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Review

PREVENTION OF PRETERM BIRTH

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Summary

Preterm birth (PTB) is a worldwide problem with great social significance because it is a leading cause of perinatal complications and perinatal mortality. PTB is responsible for more than a half of neonatal deaths. The rate of preterm delivery varies between 5-18% worldwide and has not decreased in recent years, regardless of the development of medical science. One of the leading causes for that is the failure to identify the high-risk group in prenatal care. PTB is a heterogeneous syndrome in which many different factors interfere at different levels of the pathogenesis of the initiation of delivery, finally resulting in delivery before 37 weeks of gestation (wg). The various specificities of risk factors and the unclear mechanism of initiation of labour make it difficult to elaborate standard, unified and effective screening to diagnose pregnant women at high-risk for PTB correctly. Furthermore, they make primary and secondary prophylaxis less effective and render diagnostic and therapeutic measures ineffective and inappropriate. Reliable and accessible screening methods are necessary for antenatal care, and risk factors for PTB should be studied and clarified in search of useful tools to solve issues of risk pregnancies to decrease PTB rates and associated complications.
Key words: preterm birth, high-risk group, screening

Introduction

According to the World Health Organization (WHO), preterm birth (PTB) is birth before 37 weeks of gestation (wg) or 259 days before the first day of the last menstrual period [1]. Defining the borderline between birth and abortion varies across different countries. Historically, this borderline moved from 28 wg toward earlier gestations, because of the improved survival before 28 wg following the introduction of corticosteroid prophylaxis of the respiratory distress syndrome, postnatal surfactant therapy and the advances in intensive neonatology. There are centres where this borderline moved to 22 wg. The WHO definition of PTB is based on a statistical analysis of the gestational age at birth, and this should be clearly distinguished from the concept for prematurity, which reflects the lack of maturity of different organs and systems of

the fetus at the time of birth. PTB is a leading cause of neonatal mortality and late neurological complications [2]. The rate of PTB has not decreased during the last 50 years regardless of the technological, medical, pharmaceutical, etc. advances and knowledge concerning the causes and mechanisms of PTB. Globally the complications of PTB are the leading cause of death in children under 5 in 2015 [3]. Rising rates of PTB were reported for both developing and industrially developed countries. However, there are significant differences between developing and developed countries regarding the chances of survival of premature babies. In many developing countries, the children born under 2000 grams in the 32nd wg in the absence of intrauterine growth restriction) have small chances of survival. On the contrary, the survival rate of babies born at 32 gw is similar to that of full-term babies in developed countries.

The rate of PTB in Bulgaria is estimated to be between 9 and 11%, partly because of the changing definitions of delivery and abortion in Standards of obstetrics and gynaecology. The rate is considerably high compared to the rates in the developed countries. Data from the National Delivery Registry in 2016 showed that of the 61 014 live births, 5777 were preterm and 276 babies extremely low birth weight of less than 1000 gr. The highest rates were registered in Russe – 15.8% (278 from 1758 live births), and the lowest rates were in Kardzhali, where only 5.3% or 53 from 1014 babies were born preterm. The relative share of the preterm deliveries is rising in Bulgaria – from 6.6% in1990 to 9.6% in 2007, and to 10.3% in 2008. In many regions such as Burgas, Vratza, Stara Zagora, Sliven and Yambol the relative share of preterm born children has reached 13%. In 2012, the number of preterm deliveries was 5750, which was 8.3% of those born alive, and in 2010 it was 10.3%. Almost 50% of preterm babies born before 26 wg have severe handicaps. The results in survivors at 6 years of age showed 22% severe disability (cerebral palsy, low cognitive results, blindness, and deafness), 24% had moderate degrees of disability, and 34% had a mild disability and just 20% developed almost normally.

