Chapter

Haemodynamic Changes during Preterm Birth Treatment

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Abstract

The well-being of the fetus depends on the efficiency of its circulatory system and the proper maternal-fetal exchange. Hemodynamic changes can occur due to disturbance of fetal and maternal homeostasis, malformations, pregnancy pathology, and medications. Preterm labor directly affects maternal-fetal haemodynamics, both due to uterine contractions and medications used to inhibit it. Research on maternal-fetal haemodynamics in preterm labor is currently focused mainly on the safety of the used tocolytics. In this chapter, we will discuss the basic principles of fetal haemodynamics, ultrasound methods of maternal-fetal circulation assessment, and the influence of preterm labor on maternal-fetal haemodynamics, with particular emphasis on medications used in threatening and progressive preterm labor.

Keywords: preterm labor, maternal-fetal haemodynamics, doppler

1. Introduction

During pregnancy, the maternal body undergoes significant hemodynamic changes to ensure normal fetal growth. On average, maternal cardiac output can increase up to 30%–45%, resulting mostly from the intensified metabolism, increased circulating blood mass, the appearance of an accessory placental circulatory system, and finally, a gradual increase in body weight during pregnancy. Although blood volume increases, the systemic blood pressure in a healthy mother undergoes no significant changes. This is mainly due to a decrease in total peripheral vascular resistance, primarily at the arteriolar level. The mammalian placenta is also important for the regulation of both the maternal and fetal circulations. Adequate uterine blood flow is critical to fetal growth and development [1]. Fetal heart undergoes functional changes: throughout gestation, the fetal myocardium becomes more compliant and making ventricular filling less dependent on atrial contraction. Both the increase in size and the maturational changes lead to a tremendous increase in cardiac output [2].

2. Maternal-fetal circulation

The primary heart and vascular system appear in the middle of the third week of development. On about 22nd-23rd day, the heart begins its systolic action.

Oxygenated blood, rich in nutrients, flows through the umbilical vein from the placenta to the portal sinus. The portal sinus is a wide L-shaped vessel at the terminal end of the umbilical vein, connecting two main vessels termed the right and left intrahepatic portal veins perfusing the right and left hepatic lobes. It then goes into the ductus venosus. The ductus venosus originated from the portal sinus as the latter turned at an almost right angle into the right lobe of the liver. The ductus venosus is a branchless, hourglass-shaped vessel that ascends steeply in the direction of the diaphragm. The blood flow in the ductus venosus is regulated by the sphincter mechanism. The blood then flows in the inferior vena cava and enters the right atrium of the heart. Most of the blood from the inferior vena cava is directed to the secondary septum through the oval foramen to the left atrium. There it mixes with a relatively small amount of poorly oxygenated blood returning through the pulmonary veins from the lungs. The blood from the left atrium flows into the left ventricle and leaves it through the ascending aorta. The arteries that supply the heart, head, neck and upper limbs receive well-oxygenated blood. The small amount of well-oxygenated blood from the inferior vena cava that remains in the right atrium of the heart mixes with the poorly oxygenated blood from the superior vena cava and coronary sinus and flows into the right ventricle. This blood leaves the right heart through the pulmonary trunk. Due to the high pulmonary vascular resistance during fetal life, blood flow through the lungs is low. About 10% of the blood flows to the lungs and most of it flows through the arterial duct to the fetal aorta. The blood returns to the placenta through the umbilical arteries [3, 4].

3. Vascular flow testing using Doppler ultrasonography

Doppler examination assessing the vascular flow of the maternal-fetal circulation is an important diagnostic tool in the assessment of the well-being of the fetus. The analysis of vascular flows is also used to make decisions about the further duration of pregnancy. It is often a pregnancy complicated by diseases that threaten the life of the mother and the fetus. Due to the high risk of iatrogenic prematurity, the experience of the person performing the ultrasound examination is extremely important, taking into account the factors that may affect the parameters of the vascular flow wave. Overinterpretation of the Doppler results may expose both parents and the perinatological team to unnecessary stress, medical activities and costs [5, 6].

