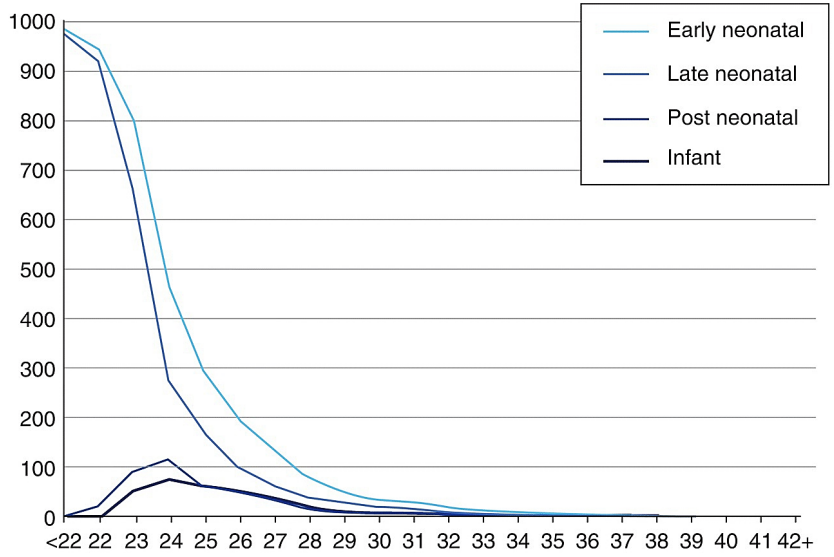


Fig. 2.2. Infant mortality rate by gestation, 2011 birth cohort, England and Wales

Source: UK Office for National Statistics

In the past, surfactant deficiency leading to neonatal respiratory distress syndrome (RDS) was the major cause of morbidity and mortality in preterm infants. Alveolar surfactant production begins at 30–32 weeks' gestation. Therefore, preterm infants born before 30 weeks are at highest risk. Over the past three decades, the impact of RDS on neonatal morbidity and mortality has been significantly reduced by the use of antenatal corticosteroids and exogenous

surfactant replacement. However, the risk of developing chronic lung disease, defined as the need for ventilation or supplemental oxygen at 36 weeks after conception, continues to increase due to the increased survival of extremely preterm infants. The fetal and neonatal brain is especially susceptible to injury between 20 and 34 weeks. The greatest risk of long- term neurodevelopmental problems is in infants born before 28 weeks or with the birth weight less than 1000 g. The Epicure study showed that approximately half infants born before 26 weeks' gestation had some disability at 30 months and approximately one-quarter had severe disability. Cerebral palsy may be related to periventricular hemorrhage, post-hemorrhagic hydrocephalus and periventricular leukomalacia. Hypoxia-ischemia is a major risk factor for neonatal cerebral damage. However, there is growing evidence for a strong relation between chorioamnionitis, fetal inflammation and the risk of periventricular leukomalacia. The overall risk of cerebral palsy associated with preterm birth at any gestational age (e.g., 23–36 weeks) is seven times that of children born at term; however, the risk increases dramatically with decreasing gestational age, with relative risks of 14, 46, and 70 times for children born before 34, 31, and 28 weeks, respectively. The risk of visual impairment due to retinopathy of prematurity is inversely related to gestational age at birth and directly related to the concentration and duration of oxygen treatment. The risk of retinopathy of prematurity rises dramatically from less than 10% at 26 weeks to above 50% in infants born at 24 weeks. About 3% of infants born before 28 weeks' gestation will require a hearing aid and 50% will be found to have learning difficulties at school requiring additional educational support. Preterm births are associated with an increased prevalence of other medical disabilities, learning difficulties, and behavioral and psychological problems even in those without cerebral palsy. The risk of autism and mental retardation is 10-fold increased in preterm infants born before 28 weeks, and that of schizophrenia is 5-fold increased. Difficulty with cognitive processes contributes to an increased risk of school problems in children born preterm. Only half of children born before 28 weeks are able to enter preschool

with their peer group. The proportion of children born preterm who experience academic difficulties increases with age as the complexity of the schoolwork increases. Even among adults born prematurely with no apparent medical problems, there are lower rates of high-level education and higher rates of low income and dependence on Social Security benefits. Mothers of infants born preterm are at increased risk of experiencing depressive symptoms. The length of time that the newborn preterm infant must stay in the hospital also affects the ability of the mother to fulfill her role in the family. Families caring for a child born preterm face long-term and multiple challenges. The impact on families is long term: parents, siblings, finances and family functioning suffer. Families will need to continue to manage the effects of prematurity when the children are toddlers, reach school age, become adolescents and, in some cases, into adulthood. Parents' marital relationships may become strained, often leading to divorce and subsequent exacerbation of parenting difficulties. Parents will experience increased levels of stress due to difficulties with childcare, peer relationships and the child's self-esteem, the impact of the child's difficulties on family routines and worries about the child's future. Siblings are affected because of the decreased attention that they receive from their parents.

Endocrinology and biochemistry of labor

To effectively predict and prevent labor requires a good understanding of the endocrinology and biochemistry underlying

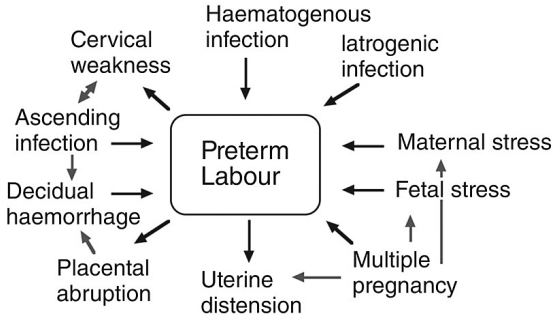


Fig. 2.3. Endocrinology and biochemistry underlying the onset of labor
Source: Evidence based medicine & ethical dilemmas in reproductive medicine

the onset of labor in humans, both at term and preterm (Fig. 2.3, p. 46). Our understanding of the mechanisms leading to the onset of labor in humans remains incomplete, in part because the mechanisms of labor onset appear to have evolved differently in different animal species, making direct extrapolation of data from animal models to humans not always valid.

LABOR AS AN INFLAMMATORY PROCESS

Throughout pregnancy the uterine cervix needs to remain firm and closed whilst the body of the uterus grows by hypertrophy and hyperplasia but without significant fundal dominant contractions. For labor to be successful the cervix needs to be converted into a soft and pliable structure that can efface and dilate and the uterus needs to become a powerful contractile organ. There is no single endocrine or biochemical switch in the human that changes the uterus from its not-in-labor state to its in-labor state. The onset of labor is a gradual process which begins several weeks before delivery itself with changes in the lower pole of the uterus which cause cervical ripening and effacement. The onset of clinically identifiable contractions is a relatively late event in this process. Cervical ripening occurs through breakdown of collagen, changes in proteoglycan concentrations and an increase in water content. The lower segment of the uterus also stretches and relaxes and behaves physiologically more like the cervix than like the contractile upper segment of the uterus. These changes in the lower segment of the uterus are associated with an increase in the production of inflammatory cytokines, particularly interleukin (IL)-8 and prostaglandins from the overlying fetal membranes and decidua and from the cervix itself. Cervical ripening is associated with an influx of inflammatory cells into the cervix which release matrix metalloproteins that contribute to the anatomical changes associated with ripening. The later increase in finally dominant contractility in the upper segment of the uterus is associated with an increase in the expression of receptors for oxytocin and prostaglandins, in gap junction proteins, which mediate electrical connectivity between myocytes, and in more complex

changes in the intracellular signaling pathways which increase the contractility of the myocytes.

Roles of progesterone, corticotropin-releasing hormone and oxytocin

In many species progesterone is thought to play an important role in suppressing the onset of labor. Progesterone has a generally anti-inflammatory action within the uterus. As discussed above, many of the biochemical events associated with cervical ripening and the onset of labor are similar to those at sites of inflammation. In most species the onset of labor is heralded by withdrawal of progesterone. So, for example, in the rodent, prostaglandin-mediated regression of the corpus luteum leads to a fall in progesterone concentrations immediately prior to the onset of labor. In the sheep increased production of cortisol from the fetal adrenal signals fetal maturation and induces placental 17α-hydroxylase, which increases synthesis of estrogen at the expense of progesterone, again leading to progesterone withdrawal immediately prior to the onset of labor. There is no systemic withdrawal of progesterone in the human prior to the onset of labor, although there is an increase in the expression of genes formerly repressed by progesterone, which has led to the hypothesis of a "functional progesterone withdrawal" mediated by changes in the expression or function of progesterone receptors or cofactors needed for the function of the progesterone receptor. Another hypothesis is that inflammatory events seen within the uterus at the time of labor are associated with increased activity of the transcription factors: nuclear factor (NF)-κB and AP-1 (transcription factors strongly associated with inflammation in other contexts such as asthma, inflammatory bowel disease or arthritis). NF-κB and AP-1 inhibit the function of the progesterone receptor and so could mediate functional progesterone withdrawal. Although in the mouse progesterone concentrations fall due to luteolysis just prior to labor, there is still sufficient circulating progesterone concentrations to activate progesterone receptors. In the mouse it appears that the final event leading to parturition is the increased production of surfactant protein A from the fetal lung, which

stimulates the activity of NF-κB within the uterus leading to an influx of inflammatory cells, an increase in inflammatory cytokine synthesis and depression of the residual function of the progesterone receptor. It is an attractive hypothesis that pulmonary maturation in humans may signal the final phase of the onset of labor, but now there is no direct evidence that this mechanism applies in humans.

Circulating levels of corticotropin-releasing hormone (CRH), synthesized in the placenta, increase progressively throughout pregnancy and especially during the weeks prior to the onset of labor. CRH-binding protein concentrations fall with advancing gestational age such that, approximately 3 weeks prior to the onset of labor the concentration of CRH exceeds that of its binding protein. Unlike in the hypothalamus, placental CRH is upregulated by cortisol. Several studies have linked placental production of CRH with the timing of birth and have demonstrated that a premature rise in CRH is associated with preterm delivery. The upregulation of CRH by cortisol suggests a mechanism by which the fetus, through increased adrenal cortisol production, may signal its maturation and control the timing of birth. For much of pregnancy the CRH receptor expressed by the myometrium is linked to second messenger systems that promote relaxation. Near the term, however, CRH may enhance the contractile response to oxytocin and may stimulate the production of prostaglandins from the fetal membranes and the placenta. In the monkey, uterine contractions occur only at night. In the days preceding labor and delivery there are nocturnal non-fundal dominant contractions which have been termed "contractures". The conversion from contractures to contractions is mediated by an increase in the production of oxytocin from the maternal posterior pituitary gland. In the monkey, therefore, while the fetus might signal its general readiness to be born through increased cortisol production from the adrenal, the precise timing of birth is signaled by the mother. This may be a mechanism of defense against predators which provides that delivery is always at night. Contrary to the experience of many obstetricians, this phenomenon does not apply to the human. There is no increase in the production of oxytocin associated with the onset or progression of either preterm or term labor. There is,

however, an increase in the expression of oxytocin receptors within the uterus and there is local production of oxytocin in the uterus, decidua and fetal membranes. Although oxytocin probably does not play an important role in the precise timing of parturition in humans, increases in the density of oxytocin receptors suggests that oxytocin does play a role in mediating contractility. Recent studies have shown that oxytocin acts not only to stimulate the uterus to contract, but also to upregulate inflammatory mediators within the uterus, therefore adding an additional "pre-labor" mechanism of action for the hormone. Oxytocin also has important postnatal functions: mediating the milk let-down reflex, contracting the uterus to prevent postpartum hemorrhage, and affecting the mother-child bond.

Causes of preterm labor

Preterm labor is not a single disease entity but is a syndrome that may have one or more causes. Research into the prognosis and prevention of preterm labor is complicated to some extent by the fact that many researchers consider this syndrome as a separate disease. With the exception of studies conducted specifically in multiple pregnancies and in populations of women with short cervixes, most clinical trials of interventions to prevent or delay preterm labor have not attempted to differentiate subjects according to the underlying cause. Similarly, many studies which have attempted to identify biomarkers for preterm labor have not taken into account its multiple etiology. Preterm labor has been connected to cervical incompetence, abnormalities of hemostasis, infection within the uterus, placental abruption or decidual hemorrhage, fetal or maternal stress and multiple pregnancy. These various factors may act together to increase the likelihood of preterm delivery or to affect the gestational age at which preterm delivery occurs. Multiple pregnancy probably leads to preterm delivery through at least three mechanisms. Over-distension of the uterus leads to premature upregulation of contraction-associated proteins and of factors which mediate cervical ripening, all of which have been shown to be sensitive to mechanical stretch. Multiple pregnancy is associated with multiple placentas and therefore with an earlier rise in placental CRH concentrations in the circulation. The development of multiple

corpora lutea may lead to increased production of relaxing and to premature cervical ripening. The incidence of multiple pregnancy has increased due to the trend of delayed childbirth, since multiple births occur with a greater frequency amongst older mothers. However, a major contributing factor has been the associated increase in the use of assisted reproductive technologies. In the UK, this problem has been addressed to some extent by limiting the number of embryos transferred by in vitro fertilization, although poorly controlled methods of ovulation induction may continue to contribute to the problem.

Cervical function

Due to improved survival in early pregnancy, there is now an overlap between second trimester pregnancy loss and preterm birth. Cervical incompetence was diagnosed in women who experienced persistent, often rapid and painless pregnancy loss at the end of the second trimester. More recently, the concept of cervical competence as a continuum has evolved. The cervical length and strength, together with the quality of the cervical mucus, contribute to cervical function, both to retain the pregnancy within the uterus and to exclude potential bacterial pathogens from ascending from the vagina. Numerous studies have demonstrated a strong relationship between cervical length and the risk of preterm delivery. The cervix may be damaged (or completely removed) by surgery in the treatment of cervical cancer or, rarely, during a difficult instrumental vaginal delivery, or cesarean section at full dilatation. There were associations between diethylstilbestrol exposure in utero and developmental anomalies in the genital tract and cervical weakness. This is no longer a problem in modern obstetric practice, as the cohort of women exposed in the 1960s is now past reproductive age. A short or partially dilated cervix can allow bacteria to ascend to the lower pole of the uterus where, acting through Toll-like receptors of the innate immune system that recognize bacterial components, stimulate the production of inflammatory cytokines, prostaglandins, and the inflammatory response. This leads to maturation and shortening of the cervix, which in turn reduces its ability to act as a mechanical or microbiological

barrier and ultimately leads to the development of localized or generalized chorioamnionitis and preterm delivery. Therefore, a short or weak cervix may contribute to preterm labor, not only leading to a simple miscarriage in the second trimester, but also contributing to the risk of ascending infection leading to more classic spontaneous preterm labor. Delivery by cesarean section with complete or near complete cervical dilatation is now recognized as a risk factor for preterm labor. The likelihood that a difficult delivery results in mechanical damage to the cervix as a result of trauma from an unsuccessful instrumental delivery, from a uterine incision made in the cervical tissue rather than the lower segment, or from damage to the cervix caused by the need to depulpate a deeply located fetal head. There is an association between risk of preterm delivery and cervical intraepithelial neoplasia (CIN). The greatest risk is in those women with CIN who have had a particularly deep large loop excision of the transformation zone (LLETZ) or a cold knife cone biopsy. In women who have had a deep LLETZ or a cold knife cone biopsy, mechanical damage to the integrity of the cervix is probably a major aetiological factor in their risk of preterm labor. However, there is a smaller underlying risk associated with CIN alone. It may be that human papillomavirus (HPV) infection is an independent risk factor for preterm birth. It is also possible that underlying factors associated with the development of CIN after HPV infection in a particular woman may also be factors that increase the risk of preterm labor.

Genital tract infection

There is a close relationship between infection in the uterus and the onset of spontaneous preterm labor. As already mentioned, activation of inflammatory mediators is a central part of the normal biology of labor. Therefore, infection in the uterus is able to activate all biochemical pathways that will ultimately lead to cervical ripening and uterine contractions. It is estimated that about 40% of all preterm births are associated with bacterial infection. The most likely source of infection is bacteria traveling from the vagina through the cervix to the lower part of the uterus. However, bacteria can also enter the amniotic cavity by hematogenous route or by introduction during

invasive procedures. After preterm labor, histologic chorioamnionitis is usually more common and severe at the site of membrane rupture than at other sites, such as over the placenta or umbilical cord. Inflammation of the fetal membranes is also seen in almost all cases of congenital pneumonia. The bacteria identified in most cases of congenital infection are often found in the lower genital tract of the mother as well, and in premature twin births, chorioamnionitis is more common and severe in the first twin than in the second (although this is not always the case). All of these factors suggest that ascending infection from the lower genital tract is the most common mechanism for the development of chorioamnionitis. The most common microbes isolated from the amniotic cavity of women with preterm labor are *Ureaplasma urealyticum, Fusobacterium and Mycoplasma hominis*. More than 50% of patients in preterm labor will have more than one microorganism isolated from the amniotic cavity. Microorganisms can be found in the fetal membranes of most women who deliver either at term or preterm. It is likely that some cases of spontaneous preterm labor are due to an excessive inflammatory response to a lesser degree of bacterial invasion of the amniotic cavity. So, for example, bacterial vaginosis (see below) may be a greater risk factor for preterm labor in women who carry a high secretory form of the tumor's necrosis factor (TNF)-α gene. There is currently considerable interest in the role of microbial communities in the vagina in the etiology of preterm labor. The collective term for the range of bacterial species in the vagina is "vaginal microbiota". A collective term for all bacterial genes present is "vaginal microbiome" (although the term "microbiome" is often used interchangeably with "microbiota" to define a microbial community occupying a fairly well-defined habitat that has distinct physicochemical properties). The study of the genes of bacteria present in the vaginal microbiome is described as metagenomics. During the reproductive years, the vaginal microbiota is usually dominated by lactobacilli, accounting for more than 90% of all bacterial species present. Lactobacilli secrete lactic acid, which maintains a low pH level that is hostile to other microorganisms and has anti-inflammatory effects. Lactobacilli also secrete specific

antimicrobial proteins. In a minority of women, the vaginal microbiota is impoverished with lactobacilli, and this can lead to overgrowth of anaerobic organisms associated with bacterial vaginosis (BV), such as Gardnerella vaginalis, which create a biofilm that allows other opportunistic bacteria to thrive. The increase in estrogen concentration during pregnancy increases the availability of vaginal mucosal glycogen, an energy source for lactobacilli. Therefore, in general, the proportion of lactobacilli in the vagina increases during pregnancy. The relationship between the structure of the vaginal microbiota and the risk of preterm labor varies from population to population. In some, but not all, US populations where lactobacillus depletion is common, lactobacillus-depleted vaginal dysbiosis microbiota is a risk factor for preterm labor. In the UK, the prevalence of vaginal dysbiosis in pregnancy is low but is probably still a risk factor. However, the predominance of one particular species, *Lactobacillus iners*, appears to be a risk factor for both cervical shortening and preterm labor. *Lactobacillus iners* has a lower ability to secrete anti-inflammatory lactic acid isomers or antimicrobial proteins and may represent a transitional organism between a healthy vaginal microbiota and vaginal dysbiosis or bacterial vaginosis.

Hemorrhage

Placental rupture can lead to the onset of preterm labor. This is thought to be due to the release of thrombin, which stimulates myometrial contractions via protease-activated receptors but independently of prostaglandin synthesis. This may explain the clinical impression that preterm labor associated with chorioamnionitis is often rapid, whereas labor associated with placental rupture is less rapid because there is no pre-maturation of the cervix. Thrombin generation may also play a role in preterm labor associated with chorioamnionitis when it is released as a result of decidual hemorrhage.

Fetal and maternal stress

There is evidence that both fetal and maternal stress may be risk factors for preterm labor. Fetal stress may arise in association with abnormal placentation and growth restriction. Maternal stress could

be due to environmental factors. In both cases it is postulated that oversecretion of cortisol leads to upregulation of CRH production in the placenta.

Prediction of preterm labor

In most cases of preterm labor, obstetric management is limited to attempts to suppress contractions in women who are already in labor. As discussed in more detail below, this strategy is essentially ineffective. Obstetric strategies to reduce perinatal morbidity and mortality associated with preterm birth should ideally include early identification of women at risk and the use of preventive therapy. Prediction of preterm birth can be considered in two broad scenarios. First, it is prognostication at a time remote from the birth event itself, intended to guide possible preventive therapy. Second, prediction of labor in symptomatic women, essentially designed to distinguish those who are actually in preterm labor from those who have preterm labor but are not at risk of imminent labor. Attempts have been made to develop risk assessment systems based on sociodemographic characteristics, anthropomorphic features, past history, patient behavior and habits, and factors of current pregnancy. None of these systems have positive predictive value or sensitivity, making them clinically useful for identifying individual women at risk. Most systems rely heavily on obstetric history and are therefore not relevant to first-time mothers. There are currently no screening tests that are routinely applied to first-time mothers or to multiparous women who are not at high risk of preterm birth. Women at high risk of preterm labor are initially identified solely on the basis of past obstetric history. A single preterm birth in the past increases the risk of preterm birth in a subsequent pregnancy 4-fold compared with women who had a previous preterm birth at term. An obstetric history consisting of preterm labor followed by preterm delivery increases the risk of preterm birth in the third pregnancy compared with an obstetric history consisting of preterm labor followed by preterm delivery. This may be because the latter group has a disproportionate number of women whose preterm labor was due to “non-recurrent” causes such as placental abruption, whereas in the former group, preterm

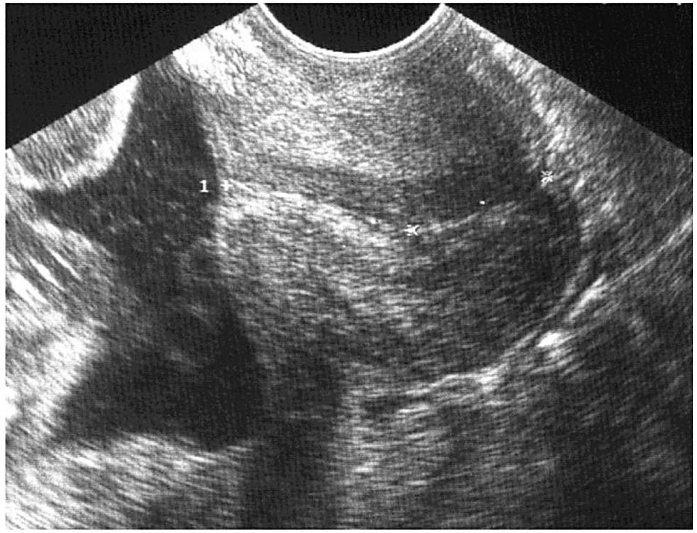
labor followed by preterm delivery may be due to cervical injury during the initial preterm labor.

Ultrasound measurement of cervical length

There is very good evidence that transvaginal sonographic measurement of cervical length can be used to identify women at risk of preterm labor in both low- and high-risk pregnancies and in women who are symptomatic (Fig. 2.4. p. 57).

Transabdominal measurement of cervical length is unreliable because of the need for a full bladder, which may compress the cervix, resulting in an overestimation of its length, and because it is more difficult to obtain an adequate view of the cervix with this technique. Transvaginal ultrasound should be performed with an emptied bladder. The transducer is placed in the anterior vaginal wall without undue pressure on the cervix, and optimally, the inner and outer echogenic endocervical mucosa should be identified along the entire length of the canal. Two strategies are now widely used to detect risk in asymptomatic women (those without symptoms of labor): a single measurement in the middle of the second trimester or serial measurement of cervical length throughout the second and early third trimesters of pregnancy.

A single measurement of cervical length, usually during a routine ultrasound scan between 18 and 22 weeks, is widely used to identify individuals at high risk of preterm labor for inclusion in intervention trials. If a screening strategy using a single ultrasound measurement of cervical length is used, a score between 21 and 24 weeks of gestation appears to be a better predictor of preterm birth risk than a score before 20 weeks' gestation. It is clear that the closer to the actual onset of preterm labor an assessment of cervical length is made, the more likely the cervix is to be short. It could be argued that identifying the risk of preterm birth at 23 weeks may be too late for any potential preventive measures to be fully effective. Furthermore, such a strategy would fail to identify any women with pregnancy loss or preterm labor occurring before 23 weeks. A large number of studies have examined the association between gestational age, cervical length and risk of preterm birth (Fig. 2.5, p. 58). Many studies have used uniform cut-off values. For example,



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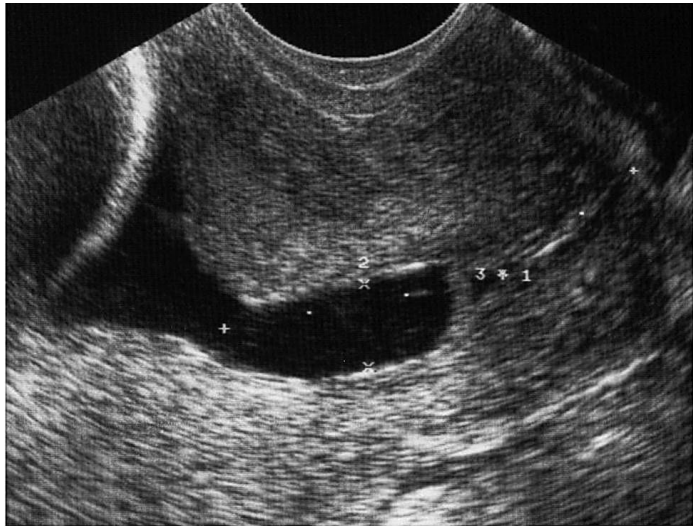

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Fig. 2.4. Transvaginal sonographic measurement of cervical length
Source: Premature Cervical Change And The Use Of Cervical Cerclage

a cervical length of 15 mm or less at 20–24 weeks predicts the risk of preterm labor before 34 weeks' gestation by approximately 50% in the low-risk group. It is the absolute cervical length, not the presence or absence of a funnel, that is the main predictor of spontaneous preterm labor (although obviously the presence of a funnel will lead to a reduction in cervical length). It has been suggested that the introduction of routine measurement of cervical length during ultrasound scans for second trimester anomalies would allow screening in low-risk groups. This concept is largely based on the assumption that there is an effective intervention (see section on progesterone and cervical cerclage). The value of routine measurement of cervical length also depends on the prevalence

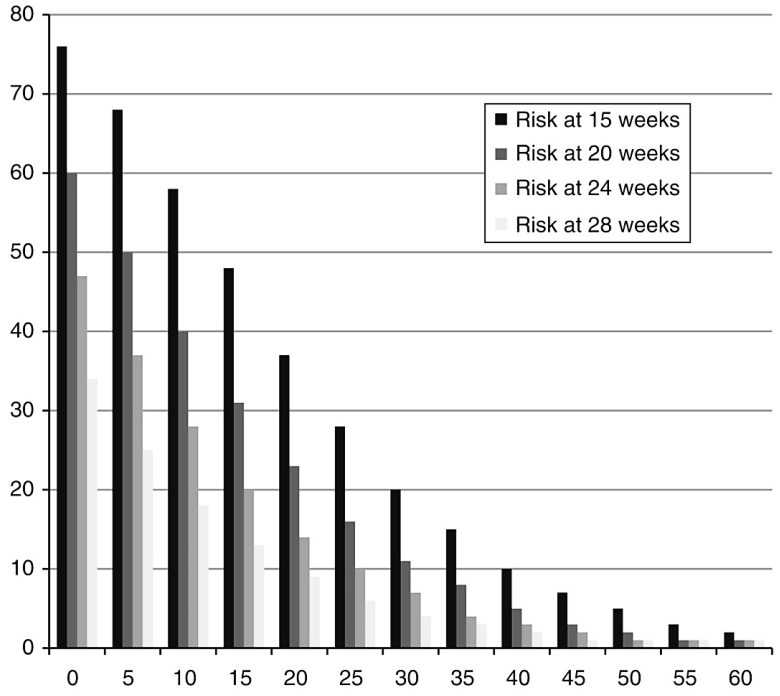


Fig. 2.5. The relationship between gestational age, cervical length and the risk of preterm delivery

of a short cervix and the incidence of preterm birth in the background population. In UK populations this approach will only detect about 15% of all preterm births, a reflection of the multi-etiological nature of the syndrome. Women at high risk of preterm birth may be offered serial measurement of cervical length to assess their risk of preterm labor. This approach appears to be superior in assessing the risk of preterm delivery. This method has been widely promoted as a way to identify women who would benefit from taking progesterone during pregnancy. It is also a particularly useful approach in women with a history of a previous preterm birth or second-trimester pregnancy loss in whom a diagnosis of cervical insufficiency or incompetence is not clear and can be used to reduce the number of unnecessary cervical cerclage procedures performed. With this management strategy, cervical cerclage is indicated either when the cervical length decreases to a fixed limit, usually 25 mm, or falls below the 10th or 3rd cervical length centile at a given gestational age. In continental Europe, it is common to perform a vaginal assessment of cervical length at every prenatal appointment, although multicenter studies have shown that this technique is not useful in predicting the risk of preterm labor.

Bacterial vaginosis (BV)

As already discussed, BV is a risk factor for preterm birth, although most studies have shown that treating BV with antibiotics does not decrease the risk. The results of studies on the risk of preterm birth associated with BV vary widely. However, it seems that overall, BV seems to roughly double the risk of preterm labor. There also appeared to be an association between gestational age at diagnosis of BV and risk of preterm labor: if BV was diagnosed early in pregnancy, it was associated with a higher risk of preterm labor. Routine screening for BV is therefore not performed in low-risk groups. Some obstetricians include screening for BV in the management of high-risk groups and it is currently performed using non-genetic methods, although the future introduction of DNA sequence-based bacteriology may change this situation. Currently, the diagnosis of BV can be made on the basis of Gram staining

of vaginal fluid using the Nugent or Spiegel criteria, gas-liquid chromatography of vaginal fluid (detection of a high ratio of succinate to lactate), or on clinical findings based on high vaginal pH, fishy odor in thin homogeneous vaginal discharge, and the presence of key cells in the discharge on a wet preparation. There is no significant difference in the ability of each of these diagnostic tests to predict preterm birth. Although there is reasonably good evidence that BV is a risk factor for preterm delivery, it is less clear that treating it with antibiotics is beneficial. This may be in part because various studies of BV have used different antibiotics in different regimens and at different times, but it may also reflect the fact that antibiotics may not necessarily result in the re-establishment of normal bacterial flora. The two antibiotics commonly used in the treatment of BV are metronidazole administered orally or clindamycin, which may be given either orally or vaginally. Clindamycin may have advantages over metronidazole since it has better activity against anaerobic bacteria and *Mycoplasma hominis* and *Ureaplasma urealyticum* which are often associated with BV. While screening of pregnant women who are at high risk for preterm delivery based on their past obstetric history or other factors might be justified, there is currently no strong evidence to recommend the routine screening and treatment of the general obstetric population.

Fetal fibronectin

Fetal fibronectin is a glycoprotein variant of the fibronectin family present in amniotic fluid, placenta and the extracellular substance of the decidua. Its synthesis and release are increased by the mechanical and inflammatory events which occur prior to the onset of labor. Fibronectin is often described as "leaking" from disruption to the fetal membranes and decidua in the lower pole of the uterus associated with the early biochemical events of parturition. However, it is also an inflammatory response gene, and therefore concentrations of fibronectin in vaginal fluid can be considered to also be a marker of inflammation (which may be pathological or a normal part of the onset of labor at term). Normally, fetal fibronectin can be detected in vaginal secretion at levels greater than 50 ng/mL before 20 weeks of gestation and

after 36 weeks of gestation. Detection before 20 weeks is possible because the amniochorion is not fully fused to the decidua until this time. Detection closer to term is a feature of the normal mechanical and biochemical events leading to normal term labor. Therefore, the presence of fibronectin in vaginal secretion at levels greater than 50 ng/mL between weeks 20 and 36 is not normal and can be used to predict the risk of preterm labor. When the fibronectin assay was introduced as a commercial test, it was intended to be used in women with preterm labor to differentiate women at risk for preterm labor. However, it is now increasingly being used to predict risk in women who are asymptomatic but at risk for other reasons, particularly cervical shortening. Currently available bedside test kits allow quantification of fibronectin concentrations in vaginal fluid, which has improved the prognostic performance of the test. For example, women with a cervical length of less than 25 mm between 22 and 28 weeks but with a fetal fibronectin concentration of less than 10 ng/mL have less than a 10% risk of preterm delivery before 34 weeks; this increases to more than 50% if the fibronectin concentration exceeds 200 ng/mL. Predictive algorithms (e.g. QUIPP, Apple Store) have now become available that combine the information of past obstetric history, gestational age, cervical length and fibronectin concentration to produce an estimate of risk delivery within a defined time period (e.g. 7 days) or prior to a defined gestational age (e.g. 34 weeks). These algorithms have been developed based on populations who had interventions if they were identified as being at high risk and therefore their general applicability, particularly to low-risk populations, is uncertain. Nevertheless, they serve as a useful guide for physicians to consider all risk factors for preterm birth, guide therapy, and counsel patients about the risks and benefits of interventions.

Prevention of preterm labor

In primiparous women with no other significant risk factors for preterm labor, there is currently no effective method for predicting preterm labor, so treatment can only be initiated at the time of acute onset of labor. However, a group of women at risk of preterm labor can be identified in the antenatal period based on their

past obstetric history, the presence of genital tract abnormalities, and the use of screening tests such as transvaginal ultrasound measurement of cervical length and fetal fibronectin in vaginal secretion. A recurrent problem in the development of treatments aimed at reducing the risk of preterm birth is the lack of suitable tools to stratify women at risk into different etiologic groups. Most studies either did not categorize interventions or selected subgroups of women, such as those with multiple pregnancies or short cervixes. However, even in these subgroups, the underlying etiology may be different. For example, it is possible that cervical damage caused by excisional treatment of CIN may result in both cervical incompetence and a physically shortened cervix. Such women may be helped by cervical cerclage. However, the cervix can compromise its structural integrity without necessarily becoming shorter, in which case cervical cerclage is beneficial. Cervical shortening may be caused by activation of inflammation in the vagina and cervix, in which case cervical cerclage may be harmful. It is possible that some of the dramatic differences in the effectiveness of interventions observed in different clinical trials are due to the fact that they involved women whose risk of preterm labor was due to different etiologies, despite a similar appearance, such as a short cervix. Currently, no prophylactic therapy has been shown to unequivocally help prevent preterm labor in the high-risk group. Commonly used therapies include cervical cerclage and progesterone. Previously, non-steroidal anti-inflammatory drugs and oral beta-sympathomimetics were used. Vaginal pessaries are currently being studied.

Cervical cerclage

The objective of the MRC/RCOG multicenter randomized trial of cervical cerclage, published in 1993, was to assess whether cervical cerclage in women deemed to be at increased risk of cervical incompetence prolongs pregnancy and thereby improves fetal and neonatal outcome. However, women were randomized only if their obstetrician was uncertain whether to recommend cervical cerclage. Therefore, cervical cerclage was compared with a policy of withholding the operation unless it was considered to be clearly indicated. In this study, the largest

ever conducted of this question, the overall preterm delivery rate was 28% and there were fewer deliveries before 33 weeks in the cerclage group (13% vs. 17%). This difference was reported to be reflected in deliveries characterized by features of cervical incompetence: painless cervical dilatation and pre-labor rupture of the membranes. The use of cervical cerclage was associated with a doubling of the risk of puerperal pyrexia. Based largely on these data, current UK guidelines suggest that history-indicated cerclage should be offered to women with three or more previous preterm births and/or second-trimester losses. Various tests, including assessment of cervical resistance index, hysterography or insertion of cervical dilators, have been found to have no benefit in predicting cervical weakness. Nevertheless, clinical examination of the cervix in women at risk is useful. It will detect any congenital or acquired abnormalities and identify women in whom cervical cerclage may be more difficult than expected before being discovered on the operating table. Many obstetricians are now using transvaginal ultrasound measurement of cervical length to assess the risk of preterm labor and to target intervention by cervical cerclage in women who have doubts about the possible benefit.

If ultrasound evidence indicates that cervical cerclage is necessary, the appropriate threshold has not yet reached universal agreement, although a length of less than 25 mm is commonly used. The presence of visible fetal membranes at the time of cervical cerclage is a strong predictor of risk of preterm labor. Visible fetal membranes are never observed at cervical lengths greater than 15 mm. A meta-analysis of individual patient data from four large studies of targeted cervical cerclage in women with short cervix, drawn from the general obstetric population without an increased background risk of preterm birth, showed that cervical cerclage was not beneficial. Therefore, it is usually concluded that cervical cerclage does not benefit women with a short cervix but without other risk factors for preterm labor. However, in this analysis, the selected cervical length for cervical cerclage ranged from less than 15 mm to less than 25 mm, and the ultrasound examinations were performed at relatively late gestational age, 22–24 weeks.

The results of this meta-analysis also contrast sharply with the results of a much smaller, earlier study that showed a significant benefit of cervical cerclage performed by a single, highly skilled obstetrician. As discussed below, there are various aspects of the technical performance of the operation that affect the outcome. It is possible that the failure to demonstrate a benefit of cervical cerclage in a large general population of women with short cervix is due in part to short cervical length, late gestational age at screening, variable operator skill and experience, and technique of the procedure. It is also probably the case that a population of women at risk of preterm birth with a short cervix at the end of the second trimester of pregnancy represents a mixture of women with genuine mechanical cervical problems, who would probably benefit from cervical cerclage, and women whose cervix is short for other reasons, who would probably not benefit and may even be harmed (see discussion on effects of suture material). There are not many studies of the role of cerclage in women with twins who have a history of second-trimester pregnancy loss or preterm delivery. However, it would be illogical to deny a woman who had previously benefited from cervical cerclage, a cerclage in a subsequent pregnancy because she was carrying twins.

Emergency "rescue" cerclage

Rescue cervical cerclage may be performed when a woman is admitted with silent cervical dilatation and bulging of the membranes into the vagina but without the onset of uterine contractions. Characteristically, such women present with slight vaginal bleeding, a watery vaginal discharge, or vague pelvic or vaginal pain. The available literature, mostly composed of case reports and small case series, suggests that rescue cerclage may delay delivery by a further 5–7 weeks on average compared with expectant management/bed rest alone, associated with a twofold reduction in the risk of delivery before 34 weeks. However, there are concerns that emergency or rescue cerclage might convert a second-trimester pregnancy loss into an early preterm delivery with its associated handicap risk, particularly in the context of chorioamnionitis. Adverse features which should contraindicate

rescue cervical cerclage include evidence of chorioamnionitis: maternal pyrexia, abdominal pain, contractions, raised white blood cell count or C reactive protein levels. Whether antibiotics are beneficial in such cases has not been established.

Non-steroidal anti-inflammatory drugs

The central role for prostaglandins and inflammatory cytokines in the onset of labor at term and in the etiology of preterm labor suggests that non-steroidal anti-inflammatory drugs (NSAIDs) may be beneficial in preventing preterm delivery. NSAIDs work largely by inhibition of the cyclooxygenase enzymes which catalises the synthesis of prostaglandins. However, various NSAIDs also have other mechanisms of action, including effects on intracellular signaling pathways and on inflammatory transcription factors such as NF-κB and AP-1. Whilst there are several studies of the use of NSAIDs in the acute management of preterm labor, there are few good randomized trials of their use as prophylaxis. NSAIDs are associated with significant fetal side effects, in particular oligohydramnios and constriction of the ductus arteriosus. Oligohydramnios occurs in up to 30% of fetuses exposed to indomethacin. The effect is dose dependent and may occur with both short-term and long-term exposure. Discontinuation of therapy usually results in a rapid return of normal fetal urine output and resolution of the oligohydramnios. Constriction of the ductus arteriosus occurs in up to 50% of fetuses exposed to indomethacin at gestational ages greater than 32 weeks. There is a relationship between dose and duration of therapy and gestational age. Ductal constriction is seen less commonly below 32 weeks and rarely below 28 weeks. Long-term indomethacin therapy, particularly after 32 weeks, is therefore associated with a significant risk of persistent pulmonary hypertension. More detailed ultrasound studies have shown that administration of indomethacin is associated with a rapid reduction in hourly fetal urine production but that oligohydramnios may develop more slowly and become significant at between 15 and 28 days. There are two major isoforms of the cyclooxygenase enzyme, COX1 and COX2. COX1 is constitutively expressed in the majority of cells whereas COX2 is inducible and catalyzes

the synthesis of prostaglandins at the sites of inflammation. Since it is likely that it is COX1 that plays an important role in fetal kidney function and ductal patency, it was hoped that the use of COX2-selective or COX2-specific NSAIDs would be associated with a lower risk of fetal side effects. However, nimesulide, which is approximately 100-fold more effective in inhibition of COX2 than COX1, is associated with an incidence of fetal oligohydramnios similar to that seen in fetuses exposed to indomethacin and there have been isolated case reports of fatal renal failure. Prophylactic use of the COX2-specific rofecoxib, although associated with weaker effects on both fetal renal function and the ductus arteriosus than indomethacin or nimesulide, is associated with an increased rate of preterm delivery. The reasons for this are unclear but probably represent an effect on anti-inflammatory as well as proinflammatory prostaglandins. Therefore, there is currently no convincing evidence that NSAIDs are beneficial when used as prophylaxis against preterm labor. They are associated with a significant risk of potentially life-threatening side effects. If NSAIDs such as indomethacin are used, perhaps as short-term therapy in combination with cervical cerclage, and especially for more than a few days after 28 weeks, ultrasound monitoring of fetal urine output, amniotic fluid index, and ductus arteriosus should be performed and therapy discontinued when fetal side effects become evident.

Progesterone

Progesterone is probably the most widely used worldwide to prevent preterm labor. Currently, two different progestin preparations are in common use. The synthetic 17α-hydroxyprogesterone caproate, which is chemically similar to testosterone and is not a natural progesterone metabolite, has been shown to reduce the risk of preterm birth in women at high risk based on past history but who do not have a short cervix. Current evidence suggests that 17α-hydroxyprogesterone caproate is not effective in the group of women whose risk of preterm birth is predicted by a short cervix, nor is it effective in women at risk of preterm birth because of multiple pregnancy. The mechanism of action of 17α-hydroxyprogesterone caproate is unclear. As mentioned above,

unlike other animal species, in humans, circulating progesterone concentrations do not fall during either term or preterm labor. There is no evidence of decreased blood or tissue progesterone concentrations in women at risk of preterm labor. The relative binding affinity of 17α-hydroxyprogesterone caproate to nuclear progesterone receptors is only about 30% of that of natural progesterone. 17α-hydroxyprogesterone caproate does not inhibit myometrial contractions in *vitro.* Several large randomized trials in multiple gestations have identified harm related to exposure to 17α-hydroxyprogesterone caproate, and the synthetic drug is therefore contraindicated in this population. In addition, 17α-hydroxyprogesterone caproate is given as a weekly intramuscular injection, which itself is very painful and therefore patient compliance may not be good. For these reasons 17α-hydroxyprogesterone caproate has not found great popularity outside the USA. Probably the most widely used progesterone for prevention of preterm birth is natural progesterone administered as a vaginal pessary. Vaginal progesterone appears to be principally effective in patients identified as at risk of preterm labor because of a short cervix. It is not effective in women at risk who have a normal cervical length, nor has it been proven to be of benefit in multiple pregnancy, although there is some evidence that it may be beneficial in women with twins who also have a short cervix. Unlike 17α-hydroxyprogesterone caproate, natural progesterone has not been associated with any maternal or fetal harm. A meta-analysis of individual patient data from five randomized controlled trials and a systematic review of 36 randomized controlled trials support the use of vaginal progesterone to reduce the incidence of preterm birth in women with singleton pregnancies at risk of preterm birth associated with a short cervix. The results of both systematic reviews are largely driven by the 2011 International Pregnancy Study, a randomised controlled trial in which pregnant women at low risk of preterm birth were screened for cervical length by transvaginal ultrasound and prescribed progesterone if their cervix was 10–20 mm. Overall, the study showed a clear benefit for progesterone in reducing risk of preterm birth in this group, although the trial also showed substantial heterogeneity across study sites.