A multicenter study in the United Kingdom (UK) reported that 80% of the children born in the 26 wg had some degree of disability at 6 years of age [4]. About one-third of those who were born between 32 and 35 wg had learning difficulties at school age, and they represented the most significant number when compared to those with lower birth weight. These disabilities have a significant impact on the educational system [5]. Newborns at highest risk of morbidity and mortality are those born before the 32nd wg, yet those born between 32 and 36 wg comprise the larger group of the prematurely born. This group (near-term infants) is subject to a significant risk for health and developmental problems, as compared to full-term infants [5, 6].

Materials and Methods

The study reviewed the literature and presented available screening tools and prophylactic measures that aim to define the risk factors and risk groups for PTB. It could serve as a basis for further research and analysis. Our goal is to elaborate an effective, simple and readily applicable algorithm to define the high-risk group in routine antenatal care. The lack of an effective screening did not allow for sufficient accuracy in identifying the high-risk group of pregnant women for PTB, thus impeding the efforts to define effective intervention for prevention. A more accurate determination of pregnant women at low risk for PTB would allow avoiding unnecessary, expensive and sometimes overwhelming side effects of interventions.

Interventions to reduce the occurrence and/or morbidity and mortality of PTB could be categorised as primary (targeting all women at reproductive age), secondary (targeting at eliminating or reducing the effect of a specific risk factor) and tertiary (aiming to improve the outcome of PTB) [16]. Most of the interventions that are currently proven to be effective in reducing the burden of PTB (morbidity and mortality) are essentially tertiary measures. These are: referring pregnant women who deliver preterm to specialised tertiary centres, antenatal corticosteroids, and tocolytics to delay delivery enough to apply the first two measures, antibiotics to reduce the risks of infections, optimising the indications for medically indicated preterm deliveries, etc.

Causes of PTB

Births before 37 wg are associated with a

spontaneous beginning of uterine contractions, with intact membranes, preterm prelabour rupture of membranes (PPROM) and following induction of labour or elective cesarean section for maternal and/or fetal indications. About 45-50% of PTBs are idiopathic, 30% occur after PPROM, and 15-30% are medically indicated deliveries. Since the outcome of pregnancy correlates with the gestational age at delivery, PTBs subdivide into:

- Extreme (born before 28 wg) – 0.25%;
- Early (28-30 wg) – 0.25%;
- Moderate (31-33 wg) – 0.6%;
- Mild- (34-36 wg) – 3.0%.

The risks of fetal handicap and death are highest in the first three groups. PPROM is defined as one occurring before 37 wg and at least one hour before the beginning of regular contractions. In most of the cases, PPROM has unclear aetiology, but it is often associated with asymptomatic or overt infection. Most of the pregnant women with PPROM usually develop uterine contractions followed by cervical changes. Since the amniotic membrane acts as a barrier against ascending infection, a rupture is often followed by infection. Spontaneous PTB with intact membranes is the spontaneous onset of regular uterine contractions followed by cervical changes before 37 wg. The aetiology and pathogenesis of this process are unclear, but it is regarded as early idiopathic activation of the birth process. Some theories explain this event, such as progesterone withdrawal, oxytocin theory, and decidual activation, among others. The role of the fetus has been described as a factor in the initiation of labour [7].

PTB is a very heterogeneous syndrome and should be regarded as such, with unclear and multifactorial aetiology, where multiple factors lead to a common end-result delivery before 37 wg. It is necessary to clarify the different phenotypes of PTB that reflect the heterogenicity of the underlying etiologies and the following pathogenetic mechanisms. Studying PTB and its rates require appropriate categorisation, considering the efforts to create effective practices that aim to reduce PTB rates. Simplification and unification of all births occurring before 37 wg impede the appropriate research of PTB and lead to empiric strategies that overlook the heterogeneity of PTB and the variety of factors concerned. Finally, such strategies have been proved as ineffective and inappropriate.

However, there are studies which describe and classify the different phenotypes of PTB syndrome [8, 9]. Deliveries after spontaneous onset of uterine contractions and spontaneous PPROM are described together as spontaneous PTB. They are regarded as syndomatic and as resulting from multiple causes which interfere in different gestations, e.g. inflammatory processes (immunological, systemic and intrauterine infections), placental (micro-) thromboses, and uterine vascular lesions associated with fetal stress, decidual haemorrhages, cervical insufficiency and uterine overdistension. Individual genetics and the environment influence all these factors. Romero et al. (2006) describe different pathological processes leading to the syndrome of PTB, such as intrauterine infection and/or inflammation, uterine ischaemia, uterine overdistension, a normal allograft reaction, allergies, cervical insufficiency and hormonal disturbances [10].

