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OBSTETRICAL PATHOLOGY: SELECTED ISSUES

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МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
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КАФЕДРА ИНОСТРАННЫХ ЯЗЫКОВ

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ПАТОЛОГИЯ В АКУШЕРСТВЕ: ИЗБРАННЫЕ ВОПРОСЫ

OBSTETRICAL PATHOLOGY: SELECTED ISSUES

Учебно-методическое пособие

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Посвящено некоторым вопросам патологического акушерства. Представлены современные данные о гипертензивных расстройствах, сахарном диабете при беременности, невынашивании и перенашивании беременности. Описана тактика ведения беременных и методы родоразрешения при этих формах патологии.

Предназначено для студентов 4–6-го курсов медицинского факультета иностранных учащихся, обучающихся на английском языке.

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HYPERTENSIVE DISORDERS IN PREGNANCY

GENERAL ISSUES

Hypertensive disorders complicating pregnancy are common and form one of the deadly triad, along with hemorrhage and infection, which contribute greatly to maternal morbidity and mortality.

TERMINOLOGY AND CLASSIFICATION

The term gestational hypertension is used to describe any form of new-onset pregnancy-related hypertension. The term emphasizes the cause-and-effect connection between pregnancy and its unique form of hypertension, preeclampsia and eclampsia.

There are five types of hypertensive disease:

1. Gestational hypertension (formerly pregnancy-induced hypertension that included transient hypertension).
2. Preeclampsia.
3. Eclampsia.
4. Preeclampsia superimposed on chronic hypertension.
5. Chronic hypertension.

An important consideration in this classification is differentiating hypertensive disorders that precede pregnancy from preeclampsia and eclampsia, which are potentially more dangerous.

DIAGNOSIS

Hypertension is diagnosed when the resting blood pressure is 140/90 mm Hg or greater. It was recommended that an incremental increase of 30 mm Hg systolic or 15 mm Hg diastolic pressure be used as diagnostic criteria, even when absolute values were below 140/90 mm Hg. These criteria are no longer recommended but women who have a rise of 30 mm Hg systolic or 15 mm Hg diastolic warrant close observation. **Edema has been excluded as a diagnostic criterion because it occurs in too many normal pregnant women to be a characteristic feature**.

GESTATIONAL HYPERTENSION

The diagnosis of gestational hypertension is made in women whose blood pressure reaches 140/90 mm Hg or greater for the first time during pregnancy but in whom proteinuria is not identified (Table 1).

Table 1

Differential Diagnosis of Gestational Hypertension from Mild Preeclampsia

Gestational hypertension	Gestation > 20 weeks
	Sustained hypertension > 140/90
	No proteinuria
Mild preeclampsia	Gestation > 20 weeks
	Sustained hypertension > 140/90
	Proteinuria ≥ 300 mg/24-hr

Gestational hypertension is also called transient hypertension if preeclampsia does not develop and the blood pressure has returned to normal by 12 weeks' postpartum. The final diagnosis that the woman does not have gestational hypertension is not made until several weeks after delivery. Thus, gestational hypertension is a diagnosis of exclusion. Some women with gestational hypertension may later develop other findings of preeclampsia, for example, symptoms such as headaches or epigastric pain, proteinuria, or thrombocytopenia, all of which influence management.

When blood pressure rises appreciably during the latter half of pregnancy, it is dangerous, especially to the fetus, because proteinuria has not yet developed. 10 % of eclamptic seizures develop before proteinuria is identified. Proteinuria is a sign of worsening hypertensive disease, specifically preeclampsia.

PREECLAMPSIA

This condition is described as a pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation. Proteinuria is an important sign of preeclampsia, and rightfully concluded that the diagnosis is questionable in its absence.

The minimum criteria for the diagnosis of preeclampsia are hypertension and minimal proteinuria (Fig. 1).

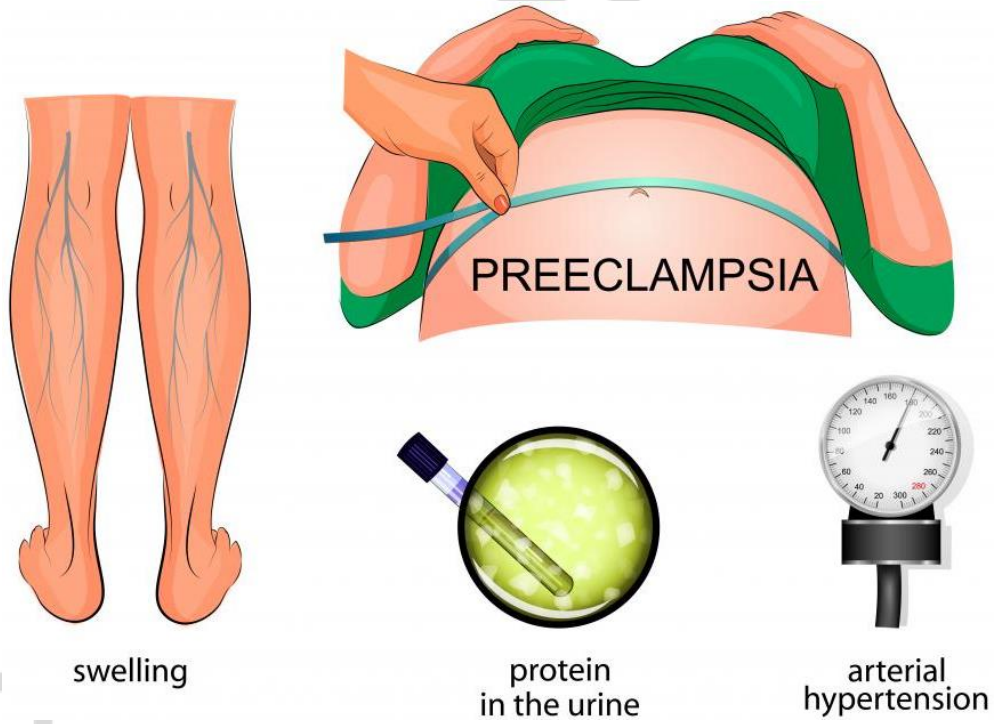

Figure 1. Signs of preeclampsia (https://www.proaist.ru)

Risk factors for preeclampsia are demonstrated in Table 2.

Table 2

Risk Factors for Preeclampsia

Demographic	Nullipara
	Age extremes (< 20 years, > 34 years)
Obstetric	Multiple gestation
	Molar pregnancy
	Non-immune hydrops
Medical	Diabetes mellitus
	Chronic hypertension
	Renal disease
	Systemic lupus erythematosus

Mild pre-eclampsia is diagnosed when a pregnant woman develops:

1. Blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on two separate readings taken at least four to six hours apart after 20 weeks' gestation in an individual with previously normal blood pressure.

2. Proteinuria ≥ 0.3 grams (300 mg) or more of protein in a 24-hour urine sample or urinary protein to creatinine ratio ≥ 0.3 or a urine dipstick reading of 1+ or greater (dipstick reading should only be used if other quantitative methods are not available).

It is recommended to obtain renal biopsy specimens from hypertensive pregnant women. They will reveal evident glomerular lesions characteristic of preeclampsia. Proteinuria and alterations of glomerular histology develop late in the course. It is apparent that preeclampsia becomes evident clinically only near the end of an unrecognized pathophysiological process that may begin as early as implantation. Key points are shown in Table 3.

Table 3

Mild Preeclampsia: Summary Table

Pathophysiology	Diffuse vasospasm
	Capillary injury
	No headache, no epigastric pain, no visual changes
	No specific findings on examination
Laboratory findings	Proteinuria (1–2+ dipsticks)
	Hemoconcentration
Management	< 36 weeks Conservative in-patient treatment
	≥ 36 weeks $MgSO_4$ (Fig. 2) and delivery *Continue 24 hrs postpartum*

Case 1: *A 22 yr-old patient (the 1st pregnancy) is seen in the out-patient clinic for routine visit at 32 weeks confirmed by 1st trimester sonography. She complains of* ***swelling in her hands*** *and feet, but denies headaches, epigastric pains or visual changes. She has gained about* ***4.5 kg over 2 weeks*** *(normal weight gain — 200–220 gr/week). Blood pressure is* ***155/95*** *mm Hg, and remains so on repeat blood pressure in 15 min. She has 3+ pedal edema and her fingers appear swollen. A spot urine dipstick shows* ***2+ protein****.*

Figure 2. $MgSO_4$ medication

There is no term "moderate preeclampsia"; it progresses from *mild* to *severe*. Mild preeclampsia requires a conservative management, severe can be managed aggressively.

Case 2: *A 22 yr-old patient (32-week 1st pregnancy confirmed by 1st trimester sonography). For 24 hrs she has had severe,* ***occipital headaches****, mid-****epigastric pain*** *not relieved by acetaminophen. She sees* ***light flashes*** *and* ***spots****. She has gained about 4.5 kg in 2 weeks (normal weight gain — 200–220 gr/week). Blood pressure is* ***165/115*** *mmHg. She has 3+pedal edema and her* ***fingers are swollen.*** *Fundal height is* ***29 cm****. Fetal heart tones are regular at 145 per minute. Urine dipstick shows* ***4+ protein****.*

A systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 110 and/or proteinuria > 5g in a 24-hour period is also indicative of **severe** pre-eclampsia. Risk factors for severe preeclampsia are the same as in mild preeclampsia (see Table 2). Diabetes mellitus over 10 years is particularly responsible for severe preeclampsia. Similarly, abnormal laboratory findings in tests of renal, hepatic, and hematological function increase the certainty of preeclampsia. Persistent premonitory symptoms of eclampsia, such as headache and epigastric pain, also increase the certainty.

Epigastric or right upper quadrant pain is thought to result from hepatocellular necrosis, ischemia, and edema that stretches the Glisson capsule. This characteristic pain is frequently accompanied by elevated serum hepatic transaminase levels and usually is a sign to induce delivery.

Thrombocytopenia is characteristic of progressing preeclampsia, and it probably is caused by platelet activation and aggregation as well as microangiopathic hemolysis induced by severe vasospasm. Evidence of gross hemolysis such as hemoglobinemia, hemoglobinuria, or hyperbilirubinemia is indicative of severe disease. Other factors indicative of severe hypertension include cardiac dysfunction with pulmonary edema as well as obvious fetal growth restriction.

Although hypertension is a requisite to diagnosing preeclampsia, absolute blood pressure alone is not always a dependable indicator of its severity. A rapid increase in blood pressure followed by convulsions is usually preceded by a severe headache or visual disturbances. For this reason, these symptoms are life-threatening.

Key points of severe preeclampsia are shown in Table 4.

Table 4

Severe Preeclampsia: Summary Table

Blood pressure	≥ 160/110 mm Hg
Proteinuria	≥ 5 grams
Symptoms	headaches epigastric pains visual changes
Signs	pulmonary edema oliguria cyanosis
Laboratory findings	DIC (dissemination intravascular coagulation) syndrome ↑ liver enzymes
Aggressive management	Intravenous (IV) $MgSO_4$ to prevent convulsions *Continue 24 hrs postpartum*
	To lower blood pressure — diastolic 90–100 mm Hg Use *Hydralazine* or *Labetalol*
	Induce labor: stable mother and fetus — intravenous *oxytocin* and *amniotomy* unstable mother and fetus — Cesarean delivery
Conservative management (there are very few patients that can be managed so)	26 – 34 weeks gestation If blood pressure is brought to < *160/110* mm Hg
	Intensive monitoring if the mother and fetus are in the *ICU* (intensive care unit)
	Continuous intravenous $MgSO_4$ *Betamethasone* for fetus lung maturation

PREECLAMPSIA SUPERIMPOSED ON CHRONIC HYPERTENSION

All chronic hypertensive disorders, regardless of their cause, predispose to development of superimposed preeclampsia and eclampsia. These disorders can create difficult problems with diagnosis and management in women who are not seen until after midpregnancy. The diagnosis of chronic underlying hypertension is made when:

1. Hypertension (140/90 mm Hg or greater) is documented before pregnancy.
2. Hypertension (140/90 mm Hg or greater) is detected before 20 weeks, unless there is gestational trophoblastic disease.
3. Hypertension persists long after delivery.

Essential or familial hypertension is the cause of underlying vascular disease in more than 90 % of pregnant women. Obesity and diabetes are other common causes. In some women, hypertension develops as a consequence of underlying renal parenchymal disease.

Case 3: *A 35 yr-old multigravida is seen in the out-patient clinic for her 1st prenatal visit. She is* ***12 weeks*** *pregnant with a blood pressure of* ***155/95*** *mm Hg.* ***Chronic hypertension*** *was diagnosed 5 years ago for which she has been treated with oral nifedipine. A urine dipstick* ***protein is 2+****. A recent 24-hour urine showed* ***1.2 g of protein****. Serum creatinine is 1.2 mg/dL. She doesn't have headaches or visual changes.*

Chronic hypertension can lead to ventricular hypertrophy and cardiac decompensation, cerebrovascular accidents, or renal damage. These complications are more likely during pregnancy if there is superimposed preeclampsia. The risk of placental abruption is also increased if there is superimposed preeclampsia. The fetuses of women with chronic hypertension are at risks for growth restriction, preterm delivery, and death.

In some women with chronic hypertension, blood pressure increases to abnormal levels, typically after 24 weeks. If accompanied by proteinuria, then superimposed preeclampsia is diagnosed. Superimposed preeclampsia develops earlier in pregnancy than "pure" preeclampsia, and it tends to be more severe and often accompanied by fetal growth restriction.

INCIDENCE AND RISK FACTORS

Gestational hypertension more often affects nulliparous women. Because of the increasing incidence of chronic hypertension with advancing age, older women are at greater risk for superimposed preeclampsia. The incidence is markedly influenced by parity; it is related to race and ethnicity and thus to genetic predisposition, and environmental factors likely also play a role.

Other risk factors associated with preeclampsia include chronic hypertension, multifetal gestation, mother's age over 35 years, obesity. The relationship between maternal weight and the risk of preeclampsia is progressive. It increases for women with a body mass index greater than 35 kg/m^2. Placenta previa also reduces the risk of hypertensive disorders in pregnancy.

ETIOLOGY

Hypertensive disorders due to pregnancy develop in women who:

1) are exposed to chorionic villi for the first time;
2) are exposed to a superabundance of chorionic villi, as with twins or hydatidiform mole;
3) have preexisting vascular disease;
4) are genetically predisposed to hypertension developing during pregnancy.

Although chorionic villi are essential, they need not be located within the uterus. The cascade of events that leads to the preeclampsia syndrome is characterized by abnormalities that result in vascular endothelial damage with vasospasm, transudation of plasma, and ischemic and thrombotic consequences.

Potential causes include the following:

1. abnormal trophoblastic invasion of uterine vessels;
2. immunological intolerance between maternal and fetoplacental tissues;
3. insufficient maternal adaptation to cardiovascular or inflammatory changes of normal pregnancy;
4. dietary deficiencies;
5. genetic influences.

Abnormal trophoblastic invasion. In normal implantation, the uterine spiral arteries undergo extensive remodeling as they are invaded by endovascular trophoblasts. In preeclampsia, there is incomplete trophoblastic invasion. In this case, decidual vessels, but not myometrial vessels, become lined with endovascular trophoblasts. The magnitude of defective trophoblastic invasion of the spiral arteries correlates with the severity of the hypertensive disorder. Early preeclamptic changes include endothelial damage, insudation of plasma constituents into vessel walls, proliferation of myointimal cells, and medial necrosis. Lipid accumulates first in myointimal cells and then in macrophages. Such lipid-laden cells and associated findings have been termed atherosis. The vessels affected by atherosis develop aneurysmal dilatation and are frequently found in association with spiral arterioles that have failed to undergo normal adaptation. Obstruction of the spiral arteriolar lumen by atherosis may impair placental blood flow. These changes cause placental perfusion to be pathologically diminished, which eventually leads to the preeclampsia syndrome.

Immunological factors. There is circumstantial evidence to support the theory that preeclampsia is immune mediated. The risk of preeclampsia is enhanced in circumstances where formation of blocking antibodies to placental antigenic sites might be impaired. This may arise in situations in which effective immunization by a previous pregnancy is lacking, as in first pregnancies; or in which the number of antigenic sites provided by the placenta is unusually great compared with the amount of antibody, as with multiple fetuses. “Immunization” from a prior abortion does not occur.