The safety of ultrasound examinations is based on the degree of fetal exposure, which depends on the amount and duration of ultrasound examinations and the energy used for the examination. It takes into account the control of the thermal and mechanical index and the superior principle of using the lowest dose of energy that allows correct imaging - ALARA (as low as reasonably achievable). The term thermal index describes the quotient of the power lost to the reference power that increases the tissue temperature by 1 °C. The mechanical index describes the amplitude of the ultrasound wave. Ensuring the safety of ultrasound examination is only possible through excellent knowledge of anatomy and embryology, as well as regular index control when changing the settings of the ultrasound machine.

The table contains the most frequently assessed vascular flows along with their correct imaging.

Vessel	Visualization	Doppler sample volume (mm)	Insonation angle	Flow velocity/ waveforms
Umbilical artery	Free loop of the umbilical cord, without fetal breathing movements	2–3	<30°	4–6 waveforms
Middle cerebral artery	Cross-section of the brain, visualization of the Willis circle, mapping on the proximal side of the transducer, Doppler gate in the 1/3 proximal course of the vessel, as little pressure as possible on the fetal head - high risk of change of intracranial pressure and flow velocity	2–3	<30°	3–10 waveforms
Ductus venosus	Sagittal or transverse section of the fetus	0,5–1	<30°	3–6, velocity > 30 cm/s
Uterine arteries	Measurement on the right and left side of the patient, after visualizing the junction with the iliac vessels, cephalic direction	2	<30°	3–6, velocity > 50 cm/s

The special structure of the fetal uteroplacental, umbilical and cerebral circulation ensures a constant vascular flow in the fetus, independent of the mother's heart cycle. This system gradually develops in the utero-fetal circulation. The significant effect of this phenomenon consists not only in the gradual increase in the end-diastolic velocity of the flow wave, but also in the accompanying decrease in pulsation, which is the difference between the components of the maximum systolic and end-diastolic velocity.

The correct shape of the flow wave of both the fetal middle cerebral artery and the umbilical cord artery is not characterized by the disappearance of the flow wave or its inversion. It is one of the disparities in the fetal circulatory system that does not give a compensatory break in the heart's work. If it occurs, it is called absent flow or reverse flow. Both of these phenomena are among the alarm signals of poor fetal condition [7].

3.1 Mistakes in Doppler examination

Due to incomplete bone calcification, the head of a premature fetus is susceptible to pressure. Excessive pressure with the transducer may indicate the disappearance of the end-diastolic wave in the assessed fetal middle cerebral artery [7, 8].

The assessment of the vascular flow spectrum should cover several fetal heartbeat cycles. One of the reasons for doing this are the breathing movements of the fetus, which can disrupt the normal flow spectrum. Similar phenomena can be observed when a pregnant woman breathes too deeply. In order to verify the correctness of the vascular flow, a patient should be asked to shorten her breath or even temporarily stop breathing.

Incorrect parameters of the ultrasound device settings may falsify the Doppler measurements.

Corticosteroids administered to the mother to stimulate the maturation of the fetal lungs in the event of impending preterm labor may temporarily "improve" the

flow waves. In that case, it is reasonable to repeat the Doppler examination approximately 48 hours after administering the medications [7, 9].

4. Medications used in the preterm labor

The use of medications should take place primarily in compliance with the principles of patient safety and the minimum risk of side effects. The problem of therapy in pregnancy is related to the limited possibility of testing the effects of the medication on the pregnant woman and the fetus, and often the lack of consent to perform such tests. Therefore, medications used in pregnancy often have limited indications and are administered taking into account the individual risks and benefits of therapy. The pharmacological action of the medication in the fetus must take into account the kinetics of its transformations in the mother's organism as well as in the placenta. The distribution of the medication and its metabolism in the mother's body determine its availability to the fetus. Since pregnancy involves profound physiological and biochemical changes, the metabolism of many medications is also significantly altered. Data from animal studies suggest that the rate of metabolism of medications in the liver decreases during pregnancy and their availability to the fetus may be greater than expected. The transfer of the medication from the mother's body to the fetus takes place from arterial blood through the intervillous spaces to the fetal capillaries in the villi and further through the umbilical vein.