Risk factors include prior PTB, black race, periodontal disease, low maternal body mass index (BMI). A PTB rate of 4% was reported in women with BMI from 25 kg/m^2 to 26 kg/m^2. The rate is up to 5% in women with obesity but rises to 5.5% in low BMI 17-18 kg/m^2 and to 7% in BMI under 17 kg/m^2. There is a linear inverse correlation with the height of the pregnant women with a rate of 6% with a height of 1.46 m, and less than 3% with a height of 1.75 m. There are racial and ethnic differences in the rate of PTB.

A previous PTB is a significant risk factor during pregnancy. The recurrence risk is increased both in spontaneous and iatrogenic PTBs, and the risk is in inversed correlation with the gestational age of the previous PTB. The risk is also related to the number of the previous PTBs.

Factors associated with the increasing PTB rates include increased number of multifetal pregnancies, increased usage and success rates of artificial reproductive technologies (ART), increase of the number of pregnancies in women after 35, increasingly and more liberal application of elective delivery indications (either induction of labor or cesarean delivery) and moving toward earlier gestations because of the improved survival of those born preterm. The risk of PTB

after ART is 10% versus 6.8% in spontaneous pregnancies even in singleton pregnancies. Multifetal pregnancies are currently amongst the leading causes of PTB. The highest rate of naturally conceived multifetal pregnancies is observed in West Africa (1 in 40), and the lowest in Japan (1 in 200). In developed countries, approximately 8% of all deliveries follow the application of ART, which is associated with a high rate of multifetal pregnancies, in spite of the trend to decrease the number of the transferred embryos. Multifetal pregnancies (2-3% of all deliveries) are associated with a high rate of PTB and account for15-20% of all PTBs. Preterm delivery occurs in about 60% of twin pregnancies, and spontaneous PTBs account 40% of these. The rest are indicated PTBs following preeclampsia or other maternal or fetal conditions.

The risks vary, regarding the number of fetuses and chorionicity. Almost all multiple pregnancies with more than two fetuses deliver preterm [11]. Genital bleeding during pregnancy as a consequence of placental abruption or placenta previa is associated with a very high risk of PTB. Genital bleeding during pregnancy which is not associated with the pathologies as mentioned above is not associated with an increased risk of PTB [12]. Amniotic fluid anomalies (polyhydramnios and oligohydramnios) are also associated with a high risk of PTB. Abdominal, and especially uterine surgeries, increase the risk of preterm initiation of labour. Chronic diseases in pregnant women, such as thyroid diseases, hypertension, and diabetes are also associated with increased risk of PTB. Cervical surgeries, such as conisation, LEETZ and tracelectomy increase the risk of PTB [13]. Globally, infections are the most common cause for PTB [14].

Indicated (iatrogenic) PTBs occur after elective induction of labour or cesarean section, various maternal and/or fetal conditions, and most commonly the consequences of abnormal placentation – preeclampsia and intrauterine growth restriction of the fetus. These conditions can be acute or chronic and require balancing between the risks of continuing the pregnancy until reaching a certain level of maturity and the risk of continuing exposition of suboptimal intrauterine environment. According to a UK epidemiological study (North West Thames database 1988-2000) between 28 and 31wg almost 50% of all deliveries were iatrogenic.

Many studies based on a sonographic determination of the estimated delivery date have shown that uncertainty of the date of the last menstrual period and variations in the length of the menstrual cycle has led to an inaccurate assessment of gestational age at delivery [15]. Changes in the definitions for abortion, delivery and neonatal death also contribute to the increase of the PTB rates.