Immune poor adaptation plays the role in the pathophysiology of preeclampsia. Beginning in the early second trimester, women destined to develop preeclampsia have a significantly lower proportion of helper T cells (Th1) compared with that of women who remain normotensive. This Th1/Th2 imbalance, with Th2 dominance, may be mediated by adenosine, which is found in higher serum levels in preeclamptic women compared with normotensive women. These helper T lymphocytes secrete specific cytokines that promote implantation, and their dysfunction may favor preeclampsia.

Vasculopathy and the inflammatory changes. In response to placental factors released by ischemic changes, or any other inciting cause, a cascade of events is set in motion. The decidua also contains an abundance of cells that, when activated, can release toxic agents. These then serve as mediators to provoke endothelial cell injury.

The endothelial cell dysfunction associated with preeclampsia can result from a "generalized perturbation of the normal, generalized maternal intravascular inflammatory adaptation to pregnancy". In this hypothesis, preeclampsia is a disease due to an extreme state of activated leukocytes in the maternal circulation. Cytokines such as tumor necrosis factor (TNF) and the interleukins may contribute to the oxidative stress associated with preeclampsia. Oxidative stress is characterized by reactive oxygen species and free radicals that lead to formation of self-propagating lipid peroxides. These in turn generate highly toxic radicals that injure endothelial cells, modify their nitric oxide production, and interfere with prostaglandin balance. Other consequences of oxidative stress include production of the lipid-laden macrophage foam cells seen in atherosis; activation of microvascular coagulation, seen in thrombocytopenia; and increased capillary permeability, seen in edema and proteinuria. These observations on the effects of oxidative stress in preeclampsia have given rise to increased interest in the potential benefit of antioxidants to prevent preeclampsia.

Nutritional factors. Blood pressure in nonpregnant individuals is affected by a number of dietary influences, including minerals and vitamins. Some studies have shown a relationship between dietary deficiencies and the incidence of preeclampsia. This was followed by studies of supplementation with various elements such as zinc, calcium, and magnesium to prevent preeclampsia. A diet high in fruits and vegetables that have antioxidant activity is associated with decreased blood pressure. The incidence of preeclampsia was doubled in women whose daily intake of ascorbic acid was less than 85 mg.

Obesity is a potent risk factor for preeclampsia. There is much evidence that obesity in nonpregnant individuals causes endothelial activation and a systemic inflammatory response associated with atherosclerosis. C-reactive protein, an inflammatory marker, is increased in obesity which in turn is associated with preeclampsia.

Genetic factors. The predisposition to hereditary hypertension is linked to preeclampsia, and the tendency for preeclampsia-eclampsia is inherited. Preeclampsia-eclampsia is highly heritable in sisters, daughters, granddaughters of eclamptic women.

PATHOGENESIS

Vasospasm. The concept of vasospasm based on direct observations of small blood vessels in the nail beds, ocular fundi, and bulbar conjunctivae. Vascular constriction causes resistance and subsequent hypertension. Endothelial cell damage causes interstitial leakage through which blood constituents, including platelets and fibrinogen, are deposited subendothelially. Disruption of endothelial junctional proteins and ultrastructural changes in the subendothelial region of resistance arteries are demonstrated in preeclamptic women. With diminished blood flow because of poor distribution, ischemia of the surrounding tissues would lead to necrosis, hemorrhage, and other end-organ disturbances characteristic of the syndrome.

Endothelial cell activation. Unknown factor(s), likely from the placenta, are secreted into the maternal circulation and provoke activation and dysfunction of the vascular endothelium. The clinical syndrome of preeclampsia results from these widespread endothelial cell changes.

Intact endothelium has anticoagulant properties, and it also weakens the response of vascular smooth muscle to agonists by releasing nitric oxide. Damaged or activated endothelial cells secrete substances that promote coagulation and increase the sensitivity to vasopressors. Further evidence of endothelial activation includes the characteristic changes in glomerular capillary endothelial morphology, increased capillary permeability, and elevated blood concentrations of substances associated with such activation. These latter substances are transferrable, and serum from women with preeclampsia stimulates cultured endothelial cells to produce greater amounts of prostacyclin than serum from normal pregnant women.

Increased pressor responses. Normally, pregnant women do not develop susceptibility to infused vasopressors. Women with early preeclampsia have increased vascular reactivity to infused norepinephrine and angiotensin II. Moreover, increased sensitivity to angiotensin II clearly precedes the onset of gestational hypertension. Normotensive nulliparas remain unsusceptible to infused angiotensin II, but those who subsequently became hypertensive lost this refractoriness several weeks before the onset of hypertension. Women with underlying chronic hypertension have almost identical responses.

– Prostaglandins. A number of prostanoids are central to the pathophysiology of the preeclampsia syndrome. Specifically, the weakened pressor response seen in normal pregnancy is at least partially due to decreased vascular responsiveness mediated by vascular endothelial prostaglandin synthesis. When compared with normal pregnancy, endothelial prostacyclin (PGI_2) production is decreased in preeclampsia. This action is mediated by phospholipase A_2. At the same time, thromboxane A_2 secretion by platelets is increased, and the prostacyclin: thromboxane A_2 ratio decreases. The net result favors increased sensitivity to infused angiotensin II, and ultimately, vasoconstriction.

– Nitric oxide. This potent vasodilator is synthesized from L-arginine by endothelial cells. It also is produced by fetal endothelium and is increased in response to preeclampsia, diabetes, and infection. Preeclampsia is associated with decreased endothelial nitric oxide synthase expression, which increases cell permeability. There is not decreased nitric oxide release or production prior to the onset of hypertension. Its production is increased in severe preeclampsia possibly as a compensatory mechanism for the increased synthesis and release of vasoconstrictors and platelet-aggregating agents. Thus, increased serum concentrations of nitric oxide in women with preeclampsia are likely the result of hypertension, not the cause.

– Endothelins. These 21-amino acid peptides are potent vasoconstrictors, and endothelin-1 (ET-1) is the primary isoform produced by human endothelium. Plasma ET-1 is increased in normotensive pregnant women, but women with

preeclampsia have even higher levels. The placenta is not the source of increased ET-1 and it likely arises from systemic endothelial activation. Treatment of preeclamptic women with magnesium sulfate lowers ET-1 concentrations.

Angiogenic factors. Several glycosylated glycoproteins are selectively mitogenic for endothelial cells and are important in mediating the preeclampsia syndrome. Two of these are vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Their secretion increases across normal pregnancy, and they promote angiogenesis and induce nitric oxide and vasodilatory prostaglandins. Placental VEGF is important in vasculogenesis and control of microvascular permeability. Paradoxically, VEGF is increased in serum from women with preeclampsia but its bioavailability is decreased.

PATHOPHYSIOLOGY

Although the cause of preeclampsia remains unknown, it begins to manifest early in pregnancy with unrecognized pathophysiological changes that gain severity across gestation. These adverse life-threatening maternal and fetal effects develop simultaneously. They are a consequence of vasospasm, endothelial dysfunction, and ischemia.

CARDIOVASCULAR SYSTEM. Severe disturbances of normal cardiovascular function are common with preeclampsia or eclampsia. These are related to:

1) increased cardiac afterload caused by hypertension;

2) cardiac preload, which is substantively affected by pathologically diminished hypervolemia of pregnancy or is iatrogenically increased by intravenous crystalloid or oncotic solutions;

3) endothelial activation with extravasation into the extracellular space, especially the lung;

4) left ventricular mass is increased relative to normal pregnancy.

Hemodynamic changes. The cardiovascular aberrations of hypertensive disorders of pregnancy vary depending on a number of factors. Some of these include severity of hypertension, presence of underlying chronic disease, whether preeclampsia is present. Variables that define cardiovascular status in women with hypertensive disorders range from high cardiac output with low vascular resistance to low cardiac output with high resistance.

Vasodilation then occurs, and as the blood volume increases, the hematocrit usually falls. Thus, women with eclampsia:

1) are unduly sensitive to aggresive fluid therapy administered in an attempt to expand the contracted blood volume to normal pregnancy levels;

2) are quite sensitive to even normal blood loss at delivery.

Blood and coagulation. Hematological abnormalities develop in some women with preeclampsia. Among these are thrombocytopenia, which at times may become so severe as to be life-threatening. In addition, the levels of some plasma clotting factors may be decreased, and erythrocytes may display strange shapes and undergo rapid hemolysis.

Platelets. Because thrombocytopenia can be induced acutely by preeclampsia-eclampsia, the platelet count is routinely measured in hypertensive pregnant women. The frequency and intensity of maternal thrombocytopenia varies and likely is dependent on the intensity of the disease process, duration of preeclampsia, and the frequency with which platelet counts are performed. Thrombocytopenia defined by a platelet count less than 100,000/μL, indicates severe disease. In most cases, delivery is indicated because the platelet count continues to decrease. After delivery, the platelet count increases progressively to reach a normal level within 3 to 5 days.

Thrombocytopenia results from platelet activation, aggregation, and consumption that is accompanied by increased mean platelet volume and decreased life span. Platelet production is increased, and thrombopoietin, a cytokine that promotes platelet proliferation from megakaryocytes, is increased in preeclampsia with thrombocytopenia.

HELLP syndrome. The clinical significance of thrombocytopenia, in addition to any impairment in coagulation, is that it reflects the severity of the pathological process. In general, the lower the platelet count, the higher the maternal and fetal death. Thrombocytopenia is accompanied by elevated serum liver transaminase levels in women with eclampsia. The combination of events that compose the HELLP syndrome is shown on Fig. 3 and this name now is used worldwide.

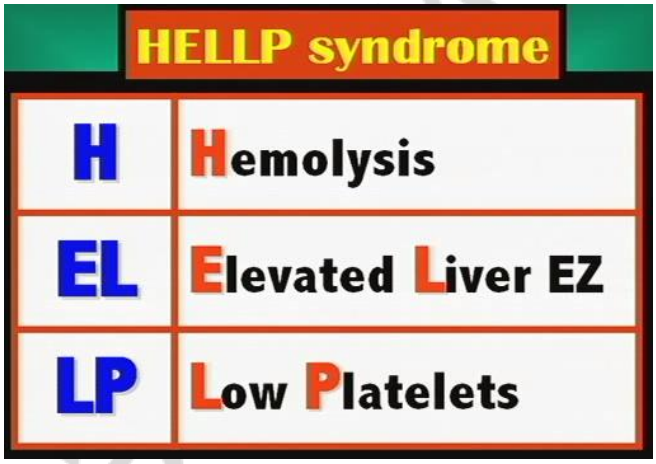

Figure 3. HELLP syndrome: abbreviation expansion

Case 4: *A 32 year-old multigravida is at 32 weeks. At a routine prenatal visit her blood pressure was* ***160/105****. Previous measurements were normal. Preeclampsia workup shows:* ***increased total bilirubin, LDH (lactate dehydrogenase), ALT, AST*** *as well as* ***platelet count of 85,000****. She has no headaches or visual changes.*

A patient can have HELLP syndrome without hypertension. HELLP syndrome gives 20 % risk of abruptio placenta. Patients are managed aggressively (Table 5).

Table 5

Management of Patients with HELLP Syndrome

Steps	Purpose
IV (intravenous) $MgSO_4$	to prevent convulsions
Induce labour	*amniotomy* and intravenous *oxytocin* — if mother and fetus are stable
Lower BP (blood pressure)	use *Hydralazine* or *Labetalol* to achieve diastolic pressure 90–100 mm Hg
Maternal steroids (dexamethasone)	to promote the normalization of mother's lab values

Coagulation. Subtle changes consistent with intravascular coagulation, and less often erythrocyte destruction, commonly are found with preeclampsia and especially eclampsia. Except for thrombocytopenia, laboratory aberrations generally are mild. Unless there is associated placental abruption, plasma fibrinogen levels do not differ remarkably from levels found in normal pregnancy, and fibrin degradation products are elevated only occasionally. Routine laboratory assessment of coagulation, including prothrombin time, activated partial thromboplastin time, and plasma fibrinogen level, is unnecessary in the management of pregnancy-associated hypertensive disorders. The thrombin time is somewhat prolonged in a third of the cases of eclampsia even when elevated levels of fibrin degradation products are not identified.

Other clotting factors. The thrombophilias are clotting factor deficiencies that lead to hypercoagulability. They may be associated with early-onset preeclampsia. Antithrombin is lower in women with preeclampsia compared with normally pregnant women and women with chronic hypertension. Fibronectin, a glycoprotein associated with vascular endothelial cell basement membrane, is elevated in women with preeclampsia. Preeclampsia causes vascular endothelial injury with subsequent hematological aberrations.

Fragmentation hemolysis. Severe preeclampsia is frequently accompanied by evidence of hemolysis indicated by elevated serum lactate dehydrogenase levels. Other evidence is from peripheral blood changes that include schizocytosis, spherocytosis, and reticulocytosis. These derangements result in part from microangiopathic hemolysis caused by endothelial disruption with platelet adherence and fibrin deposition. Increased erythrocyte membrane fluidity with HELLP syndrome predispose to hemolysis. Erythrocytic membrane changes, increased adhesiveness, and aggregation may also facilitate a hypercoagulable state.

VOLUME HOMEOSTASIS

Endocrine changes. Plasma levels of renin, angiotensin II, and aldosterone are increased during normal pregnancy. With preeclampsia, these values decrease toward the normal nonpregnant range. With sodium retention, hypertension, or both, renin secretion by the juxtaglomerular apparatus decreases. Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is then transformed into angiotensin II by angiotensin-converting enzyme (ACE). Thus, with preeclampsia, angiotensin II levels decline, resulting in a decrease in aldosterone secretion.

Deoxycorticosterone (DOC) is another potent mineralocorticoid that is increased remarkably in third-trimester plasma. This results from conversion from plasma progesterone rather than increased maternal adrenal secretion. Because of this, DOC is not reduced by sodium retention or hypertension, and it may serve to explain why women with preeclampsia retain sodium.

Vasopressin levels are normal in women with preeclampsia despite decreased plasma osmolality. During normal pregnancy, serum concentrations of atrial natriuretic peptide are maintained in the nonpregnant range despite the increased plasma volume. The peptide is released on atrial wall stretching from blood volume expansion. It is vasoactive and promotes sodium and water excretion, probably by inhibiting aldosterone, renin activity, angiotensin II, and vasopressin. Secretion of atrial natriuretic peptide is increased in women with preeclampsia. Increases in atrial natriuretic peptide following volume expansion result in comparable increases in cardiac output and decreases in peripheral vascular resistance in both normotensive and preeclamptic women.

KIDNEY. During normal pregnancy, renal blood flow and glomerular filtration rate are considerably increased. With development of preeclampsia, anumber of reversible anatomical and pathophysiological changes may occur. Renal perfusion and glomerular filtration are reduced. Plasma uric acid concentration is typically elevated, especially in women with severe disease. The elevation exceeds the reduction in glomerular filtration rate and creatinine clearance that accompanies preeclampsia. Preeclampsia is associated with diminished urinary excretion of calcium because of increased tubular reabsorption.

Mild to moderately diminished glomerular filtration may result from a reduced plasma volume resulting in plasma creatinine values up to twice those expected for normal pregnancy. In some cases of severe preeclampsia, however, severe intrarenal vasospasm is profound, and plasma creatinine may be elevated several times the nonpregnant normal value. In severe preeclampsia, oliguria develops despite normal ventricular filling pressure. In most women, urine sodium concentration is elevated. Urine osmolality, urine:plasma creatinine ratio, and fractional excretion of sodium are also indicative that a prerenal mechanism is involved. Intensive intravenous fluid therapy is not indicated for these women with oliguria.

Proteinuria. There should be some degree of proteinuria to establish the diagnosis of preeclampsia-eclampsia. Because proteinuria develops late, some women may be delivered before it appears.

Albuminuria is an incorrect term to describe proteinuria of preeclampsia. As with any other glomerulopathy, there is increased permeability to most large-molecular-weight proteins; thus, abnormal albumin excretion is accompanied by other proteins, such as hemoglobin, globulins, and transferrin. Normally, these large protein molecules are not filtered by the glomerulus, and their appearance in urine signifies a glomerulopathic process. Some of the smaller proteins that usually are filtered but reabsorbed are also detected in urine.