Despite the fact that the placenta is treated as a specific protective barrier for the fetus, it has little ability to metabolize medications. Many medications can reach the fetus in the form of metabolites, often more toxic [10]. The safety of the use of tocolytics is still a significant perinatological problem. The duration of tocolysis should be short enough to allow the full effect of steroid therapy on the fetus, with the least negative impact on the health of the mother and child [11].

The most commonly used medications that inhibit uterine contractions are discussed below, with particular emphasis on their effects on the circulatory system of the mother and the fetus.

4.1 Calcium channel blockers – nifedipine

Nifedipine contains the formula of a short- and long-acting 1,4-dihydropyridine calcium channel blocker. It prevents contraction of calcium-dependent myocytes and their vessels by blocking the influx of calcium into smooth muscle cells. The second possible vasodilatory mechanism is the inhibition of pH-dependent calcium influx by inhibiting smooth muscle carbonic anhydrase. Nifedipine is used to treat high blood pressure and chronic stable angina. At therapeutic sub-toxic concentrations, it has little effect on myocardium and conducting cells. Inhibition of calcium influx lowers smooth muscle contraction, which causes dilation of the coronary and systemic arteries, increased oxygen delivery to the muscle tissue, reduced total peripheral resistance, blood pressure and afterload.

The most common side effect of nifedipine reported by mothers is headache associated with a transient reduction in blood pressure after initiating therapy. The second common effect is tachycardia. In addition, dizziness, drowsiness, nausea, a sharp drop in blood pressure, slurred speech and weakness may occur. One in ten patients may experience palpitations and hot flushes. Severe side effects, such as myocardial infarction, maternal dyspnea, patient hypoxia, severe maternal hypotension with intrauterine fetal death, atrial fibrillation were also observed during nifedipine therapy. Pulmonary edema has been reported in a group of pregnant patients after taking nifedipine.

It is not recommended for use in patients with twin pregnancies due to the more frequent occurrence of dyspnea. It is absolutely contraindicated in the group of patients with heart disease, maternal hypertension and intrauterine infection. Dyspnea occurring in twin pregnancy is explained by a reduced blood flow and the degree of lung ventilation due to the higher elevated diaphragm dome [11–15]. Nifedipine has no effect on motor activity, heart rate and blood flow in the fetus. The occurrence of side effects is not related to the level of this medication in the patient's blood serum, so there is no need to adjust its dose based on body weight, body mass index (BMI) or gestational age [14].

In a study carried out on laboratory animals, the effect of nifedipine on the normal development of pregnancy was assessed. After administration of three and thirty times higher doses of nifedipine than recommended for humans, dilatation of blood vessels, increased vascularization of the uterus and placenta, and trophoblast hyperplasia were observed in both groups. Higher placental weights were seen in the higher dose group, but this had no effect on fetal survival or an increased risk of birth defects. Fetal weight did not differ from the control group at the lower dose, but statistically significantly lower weight was reported for the group with the higher dose of the drug. As expected, there were changes in the uterine muscle and collagen structure of the cervix during tocolysis. The authors concluded that the use of nifedipine in pregnancy in acceptable doses should not have a negative impact on the condition of fetuses and newborns, and that this therapy often improves the prognosis [16].

The optimal dose of nifedipine is still being determined. The starting dose in most studies was 10 mg either orally or sublingually. If uterine contractions were maintained, the dose was repeated every 15–20 minutes, until a dose of 40 mg was obtained in the first hour. Then, maintenance therapy is 20 mg every 6–8 hours for two to three days [14].

In a comparative study of nifedipine and another tocolytic combined with steriodotherapy, no significant risk to the fetuses was observed [17].

4.2 Beta-adrenergic receptor agonists

Ritodrine stimulates the beta-2-adrenergic receptor, increasing the level of cAMP and decreasing the concentration of intracellular calcium, which in turn leads to the relaxation of uterine smooth muscles and a reduction in the frequency of uterine contractions.