Primary prophylaxis

Measures before pregnancy

There is a wrong point of view in society that improved neonatal care for those born preterm has solved the problem with PTBs. Clarifying the fact that PTB is a leading cause for neonatal morbidity and mortality would focus the efforts to avoid the potential risk factors. Policies to reduce the risk of multifetal pregnancy were proven to be effective in Europe, Australia and USA. Measures to reduce the risks and to improve the outcome of a present pregnancy are applied in many Europen countries, e.g. paid maternity leave, maternity leave for antenatal care, restrictions to work night shifts, ensuring appropriate work conditions and eliminating harmful substances and occupational risks at the workplace. Results from these policies were presented in the European programme of occupational risks and pregnancy outcome (EUROPOP) study. According to this study, the risk of PTB was not high in working pregnant women but was substantially higher in those who work more than 42 hours a week and more than 6 hours a day [17]. Women who plan pregnancy are routinely advised to take prenatal vitamins to reduce the risk of congenital malformations (as in the case with folic acid and neural tube defects). Randomised placebo-controlled trials (RCT) have not demonstrated the effects of any food supplements on the frequency of PTB. Maternal smoking increases the risk of delivery of a low birth weight baby and unfavourable neonatal outcome. However, in the USA, the rate of PTB increased from 11.6% to 12.5% between 2000 and 2004, although the smoking rate in women between 18 and 44 years has decreased from 25% to 22% in this period [18].

Improved prenatal care

Improved access to prenatal care was regarded as a way to reduce the occurrence of PTB because of the probable association of early registration and increased number of visits with lower levels of prematurity. In a study on this association, it has been demonstrated that delayed first antenatal visit was related to unfavourable outcomes. The first visit at 14 wg was associated with PTB ($p<0.001$), but a Cochrane review has not found a significant difference in the frequency of PTBs and reduced number of antenatal visits versus the standard number of visits [19]. It is necessary to study further populational measures and to search for specific practices to decrease the rates of PTB because low-risk women deliver a more significant number of preterm infants. The content of antenatal care concerning PTB prevention should reflect the heterogeneity of this condition to expect an effect on the rate of PTB.

Periodontal care

The risk of PTB is increased in the presence of periodontal disease and increases further if the disease progresses during pregnancy. This is probably an effect from the generalisation of the inflammatory reaction during pregnancy. RCTs have not shown the effect of treating the disease during pregnancy [20].

Inflammatory processes and infections

Although infections and colonisation of the genital tract of pregnant women are associated with increased risk of PTB, treatment fails to decrease this risk. Bacterial vaginosis (BV) is present in 20% of pregnant women and is asymptomatic in most of the cases. It is associated with an increased risk of PPROM and PTB. The risk of PTB is doubled in pregnant women with BV, and is much higher if the BV is present before 16 wg. Treatment during pregnancy has not shown to reduce the risk of PTB. It is necessary to study the effect of treatment at earlier gestational age (before 16 wg). The screening and treatment for Ureaplasma urealyticum, group B streptococcus and Trichomonas vaginalis do not decrease the risk of PTB [21]. In pregnant women with asymptomatic bacteriuria, the risk of pyelonephritis and PTB is increased. Antibiotic treatment decreases the risk of pyelonephritis, but it does not influence the risk of PTB [22].

Screening of high-risk pregnancies

There are two subgroups of women which contribute to spontaneous PTBs. About 3% of all pregnant women have had a previous late miscarriage or prior preterm labour, and they account for 15% of spontaneous PTBs. The risk of recurrence is in inversely proportional to the gestation age at which the previous PTB has occurred and also in relation with their number. The other group, which includes about 85% of those who deliver preterm are either in their first pregnancy or have has deliveries at term. This latter group represents 97% of pregnant women. It is evident that preventive strategies targeting only the subgroup with previous PTB would have a minimal impact on the overall rate of PTB. There are two strategies to identify the high-risk group for PTB amongst the 97% of pregnant women who are either in their first pregnancy or already have given birth at term. They deliver 85% of those born before 34wg [23]. These strategies are an estimation of the risk by measurement of the cervical length (CL) and the use of biological markers.

