

# EXTREMELY PRETERM DELIVERY: PREDICTION AND PREVENTION

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## REZUMAT

**Context:** Dezvoltarea neonatologiei a facut posibilă supraviețuirea prematurilor extrem de mici. Sechelele nou-născuților pot fi însă serioase și din acest motiv nașterile premature sunt recunoscute a fi una din principalele probleme de sănătate publică. Este de remarcat faptul că, atât persoane neinițiate cât și unii profesioniști nu sunt familiarizați cu faptul că există posibilități de prevenție a nașterii premature atât înainte de sarcină cât și în timpul sarcinii. Există multe cauze de naștere prematură și nu toate sunt cunoscute. Din acest motiv este improbabil ca o singură metodă de prevenție sau un singur medicament să oprească efectiv nașterea prematură. Cele mai multe nașteri premature apar la grupul de gravide fără factori de risc. **Metode:** Modelele de predicție a riscului de naștere prematură utilizate în Slovenia recomandă efectuarea unor teste suplimentare. Testele de screening ar trebui utilizate pentru toate gravidele. Aceste teste îmbunătățesc puterea de predicție la grupul de paciente fără factori de risc în anamneză. Unii factori de risc identificați pot fi influențați. Alți factori de risc ca de exemplu antecedentele de naștere (nașterea prematură, conizația, etc.) nu pot fi influențați. Alți factori de risc pot fi îndepărtați înainte de sarcină prin metode chirurgicale așa cum este cazul anomaliilor uterine. În sarcină, prezența cumulată a unui col uterin scurtat și a antecedentelor obstetricale sunt un predictor pentru nașterea prematură. Exemple de măsuri de prevenție secundară sunt tratamentul cu progesteron la pacientele cu risc, tratamentul infecțiilor vaginale în sarcina precoce, cerclajul colului uterin când canalul cervical este scurtat, suportul psihologic și social. Chiar dacă nașterea prematură nu se mai poate evita, putem prelungi sarcina cu o tocoliză eficientă astfel încât să avem timp să administrăm corticosteroizi și să transferăm gravida într-un centru terțiar cu secție de terapie intensivă neonatală, centru ce poate îmbunătăți evoluția nou-născutului. Prolungirea sarcinii este permisă doar dacă nu este nocivă pentru mamă și nou-născut. **Concluzii:** Este necesar să utilizăm cunoștințele referitoare la prevenția nașterii premature. În viitor, genomica, proteomica și farmacogenomica vor face probabil posibilă o predicție și o prevenție mai specifică a nașterii premature.

**Cuvinte cheie:** naștere prematură, prematuri mici, prematuritate extremă, sechele, predicție, factori de risc.

## ABSTRACT

**Background:** The development of neonatology has led to survival of extremely preterm neonates. Sequels for the neonate might be serious, and for that reason very preterm delivery has been recognised as one of the main problems of public health. But, too many lay persons and even professionals are not aware of the fact that there are, before pregnancy as well as in pregnancy, possibilities of prevention of extremely preterm delivery. There are many causes for preterm delivery and not all are known. It is not probable that one method or one drug would effectively stop preterm labor or prevent delivery. Most of preterm deliveries occur in the group of pregnant women without risk factors. **Methods:** Prediction model for preterm delivery risk estimation is used in Slovenia with suggestion that additional tests are performed. Screening tests should be used for all pregnant women. These tests would improve the prediction in the group of pregnant population with no risk factors in their medical history. Besides, such risk factors could be found that could be influenced. Some risk factors can not be changed: previous preterm delivery and conisation, e.g. Some risk factors can be removed before pregnancy, like operative correction of uterine anomalies. In pregnancy, combination of short cervix and obstetric history is a good predictor of preterm delivery. Examples of secondary prevention are treatment with progesterone in high risk women, treatment of vaginal infection early in pregnancy, cerclage when cervix is short, psychological and social support. Even when preterm delivery is unavoidable, we can prolong pregnancy with efficient tocolysis so corticosteroids can be applied and the pregnant woman is transported to the centre with neonatal intensive care unit (tertiary prevention), which improves the outcome for the newborn. Prolongation of pregnancy is allowed only when it does not harm the mother or the fetus. **Conclusions:** We have to use the existing knowledge regarding preterm delivery prevention. In the future, genomics, proteomics and pharmacogenomics will make prediction and prevention of preterm delivery more specific.