Terbutaline is a relatively selective bronchodilator with little or no effect on alpha-adrenergic receptors. It appears to have a greater effect on stimulating the beta receptors of the bronchi, vessels and smooth muscle, including the uterus (beta-2 receptors), than at the heart receptors (beta-1). This drug relaxes smooth muscles and inhibits uterine contractions, but it can also have a stimulating effect on the heart and central nervous system.

The mechanism of action is based on the stimulation of beta-adrenergic receptors in intracellular adenylate cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic adenosine 3 ', 5'-monophosphate (c-AMP). Elevated levels of c-AMP are associated with relaxation of bronchial smooth muscles and inhibition of the release of immune system mediators, especially from mast cells.

Fenoterol stimulates beta-2 receptors in the lungs and causes bronchial smooth muscle relaxation, bronchodilation and increased air flow. Symptoms of overdose are chest pain, dizziness, dry mouth, fatigue, flu-like symptoms, headaches, heart abnormalities, high or low blood pressure, high blood glycemia, insomnia, muscle spasms, nausea, nervousness, rapid heartbeat, seizures and tremors.

4.3 Prostaglandin synthesis inhibitors – indomethacin

As an analgesic and antipyretic drug, indomethacin inhibits the secretion of prostaglandins involved in the pain reaction, fever and inflammation. Symptoms of overdose: nausea, vomiting, severe headache, dizziness, confusion or lethargy. There have been reports of paraesthesia, numbness and convulsions.

4.4 Magnesium sulfate

Magnesium sulfate reduces striated muscle contraction and blocks neuromuscular transmission, reducing the release of acetylcholine. In addition, magnesium inhibits the inflow of calcium, enhancing the relaxing effect of vascular smooth muscles [12]. It is currently treated as a mild tocolytic. Used in fetal neuroprotection in preterm labor below 32 weeks of pregnancy.

4.5 Oxytocin receptor antagonist – atosiban

It is a competitive antagonist of human oxytocin at the receptor level. In rats and guinea pigs, atosiban has been observed to bind to oxytocin receptors, reducing the frequency of contractions and the tension of the uterine muscles, thereby reducing uterine contractions. Atosiban has also been observed to bind to vasopressin receptors, reducing its effect. In animals, atosiban had no effect on the cardiovascular system. In women at risk of preterm labor, atosiban, at the recommended doses, prevents uterine contractions and induces a resting state of the uterus. Uterine relaxation following atosiban administration is rapid, uterine contractions are significantly reduced within ten minutes, and uterine quiescence of less than four contractions per hour is achieved and stable for twelve hours.

In women at risk of preterm labor receiving atosiban by intravenous infusion (300 micrograms per minute for six to twelve hours), steady-state plasma concentrations were reached within one hour of starting the infusion.

The use of atosiban below 24 and above 33 weeks of pregnancy is contraindicated. There was no evidence of fetal toxicity. Small amounts of the drug are excreted into breast milk, no effect of the drug on breastfeeding has been acknowledged.

The most common side effects of treatment with this preparation include nausea, headache and dizziness, hot flushes and an increase in heart rate [18].

4.6 Medications that relax the uterine muscles

Scopolamine (hyoscine) is an alkaloid. Along with its derivatives, it resembles atropine and has a similar effect, but with a greater influence on the nervous system. Hyoscine belongs to a group of medications called parasympatholytics. The action of cholinolytic medications is to block the stimulation of cholinergic receptors (activated by acetylcholine). Hyoscine acts on muscarinic receptors and relaxes smooth muscles of the gastrointestinal, biliary and urogenital tract.

Side effects may include dry mouth, atonic constipation, increased urination disorders, urinary retention, decreased sweat secretion, increased heart rate (tachycardia), hypotension, and visual disturbances [12, 18].

Drotaverine inhibits the activity of the phosphodiesterase IV enzyme, which leads to an increase in the concentration of cAMP and a further cascade of intracellular reactions that result in the relaxation of the muscle cell. It may also have calcium channel blocking abilities.

The relaxant effect affects the smooth muscles of the gastrointestinal tract, urogenital system, cardiovascular system and bile ducts and is stronger than that of papaverine. It is used in the case of contraction of smooth muscles of both nervous and muscular origin. Side effects are rare and similar to scopolamine [12, 18].