Asymptomatic pregnant women with positive fetal fibronectin (FFN) test are at an increased risk of PTB before 35wg, more specifically within two weeks after the positive test. FFN is thought to be positive in the subgroup of PTBs that follow inflammatory reactions. FFN is an extracellular matrix protein produced by the cytotrophoblast. It is localised between the chorion and deciduas, and acts as „glue". Placebo-controlled trials had not shown a reduction of the risk of PTB when pregnant women with a positive FFN test was treated with antibiotics. High levels of FFN could be found in cervicovaginal secretions before 22 wg. Measuring FFN in the cervicovaginal fluid between 22-24 wg has proved useful in defining the pregnant women at high risk of spontaneous PTB. In 22-24 wg, the test is positive in 5% of the pregnant women and this group includes 25% of those who deliver spontaneously preterm before 34 wg [24-26]. A routine investigation of the uterine cervix in the second trimester in low-risk singleton pregnancies by transvaginal ultrasound could identify those at high-risk for PTB, but the sensitivity is low. The CL at 20-24 wg in pregnant women who deliver at term has a normal distribution in the population with a

mean of 34 mm. In pregnancies, where delivery is before 34 wg, there is a bimodal distribution of the CL. CL less than 15 mm is seen in 1% of pregnant women, and they deliver 20% of those born before 34 wg. CL less than 25 mm is observed in 10% of the pregnant women, and they deliver 40% of those born before 34 wg [27].

Both sonographic assessment of the cervix and the FFN have a high negative predictive value (NPV) and low positive predictive value (PPV). This means that both tests r define the low-risk, rather than the high-risk group.

Secondary prophylaxis of PTB

Secondary prophylaxis targets women, identified as being of high-risk for PTB either from obstetric history (previous PTB, uterine anomalies, etc.) or because of a risk factor in the present pregnancy (multifetal pregnancy, bleeding, etc.). These groups of pregnant women are also quite heterogeneous. In an attempt to define the risk factors in healthy pregnant women, Goldenberg and colleagues report that the number and the gestational age of previous PTBs are the most reliable predictors from the obstetric history, and the presence of FFN in cervicovaginal fluid, the CL and BV most strongly correlate with the risk of spontaneous PTB in singleton pregnancies. With a baseline risk of 10-12%, the risk of recurrence in a current pregnancy after one, two and three PTBs increases to 15%, 30%, and 45%, respectively. About 85% of those who deliver preterm are either in their first pregnancy or have deliveries at term. Consequently, a screening strategy based solely on the past obstetric history would yield a very low detection rate.

Preconceptional measures

The risk of recurrence is high for both spontaneous as well for the indicated PTBs. The risk increases with the number of previous PTBs and with the increasing degree of prematurity of the previous PTB. Current risk factors could be identified in about 40% of PTBs. Having in mind that that PTB is a major perinatal problem and actively searching for risk factors would allow applying preventive strategies and procedures such as correction of uterine anomalies, treatment of urogenital and periodontal infections, abdominal cerclage, diabetes control, epilepsy, asthma or hypertension. Randomised and placebo-controlled trials, which test the effect of preconceptual administration of antibiotics have shown that antibiotics do not have an effect on recurrences. Antibiotics did not reduce the risk of PPROM or preterm delivery except in the subgroup of women with a previous PTB, who had bacterial vaginosis) [28, 29].

Postconceptional interventions

Secondary prophylaxis of spontaneous PTBs

Interventions in asymptomatic pregnant women would have different efficacy according to the population being studied. Models combining CL, obstetric history, microbiology and biological markers would provide a better prediction of spontaneous PTB than any factor alone, and the sensitivity and predictive values would be higher. The sensitivity of such screening strategies improves with higher degrees of prematurity. Despite the complete absence of evidence, bed rest and restriction from sexual activity are commonly prescribed practices to decrease the risk of PTB in pregnant women with known risk factors. Results from randomised and placebo-controlled trials have proved that there is no effect from bed rest, prophylactic administration of tocolytics, stress reduction, dietary supplements, such as iron, folate, calcium, magnesium, prenatal vitamins, omega-3 polyunsaturated fatty acids, etc. However, there might be side effects of such interventions: long-term bed rest may lead to venous thromboembolism, muscle atrophy, and stress.