Progesterone appeared to be highly effective in several studies outside the USA, but to have no significant effect on preterm birth rates in US populations. Vaginal progesterone has not been approved by the FDA for use in the U. S., in part because of the lack of a significant effect on the incidence of preterm birth in U. S. research centers. The largest randomized controlled trial of vaginal progesterone, OPPTIMUM, was undertaken in the UK and published in 2016. This included women at risk of preterm birth for a variety of reasons and was powered to include three primary outcomes: preterm birth, a composite of neonatal death or severe morbidity, or childhood neurodevelopment. It showed that vaginal progesterone did not reduce any of the primary outcomes but that there was no harm associated with progesterone use. The study did show a non-statistically significant reduction in the risk of preterm birth in women randomized to progesterone because of a short cervix and has been criticized because of a lower compliance rate than seen in other studies, and because the study was not powered to specifically study the patient with a short cervix. A meta-analysis performed after publication of OPPTIMUM continues to show a significant benefit of vaginal progesterone in women with a short cervix. The potential mechanism of action of natural progesterone is also unclear. The concentrations of progesterone in the circulation during normal pregnancy are substantially above the Kd for the nuclear progesterone receptor. There is no evidence for lower progesterone concentrations in the circulation of women at risk of preterm birth, and administration of vaginal progesterone to women at risk does not elevate circulating progesterone concentrations. It seems likely that the mechanism of action of natural progesterone is local rather than systemic, and it is possible that it may act both through the parent hormone and through metabolites. Progesterone may act to increase the volume and quality of cervical mucus, hence improving physical and biochemical barriers to ascending infection. A widely accepted hypothesis is that progesterone may act as an anti-inflammatory. In cell culture model studies, progesterone inhibits cytokine- or lipopolysaccharide-stimulated activation of inflammatory transcription factors,

prostaglandin synthetic enzymes, and the synthesis of prostaglandins and cytokines. However, clinical studies have shown that progesterone does not suppress mediators of cervical and vaginal inflammation and does not affect the vaginal microbiota. A pool of amniotic fluid greater than 2 cm is associated with a low incidence of pulmonary hypoplasia. Although many women with premature rupture of the fetal membranes go into labor fairly quickly, those women who do not go into preterm labor soon after PROM are at risk of developing chorioamnionitis. This may represent infection ascending into the uterine cavity, although in some cases PROM may follow established chorioamnionitis. In either case such infection can be harmful and potentially fatal to both mother and baby and so PROM requires careful clinical monitoring to allow early detection and treatment of in utero infection and chorioamnionitis. Accurate diagnosis of PROM is therefore important. This may be based on history, identification of a pool of liquor in the vagina and of oligohydramnios on ultrasound. Biochemical tests of PROM are available that depend on detection of nitrazine (pH), placental α-microglobulin (PAMG)-1 or insulin-like growth factor binding protein (IGFBP)-1 in vaginal fluid. Nitrazine (pH) testing does not appear to be useful in diagnosis of PROM, having a clinically useless positive predictive value. Tests for PAMG-1 or IGFBP-1 have clinically useful positive predictive values and so could be used where clinical assessment of PROM is equivocal but if clear pooling of amniotic fluid is seen are probably unnecessary. Once PROM has been confirmed the management is a balance between the risks of prematurity if delivery is encouraged versus the risks of maternal and fetal infection if there is conservative management. It is important to recognize, especially in the context of PROM, that increasing gestational age at delivery by increasing the latency period is not necessarily associated with improvements in neonatal and childhood outcomes. The association of chorioamnionitis, and especially funiculitis, with pulmonary disease and cerebral palsy suggests that deliberate retention of the fetus in an unfavorable intrauterine environment could potentially worsen early neonatal outcomes and thus the risk of cerebral palsy. The ORACLE II study from 2001 showed that

prophylactic use of erythromycin improves neonatal morbidity, reduces the risk of sepsis and is associated with a longer latency period, whereas co-amoxiclav increases the risk of necrotizing enterocolitis and should therefore be avoided. Antibiotics of any type, administered prophylactically, do not reduce the incidence of perinatal death or neonatal encephalopathy and do not affect the rates of maternal sepsis or maternal death. These findings have been confirmed by meta-analysis of subsequent studies. Follow-up of infants in the ORACLE I study showed no differences in serious infant morbidity at 7 years; in particular, there were no differences in cerebral palsy incidence between infants whose mothers did or did not receive antibiotics after PROM. Erythromycin has a number of potential advantages over other antibiotics in PROM. It can be administered orally and is effective against group B Streptococcus, other streptococcal and staphylococcal infections and Mycoplasma, all of which may be implicated in chorioamnionitis. Its use is therefore currently recommended in the UK as prophylaxis for up to 10 days following a diagnosis of PROM. However, this is not based on any stratification of PROM causes. Recent studies have demonstrated that there is a more complex relationship between the vaginal microbiota, PROM and erythromycin. In cases where the vaginal microbiota is dominated by lactobacilli, erythromycin may result in the destruction of potentially protective lactobacilli and allow a dysbiosis-like BV microbiota to establish. A dysbiosis vaginal microbiota correlates with the development of chorioamnionitis and funicity and is therefore a risk factor for later neurodevelopmental problems. It is probable that the role of erythromycin will need to be re-evaluated when diagnostic tools to assess the vaginal microbiota within clinically useful time scales become available. Management of PROM continues to be controversial. Currently, there is no consensus on how to manage women with ruptured fetal membranes at 34 to 37 weeks' gestation. Most obstetricians will institute conservative management in uncomplicated PROM before 34 weeks and many would induce labor relatively early in women whose membrane rupture occurs subsequent to 37 weeks. In any woman, labor should be induced if there is strong evidence of infection,

although making the diagnosis of chorioamnionitis can be difficult (discussed below). A large randomized controlled trial from the Netherlands, PROMEXIL (PROM Expectant Management versus Induction of Labor) published in 2012 compared immediate induction of labor or expectant management in women with PROM between 34 to 37 weeks of gestation. This found that the risk of chorioamnionitis was slightly reduced in the induction of the labor group compared with the expectant management group but there were no differences in rates of neonatal sepsis, RDS or cesarean section. Because fewer babies born to women in the pregnant group developed neonatal sepsis, the study was underpowered to assess this outcome; however, a subsequent meta-analysis of eight studies confirmed all of these findings. In 2016, the PROMT trial, a multicenter randomized controlled trial performed at 65 centers across 11 countries, showed that expectant management does not increase the risk of neonatal sepsis whilst early delivery was associated with increased risk of RDS. Mothers in the expectant management group were more likely to have evidence of sepsis at the time of delivery, but less likely to require cesarean section. From these studies it is reasonable to conclude that in the absence of signs of infection or fetal compromise, a policy of expectant management with appropriate surveillance of maternal and fetal well-being should be followed in pregnant women who present with PROM up to 37 weeks. It is likely that the later the PROM, the lower the index of suspicion for chorioamnionitis leading to induction of labor should be. Lower genital tract swabs are routinely taken in women with PROM. Positive cultures for potential pathogens do not correlate well with the risk or development of chorioamnionitis; however, they are useful for identifying pathogens after chorioamnionitis develops and for directing antibiotic therapy for both mother and preterm neonate. Conservative management should include clinical surveillance for signs of chorioamnionitis, including regular recording of maternal temperature and maternal and fetal heart rate. The role of white blood cell count (WCC) and C-reactive protein (CRP) is often misunderstood. Neither WCC nor CRP are highly specific for chorioamnionitis. There is significant overlap between cases with and without histologically

confirmed chorioamnionitis at the lower end of the range of values. Chorioamnionitis is often associated with "normal" WCC or CRP values. WCC may be normally elevated in pregnancy, will rise in response to antenatal corticosteroid therapy and has a relatively narrow range, rarely being less than 10×106/L and rarely exceeding 20×106/L, whether there is chorioamnionitis or not. CRP is the best indicator of chorioamnionitis, but is not suitable for screening for the development of chorioamnionitis because of low specificity at the cutoff values required for high sensitivity and the inability to "predict" chorioamnionitis (in other words, CRP remains low until chorioamnionitis actually develops). Most studies have used values of 5, 12, or 20 mg/L to determine CRP levels. Using low cutoff values increases sensitivity (i.e., the truest cases of chorioamnionitis are correctly identified) but decreases specificity (i.e., many women with a positive test do not actually have chorioamnionitis). As cut-off values are increased the number of false positives is reduced but at the expense of failing to identify many genuine cases of chorioamnionitis. When upper limits of CRP are set at 30, 35 or 40 mg/L, the last CRP before delivery is 90, 95 and 100% specific for chorioamnionitis. Therefore, whilst a low CRP value is not reassuring, a high value (>50 mg/mL) has a very high association with chorioamnionitis, particularly if it has risen rapidly. Chorioamnionitis should therefore be strongly suspected if there is clinical evidence (tenderness, pyrexia, maternal and/or fetal tachycardia), if there is a rapid rise in CRP values, or if a single CRP value is very high in the absence of any other clinical explanation such as pneumonia, pyelonephritis, deep vein thrombosis or pulmonary embolism. The absence of fetal movements or fetal breathing movements is also an adverse sign. The use of ultrasound measurement of cervical length in women with PROM is uncertain. Some studies have shown that cervical length is predictive of latency, others have not. Ultrasound assessment is probably preferable to digital assessment since it appears to be associated with little risk of the introduction of infection. However, at present the technique is not generally used in the management of PROM. The current evidence is that tocolytic therapy for women with preterm contractions following PROM leads

to an increase in maternal chorioamnionitis without significant benefits to the infant. The potential benefits of tocolytic drugs do not apply in the majority of cases of PROM since there is usually time for administration of corticosteroids and in utero transfer before the onset of preterm labor itself. The dilemma of when to induce labor in cases of PROM is often not resolved, as 50% of women managed conservatively go into labor within 7 days. The development of chorioamnionitis stimulates the mechanisms leading to the initiation of labor. Thus, labor itself is a marker of potential chorioamnionitis and therefore should not be inhibited.

MANAGEMENT OF SYMPTOMATIC PRETERM LABOR

Prediction of delivery risk in symptomatic preterm labor

Among women admitted to hospital with preterm labor and considered at risk of preterm labor, more than 70% remain pregnant for the next 14 days or more. As discussed in more detail below, there is little evidence that the use of tocolytics, i.e. drugs that inhibit uterine contractions, provides any significant benefit in preterm labor. The improvement in neonatal morbidity and mortality seen with advancing gestational age is often used as an argument for the potential benefit of delaying preterm labor using tocolytic agents. However, there is no evidence that tocolytic drugs provide such a benefit, and there is a real risk that intentionally prolonging pregnancy, especially in the setting of chorioamnionitis, may cause harm by keeping the fetus in an unfavorable intrauterine environment. Timely administration of magnesium sulfate (MgSO4) and corticosteroids to reduce the risk of neonatal morbidity (see below) and intrauterine transfer to a perinatal center with suitable neonatal intensive care facilities have clear advantages. Inappropriate administration of multiple courses of corticosteroids is associated with fetal harm, while unnecessary intrauterine transfer is costly and blocks obstetric and neonatal intensive care beds to the detriment of other mothers and infants who could benefit from transfer. There is therefore a clear need for predictive tests that can determine which women who present with preterm contractions are

genuinely at risk of delivery within the next 7 days and which are not. As with prognostication in asymptomatic women, two methods are now widely used: transvaginal measurement of cervical length and fetal fibronectin concentration in vaginal fluid.

Ultrasound measurement of cervical length

The use of cervical length ultrasonography in women with symptoms of threatened preterm labor varies by geographic location. In the United States, almost all obstetricians and gynecologists are proficient in cervical ultrasound measurement, and ultrasound machines are available in labor and delivery units. In the UK and most other countries in the world, most maternity units do not have ultrasound machines equipped with suitable transvaginal transducers, and most obstetric registrars do not have the necessary skills. Studies have used various cervical length cut-off values to define risk, commonly 15, 20 or 25 mm. The negative predictive value is generally stable at each defined length whilst the positive predictive value improves at 15 mm. A cervical length of 15 mm, in a woman symptomatic of preterm labor, has positive predictive values of 28 and 44% for delivery within 48 hours or 7 days with negative predictive values of 97 and 94%, respectively. A cervical length of 15 mm could therefore be reasonably used as a cut-off value at which to offer corticosteroids and in utero transfer. Studies in the United States have shown that when this strategy is used, no baby in a group considered to be at low risk of preterm birth is born prematurely without a full course of prenatal corticosteroid therapy, and overall, babies in this group have significantly lower exposure to steroids and tocolytics.

Biomarkers: fetal fibronectin, phosphorylated IGFBP-1 and PAMG-1

In the UK, the lack of transvaginal ultrasound machines in maternity units and of doctors with appropriate qualifications or experience to perform ultrasound, as well as the availability of bedside tests, means that vaginal biomarker testing is probably the optimal diagnostic test at present. Of the three methods available, fetal fibronectin detection is the most studied and probably the most widely used test. When these tests first appeared, they were recognized as "test-positive" at concentrations that provided high

negative predictive value at the expense of positive predictive value. In other words, if the test is "negative," the risk of preterm labor within the next 48 hours or 7–14 days is quite low, and in most cases it is reasonable to refrain from steroids or intrauterine transfer. In the widely used "qualitative" fetal fibronectin "test-positive" test, the cutoff is 50 ng/mL. In this case, a positive fetal fibronectin test in a symptomatic woman predicts the risk of preterm labor in the next 7 days by about 40%, and a negative fetal fibronectin test reduces this risk to less than 1%. Quantitative fetal fibronectin testing has now become available and this has improved the test. Test results can now be interpreted either by using a range of different cut-off values or by direct interpretation of the quantified results. So, for example, as screen-positive cut-off values are increased from the original 50 ng/mL to 200 and 500 ng/mL, the positive predictive value for delivery within 14 days increases from 20% to 37% and 46%, respectively, whilst the negative predictive value only decreases from 98% to 97% and 96%. Using a lower cut-off of 10 ng/mL decreases the positive predictive value to 10% with no effect on the negative predictive value. It is possible to combine the results of transvaginal measurement of cervical length and vaginal fluid fibronectin concentrations to improve risk stratification, provided that facilities for both tests are available. It is essential that the fibronectin test be performed before transvaginal ultrasound examination. Most studies have combined measures of cervical length with categorical fibronectin results based on a cut-off of 50 ng/mL and have demonstrated higher sensitivity and positive predictive value while maintaining high negative predictive value. Where qualitative fibronectin testing is used, it appears that a high fibronectin concentration has a better predictive value than a short cervical length alone. So, for example, a woman with a cervical length below 10 mm but a fibronectin concentration of 10 ng/mL has a very low risk of delivery within 7 days, whereas a woman with a cervical length of 30 mm but a fibronectin concentration above 500 ng/mL is at very high risk. However, either of these two scenarios is likely to be quite rare. The improved prognostic value of quantitative fibronectin compared with cervical length is probably

a reflection of where a particular woman is on the biochemical pathway to preterm labor. In most cases cervical shortening will precede release of fibronectin into vaginal fluid by several weeks. Fibronectin testing is therefore most useful in identifying the woman at imminent risk of preterm delivery. Measurement of cervical length is probably of better value in identifying women whose risk is more remote. Some studies of interventions to prevent preterm birth which have recruited patients based on fibronectin positivity have been, probably justifiably, criticized for enrolling patients who are too late in the processes of parturition to be helped by the intervention. The development of computed algorithms (e.g. QUIPP, Apple Store) is now allowing fetal fibronectin concentrations to be interpreted as a continuous variable and to provide individualized risk assessment taking into account the patient's history and cervical length measurements if available.

ACUTE TOCOLYSIS

Sympathomimetics

The maximum benefit to the preterm neonate from antenatal corticosteroid administration is from 24 hours to 7 days after the first dose of the course. In utero transfer has also been shown to improve neonatal morbidity and mortality and clearly time would be required to move a mother in preterm labor from one hospital to another. Suppression of uterine contractions has therefore been seen as an obvious solution to the problem of preterm labor. The use of tocolytic drugs intended to inhibit uterine contractions began with the introduction of alcohol and then beta-sympathomimetics into obstetric practice in the 1970s. The first clinical trials showed that beta-sympathomimetics were highly effective in suppressing preterm labor; manufacturers advertised them widely, and most obstetricians were under the impression that tocolysis (specifically using beta-sympathomimetics such as ritodrine and salbutamol) was an effective treatment for acute preterm labor. This impression was strengthened because of the very high placebo response rate, which implied mistakenly that the drug was being effective. More

modern studies have shown that ritodrine will delay preterm delivery in a minority of patients for 24 and 48 hours but that its use is not associated with any improvement in any marker of neonatal morbidity or in neonatal mortality rates. Ritodrine and salbutamol are associated with significant, potentially life-threatening maternal side effects (particularly if given in combination with corticosteroids) that include fluid overload, pulmonary oedema, myocardial ischemia, hyperglycemia and hypocalcemia. Numerous maternal deaths have been reported in which tocolysis using beta-sympathomimetic drugs has played a role. Beta-sympathomimetics as tocolytics are therefore now rarely used in the context of preterm labor, since safer, though not necessarily more efficacious, tocolytic drugs are now available, and their use should probably be completely abandoned. Beta-sympathomimetics continue to have a role in the suppression of excessively frequent or strong contractions stimulated by prostaglandins in the context of induction of labor at term, where short-term use poses few risks.

Non-steroidal anti-inflammatory drugs

The most widely studied NSAID as an acute tocolytic is indomethacin. Previous relatively small randomized placebo-controlled trials have suggested that indomethacin may delay preterm birth in the short term, but the total number of women enrolled in these trials was small. As discussed in previous sections, indomethacin has significant effects on fetal renal function and on the fetal cardiovascular system, particularly the fetal arterial duct. The use of indomethacin for tocolysis has also been associated with a higher incidence of necrotizing enterocolitis, intraventricular hemorrhage, and impaired hemostasis in neonates. A number of more recent studies tended to be small and of low overall quality. In some network meta-analyses and indirect comparisons, indomethacin appeared to have some benefit in delaying labor compared with placebo and beta-mimetics, and for maternal adverse effects compared with beta-mimetics and MgSO4. However, such indirect comparisons (e.g., when indomethacin is compared to salbutamol, salbutamol is compared to MgSO4, and therefore indomethacin can be indirectly compared to MgSO4) are strongly influenced by the entry

criteria and high response rates to placebo in the original studies. There is no data on long-term outcomes in children, limitations due to the small number of patients and minimal safety data. There is currently no evidence that indomethacin or any other NSAID has any advantage as a first-line tocolytic over calcium channel blockers or oxytocin antagonists, each of which has a much better maternal and fetal side-effect profile.

Oxytocin antagonists

Although there is no strong evidence for increased circulating oxytocin concentrations in preterm labor, both preterm labor and preterm delivery are associated with increased expression of the oxytocin receptor in the myometrium, and oxytocin is synthesized in the uterus itself, in the myometrium, and in the decidua. This has led to the search for drugs that antagonize the oxytocin receptor as tocolytics. Currently, there are no specific oxytocin antagonists for clinical use, although atosiban, a mixed antagonist of arginine vasopressin (AVP) and oxytocin receptors, is licensed by the European Medicines Agency for the treatment of preterm labor. Atosiban has been the subject of both comparative trials with placebo and comparisons with beta-sympathomimetic drugs. A 2000 placebo-controlled study in the USA was flawed to some extent because randomization in early pregnancy was skewed, resulting in increased neonatal mortality in very preterm infants whose mothers received atosiban compared with placebo (Fig. 2.6, p. 79). Atosiban crosses the placenta, but the drug does not accumulate in the fetus with longer infusions. Despite acting on the AVP receptor, atosiban does not affect maternal or fetal cardiovascular parameters or fetal oxygenation. Most infant deaths associated with atosiban exposure have been associated with neonates with birth weights less than 650 g, suggesting that extreme prematurity, which is not an effect of atosiban, was the cause.

The primary outcome of the placebo-controlled trial (i.e. the time between the initiation of treatment and therapeutic failure, defined as either preterm delivery or need for an alternate tocolytic) showed that atosiban was no different to placebo. For this reason, and because of failure to show overall morbidity or mortality benefit, an FDA

license was denied. There were statistically significant differences in the number of women who remained undelivered and did not require an alternative tocolytic at the specific 24-and 48-hour and 7-day time points, although this applied only in women who were beyond 28 weeks' gestation. As with all previous trials of tocolytic drugs, this trial was complicated by a very high placebo response rate. Analysis of the data shows that, for example, 48 hours after randomization, although 70% of the women randomized to receive atosiban appeared to respond to it, in reality most of them were placebo responders. It can be estimated that only 11% had a true clinical response. This is a quarter of those women who actually had preterm labor and had the potential for a real clinical response. Trials comparing atosiban with beta-sympathomimetics showed that atosiban was as clinically effective as beta-sympathomimetics but had a significantly better maternal side effect profile. However, the clinical response rate to atosiban or beta-sympathomimetics in these studies was so high (>90%) that it is likely that most of the patients included in the study did not have true preterm labor. Neither placebo-controlled studies nor comparative trials of beta-sympathomimetics have demonstrated improvement in any aspect of neonatal morbidity or neonatal mortality associated with atosiban use. More recently,

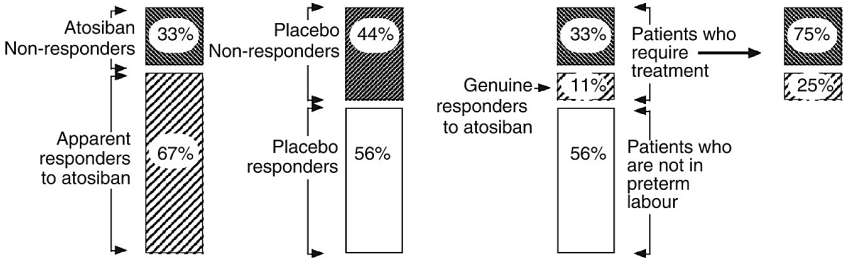


Fig. 2.6. Analysis of the 48-hour outcome data from the placebo-controlled trial of atosiban. Of all patients allocated to atosiban treatment, only 11% showed a genuine clinical response (rather than a placebo response) which represents one-quarter of those with the potential to benefit. This effect applied only in women at 28 weeks' gestational age or greater

oxytocin has been found to mediate at least two pathways through its receptors: one to stimulate contractions, the other to activate inflammatory pathways and increase synthesis of prostaglandins and cytokines. Atosiban acts as an inhibitor of contractions but as a partial activator of inflammation. A proinflammatory action in a tocolytic is not ideal and may explain the limited efficacy of atosiban. At present, second-generation oxytocin receptor antagonists are in development that are specific to the oxytocin receptor and which do not activate inflammation.

Calcium channel blockers

The central role of calcium in the biochemistry of myometrial contractions has led to the exploration of the use of calcium channel blockers, particularly nifedipine, as a tocolytic drug. Because the pharmaceutical industry was not interested in promoting nifedipine for this indication, most randomized controlled trials have been comparative trials of nifedipine versus sympathomimetics and other tocolytics. Two small studies comparing nifedipine to placebo or no treatment showed a significant reduction in the risk of labor within 48 hours associated with an increase in maternal adverse effects. The largest number of studies compared nifedipine with beta-mimetics. Meta-analyses of these studies showed fewer maternal adverse effects, increased interval between study entry and delivery, and decreased rates of preterm and very preterm birth, RDS, necrotizing enterocolitis, intraventricular hemorrhage, neonatal jaundice, and hospitalization in the neonatal intensive care unit. There have been three small and one substantial (APOSTEL III) randomized trials comparing nifedipine with atosiban. The three small trials showed contradictory results. Unlike earlier trials of tocolytic agents, APOSTEL III took advantage of cervical length and fibronectin to better define a population in threatened preterm labor. The study showed that tocolysis for 48 hours with nifedipine or atosiban resulted in similar prolongation of pregnancy and perinatal outcome rates. Discontinuation of nifedipine or atosiban due to side effects was rare, but the frequency of discontinuation did not differ between the two drugs. Currently, the obstetrician (except in the USA, where MgSO4 is still used for tocolytic action despite evidence of its

ineffectiveness) has a choice between atosiban and nifedipine, and it is probably prudent at the current level of knowledge not to use tocolytic therapy at all. More specific oxytocin antagonists are being developed, as well as drugs that affect other receptors, such as prostaglandin receptors. The disappointing results of tocolytics in most studies to date are probably due to poor study design and, in particular, the high placebo response rate when only contractions were used to diagnose preterm labor. In future trials which are able to target tocolytic drugs more specifically at women genuinely in preterm labor, for example by taking advantage of cervical length measurement or fetal fibronectin testing, may more properly define the potential value of tocolytic therapy.

Antenatal corticosteroid therapy

The potential for antenatally administered corticosteroids to accelerate lung maturity was discovered by Professor Sir Graham ("Mont") Liggins in experiments in which sheep were induced into preterm labor by injection of corticosteroids. Unlike preterm sheep delivered by cesarean section, the sheep in these experiments did not develop fatal RDS. A large number of (human) randomized trials took place during the 1970s and 1980s which, taken together, have shown that a single course of either betamethasone or dexamethasone administered to pregnant women between 24 and 34 weeks of gestation who are at risk of preterm delivery within 7 days has a beneficial significant effect on neonatal morbidity and mortality. Although the pediatric use of surfactant had a major impact on the incidence and consequence of RDS, nevertheless antenatal corticosteroid therapy is still associated with a reduction in neonatal mortality, principally due to a significant reduction in rates of RDS and intraventricular hemorrhage. Antenatal corticosteroids have a receptor-mediated effect on all the components of the surfactant system in type 2 pneumocytes. They also have effects on the structural development of the lungs, lead to accelerated maturation of the fetal intestine and have effects on the myocardium and on catecholamine responsiveness, which may explain the reduced incidence of necrotizing enterocolitis and intraventricular hemorrhage seen in extremely preterm infants that appear to be

independent of the effect on RDS. Women who are considered to be at risk of preterm delivery at between 24 and 35 weeks of gestation should be targeted for a single course of antenatal corticosteroids. Antenatal corticosteroids should also be considered for women from 23 weeks, based on estimated fetal weight and parental wishes. Although antenatal corticosteroids are most effective in reducing RDS in pregnant women who deliver within 24 hours and up to 7 days after the second dose of antenatal corticosteroids, there is an impact on neonatal mortality even if delivery occurs within the first 24 hours, so steroids should still be administered even if delivery is expected in less than 24 hours. A single course of corticosteroids is not associated with any short-term adverse maternal or fetal effects, except for destabilization of blood sugar control in diabetics or in impaired glucose tolerance during pregnancy. Diabetes mellitus should not be considered a contraindication to antenatal corticosteroid treatment for fetal lung maturation, particularly because RDS is more common in the babies of diabetic mothers. Women with impaired glucose tolerance or diabetes receiving steroids should receive supplemental insulin according to an agreed protocol and be closely monitored. The dramatic effect of a single course of corticosteroids has unfortunately led to the routine prescription of multiple courses of steroids, often at weekly intervals, to women considered to be at risk of preterm labor, especially multiple births. Concerns about the long-term consequences of continued high-dose steroid exposure, namely negative effects on development and behavior, have generally led to the abandonment of this policy. Although one or more repeated courses of corticosteroids are associated with a reduction in severe lung disease and serious neonatal morbidity, repeated courses of steroids are associated with an increased risk of intrauterine growth restriction. The obstetrician is therefore challenged to use a combination of clinical history, markers of infection or inflammation, measurement of cervical length and fetal fibronectin or other biomarkers to refine the risk assessment of preterm labor in each individual woman in order to appropriately prescribe a course of corticosteroids before delivery and reduce the number of repeated courses ideally to one or no courses. Both

dexamethasone and betamethasone were studied in randomized trials, and each had similar effects on the incidence of RDS. Studies in France have shown that betamethasone reduces the incidence of periventricular leukomalacia, whereas dexamethasone has no such protective effect; however, this may be due to the presence of sulfating agents used as preservatives in French dexamethasone preparations. A historical cohort study used multivariate logistic regression analysis to compare the two steroid-treated groups with each other, finding that the risk of neonatal death was lower with betamethasone than with dexamethasone. In other studies, dexamethasone was associated with a decreased incidence of intraventricular hemorrhage compared with betamethasone. At present, there is no clear evidence of an advantage of dexamethasone over betamethasone or vice versa. Therefore, the steroids of choice for accelerating lung maturation are either betamethasone 12 mg intravenously in two administrations or dexamethasone 6 mg intravenously in four administrations.

Magnesium sulfate

Until the 1980s, MgSO4 was widely used in the United States for the intrapartum management of pre-eclampsia and eclampsia, and the clinical impression that MgSO4 impedes induction of labor led to its evaluation as a tocolytic agent. With the withdrawal of beta-sympathomimetics from the U. S. market and the inability to obtain FDA approval for atosiban, U. S. obstetricians cannot use licensed tocolytic agents, so MgSO4 is used universally. However, randomized placebo-controlled trials of MgSO4 have shown no significant short-term delay in labor, increase in neonatal birth weight, or difference in perinatal mortality compared with placebo. MgSO4 is ineffective at delaying birth or preventing preterm birth, and has no apparent advantages for neonatal and maternal outcomes when used as a tocolytic agent. However, studies comparing MgSO4 with sympathomimetics or indomethacin have shown equal efficacy. These two conflicting results are probably due to the insufficient power of the studies to detect a significant difference between drugs with low or no efficacy and high placebo response rates. In the late 1990s, it became apparent that infants born to mothers who were given MgSO4 either for the prevention of eclampsia or for tocolysis had

a reduced risk of developing cystic periventricular leukomalacia and cerebral palsy. Since then, a series of randomized controlled trials have been conducted to confirm that the risk of cerebral palsy and significant gross motor dysfunction is reduced in infants to whom women were given MgSO4 immediately before preterm delivery. The beneficial effects of MgSO4 are greatest in women in early pregnancy, especially between 24 and 30 weeks. There is probably little or no effect in women after 34 weeks. Therefore, every effort should be made to offer intravenous MgSO4 to women at risk of preterm labor before 30 weeks and, if possible, before 32 weeks. The mechanism of action of MgSO4 in the neonatal brain is not clearly established. It may act by blocking N-methyl-D-aspartate (NMDA) receptors which mediate glial injury processes in hypoxia-ischemia. MgSO4 may also act to block calcium influx into damaged cells, to inhibit vasoconstriction, to reduce cytokine-mediated cell damage, and to interact with a wide range of cellular functions through its complex with ATP. MgSO4 has the advantage over corticosteroids of being effective when administered close to the time of preterm delivery. As with its use in the context of pre-eclampsia, MgSO4 has the potential for toxicity in the mother, leading to nausea and vomiting, lethargy, cardiac dysrhythmia, hypotension, urine retention, and respiratory and cardiac arrest. It is therefore essential that the same safeguards are put in place when it is used for cerebral palsy prophylaxis. The optimal dosing regimen for MgSO4 has not been determined. Different protocols were used in different studies, although they were usually based on protocols used in pre-eclampsia or when the drug is used as a tocolytic. A typical protocol is the administration of a 4 g bolus followed by a 1 g/hr intravenous infusion.

Antibiotics

Analysis of the use of antibiotics in symptomatic preterm labor with intact membranes in women with no clinically defined infection is dominated by the 2001 ORACLE I trial. The study showed that antibiotic administration to women in spontaneous preterm labor with intact membranes does not delay labor or improve any aspect of neonatal morbidity or mortality. The only short-term health benefit

was a reduction in maternal infection. However, a follow-up study examining the effect of antibiotics administered during pregnancy to mothers with threatened preterm labor on children at age 7 years showed an increased risk of cerebral palsy associated with antibiotic use. Surprisingly, this was mostly true for babies who were born at term. Taken together, these data suggest that antibiotics should not be administered to women with uncomplicated preterm labor without evidence of infection. However, it is important to emphasize that there are associations between preterm labor, chorioamnionitis, pneumonia, pyelonephritis, and lower urinary tract infection. These diagnoses, which require antibiotic therapy, should be carefully excluded to reduce the risk of complications of postpartum sepsis.

Management of inevitable preterm delivery

Neonatal morbidity and mortality rates are higher in babies transferred ex utero to neonatal intensive care units compared to babies born in a tertiary referral center. Therefore, every effort should be made to transfer a woman to an obstetric unit affiliated with a neonatal intensive care unit before preterm labor begins. The introduction of the fetal fibronectin test has reduced the number of unnecessary intrauterine transfers.

Cardiotocography monitoring

Except in extreme cases of prematurity (perhaps less than 26 weeks), continuous electronic fetal heart rate monitoring should be performed in most cases once preterm labor is established. The value of cardiotocography (CTG) in preterm labor is less well established than in term labor. Physiologic control of fetal heart rate differs in preterm fetuses compared with term fetuses, making CTG interpretation difficult. Baseline fetal heart rate is higher, averaging 155 beats per minute before 24 weeks compared with 140 beats per minute in term fetuses. Prematurity may normally be associated with a reduction in fetal heart rate baseline variability and be decreased secondary to the effect of fetal tachycardia but without significant hypoxia. The normal sleep-wake cycles seen at term may be absent or less common. Before 30 weeks the frequency and amplitude of accelerations are reduced, whereas fetal heart rate decelerations without contractions often occur in the healthy preterm fetus

between 20 and 30 weeks of gestation. Fetal monitoring in labor should be individualized, taking into account the context of preterm delivery, gestational age and estimated fetal weight, the likelihood of chorioamnionitis and any other complications, the overall prognosis for the neonate, and the wishes of the parents. Modern ultrasound-based CTG machines have rendered the use of fetal scalp electrodes largely redundant but they should particularly be avoided in babies below 34 weeks' gestational age.

Vaginal or cesarean section delivery

There is no evidence of benefit for routine delivery by cesarean section where the presentation is cephalic. However, hypoxia is a major risk factor for the development of cerebral damage and there should therefore be a relatively low threshold for delivery by cesarean section in the presence of abnormal fetal heart rate patterns. Nevertheless, preterm labor is usually rapid. The fetal head will be small, and therefore there will be a complete absence of the relative cephalopelvic disproportion seen at term, meaning that there is no need for molding of the fetal head. In many cases the cervix is already ripe and effaced before the onset of contractions. Preterm labor in breech presentation remains an obstetric dilemma. Although cesarean section has now been shown to be preferable for preterm deliveries, it has not been possible to conduct randomized trials of cesarean section for preterm presentation. One of the potential disadvantages of planning for preterm (or cephalic) delivery by elective cesarean section is the high incidence of "threatened" preterm labor that does not result in preterm delivery. Aggressive management of delivering preterm infants by cesarean section may lead to iatrogenic preterm labor. On the other hand, cesarean section before term, when the preterm part is already in the vagina, may be more traumatic than vaginal delivery. At present, until further evidence becomes available the mode of delivery of the preterm breech will need to be made on a case-by-case basis by the obstetrician at the time. There is no evidence of benefit from the old practice of elective forceps delivery to protect the fetal head during preterm delivery and episiotomy is rarely required. If instrumental delivery is required for the preterm infant below

34 weeks, ventose should be avoided. It is usually easy to rotate a preterm fetal head to an occipital-anterior position manually, or it can be done using Kielland's forceps by those who still have the skill. There is now good evidence for the benefit of delayed cord clamping and waiting at least 30 seconds but no longer than 3 min if the mother and baby are stable. If the preterm baby needs to be resuscitated or there is significant maternal bleeding, the umbilical cord can be briefly milked in the direction of the neonate and then clamped more quickly. If delivery by cesarean section is required, there may be a need to perform a classical cesarean section through a vertical incision in the uterus, particularly at very preterm gestational ages when the lower segment of the uterus is poorly formed. Occasionally, an incision initially made in the lower segment proves to be insufficient for delivery. In these cases, the incision can be converted to a J-shaped incision. Especially at the end of viability, the birth should be carried out as minimally traumatic as possible, ideally an en caul birth with intact membranes. This greatly reduces the risk of trauma to the fetus, and maritime folklore says that a baby born en caul will never drown at sea.

Lecture 3

EARLY GESTOSIS. HYPERTENSIVE DISORDERS DURING PREGNANCY. PRE-ECLAMPSIA. ECLAMPSIA

Relevance of the topic

The incidence of pre-eclampsia does not decrease during pregnancy (from 1.5 to 23.3% of all pregnancies). The pathology is associated with life-threatening complications of pregnancy and determines maternal and perinatal morbidity and mortality. In the structure of mortality during pregnancy, childbirth and postpartum pre-eclampsia occupy the first place. Therefore, timely diagnosis, prevention and treatment of pregnant women with pre-eclampsia and eclampsia are one of the most urgent problems of modern obstetrics and the health of mothers and newborns.

Educational material

EARLY GESTOSIS

The concept of "early gestosis" exists only in the practice of obstetricians and gynecologists. In obstetric practice abroad there is no such concept; there are conditions that are classified as "mild" complications of pregnancy or "unpleasant symptoms during pregnancy." But in HIC-10, Section XV, topic O21 includes vomiting of different severity during pregnancy, and titles O26 and O28 include other conditions associated with pregnancy. Therefore, we consider it appropriate to discuss the special condition of pregnancy under the heading "early gestosis" in a separate section.

The pathology of pregnancy is divided (according to clinical course) into two groups:

1. Early gestosis, which occurs frequently — vomiting of pregnant women, increased salivation, itching of pregnant women.

2. Early gestosis is rare — dermatoses of pregnancy, cholestatic hepatosis of pregnancy, acute liver steatosis of pregnancy, tetania of pregnancy, chorea of pregnancy, osteomalacia of pregnancy, bronchial asthma of pregnancy.

Etiology and pathogenesis of early gestosis

There are many theories explaining the causes of early gestosis (toxemic, allergic, endocrine, neurogenic, psychogenic, immunological, etc.).

Modern theories consider early gestosis to be a consequence of disorders of neurovegetative, immunological, endocrine and metabolic regulation, in which the functional state of the central nervous system plays a leading role.

The fertilized egg causes excessive irritation of areas of the hypothalamus, brain stem and organs involved in the regulation of autonomic functions and inhibition of neuronal processes in the cerebral cortex. As a consequence, there is a predominance of excitatory processes in the brain stem (especially in the vomiting center).

Risk factors for early gestosis

- Congenital or acquired defects in neuroendocrine regulation of adaptive responses (hypoxia, infection, intoxication, violation of the regime in childhood and adolescence, etc.).
- Extragenital diseases.
- Dysfunction of the nervous system, stressful situations.
- Previous interventions on the genital organs, which can lead to changes in the receptor apparatus of the uterus and the development of pathological impulses in the central nervous system.

Vomiting of pregnancy

Vomiting of pregnancy (emesis gravidarum) is a complex clinical syndrome. The act of vomiting is one of the manifestations of the disease, causing diarrhea, secretory, sensory, vascular and other disorders.

According to the severity, there are mild vomiting (less than 5 times a day), moderate (5 to 10 times) and severe vomiting (hyperemesis gravidarum) with metabolic disorders (more than 10 times a day). It should be noted that 50% of pregnant women

in the early stages of pregnancy experience "morning vomiting," which is not pathological in nature and does not require medical treatment (Table 3.1).

Table 3.1

Classification of the severity of early gestosis

Degree	Status	Frequency of vomiting	Weight loss	HR	Laboratory research
I. Mild (neurotic phase)	Satisfactorily	Up to 5 times	No more than 3 kg	Standard	Standard
II. Moderate (toxicosis phase)	Relatively satisfactory	6–10 times	More than 3 kg	Up to 100	Acetone in urine ++
III. Severe (dystrophy phase)	Severe	Up to 25 times or more	8–10 kg or more	More than 100	Acetone in urine ++++

When determining the severity of the disease, clinical manifestations are determined: the condition of the pregnant woman, dry skin, yellow sclera and skin, the presence or absence of appetite, salivation, nausea, frequency and intensity of vomiting, weight loss curve, dehydration, heart rate, blood pressure, subfebrile temperature, the amount of diuresis. Assessment of the severity of vomiting in a pregnant woman includes the results of laboratory tests: specific gravity of urine, the presence of ketonuria, the level of acetonitrile, bilirubin and creatinine in the blood.

To diagnose and monitor the effectiveness of treatment, the following studies were carried out:

- Body weight control.
- Control of diuresis.
- Blood pressure dynamics.
- Determination of hematocrit and hemoglobin.
- Urine (specific gravity, acetone, ketone bodies, protein).
- Biochemical blood test (bilirubin and its fractions, liver enzymes, creatinine).
- Determination of the level of electrolytes in the blood (K, Na, Cl).
- Determination of acid-base balance in blood.

Differential diagnosis of vomiting in pregnant women should be carried out with the following diseases: food poisoning, gastritis, pancreatitis, pyelonephritis, cholelithiasis, hepatitis, appendicitis, meningitis, brain tumors, etc.

Treatment of vomiting of pregnancy

The large number of recommended treatments reflects the majority of theories explaining the causes of vomiting in pregnancy. However, uncontrolled use of these treatments in early pregnancy may be harmful in some cases, taking into account that embryogenesis occurs early in pregnancy.

Mild vomiting. Pregnant women who experience mild vomiting are not recommended to be hospitalized. A light (5–6 times a day), balanced diet and vitamins are recommended. Patients are given easily digestible food (cookies, mashed potatoes, tea, cocoa, coffee, lean meat, fish, eggs, butter, etc.). Take them often and in small portions in the supine position, preferably in a cooled form.

Non-traditional treatment methods can be used: reflexology, hypnosis, central electroanalgesia, homeopathic therapy and others.

Moderate and severe vomiting. Pregnant women must be hospitalized and receive medical treatment.

The drug should be administered only parenterally. When the central nervous system is influenced as the main pathogenetic factor that disrupts the excitability of the vomiting center, the following drugs are prescribed: Etaperazine 0.002 g orally 3–4 times a day for 10–12 days; Torekan 1.0 ml intramuscularly or 6.5 mg in the form of tablets or rectal suppositories 2–3 times a day; Droperidol 0.5–1.0 ml intramuscularly 1–3 times a day; Cerucal 10 mg intramuscularly or orally.

To avoid hypoproteinemia and dehydration, intravenous targeted administration of protein (plasma) and Ringer-Locke solution is necessary. In general, all infusions are performed only when indicated based on laboratory tests. The amount of liquid is determined by the state of water balance.