5. Effect of preterm labor and its treatment on maternal-fetal hemodynamics

5.1 Patient's body position

Khatib et al. analyzed changes in vascular flow in the fetal circulation when changing the left lateral to supine position in pregnant women in the third trimester. Test time was approximately fifteen minutes. The authors noted a statistically significant decrease in the value of the pulsation index in the middle cerebral and umbilical artery, as well as a decrease in the maximum systolic velocity of the middle cerebral artery and the systolic-diastolic index of the umbilical artery [19]. It is most likely related to the symptom of brain sparring of the fetal circulation. As can be seen from the above studies, the mechanisms of circulatory centralization are not only activated by the pathological condition, but also by a stressful situation for the fetus, such as changing the position from a comfortable left-lateral or vertical position to a supine position, limiting the correct placental-fetal flow. The mechanism of fetal circulation centralization protects the fetus in a situation of persistent limited blood flow. Vascular resistance in the cerebral circulation is reduced, which allows blood flow to the brain to be increased.

Katwijk and Wladimiroff analyzed changes in the value of flows in the umbilical artery when the body position changes. When changing the patient's body position from vertical to lying, they noted an increase in the umbilical artery pulsation and resistance index, regardless of the gestational age, and this is explained by the flow mechanism of a lock [20].

Kinsella et al. in the group of twenty pregnant women in the third trimester did not observe any changes in the flow in the fetal umbilical artery when the patient's body position was changed [21].

Similarly, Armstrong et al. in the group of twenty-five full-term pregnant women qualified for elective cesarean section did not observe changes in vascular flow depending on the different positions of the patient's body. The authors assume that the degree of compression of the inferior vena cava and aorta in different body positions is not significant enough to disturb the vascular flow in the umbilical artery, or that these changes are so subtle that Doppler devices are unable to capture them [22].

Marx et al. monitored the vascular flow in the umbilical cord in various body positions in the early stage of labor. The systolic-diastolic index of the umbilical artery was significantly higher in the supine position compared to the left-lateral position of the patient, which in turn led to an increase in vascular resistance in the umbilical artery [23].

Inferior vena cava syndrome most often occurs in the third trimester of pregnancy, when a large weight of the pregnant uterus presses on the inferior vena cava, especially in the supine position, which disturbs the maternal-fetal flow and may lead to fainting, and consequently the fetus to hypoxia. Ryo et al. undertook studies to determine the risk of inferior vena cava syndrome in the second trimester of pregnancy and its consequences for the fetus. In a group of ninety Japanese pregnant women between the twenty-fourth and twenty-seventh weeks of pregnancy, they assessed umbilical artery flow and its relationship with uteroplacental flow.

There were no changes in the umbilical artery resistance index during the five-minute supine position of the patient [24].

In a study by Qu et al. on a group of fifty pregnant women between the twenty-seventh and forty weeks of gestation, no changes in the umbilical artery flow values were found when the patient's body position was changed [25], similarly to Backe et al. [26], while Sorensen et al. did not report changes in the systolic-diastolic index in patients with normal blood pressure [27].

Kinsella et al. and Witter and Besinger did not find statistically significant changes in uterine artery flows depending on the patient's body position and the duration of the study [21, 28].

In the group between thirty-seven and forty weeks of pregnancy, Qu et al. observed a statistically significant increase in the resistance index in the uterine arteries after changing the position of the pregnant woman [25].

Sohn et al. proved that uterine flow clearly decreases in the sitting and standing position of the pregnant woman, which is associated with an increase in vascular resistance. In the conclusions, the authors emphasize that apart from uterine contractions, there are also other factors influencing uterine flow, which may be important in the monitoring of fetuses with limited growth rate [29]. In another work, the author presents the concept of selecting a safe position of the patient's body based on the results of measurements of vascular flows in the maternal-placental circulation [30]. Similar conclusions were presented by Easterling et al. in each trimester of pregnancy [31], as well as by Ryo et al. [24].