LIVER. The commonly found characteristic lesions are regions of periportal hemorrhage in the liver periphery. In women with eclampsia, hemolysis, and thrombocytopenia elevated serum hepatic transaminase levels are observed. These changes are also seen in women with severe preeclampsia (HELLP syndrome).

Anatomical changes with extensive lesions are seldom identified with liver biopsy in nonfatal cases. Bleeding from these lesions may cause hepatic rupture, or they may extend beneath the hepatic capsule and form a subcapsular hematoma. These hemorrhages without rupture are probably more likely in women with HELLP syndrome.

BRAIN. Headaches and visual symptoms are common with severe eclampsia, and associated convulsions define eclampsia.

Anatomical pathology. There are two distinct but related types of cerebral pathology. The first is gross hemorrhage due to ruptured arteries caused by severe hypertension. These can be seen in any woman with gestational hypertension, and preeclampsia is not necessary for their development. These complications are more common in women with underlying chronic hypertension.

The second type of cerebral lesion is variably demonstrated with preeclampsia but probably is universal with eclampsia. These are more widespread, focal, and seldom fatal. The principal postmortem lesions are edema, hyperemia, ischemias, thrombosis and hemorrhage.

Neuroimaging studies. Improved computed tomography (CT) and magnetic resonance imaging (MRI) show that nearly all women with eclampsia have abnormal brain findings. Those most commonly seen with CT are hypodense areas in the cortex and correspond to the petechial hemorrhages and infarctions. The extent and location of these ischemic and petechial lesions influence the severity of the clinical picture. For example, worrisome neurological complications, such as blindness or coma, sometimes occur. These findings primarily were areas of edema.

Cerebral blood flow. Until recently, noninvasive determination of cerebral blood flow was limited to transcranial Doppler ultrasonography. This technology measures blood flow, and cerebral perfusion pressure is calculated.

MRI techniques have now been developed that allow for accurate measurement of cerebral blood flow, and these correlate with invasive procedures.

Blindness. Although visual disturbances are common with severe preeclampsia, blindness is rare with preeclampsia alone. It follows eclamptic convulsions in up to 10 % of women. Blindness has been reported to develop up to a week or more following delivery. This condition is also called amaurosis (from the Greek dimming), and affected women have evidence of extensive occipital lobe vasogenic edema on CT and MRI. Rarely, permanent visual defects, including blindness, complicate preeclampsia-eclampsia. This can be caused either by cerebral infarction or by retinal artery ischemia and infarction.

Retinal detachment may also cause altered vision, although it is usually one-sided and seldom causes total visual loss. Occasionally it coexists with cortical edema and visual defects. Detachment is obvious by examination. Surgical treatment is seldom indicated, the prognosis generally is good, and vision usually returns to normal within a week.

Cerebral edema. Clinical manifestations suggesting more widespread cerebral edema are worrisome. Clinically, these women are very susceptible to sudden and severe blood pressure elevations, which acutely worsen the widespread vasogenic edema. Thus, careful blood pressure control is essential. The treatment is with mannitol or dexamethasone.

UTEROPLACENTAL PERFUSION. Impaired uteroplacental perfusion from vasospasm is almost certainly a major cause of increased perinatal morbidity and mortality associated with preeclampsia. Assessment of human maternal and placental blood flow is difficult to perform due to inaccessibility of the placenta, the complexity of its venous effluent, and because certain investigative techniques are unsuitable for humans.

Doppler velocimetry. Measurement of blood flow velocity through uterine arteries is used to estimate resistance to uteroplacental blood flow. Vascular resistance is estimated by comparing arterial systolic and diastolic velocity waveforms. Studies were done to assess this by measuring these ratios from uterine and umbilical arteries in preeclamptic pregnancies. The findings indicated that in some cases there was increased resistance. Thus, impaired uteroplacental circulation is present in only a few women with preeclampsia.

PREDICTION

Measurement in early pregnancy of a variety of biological, biochemical, and biophysical markers implicated in the pathophysiology of preeclampsia are used to predict its development. Investigators have attempted to identify early markers of faulty placentation, reduced placental perfusion, endothelial cell activation and dysfunction, and activation of coagulation. Currently, there are no screening tests for preeclampsia that are reliable, valid, and economical.

Roll-over test. A hypertensive response induced by having women at 28 to 32 weeks assume the supine position after lying laterally recumbent can predict gestational hypertension. Women who demonstrate a positive “roll-over” test are abnormally sensitive to infused angiotensin II.

Uric acid. Elevated serum uric acid levels due to decreased renal urate excretion are frequently found in women with preeclampsia. Plasma uric acid values exceeding at 24 weeks have a positive predictive value for preeclampsia. Because uric acid levels have not even proven useful in differentiating gestational hypertension from preeclampsia, they are not widely used.

Fibronectin. Endothelial cell activation is the cause of elevated serum cellular fibronectin levels in some women with preeclampsia.

PREVENTION

A variety of strategies used to prevent or modify the severity of preeclampsia have been evaluated. In general, none of these have been found to be clinically efficacious.

Dietary manipulation. In a number of countries salt restriction is one of dietary recommendations to prevent preeclampsia, though data of studies performed in the US has showed that a sodium-restricted diet is ineffective in preventing preeclampsia. Women with low dietary calcium are at significantly increased risk for gestational hypertension.

Low-dose aspirin. Early successes of 60-mg aspirin to reduce the incidence of preeclampsia were attributed to selective thromboxane suppression with resultant dominance of endothelial prostacyclin. Subsequent multicenter randomized trials in both low-risk and high-risk women have consistently shown that low-dose aspirin was ineffective in preventing preeclampsia.

Antioxidants. Serum of normal pregnant women contains antioxidant mechanisms that control lipid peroxidation, which has been implicated in endothelial cell dysfunction. Serum of women with preeclampsia has markedly reduced antioxidant activity. Vitamin E consumption was unrelated to preeclampsia.

MANAGEMENT

Basic management objectives for any pregnancy complicated by preeclampsia are:

1. Termination of pregnancy with the least possible trauma to mother and fetus.
2. Birth of an infant who subsequently thrives.
3. Complete restoration of mother's health.

In certain women with preeclampsia, especially those at or near term, all three objectives are served equally well by induction of labor.

Early prenatal detection. Traditionally, the frequency of prenatal visits is increased during the third trimester to facilitate early detection of preeclampsia. Women with diagnosed hypertension (140/90 mm Hg or greater) are frequently admitted to the hospital for 2 to 3 days to evaluate the severity of new-onset hypertension. Women with persistent severe disease are observed closely, and many are delivered. Conversely, women with mild disease are often managed as out-patients.

Management of women without evident hypertension, but in whom early preeclampsia is suspected during routine prenatal visits, consists primarily of increased surveillance.

Antepartum hospital management. Hospitalization is considered at least initially for women with new-onset hypertension, especially if there is persistent or worsening hypertension or development of proteinuria.

A systematic evaluation is instituted to include the following:

1. Detailed daily examination for clinical findings such as headache, visual disturbances, epigastric pain and rapid weight gain.
2. Weight on admittance and every day thereafter.
3. Analysis for proteinuria on admittance and at least every 2 days thereafter.
4. Blood pressure readings in the sitting position with an appropriate-size cuff every 4 hours, except between midnight and morning.

5. Measurements of plasma or serum creatinine, hematocrit, platelets, and serum liver enzymes, the frequency to be determined by the severity of hypertension.

6. Frequent evaluation of fetal size and amnionic fluid volume either clinically or with sonography.

If these observations lead to a diagnosis of severe preeclampsia, further management is the same as described subsequently for eclampsia.

Reduced physical activity throughout much of the day is beneficial. Absolute bed rest is not necessary, and sedatives and tranquilizers are not prescribed. Ample, but not excessive, protein and calories should be included in the diet. Sodium and fluid intakes should not be limited or forced. Further management depends on:

1. Severity of preeclampsia.
2. Duration of gestation.
3. Condition of the cervix.

Termination of pregnancy. Delivery is the cure for preeclampsia. Headache, visual disturbances, or epigastric pain indicate that convulsions may be imminent, and oliguria is another warning sign. Severe preeclampsia demands anticonvulsant and usually antihypertensive therapy followed by delivery. Treatment is identical to that described subsequently for eclampsia. The prime objectives are to prevent convulsions, intracranial hemorrhage and serious damage to other vital organs, and to deliver a healthy infant.

When the fetus is preterm, the obstetrician should do their best to prolong pregnancy to reduce the risk of neonatal death or serious morbidity. Such a policy certainly is justified in milder cases. Assessments of fetal well-being and placental function have been attempted, especially when there is hesitation to deliver the fetus because of prematurity. Frequent performance of various tests is recommended to assess fetal well-being. These include the nonstress test or the biophysical profile. Measurement of the lecithin-sphingomyelin ratio in amnionic fluid may provide evidence of lung maturity. Even when this ratio is less than 2.0 respiratory distress may not develop.

With moderate or severe preeclampsia that does not improve after hospitalization, delivery is usually advisable for the welfare of both mother and fetus. Labor should be induced by intravenous oxytocin. Many clinicians favor preinduction cervical ripening with a prostaglandin or osmotic dilator (laminaria). When labor induction almost certainly does not succeed cesarean delivery is indicated for more severe cases.

For a woman near term, with a soft, partially effaced cervix, even milder degrees of preeclampsia probably carry more risk to the mother and her fetus-infant than does induction of labor by carefully monitored oxytocin infusion. If the preeclampsia is mild but the cervix is firm and closed, labor induction with oxytocin is not indicated.

Antihypertensive drug therapy. The use of antihypertensive drugs in attempts to prolong pregnancy or modify perinatal outcomes in pregnancies complicated by various types and severities of hypertensive disorders has been of considerable

interest. Unfortunately, drug treatment for early mild preeclampsia has been disappointing. Although women given labetalol have significantly lower mean blood pressures, there are no differences in terms of mean pregnancy prolongation, gestational age at delivery, or birthweight. There are studies demonstrating that β-blocking agents (atenolol, bisoprolol, Concor), labetalol, or calcium-channel blockers (nifedipine, isradipine) show no benefits of antihypertensive treatment. These studies concluded that treatment-induced decreases in maternal blood pressure may adversely affect fetal growth. The use of angiotensin-converting enzyme (ACE) inhibitors during the second and third trimesters should be avoided. Complications include oligohydramnios, fetal growth restriction, bony malformations, limb contractures, persistent patent ductus arteriosus, pulmonary hypoplasia, respiratory distress syndrome, prolonged neonatal hypotension, and neonatal death. ACE inhibitors taken during early pregnancy do not carry an adverse outlook as long as these drugs are discontinued as soon as possible.

Glucocorticoids. In attempts to enhance fetal lung maturation, glucocorticoids (betamethasone) are administered to women with severe hypertension who are remote from term. The treatment does not worsen maternal hypertension, but produces a decrease in the incidence of respiratory distress, intraventricular hemorrhage and improved fetal survival. There are insufficient data to conclude that corticosteroids are beneficial to reduce the severity of HELLP syndrome.

Summary information about preeclampsia superimposed on chronic hypertension is given in Table 6.

Table 6

Preeclampsia Superimposed on Chronic Hypertension: Summary Table

Obstetric Gynecological Key Triads	chronic hypertension	
	worsening blood pressure	
	worsening proteinuria	
Prognosis	**Good prognosis**	Blood pressure 140/90 to 179/109 mm Hg No end-organ damage (no involvement of the heart, kidneys, eyes, no left ventricle hypertrophy
	Poor prognosis (small vessels disease)	Kidneys: renal disease creatinine > 1.4 mg/dL
		Eyes: retinopathy hemorrhages, exudates, narrowing
		Heart: left ventricle hypertrophy prolonged blood pressure > 180/110 mm Hg
	Worst prognosis	Uncontrolled hypertension (250/140 mm Hg chronic hypertension + superimposed preeclampsia vessel involvement and weakening intracerebral hemorrhage
Management	Direct current antihypertensive medicines — if blood pressure < 100 mm diastolic	
	If antihypertensive medicines needed — *Methyl dopa* is drug of choice (or *Labetalol*) – safe for pregnancy	
	Serial ultrasonogrphy, nonstress test (NST) and atrial fibrillation investigation (AFI) — ↑ risk of intrauterine growth retardation (IUGR) > 30 weeks	

Table 6 (continued)

	Serial blood pressure and urine protein — watch for superimposed preeclampsia — indication for delivery	
	Uncomplicated chronic hypertension, 40 weeks — induce labor at term	
Antihypertensive medicines NEVER to use in pregnant	ACE Inhibitors*	reason: fetal renal failure Caution for ACE inhibitors in 1st trimester!
	Diuretics	reason: ↓ plasma volume
Aggressive management	Intravenous (IV) $MgSO_4$ to prevent convulsions	
	To lower blood pressure — diastolic 90–100 mm Hg Use *Hydralazine* or *Labetalol(selective)*	
	Induce labor: stable mother and fetus — intravenous *oxytocin* and *amniotomy* regardless the gestational age unstable mother and fetus — Cesarean delivery	

* ACE (angiotensin-converting enzyme) inhibitors.

ECLAMPSIA

Eclampsia is preeclampsia complicated by generalized tonic-clonic convulsions. The seizures (convulsions) are generalized and may appear before, during, or after labor. Fatal coma without convulsions is also called eclampsia. However, it is better to limit this diagnosis to women with convulsions; and deaths in nonconvulsive cases should be considered as due to severe preeclampsia. Major complications include placental abruption, neurological deficits, aspiration pneumonia, pulmonary edema, cardiopulmonary arrest, acute renal failure and maternal death.

Preeclampsia precedes the onset of eclamptic convulsions. Depending on whether convulsions appear before, during, or after labor, eclampsia is called as antepartum, intrapartum, or postpartum. Eclampsia is most common in the last trimester and becomes increasingly more frequent as term approaches. In more recent years, there has been an increasing shift in the incidence of eclampsia toward the postpartum period. This is presumably related to improved access to prenatal care, earlier detection of preeclampsia, and prophylactic use of magnesium sulfate.

The convulsive movements usually begin about the mouth in the form of facial twitchings. After a few seconds, the entire body becomes rigid in a generalized muscular contraction. This phase may persist for 15 to 20 seconds. Suddenly the jaws begin to open and close violently, and soon after, the eyelids as well. The other facial muscles and then all muscles alternately contract and relax in rapid succession. Muscular movements are so forceful that the woman may fall from her bed, and if not protected, her tongue is bitten by the violent action of the jaws. This phase, in which the muscles alternately contract and relax, may last about a minute. Gradually, the muscular movements become smaller and less frequent, and finally the woman lies motionless. Convulsions may recur every 5 minutes but usually every 20 minutes to 1 hour. The average number is from 5 to 15 attacks, but even up to over 100.

In the course of the seizure the diaphragm becomes fixed, with respiration halted. For a few seconds it seems that the woman is dying from respiratory arrest, but then she takes a long, deep, stertorous inhalation, and breathing is resumed. The first convulsion is usually the sign of others, which may vary in number from one or two in mild cases to even continuous convulsions status epilepticus in untreated severe cases. After a seizure, coma occurs. The woman does not remember the convulsion(s) or events immediately before and afterward. Over time, these memories return.

The duration of coma after a convulsion is variable. In very severe cases, the coma persists from one convulsion to another, and death may result before she awakens (mortality rate 10 %). In rare instances, a single convulsion may be followed by coma from which the woman may never emerge, although, as a rule, death does not occur until after frequent convulsions.

Respirations after an eclamptic convulsion are usually increased in rate and may reach 50 or more per minute. Cyanosis may be observed in severe cases. High fever is a very grave sign, because it is probably the consequence of a central nervous system hemorrhage.

Proteinuria is almost always present and frequently pronounced. Urine output is diminished appreciably, and occasionally anuria develops. Hemoglobinuria is common, but hemoglobinemia is observed only rarely. Often the edema is pronounced at times, massive but it may also be absent.