Complication: Excessive vomiting can lead to dehydration, fatigue, and Mallory–Weiss syndrome (rupture of the stomach lining). In some cases, it is necessary to terminate the pregnancy early. Indications

for this are the lack of effect of treatment within 7–10 days, threat to the life of the mother, persistent tachycardia, hyperthermia, proteinuria and progressive cylindruria, the presence of jaundice and acetone in the urine.

Prevention of early gestosis consists of early identification of pregnant women at risk of early development of pre-eclampsia, their rehabilitation, treatment of concomitant diseases and early registration of pregnancy.

Hypersalivation of pregnancy

Salivation (ptyalism) is seen in vomiting, sometimes in poisoning and pre-eclampsia. The amount of saliva with increased salivation can reach 1.0 liters per day. Salivation does not cause serious disturbances in the body, but it also depresses the psyche of patients and causes maceration of the skin and mucous membrane of the lips. Sometimes, to reduce the secretion of the salivary glands, intramuscular injection of 0.5 ml of a 0.1% atropine solution is prescribed twice a day. Rinse your mouth with infusions of sage, mint, chamomile, oak, measles and other astringents. Termination of pregnancy for this pathology is not required.

Pruritus gravidarum (itching of pregnancy). The most common form of dermatosis is pruritus gravidarum, which can be limited to the vulva and spread throughout the body, causing irritability and sleep disturbances.

Itching in pregnant women must be differentiated from allergic reactions, mycoses, trichomoniasis, diabetes mellitus and helminthiasis.

Antihistamines and sedatives, B vitamins and ultraviolet irradiation are used for treatment.

Rare forms of gestosis

Dermatoses in pregnant women are a group of diseases that arise in connection with pregnancy and disappear after its interruption. The prevalence is 1 in 200 pregnancies. Skin diseases during pregnancy depend on a functional imbalance between the cortex and subcortex, increased excitability of the autonomic nervous system, which is accompanied by disturbances in the innervation of the skin, as well as metabolic and microcirculatory changes. Dermatosis

in pregnant women manifests itself in the form of itchy skin, less often in the form of eczema, urticaria, erythema and papular rashes. The disease does not affect the condition of the fetus.

Treatment of dermatosis: a low in fat and protein diet, drugs that regulate the function of the nervous system and metabolism, antihistamines, rarely systemic or local corticosteroids.

Pemphigoid in pregnancy is a mild but severe disease associated with preterm birth, fetal growth restriction, fetal distress, and increased perinatal mortality. Itchy rashes first appear on the skin of the abdomen in the umbilicus area and then spread to the limbs, arms and feet. At first these are papules and plaques, after 2 weeks they turn into vesicles and dense vesicles. The diagnosis is based on the detection of complement in the basement membrane of the epidermis. Treatment: topical 1% hydrocortisone cream or systemic corticosteroids and sedating antihistamines.

Pregnancy with cholestatic hepatosis can occur at different stages of pregnancy, but most often occurs in the third trimester and occurs in 1 in 2000 pregnant women. The pathogenesis of this disease is not well understood. In development, factors such as the inhibitory effect of progesterone on the function of cholesterol, increased cholesterol production, decreased tone of the biliary system and increased bile viscosity may be important. The appearance of jaundice is preceded by the spread of severe itching of the skin. The general condition of patients with cholestatic hepatosis in pregnant women does not change significantly. Laboratory tests reveal moderate leukocytosis, neutrophilia and, somewhat more pronounced than in uncomplicated pregnancy. The level of bilirubin in the blood is increased (up to 90 mmol/l) and quickly returns to normal after childbirth. Alkaline phosphatase increases. There was no increase in liver enzymes such as ALT and AST.

Differential diagnosis should be made for damage to the liver and biliary tract under the influence of mechanical or infectious factors, as well as as a result of metabolic disorders. Jaundice can develop as a result of severe intoxication with severe early gestosis.

Treatment of cholestatic hepatosis consists of following a balanced diet (Diet No. 5) and using medications that relieve itching. The use

of ursodeoxycholic acid improves liver function. In some cases, termination of pregnancy may become necessary due to exacerbation of clinical manifestations of the disease and damage to the fetus. It is advisable to prescribe vitamin K a week before the planned birth to reduce the risk of postpartum hemorrhage.

Acute hepatic steatosis in pregnancy is one of the most severe forms of pre-eclampsia, which most often occurs in late pregnancy (33–40 weeks) with a prevalence of 1 in 100,000 pregnant women and is characterized by a very acute onset and high mortality. Morphologically, this is a pronounced fatty degeneration of hepatocytes without signs of necrosis. The clinical course of fatty liver disease is divided into two stages. Jaundice is preceded by abdominal pain, weakness, headache, nausea, debilitating heartburn and itchy skin. Jaundice aggravates the symptoms of liver and kidney failure, intoxication, encephalopathy, DIC syndrome develops, and fetal death often occurs. The immediate cause of death in a pregnant woman is cerebral edema and severe hemorrhagic coagulopathy.

Treatment of this serious complication consists of correction of coagulopathy and electrolyte imbalance, cardiovascular support, and, if possible, vaginal delivery (Fig. 3.1, p. 95).

Bronchial asthma of pregnancy

It is rare, but severe. The main symptoms of asthma in pregnant women are shortness of breath and a chronic dry cough. Bronchial asthma in pregnant women must be distinguished from the usual form of bronchial asthma, which usually occurs before the onset of pregnancy.

Treatment includes prescribing:

— calcium supplements,

— sedatives,

— vitamins.

Tetany of pregnant women

Pregnancy tetany (tetania gravidarum) can manifest itself as cramps of the upper (“obstetrician’s hands”) or lower extremities (“ballerina’s legs”) or face (“fish mouth”). The disease is associated with decreased function of the parathyroid glands, impaired

calcium metabolism and rheumatism. Parathyroidin, calcium preparations, B vitamins, calciferol (D) and tocopherol acetate (E) are used. If the disease is severe or treatment is ineffective, abortion is recommended.

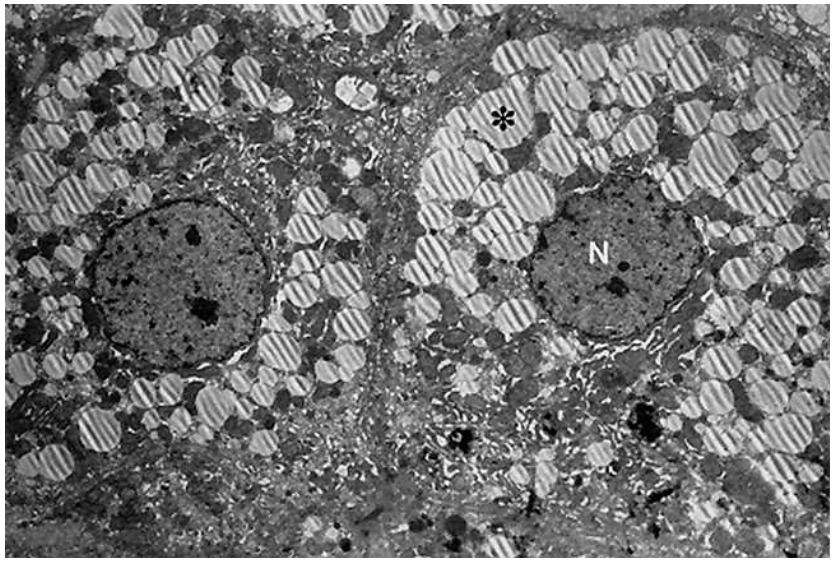


Fig. 3.1. Fatty liver of pregnancy. Electron photomicrograph of two hepatocytes containing numerous microvesicular fat droplets (*). Nuclei (N) remain centered within the cells, in contrast to macrovesicular fat deposits

Source: Courtesy of Dr. Don Wheeler

Chorea gravidarum is the term for chorea that occurs during pregnancy. It is not an etiologically or pathologically distinct disease, but rather a general term for chorea of any cause beginning during pregnancy. Chorea is an involuntary abnormal movement characterized by sharp, short, irregular, non-repetitive movements of any part of the body, often accompanied by grimaces without any pattern on the face.

Chorea may also be due to toxic drugs (eg, antiepileptic drugs, antiparkinsonian drugs, antipsychotics, steroids, and estrogens)

or due to an infectious disease such as meningovascular syphilis, Lyme disease, viral encephalitis, and many others.

Drug treatment is indicated for patients with severe, disabling chorea. Treatments include haloperidol, chlorpromazine alone or in combination with diazepam, and pimozide, another antipsychotic that may have fewer side effects than haloperidol. Valproic acid, chloral hydrate, risperidone, or phenobarbital may also be used. Psychotherapy, massage, and muscle stretching exercises relieve symptoms during an attack.

Osteomalacia gravidarum is an extremely rare and predetermined decalcification of bones and soft tissues. Most often, the bones of the pelvis and spine are affected, which is accompanied by painless stretching. When palpating the pubic symphysis, the pregnant woman feels pain. An X-ray examination of the pelvis sometimes reveals separation of the bones of the pubic symphysis, but, despite true osteomalacia, there are no destructive changes in the bones.

Treatment of osteomalacia consists of normalizing phosphorus-calcium metabolism. At the present stage, the entire exchange of mineral substances in the bones, leading to their resorption, is diagnosed using densitometry — a modern ultrasound method for studying bones. Fish oil, calciferol (vitamin D) and ultraviolet irradiation are used.

Prevention of early gestosis. Prevention of early gestosis consists in the treatment of chronic extragenital diseases of the pregnant woman, the psycho-emotional calm of the pregnant woman and reducing the influence of environmental factors.

Pregnant women with early gestosis, especially with relapse, are at risk of developing obstetric and perinatal pathologies (miscarriage, pregnancy, placental insufficiency, fetal malnutrition, pathology of the newborn), including in the prevention of these complications.

Hypertensive disorders of pregnancy

Hypertension is one of the most common medical complications during pregnancy and is a significant contributor to maternal and perinatal morbidity and mortality. High blood pressure is a sign of an underlying pathology that may have existed previously or appeared for the first time during pregnancy. Recognition of this clinical condition

and effective treatment play an important role in pregnancy outcome for both mother and child. In developing countries with inadequate prenatal care, the condition often goes undetected until serious complications occur. In Ukraine there is a different terminology for this pathology. Until then, the term “high blood pressure, pregnancy” can be considered obsolete. Modern terms are “gestosis, hypertensive disorders of pregnancy” (Tables 3.2, 3.3, Fig. 3.2, p. 98).

Table 3.2

Classification of hypertension in pregnancy (National High Blood Pressure Education Program, 2000)

Disorder	Definition	Disorder	Definition
Hypertension	Blood pressure ≥140/90 mm Hg, measured twice with at least 6-hour interval	Chronic hypertension with superimposed pre-eclampsia and eclampsia	The most common causes of chronic hypertension: (a) Essential hypertension; (b) Chronic renal disease (renovascular); (c) Coarctation of the aorta; (d) Endocrine diseases (diabetes mellitus, pheochromocytoma, thyrotoxicosis); (e) Connective tissue diseases (Lupus erythematosus). Diagnosis criteria for superinduced pre-eclampsia: (1) New-onset proteinuria >0.5 g/24-hour sample. (2) Exacerbation of hypertension. (3) thrombocytopenia or (4) increased liver enzyme activity
Proteinuria	Urinary excretion ≥0.3 g protein/24-hour sample or 0.1 g/L		
Gestational hypertension	Blood pressure ≥140/90 mm Hg for the first time during pregnancy after 20 weeks, without proteinuria		
Pre-eclampsia	Gestational hypertension with proteinuria		
Eclampsia	Women with pre-eclampsia complicated by seizures and/or coma		
Chronic high blood pressure	Known hypertension before pregnancy or newly diagnosed hypertension before 20 weeks of pregnancy		
Superimposed pre-eclampsia or eclampsia	New-onset proteinuria in women with chronic hypertension		

Source: DK Dutta, Hiralal Konar, 2013

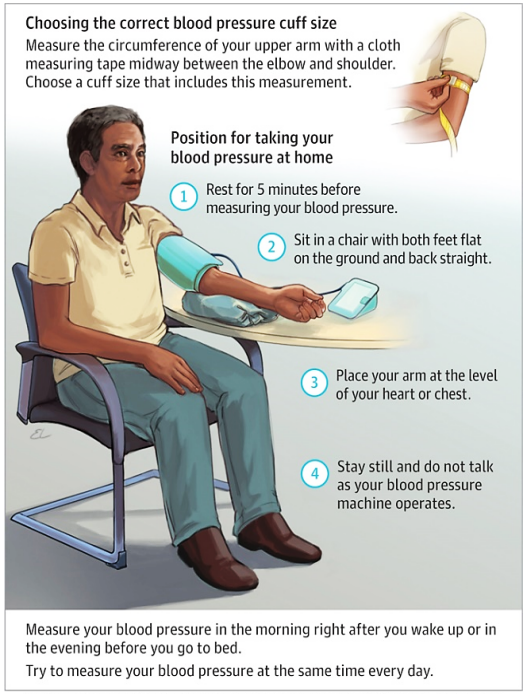


Fig. 3.2. Blood pressure measurement

Table 3.3

Treatment

Drug	Dosage	Comments
1	2	3
Labetalol	200–2,400 mg/d orally in two to three divided doses. Commonly initiated at 100–200 mg twice daily	Potential bronchoconstrictive effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia
Nifedipine	30–120 mg/d orally of an extended-release preparation. Commonly initiated at 30–60 mg once daily (extended-release)	Do not use sublingual form. Immediate-release formulation should generally be reserved for control of severe, acutely elevated blood pressures in hospitalized patients. Should be avoided in tachycardia

End of Table 3.3

1	2	3
Methyldopa	500–3,000 mg/d orally in two to four divided doses. Commonly initiated at 250 mg twice or three times daily	Safety data up to 7 years of age in offspring. May not be as effective as other medications, especially in control of severe hypertension. Use limited by side effect profile (sedation, depression, dizziness)
Hydrochlorothiazide 12.5–50 mg daily		Second-line or third-line agent

Source: ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy

PRE-ECLAMPSIA

Pre-eclampsia (PE) is a multisystem disease of pregnancy, previously defined by the onset of hypertension accompanied by significant proteinuria after 20 weeks of pregnancy. Recently, the definition of PE has been expanded. Pre-eclampsia is a leading cause of maternal and perinatal morbidity and mortality, especially when the disease occurs in the early stages. Every year, 76,000 women and 500,000 infants die from this disease worldwide. In addition, women in low-resource countries are at higher risk of developing PE than women in high-resource countries.

Pre-eclampsia HIC-10 classification: O13-O15

- Mild pre-eclampsia or gestational hypertension without significant proteinuria.
- Moderate pre-eclampsia.
- Severe pre-eclampsia.
- Pre-eclampsia unspecified.
- Eclampsia.
- Eclampsia during pregnancy.
- Eclampsia at birth.
- Eclampsia in the postpartum period.
- Eclampsia of unspecified period.
- Etiopathogenesis of pre-eclampsia.

There are about 30 different theories. Among the causes of pre-eclampsia, especially severe, extragenital, autoimmunological diseases

and endocrine diseases take first place. A number of different theories of the pathogenesis of pre-eclampsia suggest that none of them describes it completely.

An important role in the development of pre-eclampsia is played by:

1. Insufficiency of the spiral arterioles of the uterus, leading to disruption of placental circulation.
2. Endothelial dysfunction associated with pregnancy-induced autoimmune disease.

Organ changes characteristic of pre-eclampsia:

1. Cardiovascular system: generalized vasospasm, increased peripheral vascular resistance, hypovolemia.
2. Hematological changes: platelet activation, which is accompanied by consumption coagulopathy, decreased plasma volume, increased blood viscosity and hemoconcentration.
3. Kidneys: proteinuria, decreased glomerular filtration rate, decreased excretion of uric acid.
4. Liver: periportal necrosis, subcapsular hematoma.
5. Central nervous system: cerebral edema, intracranial hemorrhage (Fig. 3.3).

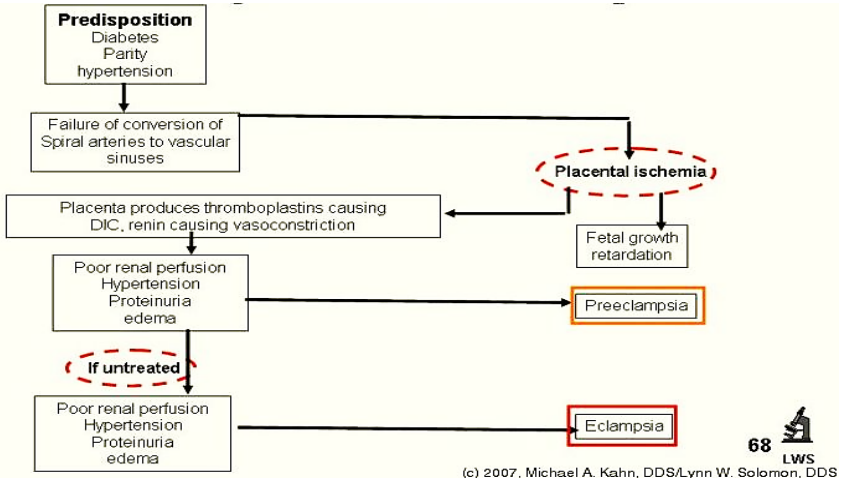


Fig. 3.3. Pathogenesis of pre-eclampsia

There is a severe form of clinical pre-eclampsia — HELLP syndrome (hemolysis — microangiopathic hemolytic anemia, increased activity of liver enzymes — increased concentration of liver enzymes in the blood plasma, decreased number of platelets — decreased number of platelets). Pathophysiological changes in HELLP syndrome occur primarily in the liver. Segmental vasospasm leads to impaired blood circulation in the liver and swelling of Glisson's capsule (pain in the upper abdomen). Hepatocellular necrosis associated with elevated levels of transaminases.

Thrombocytopenia and hemolysis occur as a result of endothelial damage during vascular changes. If this vicious circle of endothelial damage and intravascular activation of blood coagulation is not broken, WIS syndrome develops within a few hours with fatal bleeding.

Risk factors for pre-eclampsia:

1. Extragenital pathology: kidneys, liver, hypertension, chronic diseases of the lungs and bronchi, heart defects, diabetes mellitus, obesity.
2. Obstetric and gynecological risk factors:
   — presence of arterial hypertension in a family history;
   — previous history of pre-eclampsia;
   — age of the pregnant woman (less than 20, over 30 years);
   — hydramnios, twins;
   — anemia in pregnant women;
   — isosensitization to the Rh factor and the ABO system.
3. Social factors:
   — bad habits;
   — hazards in the workplace;
   — unbalanced diet.

Knowledge of the risk factors for pre-eclampsia allows you to timely identify groups at risk for pre-eclampsia.

Clinical manifestations. The classic triad of symptoms of pre-eclampsia (edema, proteinuria, hypertension), described in 1913 by the German obstetrician Zangemeister.

Headache, blurred vision, pain in the upper and lower right abdomen are clinical manifestations of severe pre-eclampsia.

Diagnosis of pre-eclampsia during pregnancy more than 20 weeks with blood pressure more than 140/90 mm Hg or with an increase in diastolic blood pressure by 15% of the initial value in the first trimester of pregnancy with proteinuria (protein in daily urine more than 0.3 g/l) and general edema (increase in pregnant body weight more than 900.0 g per week or 3 kg per week month). The diagnosis of pre-eclampsia establishes the presence of hypertension and proteinuria or general edema, or the presence of all three (Table 3.4).

Table 3.4

Diagnostic criteria for severe pre-eclampsia / eclampsia

Diagnosis	Diastolic BP mm Hg	Proteinuria g/L	Other signs
Gestational hypertension or mild pre-eclampsia	90–99	<0.3	—
Moderate pre-eclampsia	100–109	0.3–5.0	Swelling in the face, hands Sometimes a headache
Severe pre-eclampsia	≥110	>5	Swelling generalize, significant Headache Dystopia Pain in the epigastrium and/or right hypochondrium Hyperreflexia Oliguria (<500 ml/ext) Thrombocytopenia
Eclampsia	≥90	≥0.3	Convulsive attack (one or more)

NB! If a pregnant woman has at least one of the criteria for more severe pre-eclampsia, this is the basis for a diagnosis.

There are "pure" and "complicated" forms of pre-eclampsia. Complicated gestosis develops against the background of extragenital diseases (Fig. 3.4 (p. 103), 3.5 (p. 104)).

Notice as a criterion of severity! Examination of arterial hypertension in pregnant women, indications for the initiation of antihypertensive therapy and evaluation of its effectiveness based on diastolic blood pressure alone. To determine the latter,

it is necessary to take into account Korotkoff's V sound (and not IV, as before).

Additional clinical and laboratory criteria should also be defined for the diagnosis of pre-eclampsia (Table 3.4; Fig. 3.5).

The provision of assistance depends on the condition of the pregnant woman, as well as blood pressure and proteinuria.

PP-13, PAPP-A and PI as markers of pre-eclampsia

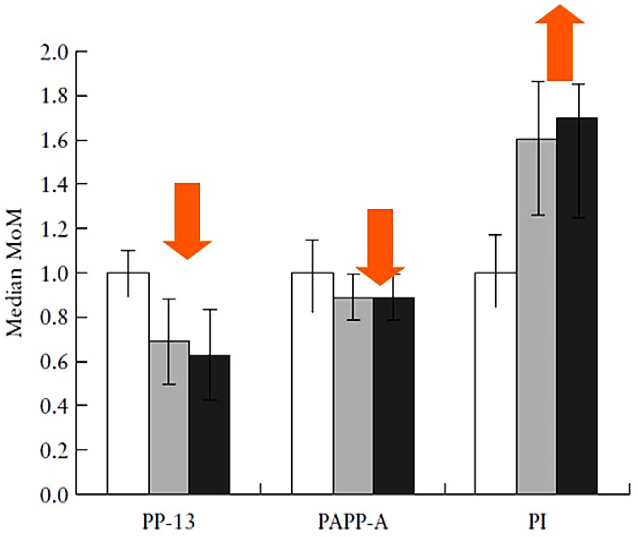


Fig. 3.4.

Source: Khalil A., 2010, Odibo JSC, 2011, Spencer K., 2007

Table 3.5

Additional clinical and laboratory criteria for pre-eclampsia

Signs of pre-eclampsia	Mild	Moderate	Severe
Uric acid, mmol/l	<0.35	0.35–0.45	>0.45
Urea, mmol/l	<4.5	4.5–8.0	>8
Creatinine, μmol/l	<75	75–120	>120 or oliguria
Platelets, 10^9/l	>150	80–150	<80

Mild pre-eclampsia

Pregnant women who meet the criteria for mild pre-eclampsia before 37 weeks of pregnancy may receive a day hospital stay. Examinations: measuring blood pressure, monitoring fluid balance and edema, checking fetal movements.

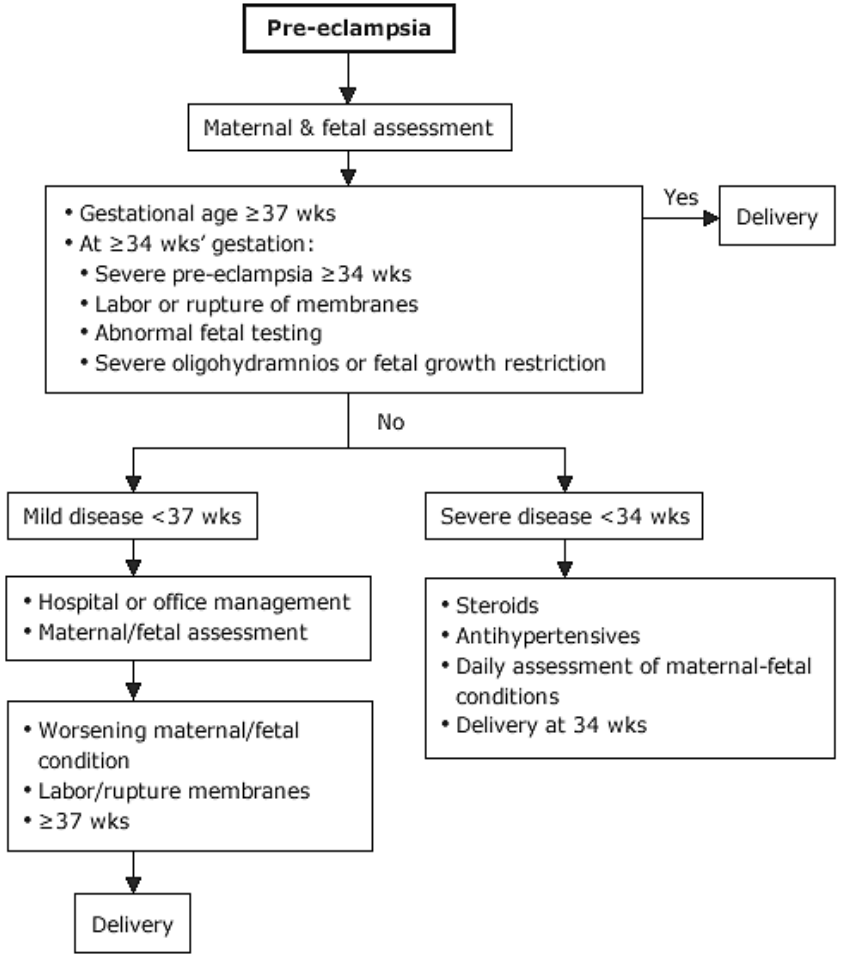


Fig. 3.5. Treatment of pre-eclampsia

Laboratory tests: general urine analysis, daily proteinuria, plasma creatinine and urea, hemoglobin, hematocrit, platelet count, coagulogram, ALT and AST, fetal determination (if possible, not a stress test). Drug therapy is not indicated. Do not limit your fluid and salt intake.

Indications for hospitalization: at least one sign of moderate gestosis, fetal hypoxia. If a woman's condition is stable and meets the criteria for mild gestosis, expectant pregnancy management is carried out. Delivery is per *vias naturalis*.

Moderate pre-eclampsia

Hospitalization of a pregnant woman. Primary laboratory tests: general blood count, hematocrit, platelet count, coagulogram, ALT and AST, blood group and Rh factor (in the absence of exact information), general urine analysis, determination of daily proteinuria, creatinine, urea, uric acid, plasma electrolytes (sodium and potassium), assessment of fetal health.

Protective mode — limiting physical and mental stress.

Diet: High protein foods, no restrictions on salt and water, and foods that do not cause thirst.

A complex of vitamins and minerals for pregnant women, iron supplements if necessary. With diastolic blood pressure >100 mm Hg antihypertensive drugs are prescribed (methyldopa 0.25–0.5 g 3–4 times a day, maximum dose — 3 g per day, and if necessary, an additional 10 mg of nifedipine 2–3 times a day, maximum daily dose — 100 mg).

During pregnancy up to 34 weeks, corticosteroids are prescribed to prevent respiratory distress syndrome (RDS) — dexamethasone 6 mg every 12 hours four times for 2 days.

The study is carried out using a fixed set of dynamic monitoring indicators:

- Blood pressure control — every 6 hours on the first day, then twice a day.
- Auscultation of the fetal heart every 8 hours.
- Urine — daily.
- Daily proteinuria.

- Hemoglobin, hematocrit, coagulogram, platelet count, ALT and AST, creatinine, urea — every three days.
- Daily fetal monitoring.

Delivery

With progression of gestosis or deterioration of the fetus's condition preparations for childbirth begins:

— in the "immature" cervix — prostaglandin E2 (locally);
— if ineffective — cesarean section;
— "mature" cervix — stimulation of contractile activity of the uterus and natural delivery.

The algorithm for carrying a pregnancy to term for severe gestosis is carried out in cases where at least one of the following symptoms increases:

- diastolic blood pressure >110 mm Hg;
- headache;
- visual impairment;
- pain in the epigastric and right hypogastric area;
- signs of liver failure;
- oliguria (<25 ml/year);
- thrombocytopenia (<100 · 109/l);
- signs of WIS syndrome;
- improvement of ALT and AST.

Severe pre-eclampsia

The pregnant woman is hospitalized in the Anesthesiology unit and level III Intensive Care Unit to assess the risk of pregnancy for the mother and fetus and choose the method of delivery within 24 hours. A separate post will be allocated for round-the-clock monitoring by medical personnel. Immediate consultation with a therapist, neurologist, ophthalmologist. Catheterization of peripheral veins. Primary laboratory tests: complete blood count, hematocrit, platelet count, coagulogram, ALT and AST, blood group and Rh factor (if absent), total urine, determination of proteinuria, creatinine, urea, total protein, bilirubin and its fractions, electrolytes.

Careful observation of dynamics:

- Blood pressure monitoring — every hour.

- Urinalysis — every 4 hours.
- Monitoring hourly urine output (bladder catheterization).
- Hemoglobin, hematocrit, platelet count, liver function tests, plasma creatinine — daily.
- Auscultation of the fetal heart — every 15 minutes.
- Fetal monitoring: number of movements per hour, heart rate (daily if possible), Doppler monitoring of blood flow in the umbilical vessels, vessels of the fetal brain, placenta and fetoplacental complex.
- Assessment of amniotic fluid and biophysical profile of the fetus.
- Cardiotocography.

Treatment

Conservative treatment (hard beds). In the term of 34 weeks corticosteroids for the prevention are prescribed — RDS-Dexamethasone 6 mg every 12 hours, 4 times during 2 days. The management is effective for delivery within the next 24 hours from the moment of diagnosis regardless of the stage of pregnancy.

Antihypertensive therapy

Treatment of hypertension is not pathogenic, but is necessary for the mother and fetus. Systolic pressure lowering is intended to prevent hypertensive encephalopathy and cerebral hemorrhage. The goal is to bring systolic pressure to a safe level (150/90–160/100 mm Hg, not lower!) to ensure the maintenance of adequate cerebral and placental blood flow. Antihypertensive therapy is carried out when diastolic pressure increases >100 mm Hg. It has been proven that drug antihypertensive therapy should not be started when blood pressure is <150/100 mm Hg. Drop of the blood pressure with medications may improve the effect of pregnancy on the mother, but not the fetus. Of antihypertensive drugs used during pregnancy the next are used: methyldopa 1.0–3.0 g per day (the drug of choice), nifedipine 5–10 mg sublingually, labetalol 10 mg intravenously, blockers, clonidine 0.5–1 ml 0.01% solution intravenously or intramuscularly or 0.15–0.2 mg sublingually 4–6 times a day, hydralazine 20 mg (1 ml) intravenously; if it is possible to study the nature of hemodynamics, antihypertensive

therapy is recommended for this purpose. For hyperkinetics, it is advisable to use a combination of labetalol with nifedipine, for hypokinetics — clonidine, nifedipine against the renewal of blood volume, for eukinetics — methyldopa and nifedipine.

The use of diuretics should be avoided, especially in cases of pre-eclampsia (exception: pulmonary edema or renal failure). ACE inhibitors and angiotensin II receptor blockers are absolutely contraindicated.

How do antiepileptic drugs interact with the antihypertensive action of magnesium sulfate, the drug of choice for the prevention and treatment of seizures occurring in hospitalized women as a result of inadequate treatment of severe pre-eclampsia? It has been absolutely proven that magnesium sulfate prevents the development of eclampsia and is the drug of choice for its treatment. All the women with eclampsia should receive magnesium sulfate during labor and for 24 hours after birth. Magnesium sulfate therapy is a bolus of 4 g dry weight magnesium sulfate (IV for 5 min) followed by a continuous intravenous infusion at a rate determined by the patient. Magnesium sulfate therapy begins upon hospitalization when diastolic blood pressure is >130 mm Hg. The purpose of magnesium sulfate therapy is to maintain the concentration of magnesium ions in the blood of pregnant women at a level necessary to prevent seizures.

Signs of magnesium intoxication are also possible against the background of therapeutic concentrations of magnesium in plasma, provided that it is combined with other drugs, especially calcium channel blockers. If signs of magnesium sulfate toxicity appear, 1 g of calcium gluconate (10 ml of a 10% solution) is prescribed intravenously, which should always be at the patient's bedside.

Monitoring a pregnant woman during antihypertensive therapy and magnesium sulfate therapy includes measuring blood pressure every 20 min, monitoring heart rate, heart rate and breathing patterns (at least 14 per minute). Determination of O_2 saturation (not less than 95%); ECG, checking knee reflexes every 2 hrs, checking urine output (not less than 50 ml/hr). In addition, the severity of symptoms of increasing pre-eclampsia: headache, visual impairment (double

vision, "flickering flies" in the eyes), pain in the upper abdomen, symptoms of possible pulmonary edema (tightness in the chest, cough, suffocating fever, increased CVP, appearance of crepitus or moist rales during auscultation), increased heart rate and signs of hypoxia, decreased fetal consciousness (hourly cardiac auscultation, fetal monitoring) (see Table 3.3).

Fluid management

A prerequisite for adequate infusion therapy is strict control of volume, fluid and diuresis. Diuresis should be at least 50 ml/hr. The total volume of fluid administered should cover the woman's daily physiological needs (on average 30–35 ml/kg) plus volumetric non-physiological costs (blood loss, etc.). The rate of fluid administration should not exceed 85 ml/hr, and urine output should not exceed 30 ml/hr. The drugs of choice for infusion therapy at the time of birth are isotonic solutions (Ringer, NaCl 0.9%). If it is necessary to resume BCC, the optimal therapy is 6% or 10% solutions of hydroxyethyl starch (Stabizol, Refortan). Hydroxyethyl starch or dextran should be administered with crystalloids in ratio 2:1. It is advisable to include fresh donor plasma in the infusion-transfusion program to avoid of hypoproteinemia (plasma protein level <55 g/l), normalize the level of anticoagulants/procoagulants in order to prevent bleeding during childbirth and the postpartum period.

Hypoosmotic solutions — 5% and 10% glucose and their mixtures with electrolytes (polarizing mixtures) should not be used, as they often cause hypoglycemia in the fetus and increase the accumulation of lactate in the mother's brain, which worsens the neurological prognosis in eclampsia. Before administering glucose solutions to patients with severe pre-eclampsia, hypoglycemia can be prevented only for absolute indications — hypoglycemia, hypernatremia and hypertensive dehydration, sometimes in patients with diabetes mellitus.

Delivery strategy

Delivery takes place with taking into account the obstetric situation. Vaginal delivery with appropriate anesthesia (epidural

or inhaled nitrous oxide) is preferred. Provided that preparation for childbirth occurs through amniotomy with induction of labor with oxytocin.

If the cervix is unprepared and there is no effect of the drug, prostaglandin is prescribed, and if arterial hypertension progresses, the threat of seizures or the condition worsens, a cesarean section is performed.

The indication for elective cesarean section with severe pre-eclampsia is the progression of pre-eclampsia or deterioration of the fetus in pregnant women with premature birth.

If the condition of the pregnant woman or fetus worsens in the second stage of labor, obstetric forceps are applied or vacuum extraction of the fetus is performed under adequate anesthesia.

In the third stage of labor uterotonics are used to prevent bleeding (oxytocin intravenously). Methylergometrine is not used!

After starting treatment, pre-eclampsia persists depending on the woman's condition, clinical symptoms and laboratory parameters. Blood pressure control and antihypertensive therapy are necessary. The dose of antihypertensive drugs is gradually reduced, but not earlier than 48 hours after birth. Magnesium sulfate therapy continues for at least 24 hours after birth.

With **postpartum pre-eclampsia** protection regimen, blood pressure control and a balanced diet are indicated. *Laboratory examination:* general blood test (hemoglobin, hematocrit, platelet count) and urine, biochemical blood test (ALT and AST, bilirubin, creatinine, urea, total protein), coagulogram.

Treatment. If antihypertensive drugs are taken during childbirth, they are continued in the postpartum period. If the effectiveness of therapy is insufficient, thiazide diuretics are added. If a patient experiences postpartum hypertension for the first time, treatment with a thiazide diuretic starts. Magnesium sulfate is prescribed according to indications with the risk of eclampsia. Uterine involution is carefully monitored. Bleeding prevention is with oxytocin.

Eclampsia

The term "eclampsia" comes from a Greek word meaning "like a flash of lightning." This can happen suddenly, without warning.

However, in most cases (more than 80%), the disease is preceded by symptoms of severe pre-eclampsia.

A high risk of developing eclampsia takes place with severe headache, high blood pressure (diastolic blood pressure >120 mm Hg), nausea, vomiting, blurred vision, pain in the right lower and/or upper abdomen.

The main goals of the emergency are:

- cessation of seizures;
- renewal of the airway entrance.

Problems of intensive care after the elimination of attacks:

- prevention of recurrent seizures;
- elimination of hypoxia and acidosis (respiration and metabolism);
- prevention of aspiration syndrome;
- emergency delivery.

Eclampsia, convulsions or seizures: seizures are epileptiform and consist of four stages:

- Premonitory stage: the patient loses consciousness. The muscles of the face, tongue and limbs twitch. The eyeballs roll or turn to the side and remain motionless. This phase lasts about 30 seconds.
- Tonic stage: The whole body falls into a tonic spasm — the trunk is opisthotonus, the limbs are bent, the hands are clenched. Breathing stops, tongue sticks out between teeth. Cyanosis occurs. The eyeballs become hard. This stage lasts about 30 seconds.
- Clonic stage: all voluntary muscles alternately contract and relax. The spasms begin in the face, then one side of the limbs is affected, and finally the whole body is involved in the spasm. It comes down to tongue biting. The breathing is stertorous, the mouth is filled with foamy secretions; cyanosis gradually disappears. This stage lasts 1–4 minutes.
- Coma stage: after an attack, the patient enters the coma stage. It may last for a brief period in some patients, but sometimes the deep coma lasts until the next attack. After a seizure the patient may appear confused and cannot remember what happened. In rare cases, coma occurs without a previous attack.

First aid for an attack of eclampsia

In the event of an attack, treatment begins immediately on the spot. The patient is taken to the intensive care unit or the anesthesia and intensive care unit of the hospital. The patient is placed on a flat surface, the airways are quickly opened, the mouth is opened and the lower jaw is pushed forward, and the contents of the oral cavity are emptied. If possible and while maintaining independent breathing, air exchange and oxygen inhalation are carried out. If persistent apnea develops, mechanical ventilation is immediately started through a nasal mask with 100% oxygen supply in positive pressure at the end of the expiratory mode. If seizures recur or the patient remains comatose, muscle relaxants are administered and the patient is placed on artificial lung ventilation (ALV) and moderate hyperventilation. Artificial lung ventilation is not the main method of treating eclampsia, but the elimination of hypoxia (an important pathogenetic factor in the development of multiple organ failure) is a necessary condition for other measures.

After complete restoration of consciousness, absence of convulsions, cessation of the use of antiepileptic drugs, stabilization of hemodynamics, stability of the hemostatic system and restoration of the oxygen capacity of the blood (hemoglobin 80 g/l), a planned cessation of ALV is carried out and accompanied by complete withdrawal of sedative therapy.

In case of cerebral hemorrhage and coma in a pregnant woman, artificial respiration is stopped no earlier than after two days. Resuscitation will continue in full.

Catheterization of peripheral veins and administration of antiepileptic drugs (magnesium sulfate — 4 g bolus over 5 minutes intravenously, then maintenance therapy 1–2 g/year) is performed under strict control of blood pressure. Bladder catheterization. All manipulations (catheterization of veins, bladder, obstetric manipulations) are performed under general anesthesia. After eliminating seizures, metabolic disorders, water-electrolyte balance and acid-base status, as well as protein metabolism are corrected. Examination by a neurologist and an ophthalmologist will be carried

out. Laboratory tests: complete blood count (platelets, hematocrit, hemoglobin, clotting time), total protein, albumin, glucose, urea, creatinine, transaminases, electrolytes, calcium, magnesium, fibrinogen and its breakdown products, prothrombin time and index, general urine analysis, daily proteinuria.

Delivery is urgent. If the obstetric situation does not allow immediate delivery through the vaginal birth canal, a cesarean section is performed. Childbirth immediately after elimination of the attack against the background of constant intake of magnesium sulfate and antihypertensive therapy. If the attacks persist, emergency delivery is performed after the patient is transferred to ALV. Artificial ventilation continues to stabilize the patient's condition after surgery. After childbirth, treatment is continued according to the postpartum condition. Therapy with magnesium sulfate should be continued for at least 48 hours.

Observation of a woman suffering from pre-eclampsia/eclampsia after discharge from the maternity hospital. In the antenatal clinic with outpatient supervision by a therapist, a woman who has had pre-eclampsia or moderate to severe eclampsia is given the following:

- nursing home;
- consultation with specialists (if necessary);
- comprehensive examination 6 weeks after birth.

Women who require treatment with antihypertensive drugs are examined weekly after discharge from the maternity hospital, and the degree of proteinuria and plasma creatinine concentrations should be monitored in the laboratory.

If arterial hypertension persists within 3 weeks after birth, the woman is hospitalized. The duration of outpatient treatment after moderate to severe pre-eclampsia or eclampsia is 1 year.

Scope and timing of the examination:

- general urine analysis — 1, 3, 6, 9 and 12 months after birth;
- general blood test — after 1 and 3 months;
- ophthalmoscopy — 1, 3 and 12 months;
- ECG — after 1 month, after that — a visit to therapist.

Women with pre-eclampsia are advised to check their blood pressure daily for one year after giving birth. Women who have had

gestational hypertension or pre-eclampsia have an increased risk of developing high blood pressure in the future, death from stroke and other cardiovascular causes.

Therefore, such follow-up examinations should be carried out under the supervision of a doctor and regular screenings (annual determination of cholesterol and glucose levels) should be carried out.

For a woman with eclampsia (as well as her husband), visiting a psychologist is of great importance, since severe complications of pregnancy often lead to post-traumatic stress disorder.

Table 3.6

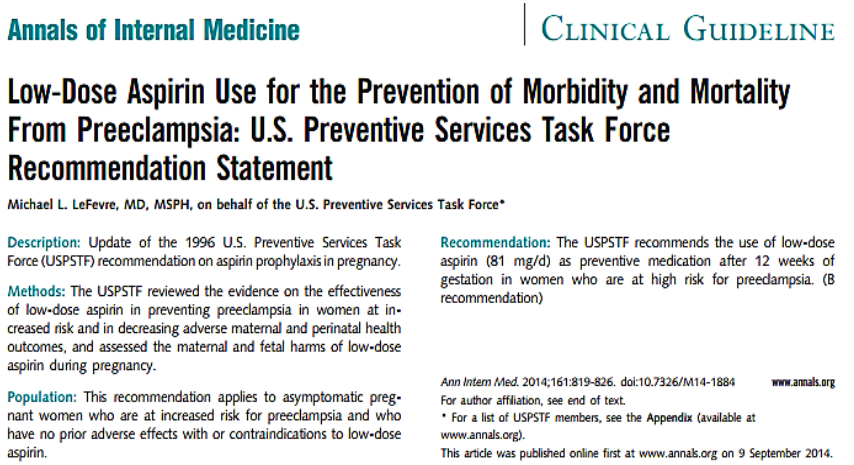
Approved drugs for the treatment of pre-eclampsia

Medicine	Dose	Comments	Start of action
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 minutes to a maximum cumulative dose of 300 mg or continuous infusion of 1–2 mg/min IV	Tachycardia occurs less frequently and there are fewer 1–2-minute side effects. Avoid use in women with asthma, pre-existing myocardial disease, congestive heart failure, heart block, and bradycardia	1–2 minutes
Hydralazine	5 mg IV or IM, then 5 to 10 mg IV every 20 to 40 minutes to a maximum cumulative dose of 20 mg; or continuous infusion of 0.5–10 mg/hr	Higher or more frequent dosing is associated with maternal hypotension, headache, and abnormal fetal heart rate measurements; may occur more frequently than with other agents	10–20 minutes
Nifedipine (immediate release)	10–20 mg orally, repeat after 20 minutes if necessary; then 10–20 mg every 2–6 hours; the maximum daily dose is 180 mg	Reflex tachycardia and headache may occur	5–10 minutes

Source: Obstetrics and Gynecology

Prevention of pre-eclampsia and eclampsia

An effective prevention of pre-eclampsia with proven effectiveness is the use of antiplatelet therapy and calcium intake (Fig. 3.6).