5.2 The influence of tocolytics on vascular flows

In the study by Bednarek et al. on the safety of tocolytic medications in preterm labor, mean values of vascular flow measurements before the initiation of therapy that inhibits premature uterine contraction and at least one day after their initiation, subjected to statistical analysis, did not show significant changes in most of the parameters studied. The changes mainly concerned the systolic-diastolic index in the umbilical artery, where its decrease was noted, the peak systolic velocity in the middle cerebral artery increased, and the pulsation index decreased. The patients' therapy mainly included nifedipine. The lack of statistically significant changes in the value of vascular flows may indirectly confirm the safety of this medication and the lack of negative impact on the well-being of the mother and the fetus. No patients experienced life-threatening or health-threatening symptoms, and the reported side effects were mainly periodic headache during the first day of therapy and transient reddening of the skin. There was no significant decrease in blood pressure in patients undergoing treatment. This significantly increases the benefits associated with the use of this therapy, especially in relation to therapy with beta-mimetics, especially fenoterol.

Cornette et al. analyzed the effect of nifedipine on the values of vascular flow in the cerebral and placental-fetal circulation. They found no statistically significant changes in the vascular flow of the fetal middle cerebral artery, umbilical cord, uterine arteries and ductus venous. The study was conducted in pregnant women between the thirty-fifth and thirty-seventh week of gestation in a group of fifteen healthy pregnant women, after administering 20 milligrams of nifedipine orally and assessing vascular flow one hour after dosing. The authors emphasize the mechanisms counteracting the disturbance of the uterine circulation despite the significant reduction of maternal afterload under the influence of nifedipine, which means that in healthy pregnant women with normal arterial pressure, trophoblast invasion lowers uterine vascular resistance to such an extent that administration of nifedipine, which has the ability to lower peripheral vascular resistance, is no longer

able to lower uterine resistance. Adverse effects of nifedipine have been reported in the situation of significantly lowered blood pressure in pregnant women, therefore it is important that the use of this medication as an inhibitor of uterine contractions ought to be considered only in pregnant women with normal blood pressure [32].

The study by Lima et al. was based on the administration of nifedipine in a dose of 20 milligrams sublingually every twenty minutes to a pregnant woman with uterine contraction, until the activity subsided. Thereafter, 20 milligrams of nifedipine was orally administered every six hours, until a total dose of 120 milligrams per day. Vascular flow in the fetal and maternal circulation was assessed before the initiation of nifedipine, five and twenty-four hours after the initiation of the therapy. Five and twenty-four hours after the initiation of the therapy, there was no change in the resistance index from pre-treatment measurements, while a decrease in the resistance index in the fetal central artery was observed between five and twenty-four hours after the initiation of the therapy.

The value of the peak systolic velocity of the middle cerebral artery was also analyzed. In the Lima study, there was a decrease after five hours, while comparing the measurements before and 24 hours after starting the treatment, no statistically significant changes were noted [33]. In the study by Bednarek et al., the peak systolic velocity of the middle cerebral artery increased statistically significantly after the initiation of the therapy. It is noteworthy, however, that the measurements were made at least twelve hours after the initiation of the therapy. Similarly, Grzesiak et al. reported a decrease in the peak systolic velocity in the middle cerebral artery, with no changes in the remaining parameters during the day after the initiation of oral nifedipine therapy [34].

The special structure of the fetal uteroplacental, umbilical and cerebral circulation ensures constant vascular flow independent of the heart cycle. This system gradually develops in the utero-fetal circulation. A significant effect of this phenomenon consists not only in the gradual increase in the velocity of the end-diastolic flow wave, but also in the accompanying decrease in the pulsation index, which is the difference between the components of the maximum systolic velocity and the end-diastolic velocity [33].

Similarly, Guglu et al. observed a decrease in the pulse index of the central cerebral artery one day after the initiation of nifedipine therapy. The authors note that nifedipine reduces blood pressure while keeping the maternal heart rate unchanged. Moreover, they acknowledged a decrease in resistance in the uterine circulation. The mechanism of increased resistance in the umbilical artery with an accompanying decrease in the pulse index in the central artery of the brain prevents diastolic changes in the fetal heart [35, 36]. It is noteworthy that the maternal-fetal circulation has mechanisms that protect the fetus against changes in flow that may be a real threat to its well-being.