As with severe preeclampsia, after delivery an increase in urinary output is usually an early sign of improvement. Proteinuria and edema ordinarily disappear within a week. In most cases, blood pressure returns to normal within a few days to 2 weeks after delivery. The longer hypertension persists postpartum, the more likely that it is the consequence of chronic vascular disease.

If the convulsion occurs during labor, contractions may increase in frequency and intensity, and the duration of labor may be shortened. Because of maternal hypoxemia and lactic acidemia caused by convulsions, it is usual for fetal bradycardia to follow a seizure. This usually recovers within 3 to 5 minutes; if it persists more than about 10 minutes, another cause, such as placental abruption or imminent delivery, must be considered.

Pulmonary edema may follow eclamptic convulsions. This may be caused by aspiration pneumonitis from inhalation of gastric contents if simultaneous vomiting accompanies convulsions. Alternatively, it may be caused by cardiac failure as the result of a combination of severe hypertension and vigorous intravenous fluid administration.

In some women with eclampsia, sudden death occurs synchronously with a convulsion or follows shortly thereafter, as the result of a massive cerebral hemorrhage. Hemiplegia may result from sublethal hemorrhage. Cerebral hemorrhages are more frequent in older women with underlying chronic hypertension. Rarely they may be due to a ruptured berry aneurysm or arteriovenous malformation.

In some women, some degree of blindness follows a seizure. Blindness seldom develops spontaneously with preeclampsia. Women may have substantively altered consciousness, including persistent coma, following a seizure. Rarely, eclampsia is followed by psychosis, and the woman becomes violent. This usually lasts for several days to 2 weeks, but the prognosis for return to normal is good, provided there was no preexisting mental illness.

Case 5: *A 21 year-old primigravida is brought to the emergency department after a* ***generalized tonic-clonic seizure*** *at 32 weeks. The seizure was preceded by a* ***severe headache****. She lost control of her bowels and bladder. She has gained* ***about 4.5 kg in 2 weeks****. On exam she is unresponsive in a post-ictal* state. Blood pressure is* ***185/115*** *and a spot urine dipstick shows* ***4+ protein****.*

(*altered state of consciousness after an eclamptic seizure. It usually lasts between 5 and 30 minutes, but sometimes longer in the case of larger or more severe seizures, and is characterized by drowsiness, confusion, nausea, hypertension, headache or migraine, and other disorienting symptoms. Additionally, emergence from this period is often accompanied by amnesia or other memory defects.)

Differential diagnosis. Generally, eclampsia is diagnosed too frequently rather than overlooked, because epilepsy, encephalitis, meningitis, cerebral tumor, cysticercosis, and ruptured cerebral aneurysm during late pregnancy and the puerperium may simulate eclampsia. Until other such causes are excluded, all pregnant women with convulsions should be considered to have eclampsia.

Prognosis. The prognosis for eclampsia is always serious; it is one of the most dangerous conditions in pregnancy. Fortunately, maternal mortality due to eclampsia has decreased from four decades ago.

Magnesium sulfate to control convulsions. In more severe cases of preeclampsia and eclampsia, magnesium sulfate administered parenterally is an effective anticonvulsant agent without depressing central nervous system in either the mother or the infant. It may be given intravenously by continuous infusion. The dosage schedule for severe preeclampsia is the same as for eclampsia. Because convulsions develop more frequently during labor and delivery, women with preeclampsia-eclampsia usually are given magnesium sulfate during labor and for 24 hours postpartum. Magnesium sulfate is not given to treat hypertension.

Based on extensive clinical observations, magnesium most likely exerts a specific anticonvulsant action on the cerebral cortex. Usually, the mother stops convulsing after the initial administration of magnesium sulfate and, within an hour or two, regains consciousness sufficiently to be oriented as to place and time.

When magnesium sulfate is given to arrest and prevent recurrent eclamptic seizures, some women have a subsequent convulsion. An additional 2-g dose of magnesium sulfate in a 20 % solution is administered slowly intravenously. In a small woman, an additional 2-g dose may be used once, and twice if needed in a larger woman. Sodium amobarbital is given slowly intravenously in doses up to 250 mg in women who are excessively agitated in the postconvulsion phase. Thiopental is suitable also. Maintenance magnesium sulfate therapy for eclampsia

is continued for 24 hours after delivery. For eclampsia that develops postpartum, magnesium sulfate is administered for 24 hours after the onset of convulsions.

Pharmacology and toxicology of magnesium sulfate. Magnesium sulfate (United States Pharmacopoeia) is $MgSO_4$ $7H_2O$ and not $MgSO_4$. Parenterally administered magnesium is cleared almost totally by renal excretion, and magnesium intoxication is avoided by ensuring that urine output is adequate, the patellar or biceps reflex is present, and there is no respiratory depression. Eclamptic convulsions are almost always prevented by plasma magnesium levels maintained at 4.8 to 8.4 mg/dL (or 2.0 to 3.5 mmol/L).

The initial intravenous infusion of 4 to 6 g is used to establish a prompt therapeutic level that is maintained by continuous infusion at 2 to 3 g per hour. With these dosage schedules, therapeutically effective plasma levels of 4.8 to 8.4 mg/dL are achieved compared with pretreatment plasma levels.

At magnesium plasma levels higher than about 12 mg/dL, respiratory depression develops. Treatment with calcium gluconate, 1 g intravenously, along with postponing further magnesium sulfate usually reverses mild to moderate respiratory depression. Unfortunately, the effects of intravenously administered calcium may be short-lived. For severe respiratory depression and arrest, prompt tracheal intubation and mechanical ventilation are lifesaving. Direct toxic effects on the myocardium from high levels of magnesium are not common.

Because magnesium is cleared almost exclusively by renal excretion, plasma magnesium concentration, using the doses described previously, is excessive if glomerular filtration is decreased substantively. The initial standard dose of magnesium sulfate can be safely administered without knowledge of renal function. Renal function is thereafter estimated by measuring plasma creatinine, and whenever it is 1.3 mg/dL or higher, only half of the maintenance intramuscular magnesium sulfate dose is given. With this renal impairment dosage, plasma magnesium levels are usually within the desired range of 4 to 7 mEq/L. When magnesium sulfate is being given intravenously by continuous infusion, serum magnesium levels are used to adjust the infusion rate. With either method, when there is renal insufficiency, plasma magnesium levels must be checked periodically.

Uterine effects. Magnesium ions in relatively high concentration depress myometrial contractility both in vivo and in vitro.

Fetal effects. Magnesium administered parenterally to the mother promptly crosses the placenta to achieve equilibrium in fetal serum and less so in amnionic fluid. Neonatal depression occurs only if there is severe hypermagnesemia at delivery. Neonatal compromise after therapy with magnesium sulfate has not been reported. Whether magnesium sulfate affects the fetal heart rate pattern, specifically beat-to-beat variability, is controversial.

Hydralazine to control severe hypertension. Hydralazine is given intravenously whenever the diastolic blood pressure is 105 mm Hg or higher or the systolic blood pressure is more than 160 mm Hg.

A number of regimens have been used. Hydralazine is administered in 5- to 10-mg doses at 15- to 20-minute intervals until a satisfactory response is achieved.

A satisfactory response antepartum or intrapartum is defined as a decrease in diastolic blood pressure to 90-100 mm Hg, but not lower lest placental perfusion be compromised. Hydralazine so administered is remarkably effective in the prevention of cerebral hemorrhage. Seldom was another antihypertensive agent needed because of poor response to hydralazine. The tendency to give a larger initial dose of hydralazine when the blood pressure is higher must be avoided. The response to even 5- to 10-mg doses cannot be predicted by the level of hypertension; thus, we always give 5 mg as the initial dose.

Labetalol. Labetalol lowers blood pressure more rapidly, and associated tachycardia is minimal, but hydralazine lowers mean arterial pressure to safe levels more effectively. The protocol recommends starting with a 20-mg intravenous bolus. If not effective within 10 minutes, this is followed by 40 mg, then 80 mg every 10 minutes but not to exceed a 220-mg total dose per episode treated.

Other antihypertensive agents. Nifedipine in a 10-mg oral dose is recommended to be repeated in 30 minutes if necessary. The calcium antagonist, verapamil is administered by intravenous infusion at 5 to 10 mg per hour.

Diuretics and hyperosmotic agents. Potent diuretics further compromise placental perfusion, because their immediate effects include intravascular volume depletion, which most often is already reduced compared with that of normal pregnancy. Therefore, diuretics are not used to lower blood pressure lest they enhance the intensity of the maternal hemoconcentration and its adverse effects on the mother and the fetus. Antepartum administration of furosemide or similar drugs typically is used in the rare instances in which pulmonary edema is identified or strongly suspected. Once delivery is accomplished, there is a spontaneous diuresis that usually begins within 24 hours in almost all cases of severe preeclampsia and eclampsia. This diuresis results in the disappearance of excessive extravascular fluid over the next 3 to 4 days. With infusion of hyperosmotic agents, the potential exists for an appreciable intravascular influx of fluid and, in turn, subsequent escape of intravascular fluid in the form of edema into vital organs, especially the lungs and brain. Moreover, an osmotically active agent that leaks through capillaries into lungs and brain promotes accumulation of edema at these sites.

Fluid therapy. Lactated Ringer solution is administered routinely at the rate of 60 mL to no more than 125 mL per hour unless unusual fluid loss from vomiting, diarrhea, or excessive perspiration, or excessive blood loss at delivery has occurred. Infusion of large fluid volumes could and does enhance the maldistribution of extravascular fluid and thereby appreciably increases the risk of pulmonary and cerebral edema.

Pulmonary edema. Women with severe preeclampsia-eclampsia who develop pulmonary edema most often do so postpartum. Aspiration of gastric contents, the result of convulsions or perhaps from anesthesia, or oversedation, should be excluded, however, the majority of these women have cardiac failure. Importantly, plasma oncotic pressure decreases appreciably in normal term pregnancy because of decreases in serum albumin, and oncotic pressure falls even

more with preeclampsia. Increased extravascular fluid oncotic pressure in women with preeclampsia favors capillary fluid extravasation. Capillary permeability in women with preeclampsia is also increased. The frequent findings of hemoconcentration, as well as the identification of reduced central venous and pulmonary capillary wedge pressures in women with severe preeclampsia require the infusion of various fluids, starch polymers, or albumin concentrates to expand blood volume and relieve vasospasm and reverse organ deterioration.

DELIVERY

To avoid maternal risks from cesarean delivery, steps to effect vaginal delivery are used initially in women with eclampsia. After an eclamptic seizure, labor often ensues spontaneously or can be induced successfully even in women remote from term. An immediate cure does not immediately follow delivery by any route, but serious morbidity is less common during the puerperium in women delivered vaginally.

Blood loss at the delivery. Hemoconcentration, or lack of normal pregnancy-induced hypervolemia, is a feature of severe preeclampsia-eclampsia. These women, who consequently lack normal pregnancy hypervolemia, are much sensible to blood loss than are normotensive pregnant women. It is important to know that an appreciable fall in blood pressure very soon after delivery most often means excessive blood loss. When oliguria follows delivery, the hematocrit should be evaluated frequently to help detect excessive blood loss that, if identified, should be treated appropriately by careful blood transfusion.

Analgesia and anesthesia. In the past, both spinal and epidural analgesia were avoided in women with severe preeclampsia and eclampsia. The primary concern centered on the hypotension induced by sympathetic blockade and, in turn, on dangers from pressor agents or large volumes of intravenous fluid used to correct iatrogenically induced hypotension. For example, rapid infusion of large volumes of crystalloid or colloid, given to counteract maternal hypovolemia caused by a variety of factors, including epidural analgesia, has been implicated as a cause of pulmonary edema. There have also been concerns about fetal safety, because sympathetic blockade-induced hypotension can dangerously lower uteroplacental perfusion. Pharmacological restoration of blood pressure (with vasopressor) may be hazardous because women with preeclampsia are very sensitive to such agents. As regional analgesia techniques improved, epidural analgesia for women with severe preeclampsia can improve vasospasm and lower blood pressure. General anesthesia is inadvisable because stimulation caused by tracheal intubation may result in sudden hypertension, pulmonary edema, cerebral edema, or intracranial hemorrhage. Tracheal intubation may be particularly hazardous in women with airway edema due to preeclampsia. Most authorities believe that epidural analgesia used in the cesarean delivery of women with severe preeclampsia is the preferred method due to its safety.

Summary information about eclampsia is given in Table 7.

Table 7

Eclampsia

Risk factors	Same as Preeclampsia (see Table 2)
Pathophysiology	Cerebral vasospasm
	Ischemia
	Brain edema (on MRI)
Symptoms	Tonic-clonic seizures
Laboratory findings	Proteinuria
	Hemoconcentration
	DIC (dissemination intravascular coagulation) syndrome
	↑ liver enzymes
Management	Stop convulsions (intravenous $MgSO_4$)
	Avoid diuretics and limit intravenous fluid administration unless fluid loss is excessive. Hyperosmotic agents are avoided.
	Lower diastolic blood pressure 90–100 mm Hg (intermittent intravenous or oral administration of an antihypertensive medication) *Continue intravenous $MgSO_4$ for 24 hours postpartum.*
	Prompt delivery at any gestational age

LONG-TERM CONSEQUENCES

Women who develop hypertension during pregnancy should be evaluated during the immediate postpartum months and counseled about future pregnancies and also their cardiovascular risk later in life. The longer hypertension diagnosed during pregnancy persists postpartum, the greater the likelihood that the cause is underlying chronic hypertension. Hypertension attributable to pregnancy must resolve within 12 weeks of delivery. Hypertension persisting longer than this period of time is the evidence of chronic hypertension. Many reports confirm the risk of recurrence of hypertension during a subsequent pregnancy in women affected during a prior pregnancy.

Counseling for future pregnancies. Women who have had preeclampsia are more prone to hypertensive complications in future pregnancies. Generally, the earlier preeclampsia is diagnosed during any pregnancy, the greater the likelihood of recurrence. Multiparous women who develop preeclampsia are at increased risk for recurrence of preeclampsia in subsequent pregnancy compared with nulliparas who develop preeclampsia. Women with early-onset severe preeclampsia may have underlying thrombophilias. These disorders not only complicate subsequent pregnancies but also have an impact on overall long-term health.

PREMATURE AND LATE DELIVERY

PRETERM BIRTH

Low birthweight defines neonates who are born too small, and *preterm* or *premature* birth are the terms used to define neonates who are born too early. With respect to gestational age, a newborn may be preterm, term, or post-term. With respect to size, a newborn may be normally grown or appropriate for gestational age, small in size or small-for-gestational age, or overgrown and consequently large-for-gestational age (Fig. 4). The preterm *appropriate-for-gestational age* designates newborns whose weight is between the 500 g and 2500 g. Thus, infants born before term can be small- or large-for-gestational age but still fit the definition of preterm. Preterm birth is defined as delivery in the period of 22–37 completed weeks (Fig. 5).