Annals of Internal Medicine | CLINICAL GUIDELINE

Low-Dose Aspirin Use for the Prevention of Morbidity and Mortality From Preeclampsia: U.S. Preventive Services Task Force Recommendation Statement

Michael L. LeFevre, MD, MSPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 1996 U.S. Preventive Services Task Force (USPSTF) recommendation on aspirin prophylaxis in pregnancy.

Methods: The USPSTF reviewed the evidence on the effectiveness of low-dose aspirin in preventing preeclampsia in women at increased risk and in decreasing adverse maternal and perinatal health outcomes, and assessed the maternal and fetal harms of low-dose aspirin during pregnancy.

Population: This recommendation applies to asymptomatic pregnant women who are at increased risk for preeclampsia and who have no prior adverse effects with or contraindications to low-dose aspirin.

Recommendation: The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia. (B recommendation)

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For author affiliation, see end of text.

* For a list of USPSTF members, see the Appendix (available at www.annals.org).

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Fig. 3.6. Preventing Pre-eclampsia and Eclampsia

Source: Michael L. Lefebvre, MD, MSPH. 2014

The American Congress of Obstetricians and Gynecologists recommends the use of low-dose aspirin (60–80 mg/day) at the end of the first trimester to prevent pre-eclampsia in women with a history of early-onset pre-eclampsia and preterm birth (<34 weeks) or pre-eclampsia in more than 1 pregnancy.

The World Health Organization recommends low-dose aspirin (75 mg/day) as early as 12–20 weeks of pregnancy for women at high risk (i.e., women with pre-eclampsia, diabetes, chronic hypertension, kidney or autoimmune disease, or multiple pregnancies). There are limited data on the benefit of low-dose aspirin in other subgroups of high-risk women.

The National Institute for Health and Care Excellence recommends that women at high risk for pre-eclampsia (i.e., women with hypertension in a previous pregnancy, chronic kidney disease, autoimmune disease, type 1 or type 2 diabetes, or chronic

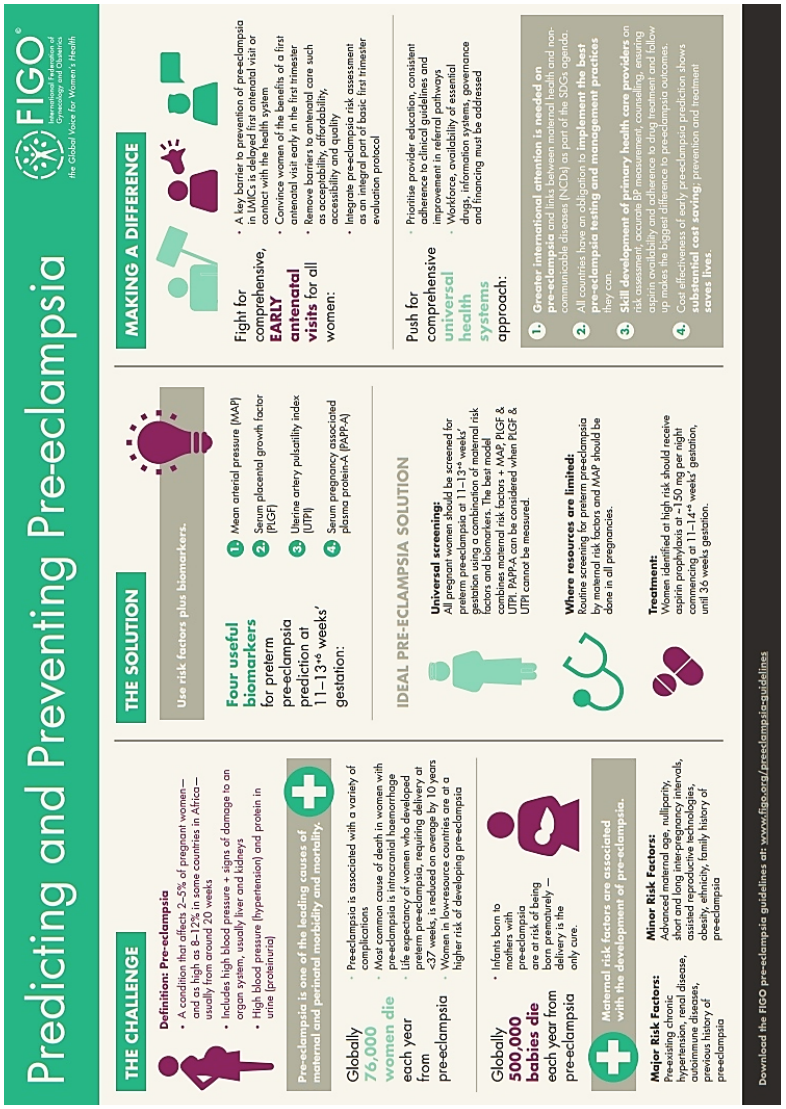


Fig. 3.7. Medicines recommended for the treatment of pre-eclampsia

hypertension) being tested during pregnancy from 12 weeks before delivery take 75 mg of aspirin daily. The same is true for women with more than one moderate risk factor (first pregnancy, age ≥40 years, gestation interval >10 years, body mass index ≥35 kg/m^2, family history of pre-eclampsia or multiple pregnancies).

The American Heart Association and the American Stroke Association recommend a low-dose aspirin from 12 weeks before delivery for women with chronic primary or secondary hypertension or hypertension caused by a previous pregnancy.

The American Academy of Family Physicians recommends low-dose aspirin (81 mg/day) after 12 weeks of pregnancy for women at high risk of pre-eclampsia (Fig. 3.7, p. 116).

Lecture 4

ANTE-, INTRA- AND POSTPARTUM HEMORRHAGES

Topic Relevance

The incidence of obstetric hemorrhage is 5–10%, but it is the most common cause of maternal disease, disability and mortality (20–25%). One of the most important factors is the increase in the number of cesarean sections. The profuse obstetrical hemorrhage during some minutes can become fatal because of belated elimination of blood and its components deficiency. In hemorrhage in the III trimester of pregnancy, acute fetal hypoxia often occurs, requiring immediate delivery, when there is no time to wait for persistent normalisation of haemodynamic parameters and the full volume of infusion and transfusion therapy is performed. Physiological postnatal hemorrhage after the ending of the III labor stage should be lower than 0.5% of a woman's body weight (>0.5% — pathological). All other bleeding during pregnancy is pathological. Massive obstetric hemorrhage is more often associated with placenta previa or premature placental abruption, anomalies of placentation, postnatal hypo- and atony of uterus, embolism by amniotic fluids, uterus rupture. The profuse obstetrical hemorrhage can lead to hemorrhagic shock or be accompanied by disorders of the homeostasis system.

Educational Materials

SPONTANEOUS ABORTION (MISCARRIAGE)

Abortion is the expulsion or removal from the mother's body of an embryo or fetus weighing 500 g or less when it is incapable of independent survival (WHO). This 500 g fetal weight is reached at about 22 weeks (154 days) of pregnancy. The expelled embryo or fetus is called an abortion. The term 'miscarriage' is the recommended terminology for spontaneous abortion (Fig. 4.1, p. 119).

1. Threatened abortion (abortus imminens).
2. Incipient abortion.
3. Inevitable spontaneous abortion *(abortus protrahens)*.
4. Incomplete spontaneous abortion.
5. Complete spontaneous abortion.
6. Abortion which did not take place (missed abortion).

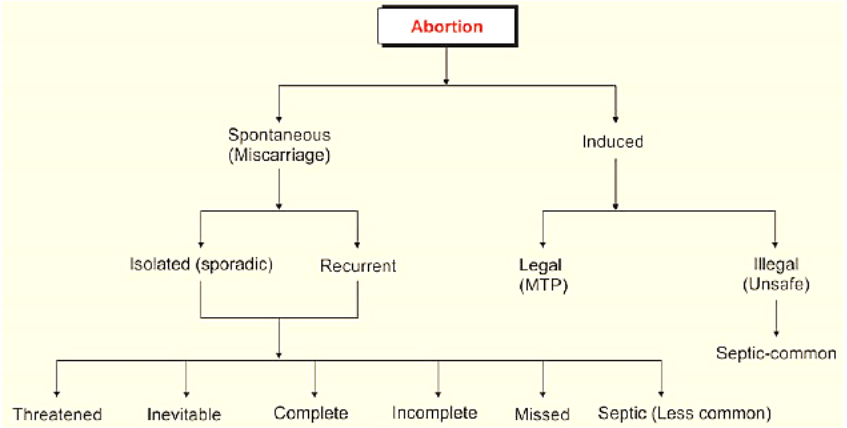


Fig. 4.1.

Source: Chapter-15 Hemorrhage in Early Pregnancy Book title: D C Dutta's Textbook of Obstetrics

The etiology of miscarriage is often complex and obscure. The following factors (embryonic or parental) are important:

- Genetic.
- Endocrine and metabolic.
- Anatomic.
- Infection.
- Immunological.
- Antifetal antibodies.
- Thrombophilias.
- Others.

Common Causes of Miscarriage:

First trimester: (1) genetic factors (50%); (2) endocrine disorders (LPD, thyroid abnormalities, diabetes); (3) immunological disorders (autoimmune and alloimmune); (4) infection and (5) unexplained.

Second trimester:

1. Anatomic abnormalities:
   (a) Cervical incompetence (congenital or acquired);
   (b) Mullerian Fusion defects (bicornuate uterus, septate uterus);
   (c) Uterine synechiae;
   (d) Uterine fibroid.
2. Maternal medical illness.
3. Unexplained.

Mechanism of miscarriage. In the early weeks, death of the ovum occurs first, followed by its expulsion. In the later weeks, maternal environmental factors are involved leading to expulsion of the fetus which may have signs of life but is too small to survive.

- Before 8 weeks: The ovum, surrounded by the villi with the decidual coverings, is expelled out intact. Sometimes, the external os fails to dilate so that the entire mass is accommodated in the dilated cervical canal and is called cervical miscarriage.
- 8–14 weeks: Expulsion of the fetus commonly occurs leaving behind the placenta and the membranes. A part of it may be partially separated with brisk hemorrhage or remains totally attached to the uterine wall.
- Beyond 14th week: The process of expulsion is similar to that of a "mini labor". The fetus is expelled first followed by expulsion of the placenta after a varying interval.

Clinical and diagnostic criteria

Symptoms of a miscarriage:

— pain syndrome: pain, connected to the contraction of the uterus;
— increased uterus tone;
— bleeding of different degree of severity;
— structural changes in the uterine cervix.

The last two symptoms are the basis for the differential diagnostics of the stages of a miscarriage. During a threat of an abortion there are no bleeding and structural changes in the cervix.

Bleeding during spontaneous abortion, incipient abortion, inevitable abortion, incomplete spontaneous abortion.

THREATENED MISCARRIAGE

It is a clinical phenomenon where the process of miscarriage has begun but has not progressed to a state from which it is impossible to recover.

Clinical features

The woman having symptoms suggestive of pregnancy complains of: bleeding per vagina (usually slight, may be brown or bright red in color). On rare occasions, the bleeding may be brisk, especially in the late second trimester. The bleeding usually stops spontaneously.

Hemorrhage in early pregnancy. Bleeding is usually painless but there may be mild back ache or dull pain in the lower abdomen. Pain appears usually following hemorrhage. Pelvic examination should be done as gently as possible. Examination with gynecologic speculum reveals that the hemorrhage, if any, comes out through the external orifice.

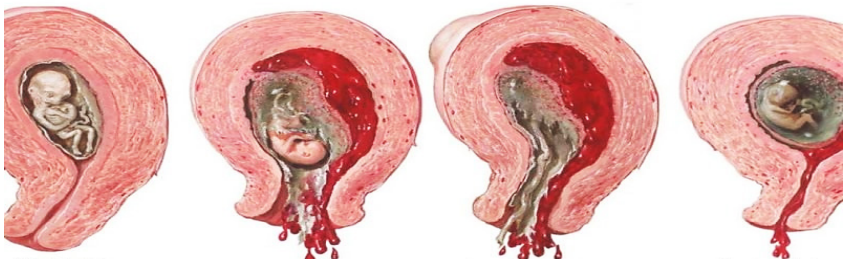
Differential diagnosis includes cervical ectopy, polyps or carcinoma, ectopic pregnancy and molar pregnancy. Digital examination reveals the closed external os. The uterine size corresponds to the period of amenorrhea.

Routine examination includes:

- Blood analysis (hemoglobin, hematocrit, AB0 and Rh group). Blood transfusion may be required if abortion becomes inevitable and anti-D gamma globulin has to be given in Rh negative non-immunized women.
- Urine analysis for the immunological test of pregnancy is not helpful as the test remains positive for a variable period even after the fetal death.
- Ultrasonography findings: a well-formed gestation ring with central echoes from the embryo indicating healthy fetus.

Observation of fetal cardiac motion. With this, there is a 98% chance of continuation of pregnancy. A blighted ovum is evidenced by loss of definition of the gestational sac, smaller mean gestational sac diameter, absent fetal echoes and absent fetal cardiac movements (Fig. 4.2).

- Serum progesterone value of 25 ng/mL or more generally indicates a viable pregnancy in about 95% of cases. Serial serum chorionic gonadotropin (hCG) level is helpful to assess the fetal wellbeing.



Missed abortion *Inevitable abortion* *Incomplete abortion* *Threatened abortion*

Fig. 4.2. Clinical variants of abortion

INEVITABLE MISCARRIAGE

It is a clinical type of abortion where changes progress to a state where continuation of the pregnancy is not possible.

Clinical features: The patient having the features of threatened miscarriage develops the following manifestations:

- Increased vaginal bleeding.
- Aggravation of pain in the lower abdomen which may be colicky in nature.
- Internal examination reveals dilated internal os of the cervix through which the products of conception are felt.

On occasion, the features may develop quickly without prior clinical evidence of threatened miscarriage.

General measures: excessive bleeding should be promptly controlled by administering methergine 0.2 mg if the cervix is dilated and the size of the uterus is less than 12 weeks.

The blood loss is corrected by intravenous fluid therapy and blood transfusion.

Active treatment

- Before 12 weeks: Dilatation and evacuation followed by curettage of the uterine cavity by blunt curette using analgesia or under general anesthesia. Alternatively, suction evacuation followed by curettage is done.
- After 12 weeks: The uterine contraction is accelerated by oxytocin drip (10 units in 500 mL of normal saline) 40–60 drops per minute. If the fetus is expelled and the placenta is retained, it is removed by ovum forceps, if lying separated. If the placenta is not separated, digital separation followed by its evacuation is to be done under general anesthesia.

COMPLETE MISCARRIAGE

Clinical features

There is history of expulsion of a fleshy mass per vagina followed by:

- Subsidence of abdominal pain.
- Vaginal bleeding becomes slight or absent.
- Internal examination reveals: uterus is smaller than the period of amenorrhea and a little firmer, cervical os is closed, trace of bleeding. Examination of the detached fleshy mass reveals a complete abortion.

Rh-negative women: A Rh-negative patient without antibody in her system should be protected by Anti-D gamma globulin 50 mcg or 100 mcg intramuscularly in cases of early miscarriage or late miscarriage respectively within 72 hours. However, Anti-D may not be required in a case with complete miscarriage before 12 weeks' gestation where no instrumentation has been done.

INCOMPLETE MISCARRIAGE

Definition. When the entire products of conception are not expelled, instead a part of it is left inside the uterine cavity, it is called incomplete miscarriage.

Clinical features

- Continuation of pain lower abdomen.
- Persistence of vaginal bleeding.
- Internal examination reveals: (a) uterus smaller than the period of amenorrhea, (b) patulous cervical os often admitting tip of the finger, and (c) varying amount of bleeding on examination, the expelled mass is found incomplete.

Complications. The retained products may cause: profuse bleeding, sepsis or placental polyp.

Treatment. In recent cases — evacuation of the retained products of conception (ERCP) is done. It should be resuscitated before any active treatment is undertaken.

- Early abortion: dilatation and evacuation under analgesia or general anesthesia is to be done.
- Late abortion: the uterus is evacuated under general anesthesia and the products are removed by ovum forceps or by blunt curette. In advanced cases, dilatation and curettage surgery is performed to remove pieces of tissue left behind after surgery. The removed materials are subjected to a histological examination. Medical management of incomplete miscarriage may be done. Tablet Misoprostol 200 µg is used vaginally every 4 hours.

MISSED MISCARRIAGE

Definition. When the fetus is dead and retained inside the uterus for a variable period, it is called missed miscarriage or early fetal demise.

Pathology. The causes of prolonged retention of the dead fetus in the uterus is not clear. Beyond 12 weeks, the retained fetus becomes macerated or mummified. The liquor amnii gets absorbed and the placenta becomes pale, thin and may be adherent. Before 12 weeks, the pathological process differs when the ovum is more or less completely surrounded by the chorionic villi.

Carneous Mole (Syn: blood mole, fleshy mole).

It is the pathological variant of missed miscarriage affecting the fetus before 12 weeks. Small repeated hemorrhages in the choriodecidual space disrupt the villi from its attachments. The bleeding is slight, so it does not cause rupture of the *decidua capsularis*. The clotted blood with the contained ovum is known as a blood mole. By this time, the ovum becomes dead and is either completely absorbed or remains as a rudimentary structure. Gradually, the fluid portion of the blood surrounding the ovum gets absorbed and the wall becomes fleshy, hence the term fleshy or carneous mole.

Clinical features

- Persistence of brownish vaginal discharge.
- Subsidence of pregnancy symptoms.
- Retrogression of breast changes.
- Cessation of uterine growth which in fact becomes smaller in size.
- Nonaudibility of the fetal heart sound even with Doppler ultrasound if it had been audible before.
- Cervix feels firm.
- Immunological test for pregnancy becomes negative.
- Real time ultrasonography reveals an empty sac early in the pregnancy or the absence of fetal motion or fetal cardiac movements.

Treatment

- Uterus is less than 12 weeks:

Expectant management — many women expel the conceptus spontaneously.

Medical management. Prostaglandin E1 (Misoprostol) 800 mg vaginally in the posterior fornix is given and repeated after 24 hours if needed. Expulsion usually occurs within 48 hours.

Suction evacuation or dilatation and evacuation is done either as a definitive treatment or it can be done when the medical method fails. The risk of damage to the uterine walls and brisk hemorrhage during the operation should be kept in mind.

- Uterus more than 12 weeks:

Induction is done by the following methods: prostaglandins are more effective than oxytocin in such cases.

The methods used are:

A. Prostaglandin E1 analogue (misoprostol) 200 µg tablet is inserted into the posterior vaginal fornix every 4 hours for a maximum of 5 ones.
B. Oxytocin — 10–20 units of oxytocin in 500 mL of normal saline at 30 drops per minute is started. If fails, escalating dose of oxytocin to the maximum of 200 mlU/min, may be used with monitoring.
C. Many patients need surgical evacuation following medical treatment. Following medical treatment, ultrasonography should be done to document empty uterine cavity. Otherwise evacuation of the retained products of conception (ERPC) should be done.
D. Dilatation and evacuation is done once the cervix becomes soft with use of PGE1. Otherwise the cervical canal is dilated using mechanical dilators or by a laminaria tent. Evacuation of the uterine cavity is done thereafter slowly (Fig. 4.3).

MOLAR PREGNANCY

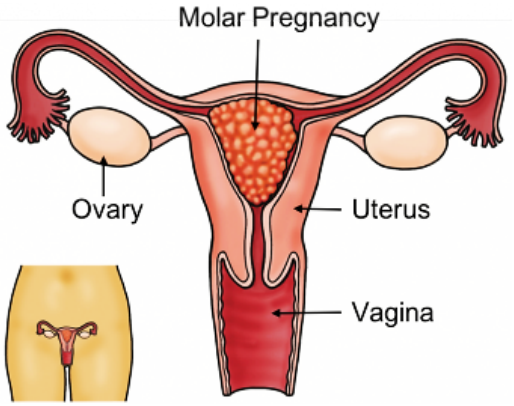


Fig. 4.3.
Source: NHS The Leeds Teaching Hospitals

A molar pregnancy is an abnormal form of pregnancy in which a non-viable fertilized egg implants in the uterus and converts a normal pregnancy into an abnormal one. It is a gestational trophoblastic disease in which changes in the chorion are expressed by a dramatic increase in the size of the villi, which grow in bunches resembling grapes.

Classification of hydatidiform mole:

Hydatidiform mole:

1. Complete.
2. Incomplete.

Gestational trophoblastic neoplasia:

1. Destructive invasive malignancy mole.
2. Choriocarcinoma.

Clinical classification of choriocarcinoma

I stage — is limited in the uterus.
II stage — spreads beyond the uterus, but is limited to the genitals.
III stage — metastasis to the lungs.
IV stage — metastasis involves of other organs.

Risk factors

- Maternal age. A molar pregnancy is more typical for women older than 35 or younger than 20 years old.
- Previous molar pregnancy. If you've had one molar pregnancy, you're more likely to have one more.
- Previous inflammatory diseases or ovarian hormonal disorders.
- Previous abortions.
- Using birth control pills.
- Asian ethnicity.

Symptoms

- Missed period 2–3 months.
- Morning sickness.
- Vaginal bleeding.
- A uterus is larger than normal.
- Severe nausea and vomiting.
- Uncomfortable feeling in the pelvis.

- Vaginal discharge of tissue that is shaped like grapes. This is usually a sign of molar pregnancy.

Diagnosis

The early symptom of toxicity is usually a moderate or severe vomiting. Early symptoms of late toxicity: edema, proteinuria, later hypertension appears. Blood tests will show very high levels of human chorionic gonadotropin (hCG) >1000 times.

On ultrasound, the mole resembles a bunch of grapes ("cluster of grapes" or "honeycombed uterus" or "snow-storm" (Fig. 4.4).

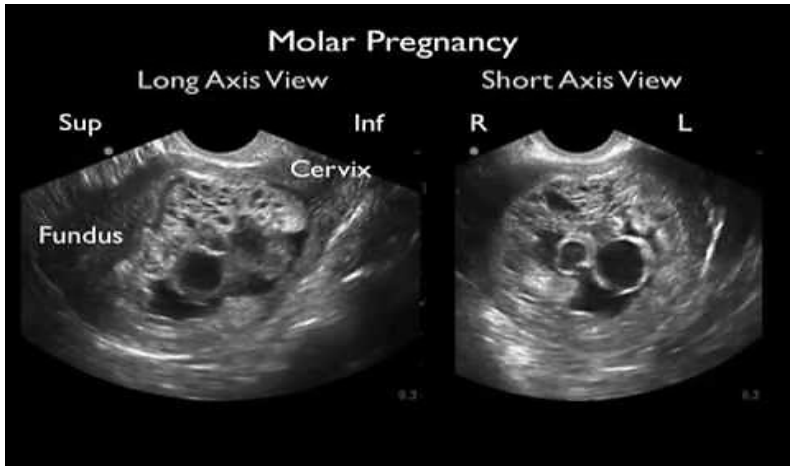


Fig. 4.4.

Source: SonoSpot: Topics in Bedside Ultrasound Share & highlight US cases, tips & tricks, research, news, people and events

Treatment. A molar pregnancy is treated by evacuating the uterus by uterine suction or by surgical curettage, in order to avoid the risks of choriocarcinoma.

Patients are followed up until the serum hCG level falls down to an undetectable level.

Invasive or metastatic moles may require chemotherapy and methotrexate-dactinomycin-cyclophosphamide. The response to treatment is nearly 100%.

Patients are advised to avoid the next pregnancy for one year after molar pregnancy, check-up during 4 years.

Extra-uterine pregnancy (ectopic, EP) takes place when the fertilized ovum is implanted and develops outside the normal endometrial cavity (Fig. 4.5).

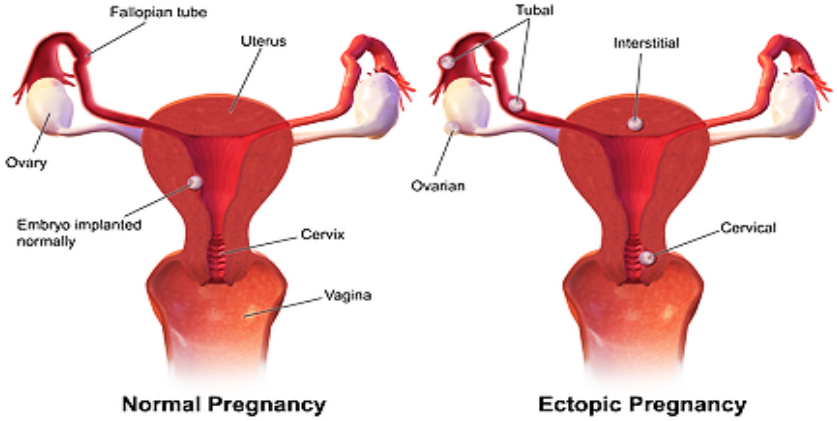


Fig. 4.5.

Source: Medium. Ectopic Pregnancy: Causes, Symptoms, Risks and Treatment

Classification

1. By the ICD-10

O00 Abdominal pregnancy
O00.1 Tubal pregnancy
Pregnancy in the fallopian tube
Rupture of the fallopian tube due to the pregnancy
Tubal abortion
O00.2 Ovarian pregnancy
O00.8 Other forms of extra-uterine pregnancy
Cervical
Combined
In the uterus wall (interstitial, intramural)
Intraligamentous
In the uterine horn
O00.9 Unspecified extra-uterine pregnancy

2. *By the course:*
   — progressing;
   — interrupted (aborted);
   — miscarriage.

Risk factors

- Inflammatory diseases of the uterus and uterine appendages in the anamnesis.
- Cicatricial adhesions in the pelvic organs due to past operations on the internal genitals organs, pelviperitonitis, abortions.
- Hormonal ovarian dysfunction.
- Genital infantilism.
- Endometriosis.
- Prolonged use of intrauterine contraceptives.
- Assisted reproductive technologies.

Clinical signs

1. *Signs of pregnancy:* delay or missed menstruation, breast swelling, change in taste, smell and other sensations characteristic of pregnancy, signs of early gestosis (nausea, vomiting, etc.), positive immunological reactions to pregnancy (hCG in blood serum and urine).

2. *Menstrual dysfunction:* spotting, bloody vaginal discharge — after a delay in menstruation; with the beginning of the next menstruation; before the next expected menstruation.

3. *Pain syndrome:* unilateral spastic or persistent pain in the lower abdomen; sudden intensive pain in the lower abdomen; peritoneal symptoms in the lower abdomen of different severity; irradiating pain to the rectum, perineum and sacrum.

4. *Signs of intra-abdominal bleeding (in case of EP):* dullness of percussion sound in the flanks and abdomen; positive Kulencampf's symptom (signs of peritoneal irritation with the absence of local muscle pressure in the lower abdomen); when the patient is in horizontal position there is a positive bilateral "phrenicus" symptom, and in a vertical position — dizziness, loss of consciousness; in case of considerable hemoperitoneum — positive Blumberg symptom; progressing decrease in hemoglobin, erythrocytes, hematocrit from blood analysis results.

5. *Impairment in the patient's general condition (in case of EP):* weakness, dizziness, loss of consciousness, cold sweats, collapse, hemodynamic dysfunction, faintness, reflex vomiting, flatulence, and diarrhea.

Gynecologic exam: cyanosis of the vaginal mucosa and cervix, the size of the uterus is smaller than at the expected gestational term, unilateral increase and tenderness of the uterine appendages, acute pain during palpation of the posterior vaginal fornix ("Douglas' cry"), pain during cervical excursion.

Specific laboratory tests: qualitative or quantitative test for hCG.

Instrumental methods of examination: ultrasound (absence of the fetal egg in the uterine cavity; visualization of the embryo outside the endometrial cavity; detection of a non-uniform structure in the field of projection of the fallopian tubes; significant amount of free fluid in the Douglas pouch); laparoscopy (retro-shaped thickening of the fallopian tubes with a crimson-cyanotic color; rupture of the fallopian tubes, bleeding from the ampular opening or from a ruptured place in the fallopian tubes, presence of coagulated or fresh blood in the abdominal cavity and in the Douglas pouch, presence of elements of the fetal egg in the abdominal cavity) (Fig. 4.6, 4.7, p. 132).

Diagnostic curettage of the walls of the uterine cavity:

- absence of elements of the fetal egg in the curettage material;
- presence of decidual tissue in the curettage material.

Diagnostic curettage of the walls of the uterine cavity is performed in the absence of an ultrasound and with informed consent from the patient for this manipulation.

With a short period of delayed menstruation and the woman's interest in preserving uterine pregnancy and the absence of symptoms of intra-abdominal hemorrhage, it is necessary to choose conservative tactics, observing clinical signs, ultrasound in dynamics, serum hCG level.

Puncture of abdominal cavity through the posterior vaginal fornix (Fig. 4.8, p. 133) performed when there is no ultrasound to diagnose tubal abortion. The presence of fresh blood in punctate is one of the signs of EP.

In case of clinical signs of an intra-abdominal bleed, puncture of the abdominal cavity through the posterior vaginal fornix is not performed — it delays the beginning of laparotomy.

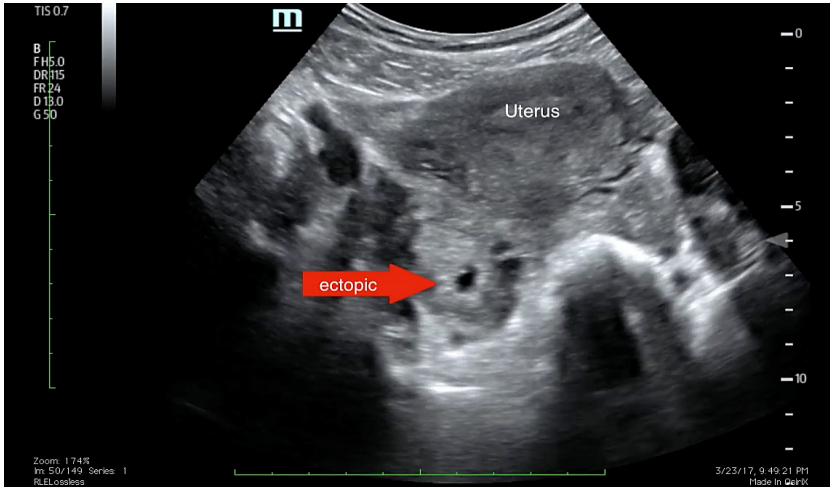


Fig. 4.6. US of ectopic pregnancy

Source: Ectopic Pregnancy, Ultrasound Still Image, Annotated. JETem 2017

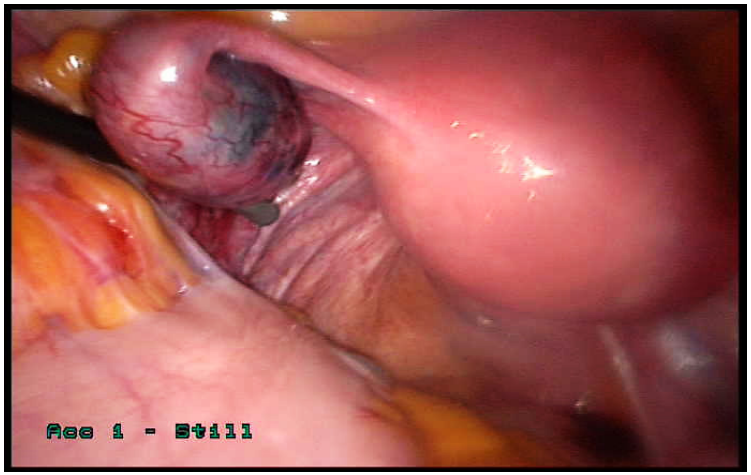


Fig. 4.7. Tubal ectopic pregnancy

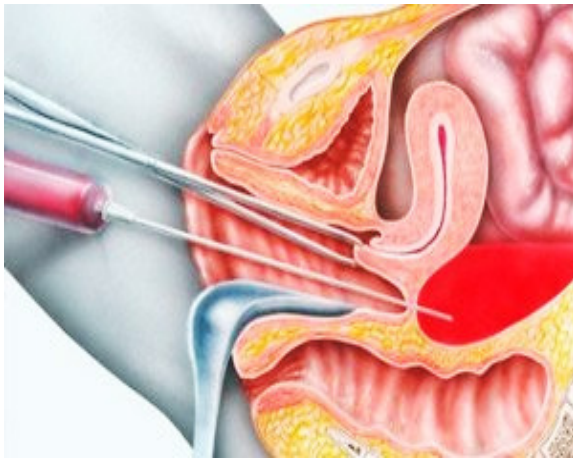


Fig. 4.8. Puncture of the posterior vaginal fornix

Differential diagnostics

Diagnosis of ectopic pregnancy is easy in patients with amenorrhoea, signs of pregnancy, lower abdominal pain and bleeding. But it is necessary to exclude the following conditions:

1. Twisting of an ovarian cyst or acute appendicitis.
2. Aborted uterine pregnancy.
3. Hemorrhage into the corpus luteum.

Table 4.1

Diagnostic signs of various forms of tubal pregnancies

Clinical signs	Progressing ectopic pregnancy	Tubal abortion	Rupture of the fallopian tubes
1	2	3	4
Signs of pregnancy	Positive	Positive	Positive
Patient's general condition	Satisfactory	Periodically worsens, short-term losses of consciousness, long periods of satisfactory general condition	Collaptoid state, clinic picture for massive blood loss, progressive deterioration of the general condition

End of Table 4.1

1	2	3	4
Pain	Absent	Attacks which periodically repeat	Present in the form of acute attack
Discharge	Absent or insignificant bloody discharge	Dark bloody discharge, which appears after pain attack	Absent or insignificant bloody discharge
Vaginal examination	Uterus does not fit the estimated pregnancy term, near the uterus is a retro-shaped formation, non-tender, fornix is free	The same, pain when the uterus is shifted, formation without clear contours, posterior fornix is smooth	The same, "floating uterus" symptoms, pain in the uterus and uterine appendages on the affected side, bulging of the posterior fornix
Additional methods of examination	Ultrasound, levels of β-hCG, laparoscopy	Culdocentesis, laparoscopy	Not performed

Treatment of ectopic pregnancy

Principles for management of patients with ectopic pregnancy:

1. Suspected ectopic pregnancy is an indication for urgent hospitalization.

2. Early diagnosis helps to reduce complications and enables alternative treatments.

3. Urgent surgical intervention (laparoscopy, laparotomy) is necessary for ectopic pregnancy. Surgical treatment is optimal. In modern practice, conservative methods of treatment are possible.

4. In case of ectopic pregnancy and the presence of hemodynamic dysfunctions, hypovolemia, the patient should be immediately hospitalized for emergency surgery using the laparotomy access. If the clinical picture is not clear, there are no signs of hypovolemia and internal bleeding — ultrasound of the pelvic organs and/or laparoscopy.

5. Infusion therapy (volume, speed of introduction of solutions) depends on the stage of hemorrhagic shock.

6. Poor condition of the patient, presence of pronounced hemodynamic dysfunctions (hypotension, hypovolemia, hematocrit

less than 30%) are absolute indications for operative intervention by laparotomy access with the removal of the fallopian tubes and anti-shock therapy.

7. A complex approach to the treatment of women with an ectopic pregnancy is provided, which includes:

a) surgical treatment;
b) control of bleeding, hemorrhagic shock, blood loss;
c) conducting the postoperative period;
d) rehabilitation of reproductive function.

8. Operative treatment can be provided with laparotomy or laparoscopic access. Advantages of laparoscopic access include:

— decrease of the duration of the operation;
— decrease of the duration of the postoperative period;
— decrease of the duration of the hospital stay;
— decrease of the cicatricial changes in the anterior abdominal wall;
— cosmetic effect.

9. Organ-preserving operations in EP are accompanied by the risk of trophoblast persistence in the postoperative period, which is the result of its incomplete removal from the fallopian tubes and abdominal cavity. The most effective method of prevention of this complication is thorough lavage of the abdominal cavity with 2–3 liters of physiological solution and a single injection of 7.5–100 mg of methotrexate IM in the first 24–48 hours after surgery.

Operations used in the case of tubal pregnancy

1. Salpingostomy (tubectomy). Longitudinal salpingostomy is performed. After the removal of the fetal egg, salpingostomy is usually not sutured. In the case the chorionic villi do not grow into the muscular membrane of the fallopian tube, only curettage is performed.

2. Segmentary resection of the fallopian tubes. The segment of the fallopian tubes is removed where the fetal egg is located, then an anastomosis is made between two ends of the tube. If it is impossible to perform salpingo-salpingo anastomosis then it is possible to tie off both ends and perform anastomosis later.

3. Salpingectomy. This operation is performed for a tubal pregnancy accompanied by massive bleeding. The operation and hemotransfusion is performed in that case simultaneously (Fig. 4.9).

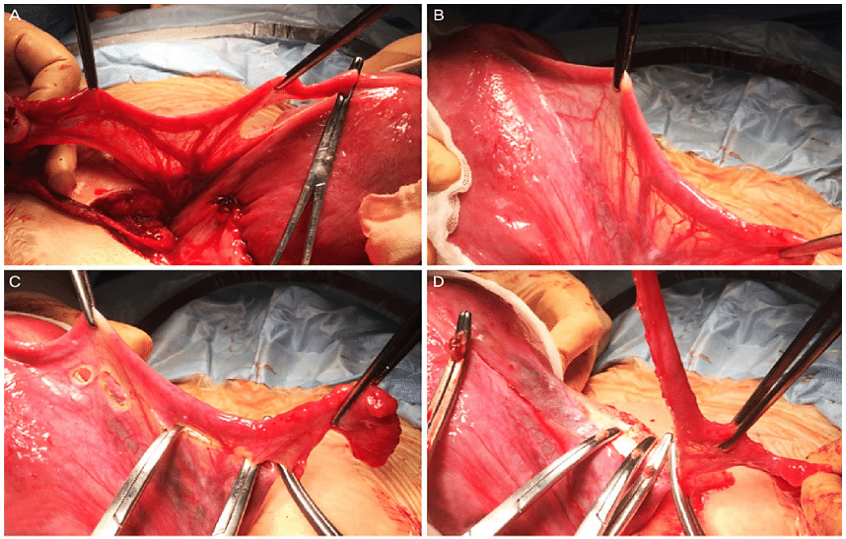


Fig. 4.9. Salpingectomy with tubal pregnancy

Source: Bilateral salpingectomy to reduce the risk of ovarian/ fallopian/peritoneal cancer in women at average risk: A position statement of the Korean Society of Obstetrics and Gynecology (KSOG)

Conservative treatment of ectopic pregnancy

Treatment of progressing EP with methotrexate can be done only in third level institutions of public health services where it is possible to determine β-subunit of hCG in blood serum and perform a transvaginal ultrasound.

Indications for the use of methotrexate in the case of ectopic pregnancy

In order to avoid the introduction of methotrexate during a normal uterine pregnancy or an abortion which has not taken place, it is prescribed only in the following cases:

1. Increased level of β-subunit of hCG in blood serum after organ-saving operations on the fallopian tubes, performed due to progressing extra-uterine pregnancy.

2. Stabilization or increased level of β-subunit of hCG in blood serum during 12–24 hours after separate diagnostic curettage or vacuum aspiration if the size of the fetal egg at the area of the uterine appendages does not exceed 3.5 cm.

3. During trans-vaginal ultrasound it is discovered that the fetal egg has a diameter no more than 3.5 cm at the area of the uterine appendages and the level of β-subunit of hCG is 1500 IU/l, the absence of the fetal egg in the uterine cavity.

Table 4.2

Use of methotrexate in the case of EP

Day	Treatment-diagnostic approach
1st	Determine the level of β-subunit of hCG in blood serum
2nd	General blood analysis, determine the woman's blood type and Rh-factor, liver enzymes
5th	Methotrexate 75–100 ml IM
8th	Determine the level of β-subunit of hCG in blood serum

If the level of β-subunit of hCG in blood serum has decreased less than 15% on the eighth day, methotrexate can be introduced again in the same dose.

If the serum hCG β-subunit level has increased by more than 15%, the patient is monitored, and the serum hCG β-subunit level is determined every week until it is at least 10 IU/L.

OVARIAN PREGNANCY

It develops if the ovum is fertilized in the follicle cavity. Ovarian pregnancy makes up 0.5–1% of all ectopic pregnancies. The use of intrauterine contraceptives is the only risk factor for this type of EP.

Clinical signs and symptoms are similar to those for tubal pregnancy. If ovarian pregnancy ruptures, the clinical picture of hemorrhagic shock develops. In 75% of cases, ovarian pregnancy is misdiagnosed with ovarian apoplexy.

Ultrasound of the pelvic organs helps in diagnostics, especially transvaginal ultrasound, when the fetal egg is visualized at the area of the ovary and there is a positive reaction for hCG.

Ultrasound signs for ovarian pregnancy:

- the fallopian tube on the affected side is intact;
- the fetal egg is in the ovary;
- the fetal egg is connected to the uterus by the ovarian ligament;
- amongst the fetal membrane, ovarian tissue is seen.

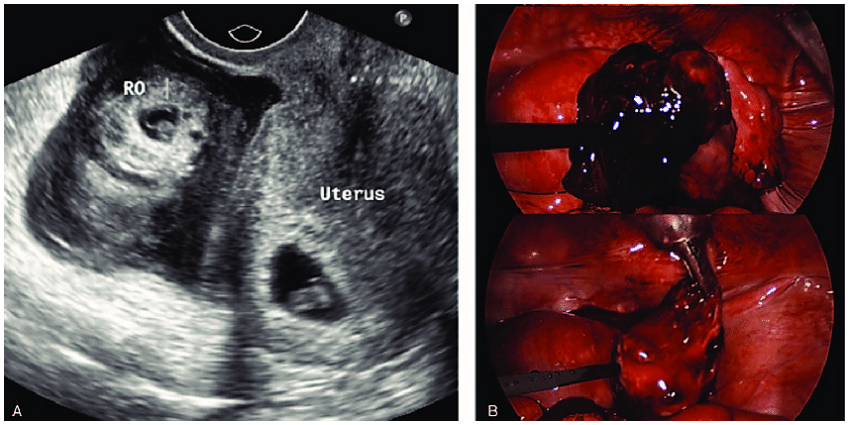


Fig. 4.10. Ovarian pregnancy

Source: The risk factors of miscarriage and obstetrical outcomes of intrauterine normal pregnancy following heterotopic pregnancy management

Treatment

Surgical treatment includes removal of the fetal egg and wedge resection of the ovary. In the case of massive defects of the ovary and considerable intra-abdominal bleeding, ovariectomy is performed.