Beta-memetic therapy is now used much less frequently in suppressing preterm labor. Despite the lack of obvious adverse effects on vascular flow in the fetal circulation, side effects in the mother are significant enough to minimize this method of treatment [37–39]. In a study with ritodrine, an increase in the pulse index in the middle artery of the fetal brain was noted, with a decrease in the pulse index in the umbilical artery [40]. Friedman et al. claim that therapy with ritodrine does not increase the resistance to placental circulation, does not lead to fetal hypoxia, changes in the fetal heart rate or preload on the fetal heart, but shortens the systolic fraction of the heart, which may lead to an increase in vascular resistance in the fetal circulation or reduce contractility of the heart muscle [41, 42]. Similarly, terbutaline increases vascular flow through the fetal heart, thus increasing its load [43]. Beta-agonist therapy should be limited as much as possible due to the side effects of these medications on both the mother and the fetus.

Oxytocin receptor blockers are a new class of tocolytic drugs. The oxytocin antagonist atosiban has less side effects than beta-agonists [44]. Atosiban crosses the placenta. Drug concentrations in the fetal circulation do not increase with longer infusion rates, suggesting that the drug does not accumulate in the fetus. Atosiban has the best maternal and fetal safety profile; however, its costs are considerable. Maternal heart rate and blood flow in (R-UtA/L-UtA) were not altered significantly during atosiban administration. No significant changes in FHR as well as Doppler parameters (resistance index, pulsality index, peak systolic velocity) in umbilical artery and middle cerebral artery were recorded after 24/48 hours of tocolytic treatment. The mean values of cerebroplacental ratio (CPR) remained unaltered during treatment. Detailed evaluation of fetal cardiac function parameters (E/A, SF, MPI) calculated independently for both ventricles, revealed no significant changes over the time [45].

Tocolytic treatment with atosiban is associated with elevation of oxidative stress markers after a 48 hours administration. This effect of atosiban may reduce its potency as a tocolytic agent and therefore should be considered with respect to its clinical use, especially because of its connection with the occurrence of premature birth [46].

Indomethacin used as a substance inhibiting premature uterine contractile activity does not negatively affect the cerebral flow in the fetus, however, it should be remembered that long-term therapy with non-steroidal anti-inflammatory medications may lead to blood flow disorders in the arterial duct [47, 48].

Intravenous magnesium sulfate is also allowed in the treatment of preterm labor. Keeley et al. analyzed the effect of this medication on vascular flow and found a decrease in the flow velocity in the fetal middle cerebral artery and an increase in flow velocity in the uterine arteries. There were no disturbances in the flow in the umbilical artery. During the study, the blood circulation was normalized, which the authors associate with the beneficial effects of magnesium sulphate also on the fetus and the tocolytic effect [49]. This is also confirmed by the studies of Pezzati et al., who assessed the fetal and neonatal circulation in the first hours of life of children in the therapy of magnesium sulphate and ritodrine [50].

When analyzing the safety of tocolytic medications, it should be remembered that in most patients, steroid therapy is started parallel to stimulate the fetal respiratory system. In the study by Bednarek et al. no significant haemodynamic changes were found after steroid therapy, however, other authors observed a transient decrease in the pulse index of the fetal middle cerebral artery [51, 52]. It cannot be ruled out that these differences result from the different tocolitics analyzed. Corticosteroids administered to the mother to stimulate the maturation of the fetal lungs in the event of impending preterm labor may temporarily "improve" the flow waves. In such a situation, it is reasonable to repeat the Doppler examination approximately 48 hours after administration [34].

Brar et al. reported lower efficacy of tocolysis in patients with abnormal flows in the maternal-fetal circulation before the therapy, which increases the risk of preterm labor [53].

Summing up, it should be emphasized that drugs inhibiting uterine contractions do not have a significant, long-term and permanent effect on the vascular flow of the maternal-fetal circulation. When considering the efficacy of tocolysis, other factors disrupting normal vascular flow should be taken into account, which may reduce the effectiveness of tocolytic drugs and increase the risk of preterm labor.