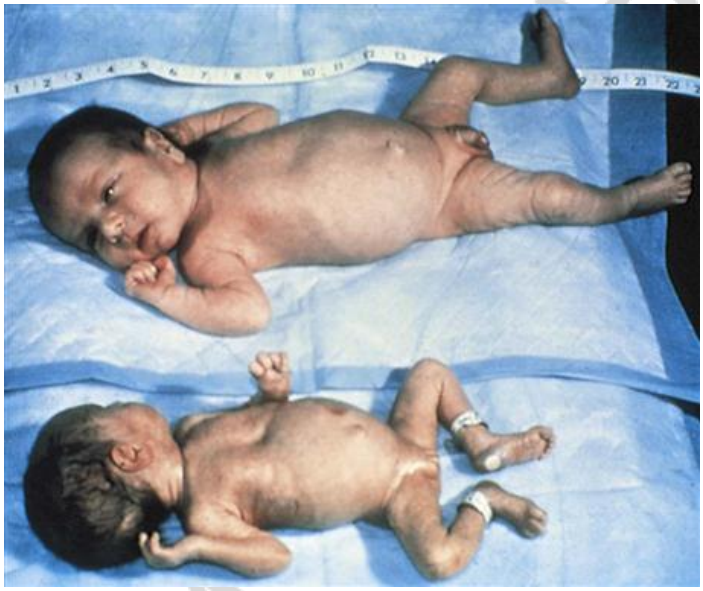

Figure 4. Preterm and post term newborns (https://nursekey.com/wp-content/uploads/2016/08/F000139f013-001-9781437708240.jpg)

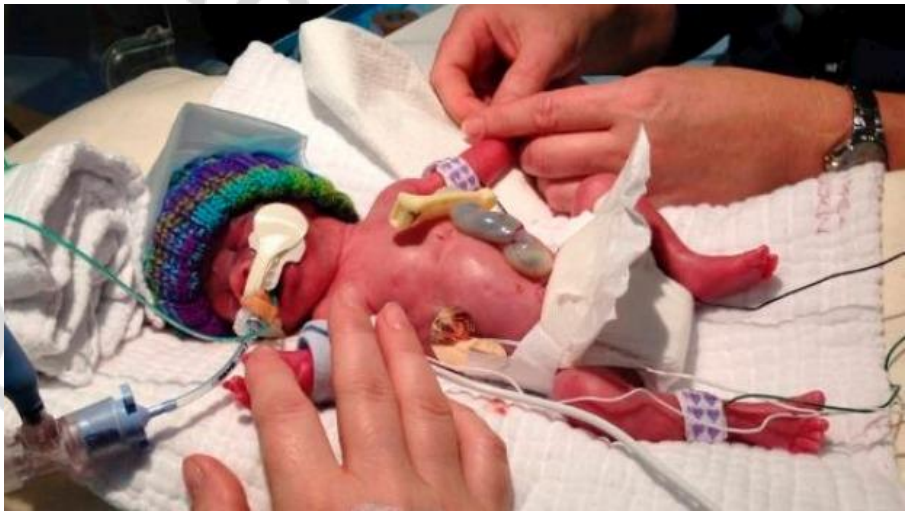

Figure 5. Preterm newborn https://www.essentialbaby.com

Approaches to preterm labor and delivery currently are guided by expectations for survival of the neonate. The most accurate estimates of gestational age are made from last menses, obstetrical parameters, and ultrasonographical examination. Perinatal mortality and morbidity decrease markedly from 24 to 26 weeks gestation. Survival increases from approximately 20 % at 24 weeks up to 50 % at 25 weeks. Neonatal morbidity and mortality are primarily influenced by gestational age and thus maturity, and less so by birth weight.

CAUSES OF PRETERM BIRTH

Medical and obstetrical complications include several factors: preeclampsia, fetal distress, fetal growth restriction, placental abruption, fetal death and spontaneous preterm labor with or without prematurely ruptured membranes.

Threatened abortion. Vaginal bleeding in early pregnancy is associated with increased adverse outcomes. Both light bleeding (described as spotting) and heavy bleeding (similar to menses) are associated with subsequent pregnancy loss prior to 24 weeks, preterm labor, and placental abruption.

Life style factors. Cigarette smoking, inadequate maternal weight gain during pregnancy and illicit drug use play important roles in both the incidence and the outcome of low birth weight neonates. Other maternal factors implicated include young or advanced maternal age; poverty; short stature; Vitamin C deficiency; and occupational factors such as prolonged walking or standing, strenuous working conditions, and long weekly work hours (Fig. 6). No increased incidence of recurrent preterm birth was found in women with a history of preterm birth and whose work during their current pregnancies was outside the home or required physical exertion.

Figure 6. Life style factor for preterm delivery

Both stress and higher levels of maternal serum cortisol have been associated with spontaneous preterm birth. A significant link between low birthweight and preterm birth is found in women injured by physical abuse. Depression is not associated with birth prior to 35 weeks.

The association of cigarette smoking and fetal growth restriction is evident. Smoking increased the incidence of ectopic pregnancy, placental abruption, and placenta previa.

Genetic factors. The recurrent, familial, and racial nature of preterm birth has led to the suggestion that genetics may play some role. The gene for decidual relaxin, fetal mitochondrial trifunctional protein defects or polymorphism in the interleukin-1 gene complex, β_2-adrenergic receptor, or tumor necrosis factor-α (TNF-α) may also be involved in preterm membrane rupture.

Infections of the membranes and amnionic fluid caused by a variety of microorganisms may explain some cases of ruptured membranes, preterm labor, or both. Bacteria and viruses are recovered by transabdominal amniocentesis from as many as 20 % of women in preterm labor without evident clinical infection and with intact fetal membranes.

Infection is not limited to amnionic fluid. The recovery of organisms from the chorioamnion is significantly increased with spontaneous preterm labor. Recovery of pathogens also correlates with gestational age.

Escherichia coli can permeate living membranes; they are not an absolute barrier to ascending infection. Another pathway for bacterial initiation of preterm labor may not require bacteria in the amnionic fluid. The cytokine network of cell-mediated immunity can be activated within the decidual tissue that lines the presenting fetal membranes. In this scheme, bacterial products such as endotoxin stimulate decidual monocytes to produce cytokines, which in turn stimulate arachidonic acid and then prostaglandin production. Prostaglandins E_2 and $F_{2\alpha}$ stimulate adjacent myometrium to contract.

SIGNS AND SYMPTOMS

In addition to painful or painless uterine contractions, symptoms such as pelvic pressure, menstrual-like cramps, watery vaginal discharge, and pain in the low back are associated with impending preterm birth. Such symptoms are common in normal pregnancy and therefore often dismissed by patients, clinicians, and nurses. True signs and symptoms signaling preterm labor, including uterine contractions appear only within 24 hours of preterm labor.

RISK FACTORS FOR SPONTANEOUS PRETERM LABOR

Prior preterm birth. Prior preterm delivery strongly correlates with subsequent preterm labor. The causes of prior preterm delivery (i.e., preterm labor with intact membranes, preterm membrane rupture, or indicated delivery) also recur.

Incompetent cervix is a clinical diagnosis characterized by recurrent, painless cervical dilatation and spontaneous midtrimester birth in the absence of spontaneous membrane rupture, bleeding, or infection

Asymptomatic cervical dilatation after midpregnancy may be a predictor of increased risk of preterm delivery.

Ultrasonographic measurement of cervical length. It seems that the use of ultrasonographic cervical measurements can increase the ability to predict spontaneous birth prior to 35 weeks in high-risk women. The mean cervical length at 24 weeks is about 35 mm, and those women with progressively shorter cervices experience increased rates of preterm birth. Dilatation of 2 to 4 mm identified during second-trimester cervical ultrasonographic scanning predicts an increase in births prior to 35 weeks.

Fetal fibronectin. This glycoprotein is produced in 20 different molecular forms by a variety of cell types, including hepatocytes, fibroblasts, and endothelial cells, and by fetal amnion. Present in high concentrations in maternal blood and in amnionic fluid, it plays a role in intercellular adhesion during implantation and in the maintenance of placental adhesion to the decidua. Fetal fibronectin is detected in cervicovaginal secretions in women who have normal pregnancies with intact membranes at term, and it reflects stromal remodeling of the cervix prior to labor.

Fibronectin detection in cervicovaginal secretions prior to membrane rupture is a possible marker for impending preterm labor. Fetal fibronectin is measured using an enzyme-linked immunosorbent assay, and values exceeding 50 ng/mL are considered positive. Contamination of the sample by amnionic fluid and maternal blood should be avoided. A positive value for cervical or vaginal fetal fibronectin assay as early as 8 to 22 weeks is a powerful predictor of subsequent preterm birth. The less informative positive predictive value likely results from factors such as cervical manipulation and infection, which can stimulate fetal fibronectin release. These findings may implicate infection in the initiation of preterm labor in some women.

Bacterial vaginosis. Bacterial vaginosis is not an infection but rather a condition in which the normal, hydrogen peroxide-producing lactobacillus-predominant vaginal flora is replaced with anaerobes, *Gardnerella vaginalis*, *Mobiluncus* species, and *Mycoplasma hominis*.

Bacterial vaginosis is associated with spontaneous abortion, preterm labor, preterm ruptured membranes, chorioamnionitis, and amnionic fluid infection. Bacterial vaginosis may precipitate preterm labor by a mechanism similar to that proposed for amnionic fluid infection.

Environmental factors are important in the development of bacterial vaginosis. Exposure to chronic stress, ethnic differences, and frequent or recent douching have all been associated with increased rates of the condition.

There is no doubt that adverse vaginal flora, such as in bacterial vaginosis, is associated with spontaneous preterm birth. Unfortunately screening and treatment with metrnidazole do not prevent preterm birth.

Lower genital tract infection. Women who have *Trichomonas* or *Candida* species are not at greater risk for preterm birth. Conversely, it is found that the neonates of women with *Trichomonas* have increased risk of having low-birthweight, an increased risk of preterm birth, and a risk of perinatal death. *Chlamydia trachomatis* likely does not play a role in increased preterm delivery. No association of preterm birth with midtrimester chlamydial infection has been

found. The incidences of preterm delivery in women with and without chlamydial or trichomonal infection are similar. Currently, screening and treatment to prevent preterm birth in women with either *C trachomatis* or *Trichomonas vaginalis* is not recommended.

Periodontal disease. Oral bacteria, especially *Fusobacterium nucleatum* and *Capnocytophaga* species, have been associated with upper genital tract infection in pregnant women. It is found that women with periodontitis have a high risk of preterm birth.

ROLE OF PROGESTERONE IN THE MAINTENANCE OF PREGNANCY

It is accepted that in human pregnancy progesterone withdrawal does not cause the initiation of parturition. Maternal plasma progesterone levels increase throughout pregnancy. Despite this, the use of progesterone to maintain normal uterus and to "block" labor initiation deserves continued evaluation. Progesterone and estrogen levels vary directly but markedly with gestational age. Progesterone antagonists given at term increase the rate of spontaneous labor. The most commonly used progestin in human clinical trials is 17α-hydroxyprogesterone caproate. 100-mg vaginal suppository of natural progesterone to reduce preterm delivery is effective in high-risk women.

MANAGEMENT OF PRETERM RUPTURED MEMBRANES AND PRETERM LABOR

Women at risk for preterm birth and women who present with signs and symptoms of preterm labor are candidates for a number of interventions intended to improve neonatal outcomes. In the absence of maternal or fetal indications justifying intentional delivery, interventions are intended to prevent preterm birth.

Preterm ruptured membranes. Prior to term, the precision of this diagnosis is of great importance. A history of vaginal leakage of fluid, either continuously or as a gush, should prompt a sterile speculum examination to visualize gross vaginal pooling of amnionic fluid, clear fluid from the cervical canal, or both. Confirmation of ruptured membranes is usually accompanied by ultrasonographic examination to assess amnionic fluid volume; to identify the presenting part; and if not previously determined, to estimate gestational age.

Management may be to effect delivery or to await spontaneous labor. It may necessary to decide about administration of either antimicrobials, corticosteroids, or both.

Risks of expectant management. Maternal and fetal risks vary with the gestational age at membrane rupture and include the consequences of uterine infection and sepsis. When contemplating expectant management before 25 weeks, additional consideration is given to fetal risks of oligohydramnios with resultant pulmonary hypoplasia and compression deformities of the extremities. The volume of amnionic fluid remaining after rupture is of prognostic importance in pregnancies before 26 weeks.

Clinical chorioamnionitis. If there are no untoward perinatal outcomes from an entangled or prolapsed cord or from placental abruption, prolonged membrane rupture is associated with increased infectious morbidity. If chorioamnionitis is diagnosed, prompt efforts to effect delivery, preferably vaginally, are initiated. Fever is the only reliable indicator for this diagnosis. A temperature of 38 °C or higher accompanying ruptured membranes implies infection. Maternal leukocytosis alone is not a reliable sign. During expectant management, monitoring for sustained maternal or fetal tachycardia, for uterine tenderness, and for a malodorous vaginal discharge is necessary. With chorioamnionitis, fetal and neonatal morbidity is substantively increased.

Newborns in the infected group have a higher incidence of sepsis, respiratory distress syndrome, intraventricular hemorrhage, and periventricular leukomalacia. Very-low-birthweight neonates are susceptible to neurological injury attributable to chorioamnionitis such as cerebral palsy. Maternal fever during labor is a strong predictor of infection-related death in both term and preterm neonates.

Antimicrobial therapy. Antimicrobial-treated women with a 7-day course of either ampicillin, amoxicillin plus erythromycin, have significantly fewer newborns with respiratory distress syndrome, necrotizing enterocolitis, and composite adverse outcomes. Neither tocolytics nor corticosteroids are given. There is also significant prolongation of pregnancy at 14 and 21 days. Cervicovaginal group B streptococcal colonization does not alter these results.

More recent studies have examined the efficacy of shorter treatment lengths and other antimicrobial combinations. Three-day treatment compared with 7-day regimens using either ampicillin or ampicillin-sulbactam is equally effective in regard to perinatal outcomes. Similarly, erythromycin compared with placebo offers a range of significant neonatal benefits. The amoxicillin-clavulanate regimen is not recommended because of its association with an increased incidence of necrotizing enterocolitis. Prolonged antimicrobial therapy in such pregnancies may have unwanted consequences. A number of specialists caution that such therapy potentially increases the risk for selection of resistant bacteria.

Management of preterm membrane rupture. After a confirmation of ruptured membranes, the following steps are taken:

1. Cervical dilatation and effacement are estimated visually during a sterile speculum examination.

2. For pregnancies less than 34 weeks, if there are no maternal or fetal indications for delivery, the woman and her fetus are initially observed in the labor unit. Broad-spectrum parenteral antimicrobials are begun to prevent chorioamnionitis. Fetal heart rate and uterine activity are monitored for cord compression, fetal compromise, and early labor.

3. For pregnancies less than 32 weeks, betamethasone (two 12-mg doses intramuscularly 24 hours apart) or dexamethasone (5 mg intramuscularly every 12 hours for four doses) is given.

4. If the fetal status is reassuring, and if labor does not ensue, the woman is usually transferred to an antepartum unit and observed for labor, infection, or fetal jeopardy. We do not use continuous fetal monitoring.

5. For pregnancies 34 weeks or beyond, if labor does not begin spontaneously, then it is induced with intravenous oxytocin unless contraindicated. Cesarean delivery is performed for usual indications, including failed induction of labor.

6. During labor or induction, a parenteral antimicrobial is given for prevention of group B streptococcal infection.

Adverse effects of corticosteroids. Adverse immediate and long-term effects have now been reported with multiple-course treatment. Investigators have found that early-onset neonatal sepsis, chorioamnionitis, and neonatal death are associated with multiple courses of betamethasone therapy.

Short-term maternal adverse effects include pulmonary edema, infection, and more difficult glucose control in diabetic women. No long-term adverse maternal effects have been reported.

PRETERM LABOR WITH INTACT FETAL MEMBRANES

Diagnosis. Early differentiation between true and false labor is difficult before there is demonstrable cervical effacement and dilatation. Uterine activity alone can be misleading because of *Braxton Hicks contractions*. These contractions, described as irregular, non-rhythmical, and either painful or painless, can cause considerable confusion in the diagnosis of preterm labor. Frequently, women who deliver before term have uterine activity that is attributed to Braxton Hicks contractions, prompting an incorrect diagnosis of false labor. Because uterine contractions alone may be misleading, the following criteria to document preterm labor are proposed:

1. Contractions of four in 20 minutes or eight in 60 minutes plus progressive change in the cervix.

2. Cervical dilatation greater than 1 cm.

3. Cervical effacement of 80% or greater.

Management. Women with signs and symptoms of preterm labor with intact membranes are managed much the same as described above for those with preterm ruptured membranes. The cornerstone of treatment is to avoid delivery prior to 34 weeks, if possible. Drugs to abate or suppress preterm uterine contractions are administered.

Amniocentesis to detect infection. It has not been shown that amniocentesis to diagnose infection is associated with improved pregnancy outcomes in women with or without membrane rupture.

INTERVENTIONS TO DELAY PRETERM BIRTH

Antimicrobials. Antimicrobial treatment of women with preterm labor for the sole purpose of preventing delivery is generally not recommended.

Emergency cerclage. If cervical incompetence is recognized in threatened preterm labor, emergency cerclage can be attempted, but an appreciable risk of infection and pregnancy loss should be taken into account. Currently, pessaries are widely used to prolong pregnancy.