In pregnant women with previous spontaneous PTB, singleton pregnancy and CL less than 25 mm, cervical cerclage significantly prevents PTB and perinatal morbidity and mortality [30]. In such cases, cerclage decreases the risk of PTB before 34 wg by 25%. There are two options in such cases. Elective cerclage after 14 wg, or follow up of the CL and placing the cerclage if CL becomes shorter than 25 mm. The overall rate of PTB is the same with the two approaches but the second approach decreases cases of placing cerclages by 50%. Many studies show a decreased rate of spontaneous PTB in women with previous PTB with the application of progesterone. Several possible pharmacological effects of progesterone have been studied,

including the decreased formation of gap-junctions between muscle cells, antagonism and decreased susceptibility to endogenous oxytocin, and anti-inflammatory effects. Prophylactic application of progesterone between 20 and 34 wg decreases the risk of spontaneous PTB before 34 wg by 25%. It could be applied as natural progesterone vaginally (200 mg) every night, or intramuscularly as a synthetic 17-alpha-hydroxiprogesteron caproate (250 mg). Natural progesterone is preferable because of the fewer side effects, such as sleepiness, weakness and headache. Progesterone, however, is not uniformly effective in all populations of high-risk pregnant women. This indicates that some pathogenetic mechanisms of recurring PTB progesterone application unsuitable. In pregnant women without prior PTB but with a positive screening test in the current pregnancy, such as positive FFN, the application of antibiotics does not decrease the rate of spontaneous PTBs.

The effect of eradication of BV in earlier gestations (before 16 wg) needs to be studied. Cerclage placement in pregnant women with short cervix below 25 mm between 20-24 wg decreases the rate of PTB before 34 wg by 15%, and vaginal application of progesterone (200 mg) decreases the risk of PTB by 35-40% [31, 32]. The rate of PTB before 34 wg in singleton pregnancies is about 2%, and 15% in twin pregnancies. In both singleton and multifetal pregnancy, the risk of PTB increases because the CL decreases in 20-24 wg. In case of twin pregnancy combined with a CL less than 25 mm in 20-24 wg, vaginal application of progesterone between 20-34 wg could decrease the rate of spontaneous PTB before 34 wg up to 30% [33]. In twin gestation with a short cervix, treatment with cervical cerclage may reduce the rate of early PTB, but there is a need of well-designed randomised controlled trials on cerclage applied in twin gestations with a short cervix to confirm this effect [34]. There are many studies on the efficacy of vaginal pessaries as an alternative to cerclage, and they have reported contradictory results both in singleton and multifetal pregnancies. These are flexible silicone rings that are placed into the vagina in early pregnancy, avoiding invasive cerclages. The rings can be removed easily near term [35-37].

Tertiary interventions for women at acute risk for PTB

Diagnosing situations which immediately precede preterm labour gives a chance to intervene and to improve the outcome. The most common symptoms of threatening PTB are frequent and sometimes painful uterine contractions, spontaneous amniotic rupture, genital spotting or bleeding. Early recognition of the signs of threatening PTB is usually challenging because the symptoms are often discrete and similar to common pregnancy complaints. Most pregnant women who present (about 70%), with regular contractions between 24-36 wg are in false labour and do not deliver in the subsequent seven days. Diagnosing threatening preterm labour by measuring the CL and/or testing cervicovaginal fluid for FFN discriminates false and true labour, and gives the chance to avoid unnecessary hospitalisations [38, 39]. In a meta-analysis, Boots et al. (2014) found that, in symptomatic patients, positive FFN, the absence of fetal breathing movements, and CL have diagnostic use as predictors of delivery within 48 hours and 7 days of testing. The absence of fetal breathing movements appears to be the best test for predicting PTB [40]. Levine et al. (2018) studied the efficacy of CL and FFN test as predictors of spontaneous preterm labour in symptomatic pregnancies in a prospective study by stratifying the results by obstetric history and parity. In primiparous women, the rising levels of FFN were associated with high-risk of spontaneous preterm labour with a positive predictive value (PPV) of 26.5%, when FFN levels were above 20 ng/mL, to 44.4% with levels of 200 ng/mL. The cut-off of 20 ng/mL had higher sensitivity (69.2%) and higher negative predictivity (96.8%), forming the group of low-risk of preterm labour. The authors found that FFN was not informative in parous pregnant women. In primiparous and parous pregnant women, CL less than 20 mm optimises the test with a PPV of 25 and 20% respectively, and NPVof 95.5 and 92.7%. In parous women, CL less than 25 mm discriminates between the low and high-risk groups. In parous pregnant women, the FFN test is ineffective, and CL should be applied. Irrespective of the parity the PPV of the CL and FFN remains low [41]. In pregnant