5.3 Preterm labor ended with cesarean section

Nakayi et al. analyzed the vascular flow of the uterine arteries on the third, sixth and ninth day after cesarean section. They found no significant changes in the resistance index in these vessels [54].

The assessment of uterine artery flow seems to be useful in vaginal bleeding in puerperal patients after cesarean section, as one of the complications of this operation may be rupture of the intraoperatively developed pseudoaneurysm of the uterine artery [55].

5.4 Infection in preterm labor

Caroll et al. assessed the flow in the middle cerebral and umbilical arteries of fetuses and in the uterine arteries of patients with premature rupture of the membranes with or without intrauterine infection. They found no changes in vascular flow, which means that Doppler examination is not useful for monitoring the developing intrauterine infection associated with premature drainage of amniotic fluid [56].

Different results were obtained by Yücel et al. They analyzed vascular flows in patients after premature drainage of amniotic fluid with histopathologically confirmed placental inflammation. The researchers proved that an increase in the systolic-diastolic index in the uterine artery can be considered as a marker of developing intrauterine infection [57].

5.5 Ultrasound features of the cervix shortening

Bednarek et al. observed no statistically significant changes depending on the length of the cervix. Similar results were established by Klemm et al. analyzing uterine flows after radical trachelectomy. There were no changes in the uterine arterial resistance index in relation to the control group [58].

The three-dimensional evaluation of the cervical circulation accounts for a new diagnostic possibility. Samutchaikij et al. established reference values for certain measurements of the cervical vascular bed, and De Diego et al. analyzed three-dimensional images of the cervix in patients at risk of preterm labor. The authors found differences in the parameters of cervical vascularization in patients with preterm labor in comparison to asymptomatic patients with a comparable length of the cervix. It is possible that three-dimensional ultrasound will become a practical tool for the actual assessment of cervical insufficiency [59, 60].

5.6 Pregnancy duration and vascular flows

The study by Bednarek et al. involved the division of the study group into preterm labor below and above 32 weeks of pregnancy. Vascular flow differences were found in the umbilical artery. The pulsation, resistance and systolic-diastolic index values were higher in the younger group. Similar conclusions were presented by Chanprapaph et al. in the analysis of measurements in over three hundred healthy pregnant women. This phenomenon should be explained by the progressive increase in end-diastolic velocity with increasing gestational age, which directly translates into a decrease in the pulsation index. The authors draw attention to the fact that the value of the systolic-diastolic index above three, in a pregnancy above the thirtieth week, is more often associated with complications of low fetal body weight and birth disorders - the presence of meconium in the amniotic fluid, cesarean section and worse birth condition of the newborn [61–64].

Mari and Deter draw attention to the parabolic shape of the curve of changes in the flow rates of the central artery of the brain, the values of which are maintained in newborns until the first month of life. The curves established by the authors are applicable to the monitoring of fetuses with low body weight [65].

Degani found a clear decrease in the value of the middle cerebral artery pulsation index after the thirty-sixth week of pregnancy, which is related to the compensation mechanism that protects the fetus against a progressive decrease in oxygen tension [66].

Gadelha da Costa et al. assessed the increase in fetal middle cerebral artery resistance index up to the twenty-sixth week of pregnancy, and then a decrease to the period of full-term pregnancy [67, 68].

The lack of vascular changes in the uterine arteries in pregnant women with pre-term labor confirms the assumption that the assessment of the flow of these vessels is justified in pregnancies with placental abnormalities, such as intrauterine growth restriction, arterial hypertension or diabetes [69, 70].

6. Summary

Research on maternal-fetal haemodynamics in preterm labor is currently focused mainly on the safety of the used tocolytics. The reduction of the use, and often the elimination of beta-agonists, undoubtedly increased the safety of the mother and the fetus. The above literature review proves that despite some influence of medications on maternal-fetal blood flow values, tocolysis does not significantly disturb haemodynamics. However, it is worthwhile to remember about safety rules during ultrasound examinations with the use of Doppler technique.

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