CERVICAL PREGNANCY

This is a rare (1 in 16,000 pregnancies) variant of ectopic pregnancy when the implantation occurs in the cervical canal at or below the internal os. Erosion of the walls by the trophoblasts occurs resulting in thinning and distension of the canal. The condition is commonly confused with cervical abortion. In cervical pregnancy,

the bleeding is painless and the uterine body lies above the distended cervix. Intractable bleeding following evacuation or expulsion of the products brings about suspicion. The morbidity and mortality is high because of profuse hemorrhage (Fig. 4.11).

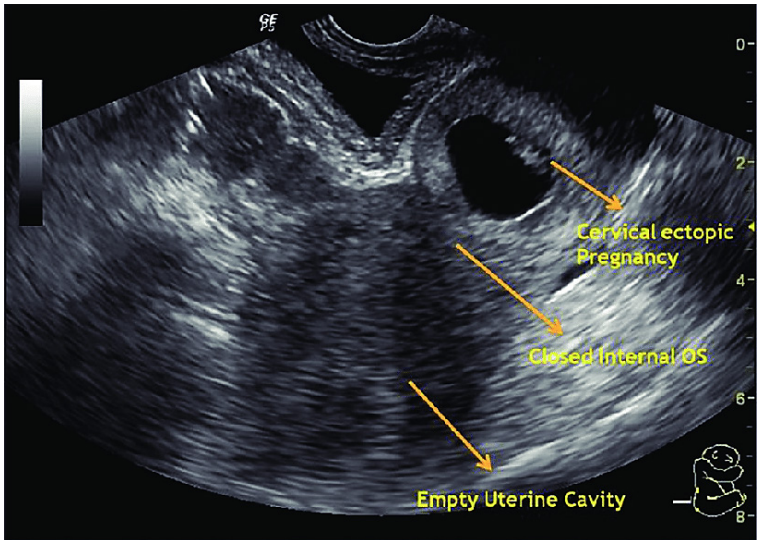


Fig. 4.11. Cervical pregnancy

Source: In book: Non-tubal Ectopic Pregnancy: Incidence and Diagnosis

Clinical diagnostic criteria for cervical pregnancy are:

- Anamnesis, including gynecological. Pay attention to the number of abortions and the course of the post-abortion period, inflammatory diseases of the internal genital organs, including the cervix.
- Soft, enlarged cervix the same size or larger than the fundus.
- Visualized cyanotic barrel-shaped cervix.
- Uterine bleeding following amenorrhea, without cramping pain.
- Products of conception entirely confined within and firmly attached to endocervix.
- A closed internal cervical os and a partially opened external os.

Ultrasound reveals the pregnancy in the cervical canal and an empty uterine cavity.

- Hyperechoic endometrium (decidual tissue).
- Heterogeneous myometrium.
- Uterus in the form of hourglass.
- Dilated cervical canal.
- Fetal egg in the cervical canal.
- Placental tissue in the cervical canal.
- Closed internal uterine os.

Differential diagnostics

Cervical pregnancy differentiates with spontaneous abortion, myoma, cervical cancer, prolapsed submucous myoma on a leg, trophoblastic tumor, placental presentation and low placental location. An ultrasound allows accurate enough differential diagnostics from other obstetrical-gynecological pathologies.

Treatment

1. Curettage of the walls of the uterine cavity in the case of diagnosed cervical pregnancy is forbidden because it can lead to profuse bleeding.

2. The treatment method for cervical pregnancy is surgical (hysterectomy). Hysterectomy is often required to stop bleeding. An attempt to preserve the uterus may be made by intracervical plugging. Uterine artery embolization with gelfoam can control hemorrhage. Confirmation is done by histological evidence of the presence of villi inside the cervical stroma.

3. After verification of the diagnosis, determine the woman's blood type and Rh-factor, insert venous catheter, obtain the patient's written consent to perform hysterectomy. The transfusion department prepares type-specific blood, fresh frozen plasma, fresh frozen erythrocytes mass, and hydroxyethyl starch.

ABDOMINAL PREGNANCY

Abdominal pregnancy makes up 0.003% of all the cases of extra-uterine pregnancy. Primary and secondary abdominal pregnancies are distinguished.

Primary pregnancy is the implantation of a fertilized ovum in the abdominal cavity.

Secondary one is formed, when the fetal egg is in the abdominal cavity after a tubal abortion. Maternal death rate for abdominal pregnancy is 7–8 times higher than for tubal, and is 90 times higher than for uterine pregnancy.

Symptoms:

History suggestive of disturbed tubal pregnancy during early months (pain lower abdomen and vaginal bleeding) is often present.

Minor ailments of normal uterine pregnancy are often exaggerated, such as nausea, vomiting, constipation, pain in the abdomen and increased fetal movements.

Clinical picture depends on the pregnancy term:

1. In the first trimester and in the beginning of the second trimester they differ a little from the symptoms for tubal pregnancy.

2. In later terms, the pregnant woman complains of pains during fetal movement, sensation of fetal movement in the epigastric area or suddenly not feeling fetal movement.

3. During bimanual examination, soft fetal parts and separately a small uterus are easily palpated. Abdominal pregnancy also is diagnosed when there are no uterine contractions after introducing oxytocin.

4. Ultrasound is also used for diagnostics. It is commonly performed. Suggestive features are absence of uterine wall around the fetus, abnormally high position of fetus with abnormal attitude, fetal parts with close approximation to maternal abdominal wall and visualization of the uterus separately. Diagnostic error could reach more than 40%.

If ultrasound is not informative, the diagnosis can be confirmed with X-ray, CT and MRI.

X-ray examination reveals:

- Abnormally high position of the fetus with absence of outline of uterine shadow.
- Superimposition of gas shadow on the fetal skeleton.
- Lateral X-ray on standing position shows superimposition of fetal skeleton shadow with the maternal spinal shadow.

On the X-ray of the abdominal cavity, taken from lateral projection, a shadow of the fetal skeleton is visualized, which lies on the top of the mother's spine image.

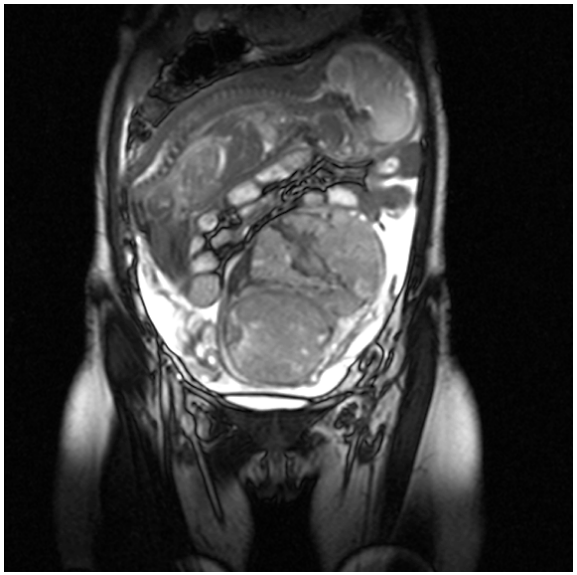


Fig. 4.12. Abdominal pregnancy

Source: Advanced Secondary Abdominal Pregnancy: A Complication of Induced Abortion

Internal examination. The uterus is difficult to separate from the abdominal mass. If it does, it is enlarged (12–16 weeks) but the cervix is not typically soft and is usually displaced depending upon the position of the sac.

The risks of continuation of pregnancy are:

- Catastrophic hemorrhage.
- Fetal death.
- Increased fetal malformation.
- Increased neonatal loss (50%).

Treatment

Considering the high risk of maternal death rate, immediately after the diagnosis is established, surgical treatment is performed. During

operative treatment, the vessels, which deliver blood to the placenta, are tied off and if necessary removed. If it is impossible because of heavy bleeding, the placenta is tamponaded. Tampons are removed in 24–48 hours.

Complications include secondary hemorrhage, intestinal obstruction and infection.

Bleeding during the second half of the pregnancy:

- placenta previa;
- premature detachment of placenta in its normal presentation;
- rupture of the uterus.

PLACENTA PREVIA

ICD-10 code — O44

044.0 — Determined placenta previa without bleeding

044.1 — Placenta previa with bleeding

Placenta previa is a pregnancy complication in which the placenta is located in the lower uterine segment below the presenting part, blocking all or part of the internal cervical os. In physiological pregnancy, the lower edge of the placenta does not approach the inner membrane by more than 7 cm. Placenta previa is seen in 0.2–0.8% of all deliveries.

Classification of placenta previa

1. Complete presentation — the placenta completely blocks the internal os.

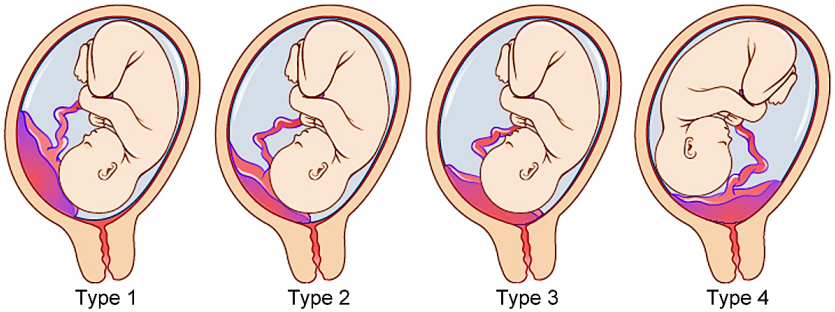
2. Incomplete presentation — the placenta partially blocks the internal os:

a) Lateral presentation — 2/3 of the area of the internal os is blocked;

b) Marginal presentation — the edge of the placenta meets the internal os.

3. Low placenta previa (placement) — the placenta is implanted in the lower uterine segment less than 7 cm from the internal os without blocking it.

In connection with migration of the placenta or its growth, the type of presentation can change as the pregnancy continues (Fig. 4.13, p. 144).



Classifications

Classical	*Contemporary*	*Ultrasound*
Type 1	Marginal	Minor
Type 2	Lateral	
Type 3	Central	Major
Type 4		

Fig. 4.13. Types of placental location

Source: Dr Rukhsana Tariq

Etiology

The exact cause of the implantation of the placenta in the lower segment is not known. The following theories have been put forward:

Dropping down theory. The fertilized ovum drops down and is implanted in the lower segment. Poor decidual reaction in the upper uterine segment may be the cause. Failure of zona pellucida to disappear in time can be a hypothetical possibility. This explains the formation of central placenta previa.

- Persistence of chorionic activity in the decidua capsularis and its subsequent development into capsular placenta which comes in contact with decidua vera of the lower segment can explain the formation of lesser degrees of placenta previa.
- Defective decidua, results in spreading of the chorionic villi over a wide area in the uterine wall to get nourishment. During this process, not only the placenta becomes membranous but encroaches onto the lower segment. Such a placenta previa may invade the underlying decidua or myometrium to cause placenta accreta, increta or percreta

- Big surface area of the placenta as in twins may encroach onto the lower segment.

The cause of hemorrhage. As the growth of the placenta slows down in the last months, and the lower segment continues to expand, the inelastic placenta detaches from the wall of the lower segment. This leads to the opening of the uteroplacental vessels and, consequently, to bleeding. Since this is a physiological phenomenon that leads to placental abruption, bleeding is considered inevitable. However, placental abruption can also be triggered by trauma, such as a vaginal examination, sexual intercourse, external variant or high rupture of the membranes. The blood is almost always maternal, although fetal blood may escape from the torn villi especially when the placenta is separated during trauma.

Clinical symptoms. The only symptom of placenta previa is vaginal bleeding. The classical features of bleeding in placenta previa are sudden onset, painless, apparently causeless and recurrent. In about 5% cases, it occurs for the first time during labor, especially in primigravidae. In about one-third of cases, there is a history of "warning hemorrhage" which is usually slight. The bleeding is unrelated to activity and often occurs during sleep and the patient becomes frightened on awakening to find herself in a pool of blood. The bleeding is unassociated with pain unless labor starts simultaneously. Obvious causes for the placental separation such as trauma or hypertension are usually absent. However, pre-eclampsia may complicate a case of placenta previa. The first bout of bleeding is usually not alarming but subsequent bouts may be heavier than the previous one due to separation of fresh areas of placenta. In the majority of cases, bleeding occurs before 38 weeks and earlier bleeding is more likely to occur in major degrees. However, there may not be any bleeding in central placenta previa until labor starts. Anemia, as a result of bleeding.

Abdominal examination:

The size of the uterus is proportionate to the period of gestation. Note the effective reduction of the antero-posterior diameter of the inlet in contrast to type II anterior placenta previa.

- The uterus feels relaxed, soft and elastic without any localized area of tenderness.
- Persistence of malpresentation like breech or transverse or unstable lie is more frequent. There is also increased frequency of twin pregnancy.
- The head is floating in contrast to the period of gestation. Persistent displacement of the fetal head is very suggestive. The head cannot be pushed down into the pelvis.
- Fetal heart sound is usually present, unless there is major separation of the placenta with the patient in exsanguinated condition. Slowing of the fetal heart rate on pressing the head down into the pelvis which soon recovers promptly as the pressure is released is suggestive of the presence of low lying placenta especially of posterior type (Stallworthy's sign). But this sign is not always significant because it may be due to fetal head compression even in an otherwise normal case. Frequently, incorrect positioning of the fetus occurs: diagonal, transverse, breech presentation, incorrect insertion of the head. Premature birth is possible.

Diagnosis

1. Anamnesis.

2. Clinical displays — occurrence of repeated bleeding, not accompanied by pain and increased uterus tonus.

Obstetrical examination:

a) External examination:
   - High standing of the presented part;
   - Diagonal, transverse fetal position;
   - The tonus of the uterus is not increased;

b) Internal examination (performed only in the conditions of an operation room):
   - Doughy tissue in the fornix, swelling, pulsation of vessels;
   - Impossible to palpate the presented part through the fornix.

In case of bleeding of a specific character, the presentation is not meaningful because the obstetrical management is determined by the volume of blood loss and the condition of the woman.

Table 4.3

Distinguishing features of placenta previa and abruptio placentae

	Placenta previa	**Abruptio placentae**
Clinical features: Nature of bleeding	(a) Painless, apparently causeless and recurrent (b) Bleeding is always revealed	(a) Painful, often attributed to pre-eclampsia or trauma and continuous (b) Revealed, concealed or usually mixed
Character of blood	Bright red	Dark colored
General condition and anemia	Proportionate to visible blood loss	Out of proportion to the visible blood loss in concealed or mixed variety
Features of pre-eclampsia	Not relevant	Present in one-third cases
Abdominal examination: Height of uterus	Proportionate height to gestational age	May be disproportionately enlarged in concealed type
Palpating uterus	Soft and relaxed	May be tense, tender and rigid
Malpresentation	Malpresentation is common. The head is high floating	Unrelated, the head may be engaged
FHS	Usually present	Placenta in the upper segment
Placentography (USG)	Placenta in lower segment	Placenta in upper segment
Vaginal examination	Placenta is felt on the lower segment	Placenta is not felt on the lower segment. Blood clots should not be confused with the placenta

Placenta previa with bleeding is an urgent indication for hospitalization.

Algorithm of examining a pregnant woman with bleeding in the hospital:

- Specify the anamnesis.
- Evaluate the general condition, volume of blood loss.
- General instrumental tests (blood type, Rhesus factor, general blood analysis, coagulogram).
- External obstetrical examination.
- Examination of the uterine cervix and vagina in an operational room with the help of vaginal mirrors to exclude such reasons

for bleeding as cervical polyp, cervical cancer, rupture of a varicose node, evaluate vaginal discharge.

- Additional methods of examination (US) if indicated, if there is no need for urgent delivery.

Treatment

Treatment management depends on the volume of blood loss, conditions of the patient and fetus, character of the presented part, term of the pregnancy, maturity of the fetus's lungs.

Principles for conducting patients with placenta previa:

1. In case of small blood loss (250 ml), absence of symptoms of hemorrhagic shock, fetal distress, absence of labor activity, immaturity of the fetus's lungs before 37 weeks' term — waiting tactics.

2. Bleeding that has stopped — US, prepare the fetus's lungs. The purpose of waiting tactics — prolong the pregnancy to term of a viable fetus.

3. In case of progressing uncontrollable bleeding (more than 250 ml), accompanied by symptoms of hemorrhagic shock, fetal distress, regardless of the pregnancy term, condition of the fetus (live, distress, dead) — urgent (emergency) delivery.

Clinical variants

1. Blood loss (up to 250 ml), there are no symptoms of hemorrhagic shock, fetal distress, term of pregnancy — less than 37 weeks:

- hospitalization;
- tocolytic therapy when indicated;
- quicken the maturing of the fetus's lungs before 34 weeks of pregnancy (dexamethasone 6 mg every 12 hours for 2 days);
- monitoring the woman and fetal condition;
- if bleeding progresses more than 250 ml — delivery by Cesarean section.

2. Considerable blood loss (more than 250 ml) with premature term of pregnancy — regardless of the presented part — emergency Cesarean section.

3. Blood loss (up to 250 ml) with mature pregnancy:

Under the conditions of an operational room, determine the presentation:

- In case of partial placenta previa, intact amniotic sac and cephalic presentation, active uterine contractions, perform amniotomy. If the bleeding stops, delivery can be performed vaginally. After the birth of the baby — IM administration of 10 units of oxytocin, carefully observe the contractions of the uterus and character of vaginal discharge. If bleeding continues — cesarean section.
- In case of complete or incomplete placenta previa, wrong fetal position (pelvic, diagonal or transverse) perform cesarean section.
- In case of incomplete placenta previa, dead foetus, amniotomy is performed, vaginal delivery is performed if bleeding stops.

4. Blood loss (more than 250 ml) mature pregnancy regardless of the presentation — an urgent cesarean section.

5. Complete placenta previa: diagnosed by US, without bleeding — hospitalization till mature term for delivery, cesarean section at 37–38 weeks.

In the early postnatal period — careful supervision of the woman's condition. If the bleeding reoccurs after Cesarean section and the volume of blood loss is more than 1% of body weight — urgent relaparotomy, hysterectomy without the appendages, if necessary — ligation of the internal iliac arteries by an expert.

Compensation for the blood loss, treatment of hemorrhagic shock and DIC-syndrome is performed when indicated.

PREMATURE DETACHMENT OF A NORMALLY LOCATED PLACENTA

Code number — 045 Premature detachments (tearing away of the placenta)

045.0 Premature detachment of the placenta with coagulation dysfunction

045.8 Other premature detachment of the placenta

045.9 Premature non-specified detachment of the placenta

Premature detachment of a normally located placenta is the premature pathological detachment from the uterine walls during the pregnancy or during the I–II periods of labor.

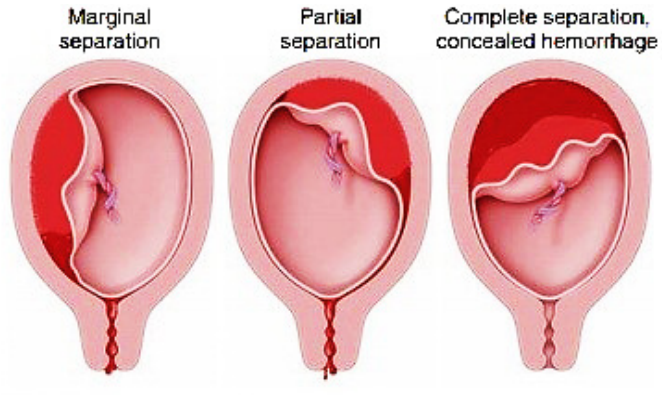


Fig. 4.14. Types of placental abruption

Source: BrainKart.com

Etiology

The exact cause of separation of a normally located placenta remains obscure in the majority of cases. The prevalence is more with:

— high birth order pregnancies with gravida 5 and above — three times more common than in first birth;
— advanced age of the mother;
— poor socio-economic condition;
— malnutrition;
— smoking (vasospasm).

- Hypertension in pregnancy is the most important predisposing factor. Pre-eclampsia, gestational hypertension and essential hypertension, all are associated with placental abruption.
- Trauma. Traumatic separation of the placenta usually leads to its marginal separation with escape of blood outside. The trauma may be due to:
  — attempted external cephalic version specially under anesthesia using great force;
  — road traffic accidents or blow on the abdomen;
  — needle puncture at amniocentesis.
- Sudden uterine decompression of the uterus leads to diminished surface area of the uterus adjacent

to the placental attachment and results in separation of the placenta. This may be provoked by following:
  — delivery of the first baby of twins;
  — sudden escape of liquor amnii in hydramnios and;
  — premature rupture of membranes.
- Short cord, either relative or absolute, can bring about placental separation during labor by mechanical pull.
- Supine hypotension syndrome. In this condition which occurs in pregnancy there is passive engorgement of the uterine and placental vessels resulting in rupture and extravasation of the blood.
- Placental anomaly. Circumvallate placenta
- Sick placenta. Poor placentation, evidenced by abnormal uterine artery Doppler waveforms is associated with placental abruption.
- Uterine factor. Placenta implanted over a septum (Septate Uterus) or a submucous fibroid. Torsion of the uterus leads to increased venous pressure and rupture of the veins with separation of the placenta:
  — isoimmune conflict between the mother and fetus;
  — overdistension of the uterus (hydramnion, multiple pregnancy, large fetus);
  — diabetes;
  — kidney disease;
  — inflammatory processes of the uterus, placenta.

Classification:

1. Complete detachment (the whole placenta detaches).
2. Partial detachment:

— marginal;
— central.

Clinical symptoms

1. Pain syndrome: sharp pain at the location of the placenta which then extends to the whole uterus, abdomen, back and becomes diffuse. The pain is most expressed during central detachment and can be not as expressed for marginal detachment. For detachment of a placenta located on the posterior uterine wall, the pain can simulate renal colic.

2. Hypertonus of the uterus up to tetany, which does not decrease with spasmolytic, tocolytic agents.

3. Vaginal bleeding can vary depending on the severity and character (marginal or central) from insignificant to massive. If the hematoma is formed retroplacenta, external bleeding can be absent.

Diagnosis

1. Condition of the pregnant woman will depend on the size of the detachment, volume of blood loss, occurrences of symptoms of hemorrhagic shock or DIC-syndrome.

2. External obstetrical examination:
   — hypertonus of the uterus;
   — the uterus is increased in size, can be deformed with local bulging if the placenta is located on the anterior wall;
   — pain, tenderness during palpation;
   — difficult or impossible palpation and auscultation of the fetal heartbeat;
   — occurrence of symptoms of fetal distress or its death.

3. Internal obstetrical examination:
   — strained amniotic sac;
   — amniotic fluid with blood;
   — bleeding from the uterus.

4. US (echo-negative shadow between the uterus and placenta), but this method cannot be an absolute diagnostic criterion, because a hypoechogenic zone can be seen in patients without detachments.

In case of absence of external bleeding the diagnosis of premature detachment of placenta is based on increased uterus tonus, local tenderness, deterioration of the fetal condition. Blood from retroplacental hematomas penetrates the wall of the uterus and forms Couvelaire's uterus (utero-placental apoplexy) which then loses the ability to contract, which leads to the development of bleedings with massive blood loss as a result of coagulopathy and hypotonus.

Treatment

Unreasonably overdue delivery leads to the death of the fetus, development of Couvelaire's uterus, massive blood loss, hemorrhagic shock and DIC-syndrome, loss of reproductive function (Fig. 4.15, p. 153).

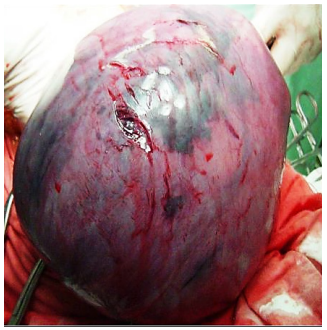


Fig. 4.15. Couvelaire's uterus

Source: Couvelaire Uterus Without Placental Abruption: A Rare Case Report

1. In case of progressing premature detachment of the placenta during the pregnancy, or in the first period of labor, with the occurrence of symptoms of hemorrhagic shock, DIC-syndrome, signs of fetal distress, regardless of the pregnancy term — urgent delivery by Cesarean section. In the presence of signs of Couvelaire's uterus — hysterectomy without the uterine appendages.

2. Restore the blood loss, treatment of hemorrhagic shock and DIC-syndrome.

3. In case of non-progressing detachment of the placenta, possible dynamic supervision for premature pregnancy till 34 weeks (carrying out therapy for the maturing of the fetus's lungs), in establishments where there is round-the-clock watch of qualified OBGYN doctors, anesthesiologists, neonatologists. Monitoring of the woman's condition and fetal condition, CTG, US in dynamics are done.

Features of the Cesarean section:
— prior to the operation — amniotomy (if there are conditions);
— obligatory revision of the uterine walls (especially the external surface) for the purpose of an excluding utero-placental apoplexy;
— in case of diagnosing of Couvelaire's uterus — hysterectomy without the uterine appendages;
— if there is a small area of apoplexy — 2–3 foci of small diameter 1–2 cm, or one — up to 3 cm), and the ability of the uterus

to contract, absence of bleeding and signs of DIC-syndrome, if necessary to keep reproduction function (first childbirth, dead fetus), there is questions about preserving the uterus. Surgeons observe the condition of the uterus for some time (10–20 min) with the abdominal cavity still open, in the absence of bleeding the abdominal cavity is drained for hemostasis control. Such management in unusual cases is performed only in hospitals having a round-the-clock watch of doctors OBGYN, anesthesiologist;

— in the early postoperative period — careful supervision of the woman's condition.

Management for placental detachment at the end of the I or during the II stages of labor

- Immediate amniotomy, if the amniotic sac is intact.
- If cephalic fetal presentation — apply obstetrical forceps.
- If breech presentation — extraction of the fetus by the pelvic.
- If transverse position of the second twin — perform an obstetrical turn with extraction of the fetus by the leg. In some cases, more reliable will be cesarean section.
- Manual detachment of the placenta and removal of the placenta.
- Contractive agents — IV 10 units of oxytocin, in the absence of effect — 800 mcg of misoprostol (rectal).
- Careful dynamic supervision at the postpartum period.
- Restore the blood loss, treatment of hemorrhagic shock and DIC-syndrome.

Reasons for bleeding at the third stage of labor and early postpartum periods (stages)

1. Anomaly of placental abruption processes:
   — insufficient contractility of the myometrium;
   — anomalies of placentation;
   — strong attachment of the placenta (partial);
   — placenta adherens (partial);
   — ruptured uterus (complete, incomplete).
2. Anomaly in the processes of expulsion of the placenta:
   — hypotension of the uterus;
   — delay of the placenta in the lower segment of the uterus;

   — incorrect methods of removing the placenta;
   — irrational introduction of uterotonics drugs.
3. Trauma to the genital tract, in particular the uterus.
4. Placental defects, delay of parts of the placenta, its membranes.
5. Hemostasis dysfunction, induced by a complicated course of pregnancy and labor (coagulopathy).

Blood loss during labor should be no more than 0.5% of the woman's body weight. This is physiological!

Postpartum bleeding — blood loss more than 0.5% of the woman's body weight after the birth of the baby. Bleeding in some minutes or hours after the delivery is a serious and potentially fatal complication. Bleeding can be sudden and profuse, or slow and long.

Classification

072.0 — Bleeding at the third stage of labor

072.1 — Other bleedings in the early postpartum period

072.2 — Late or secondary postpartum hemorrhage

072.3 — Postpartum coagulation disorder

Types of postpartum hemorrhage:

1. Hemorrhage at the third stage of labor.
2. Primary (early) postpartum hemorrhage which occurs at the early postpartum period or within 24 hours after delivery.
3. Secondary (late) postpartum hemorrhage which occurs after 24 hours and up to 6 weeks after delivery.

Risk factors of postpartum hemorrhage:

— burdened obstetrical anamnesis (bleedings in previous deliveries, abortions, miscarriages);
— pre-eclampsia;
— big fetus;
— polyhydramnios;
— multiple pregnancy;
— uterus myoma;
— seam on the uterus;
— chronic DIC-syndrome;
— thrombocytopathy;
— antenatal death of the fetus.

Bleeding at the third stage of labor

Reasons

— delay of parts of the placenta or its membranes;
— pathological attachment of the placenta;
— pinching of the placenta.

The amount of blood loss depends on the type of placental attachment disorder: complete, partial adhesion of the placenta (Fig. 4.16).

Classification of anomalies of placentation

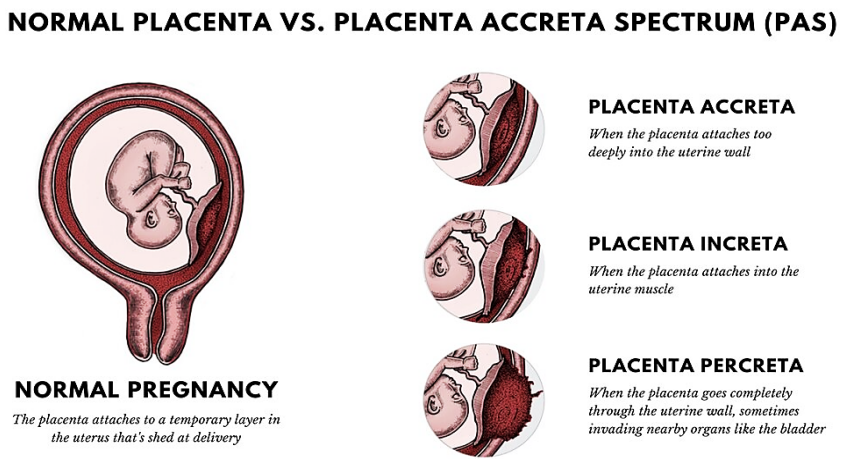


Fig. 4.16. Classification of placenta accrete spectrum
Source: healthpally.com/

Firm (compact) attachment of the placenta:

placenta accreta — pathological attachment of the placenta to the endometrium (porous layer is absent).

Penetration of the placenta:

placenta increta — penetration into the myometrium; *placenta percreta* — invasion of the placenta the whole myometrium.

The firm attachment of the placenta or its penetration can be complete (not accompanied by bleeding) and partial (accompanied by considerable bleeding due to detachment of parts of the placenta).

Reasons for pathological attachment of the placenta — changes in the structure of the porous layer of the basal decidual membrane due to:

— chronic endometritis;
— cicatricial and dystrophic changes after previous abortions or intra-uterine interventions;
— insufficient development of the uterus;
— decrease in the activity of trophoblast enzymes;
— pathological location of the placenta.

Clinical displays

1. There are no signs of detachment of the placenta for 30 minutes without considerable blood loss — pathology of adherent or penetrated placenta.
2. Bleeding begins right after the birth of the afterbirth — delay of parts of the placenta or its membranes.
3. Bleeding begins after the birth of the child without detachment of the placenta — pinched placenta, an incomplete penetration of the placenta.

Algorithm for medical help

1. Catheterization of a peripheral or central vein depending on the volume of blood loss and conditions of the woman.
2. Empty the bladder.
3. Check for signs of detachment of the placenta and deliver the placenta using manual maneuvers.

Signs of placental separation:

- The uterus becomes firm, round in shape and rises up.
- Lengthening of the umbilical cord.
- Sudden gush of blood (Fig. 4.17, p. 158).

4. In case of delay of parts of the placenta or its membranes — manual examination of the uterus cavity under intravenous narcosis.
5. If placental separation has not occurred and there is no bleeding, wait for 30 minutes; manual detachment of the placenta and delivery of the placenta.
6. If bleeding occurs — urgent manual detachment of the placenta and deliver the placenta under IV narcosis.
7. Introduction uterotonic agents — 10–20 units of oxytocin IV in 400 ml of physiological solution by droplets.

8. If true adherence or penetration of the placenta — laparotomy, hysterectomy without the uterine appendages.

9. Evaluate the volume of blood loss and restore the blood volume (treatment of hemorrhagic shock).

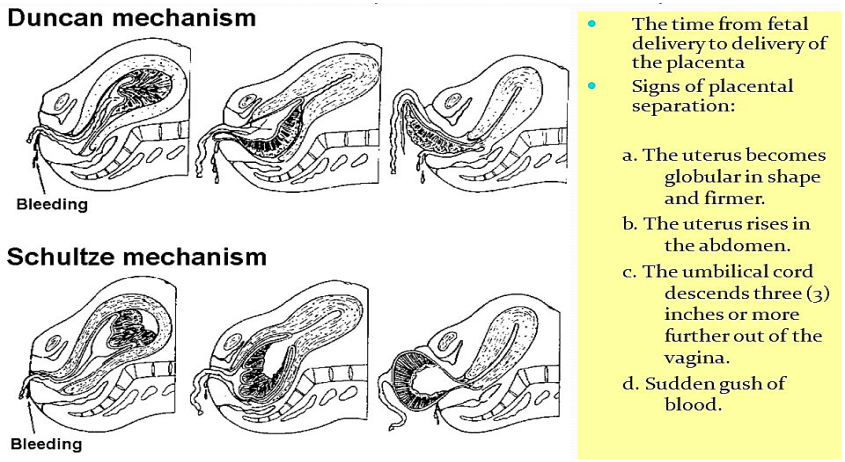


Fig. 4.17. Mechanisms of placental detachment

Source: Slide by the theme Labor Labor is the physiologic process by which a fetus is expelled from the uterus to the outside world. It involves the sequential integrated changes

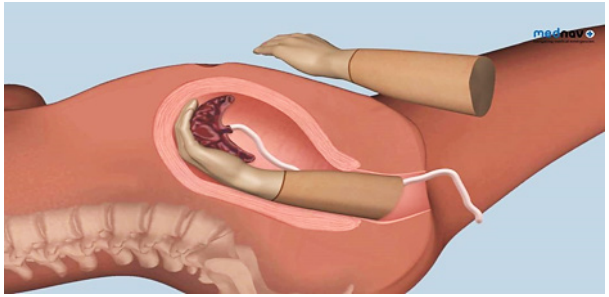


Fig. 4.18. Manual detachment

Early (primary) postpartum hemorrhage

Reasons for early postpartum hemorrhage:

- hypotonic and atonic uterus (in 90% of the cases);
- delay of parts of the placenta or membranes;
- trauma to the birth canal;
- coagulation disorders (afibrinogenemia, fibrinolysis);
- Blood coagulation disorders.

Reasons of hypotonic and atonic uterus

— disorder of the functional ability of the myometrium (pre-eclampsia, endocrinopathy, somatic diseases, tumors of the uterus, seam on the uterus, big fetus, polyhydramnios, multiple pregnancy and others);

— overexcitation with the following exhaustion of the function of the myometrium (prolonged labor), operative labor, taking drugs that reduce the tone of the myometrium (spasmolytic, tocolytics, hypoxia during delivery, etc.);

— disorder of the contractive functions of the myometrium due to disorder of biochemical processes, correlation of neurohumoral factors (estrogen, acetylcholine, oxytocin, choline esterase, progesterone, prostaglandin);

— disorders in the process of attachment, detachment and discharge of the placenta and its membranes;

— idiopathic (not established).

Hemorrhage can be of 2 types:

- Bleeding begins immediately after childbirth, massive (after a few minutes >1000 ml); the uterus remains hypotonic, does not contract, hypovolemia, hemorrhagic shock develops rapidly.
- Bleeding begins after contraction of the uterus, blood flows in small portions, blood loss gradually increases. The alternation of uterine hypotonia with restoration of tone is characteristic. The bleeding stops and starts again.

Steps of management

1. General observation:
   — evaluation of blood loss;

— evaluation of the condition of the woman: complaints, BP, pulse rate, color of the skin and mucous membranes, amount of urine, presence and stage of hemorrhagic shock.

2. Urgent laboratory tests:
   — determine the level of hemoglobin, hematocrit;
   — coagulogram (amount of thrombocytes, prothrombin index, level of fibrinogen, coagulation time of blood);
   — blood type and Rhesus factor;
   — biochemical test if indicated.
3. Catheterization of peripheral or central vein depending on the size of blood loss and conditions of the woman.
4. Empty the urinary bladder.
5. Begin or continue introducing uterotonics: 10–20 units of oxytocin IV in 400 ml of physiological solution.
6. Perform manual inspection of the uterine cavity under intravenous narcosis (evaluation of the integrity of the uterine walls, especially the left wall, remove clots of blood or the rest of the placenta or its membranes).
7. Examine the birth canal and restore its integrity.
8. External massage of the uterus.

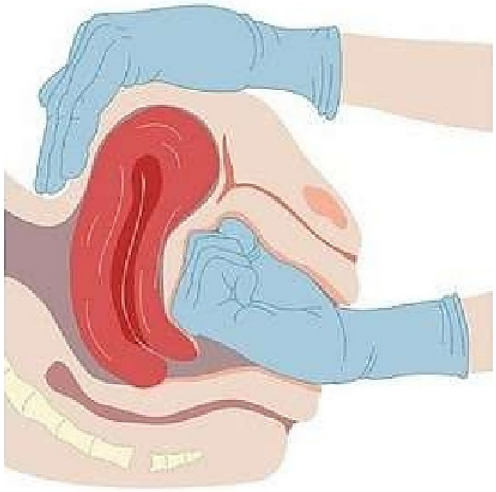


Fig. 4.19. Bimanual compression of the uterus

9. In case of continuation of bleeding, 800 mcg of misoprostol are administered rectally.
10. Restore blood volume and *blood* loss (treatment of hemorrhagic shock).
11. If bleeding continues, blood loss is 1.5% or more of the woman's body weight — treatment is operative: hysterectomy without the uterine appendages, if the bleeding continues — ligation of the internal iliac arteries (Fig. 4.20).

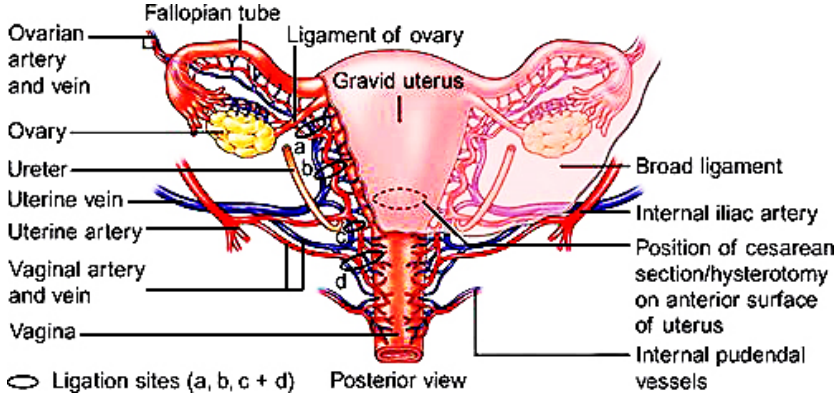


Fig. 4.20. Uterine blood supply

12. During preparation for operative treatment, to reduce blood loss, bimanual external or internal compression of the uterus (Fig. 4.22, *b*, p. 166).
13. If bleeding continues after hysterectomy — hard tamponade of the abdominal cavity and vagina (the abdominal cavity is not sutured up until the bleeding stops).

Postpartum secondary (late) hemorrhage

Main causes for late postpartum hemorrhage:
— delay of parts of the placenta or its membranes;
— discharge of necrotic tissue after delivery;
— separation of sutures on the wound on the uterus (after C-section or ruptured uterus).

Late postpartum hemorrhage occurs 7–12 days after delivery.

Steps of management:

1. Evaluation of blood loss.
2. Catheterization of peripheral or central veins.
3. Instrumental revision of the uterine cavity under IV narcosis.
4. IV introduction of uterotonics (oxytocin 10–20 units in physiological solution — 400.0 or 0.5 mcg of methylergometrine).
5. If the bleeding continues — misoprostol 800 mcg rectally.
6. Restore blood volume.
7. If blood loss >1.5% of the woman's body weight — laparotomy, hysterectomy, if it still continues — ligation of the internal iliac arteries.

Blood coagulation disorders (postpartum afibrinogenemia, fibrinolysis):

— restore blood volume;
— correct hemostasis.

Table 4.4

Factors which assist in the occurrence of hemorrhage in the postpartum period

Previous pregnancy	Factors, which occurred during the pregnancy	Factors, which occurred during the delivery
Primipara	Complete placental presentation	Stimulation of delivery
More than 5 deliveries in anamnesis	Placental detachment	Long or difficult delivery
Pathology in detachment or discharge of the placenta	Hydramnion	Fast delivery
Operations on the uterus in the anamnesis, including C-sections	Multiple pregnancy	Emergency Cesarean section
Long or difficult delivery in anamnesis	Intrauterine fetal death	Delivery with obstetrical forceps
Background diseases – cardio-vascular diseases, diabetes, coagulation disorders	Severe pre-eclampsia, eclampsia	Chorioamnionitis
Anemia	Hepatitis	DIC-syndrome
Hysteromyoma	Conditions connected with anemia	General or epidural anesthesia

Prevention of postpartum hemorrhage

1. During pregnancy:

evaluate the risk factors for the occurrence of hemorrhage

Diagnosis

— diagnosis and treatment of anemia;
— hospitalization, readiness to give medical help to pregnant women of high risk for hemorrhage: antenatal hemorrhage, hemorrhage in labor, polyhydramnios, multiple pregnancy, big fetus.

2. During delivery:

— anesthesia during labor;
— avoid prolong labor;
— active management of the third stage of labor. The underlying principle in active management is to excite powerful uterine contractions within one minute of delivery of the baby (WHO) by giving parenteral oxytocic. This facilitates not only early separation of the placenta but also produces effective uterine contractions following its separation. The advantages: (a) to minimize blood loss in the third stage approximately to 1/5th and (b) to shorten the duration of the third stage to half;

Injection oxytocin 10 units IM (preferred) or methergine 0.2 mg IM is given within 1 minute of delivery of the baby (WHO). The placenta is expected to be delivered soon following delivery of the baby. If the placenta is not delivered thereafter, it should be delivered forthwith by controlled cord traction (BrandtAndrews) technique after clamping the cord while the uterus still remains contracted. If the first attempt fails, another attempt is made after 2–3 minutes failing which another attempt is made after 10 minutes. If this still fails, manual removal is to be done. Oxytocic may be given with crowning of the head, with delivery of the anterior shoulder of the baby or after the delivery of the placenta. If the administration is mistimed as might happen in a busy labor room, one should not be panicky but conduct the third stage with conventional watchful expectancy.

Controlled cord traction (modified Brandt–Andrews method) — the palmar surface of the fingers of the left hand is placed (above the symphysis pubis) approximately at the junction of upper and lower uterine segments (Fig. 4.20). The body of the uterus is pushed upwards and backwards, toward the umbilicus while by the right hand steady tension (but not too strong traction) is given in downward and backward direction holding the clamp until the placenta comes outside the introitus.

Fundal pressure. The fundus is pushed downwards and backwards after placing four fingers behind the fundus and the thumb in front using the uterus as a sort of piston. The pressure must be given only when the uterus becomes hard. If it is not, make it hard by gentle rubbing. The pressure is to be withdrawn as soon as the placenta passes through the introitus.