women with threatening preterm labour, the probability of delivery in the next 7 days is in inverse correlation with the CL. CL less than 20 mm is measured in 20% in pregnant women with threatening preterm labour, and 75% of those who deliver in the next 7 days fall into this group. With a CL above 20 mm, the risk of delivery in the next seven days is 3%. The FFN test is positive in about 20% of pregnant women with threatening PTB, and this group includes about 75% of those who deliver in the next seven days. In those with a negative test, the risk of delivery in the next seven days is 3%. Combining CL and FFN could decrease the rate of the high-risk group for delivery in the next seven days to 5% (versus 20% with each test alone), and decrease the risk of delivery with a negative test to 1% [42, 43]. Educational programs targeting early identification of the symptoms of threatening preterm labour were shown to be ineffective in randomised trials. Similar are the results from daily electronic monitoring of the uterine activity in pregnant women at risk for PTB [44].

Placental alpha-microglobulin-1 (PAMG -1 is another biological marker. This protein is found in high concentrations in amniotic fluid, while its concentration is very low in cervicovaginal secretions. Wing et al. compared the efficacy of PAMG-1 and FFN tests in predicting preterm labour in the next seven days after the test gets positive and found better PPV of PAMG-1. The test is most useful in situations, in which the CL is between 15 and 30 mm, and the predictivity of CL alone is low [45]. Another test is based on the presence of specific monoclonal antibodies connecting the phosphorylated form of the insulin-like growth factor binding protein-1 (phIGFBP-1), which is produced by decidua but leaks in the cervicovaginal fluid, when the connection between the chorion and decidua breaks. The test possesses a 98% NPV for delivery in the following 7-14 days. Unlike FFN, the test could be done even if the sample is contaminated with urine, drugs, etc. [46]. A model comparing the efficacy of the FFN and albumin vitamin D-binding protein (Albumin/VDBP) in cervicovaginal secretions of pregnant women with threatening preterm labor showed that the double biochemical model (Albumin/VDBP) had 66.7% sensitivity, 100% specificity, 100% PPV, and 96.7% NPV as compared to FFN – 66.7%, 87.9%, 36.4% and 96.2%, respectively [47]. The biomarker tests for threatening preterm labour are currently the most useful because of their negative predictivity, making it possible to avoid unnecessary interventions, as well as to take timely measures, such as antenatal corticosteroids, etc. in those considered to be at risk.

Conclusions

PTB, the ability to accurately identify the risk groups and clarification of the interventions and the groups of pregnant women who can benefit from them are amongst the major challenges in modern obstetrics. There is a necessity to elaborate algorithms applicable in daily antenatal care to identify high-risk pregnant women, thus allowing for precise application of specific preventive measures. Because of the heterogeneity of the PTB syndrome, it might be necessary to apply different screening tools to categorise different phenotypes, eventually benefiting from specific interventions correctly. Measurement of the CL and combining it with obstetric history and microbiology of the vaginal microflora should be established as a baseline population screening. Biological markers are still costly and are most useful in selected cases, especially in cases with threatening preterm labour.

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