Treatment for bacterial vaginosis. Bacterial vaginosis is associated with excess rates of preterm birth. The effects of various antimicrobials on its eradication were studied in a number of studies. To treat bacterial vaginosis oral metronidazole may be administered. The incidence of preterm birth was lower in women treated with either metronidazole plus erythromycin or metronidazole plus azithromycin. Intravaginal clindamycin cream and oral clindamycin may be used to treat bacterial vaginosis and intermediate flora.

Beta-adrenergic receptor agonists. A number of compounds react with β-adrenergic receptors to reduce intracellular ionized calcium and prevent activation of myometrial contractile proteins. In the United States, ritodrine and terbutaline have been used in obstetrics, but only ritodrine had been approved for preterm labor by the U.S. Food and Drug Administration.

Ritodrine. Neonates whose mothers were treated with ritodrine for presumed preterm labor had less mortality and respiratory distress, and they achieved a gestational age of 36 weeks or a birthweight of 2500 g more often than did those of untreated mothers. The short-term tocolytic effects of ritodrine and its failure to arrest labor may be due to β-adrenergic receptor desensitization.

The infusion of β-adrenergic agonists has resulted in frequent and at times, serious and fatal side effects. The cause of pulmonary edema is multifactorial, and risk factors include tocolytic therapy with β-adrenergic receptor agonists, multifetal gestation, concurrent glucocorticoid therapy, tocolysis for more than 24 hours, and large intravenous crystalloid volume infusion.

Because β-agonists cause retention of sodium and water, with time (usually 24 to 48 hours), they can lead to volume overload. The drugs may cause increased capillary permeability, disturbance of cardiac rhythm, and myocardial ischemia. Maternal sepsis increases this risk. Due to the high risk of complications, ritodrine was withdrawn voluntarily in 2003 by its manufacturer and is not available in the United States.

Terbutaline. This β-agonist is commonly used to inhibit preterm labor. Like ritodrine, it can cause pulmonary edema. Adverse reports concerning terbutaline pumps describe a sudden maternal death and a newborn with myocardial necrosis. Terbutaline does not significantly prolong pregnancy, prevent preterm delivery, or improve neonatal outcomes. Oral terbutaline therapy to prevent preterm delivery is not effective.

Magnesium sulfate. Ionic magnesium in a sufficiently high concentration can alter myometrial contractility acting as a calcium antagonist. Clinical observations are that magnesium in pharmacological doses may inhibit labor. Intravenously administered magnesium sulfate (a 4-g loading dose followed by a continuous infusion of 2 g/hr) usually arrests labor. Women given magnesium sulfate must be monitored closely for evidence of hypermagnesemia. Some studies

showed that magnesium-treated women and their fetuses had identical outcomes as those given placebo. Because of these findings, this method of tocolysis is not used any more at some US hospitals and European countries.

Neonatal effects of magnesium. Very-low-birthweight neonates (less than 1500 g) whose mothers were treated with magnesium sulfate for preterm labor or preeclampsia had a reduced incidence of cerebral palsy at 2 years. Neonatal mortality and cerebral palsy, substantial motor dysfunction at 2 years of age were less frequent in infants whose mothers have received magnesium therapy.

Prostaglandin inhibitors. Drugs that inhibit prostaglandins have been of considerable interest because prostaglandins are involved in contractions of normal labor. Antagonists inhibit prostaglandin synthesis or block their action on target organs. A group of enzymes collectively termed *prostaglandin synthase* is responsible for the conversion of free arachidonic acid to prostaglandins. A number of drugs block this system, including acetylsalicylate and indomethacin.

Indomethacin is effective in stopping contractions and delaying preterm birth. The comparison of indomethacin with either ritodrine or magnesium sulfate found no difference in their efficacy to prevent preterm delivery.

Indomethacin is administered orally or rectally. A dose of 50 to 100 mg is followed by a total 24-hour dose not greater than 200 mg. Indomethacin use should be limited to 24 to 48 hours because of possible oligohydramnios, which can develop with these doses. If amnionic fluid is monitored, oligohydramnios can be detected early, and it is reversible with discontinuation of indomethacin.

Neonatal complications may be necrotizing enterocolitis, higher incidence of intraventricular hemorrhage and patent ductus arteriosus, sepsis or neonatal death, but there are no reliable evidences which associate indomethacin use with these complications.

Calcium channel blockers. Myometrial activity is directly related to cytoplasmic free calcium, and contractions are inhibited by the reduction in its concentration. Calcium channel blockers inhibit the entry of calcium through channels in the cell membrane. They were developed to treat hypertension. Their use in the arrest of preterm labor has been the subject of research since the late 1970s.

According to the Cochrane Database, nifedipine treatment reduces births of neonates of less than 2500 g although significantly more of these need intensive therapy. Other investigators have also concluded that calcium channel blockers, especially nifedipine, are safer and more effective tocolytic agents than beta-mimetics.

Nifedipine-induced decreased vascular resistance can lead to hypotension and decreased uteroplacental perfusion. The combination of nifedipine with magnesium for tocolysis is potentially dangerous. Nifedipine enhances neuromuscular blocking effects of magnesium that can interfere with pulmonary and cardiac function. Nifedipine is effective for severe gestational hypertension.

Atosiban. This non-apeptide oxytocin analogue is a competitive antagonist of oxytocin-induced contractions. In randomized clinical trials, however, atosiban failed to improve relevant neonatal outcomes and was linked with significant

neonatal morbidity. U.S. Food and Drug Administration approval for atosiban use to arrest preterm labor was denied because of concerns regarding efficacy and fetal-newborn safety.

Summary of tocolytic use for preterm labor. In many women, tocolytics stop contractions temporarily but rarely prevent preterm birth. Most practitioners do not recommend use of tocolytics at or after 34 weeks.

Corticosteroids are not generally used after 33 weeks.

RECOMMENDED MANAGEMENT OF PRETERM LABOR

The following considerations should be given to women in preterm labor:

1. Confirmation of preterm labor.
2. For pregnancies less than 34 weeks in women with no maternal or fetal indications for delivery, close observation with monitoring of uterine contractions and fetal heart rate is appropriate, and serial examinations are done to assess cervical changes.
3. For pregnancies less than 34 weeks, glucocorticoids are given for enhancement of fetal lung maturation.
4. For pregnancies less than 34 weeks in women who are not in advanced labor, attempts to inhibit contractions are made to delay delivery while the women are given glucocorticoid therapy and group B streptococcal prophylaxis.
5. For pregnancies at 34 weeks or beyond, women with preterm labor are monitored for labor progression and fetal well-being.
6. For active labor, an antimicrobial is given for prevention of neonatal group B streptococcal infection.

INTRAPARTUM MANAGEMENT

In general, the more immature the fetus, the greater the risks of labor and delivery.

Labor. Whether labor is induced or spontaneous, the doctor should examine the patient for abnormalities of fetal heart rate and uterine contractions. Continuous electronic monitoring is carried out. Fetal tachycardia, especially with ruptured membranes may be caused by sepsis. There is some evidence that intrapartum acidemia may intensify some of the neonatal complications usually attributed to preterm delivery. It was observed that intrapartum acidosis (umbilical artery blood pH less than 7.0) had an important role in neonatal complications. Increasing umbilical artery blood acidemia is related to more severe respiratory disease in preterm neonates.

To prevent neonatal group B streptococcal infections either penicillin G (benzylpenicillin) or ampicillin intravenously every 6 hours until delivery for women in preterm labor are recommended.

Delivery. In the absence of a relaxed vaginal outlet, an episiotomy for delivery may be necessary once the fetal head reaches the perineum. Perinatal outcome data do not support routine forceps delivery. Nowadays cesarean section

is recommended for pregnant women with gestational age under 34 weeks. Staff experienced in resuscitative techniques appropriate to the gestational age of the newborn and fully oriented to any specific problems should be present at delivery.

POST-TERM PREGNANCY AND DELIVERY

Post-term pregnancy is a pregnancy that extends to 42 weeks and longer. The incidence of post-term pregnancy is about 3–12 %. Risk factors for post-term pregnancy include primiparity, prior post-term pregnancy, endocrine disorders (low estrogen), mother's obesity, male gender of the fetus and genetic factors. Maternal but not paternal genetic factors are responsible for the rate of post-term pregnancies.

Although the last menstrual period (LMP) has been traditionally used to calculate the estimated due date (EDD), many inaccuracies exist using this method in women who have irregular cycles, have been on recent hormonal birth control, or who have first trimester bleeding. Not only the LMP date, but the regularity and length of cycles must be taken into account when estimating gestational age.

Management plan for a coming post-term pregnancy (> 40 weeks of gestation but < 42 weeks), may include 3 options:

1. Elective induction of labor. If the pregnancy is at risk for an adverse outcome from previous chronic maternal or fetal condition, the labor may be induced without confirmed lung maturity.

2. Expectant management of the pregnancy;

3. Antenatal testing.

Each of these three options may be used at any particular time during this 2-week period.

Post term infant characteristics are: newborn emaciated, meconium stained, hair and nails long (Fig. 7, *a*, *b*), dry peeling skin, creases cover the whole body, especially hands and soles (Fig. 8), limited vernix and lanugo (Fig. 9), rigid cranial cartilage sutures, macrosomia.

a ***b***

Figure 7. Long nails (*a*) and hair (*b*) in post term infants

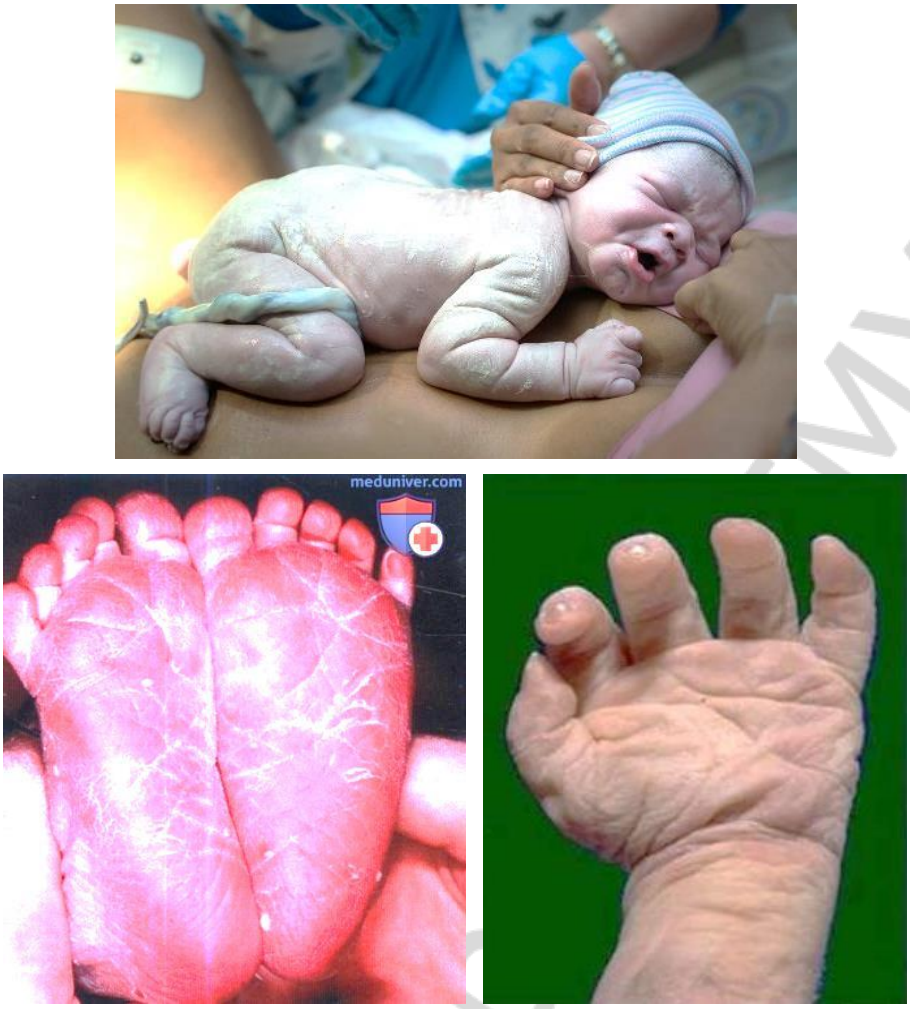

Figure 8. Post term baby's skin

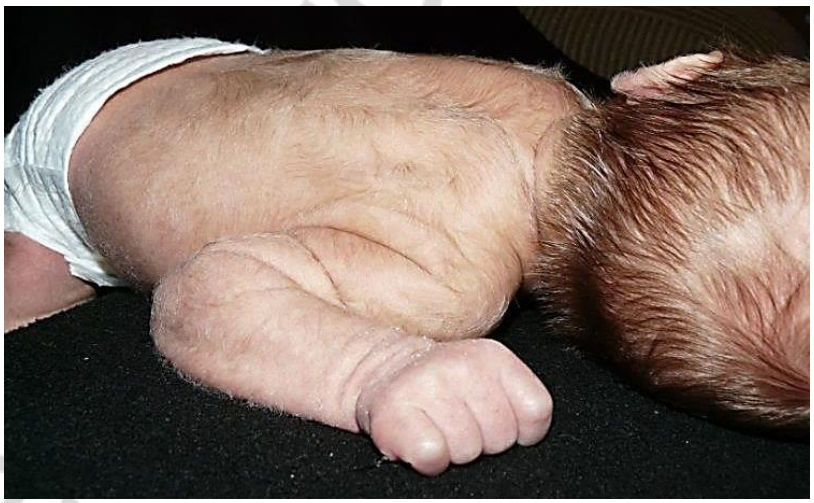

Figure 9. Baby covered in lanugo

Fetal and neonatal risks. Antepartum stillbirths account for more perinatal deaths than either complications of prematurity or sudden infant death syndrome. Perinatal mortality (stillbirths + early neonatal deaths) at 42 weeks of gestation is twice that at 40 weeks and increases 4-fold at 43 weeks and 5- to 7-fold at 44 weeks.

Infant asphyxia (with and without meconium), uteroplacental insufficiency, intrauterine infection and anencephaly contribute to perinatal deaths.

Severe morbidities such as meconium and meconium aspiration, neonatal acidemia, low Apgar scores, macrosomia and birth injury are greater in infants born to post-term pregnancies progressing to and beyond 41 weeks gestation. Since post-term infants are larger than term infants, they are at greater risk of fetal macrosomia including prolonged labor, cephalopelvic disproportion and shoulder dystocia with resultant risks of orthopedic or neurologic injury.

Approximately 20 % of post-term fetuses have fetal dysmaturity (postmaturity) syndrome, which describes infants with characteristics of chronic intrauterine growth restriction from uteroplacental insufficiency. These pregnancies are at increased risk of umbilical cord compression from oligohydramnios, intrauterine passage of meconium, and short-term neonatal complications such as hypoglycemia, convulsions and respiratory insufficiency. Post-term pregnancy is also a risk factor for neonatal encephalopathy, cerebral palsy and for death in the first year of life.

Maternal risks and mode of delivery. The maternal risks of post-term pregnancy include an increase in labor dystocia, an increase in severe perineal injury due to macrosomia and operative vaginal delivery. The rate of cesarean delivery doubles. It is associated with higher risks of chorioamnionitis, endometritis, postpartum hemorrhage and thromboembolic disease.

Timing of delivery. Routine induction of labor at 40 weeks has few benefits, and there are multiple reasons not to allow a pregnancy to progress beyond 42 weeks.

Routine induction of labor at 41 weeks of gestation does not increase the cesarean delivery rate and may decrease it without negatively affecting perinatal morbidity or mortality. It is associated with a lower rate of adverse outcomes, including shoulder dystocia and meconium aspiration syndrome.

Prevention of post-term pregnancy. Minimally invasive interventions, e.g. membrane stripping, have been recommended to encourage the onset of labor at term and prevent post-term pregnancy. Stripping or sweeping of the fetal membranes is digital separation of the membranes from the wall of the cervix and lower uterine segment. This technique requires the cervix to be sufficiently dilated to admit the practitioner's finger.

Cervical ripening, ante- and intrapartum management. The majority of patients who reach 42 weeks' gestation have an unfavorable cervical examination (Bishop Score < 7).