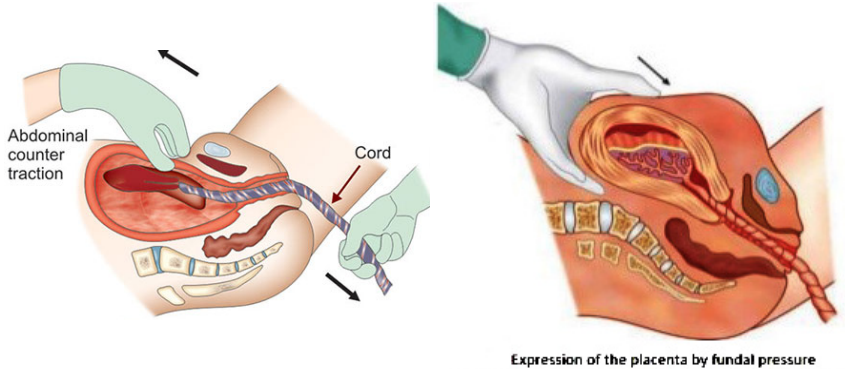


Fig. 4.21. Traction-countertraction of the cord; external uterine massage

— use uterotonic during the third period of labor;
— routine observation and evaluation of the integrity of the placenta and its membranes;
— prevention of trauma during labor.

3. After labor:
— inspection and examination of the birth canal;
— attentive supervision throughout 2 hours after delivery;
— in women of high risk — IV introduction of 20 units of oxytocin for 2 hours after the delivery.

Methods for determining the volume of blood loss

1. Libov's method.

Volume of blood loss is determined by weighing the napkins used, which are soaked in blood.

Volume of blood loss=B/2×15% (blood loss less than 1000 ml) or × 30% (blood loss more than 1000 ml).

Where B — weight of the napkins, 15% and 30% — error size (amniotic fluid, physiological solution).

2. Nelson's formula.

The percentage ratio of the total amount of blood loss is figured:

$$\frac{0.036 \times \text{original blood volume}}{\text{body weigh t}} \times \text{hematocrit}$$

$$\text{original blood volume (ml/kg)} = \frac{24}{0.86 \times \text{original hematocrit}} \times 100.$$

3. Determine the blood loss by the density of blood and the hematocrit (Table 4.5).

Table 4.5

Blood loss by the density of blood and the hematocrit

Blood density, kg/ml	Hematocrit	Volume of blood loss, ml
1057–1054	44–40	Up to 500
1053–1050	38–32	1000
1049–1044	30–22	1500
Less than 1044	Less than 22	More than 1500

4. Algover's Shock index:

$$\text{Shock index} = \frac{\text{Heart rate}}{\text{BPs}},$$

where BPs — systolic blood pressure

Normally Algover's index = 1.

By determining the index size, it is possible to conclude about the size of blood loss (Table 4.6).

Table 4.6

Evaluation of the blood loss according to Algover's index

Algover's index	Volume of blood loss (% of blood volume)
0.8 and less	10
0.9–1.2	20
1.3–1.4	30
1.5 and more	40

NB! Algover's index is not informative in patients with hypertension

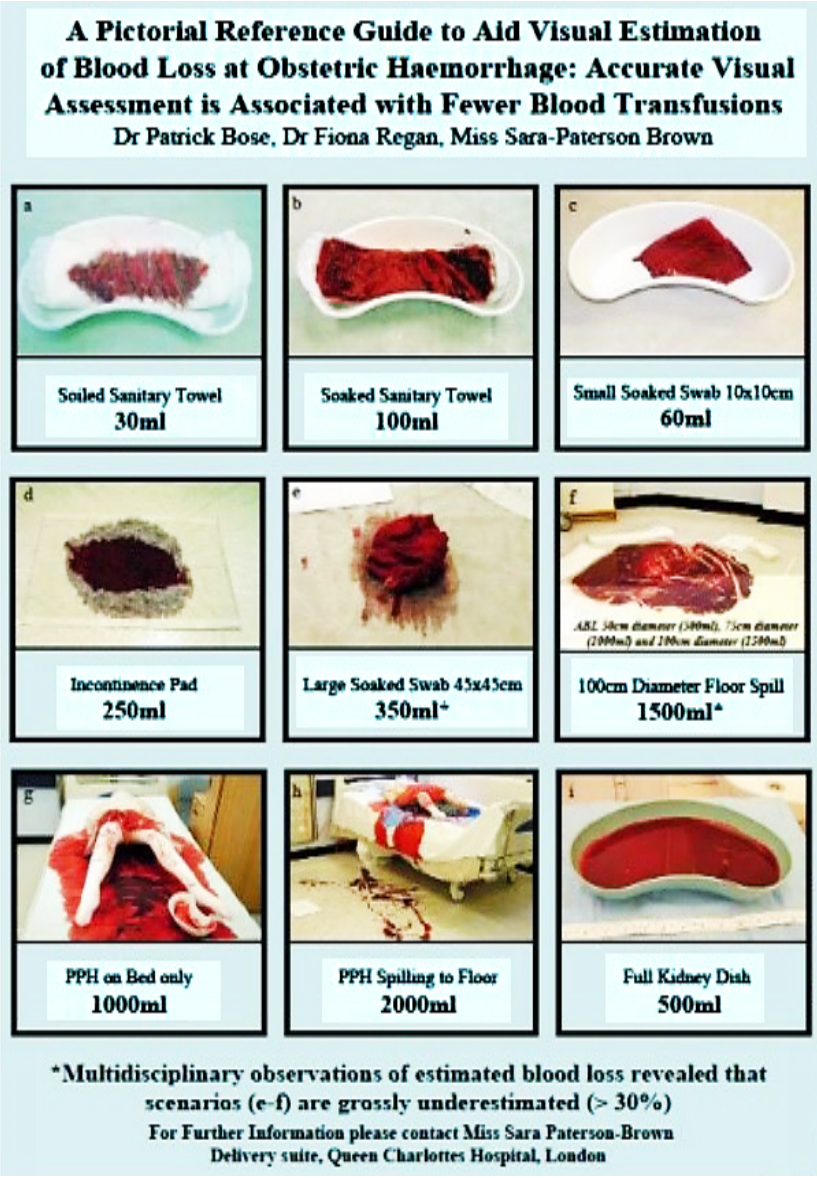


Fig. 4.22. Evaluation of the blood loss

5. Moore's hematocrit method:

$$BL = BV\,(n) \times (H\,(n) - Ht\,(a)) \,/\, Ht\,(n),$$

where:

BL — blood loss; BV (n) — normal blood volume; Ht (n) — normal hematocrit (in woman — 42);

Ht (a) — actual hematocrit determined after blood loss is stopped and hemodynamics are stabilized.

For rough amount of blood loss in pregnant women it is possible to use the modified Moore's formula:

$$BL = M \times 75 \times \frac{0.42 - Ht(a)}{0.42},$$

where: BL — blood loss (ml); M — woman's body weight (kg); Ht (a) — patient's actual hematocrit (l/l).

Coagulopathy bleedings

Any congenital or acquired coagulopathies can lead to profuse postnatal bleeding (delay of dead fetus in the uterus, amniotic fluid embolism, premature detachment of a normally located placenta, rupture of the uterus, sepsis, massive transfusions, severe pre-eclampsia and eclampsia, extragenital pathology). Therapy can result in disorder in the system of hemostasis during delivery with use of anticoagulants, long hemodilution. It should be remembered that profuse bleeding can lead to coagulopathy.

Bleeding due to intrauterine death of the fetus

If childbirth does not occur right after death of the fetus, severe coagulopathy can develop, caused by the discharge of thromboplastin from the tissue of the fetus. Treatment is immediate delivery and correction of the coagulation disorder. Induction of labor is conducted by intravenous introduction of oxytocin or prostaglandin. It is necessary to avoid hyperstimulation of labor, especially after 28 weeks, in connection with risk of rupture of the uterus in such patients.

Managing Maternal Hemorrhage

Vital Signs

Airway

- Provide adequate ventilation.
- Assess need for intubation.

Breathing

- Supplemental O_2 5–7 L/min by tight face mask.

Circulation.

- Pallor, delayed capillary refill, and decreased urine output can indicate compromised blood volume without change in BP or HR.
- Decreased urine output, decreased BP, and tachycardia may be late signs of compromise.

Actions

- Notify team.
- Bring cart & medications to patient room.
- Activate Massive Transfusion Protocol.

Infusions

- Start 2nd large bore IV (16 gauge if possible).
- Ringers lactate (RL) replaces blood loss at 2:1.
- Prepare for transfusion.
- Blood coagulation factors.
- Warm blood products and infusions to prevent hypothermia, coagulopathy, and arrhythmias.

Medication for Uterine Atony

— oxytocin (Pitocin) 10–40 units per 500–1000 mL solution;

— methylergonovine (Methergine) 0.2 micrograms IM.

Avoid in hypertension, prostaglandin f2 alpha (Hemabate) 250 micrograms IM (may repeat in q15 minutes, maximum 8 doses).

Avoid in asthma; use with caution in hypertension misoprostol (Cytotec) 800–1000 micrograms PR, 600 micrograms PO, or 800 micrograms SL (Table 4.7, p. 169).

Table 4.7

Medication for uterine atony

First stage (blood loss <1000 ml)				
Etiology	Tone	Manual inspection of the uterine walls		Simultaneously
	Tissue	One-time		
	Trauma	Suturing, laparotomy		
	Thrombin	Transfusion of coagulation factors		
Priority	Carbetocin, oxytocin	Methylergometrine	prostaglandins	
Primary dose	—Carbetocin-100 mcg IV once Oxytocin 10 units IM	Methylergometrine 0.2 mg IM or IV	Misoprostol 800 mcg per rectum	
Repeated dose absence of bleeding	Oxytocin 10 units IV in 500 ml solution 60 min	Methylergometrine 0.2 mg IM or IV every 4 hrs	—	
Max dose	Not more 3 l liq. in day, oxytocin	3 doses (1.0 mg)	Misoprostol 800 mcg per rectum	
Contraindication	—	pre-eclampsia hypertension heart diseases	pre-eclampsia asthma glaucoma	
	10 min	10 min	10 min	
Second stage-between conservative and hemostasis				
Balloon tamponade, two handed uterine compression, abdominal aorta compression				
Third stage — surgical laparotomy				
	≥1500 ml	>1500 ml		Angiographic embolization
Injection of prostaglandins in the myometrium, local uterine hypothesis				
Ligatures on ovarian uterine vessels Compression suture on the uterus		Ligation of a lacerated iliac artery, ovarian vessels		
Tight tamponade of the pelvis and vagina		Total subtotal hysterectomy		

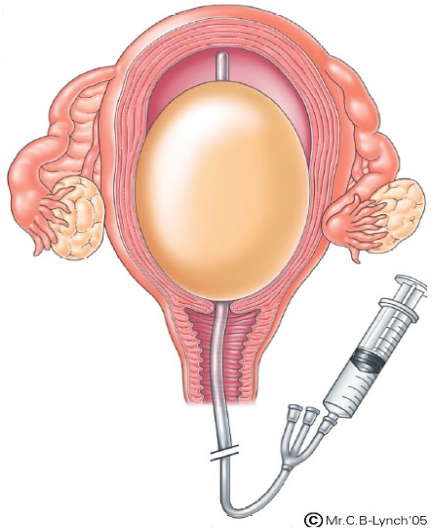


Fig. 4.23. Balloon tamponade of uterus

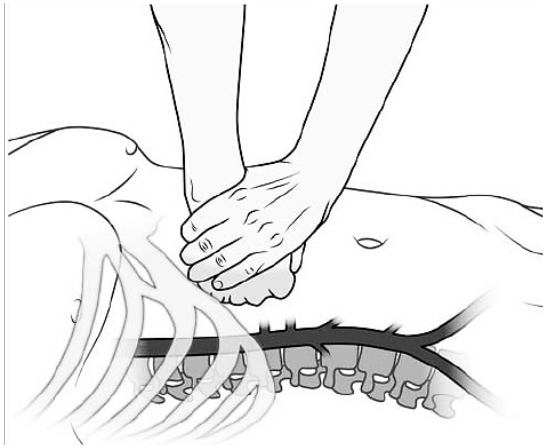


Fig. 4.24. Compression of the aorta

Surgical intervention may be a life-saving measure and should not be delayed pending correction of coagulopathy, the most common reason for the delay.

Table 4.8

Infusion transfusion therapy of obstetric hemorrhage

Blood loss			Total Transfusion of circ-blood	Infusion and transfusion environment						
				Crystalloids	Colloids					
					Synthetic (Gelofusine)	Natural				
						Plasma	Albumin 10%	Weight	Thrombocyte concentrate	
Volume of Circ-blood	% of W.body	Blood loss (ml)								
10–20%	1–1.5%	500–1000	200–300 (2.5L)	10–15 ml/kg	10 ml/kg	——	——	——	——	
20–30%	1.5–2%	1000–1500	200 (3L)	10 ml/kg	10 ml/kg	5–10 ml/kg	——	5 ml/kg	——	
30–40%	2–2.5%	1500–2000	180(4L)	7 ml/kg	7 ml/kg	10–15 ml/kg	200 ml	10–20 ml/kg	cryoprecipitate	
40–70%	2.5–3.6%	2500–3000	170 (5L)	7 ml/kg	10–15 ml/kg	15–20 ml/kg	200 ml	30 ml/kg	cryoprecipitate	
>70%	>3.6%	>3000	150 (>6L)	10 ml/kg	20 ml/kg	>20 ml/kg	>200 ml	>30 ml/kg	4–10 units	

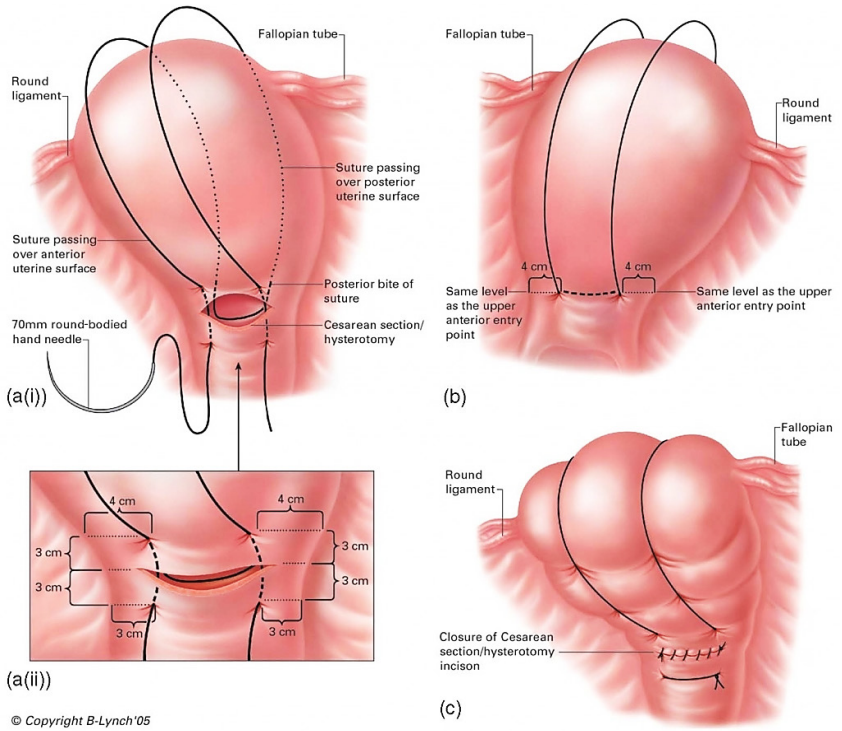


Fig. 4.25. B-lynch suture

Hemorrhagic shock

Hemorrhagic shock is a condition connected with acute and profuse bleeding during pregnancy, birth and postnatal period, which is expressed as a sharp decrease in blood volume (BV), cardiac emission and tissue perfusion due to the decompensation of protective mechanisms.

The BV in a pregnant woman is about 6.5% of the body weight.

As a rule, obstetrical bleedings exceeding 1,000 ml, i.e. more than 20% of the BV (or 15 ml of blood for 1 kg of the body weight) results in the development of shock.

Continued bleedings exceeding 1,500 ml (more than 30% of BV) are considered massive and threaten the woman's life (Fig. 4.26, p. 173).

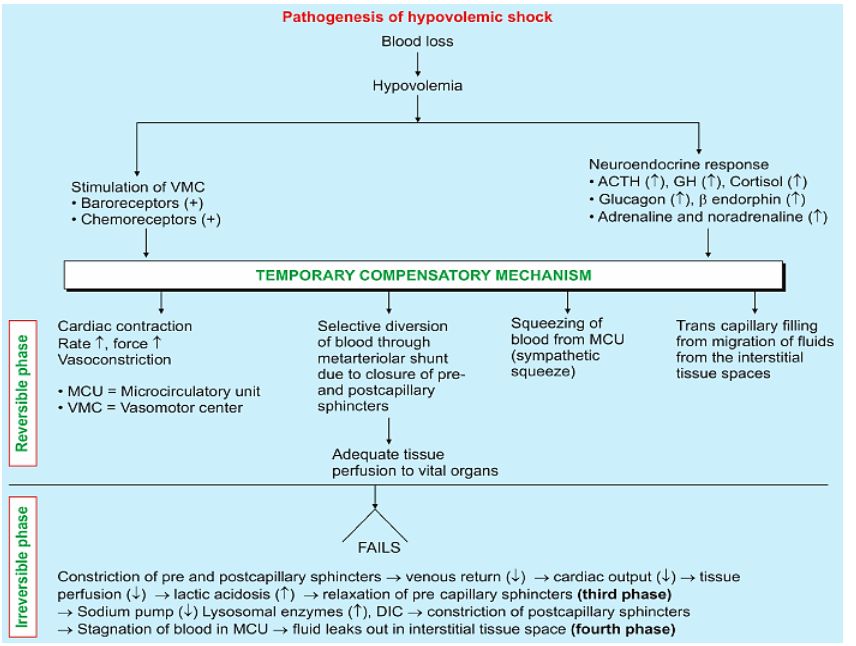


Fig. 4.26.

Source: book title: DC Dutta's Textbook of Obstetrics

Clinical course

In modern clinical practice, three stages of hemorrhagic shock are distinguished (Fig. 4.24):

I — compensated shock;

II — decompensated reversible shock;

III — irreversible shock.

Early phase (compensatory). In the early phase there is mild vasoconstriction and with the compensatory mechanism operating, the patient has relatively normal blood pressure, tachycardia and diaphoresis. Extremities remain warm. Patient appears restless and anxious. This phase can be easily managed by volume replacement.

Intermediate phase (reversible). If the early phase remains untreated, the patient passes into the state of hypotension.

Patient progressively becomes pale; tachycardia persists and due to intense vasoconstriction, the periphery becomes cold and there may be sweating. Due to diversion of blood to vital organs, the patient remains conscious and the urine output is within normal limits. Still with adequate management, the shock state can be reversed.

Table 4.9

Presenting features of shock (hemorrhagic and septic)

	Early		Late
Organ system	**Hemorrhagic (Hypovolemic)**	**Septic**	**Hemorrhagic and Septic**
BP	Normotensive or hypotensive, narrow pulse pressure	Normotensive or hypotensive widened pulse pressure	Hypotension (extravascular pooling)
Pulse	Tachycardia, thready pulse	Tachycardia, bounding pulse	Tachycardia — due to myocardial ischemia, ↓ ejection fraction
Respiratory	Normal or tachypnea (sympathetic response)	Tachypnea, pulmonary edema, acidosis	Tachypnea, ARDS
Renal	Oliguria (↓ Perfusion)	Oliguria (afferent arteriolar vasoconstriction)	Oliguria due to acute renal failure
Skin	Cold, clammy (vasoconstriction) → sympathetic response	Warm (febrile response)	Cold, clammy — due to vasoconstriction
Mental status and others	Normal	Normal • Fever or hypothermia (endotoxin)	Disorientation, obtundation due to hypoxia, cerebral edema **Other:** multiple organ dysfunction, anaerobic metabolism, coagulopathy, thrombocytopenia

Table 4.10

Classification of hemorrhagic shock (based on total blood volume 6l)

Parameter	Class 1	Class II	Class III	Class IV
Blood volume	<15	15–30	30–40	>40
Loss % (mL)	(<750 mL)	(750–1500)	(1500–2000)	(>2000)
Heart rate (bpm)	No change	Tachycardia	Moderate tachycardia	Marked tachycardia
Blood pressure	Normal	Normal	Decreased	Decreased
Respirations	Normal	Tachypnea	Tachypnea	Marked tachypnea
Mean arterial pressure	Normal	Mildly decreased	<60 mm Hg	Decreased
Cardiac output	Normal	Mildly reduced	Reduced	Markedly reduced
Systemic vascular	Normal	Increased	Increased	Increased resistance
Urine output (mL/hr)	>30	20–30	5–15	Anuric
Mental status	Normal	Anxious	Confused	Obtunded

Table 4.11

Criteria of hemorrhagic shock severity

Indicators	The shock degree			
Blood loss (ml)	750–1000	1000–1500	1500–2000	>2500
Volume of circulating blood%	15–20	21–30	31–40	>40
Body weight (%)	0.8–1.2	1.3–1.8	1.9–2.4	>2.4
Pulse	100–110	110–120	120–140	>140
Blood pressure	>90	90–70	70–50	≤50
Shock index	0.8–1	1–1.5	1.5–2	>2.0
White spot test (sec)	2	>2	>3	Undecided
Freq of breathing (in min)	20–25	25–30	30–40	>40
Diuresis (ml in hour)	30–50	25–30	5–15	Anury
State of consciousness	clear	clear	excitation	Inhibited
Mental status	tranquility	Worry or anxiety	Fear or anxiety	Confusion or coma

Late stage (irreversible). Hypotension continues and cannot be reversed by fluid replacement because of stagnation of blood at the microvascular level. Extremities become cold and clammy because of vasoconstriction due to sympathetic stimulation. For the same reason, the color of the skin becomes ashen gray. Metabolic acidosis, coagulopathy and thrombocytopenia are associated. Practically imperceptible low volume pulse, oliguria, mental confusion (multiple organ failure) are the combined results of circulatory failure and anaerobic metabolism. Treatment of any kind is practically useless in this phase and mortality varies between 3% and 100%.

Diagnosis is based on a complex of the following parameters:

1) characteristic of skin color and skin temperature, especially the extremities;
2) pulse, BP, CVP, shock index, haematocrit numbers;
3) determining the volume of blood loss;
4) revealing of the hourly diuresis;
5) change in the acid-base condition (ABC) of the blood.

Algover's shock index — the relation between the pulse rate and the value of the systolic arterial pressure — is a simple and sufficient informative parameter of the volume of blood loss and degree of oligemia. Normally this index is less than 1; due to a decrease in the VCB by 20–30% it increases to 1.0–1.2; in case of the loss of 30–50% of the VCB it equals 1.5.

It is possible to use Barashkov's method (by the parameters of the relative density of the blood and haematocrit numbers). So, with blood loss of up to 1 l. of blood, the haematocrit number is no less than 0.32; up to 1500 ml — from 0.32 to 0.2; if the blood loss is more than 1500 ml, the haematocrit number — less than 0.22. An increase in the haematocrit number for III stage of shock testifies of its irreversibility.

An important parameter describing the organ blood flow is the hourly diuresis. A decrease in the diuresis to 30 ml/hr testifies of the insufficiency of the peripheral blood circulation, and down to 15 ml/hr — of the approach of irreversible decompensated shock.

Normal parameters of CVP are 0.49–1.2 kPa (50–120 mm Hg) (Fig. 4.27, p. 177).

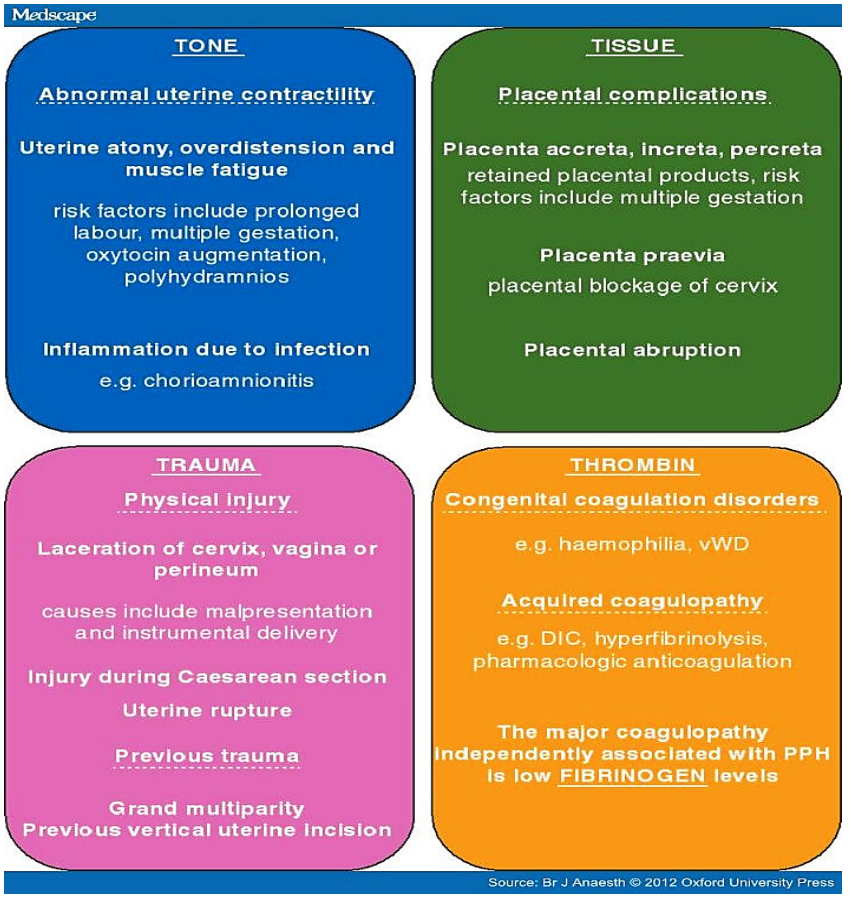


Fig. 4.27. Reasons for postpartum hemmorhage 4 T's

SHOCK MANAGEMENT

Hemorrhagic shock

The main treatment for hemorrhagic shock is to stop the bleeding and replace the lost volume. If there is no multiorgan failure, timely diagnosis and immediate resuscitation are required.

Restore circulating blood volume (infusion and transfusion). Blood should be transfused specifically for hemorrhagic shock as soon as it is available.

Crystalloids. For immediate volume replacement, saline solution should be administered first. However, crystalloids are quickly lost from the circulation. Colloids: Polygelatin solutions (Hemaccel, Gelofusine) are isosmotic with plasma. They have no effect on the blood coagulation system. Large quantities can be injected. They promote osmotic diuresis. Dextrans: These are multimolecular polysaccharides. They interfere with cross-comparison and are avoided. Human albumin solutions (4.5%) — are not normally used for volume replacement.

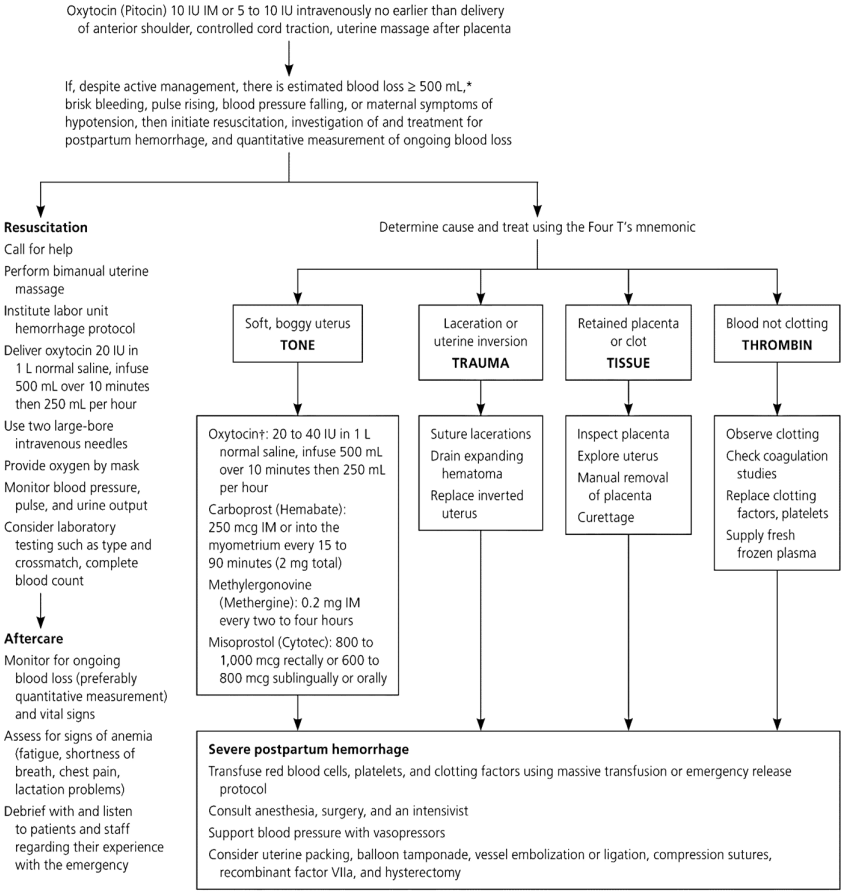
Maintenance of cardiac efficiency. When a large volume of fluid or blood is to be administered, the cardiac competence or efficiency should be ascertained — otherwise there is a risk of overloading the circulation and cardiac failure. Loss of 1 liter of plasma volume requires 6 liters of crystalloids. One or two large bore (14 or 16 gauge) cannulas are inserted for volume replacement. Packed red blood cells (specific blood component), combined with normal saline, are used for hemorrhagic shock. Hemodynamic monitoring is aimed to maintain systolic BP>90 and MAP>60 mm Hg, CVP 12–15 cm H_2O and pulmonary capillary wedge pressure 14–18 mm Hg.

Administration of oxygen to avoid metabolic acidosis. In the initial phase, administration of oxygen by nasal cannula at a rate of 6–8 liters per minute is enough but in the later phases, ventilation by endotracheal intubation may be necessary. Oxygen delivery should be continued to maintain O_2 saturation >92%, PaO_2 80–100 mm Hg, $PaCO_2$ 30–35 mm Hg and pH>7.35. Endotracheal intubation and mechanical ventilation may be needed for patients with septic shock. Indications of mechanical ventilation are: severe tachypnea (RR>40/min), altered mental status, severe hypoxemia, despite O_2 supplementation.

Pharmacological agents. Use of vasopressor drugs should be kept to a minimum, since peripheral vasoconstriction is already present. The role of vasoactive drugs, inotropes and corticosteroids

in shock has been discussed in detail in connection with management of endotoxic shock.

Control of hemorrhage. Specific surgical and medical treatment for control of hemorrhage should start along with the general



**—The American College of Obstetricians and Gynecologists defines early postpartum hemorrhage as blood loss of 1,000 mL or more accompanied by signs and symptoms of hypovolemia; cumulative blood loss of 500 to 999 mL alone should trigger increased supervision and potential interventions as clinically indicated.*

†—Oxytocin should be used as a first-line agent, with other agents added only if needed to control hemorrhage.

Fig. 4.28. Active management of the third stage of labor

Source: American Family Physician

management of shock. The specific management of each variety of obstetric hemorrhage has been outlined in the related chapters.

Monitoring. Clinical parameters like skin temperature, visible peripheral veins can be helpful to assess the degree of tissue perfusion. Urine output (>30 mL/hr) is a useful guide. Arterial blood pressure is a poor indicator to assess tissue perfusion. Invasive monitoring may not be needed in a straightforward case. In a critically ill patient, however, measurement of central venous pressure (CVP), to assess the adequacy of the patient's circulating volume and the contractile state of the myocardium, is essential. Pulse oximeter and blood gas analysis are useful to assess tissue perfusion. Measurement of left atrial pressure (pulmonary artery occlusion pressure) by 'Swan-Ganz' catheters could be done in selected cases (see Table 4.9).

Treatment

To maintain effective treatment, it is necessary to unite the efforts of the doctor-obstetrician, anaesthesiologist and if needed, hematologist. Treatment should be started as soon as possible.

Bringing the patient out of the condition of shock should be carried out simultaneously with actions for stopping the bleeding. The volume of operative intervention should provide reliable hemostasis.

If the patient's condition is severe, operative intervention is performed in 3 stages:

1) laparotomy, hemostasis (extirpation of the uterus, clamping of the great vessels);
2) resuscitation measures;
3) continuation of operations.

The main directions of hemorrhagic shock treatment are following:

1) infusion-transfusion therapy to restore the central nervous system and eliminate oligemia;
2) increase the volume of oxygen in the blood;
3) normalization of the rheological properties of blood and elimination of microcirculation and blood coagulation disorders;
4) correction of biochemical and colloid osmotic disorders.

For successful infusion-transfusion therapy, it is important to take into account the quantitative ratio of injected components

and blood products, volumetric rate and duration of transfusion. Taking into account the deposition of blood in shock, it is necessary to enter a volume of fluid that exceeds the volume of possible blood loss, namely: with blood loss of 1000 ml — 1.5 times more; 1500 ml of blood — 2 times, with more significant blood loss — 2.5 times. It is desirable that about 70% of the lost VCB be recovered in the first 1–2 hours.

The criterion of treatment efficiency is positive dynamics of the clinical symptoms of shock:

Conserved blood components (erythrocyte mass, washed frozen erythrocytes) remain the most important infusion means for treatment of hemorrhagic shock, because only with their help is it possible to restore the functional disorder of transportation of oxygen in the organism. Transfusion of fresh conserved blood (period of storage no more than 3 days) is allowable. With massive bleeding, erythrocyte mass should be 0.5–0.8 of the volume of blood loss, however during continuous treatment it is not necessary to transfuse more than 3 liters of blood in connection with the danger of developing massive transfusion syndrome.

For observing the regime of controlled haemodilution blood transfusions are necessary to combine with the introduction of colloid and crystalloid solutions in a ratio of 1:1 or 2:1. This ratio is explained by the adaptive properties of osmoregulation in pregnant women. In case of hydremia (hemodilution), you can use any solution that improves the rheological properties of blood, reduces the aggregation of cellular elements and thereby returns deposited blood to the active circulation and improves peripheral blood flow (polyglucin, reopolyglucin). Starch solutions — oxyethylamine (refortan) — are increasingly used. In the adequate treatment of hemorrhagic shock, not only the quantity but also the significant rate of administration of solutions (volumetric rate) plays an important role. In the severe condition of the patient, the volumetric rate of solution administration should be 250–500 ml/min; in case of stage II shock, solutions must be administered at a rate of 100–200 ml/min. This speed can be achieved by jet injection of solutions into several peripheral veins or by catheterization of central veins. To gain time, it is recommended

to start the infusion with a puncture in the ulnar veins and immediately start catheterization of the subclavian vein, which allows for long-term infusion — transfusion therapy.

The rate of fluid infusion, the ratio of blood and injected blood substitute, as well as the elimination of excess fluid should be carried out under constant monitoring of the general condition of the patient, as well as on the basis of an assessment of hematocrit and central venous pressure indicators, ABC, electrocardiogram. The duration of infusion therapy should be adjusted individually.

If there is doubt in determining the extent of hemorrhagic shock, the following ratio of infusion components is recommended: 1 (erythrocytes) : 0.2 (albumin) : 1 (dextran) : 1 (crystalloid).

When the patient's condition stabilizes, which is manifested by the restoration of the systolic blood pressure level to at least 90 mmHg, satisfactory filling of the pulse, disappearance of shortness of breath, hourly diuresis of at least 30–50 ml and with an increase in hematocrit number to 0.3, you can switch to drop introduction of blood and fluid in a ratio of 2:1, 3:1 until the hemodynamic parameters are completely stabilized. Metabolic acidosis is corrected by intravenous drop infusion of 150–200 ml of 4% sodium bicarbonate solution. To improve redox processes, 200–300 ml of 10% glucose solution with sufficient insulin, cocarboxylase, B vitamins and ascorbic acid are recommended.

After elimination of oligemia against the background of improving the rheological properties of blood, an important component of the normalization of microcirculation is the use of drugs that eliminate spasms of peripheral vessels — antispasmodics (papaverine, aminophylline) or ganglion blockers (0.5–1 ml of 0.5% pentamine solution dropwise with isotonic sodium chloride solution),. The introduction of a glucose-novocaine mixture (150–200 ml of a 0.5% novocaine solution with a 20% glucose solution or in a ratio of 1:1 or 2:1) is effective. To improve renal blood flow, 150–200 ml of a 10% solution of the osmodiuretic mannitol is recommended. If necessary, saluretics (Lasix) are additionally prescribed.

The introduction of antihistamines (diphenhydramine, deprazine, suprastin) contributes to the normalization of microcirculation

and metabolic disorders. To improve myocardial function, cardiac glycosides and corticosteroids are administered (single dose of hydrocortisone — 125–250 mg, daily dose — 1–1.5 g).

Disorders of the blood coagulation system, due to their great variety, should be corrected according to the coagulogram. So, in hemorrhagic shock of stages I and II, an increase in blood coagulation properties is noted. In stage III, coagulopathy may develop due to a sharp decrease in the content of procoagulants and a pronounced activation of fibrinolysis. Inadequate use of infusion solutions leads to an increased loss of blood coagulation factors, the level of which decreases due to bleeding. Restoration of the coagulation properties of the blood should be carried out by the administration of procoagulants that are lacking in the blood (fresh citrated blood, frozen plasma, antihemophilic plasma, fibrinogen preparations or cryoprecipitate). To neutralize thrombin, some authors recommend the use of direct anticoagulants — heparin, and to reduce fibrinolysis — inhibitors of proteolytic enzymes (Contrical, Gordox).

In the treatment of patients with hemorrhagic shock, the time factor is often of great importance. The sooner treatment is started, the less effort and money is required to bring the patient out of the state of shock, and the better the immediate and long-term prognosis. Therefore, in patients with compensated shock, it is enough to restore blood volume, prevent acute renal failure, and in some cases normalize the ABC. To treat patients with decompensated reversible shock, it is necessary to use the entire arsenal of therapeutic measures. If the patient has stage III shock, often all the doctor's efforts are unsuccessful.

The first stage of treatment is to remove the patient from a critical condition caused by hemorrhagic shock. Over the next few days, the therapy is aimed at eliminating the consequences of massive bleeding and preventing new complications. The doctor's actions should be aimed at supporting the functions of the kidneys, liver and heart, normalizing water and electrolyte balance, preventing anemia and infections.

Lecture 5

INTRAUTERINE GROWTH RESTRICTION. FETAL DISTRESS

Fetal growth restriction (FGR) is defined as the failure of the fetus to meet its growth potential due to a pathological factor, most commonly placental dysfunction. Worldwide, FGR is a leading cause of stillbirth, neonatal mortality, and short- and long-term morbidity. Ongoing advances in clinical care, especially in definitions, diagnosis, and management of FGR, require efforts to effectively translate these changes to the wide range of obstetric care providers.

Educational materials

FETAL GROWTH RESTRICTION

Fetal growth restriction **is** defined as the failure of the fetus to meet its growth potential due to a pathological factor, most commonly placental dysfunction. Clinically, this is reflected by a drop in fetal size percentiles over the course of gestation. However, fetal growth potential is difficult to determine, and serial assessments of fetal size to detect a drop in fetal weight percentile are usually not available. Instead, care providers most commonly have only a "snapshot" of fetal weight estimation at a given point in time. Therefore, in clinical practice, small for gestational age (SGA), defined as estimated fetal weight (EFW) or abdominal circumference below a certain threshold such as the 10th or 3rd percentile, is most commonly used to suspect FGR.

The use of SGA as a proxy for FGR has several limitations that need to be recognized. First, most SGA fetuses are constitutionally healthy small fetuses, whose smallness is merely the result of their predetermined growth potential (i.e. false-positive diagnosis of FGR). Second, some growth-restricted fetuses, depending on their original growth potential and timing of insult, may remain above

the percentile threshold described above and may thus not be SGA (i.e. false-negative diagnosis of FGR). Third, the use of SGA as a proxy for FGR is limited by the accuracy of sonographic fetal weight estimation, which has an estimation error of up to ±15–20%. Finally, the diagnosis of SGA is highly dependent on the growth chart being used, which can therefore have a considerable effect on the proportion of fetuses or infants flagged as SGA in a given population.

It should be noted that there is inconsistency in the literature regarding the terminology described above, where some use the term FGR to describe a fetus with an estimated weight below the 10th percentile for gestational age and the term SGA to describe an infant with birth weight below the 10th percentile for gestational age. However, for the purpose of this article, the term SGA is used to indicate an EFW or birth weight below the 10th percentile for gestational age, and the term FGR to refer to a small fetus that has failed to achieve its growth potential because of a pathologic process.

Consensus-based definition of placenta-related fetal growth restriction

The major member societies of FIGO follow a definition using the 10th percentile as a means of diagnosing an SGA fetus, which then leads to further testing, assessment, and follow-up. There are proposals to address the limitations of this definition, but their validity regarding reduction in adverse outcomes needs to be tested. For example, in an attempt to overcome some of the limitations described above, a consensus-based definition for placenta-mediated FGR has been proposed via a Delphi procedure. To decrease the likelihood of false-positive and false-negative diagnosis of FGR, the consensus definition was based on a combination of measures of fetal size (fetal weight estimation and abdominal circumference) and abnormal Doppler findings in the umbilical, uterine, and middle cerebral arteries, as described in Table 5.1. The implementation of this definition is limited by the lack of a recommendation on which growth chart should be used to define the 10th and 3rd percentiles for EFW and fetal abdominal circumference. In addition, further research is needed to correlate this definition with adverse perinatal outcomes (Fig. 5.1 A, B, 5.2, p. 186–187).