Many options are available for cervical ripening. Currently available chemical preparations include prostaglandin E1 tablets for oral or vaginal use (misoprostol), prostaglandin E2 gel for intracervical application (dinoprostone cervical [Prepidil]), and a prostaglandin E2 vaginal insert (dinoprostone [Cervidil]). Cervidil contains 10 mg of dinoprostone and has a lower constant release of medication than Prepidil. In addition, this vaginal insert device allows for easier removal in the event of uterine hyperstimulation.

Another method for ripening the cervix is by mechanical dilation. These devices may act by a combination of mechanical forces and by causing release of endogenous prostaglandins. Foley balloon catheters placed in the cervix, extra-amniotic saline infusions and laminaria are effective.

In patients with a scarred uterus the use of these agents is dangerous. Care should also be taken when using combinations of mechanical and pharmacologic methods of cervical ripening.

The further the pregnancy progresses beyond 40 weeks, the more likely it is that significant amounts of meconium will be present. Traditionally, saline amnioinfusion and aggressive nasopharyngeal and oropharyngeal suctioning at the perineum were used to decrease the risk of meconium aspiration syndrome. Recent studies contradict this standard practice.

Fetal macrosomia can lead to maternal and fetal birth trauma and to arrest of both first- and second-stage labor. Macrosomia increases the risk of shoulder dystocia in the 2-nd stage of labor. In this case a practitioner should apply suprapubic pressure and maneuvers to reduce the shoulder dystocia.

Antepartum fetal surveillance is suggested in post-term pregnancies when delivery is not performed. Techniques include a nonstress test, contraction stress test, full biophysical profile, modified biophysical profile (nonstress test and amniotic fluid index), or a combination of these modalities. Doppler ultrasonography to evaluate the amniotic fluid level, utero-placental and feto-placental circulation is especially important. In case of any abnormality in the findings cesarean section is indicated.

Intrapartum fetal surveillance includes auscultation and fetal heart rate monitoring. Fetal scalp stimulation and/or fetal scalp blood sampling may also be used. If the findings show fetal intolerance to labor, the induction of labor should be discontinued and cesarean delivery is recommended.

DIABETES IN PREGNANCY

The prevalence of diagnosed diabetes is increasing. This increase primarily is due to type 2 diabetes, which is also referred to as *diabesity*, because of the strong relationship with the current epidemic of obesity. The increasing prevalence of type 2 diabetes in general, and in younger people in particular, has led to an increasing number of pregnancies with this complication.

PRECONCEPTION COUNSELING

Starting at puberty and continuing in all women with diabetes and reproductive potential, preconception counseling should be incorporated into routine diabetes care.

Family planning should be discussed, and effective contraception (with consideration of long-acting, reversible conception) should be prescribed and used until a woman's treatment regimen and average levels of blood glucose (A1C) are optimized for pregnancy.

Preconception counseling should address the importance of achieving glucose levels as close to normal as is safely possible, ideally A1C < 6.5 % (48 mmol/mol), to reduce the risk of congenital anomalies, preeclampsia, macrosomia and other complications.

Women with preexisting diabetes who are planning a pregnancy should ideally be managed beginning by a team of an endocrinologist and maternal-fetal medicine specialist. In addition to focused attention on achieving glycemic levels, standard preconception care should be combined with extra focus on nutrition, diabetes education and screening for diabetes comorbidities and complications.

Women with preexisting type 1 or type 2 diabetes should be counseled on the risk of development and/or progression of diabetic retinopathy. Dilated eye examinations should be performed before pregnancy or in the first trimester. Then patients should be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy and as recommended by the ophthalmologist.

Fasting and postprandial (after-meal) self-monitoring of blood glucose are recommended in both gestational diabetes mellitus and preexisting diabetes in pregnancy to achieve optimal glucose levels. Continuous glucose monitoring can reduce macrosomia and neonatal hypoglycemia in pregnancy complicated by type 1 diabetes.

CHECKLIST FOR PRECONCEPTION CARE FOR WOMEN WITH DIABETES

Preconception education should include:

- Comprehensive nutrition assessment and recommendations for:
  - Overweight/obesity or underweight
  - Meal planning
  - Correction of dietary nutritional deficiencies
  - Caffeine intake
  - Safe food preparation technique
- Lifestyle recommendations for:
  - Regular moderate exercise
  - Avoidance of hyperthermia (hot tubs)
  - Adequate sleep
- Comprehensive diabetes self-management education
- Counseling on diabetes in pregnancy per current standards, including: natural history of insulin resistance in pregnancy and postpartum; preconception glycemic targets; avoidance of DKA/severe hyperglycemia; avoidance of severe hypoglycemia; progression of retinopathy; PCOS (if applicable); fertility in patients with diabetes; genetics of diabetes; risks to pregnancy including miscarriage, still birth, congenital malformations, macrosomia, preterm labor and delivery, hypertensive disorders in pregnancy, etc.

● Supplementation:
– Folic acid supplement (400 mg routine)
– Appropriate use of over-the-counter medications and supplements

Medical assessment and plan should include:

● General evaluation of overall health

● Evaluation of diabetes and its comorbidities and complications, including: DKA/severe hyperglycemia; severe hypoglycemia/hypoglycemic unawareness; barriers to care; comorbidities such as hyperlipidemia, hypertension, NAFLD, PCOS, and thyroid dysfunction; complications such as macrovascular disease, nephropathy, neuropathy (including autonomic bowel and bladder dysfunction), and retinopathy

● Evaluation of obstetric/gynecologic history, including history of: cesarean section, congenital malformations or fetal loss, current methods of contraception, hypertensive disorders of pregnancy, postpartum hemorrhage, preterm delivery, previous macrosomia, Rh incompatibility, and thrombotic events (DVT/PE)

● Review of current medications and appropriateness during pregnancy

Screening should include:

● Diabetes complications and comorbidities, including: comprehensive foot exam; comprehensive ophthalmologic exam; ECG in women starting at age 35 years who have cardiac signs/symptoms or risk factors, and if abnormal, further evaluation; lipid panel; serum creatinine; TSH; and urine protein-to-creatinine ratio

● Anemia

● Genetic carrier status (based on history):
– Cystic fibrosis
– Sickle cell anemia
– Tay-Sachs disease
– Thalassemia
– Others if indicated

● Infectious disease
– *Neisseria gonorrhea/Chlamydia trachomatis;*
– Hepatitis C
– HIV
– Pap smear
– Syphilis

Immunizations should include:

● Rubella.
● Varicella
● Hepatitis B
● Influenza
● Others if indicated

Preconception plan should include:

● Nutrition and medication plan to achieve glycemic targets prior to conception, including appropriate implementation of monitoring, continuous glucose monitoring, and pump technology

● Contraceptive plan to prevent pregnancy until glycemic targets are achieved

● Management plan for general health, gynecologic concerns, comorbid conditions, or complications, if present, including: hypertension, nephropathy, retinopathy; Rh incompatibility; and thyroid dysfunction

DKA — diabetic ketoacidosis
DVT/PE — deep vein thrombosis/pulmonary embolism
ECG — electrocardiogram
NAFLD — nonalcoholic fatty liver disease
PCOS — polycystic ovary syndrome
TSH — thyroid-stimulating hormone

CLASSIFICATION AND DIAGNOSIS OF DIABETES

Classification of diabetes is based on the pathogenic processes involved. Type 1 diabetes is characterized by an absolute insulin deficiency, whereas type 2 diabetes is characterized by a defective insulin secretion or insulin resistance. Modern classification does not consider the patient's age because cell destruction can occur at any age. World Health Organization suggests the following criteria to diagnose diabetes mellitus (Table 8).

Table 8

WHO Diabetes Diagnostic Criteria

Condition	**2 hour glucose**	**Fasting glucose**	**HbA_{1c}**	
Unit	*mmol/L (mg/dL)*	*mmol/L (mg/dL)*	*mmol/mol*	*DCCT % (Diabetes control and complications trial)*
Normal	< 7.8 (< 140)	< 6.1 (< 110)	< 42	< 6.0
Impaired fasting glycaemia	< 7.8 (< 140)	≥ 6.1 (≥ 110) and < 7.0 (< 126)	42–46	6.0–6.4
Impaired glucose tolerance	≥ 7.8 (≥ 140)	< 7.0 (< 126)	42–46	6.0–6.4
Diabetes mellitus	**≥ 11.1 (≥ 200)**	**≥ 7.0 (≥ 126)**	**≥ 48**	**≥ 6.5**

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following:

1) fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL);

2) plasma glucose ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test;

3) symptoms of high blood sugar and casual plasma glucose ≥ 11.1 mmol/L (200 mg/dL);

4) glycated hemoglobin (HbA_{1c}) ≥ 48 mmol/mol (≥ 6.5 DCCT%).

Classification of diabetes mellitus according to the degree of the condition severity. Mild diabetes (degree I) is characterized by a low level of glycaemia not exceeding fasting level 8mmol/L and insignificant glycosuria (trace or up to 20 g/L). No significant alterations of plasma glucose level in 24h period are observed. In mild diabetes functional or pre-clinical angioneuropathy may be diagnosed.

In moderate diabetes (degree II) fasting plasma glucose level increases to 14 mmol/L. Glycaemia alterations and glycosuria not exceeding 40 g/L are observed in 24h period. There episodes of ketosis or ketoacidosis. Diabetic angioneuropathy of various localization and functional degree may be revealed.

Severe diabetes (degree III) is characterized by high levels of fasting plasma glucose (> 14 mmol/L). In 24h period, significant alterations of plasma glucose level and glycosuria (> 40–50 g/L) are observed. Different kinds of angioneuropathy are present.

Classification of diabetes during pregnancy. Diabetes is the most common medical complication of pregnancy. Women can be separated into those who were known to have diabetes before pregnancy (*pregestational* or *overt*) and those diagnosed during pregnancy (*gestational*).

The two subtypes of gestational diabetes under this classification system are:

1) Type A1: abnormal oral glucose tolerance test (OGTT), but normal blood glucose levels during fasting and two hours after meals; diet modification is sufficient to control glucose levels.

2) Type A2: abnormal oral glucose tolerance test (OGTT) compounded by abnormal glucose levels during fasting and/or after meals; additional therapy with insulin or other medications is required.

Diabetes present before pregnancy pregestational (overt) is classified into:

1) Type B: onset at age 20 or older and duration of less than 10 years.

2) Type C: onset at age 10–19 or duration of 10–19 years.

3) Type D: onset before age 10 or duration greater than 20 years.

4) Type E: pregestational (overt) diabetes mellitus with calcified pelvic vessels.

5) Type F: diabetic nephropathy.

6) Type R: proliferative retinopathy.

7) Type RF: retinopathy and nephropathy.

8) Type H: ischemic heart disease.

9) Type T: prior kidney transplant.

An early age of onset or long-standing disease comes with greater risks (types B, C, D).

Diagnosis of pregestational (overt) diabetes during pregnancy. Diagnosis of diabetes is based on high plasma glucose levels, glucosuria, and ketoacidosis. Similarly, women with a random plasma glucose level greater than 200 mg/dL plus classic signs and symptoms such as polydipsia (increased thirst), polyuria (increased urination), polyphagia (increased hunger) or a fasting glucose exceeding 125 mg/dL (12.5 g/L) are considered to have overt diabetes. The new diagnostic value for overt diabetes of a fasting plasma glucose of 126 mg/dL or

higher is used because data indicate that the risk of retinopathy rises dramatically at that fasting level. The risk of impaired carbohydrate metabolism is increased in women with a strong familial history of diabetes, large infants, persistent glucosuria, or unexplained fetal losses.

Detection of gestational diabetes. Gestational diabetes is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy.

Screening. *The selective screening* for gestational diabetes should be performed between 24 and 28 weeks in women with unknown glucose intolerance earlier in pregnancy.

There is not international agreement for the glucose tolerance test. In some countries, plasma glucose level is measured 1 hour after a 50-g glucose load without regard to the time of day or time of last meal. A value of 140 mg/dL (7.8 mmol/L) or higher identifies women with gestational diabetes. The World Health Organization has recommended the 75-g 2-hour oral glucose tolerance test, and this approach is often used in Europe. In the United States, the 100-g 3-hour oral glucose tolerance test performed after an overnight fast remains the standard (American College of Obstetricians and Gynecologists).

GESTATIONAL DIABETES. MATERNAL AND FETAL EFFECTS

There has been an important shift in focus concerning adverse fetal consequences of gestational diabetes. Gestational diabetes with elevated fasting glucose class A2 has been associated with unexplained stillbirth similar to pregestational (overt) diabetes. The American Diabetes Association has concluded that fasting hyperglycemia more than 105 mg/dL may be associated with an increased risk of fetal death during the last 4 to 8 weeks of gestation. Adverse maternal effects include an increased frequency of hypertension and cesarean delivery.

Macrosomia. Fetal macrosomia is defined as infants whose birth weight exceeds 4500 g. In patients with gestational diabetes and fetal macrosomia the delivery is often associated with concomitant birth trauma due to shoulder dystocia. Macrosomia affects most fetal organs except for the brain. Macrosomic infants of diabetic mothers are anthropometrically different from other large-for-gestational age infants (Fig. 10). They have excessive fat deposition on the shoulders and trunk, which predisposes to shoulder dystocia. Fat infants of diabetic women more often required cesarean delivery for cephalopelvic disproportion.

Macrosomia is compatible with the long-recognized association between fetal hyperinsulinemia resulting from maternal hyperglycemia, which in turn stimulates excessive somatic growth. Similarly, neonatal hyperinsulinemia may provoke hypoglycemia within minutes of birth. Values less than 35 mg/dL at term are abnormal. A lower value is considered abnormal in preterm infants, because glycogen stores have not reached term levels. 4 % of infants of women with gestational diabetes require intravenous glucose therapy for hypoglycemia.

Figure 10. Macrosomic infant

Maternal obesity is an independent and more important risk factor for large infants in women with gestational diabetes than is glucose intolerance. Maternal obesity is an important confounding factor in the diagnosis of gestational diabetes.

MANAGEMENT

Lifestyle behavior change is an essential component of management of gestational diabetes mellitus and may suffice for the treatment of many women.

Women with gestational diabetes can be divided into two functional classes using fasting glucose.

Insulin therapy is usually recommended when standard dietary management does not maintain the fasting plasma glucose at less than 95 mg/dL or the 2-hour plasma glucose after meals is less than 120 mg/dL.

Diet. The most agreed-upon recommendation is for the diet to be low in sugar and refined carbohydrates, while relatively high in dietary fiber, especially soluble fiber. Likewise, people with diabetes may be encouraged to reduce their intake of carbohydrates that have a high glycemic index (GI). In cases of hypoglycemia, they are advised to have food or drink that can raise blood glucose quickly, followed by a long-acting carbohydrate (such as rye bread) to prevent risk of further hypoglycemia.)

It has suggested that obese women with a body mass index greater than 30 kg/m^2 may benefit from a 30- to 33 % caloric restriction. This should be monitored with weekly tests for ketonuria, because maternal ketonemia is linked with impaired psychomotor development in their children.

Insulin. Insulin is the preferred medication for treating hyperglycemia in gestational diabetes mellitus. Most practitioners initiate insulin therapy in women with gestational diabetes if fasting glucose levels exceeding 105 mg/dL persist despite diet therapy. A total dose of 20 to 30 units given once daily, before breakfast, is commonly used to initiate therapy. The total dose is usually divided into two thirds intermediate-acting insulin and a third short-acting insulin.

Oral hypoglycemic agents are not recommended during pregnancy. *Metformin* used as a treatment for infertility due to polycystic ovarian disease also reduces the incidence of gestational diabetes in women. It is usually recommended that metformin be discontinued once pregnancy is diagnosed (by the end of the first trimester). Metformin and glyburide should not be used as first-line agents, as both cross the placenta to the fetus. Other oral and noninsulin injectable glucose-lowering medications lack long-term data.

Obstetrical management. Women with gestational diabetes who require insulin seldom require early delivery or other interventions. Cesarean delivery should be recommended in women with a sonographically estimated fetal weight of 4000 grams or more. Women who require insulin therapy for fasting hyperglycemia, however, typically undergo fetal testing and are managed as if they had overt diabetes.

PREGESTATIONAL (OVERT) DIABETES

Unlike gestational diabetes, it is unquestioned that overt diabetes has a significant impact on pregnancy outcome. The embryo, the fetus, and the mother can experience serious complications due to diabetes. Successful outcomes with overt diabetes are related somewhat to the degree of glycemic control, but underlying cardiovascular or renal diseases significantly increase the risk of complications during the delivery. Women in the more advanced classes of overt diabetes increasingly develop preeclampsia.

FETAL EFFECTS

Abortion. First-trimester abortion is associated with poor glycemic control.

Preterm delivery. Pregestational diabetes is a risk factor for preterm birth.

Malformations. The incidence of major malformations in women with type 1 diabetes is about 5 %. Fetal anomalies account for almost half of perinatal deaths in diabetic pregnancies. Importantly, diabetes is not associated with increased risk for fetal chromosomal abnormalities.

Unexplained fetal death. Stillbirths without identifiable causes are a phenomenon found in pregnancies complicated by pregestational diabetes. They are declared “unexplained” because no factors such as obvious placental insufficiency, abruption, fetal growth restriction, or oligohydramnios are apparent. These infants are typically large-for-gestational age and die before labor, usually at 35 weeks or later. Investigations using cordocentesis have provided new insights into acid-base metabolism in fetuses of diabetic mothers.

Decreased fetal pH and increased Pco_2, lactate, and erythropoietin were determined in diabetic pregnancies. Such findings confirmed the hypothesis that hyperglycemia-mediated chronic aberrations in transport of oxygen and fetal metabolites may account for unexplained fetal deaths.

Explicable stillbirths due to placental insufficiency also occur with increased frequency in women with overt diabetes, usually in association with severe preeclampsia. This, in turn, is increased in women with advanced diabetes and vascular complications.

Similarly, ketoacidosis can cause fetal death.

Hydramnios. Although diabetic pregnancies are often complicated by hydramnios, the cause is unclear. A possible explanation is fetal polyuria resulting from fetal hyperglycemia. Amnionic fluid index parallels the amnionic fluid glucose level among women with diabetes. Hydramnios associated with diabetes is a result of increased amnionic fluid glucose concentration.

EFFECTS IN NEONATES

There is still an increased frequency of preterm delivery in women with diabetes. Most preterm births are associated with advanced diabetes and associated with preeclampsia.

Modern neonatal care has largely eliminated neonatal deaths due to immaturity. However, neonatal *morbidity* due to preterm birth continues to be a serious consequence. Clinicians consider that some of the morbidities in these infants are directly related with disorders in maternal glucose metabolism.

Respiratory distress. In diabetic pregnancies, fetal lung maturation may be delayed and these infants are at increased risk for respiratory distress. Subsequent observations have suggested that gestational age rather than overt diabetes is the most significant factor associated with neonatal respiratory distress.

Hypoglycemia. A rapid decrease in plasma glucose concentration after delivery is characteristic of the infant of a diabetic mother. It is due to hyperplasia of the fetal-islet cells induced by chronic maternal hyperglycemia. Prompt recognition and treatment of the hypoglycemic infant minimize the consequences.

Hypocalcemia. Hypocalcemia (serum calcium concentration less than 7 mg/dL) is one of the serious metabolic disorders in infants of diabetic mothers. Its cause has not been explained. Theories include aberrations in magnesium-calcium economy, asphyxia, and preterm birth.

Hyperbilirubinemia. The pathogenesis of hyperbilirubinemia in infants of diabetic mothers is uncertain. Factors implicated have included preterm birth and polycythemia with hemolysis. Venous hematocrits of 65 to 70 volume percent is observed in 40 % of these infants. Renal vein thrombosis also results from polycythemia.

Cardiac hypertrophy. Infants of diabetic pregnancies may have hypertrophic cardiomyopathy that sometimes progresses to congestive heart failure. These infants typically have macrosomia, and fetal hyperinsulinemia has been implicated in the pathogenesis of heart disease. Cardiomyopathy generally disappears by 6 months of age.

Inheritance of diabetes. Infants born to women with overt diabetes have a low risk of developing type 1 diabetes; the incidence ranges 1–3 %. The risk is

6% if only the father has overt diabetes. If both parents have type 1 diabetes, the risk is 20%. Older maternal age and maternal type 1 diabetes are important risk factors. Breast feeding by diabetic mothers may be implicated in the genesis of childhood diabetes.

Altered fetal growth. The incidence of macrosomia rises significantly when mean maternal blood glucose concentrations exceed 130 mg/dL.

MATERNAL EFFECTS

Diabetes and pregnancy suppose the risk for maternal health. Pregnancy does not affect the long-term course of diabetes with the possible exception of diabetic retinopathy. Maternal deaths in women with diabetes are still increased. They most often result from ketoacidosis, hypertension, preeclampsia, and pyelonephritis. Women with coronary artery disease (class H diabetes, ischemic heart disease) are at particular risk.

Diabetic nephropathy. The incidence of renal failure is nearly 30 % in individuals with type 1 diabetes and ranges 4–20 % in those with type 2 diabetes. Clinically detectable nephropathy in type 1 disease begins with microalbuminuria (30 to 300 mg/24 h of albumin). It may manifest as early as 5 years after the onset of diabetes. After another 5 to 10 years, overt proteinuria (more than 300 mg/24 h of albumin) will develop into end-stage renal disease. During this period, hypertension and renal failure typically develop in the next 5 to 10 years. Approximately 5 % of pregnant women with diabetes have diabetic nephropathy (class F). These women have significantly increased preeclampsia and indicated preterm delivery.

Diabetic retinopathy. Retinal vasculopathy is a highly specific complication of both type 1 and type 2 diabetes. Its prevalence is related to duration of diabetes. After 20 years, nearly all patients with type 1 diabetes and more than 60 % of those with type 2 diabetes have some degree of retinopathy. Laser photocoagulation and good glycemic control during pregnancy minimize the risk of eye pathology.

Diabetic neuropathy. Some pregnant women have peripheral symmetrical sensorimotor diabetic neuropathy. A form of this, known as *diabetic gastropathy*, is very troublesome in pregnancy because it causes nausea and vomiting, nutritional problems, and difficulty with glucose control. Treatment with metoclopramide and H_2-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) is sometimes successful.

Infections. Almost all types of infections are increased in diabetic pregnancies. Common infections include candida vulvovaginitis, urinary infections, respiratory tract infections, and puerperal pelvic infections.

MANAGEMENT

Management preferably should begin before pregnancy and include specific goals during each trimester. To prevent early pregnancy loss as well as congenital malformations in infants of diabetic mothers, optimal medical care and patient education are recommended before conception.

First Trimester. Careful monitoring of glucose control is essential. These women are hospitalized during early pregnancy to work out an individualized glucose control program and to provide education concerning the whole course of pregnancy. It also helps to assess the extent of vascular complications of diabetes and to establish gestational age more precisely.

Dosage monitoring and administration regimens are adjusted based on individual response to nutrition interventions, exercise and insulin administration techniques. For a woman who first presents during pregnancy for care, whether she has type 1, type 2 or gestational diabetes, an insulin dose based on gestational age and current weight provides a starting point (total daily dose) for further adjustments based on activity, meal plan and other factors (Table 9).

Table 9

Suggested Starting Total Daily Insulin during Pregnancy

Gestation weeks	Total daily insulin
Week 1–18	0.7 U/kg actual body weight
Weeks 18–26	0.8 U/kg actual body weight
Weeks 26–36	0.9 U/kg actual body weight
Weeks 36–40	1.0 U/kg actual body weight

Stress, sepsis, steroids, obesity and advancing pregnancy increase insulin needs. Multiple daily injections provide the most optimal control during pregnancy. Oral hypoglycemic agents are not usually used because they may cause fetal hyperinsulinemia. Increased rates of congenital malformations, especially ear defects, were demonstrated in infants of women treated during early pregnancy with oral hypoglycemic drugs.

New technology under development may provide noninvasive glucose monitoring. Such an automatic and painless means to obtain blood glucose information would undoubtedly greatly facilitate patient compliance. It extracts glucose through the skin using electrical potentials, a process known as iontophoresis. It then measures glucose concentrations in the extracted sample. The device provides up to three glucose readings per hour and causes only transient mild skin irritation at the sensor site. Subcutaneous insulin infusion by a calibrated pump (Fig. 11) may be used during pregnancy. Patients who use an insulin pump must be highly motivated and compliant to minimize the risk of nocturnal hypoglycemia.

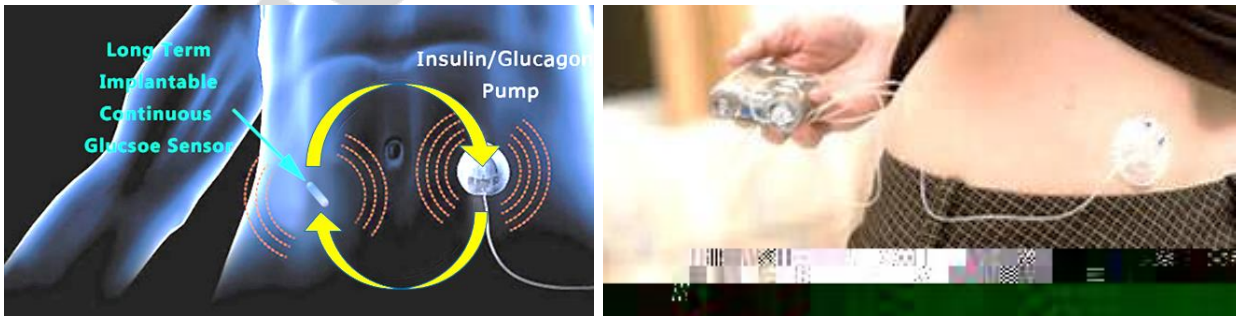

Figure 11. Calibrated insulin pump

Euglycemia based on normal pregnancy blood glucose values is the goal in management of women with overt diabetes, but achieving this goal is not always possible. Thus, individualized programs are often necessary to avoid both excessive hyperglycemia as well as frequent episodes of hypoglycemia. Diabetes tends to be unstable in the first trimester, followed by a stable period, and then by an increase in insulin requirement after about 24 weeks. This rise is due to the increased production of pregnancy hormones, which are insulin antagonists.

Women with type 1 or type 2 diabetes mellitus should be prescribed low-dose aspirin 60–150 mg/day (usual dose 81 mg/day) by the end of the first trimester in order to lower the risk of preeclampsia.

Second trimester. Maternal serum alpha-fetoprotein concentration at 16 to 20 weeks is used in association with targeted ultrasound at 18 to 20 weeks in an attempt to detect neural-tube defects and other anomalies. Maternal alpha-fetoprotein levels may be lower in diabetic pregnancies.

Third trimester and delivery. In the woman with overt diabetes in the class B or C, cesarean delivery is commonly used to avoid traumatic birth of a large infant at or near term. In women with more advanced diabetes, especially those with vascular disease, cesarean delivery is recommended. Labor induction may be attempted when the fetus is not excessively large and the cervix is considered favorable. Cesarean delivery reduces the perinatal mortality.

It is important to considerably reduce or delete the dose of long-acting insulin given on the day of delivery. Regular insulin should be used to meet most or all of the insulin needs of the mother at this time, because insulin requirements typically drop markedly after delivery. Constant insulin infusion by calibrated pump is most satisfactory.

During labor and after either cesarean or vaginal delivery, the woman should have intravenous infusions to maintain fluid balance. Glucose in sufficient amounts should be given to maintain its normal level. Capillary or plasma glucose levels should be checked frequently, and regular insulin should be administered accordingly. Infection must be promptly detected and treated.

Postpartum care. Insulin resistance decreases significantly immediately postpartum, and insulin requirements need to be evaluated and adjusted as they are often roughly half the pre-pregnancy requirements for the initial few days postpartum.

A contraceptive plan should be discussed and implemented with all women with diabetes of reproductive potential.

Women with a recent history of gestational diabetes should be screened at 4–12 weeks postpartum, using the 75-g oral glucose tolerance test and clinically appropriate nonpregnacy diagnostic criteria.

Women with a history of gestational diabetes mellitus found to have prediabetes should receive intensive lifestyle interventions and/or metformin to prevent diabetes.

Women with a history of gestational diabetes mellitus should have lifelong screening for the development of type 2 diabetes or prediabetes at least every 3 years.

Women with a history of gestational diabetes mellitus should seek preconception screening for diabetes and preconception care to identify and treat hyperglycemia and prevent congenital malformations.

Postpartum care should include psychosocial assessment and support for self-care.

Lactation. In the light of the immediate nutritional and immunological benefits of breastfeeding for the baby, all women including those with diabetes should be supported in attempts to breastfeed. Breastfeeding may also confer longer-term metabolic benefits to both mother and baby. However, lactation can increase the risk of overnight hypoglycemia, and insulin dosing may need to be adjusted.

REFERENCES

1. *Abbott, J.* Obstetrics and gynaecology an evidence-based guide / J. Abbott, L. Bowyer. Melbourne : Mosby, 2014. 658 p.

2. *Beischer &* Mackay's Obstetrics, Gynecology and the newborn. Philadelphia : Elsevier, 2015. 900 p.

3. *Clinical* obstetrics and gynaecology / ed. B. Magowan, P. Owen, A. Thomson. London : Saunders, 2014. 464 p.

4. *Hee, L.* Overview of the methods available for biomechanical testing of the uterine cervix in vivo / L. Hee // Acta Obstet. et Gynecol. Scand. 2014. Vol. 93, N 12. P. 1219–1237.

5. https://www.medscape.com. [Электронный ресурс]. Режим доступа : https://www.medscape.com/womenshealth. Дата доступа : 27.10.2020.

6. *Hypertensive* disorders of pregnancy. ISSHP classification, diagnosis, and management recommendations for international practice. American Heart Association Journals // Hypertension. 2018. Vol. 72, N 1. P. 24–43 [Электронный ресурс]. Режим доступа : https://www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.117.10803.

7. *Izquierdo, L. A.* Fetal surveillance in late pregnancy and during labor / L. A. Izquierdo, N. Yonke // Obstet. and Gynecol. Clin. of North Am. 2014. Vol. 41, N 2. P. 307–315.

8. *Management* of Diabetes in Pregnancy: Standards of Medical Care in Diabetes – 2020 American Diabetes Association Diabetes Care 2020 Jan; 43 (Supplement 1): S183-S192. [Электронный ресурс]. Режим доступа : https://doi.org/10.2337/dc20-S014.

9. *Merk* Manual. [Электронный ресурс]. Режим доступа : https://www.merckmanuals.com. Дата доступа : 27.10.2020.

10. *Middle* cerebral artery Doppler pulsatility index as a predictor of intrapartum meconium release in prolonged pregnancies / M. J. Canto [et al.] // Journal of Neonatal-Perinatal Medicine. 2020. Vol. 13, N 3. P. 339–344.

11. *Obstetrics* and Gynecology / R. B. Beckmann [et al.]. 7 ed. Philadelphia : Lippincott Williams & Wilkins, 2013. 528 p.

12. *Precocious* cervical ripening as a screening target to predict spontaneous preterm delivery among asymptomatic singleton pregnancies: a systematic review / Q. Li [et al.] // Am. J. of Obstet. and Gynecol. 2015. Vol. 212, N 2. P. 145–156.

13. *Preterm* birth / ed. O. Erez. London : Chapters published, 2013. 198 p.

14. *Progestogens* in Obstetrics and Gynecology / ed. H. J. A. Carp. Berlin : Springer Int. Publ, 2015. 202 p.

15. *Radiological* Interventions in Obstetrics and Gynaecology / ed. J. Reidy, N. Hacking, B. McLucas. Berlin : Springer Heidelberg, 2014. 180 p.

16. *The contribution* of genetic and environmental factors to the duration of pregnancy / T. P. York [et al.] // Am. J. of Obstet. and Gynecol. 2014. Vol. 210, N 5. P. 398–405.

17. *The global* epidemiology of preterm birth / J. P. Vogel [et al.] // Elsevier Best Practice & Research Clinical Obstetrics & Gynaecology. 2018. Vol. 52. P. 3–12 [Электронный ресурс]. Режим доступа : https://doi.org/10.1016/j.bpobgyn.2018.04.003.

18. *Williams* Obstetrics. 25th ed. Copyright by McGraw-Hill Education, 2018.

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