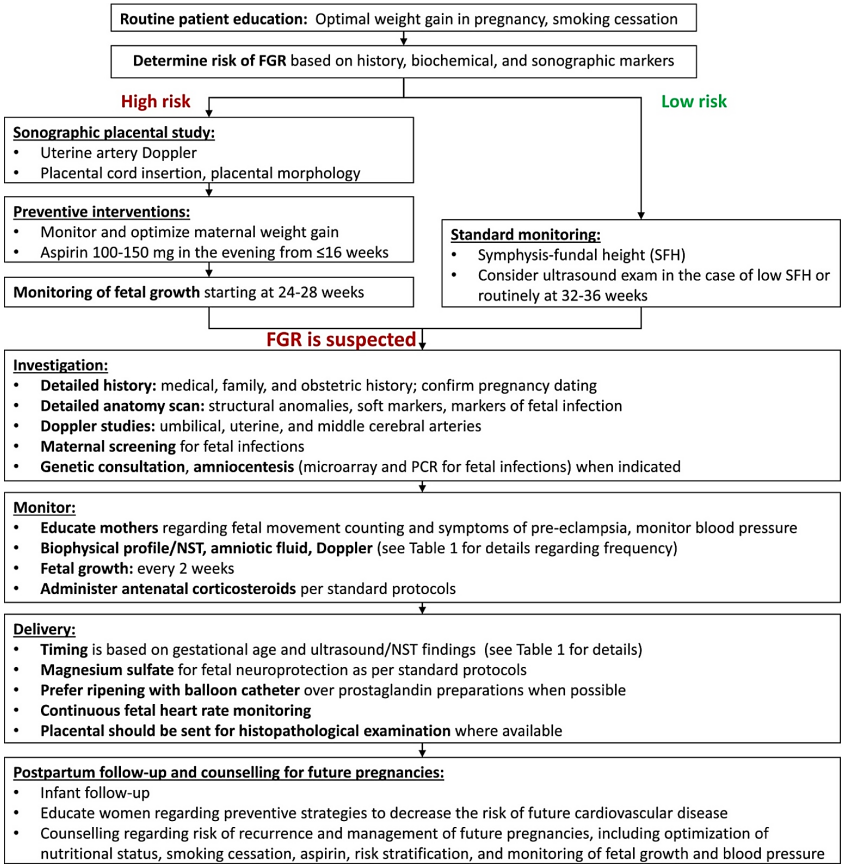


Fig. 5.1. A — Approach to screening, diagnosis, and management of fetal growth restriction in high-resource settings — FGR, fetal growth restriction; NST, nonstress test; PCR, polymerase chain reaction; SFH, symphysis-fundal height

Source: FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

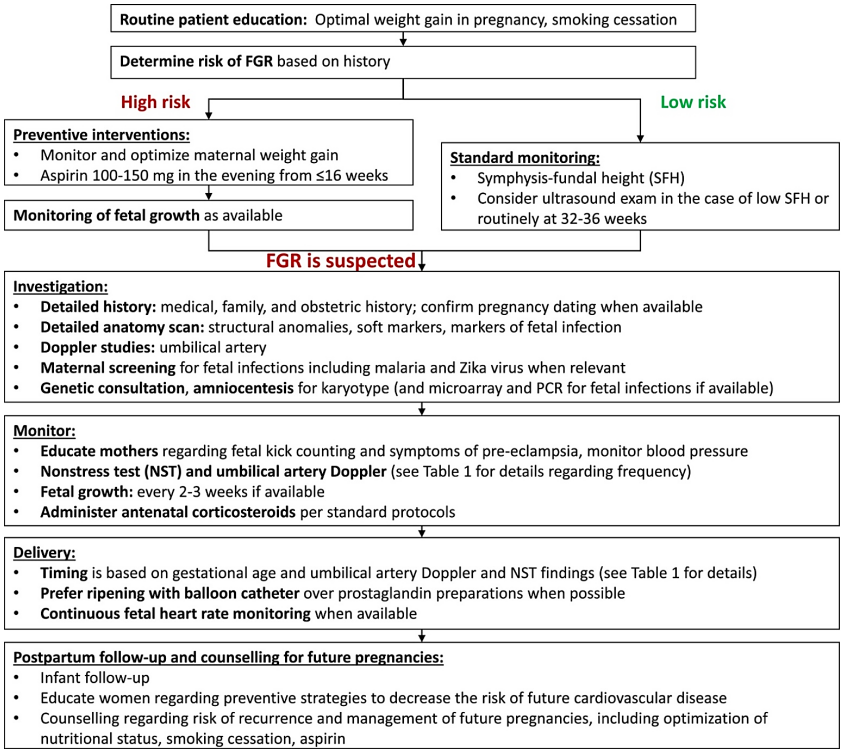


Fig. 5.1. B — Approach to screening, diagnosis, and management of fetal growth restriction in low-resource settings — FGR, fetal growth restriction; NST, nonstress test; PCR, polymerase chain reaction; SFH, symphysis–fundal height

Source: Europe PMC. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

Table 5.1

Consensus-based definitions for early and late fetal growth restriction

Early-onset FGR (<32 weeks)	Late-onset FGR (≥32 weeks)
• EFW or AC<3rd percentile • or UA with AREDV • or EFW • or AC<10th percentile, combined with one or more of the following: a. UA PI>95th percentile b. UtA PI>95th percentile	• EFW or AC<3rd percentile • Or ≥2 of the following 3 criteria: a. EFW or AC<10th percentile b. EFW or AC crossing percentiles >2 quartiles on growth percentiles c. CPR<5th percentile or UA PI>95th percentile

Note: AC, fetal abdominal circumference; AREDV, absent or reversed end-diastolic velocity; CPR, cerebroplacental ratio; EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery. (Adapted from Gordijn et al.)

Recommendations

Postpartum assessment and counselling for future pregnancies in women with a history of fetal growth restriction (FGR)

Recommendation	Quality of evidence	Strength of recommendation
1. Growth restricted infants are at an increased risk of short- and long-term morbidity and should be followed postnatally more closely than normally grown infants.	⊕⊕○○	Strong
2. Women with a history of placenta-mediated pregnancy complications including FGR are at an increased risk of future cardiovascular morbidity and should be advised regarding preventive strategies as reviewed in detail in the FIGO postpregnancy initiative on long-term maternal implications of pregnancy complications and follow-up considerations.[4]	⊕⊕⊕○	Strong
3. Women with a history of FGR should be counselled regarding the risk of recurrence based on timing of onset, severity of FGR, and placental histopathological findings.	⊕⊕○○	Strong
4. Women with a history of FGR should *not* be routinely screened for antiphospholipid antibodies in the absence of a history of thromboembolism or pregnancy loss.	⊕⊕⊕○	Strong
5. There is no role for screening for hereditary thrombophilias in women with a history of FGR.	⊕⊕⊕○	Strong
6. The following preventive interventions are recommended in women with a history of placenta-mediated FGR and those at risk of pre-eclampsia: smoking cessation, aspirin at a dose of 100–150 mg taken in the evening starting at 12–16 weeks.	⊕⊕○○	Strong
7. Low-molecular-weight heparin is not recommended for the prevention of FGR in women with a history of placenta-mediated FGR.	⊕⊕⊕○	Strong
8. In women with antiphospholipid syndrome and a history of placenta-mediated FGR, low-molecular-weight heparin may be considered in selected cases, such as in women who have experienced recurrent complications despite aspirin treatment (aspirin failure).	⊕⊕○○	Weak
9. Women with a history of FGR should undergo close surveillance of fetal growth starting at 24–28 weeks.	⊕⊕⊕○	Strong

Postpartum assessment and counseling for future pregnancies in women with a history of fetal growth restriction (FGR)

Recommendation	Quality of evidence	Strength of recommendation
1. Growth-restricted infants are at an increased risk of short- and long-term morbidity and should be followed postnatally more closely than normally grown infants.	⊕⊕○○	Strong

End of Table

Recommendation	Quality of evidence	Strength of recommendation
2. Women with a history of placenta-mediated pregnancy complications including FGR are at an increased risk of future cardiovascular morbidity and should be advised regarding preventive strategies as reviewed in detail in the FIGO postpregnancy initiative on long-term maternal implications of pregnancy complications and follow-up considerations.	⊕⊕⊕○	Strong
3. Women with a history of FGR should be counseled regarding the risk of recurrence based on timing of onset, severity of FGR, and placental histopathological findings.	⊕⊕○○	Strong
4. Women with a history of FGR should *not* be routinely screened for antiphospholipid antibodies in the absence of a history of thromboembolism or pregnancy loss.	⊕⊕⊕○	Strong
5. There is no role for screening for hereditary thrombophilias in women with a history of FGR.	⊕⊕⊕○	Strong
6. The following preventive interventions are recommended in women with a history of placenta-mediated FGR and those at risk of pre-eclampsia: smoking cessation, aspirin at a dose of 100–150 mg taken in the evening starting at 12–16 weeks.	⊕⊕○○	Strong
7. Low-molecular-weight heparin is not recommended for the prevention of FGR in women with a history of placenta-mediated FGR.	⊕⊕⊕○	Strong
8. In women with antiphospholipid syndrome and a history of placenta-mediated FGR, low-molecular weight heparin may be considered in selected cases, such as in women who have experienced recurrent complications despite aspirin treatment (aspirin failure).	⊕⊕○○	Weak
9. Women with a history of FGR should undergo close surveillance of fetal growth starting at 24–28 weeks.	⊕⊕⊕○	Strong

Source: Europe PMC. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

Early versus late onset FGR

It has been suggested that FGR should be broadly classified, based on gestational age at the time of diagnosis, into early-onset FGR (<32 weeks) and late-onset FGR (≥32 weeks). The rationale underlying this classification is based on differences between these two phenotypes of FGR in severity, natural history, Doppler findings, association with hypertensive complications, placental findings, and management.

Early-onset FGR has a prevalence of 0.5–1%, is usually more severe, and is more likely to be associated with abnormal umbilical artery Doppler than late-onset FGR. The underlying placental pathology is frequently similar to that observed in cases of early-onset pre-eclampsia (maternal vascular malperfusion), which explains the strong association of early-onset FGR with pre-eclampsia. Therefore, early-onset FGR is usually easier to detect, and the natural history tends to follow a predictable sequence of Doppler changes in the umbilical artery and ductus venosus. The main challenge in cases of early-onset FGR is management (i.e. timing of delivery), by attempting to determine the optimal balance between the opposing risks of stillbirth and prematurity.

Late-onset FGR is more common than early-onset FGR with a prevalence of 5–10%. In contrast to early-onset FGR, it is usually milder, is less likely to be associated with pre-eclampsia, and is usually associated with normal umbilical artery Doppler. Therefore, the main challenge with regard to late-onset FGR is diagnosis, while management (i.e. delivery) is relatively simple given that the diagnosis is commonly made during the late-preterm or term periods, where the risks associated with delivery are relatively small. The diagnosis of late-onset FGR mainly relies on adaptive changes in the cerebral circulation ("redistribution" or "brain-sparing effect"), which is reflected by low resistance to flow in the middle cerebral artery thereby generating a low cerebroplacental ratio. Given that the umbilical artery and ductus venosus Doppler studies are usually normal in cases of late-onset FGR, the natural history in these cases is less predictable and there is a risk of sudden decompensation and stillbirth.

Etiology of fetal growth restriction

FGR is often the result of one or more maternal, placental, or fetal disorders that interfere with the normal mechanisms regulating fetal growth. The most common etiologies of FGR are listed below. It is important to note that there is often confusion in the literature between "etiologies" (or pathogenetic pathways) and "risk factors" for FGR. For example, although maternal conditions such as chronic hypertension, kidney disease, systemic lupus erythematosus, and long-standing diabetes are often listed as "maternal etiologies" for FGR, these conditions should probably be viewed instead as maternal risk factors for abnormal placentation that may result in placenta-mediated FGR.

COMMON ETIOLOGIES FOR FETAL GROWTH RESTRICTION

I. Suboptimal uteroplacental perfusion and fetal nutrition:

a) maternal (preplacental) factors:
   - hypoxemia (chronic lung disease, high altitude);
   - anemia;
   - smoking, substance abuse (cocaine, methamphetamines);
   - malabsorption, poor weight gain;
   - environmental toxins: air pollution, heavy metals (lead, mercury), perfluorooctanoic acid (PFOA);

b) placental factors:
   - maternal vascular malperfusion pathology (infarction, fibrin deposition, chronic abruption);
   - fetal vascular malperfusion pathology;
   - chronic placental inflammation (e.g. villitis of unknown etiology);
   - confined placental mosaicism;

c) umbilical cord (postplacental) factors:
   - increased coiling;
   - increased cord length;
   - true cord knot;
   - single umbilical artery;
   - marginal or velamentous cord insertion.

II. Fetal disorders:

a) genetic disorders (chromosomal, micro deletions/duplications, single site mutations, epigenetic disorders);
b) structural anomalies (e.g. congenital heart disease, gastroschisis);
c) congenital infections (cytomegalovirus, toxoplasmosis, herpes, rubella, syphilis, Zika virus, malaria);
d) teratogen exposure (drugs, toxins).

Given that maternal nutrition and fetal growth are closely related, maternal undernutrition is an important cause of FGR worldwide. The impact of maternal undernutrition on fetal growth depends on its timing and severity. To date, maternal interventions in dietary advice and modifications have lacked significant success in preventing FGR. While the mechanisms by which maternal anemia contribute to FGR are unclear, both impaired nutrient transport to the fetus and abnormal placental adaptation to low maternal hemoglobin have been suggested as potential mechanisms.

Abnormal placentation is a common cause of FGR, which is often diagnosed by ultrasound Doppler studies and typical histopathological placental findings.

Chromosomal abnormalities have been suggested to contribute to up to 5% of FGR cases; triploidy and trisomy 13 and 18 are important considerations in early-onset FGR and the risk of many aneuploidies is higher in the presence of structural fetal anomalies. In 1–6% of cases of FGR with normal karyotype, submicroscopic (micro) duplications/deletions can be found using chromosomal microarray analysis, even when FGR is an apparently isolated finding. FGR is also more prevalent in fetuses with structural malformations, and the risk increases when multiple anomalies are present.

FGR is related to intrauterine infection in up to 5% of cases. Viral agents such as rubella, cytomegalovirus, HIV, and Zika are common causes of infection-related FGR. Protozoan infections like toxoplasmosis and malaria are another important cause, especially in endemic areas. The main mechanism involved in the pathogenesis of FGR in these cases is a decline in cell population. Finally, maternal

exposure to teratogens such as radiation, illicit drugs, and alcohol is another important etiology for FGR.

Risks associated with fetal growth restriction

The main short- and long-term risks associated with FGR are listed below. It is associated with both fetal and obstetric complications. The most devastating complication is stillbirth, and there is a well-established inverse relationship between weight percentile and the risk of stillbirth, which is more pronounced in the early preterm period than at term. FGR is an important cause of iatrogenic preterm birth, as early delivery remains the main and perhaps only strategy for the prevention of stillbirth in cases of severe FGR. FGR is also an independent risk factor for spontaneous preterm birth. Other obstetric complications associated with FGR include pre-eclampsia and placental abruption, as the pathophysiology of these conditions is often closely related.

RISKS ASSOCIATED WITH FETAL GROWTH RESTRICTION

I. Antenatal:

- Stillbirth.
- Pre-eclampsia.
- Placental abruption.
- Preterm birth.

II. Neonatal (short term):

- Neonatal mortality.
- Neonatal morbidity (hypoglycemia, hyperbilirubinemia, hypothermia, necrotizing enterocolitis, respiratory morbidity, intraventricular hemorrhage).

III. Neonatal (long term):

- Neurodevelopmental disorders.
- Metabolic syndrome (obesity, hypertension, diabetes, cardiovascular.

Despite ongoing improvements in neonatal care, FGR is associated with increased neonatal mortality and short-term morbidity. The risk of perinatal mortality in term FGR is reported to be five- to 10-fold

higher than in appropriately grown neonates. The severity of FGR, Doppler abnormalities, and associated prematurity are independent predictors of neonatal complications. Among preterm infants, the co-presence of FGR further increases the risk of certain prematurity-related complications such as respiratory morbidity, intraventricular hemorrhage, necrotizing enterocolitis, and metabolic disorders. Among term infants, FGR increases the risks of low cord artery pH, low Apgar score, and neonatal complications such as hypoglycemia, hypothermia, and jaundice.

Growth-restricted infants are also at risk of long-term complications including neurodevelopmental impairment and noncommunicable diseases.

Recommendations

FIGO recommends the following for the definition of fetal growth restriction (FGR)

Recommendation	Quality of evidence	Strength of recommendation
1. Small for gestational age (SGA) is defined as an estimated fetal weight or birth weight below the 10th percentile for gestational age.	⊕⊕⊕⊕	Strong
2. The definition of FGR should be based on a combination of measures of fetal size percentile and Doppler abnormalities.	⊕⊕◯◯	Strong

Source: Europe PMC. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

EARLY PREDICTION AND PREVENTION OF FETAL GROWTH RESTRICTION

Early prediction of FGR is important as it can identify women at high risk of FGR who may benefit from preventive interventions and close monitoring during pregnancy. While the predictive value of individual risk factors is low, clinical prediction models that are based on combinations of the risk factors outlined below can considerably improve the prediction of FGR. One important

limitation of most of the studies on early prediction of FGR is the lack of a gold standard for the antenatal or postnatal diagnosis of FGR. As such, there is wide variation among studies regarding the outcomes being predicted, including either SGA (birth weight below the 10th or 3rd percentile) or adverse perinatal outcomes that are associated with (but are not specific to) FGR. As many SGA infants are constitutionally small and healthy, differentiating between healthy small fetuses and those that are small due to FGR is critically important. As a rule, the prediction of early-onset severe FGR is better than of late-onset FGR.

RISK FACTORS FOR FETAL GROWTH RESTRICTION

I. History-based risk factors:

a) maternal demographics:
- advanced age;
- underweight;
- living in high altitude;
- severe anemia, hemoglobinopathies;
- environmental factors (air pollution, heavy metals, heat);

b) medical conditions:
- chronic hypertension;
- chronic kidney disease;
- systemic lupus erythematosus;
- inflammatory bowel disease;
- antiphospholipid syndrome;
- pregestational diabetes (long standing);

c) obstetric history:
- previous pregnancy affected by FGR or pre-eclampsia.

II. Biochemical markers:
- low PlGF;
- low PAPP-A;
- high AFP.

III. Ultrasound-based markers:
- uterine artery: pulsatility index >95th percentile;
- uterine artery: bilateral notching;
- marginal or velamentous cord insertion;

- two-vessel cord (single umbilical artery);
- abnormal placental morphology;
- decreased fetal growth velocity.

Note — [a]Refers to placental dimension (short-based thick placenta) and texture (calcifications, echogenic cystic lesions).

History-based risk factors

Several maternal factors influence fetal growth and the risk of FGR: advanced maternal age, racial/ethnic origin (e.g. South Asian), consanguinity, low body mass index, nulliparity, use of recreational drugs and alcohol, assisted reproductive technology, and medical disorders such as chronic hypertension, diabetes mellitus, and autoimmune conditions. Cigarette smoking is a common risk factor for FGR and reduces birth weight by an average of 200 g in a dose-response manner.

Some risk factors for FGR are especially relevant in low-resource countries. In a recent review from Africa, the main risk factors reported were low maternal nutritional status, HIV infection, malaria, and hypertensive diseases. Based on these findings, the authors concluded that to a large extent FGR in Africa is preventable through established interventions for malaria, HIV, and maternal undernutrition. In addition, exposure during pregnancy and lactation to toxic environmental chemicals and heavy metals has become a growing problem, especially in low-resource countries.

Biochemical markers

At this point there is no role for routine screening with serum biomarkers for FGR. However, when biochemical markers are available as part of prenatal genetic screening for trisomy 21, it may be reasonable to use this information for the purpose of risk stratification for FGR.

The placenta releases multiple factors into maternal circulation from the early stages of pregnancy, and first-trimester serum levels of some of these factors have been shown to be associated with subsequent placenta-mediated complications. Low levels of pregnancy-associated plasma protein-A (PAPP-A), a placental glycoprotein produced by the syncytiotrophoblast

layer, have been associated with adverse pregnancy outcomes including SGA. Thus, although women with low PAPP-A are at increased risk for FGR, the majority of these women will have a normal pregnancy outcome, especially as an isolated biomarker in healthy women. However, a low PAPP-A level is often considered an indication for closer monitoring of fetal growth. Elevated second-trimester maternal serum levels of alpha-fetoprotein are thought to reflect abnormal placental permeability and are associated with increased risk of placenta-mediated complications including FGR and stillbirth. The combination of low PAPP-A in the first trimester and high alpha-fetoprotein in the second trimester is particularly predictive of severe FGR. Elevated human chorionic gonadotropin (hCG) levels greater than 2.5 MoM in the second trimester, alone or combined with high alpha-fetoprotein levels, are also associated with an increased risk of SGA.

Angiogenic factors play a key role in the regulation of placental vascular development. Placental growth factor (PlGF) is a proangiogenic factor highly expressed in the syncytiotrophoblast and the maternal endothelium. Impaired placentation is associated with reduced placental production of this protein. Low first-trimester PlGF levels have been shown to be associated with adverse pregnancy outcomes including pre-eclampsia and SGA.

Findings are less consistent for soluble fms-like tyrosine kinase-1 (sFlt-1), an antiangiogenic factor released from the placenta that results in maternal endothelial dysfunction characteristic of pre-eclampsia. Therefore, the sFlt-1:PlGF ratio test used to diagnose pre-eclampsia should not be used in the first trimester as a screening test for FGR.

Ultrasound markers

Several ultrasound-based markers have been shown to be predictive of FGR, including uterine artery Doppler, placental morphology, and placental volumes. However, given their modest predictive accuracy, they cannot be recommended for universal screening for FGR.

Increased uterine artery resistance largely reflects a failure of extravillous cytotrophoblast invasion and transformation of the spiral arteries and is associated with the development of pre-eclampsia and FGR due to maternal vascular malperfusion of the placenta.

The first- and second-trimester abnormal uterine artery Doppler waveforms, defined as mean pulsatility index above the 95th percentile, have been shown to be associated with FGR. Although uterine artery Doppler shows promise, especially for the prediction of early-onset FGR, current evidence does not support routine screening with uterine artery Doppler for FGR in low- or high-risk pregnancies.

Sonographic evaluation of the placenta is a routine part of the obstetric ultrasound examination. A method for systematic two-dimensional (2D) placental ultrasound examination has been described, often in combination with other parameters. Abnormal placental morphology is defined by placental dimensions, shape, texture, and cord insertion. Placental shape is considered abnormal when the placental thickness is above 4 cm or greater than 50% of placental length. Placental texture is defined as normal when it is homogenous, and abnormal when the placenta is heterogeneous and contains multiple echogenic cystic lesions or has a jelly-like appearance with turbulent uteroplacental flow. Placental cord insertion is defined as central (>2 cm from placental disc margin), marginal (within 2 cm of margin), or velamentous (inserting into the surrounding membranes). However, the use of 2D placental imaging has significant limitations, including difficulty in assessing nonanterior placentas and a wide variability in the morphology of normal placentas. Furthermore, there are no large-scale prospective studies validating the use of this modality for prediction of FGR.

Improvements in ultrasonographic imaging provide a tool for estimating placental volume using three- and four-dimensional scanning techniques. Placental volume has been proposed as a marker for various obstetric complications related to defective placental function, including FGR. The discriminatory ability of placental

volume alone for SGA appears to be modest, but may be integrated into a multivariable screening model. However, the use of 3D placental volume as a routine screening tool for FGR is limited by the need for proper equipment and training required to obtain these measurements in a reproducible manner.

Prevention of fetal growth restriction in high-risk populations

Lifestyle modifications

Ideally, all women should plan their pregnancies, adopting a healthy lifestyle and optimizing any medical conditions and their body mass index. The preconception period provides an opportunity for health promotion with the aim of reducing accepted risk factors, including those associated with FGR.

Insufficient gestational weight gain has been associated with an increased risk of FGR, especially in women with low body mass index (BMI, calculated as weight in kilograms divided by height in meters squared). As recommended by the 2009 Institute of Medicine guidelines a total gestational weight gain of 12.5–18 kg (28–40 lb) for underweight women (BMI<18.5); 11.5–16 kg (25–35 lb) for the normal weight group (BMI 18.5–24.9); 7–11.5 kg (15–25 lb) for overweight women (BMI 25.0–29.9); and 5–9 kg (11–20 lb) for obese women (BMI≥30).

Substance use, including smoking, alcohol, and illicit drugs, is associated with low birth weight and increased perinatal morbidity and mortality. Women should be advised that smoking cessation at any point in gestation is of benefit, and that the greatest benefit is associated with cessation before 15 weeks of pregnancy. The risk of SGA with alcohol intake is increased with as little as one drink per day.

Medical interventions

Most studies on early prevention of placental complications have focused on pre-eclampsia, with the results often being extrapolated to FGR due to the common pathophysiology. However, to date, other than lifestyle modifications, no medical interventions to prevent FGR have been clearly established.

Aspirin is recommended for women at increased risk of pre-eclampsia, but there is some evidence that it may also reduce the risk of FGR. In women at high risk of pre-eclampsia, the administration of aspirin starting at less than or equal to 16 weeks of pregnancy reduced the risk of FGR by nearly half, with higher doses of aspirin associated with a greater reduction, favoring a dose of 100–150 mg. However, it should be emphasized that most of the available data on aspirin come from studies that focused on the prevention of pre-eclampsia as the primary outcome in women at high risk of pre-eclampsia, with the prevention of FGR considered only as a secondary outcome. Furthermore, in the largest trial to date on the use of aspirin for the prevention of pre-eclampsia (ASPRE trial), aspirin was not associated with a reduction in the risk of SGA below the 10th, 5th, or 3rd percentile. However, we believe that given the safety of aspirin and the overlap in the risk factors and pathogenesis of pre-eclampsia and FGR, it is reasonable to recommend aspirin to women at high risk of FGR, using the same regimen of aspirin used for women at high risk of pre-eclampsia. Most international guidelines recommend 100–150 mg aspirin to prevent FGR in women at high risk.

The adjunct role of heparin in combination with aspirin to prevent placenta-mediated complications in high-risk situations was originally attributed to its anticoagulant properties and the speculative prevention of placental thrombosis. However, in vitro and in vivo data suggest heparins may have other biological properties including anti-inflammatory, complement inhibition, and proangiogenic activities. Therefore, based on the most up-to-date evidence, LMWH cannot be recommended for the prevention of FGR in women at high risk of placenta-mediated complications. Its use for the prevention of FGR should therefore be limited to research settings, for example in women already on aspirin who are found to have abnormal levels of angiogenic markers prior to fetal viability.

Recommendations

FIGO recommends the following for prediction and prevention of fetal growth restriction (FGR)

Recommendation	Quality of evidence	Strength of recommendation
1. Women should undergo risk stratification for FGR (and other placenta-mediated complications) at the time of the first-trimester antenatal visit using history-based (medical and obstetric) risk factors.	⊕⊕⊕○	Strong
2. There is no evidence to support the routine use of biochemical markers for the prediction of FGR. However, when such information is available as part of prenatal genetic screening for trisomy 21, it may be reasonable to use this information for the purpose of risk stratification for FGR (and other placenta — mediated complications).	⊕⊕⊕○	Strong
3. Ultrasound-based markers and multiparameter algorithms have only a moderate predictive accuracy for FGR, and therefore currently cannot be recommended for universal screening.	⊕⊕⊕○	Strong
4. Women at high risk for FGR should undergo close surveillance of fetal growth starting at 24–28 weeks. In low-resource settings, the frequency and type of monitoring may be limited by the availability of obstetric ultrasound.	⊕⊕⊕○	Strong
5. Women should be advised that smoking cessation and elimination of alcohol and illicit drugs can decrease the risk of FGR.	⊕⊕⊕○	Strong
6. Women should be advised on the association of insufficient gestational weight gain with FGR and be informed regarding their target weight gain range.	⊕⊕⊕○	Strong

End of Table

Recommendation	Quality of evidence	Strength of recommendation
7. There is insufficient data to recommend routine treatment with aspirin in all women at high risk of FGR. Treatment with aspirin at a dose of 100–150 mg starting at 12–16 weeks may be considered in selected cases such as women who are at high risk of pre-eclampsia or those with a history of placenta-mediated FGR.	⊕⊕○○	Strong
8. Low-molecular-weight heparin is not recommended for the prevention of FGR in women at high risk of FGR and its use should be limited to research settings.	⊕⊕⊕○	Strong

Source: Europe PMC. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

DETECTION OF FETAL GROWTH RESTRICTION

Detection of FGR is based on the identification of a fetus that is smaller than expected for gestational age, through either physical examination (symphysis-fundal height, SFH) or ultrasound.

Symphysis-fundal height. Measurement of SFH using a tape is a simple, inexpensive, and widely used strategy to screen for FGR SFH is measured with the woman in a supine position using a nonelastic metric tape after she has emptied her bladder. To decrease the interobserver variability, a standardized technique for measuring SFH should be followed. SFH is defined as the distance from the upper border of the symphysis pubis bone to the top of the uterine fundus. SFH measured in centimeters between 24 and 38 weeks of gestation approximates the gestational age. However, the accuracy of SFH measurement in predicting SGA (EFW<10th percentile) is limited, and there are no randomized controlled trials that compare SFH measurement with serial ultrasound evaluation of fetal biometry. It is important to acknowledge that factors such as maternal obesity, uterine leiomyomas, and polyhydramnios may further limit the accuracy of SFH as a screening tool.

Sonographic fetal weight estimation. Sonographic fetal biometry is the cornerstone for detection of fetal growth disorders. Standard fetal biometry includes assessment of head circumference (HC), biparietal diameter, abdominal circumference (AC), and femur length (FL). Measurement of these biometric indices should be obtained by an experienced individual and in a standardized manner. Fetal weight is estimated based on various combinations of the four biometric indices described above, using one of many published equations. The accuracy of most equations falls within the range of ±10%, and the error has been shown to be greater at the extremes of birth weight, and to be affected by factors such as fetal sex, presentation, and plurality (greater in twin gestations). It was found that the Hadlock equation, based on three indices (HC, AC, and FL: Log10 weight=1.326 – 0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL), provided the greatest accuracy. Since the accuracy of the various equations may vary between different populations, it may be reasonable for radiologists, sonographers, or care providers to choose an equation that has been validated within their local population and within the gestational age range in which it will be used. However, if such information is not available — a very frequent scenario — it seems reasonable to use the Hadlock equation as described above.

Recommendations

FIGO recommends the following for detection of fetal growth restriction (FGR)

Recommendation	Quality of evidence	Strength of recommendation
1. Symphysis-fundal height is a simple and inexpensive tool that can be used as the primary screening strategy for FGR in low-risk pregnancies in both low- and high-resource settings.	⊕⊕⊕○	Strong
2. There is no evidence to support routine third-trimester ultrasound for the detection of FGR, as this practice has not been shown to be associated with improved perinatal outcomes.	⊕⊕⊕⊕	Strong

End of Table

Recommendation	Quality of evidence	Strength of recommendation
3. The choice of the equation used for sonographic fetal weight estimation may be based on validation within the local population. If this information is not available, we recommend that the following equation of Hadlock (based on head circumference [HC], abdominal circumference [AC], and femur length [FL]) should be used: *LogO weight = 1.326 – 0.00326*AC*FL + 0.0107*HC + 0.0438*AC + 0.158*FL.*	⊕⊕⊕○	Strong
4. Growth standards that are based on sonographic fetal weight estimation should be preferred over growth references and over charts that are based on birth weight.	⊕⊕⊕○	Strong
5. We support the recommendation of the FIGO Safe Motherhood and Newborn Health Committee that local or regional growth charts should be preferred over universal charts. Alternatively, universal standards may be used with locally adjusted thresholds to avoid under— or overdetection of FGR.	⊕⊕⊕○	Strong
6. The decision regarding which growth chart to use may be further guided by comparing the performance of the various charts in the population of interest, using local data sets.	⊕⊕○○	Weak
7. Based on the available evidence it seems reasonable to use twin-specific charts for the assessment of fetal growth in twin gestations as this has the potential to avoid overdiagnosis of FGR in this population.	⊕⊕○○	Weak
8. In twin gestations, the diagnosis of FGR should also take into consideration intertwin size discordance, especially in the case of monochorionic placentation.	⊕⊕⊕⊕	Strong

Source: Europe PMC. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

Once FGR is suspected, a systematic investigation should be performed aimed at identifying the underlying etiology for fetal smallness, with the most important reasons being constitutional SGA, placental dysfunction, and fetal conditions such as genetic or infectious disorders. Establishing the most likely etiology is essential to allow for proper counseling, surveillance, and interventions. The investigation should consist of detailed history, evaluation of screening test results for trisomy 21 and biochemical markers, detailed sonographic assessment for structural anomalies and Doppler studies, and additional testing directed at genetic or infectious etiologies when they are suspected.

Detailed history

A detailed maternal and family history is essential to correctly identify the etiology of FGR. This should include information on maternal age, racial/ethnic group, height and weight, nutritional status, socioeconomic status, medications, cigarette smoking and use of recreational drugs, chronic medical conditions, personal or family history suggestive of thrombophilia, genetic disorders or consanguinity, obstetric history including birth weight of previous children, and confirmation of pregnancy dating by first-trimester ultrasound.

Advanced maternal age has been associated with FGR, with risk increasing for women over the age of 35 years. Maternal social issues, low income, and domestic violence during pregnancy have been shown to be associated with low birth weight. Poor nutritional status due to conditions such as celiac disease and eating disorders is a potentially treatable cause of FGR. Maternal smoking is an important and potentially modifiable risk factor for FGR.

History should also address the risk of congenital fetal infection with cytomegalovirus, toxoplasmosis, syphilis, Zika virus, and varicella-zoster virus. Relevant questions include a history of febrile disease or rash in pregnancy or the periconceptional period, recent travel history to endemic areas (e.g. for Zika virus), and frequent exposure to young children (cytomegalovirus) or to domestic animals (toxoplasmosis).

Accurate dating of pregnancy is essential for the correct interpretation of estimated fetal size and to avoid a false diagnosis

of FGR. Determining gestational age based on menstrual history is often unreliable. Therefore, with the exception of pregnancies achieved by assisted reproductive technology, the crown–rump length measured at the time of first-trimester ultrasound is the most accurate method to date pregnancy, and establishes gestational age with a precision of 5 days in 95% of cases. Crown–rump length is most accurate for the purpose of dating when in the range of 7–60 mm. Therefore, confirmation of gestational age based on first-trimester ultrasound (when available) should be the first step when FGR is suspected. If more than one scan is performed in the first trimester, the earliest scan with a crown–rump length of at least 10 mm should be used.

Detailed anatomy scan

Detailed anatomy scan should be routinely performed when FGR is suspected, especially in cases of early-onset severe FGR. The presence of major structural anomalies, soft sonographic markers, or disorders of amniotic fluid (e.g. polyhydramnios) may raise the possibility of chromosomal, subchromosomal, or single gene abnormalities as the cause of FGR. The presence of very shortened fetal long bones (shorter than –2SD and especially –4SD below the mean) should raise the possibility of skeletal dysplasia and indicates targeted genetic assessment. Attention should also be given to findings that are associated with congenital infections, especially in women with a relevant history, as described above. Examples of such sonographic findings include small head circumference, ventriculomegaly, brain or liver calcifications, periventricular hyperechogenicity, cortical brain malformations, echogenic bowel, hydrops, or placentomegaly.

Doppler studies

Doppler assessment is an integral part of the diagnostic process and management of FGR. The presence of abnormal Doppler findings in the uterine, umbilical, or middle cerebral arteries is highly suggestive of placental dysfunction as the underlying etiology of FGR.

It should be noted that umbilical artery Doppler findings may be normal in the early stages of placental FGR. Therefore, normal umbilical artery Doppler studies do not rule out placental dysfunction, and therefore serial monitoring is recommended in all

cases of suspected FGR. At the same time, abnormal umbilical artery Doppler is not pathognomonic of placental dysfunction, as certain genetic conditions (e.g. triploidy) may mimic early-onset placental FGR, including the presence of abnormal umbilical artery Doppler, most likely due to concomitant placental insufficiency secondary to the abnormal placental karyotype. In contrast to umbilical artery Doppler, uterine artery Doppler is less likely to be abnormal among fetuses with FGR and abnormal karyotype, and should therefore be considered to be more specific for primary placental FGR, especially in the presence of abnormal angiogenic markers in maternal blood.

Additional testing

Screening for congenital infections should be offered when FGR is suspected, especially in cases of early-onset FGR or when infection is possible based on history of ultrasound findings. Testing should be focused on cytomegalovirus and toxoplasmosis, but may also include rubella, varicella, and syphilis in cases at high risk for these infections. Testing for Zika virus and malaria should also be considered in the relevant travel history or location context. However, it should be noted that interpretation of serology results may be challenging due to limited specificity and cross-reactivity of some of the assays, especially when baseline serology results prior to pregnancy or from early pregnancy are not available. When fetal infection is highly suspected based on serology results or clinical findings, further testing should be offered by means of amniocentesis for the detection of viral DNA in the amniotic fluid using polymerase chain reaction. In these cases, amniocentesis should be delayed until after 21 weeks of gestation and at least 6–8 weeks following the estimated onset of maternal infection to minimize the risk of false-negative results.

Genetic consultation and genetic testing by amniocentesis should be offered to women with FGR, especially in cases of early-onset or severe FGR (<3rd percentile), co-presence of sonographic findings (such as structural anomalies, soft markers, or polyhydramnios), and the absence of obvious signs of placental dysfunction such as abnormal uterine or umbilical artery Doppler. In addition, women should be counseled about the risk of a genetic etiology even in the presence of "isolated" FGR (i.e. without associated fetal anomalies).

Recommendations

FIGO recommends the following for investigation of fetal growth restriction (FGR)

Recommendation	Quality of evidence	Strength of recommendation
1. Women with suspected FGR should undergo systematic assessment that includes the following: (1) detailed history; (2) detailed sonographic assessment for structural anomalies, soft markers, and sonographic signs related to fetal infection; (3) Doppler studies that include at least the umbilical artery and, when available, also the uterine and middle cerebral arteries; and (4) maternal screening for relevant congenital infections, which should be focused on cytomegalovirus and toxoplasmosis, but may also include rubella, herpes, syphilis, malaria, and Zika virus in cases at high risk. The extent of investigation may be limited by available resources. Assessment should include screening for infections such as malaria and Zika virus in endemic areas.	⊕⊕⊕⊕	Strong
2. Confirmation of gestational age should be the first step when FGR is suspected. With the exception of pregnancies achieved by assisted reproductive technology, first-trimester crown-rump length is the most accurate method to date pregnancy when in the range of 7–60 mm. If more than one scan is performed in the first trimester, the earliest scan with a crown-rump length of at least 10 mm should be used. In low-resource settings, dating may need to be based on menstrual history or symphysis-fundal height.	⊕⊕⊕⊕	Strong
3. Amniocentesis for karyotype (as well as microarray and polymerase chain reaction for infectious agents when available) should be offered to women with suspected FGR, especially in cases with early-onset severe (estimated fetal weight<3rd percentile) FGR, in the presence of sonographic findings	⊕⊕⊕○	Strong

End of Table

Recommendation	Quality of evidence	Strength of recommendation
associated with genetic or infectious etiologies, no obvious signs of placental dysfunction, and when the findings are likely to affect management. The availability of genetic testing may be limited by available resources.		

Source: Europe PMC. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

MANAGEMENT OF PREGNANCIES WITH FETAL GROWTH RESTRICTION

Management of pregnancy with FGR depends in part on the results of the investigation. In cases of fetal abnormalities (genetic or infectious) the management (expectant versus pregnancy termination) should be individualized based on the nature of the disorder, the expected prognosis, gestational age, parental wishes, and local policies.

The most common underlying etiology for FGR is placental dysfunction. In early-onset FGR (<32 weeks), increased resistance in umbilical artery Doppler is the primary rate-limiting step to subsequent deterioration of cardiovascular and biophysical parameters. The primary management challenge arises from the risk of fetal deterioration and stillbirth in pregnancies undergoing surveillance versus the neonatal morbidity and mortality associated with preterm delivery. In late-onset FGR (≥32 weeks), cardiovascular deterioration in response to fetal hypoxia is predominantly confined to the cerebral circulation with little umbilical artery Doppler changes. Pregnancies complicated by late-onset FGR are major contributors to adverse perinatal outcome attributable to FGR because of misdiagnosis and challenges in detecting deterioration during fetal surveillance.

There is no effective antenatal treatment for placental dysfunction and therefore once FGR has been identified,

the principal management steps are institution of fetal surveillance and determination of appropriate thresholds for delivery. The recommendations for monitoring, timing and mode of delivery, and potential treatments for placenta-mediated FGR are described below and summarized in Table 5.2 (p. 211–212) and Fig. 5.2.

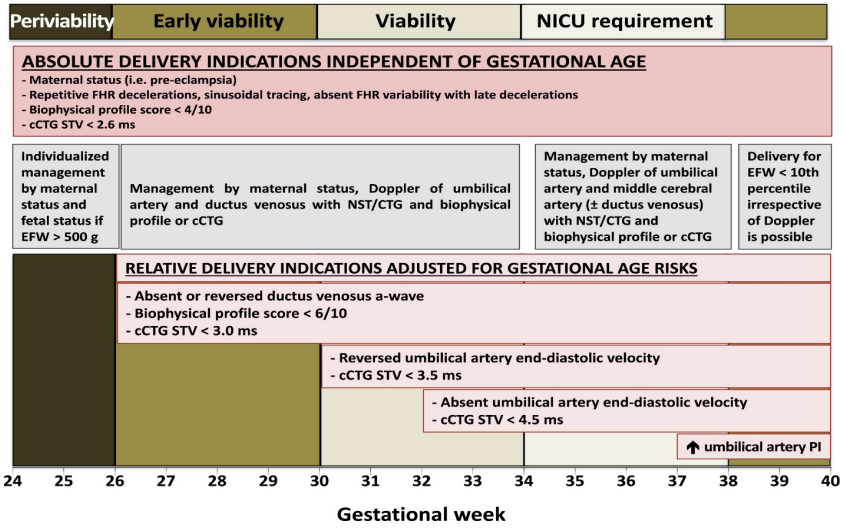


Fig. 5.2. Delivery criteria for fetal growth restriction. Delivery criteria are based on monitoring with umbilical artery, ductus venosus, and middle cerebral artery Doppler at specified gestational ages with traditional nonstress testing or computerized CTG (cCTG) if available: NICU — neonatal intensive care unit; FHR, fetal heart rate; CTG, cardiotocogram; STV, short-term variation; ms, milliseconds; EFW, estimated fetal weight; PI, pulsatility index

Source: Screening, diagnosis and treatment of growth-restricted fetuses Figo 2021

Monitoring

The primary goal of fetal monitoring is prevention of stillbirth by detection of fetal deterioration that precedes irreversible compromise. To achieve this goal, monitoring tests need to be accurate in identifying fetal risks that favor delivery and, for pregnancies

Table 5.2

Recommendations for monitoring, timing, and mode of delivery in cases with suspected fetal growth restriction

Findings	Risk of stillbirth	Suggested monitoringa	Timing and mode of delivery
GA (EFW at 3rd–9th percentile, normal fluid and Doppler studies)	Low	Doppler (UA, MCA) every 1–2 weeks Growth every 2 weeks At ≥37 weeks consider BPP/NST 1–2 times per week	37–39 weeks Mode of delivery: induction
Uncomplicated FGR at <3rd percentile (normal fluid and Doppler studies)	Low	Doppler (UA, MCA) 1–2 times per week Growth every 2 weeks At ≥37 weeks consider BPP/NST 1–2 times per week	36–38 weeks Mode of delivery: induction
FGR with mild abnormalities Early Doppler changes: a. UA PI>95th percentile, or b. MCA PI<5th percentile, or c. CPR<5th percentile, or d. UtA PI>95th percentile Oligohydramnios Suboptimal interval growth Suspected pre-eclampsia	Low	Consider inpatient monitoring Consider steroids for fetal lung maturation BPP/NST 1–2 times per week Doppler (UA, MCA, DV) 1–2 times per week Growth every 2 weeks	34–37 weeks Mode of delivery: cesarean section or induction
FGR with umbilical artery AEDV/REDV	Overall risk of stillbirth: a. AEDV: 6.8%, OR 3.6 [2.3–5.6] b. REDV: 19%, OR 7.3 [4.6–11.4] Risk of stillbirth with strict monitoring protocol with a safety net:	Inpatient monitoring Steroids for fetal lung maturation BPP/NST 1–2 times per day Doppler (UA, MCA, DV) every 1–2 days	AEDV: 32–34 weeks REDV: 30–32 weeks Mode of delivery: cesarean section

End of Table 5.2

Findings	Risk of stillbirth	Suggested monitoringa	Timing and mode of delivery
	a. AEDV: 0–1% b. REDV: 1–2% Median time for deterioration: a. AEDV: 5 days b. REDV: 2 days	Growth every 2 weeks	
FGR with abnormal ductus venosus Doppler	Overall risk of stillbirth: 20%, OR 11.6 (6.3–19.7) Risk of stillbirth with strict monitoring protocol with a safety net: a. Elevated DV PIV: 2% b. Absent-reverse a-wave in DV: 4%	Inpatient monitoring Steroids for fetal lung maturation BPP/NST twice per day Daily Doppler	26–30 weeks Mode of delivery: cesarean delivery

where delivery thresholds are not met, follow-up monitoring needs to be frequent enough to provide a safety net against unanticipated deterioration or stillbirth. Fetal surveillance tests include maternal monitoring of fetal movements, cardiotocography, ultrasound evaluation of amniotic fluid volume and fetal activity, and Doppler ultrasound of the fetal arterial and venous circulations.

Fetal movement counting. Fetal activity is established from the first trimester onward and as gestational age advances becomes organized into coordinated behavioral states. Progressive fetal hypoxemia is accompanied by a reduction of fetal activity that can be perceived most accurately by the mother when she is lying down and paying focused attention to fetal movements. Decreased fetal movement is often defined as less than 10 movements in 2 hours during focused maternal counting. Fetal movement counting is a simple and inexpensive tool that may provide a safety net between scheduled outpatient monitoring visits, it seems reasonable to use movement counting as an adjunct to monitoring in FGR. The mother should be provided with clear behavioral instructions and confirmatory monitoring should be performed for patients presenting with decreased fetal movements.

Fetal heart rate monitoring. Fetal heart rate monitoring is universally recommended to monitor pregnancies complicated with FGR. Antepartum cardiotocography (CTG), also known as a nonstress test (NST), can be performed as a standalone evaluation or in conjunction with measurement of amniotic fluid volume (modified biophysical profile), or a five-component biophysical profile (BBP).

Some heart rate characteristics reflect fetal oxygenation, gestational age, and maturational state of the nervous and cardiovascular systems. The normal heart rate baseline is between 110 and 160 beats per minute (bpm) and decreases with advancing gestation. Periodic accelerations of fetal heart rate (FHR) usually coincide with fetal movements, are observed from the early second trimester, and increase in magnitude and duration with advancing gestation. These are defined as increases in FHR over the baseline of at least 15 bpm and 15 seconds' duration. Two or more of these accelerations define a "reactive" pattern. Recognizing that

the frequency of reactivity increases from 50% at 24–28 weeks to 85% at 28–32 weeks of gestation, criteria of greater than or equal to 10 bpm amplitude and greater than 10 seconds' duration are recommended at earlier gestational ages. A "nonreactive" FHR pattern is one that does not display accelerations over an observation period of 40 minutes. In addition to reactivity, FHR patterns display "variability" — the average oscillations in the FHR signal, evaluated in bpm in 1-minute windows. Reduced variability appears later than absent reactivity in the process of progressive fetal hypoxia. It reflects reduced sympathetic–parasympathetic activity, secondary to diminished brainstem oxygenation.

Without any additional information, the empirically recommended minimum frequency is twice weekly CTG/NST. The frequency may be increased when evaluation of amniotic fluid or Doppler parameters indicate a more advanced degree of fetal compromise and delivery criteria have not yet been met. A nonreactive CTG/NST has low specificity for hypoxia and requires additional tests to determine fetal status and distinguish FHR pattern variations caused by fetal behavior, while reduced variability is a much stronger predictor of central nervous system hypoxia.

Computerized fetal heart rate monitoring. Some professional societies recommend computerized fetal heart rate monitoring (cCTG) as the preferred modality to analyze CTG/NST tracings. Inconsistency in visual assessment, particularly FHR variability, is a major contributor to interobserver variations in interpretation of CTG/NST tracings. cCTG evaluates FHR parameters such as baseline, accelerations, decelerations, and variability in an objective and quantifiable way. The Sonicaid cCTG system (Huntleigh Healthcare, Cardiff, UK) provides the parameter "short-term variation" (STV) in milliseconds, while others quantify variability in a more traditional way in bpm. In contrast to visual FHR analysis, cCTG decreases observer variability and allows longitudinal numerical analysis of variability.

FHR variability increases with gestational age; after 29 weeks of gestation, below 4.0 ms or below 3.0 ms meet criteria for reduced or very low STV, respectively. Before 29 weeks of gestation, STV below 3.5 ms is considered reduced, and below 2.6 ms is considered

very low. STV below 3 ms has a 77% positive predictive value for fetal acidemia.

Similar to CTG/NST, cCTG does not predict fetal deterioration. In early-onset FGR the daily risks for abnormal STV are 4–5% but are unpredictable by additional monitoring tests. Accordingly, CTG/NST or cCTG monitoring needs to be performed more frequently than Doppler assessments. In patients receiving inpatient monitoring, a minimum frequency of daily cCTG/CTG/NST is recommended.

Ultrasound measurement of amniotic fluid volume. Professional societies do not recommend inclusion of isolated amniotic fluid volume assessment into management decisions for FGR. A decrease in amniotic fluid volume can occur as a result of fetal oliguria in response to progressive placental dysfunction and hypoxia, as well as rupture of membranes. Accordingly, additional evaluation is required to determine the significance of decreased amniotic fluid volume. Oligohydramnios can be defined as an ultrasound measured four-quadrant amniotic fluid index below or equal to 5 cm, or a maximum vertical amniotic fluid pocket below or equal to 2 cm. Use of the latter reduces overdiagnosis of oligohydramnios and is preferred. Oligohydramnios is associated with an increased rate of intrapartum FHR abnormalities, need for cesarean section, and low 5-minute Apgar scores, but not acidosis at birth.

Biophysical profile scoring. Biophysical profile (BPP) scoring is not universally recommended as the primary surveillance tool for FGR and is predominantly utilized in Canada and North America where the concept was first developed for fetal surveillance in the later part of the third trimester. The modified BPP refers to combined use of the CTG/NST as a short-term indicator of fetal acid-base balance and the maximum amniotic fluid pocket as an indicator of long-term placental function. The five-component BPP comprises fetal breathing movements, gross body movements, and tone, in addition to CTG/NST and maximum amniotic fluid pocket, and therefore includes four indicators of short-term acid-base balance.

The modified BPP is considered abnormal when either the CTG/NST is nonreactive, or the maximum amniotic fluid pocket is below 2 cm. The most common reason for an abnormal modified

BPP is a nonreactive CTG/NST, requiring additional ultrasound observation to complete a five-component BPP and determine fetal acid-base balance. The BPP is scored over a 30-minute ultrasound observation period of the fetus. Fetal breathing movements are considered present if one or more episodes of 30 seconds of breathing or hiccups are observed. Fetal body movement is present when three or more discrete body or limb movements are observed. Fetal tone is present when one or more episodes of extension and flexion of the fetal extremities are observed. Each component of the BPP receives a score of 2 for its presence and 0 for its absence. Scores of 8–10, 6, and 4 or less are considered normal, equivocal, and abnormal, respectively.

BPP is a more accurate predictor of fetal acid-base status at the time of testing than CTG/NST and has the same accuracy as cCTG. Thus, the five-component BPP can be used to assess fetal acid-base status when non-reactive CTG/NST is taken. The frequency of BPP testing is determined according to the same principles as the timing of fetal heart rate measurements.

Dopplerography of the umbilical artery. Umbilical artery Doppler sonography is often recommended for monitoring FGR because it allows assessment of the hemodynamic aspect of placental dysfunction. It is estimated that approximately one-third of the villous circulation must be damaged before a decrease in umbilical artery end-diastolic velocity occurs. Absence or alteration of umbilical artery end-diastolic velocity corresponds to malperfusion of 50–70% of the villous vascular tree. Since increased resistance to villous blood flow is predominantly associated with placental pathology in early-onset FGR, umbilical artery Doppler sonography cannot reliably predict the outcome of late-onset FGR.

In patients with normal umbilical artery Doppler, the recommended frequency of Doppler monitoring is weekly to biweekly. However, Doppler monitoring is recommended at least twice a week in AEDV and at least three times a week in REDV if delivery criteria are not met.

Dopplerography of the cerebral arteries. Most professional societies now recommend middle cerebral artery Doppler ultrasound

for monitoring late-onset FGR. Simultaneous measurement of the umbilical artery and middle cerebral artery pulsatility index allows calculation of the cerebroplacental Doppler coefficient. Both the cerebroplacental ratio and the middle cerebral artery pulsatility index are reduced as a hemodynamic response to fetal hypoxemia and therefore reflect placental dysfunction even in pregnancies in which villous flow resistance is not sufficiently increased to cause an abnormal umbilical artery pulsatility index. The cerebroplacental Doppler coefficient is more closely related to fetal hypoxia than its individual components, but has equal accuracy in predicting perinatal death, fetal distress, or poor neonatal transition as the umbilical artery pulsatility index.

Cardiovascular disease in late-onset SRD is characterized by abnormal cerebral artery Doppler. Therefore, an important role of middle cerebral artery Doppler is in assessing perinatal risk in patients with normal umbilical artery Doppler. Due to the higher risk of an adverse outcome within 1 week of a reduced middle cerebral artery pulsatility index, monitoring at least twice weekly is recommended in this situation.

Ductus venosus Doppler. The few professional societies that recommend Doppler assessment of the ductus venosus indicate that it should be performed in specialized centers with experience in the comprehensive perinatal management of early-onset FGR. The relative forward flow into the atrial systole in the ductus venosus decreases with deterioration of placental function or reduced fetal cardiac function, resulting in an increase in the venous pulsatility index, absence or reversal of the a-wave.

Abnormal ductus venosus Doppler sonography occurs primarily in early onset FGR and can allow assessment of fetal acid-base balance and risk of stillbirth. Abnormal ductus venosus on Doppler testing is also indicative of fetal decompensation with abnormal BPH, reduced CTG variability, or stillbirth. In fetuses with increased ductus venosus pulsatility index in the veins but with direct flow during atrial systole, the mean interval to progressive deterioration of venous Doppler may be as short as 2 days. In patients who do not yet meet delivery criteria, it is recommended to perform Doppler ultrasound of the ductus

venosus at least twice weekly in patients with AEDV and three times weekly in patients with REDV. If ductus Doppler readings increase, the frequency of monitoring should be increased even further.

Monitoring strategy

Monitoring in pregnancies with FGR is intended to prevent fetal compromise or stillbirth, and the choice of tests and their timing depend largely on gestational age. A sound plan is important because expectant management with continuous monitoring, particularly in early FGR, can result in a three- to five-fold higher rate of stillbirth compared with immediate delivery, depending on the degree of cardiovascular risk until the onset of labor is permitted. The optimal frequency of monitoring for FGR has not been established due to the varying circumstances of gestational age and severity of FGR. A combination of monitoring methods is needed to accurately determine fetal acid-base status at the time of testing and to predict future deterioration. Accurate prediction of fetal acid-base status is important to avoid unnecessary interventions and unnecessary labor. Anticipation of deterioration dictates subsequent monitoring intervals, which provide protection against unexpected fetal acidosis and asphyxia. The combination of biophysical (CTG/NST, cCTG, BPP) and cardiovascular parameters (umbilical artery, middle cerebral artery and ductus venosus, Doppler ultrasound) is considered a reliable approach to monitor FGR. Among these methods, the combination of CTG/NST and umbilical artery Doppler is widely recommended.

Delivery terms

The timing of delivery in FGR is determined by gestational age, severity of FGR, results of fetal surveillance studies, and maternal factors such as pre-eclampsia. Evidence for delivery can be considered absolute if it does not depend on gestational age and relative if the threshold for delivery based on observational evidence varies with gestational age.

Risks of fetal growth restriction related to gestational age

As gestational age increases, there are several important changes in the relative risks of delivery compared with continuous monitoring that determine delivery thresholds.

During 24 to 28 weeks of gestation, each day of gestational prolongation results in approximately a 2% reduction in neonatal mortality as well as major neonatal complications including bronchopulmonary dysplasia, high-grade intraventricular hemorrhage, and surgical necrotizing enterocolitis. The effects of prematurity, neonatal weight less than 500 g, difficulties in resuscitation, and reduced tolerance to low Apgar scores result in average neonatal survival rates of less than 50% and intact survival rates of less than 50% to 26 weeks.

Between 28 and 30 weeks of gestation, the daily increase in survival is about 0.7%. After 30 weeks, neonatal survival exceeds 90%, there is a significant reduction in major neonatal complications from about 35% at 30 weeks to less than 10% at 34 weeks, and the risk of neurodevelopmental delay in the newborn is reduced. delivered after this time. In infants with FGR born before 30 weeks, the rate of developmental disabilities is three times higher and the rate of cerebral palsy is up to eight times higher.

At 34 to 38 weeks' gestation, newborns are more likely to be admitted to the NICU, but the risk of serious neonatal complications is lower. For SGA fetuses who are still nulliparous at 38 weeks, the risk of stillbirth doubles each week, reaching 60/10,000 for pregnancies that continue beyond their due date.

Gestational age management strategy

The balance between the risks to the fetus and the newborn determines the predominant management strategy at different stages of pregnancy. Accordingly, the goal of treatment shifts from achieving fetal viability at 26 weeks to progressively improving survival, neonatal morbidity and neurodevelopment by delaying delivery to 34–36 weeks. The increasing frequency of stillbirths in preterm infants increasingly favors delivery from 36 weeks.

The timing of delivery in FGR has been assessed in three randomized trials. In the Growth Restriction Intervention Trial (GRIT), pregnant women with abnormal fetal biometry and umbilical artery Doppler studies performed as part of clinical management were randomized to immediate delivery after completion of a course of steroids compared with delivery when the primary care

physician was no longer satisfied with conservative management. The monitoring protocol and delivery criteria were not specified. The study showed that in the absence of specific criteria, each management approach resulted in the same perinatal outcome. Delayed delivery increased the risk of stillbirth, whereas earlier births resulted in a higher rate of complications related to preterm birth resulting in either neonatal death or an increased risk of developmental delay.

The Disproportional Intrauterine Growth Intervention Trial at Term (DIGITAT) randomized SGA fetuses according to several biometric criteria, regardless of umbilical artery Doppler pattern, to undergo induction or pregnancy monitoring between 36 and 41 weeks of gestation. The study found that while elective induction did not affect neonatal or obstetric outcomes, delivery before 38 weeks resulted in a higher rate of neonatal intensive care unit (NICU) admission.

These studies suggest that the relative risk of neonatal complications requires clear indications for delivery before 38 weeks' gestation. After this time, delivery according to FGR indications is likely to prevent one stillbirth in an ongoing pregnancy. A sustained reduction in neonatal risk requires that early pregnancy indications occur at a higher fetal risk threshold than at 30–32 weeks.

Absolute delivery criteria for fetal growth restriction (regardless of gestational age)

- Absolute delivery criteria are those that pose significant risks to the health of the mother or fetus and therefore require delivery regardless of gestational age.
- The biophysical parameters of the fetus are strongly influenced by the oxygen tension in the regulatory centers. A 30-minute blood pressure reading of 0 or 2 or a 60-minute blood pressure reading of 4 indicates a prenatal fetal pH of less than 7.20 and requires delivery to prevent fetal death.
- Recurrent heart rate slowing, sinusoidal heart rate, lack of variability with recurrent late decelerations, or bradycardia are predictors of fetal acidemia and poor perinatal outcome and require delivery if the causative stimulus cannot be eliminated.

When using cCTG, a transient change in duration of less than 2.6 ms is below the 5th percentile regardless of gestational age and requires delivery due to its strong association with fetal acidemia.

- Severe maternal pre-eclampsia complicates up to 30% of pregnancies with FGR, with a higher proportion occurring in early-onset FGR. In the absence of effective treatment other than delivery, pre-eclampsia with uncontrolled severe hypertension, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), or other signs of end-organ damage (e.g., oliguria or acute kidney injury other than proteinuria, pulmonary edema, or eclampsia) requiring delivery.

Relative delivery criteria for fetal growth restriction (adjusted for gestational age)

- The Umbilical and Fetal Bleeding Study in Europe (TRUFFLE) evaluated two monitoring strategies and specific delivery criteria for early-onset FGR, with the primary outcome being neurodevelopment-free survival at 2 years of age. CTG and umbilical artery Doppler monitoring was universal in all patients, while ductus venosus Doppler was added in only two study groups. Patients were randomized to one of three specific delivery criteria: (1) abnormal cCTG STV; (2) mild ductus venosus abnormalities and (3) severe ductus venosus abnormalities with absent or altered wave. Since heart rate was also monitored in patients with ductus venosus Doppler monitoring, cCTG-based safety criteria were also applied in these groups. These include STV less than 2.6 ms regardless of gestational age and less than 3.0 ms from 29 weeks. In addition, umbilical artery Doppler results were used as relative criteria for delivery, starting at 30 weeks for REDV and 32 weeks for AEDV. The choice of these thresholds is supported by a recent meta-analysis that showed that REDV in the umbilical artery carries a stillbirth rate of 19% in unborn pregnancies with FGR, which is higher than the mortality rate of newborns born from 30 weeks, while AEDV carries

a stillbirth risk of 6.8%, favoring delivery from 32 weeks due to lower neonatal mortality.

- The TRUFFLE trial showed that a predetermined management strategy resulted in better than expected outcomes in all pregnancies with FGR. The primary endpoint was observed less frequently in patients randomized to delivery for late ductus venosus anomaly. Overall, cCTG was the most common inducer of labor. Across all three groups, labor was due to abnormal STV in 11–51% of participants, and visually apparent heart rate slowing induced labor in 22–31% of participants. Although the strategy of waiting for the absence or reversal of the ductus venosus A wave to detect labor resulted in better trial outcomes, it is noteworthy that the stillbirth rate increased fourfold compared to patients monitored with CTG and umbilical artery Doppler. Furthermore, the absence of a ductus venosus A wave induced labor in only 10% of participants in this study group. The frequency of birth decisions based on FHR abnormalities underscores the importance of concurrent monitoring of growth-restricted fetuses in more than one way.
- Because cCTG is not widely available, most healthcare providers must rely on traditional CTG/NST monitoring. Although BPP has not been studied in randomized intervention trials in FGR, it is an established monitoring tool to check fetal status in patients with non-reactive tracking. In FGR, abnormal DPP predicts abnormal arterial pH with similar accuracy to cCTG and is an independent delivery trigger with a frequency comparable to cCTG. Therefore, it is recommended that FGR fetuses with unsatisfactory CTG/NST who have not yet met delivery criteria undergo FPP to determine fetal status. If specialists are not available to perform BPP, it may be necessary to extend CTG/NST or increase testing frequency to determine the need for delivery.
- Optimal delivery criteria for FGR after 32 weeks' gestation have not been evaluated in randomized trials and are based on expert consensus. If local neonatal outcomes are consistently

more favorable for infants with FGR, relative indications for delivery earlier in pregnancy than indicated may be made. For example, improved neonatal survival may justify REDV starting at 30 weeks.

Type of delivery and characteristics of the intranatal period

- FGR itself is not an indication for cesarean section. However, in selected cases of severe FGR, primary cesarean section may be considered when the likelihood of successful vaginal delivery is low.
- Fetuses with placental-mediated FGR are less likely to experience labor-related distress and are at increased risk of requiring emergency cesarean section during labor because of disappointing FGR monitoring. Therefore, in some cases of FGR, attempted labor is unlikely to be successful and may pose such great risks to the fetus that a primary cesarean section should be preferred. This depends on several factors, including gestational age, severity of FGR, Doppler changes, concomitant pre-eclampsia, parity, cervical Bishop score and patient preference.
- In cases of early FGR, the primary goal is to prolong pregnancy and maximize fetal maturation by expectant management with close monitoring until signs of late umbilical artery Doppler changes (AEDV or REDV), ductus venosus changes, or FHR abnormalities. Therefore, by the time delivery is indicated in cases of severe early FGR, the fetus may already have some degree of hypoxia or acidosis. In this case, the likelihood of the fetus surviving labor is low and the cesarean section rate is reduced. it is reported to be over 80%. Furthermore, induction of labor in preterm labor is generally less successful. For these reasons, primary cesarean section is usually the preferred option when delivery is indicated in severe early FGR.
- In contrast, late-onset FGR is usually less severe and fetal hypoxia or acidosis is less likely at the time of indication for labor. Indeed, in the DIGITAT trial, vaginal delivery rates in SGA pregnancies with normal umbilical artery Doppler were over

80% after 36 weeks' gestation. This observation suggests that the majority of full-term SGA fetuses with normal umbilical artery Doppler can tolerate labor and that the presence of late-onset FGR in the absence of additional factors does not preclude induction of labor. Several studies have attempted to individualize the decision regarding mode of delivery by developing models to predict emergency cesarean section in women with late-onset GAS undergoing induction of labor. The factors most likely to predict urgent cesarean section included gestational age, SGA severity (EFW <3rd percentile), cerebral Doppler (middle cerebral artery and cerebro-placental ratio), and Bishop score.

- The optimal approach to cervical ripening in women undergoing FGR induction remains unclear. In a recent meta-analysis of 12 studies of cervical ripening in pregnancies complicated by SGA or FGR, the authors concluded that mechanical methods (such as balloon catheters) appear to be associated with a lower risk of cesarean section and intrapartum complications compared with alternatives such as dinoprostone. Given these data, it seems reasonable to prefer a balloon catheter over prostaglandin agents for cervical ripening in suspected FGR, whenever possible. If prostaglandin agents are used, a reversible method (e.g., vaginal dinoprostone) should be preferred.
- Continuous heart rate monitoring is recommended during labor. Delivery should occur in a facility where the level of neonatal care is appropriate for the gestational age and expected needs of the newborn.
- After delivery, it is recommended to send the placenta for histological examination. Ideally, this should be done in accordance with the consensus statement of the Amsterdam Workshop. A qualitative assessment of placental pathology not only increases the accuracy of the diagnosis but also provides information on the risk of recurrence.

Antenatal corticosteroids

The efficacy of antenatal corticosteroids in cases of FGR has been questioned, based on reports of elevated endogenous cortisol levels in this population when compared with normally grown fetuses. In addition, the unique cardiovascular, hormonal, and metabolic changes characteristic of growth-restricted fetuses have raised concerns that exposure to exogenous steroids may produce potentially harmful cardiovascular and metabolic effects in these already compromised fetuses. Indeed, exposure to corticosteroids has been shown to result in Doppler changes in growth-restricted fetuses such as transient increase in diastolic flow in the umbilical artery and the middle cerebral artery, which have been attributed to peripheral vasodilatation or an increase in cardiac output and circulatory stress. Despite this, recent data support the efficacy and safety of antenatal corticosteroids in the subgroup of SGA fetuses, which should be administered when delivery is anticipated, ideally within 1–7 days before birth. When administered in cases of severe FGR with late Doppler changes, an inpatient setting is advised where the fetus can be closely monitored. Finally, it is important to recognize that the "improvement" in umbilical artery Doppler that is often seen following administration of antenatal corticosteroids is transient, and is thought to be the result of vasodilation of the fetoplacental arterial tree and increased fetal cardiac output rather than a true decrease in placental resistance. Therefore, these transient changes should not be interpreted as an improvement in fetal status and should not affect the management plan. Of note, the absence of any change in end-diastolic flow in response to antenatal corticosteroids is a concern and predicts subsequent fetal deterioration.

Magnesium sulfate for neuroprotection

Administration of magnesium sulfate to women at risk of preterm birth has been shown to have a neuroprotective role, with a decrease in the risk of perinatal mortality, cerebral palsy, and gross motor dysfunction. Possible mechanisms thought to be involved in the beneficial effects of magnesium sulfate include reducing intracellular calcium levels, stabilizing blood pressure, normalizing cerebral blood flow, blocking the effects

of excitatory neurotransmitters such as glutamate, and antioxidant and anti-inflammatory effects. However, the optimal protocol for the administration of magnesium sulfate for the purpose of neuroprotection remains unclear and available protocols vary with regard to the timing of administration, upper gestational age limit, dose, duration, and need for repeat doses.

The observation that term FGR infants have higher cord blood magnesium levels compared with normally grown infants raises the theoretical concern that maternal administration of magnesium sulfate in cases of FGR might result in toxic magnesium levels in the fetus. However, there is currently no data on the efficacy and safety of magnesium sulfate in FGR fetuses that can support or refute these theoretical concerns. Therefore, there is currently no evidence in favor or against recommending administration of magnesium sulfate for neuroprotection in women at risk of preterm birth with suspected FGR. We believe that, at the current time, it is reasonable to extrapolate the efficacy of magnesium sulfate to specific subgroups of pregnancies, including those complicated by FGR, especially given that FGR is an independent risk factor for cerebral palsy.

Recommendations

FIGO recommends the following for the management of fetal growth restriction (FGR)

Recommendation	Quality of evidence	Strength of recommendation
1. Fetal movement counting is a simple and inexpensive tool that may decrease the risk of stillbirth in pregnancies with FGR in both high and low-resource settings.	⊕⊕○○	Strong
2. Surveillance in pregnancies with FGR should follow a uniform protocol that is based on a combination of biophysical (cardiotocogram/nonstress test [CTG/NST], computerized fetal heart rate monitoring [cCTG], biophysical profile) and cardiovascular (umbilical artery and middle cerebral artery, with or without ductus venosus Doppler) parameters along with predetermined thresholds	⊕⊕⊕○	Strong

Continuation of Table

Recommendation	Quality of evidence	Strength of recommendation
for delivery. In low-resource settings, the combination of CTG/NST and umbilical artery Doppler provides sufficient accuracy for the detection of fetal deterioration.		
3. In late-onset FGR, middle cerebral artery Doppler and the cerebroplacental ratio can provide additional information on fetal deterioration and should be included as part of the Doppler assessment. In cases when middle cerebral artery Doppler is unavailable, twice weekly CTG/NST monitoring in cases of late FHD with normal umbilical artery Doppler provides the same safety as middle cerebral artery Doppler.	⊕⊕○○	Strong
4. Absolute indications for delivery irrespective of gestational age include biophysical profile or CTG/NST abnormalities (reduced variability and/or repetitive late decelerations), or severe pre-eclampsia with uncontrolled hypertension, HELLP syndrome, or other types of end organ damage.	⊕⊕⊕⊕	Strong
5. In cases of isolated mild SGA (estimated fetal weight at 3rd–9th percentile) with no additional abnormalities (i.e. normal fluid and Doppler studies), delivery may be deferred until 37–39 weeks. Until then, monitoring should include umbilical artery and middle cerebral artery Doppler at an interval of 1–2 weeks. For mild SGA at term (>37 weeks), monitoring with CTG/NST and/or biophysical profile 1–2 times per week may be considered in addition to Doppler studies.	⊕⊕⊕○	Strong
6. In cases of isolated severe SGA (estimated fetal weight <3rd percentile) with no additional abnormalities, delivery may be deferred until 36–38 weeks. Until then, monitoring should include umbilical artery and middle cerebral artery Doppler 1–2 times per week. For severe SGA at term	⊕⊕⊕○	Strong

Continuation of Table

Recommendation	Quality of evidence	Strength of recommendation
(>37 weeks) monitoring with CTG/NST and/or biophysical profile 1–2 times per week may be considered in addition to Doppler studies.		
7. In cases of FGR with early Doppler changes or mild associated abnormalities (oligohydramnios, suboptimal interval growth, pre-eclampsia), delivery may be deferred until 34–37 weeks. Until then, monitoring should include CTG/NST and/or biophysical profile twice per week and Doppler 1–2 times per week.	⊕⊕○○	Strong
8. In cases of FGR with umbilical artery absent end-diastolic velocity (AEDV), delivery may be deferred until 32 weeks. Until then, inpatient monitoring is recommended with CTG/NST and/or biophysical profile 1–2 times per day and Doppler 3 times per week.	⊕⊕○○	Strong
9. In cases of FGR with umbilical artery reversed end-diastolic velocity (REDV), delivery may be deferred until 30 weeks. Until then, inpatient monitoring is recommended with CTG/NST and/or biophysical profile twice per day and daily Doppler.	⊕⊕○○	Strong
10. In cases of FGR with abnormal ductus venosus Doppler, delivery may be recommended as early as 26–30 weeks. Timing should be individualized based on local neonatal outcomes. Intensive inpatient monitoring is recommended with CTG/NST and/or biophysical profile twice per day and daily Doppler. Before 26 weeks, careful and shared decision making with the parents and neonatology team is recommended.	⊕⊕○○	Weak
11. FGR alone is not an indication for cesarean section. Primary cesarean section may be considered in cases of early-onset FGR with late umbilical artery (AEDV/REDV) or ductus venosus Doppler changes,	⊕⊕○○	Strong

End of Table

Recommendation	Quality of evidence	Strength of recommendation
abnormal CTG/NST or biophysical profile, maternal indications such as severe pre-eclampsia, or contraindications for vaginal birth. In the absence of these conditions, induction of labor should be preferred.		
12. Delivery of FGR fetuses should ideally take place at centers with the appropriate level of neonatal care for the gestational age and with the ability to perform urgent cesarean section if needed. During labor, continuous fetal heart rate monitoring is recommended.	⊕⊕⊕⊕	Strong
13. The placenta should be sent for histopathological examination where available as it may provide useful information for counselling regarding future pregnancies.	⊕⊕○○	Strong
14. The administration of antenatal corticosteroids in FGR pregnancies should follow the same protocol used in pregnancies not affected by FGR. Close fetal monitoring should be considered when antenatal corticosteroids are administered in fetuses with severe FGR with late Doppler changes.	⊕⊕⊕○	Strong
15. The administration of magnesium sulfate for neuroprotection in preterm FGR pregnancies should follow the same protocol used in pregnancies not affected by FGR.	⊕⊕○○	Strong
16. There are currently no proven treatments for FGR.	⊕⊕⊕○	Strong

Source: Europe PMC. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

POSTPARTUM ASSESSMENT AND COUNSELING FOR FUTURE PREGNANCIES

Infant follow-up

Growth-restricted infants are at increased risk of both immediate and long-term complications, and therefore require closer follow-up than normally grown infants in the first years of life.

Growth-restricted infants have lower survival rates compared with those appropriate for gestational age. Although this may be attributed in part to prematurity that is often associated with FGR, birth weight has been shown to be an independent prognostic factor for neonatal mortality, irrespective of gestational age.

FGR can affect postnatal growth. In cases of mild FGR, infants tend to achieve normal height during the first year of life. In cases affected by severe FGR, however, height in the late teens is lower than those born appropriate for gestational age.

FGR infants are also at increased risk of adverse long-term neurodevelopmental outcomes. A systematic review of this topic found that FGR infants are at higher risk of poor neurodevelopmental outcomes measured up to 3 years of age; however, high levels of heterogeneity in primary outcomes were reported in the studies included in the review. Of note, adverse neurodevelopmental outcomes may at least partly be related to coexisting increased prematurity rates.

In line with the developmental origins of health and disease hypothesis, FGR has been associated, in both animal and human studies, with an increased risk of future noncommunicable diseases including obesity, diabetes, hypertension, and cardiovascular disease. The risk is especially high in those infants who experience rapid catch-up growth in the first few years of life. The mechanisms underlying these associations are not entirely clear. However, fetal programming by means of epigenetic changes as well as direct organ damage are thought to play a role. Ongoing studies are investigating the optimal follow-up and prevention strategies to decrease the risk of these complications.

Maternal follow-up

It is well established that women with a history of pregnancy complicated by FGR or other placenta-mediated complications such

as pre-eclampsia are at an increased risk of future cardiovascular disease, especially in the presence of early-onset disease. Moreover, a combination of FGR, pre-eclampsia, and preterm delivery amplified the risk of disease seven-fold. For a detailed review of the evidence supporting these associations, their underlying mechanisms, and recommendations on maternal follow-up and prevention strategies please refer to the recently published FIGO post pregnancy initiative on long-term maternal implications of pregnancy complications and follow-up considerations.

Counseling regarding future pregnancies

The most frequent and relevant question that care providers are being asked by couples whose prior pregnancy was complicated by FGR relates to the likelihood of a similar complication in subsequent pregnancies. The answer to this question is often difficult and depends on several factors, namely the underlying etiology, severity and timing of onset, and the presence or absence of modifiable risk factors (e.g. maternal medical conditions or smoking). In cases of placenta-mediated FGR, the results of the placental histopathological examination may provide valuable information that can assist care providers in counseling patients regarding the risk of recurrence, role of further investigation, and potential preventive interventions in subsequent pregnancies.

Risk of recurrence based on severity and onset

Most of the data on the risk of recurrence of placenta-mediated complications come from studies evaluating hypertensive complications of pregnancy. Thus, couples with FGR in the first pregnancy can be reassured that the overall chance of recurrence in subsequent pregnancies is less than 25%. Therefore, counselling regarding the risk of recurrence should be further refined based on the risk factors of the individual patient, severity of FGR as reflected by timing of onset and Doppler findings, the co-presence of pre-eclampsia, and placental histopathological findings.

Risk of recurrence based on placental histopathology

The results of the placental histopathological examination are important for two main reasons. First, they may assist care providers in counseling couples regarding the most likely etiology

of FGR, especially when the clinical presentation and Doppler findings were inconclusive. Second, placental findings may provide valuable information regarding the risk of recurrence, as certain types of placental pathologies are associated with a relatively high recurrence rate. The main types of placental pathologies, the clinical phenotypes associated with these pathologies, and their estimated risks of recurrence are summarized in Table 5.3 (p. 233–234).

Role of thrombophilia screening

Whether women who experienced placenta-mediated pregnancy complications should be screened for antiphospholipid syndrome is a matter of debate. Although the consensus criteria for antiphospholipid syndrome include premature birth before 34 weeks for severe pre-eclampsia or features consistent with placental insufficiency including birth weight below the 10th percentile, the association of antiphospholipid (aPL) antibodies with these conditions is relatively weak and conflicting, especially for FGR. In addition, although some care providers recommend treatment with LMWH during pregnancy to women with aPL syndrome and previous preterm birth for placenta-mediated complications, this practice is mostly extrapolated from women with aPL syndrome and recurrent pregnancy loss, where there is some evidence in favor of LMWH. However, the only trial on LMWH in women with aPL syndrome and prior placenta-related complications (FRUIT trial) found no evidence that LMWH improves outcomes in these cases. Given the above, there is insufficient evidence to justify routine screening for aPL antibodies in women with prior FGR. However, screening for aPL antibodies is recommended in women with a history of thromboembolism or recurrent pregnancy loss (or ≥1 late fetal loss), and may be considered in selected cases of women with a history of severe FGR associated with severe early-onset pre-eclampsia, when placental examination shows features of severe maternal vascular malperfusion, especially central or multiple areas of villous infarction that are due to multiple spiral artery thromboses.

Management of women already diagnosed with antiphospholipid syndrome based on a history of placenta-mediated complications

Table 5.3

Phenotypes and risk of recurrence associated with specific types of placental pathologies

Placental pathology	Incidence	Common placental findings	Pathophysiology	Phenotype	Risk of recurrence	Recommendations for investigation and prevention in next pregnancy
Maternal vascular malperfusion (MVM)	Common	Decidual arteriopathy, agglutinated villi, increased syncytial knots, intervillous fibrin deposition, villous infarcts	Placental malperfusion due to shallow trophoblast invasion and failure of remodeling of spiral arteries	Early or late-onset FGR, pre-eclampsia, placental abruption	10–25%	Screening for antiphospholipid antibodies may be considered in selected cases of severe early-onset FGR, when placental examination shows features of severe MVM such as especially central or multiple areas of villous infarction Consider aspirin in subsequent pregnancy, especially if associated with pre-eclampsia
Fetal vascular malperfusion (FVM)	Relatively common	Avascular villi, chorionic plate or stem villous thrombi, obstructive lesions of umbilical cord	Most common cause: chronic / intermittent cord obstruction due to cord compression, entanglement, or hypercoiling. Possible association with hereditary thrombophilia	FGR, fetal CNS injury, stillbirth	Low	Consider screening of the infant or the mother for hereditary thrombophilia

End of Table 5.3

Placental pathology	Incidence	Common placental findings	Pathophysiology	Phenotype	Risk of recurrence	Recommendations for investigation and prevention in next pregnancy
Chronic inflammation						
Villitis of unknown etiology (VUE)	Relatively common (5–10% of term placentas)	Rare	Chronic T-cell mediated inflammation of villous stroma	Late-onset FGR, abnormal neurodevelopmental outcome, stillbirth	10–50%	
Chronic histiocytic intervillositis	Rare		Maternal histiocytic infiltrate in the intervillous space	Recurrent miscarriages, recurrent severe early-onset FGR, stillbirth	70–100%	Suggested interventions include prednisone, hydroxychloroquine, aspirin, low-molecular-weight heparin Associated with increased levels of serum alpha-fetoprotein and alkaline phosphatase
Massive perivillous fibrinoid deposition (maternal floor infarction)	Rare	Large amounts of fibrinoid matrix surrounding villi	Unclear	Recurrent miscarriages, recurrent severe early-onset FGR, stillbirth	40–60%	Consider screening for antiphospholipid antibodies, hereditary thrombophilia Anecdotal reports of treatment with aspirin, heparin, and IVIG

is also under debate. Based on the evidence from the FRUIT trial described above, some only recommend treatment with aspirin in this setting, while others recommend either surveillance or LMWH during the antepartum and postpartum periods. Based on available evidence we only recommend treatment with aspirin, and suggest that LMWH be considered only in selected cases, such as for women who have experienced recurrent complications despite aspirin treatment (aspirin failure).

The findings are clearer for inherited thrombophilias. Most prospective studies found no significant association between inherited thrombophilia and placenta-mediated complications. Furthermore, the TIPPS and FRUIT trials found no benefit of LMWH in women with thrombophilia and a history of placenta-mediated pregnancy complications. These findings were confirmed by a recent individual patient data meta-analysis that found no benefit of LMWH in decreasing the risk of recurrence of placenta-mediated complications, including in women with thrombophilia. Therefore, there is no indication for routine screening for inherited thrombophilia in women with prior FGR.

Preconception counseling and management of future pregnancies

Given the considerable risk of recurrence of FGR, efforts should be made to decrease this risk in future pregnancies. Modifiable risk factors for FGR such as smoking or poor nutritional status should be identified as early as possible and managed accordingly, as discussed earlier.

There is some evidence that administration of aspirin can reduce the risk of FGR. However, most available data focused on the prevention of pre-eclampsia as the primary outcome in women at high risk of pre-eclampsia, with the prevention of FGR being considered a secondary outcome. Data on the prevention of recurrence of FGR in women with a history of FGR are limited. Therefore, some recommend that aspirin should be considered in women with past FGR only if they have risk factors for pre-eclampsia at the time of the next pregnancy. However, given the safety of aspirin and the overlap in pathogenesis of pre-eclampsia and

FGR, it is reasonable to recommend aspirin to women with a history of placenta-mediated FGR in the previous pregnancy, using the same regimen of aspirin used for the prevention of pre-eclampsia. This recommendation is shared by most professional societies.

Data on the role of LMWH to prevent recurrence of placenta-mediated complications including FGR are conflicting. Based on available data, LMWH therapy should not be used in women with a past history of FGR except in a research setting.

Given the association of insufficient gestational weight gain with FGR, it is recommended monitoring of weight gain and informing women about their target weight gain range. Other interventions, such as bed rest or nutritional supplements are of unproven benefit and should not be routinely offered. The risk of recurrence can be further stratified in early pregnancy by means of prenatal screening with biochemical markers (PAPP-A, beta hCG, alpha-fetoprotein, and PlGF) as well as by uterine artery Doppler. Due to the increased risk of recurrence, pregnant women with a history of FGR in a previous pregnancy should be managed in a high-risk pregnancy clinic and should receive closer antenatal surveillance, including close monitoring of fetal growth and maternal blood pressure.

Recommendations

FIGO recommends the following for postpartum assessment and counseling for future pregnancies in women with a history of fetal growth restriction (FGR)

Recommendation	Quality of evidence	Strength of recommendation
1. Growth-restricted infants are at an increased risk of short- and long-term morbidity and should be followed postnatally more closely than normally grown infants.	⊕⊕○○	Strong
2. Women with a history of placenta-mediated pregnancy complications including FGR are at an increased risk of future cardiovascular morbidity and should be advised regarding preventive strategies as reviewed in detail in the FIGO	⊕⊕⊕○	Strong

End of Table

Recommendation	Quality of evidence	Strength of recommendation
postpregnancy initiative on long-term maternal implications of pregnancy complications and follow-up considerations.		
3. Women with a history of FGR should be counseled regarding the risk of recurrence based on timing of onset, severity of FGR, and placental histopathological findings.	⊕⊕○○	Strong
4. Women with a history of FGR should *not* be routinely screened for antiphospholipid antibodies in the absence of a history of thromboembolism or pregnancy loss.	⊕⊕⊕○	Strong
5. There is no role for screening for hereditary thrombophilias in women with a history of FGR.	⊕⊕⊕○	Strong
6. The following preventive interventions are recommended in women with a history of placenta-mediated FGR and those at risk of pre-eclampsia: smoking cessation, aspirin at a dose of 100–150 mg taken in the evening starting at 12–16 weeks.	⊕⊕○○	Strong
7. Low-molecular-weight heparin is not recommended for the prevention of FGR in women with a history of placenta-mediated FGR.	⊕⊕⊕○	Strong
8. In women with antiphospholipid syndrome and a history of placenta-mediated FGR, low-molecular— weight heparin may be considered in selected cases, such as in women who have experienced recurrent complications despite aspirin treatment (aspirin failure).	⊕⊕○○	Weak
9. Women with a history of FGR should undergo close surveillance of fetal growth starting at 24–28 weeks.	⊕⊕⊕○	Strong

Source: Europe PMC. FIGO initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction

FGR is an important cause of stillbirth, neonatal mortality, and short- and long-term neonatal morbidity. Early prediction and preventive strategies, timely diagnosis, and management using a standardized protocol to determine the proper monitoring and timing of delivery can decrease the risk of stillbirth and improve perinatal outcomes in pregnancies complicated by FGR.

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3. https://www.acog.org/
4. https://www.uptodate.com
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7. https://pubmed.ncbi.nlm.nih.gov/
8. https://www.thelancet.com/
9. https://www.rcog.org.uk/
10. https://www.npwh.org/
11. https://www.nice.org.uk/guidance
12. https://www.figo.org/
13. https://www.isuog.org/

У навчальному посібнику на сучасному науковому рівні наведено основні лекції з фізіологічного та патологічного акушерства. Головну увагу приділено проблемам вагітності та передчасних пологів, гестозу, кровотечам в акушерстві, дистресу плода. У підготовці матеріалу використовували клінічні рекомендації європейських і американських спільнот.

Навчальний посібник відповідає робочим програмам з акушерства і може бути рекомендований як додаткове джерело для підготовки здобувачів вищої освіти 5-го та 6-го курсів.

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