**Key Words:** Very preterm delivery, extremely preterm delivery, sequels, prediction, risk factors.

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## INTRODUCTION

The rate of preterm delivery (PTD) is rising.<sup>1</sup> The reasons are several and different for different populations, among them the artificial reproductive techniques (ART), worse maternal health because of increasing age at parturition, poverty, no health insurance etc.<sup>2,3</sup> PTD is in 75 % responsible for neonatal mortality and morbidity; more than two thirds

of affected neonates are born before 32 weeks of pregnancy (w.p.), i.e. very preterm. In the prospective observational study the survival up to 25 w.p. was 39 % and the long term morbidity of survivors was very high.<sup>4,5</sup> Those born with birth weight under 1500 g, of whom most are preterm babies, have 60 to 80 times more cerebral palsy.<sup>6</sup>

It can also be expressed financially: in U.S.A. to care for preterm neonate is 28 times more expensive than for a term one (280,146 \$ vs. 9,803 \$).<sup>3</sup> For the first ten years of children born after extremely preterm delivery (before 28 w.p., EPTD), the expenses were 443% compared to expenses for a term neonate.<sup>7</sup> It is relatively easy to calculate expenses. It is, however, impossible, to quantify consequences for the child and family.

For the whole Slovenia, there are – since 1987 – more than 100 items entered in the National Perinatal Information System (NPIS) database for each mother-neonate pair at delivery.

The percentages of PTD (before 37 w.p.) and very preterm deliveries (before 32 w.p., VPTD) are shown in Table 1; there were on average 0.49% of EPTD in those years.

**Table 1.** Slovenia 2002 – 2006: percentage of preterm deliveries

Year	Deliveries before 32 wk of pregnancy n		Deliveries before 37 wk of pregnancy n		All deliveries n
2002	217	1,3 %	1101	6,3 %	17347
2003	199	1,2 %	1053	6,2 %	16904
2004	211	1,2 %	1143	6,5 %	17629
2005	227	1,3 %	1166	6,5 %	17887
2006	207	1,1 %	1197	6,4 %	18661

The percentage of EPTD is twice that reported for seven hospitals in London, where it was 0.23% for years 1998 to 2006 and more than twice that of the rate in Scotland, where it was 0.19% between 1985 and 2005.<sup>8</sup> (Table 1)

The ratio between spontaneous and iatrogenic EPTD was 3.6:1, and 1:1 for VPTD.

So we have two goals:<sup>9</sup>

- To find the group of pregnant women who are at high risk for PTD (with help of *Prediction model for preterm delivery risk estimation* and additional tests);

- To use all known management options to prolong pregnancies over 28 w.p. when prolongation is not dangerous for the mother or the baby.

## **PRETERM DELIVERY RISK PREDICTION**

The process of labour and delivery starts much earlier than the clinical signs are recognisable.<sup>3</sup> There are many schemes for prediction of risk for PTD. Verdenik has, on the basis of almost 150 000 deliveries in Slovenia from the NPIS database, elaborated *Prediction model for preterm delivery risk estimation*.<sup>10,11</sup>

**Table 2.** Scoring system for very preterm delivery risk for factors present before pregnancy.

Risk factor	Score	Risk factor	Score
Conisation	16	First visit before 7w.p.**	4
Previous PTD*	12	12 years of education	3
Uterine anomalies	11	8 or less years of education	3
Primipara < 18 years	10	Primipara 19-32 years	3
Primipara > 33 years	10	Smoking > 10/ day	3
Hypertension	10	Living together not married	2
Diabetes mellitus	8	Single	2
Uterine operations	7	Previous induced abortions	2
Multipara > 36 years	5	Smoking < 10/ day	2
Chronic renal disease	5	IVF – ET	2
Previous spontaneous abortions	4	First visit after 19w.p.	1

\*PTD – preterm delivery, \*\*w.p. – week of pregnancy

**Table 3.** Scoring system for very preterm delivery risk for factors present in pregnancy.

Risk factor	Score
(Suspected) fetal anomaly	32
2 <sup>nd</sup> trimester bleeding	17
3 <sup>rd</sup> trimester bleeding	17
Less secure employment	8
Very reduced housework	7
1 <sup>st</sup> trimester bleeding	6
Hypertension	5
No paid work in pregnancy	4
Reduced housework	3
Early amniocentesis	3

The model was validated on another group of women, who also delivered in Slovenia.<sup>10,12</sup> Risk factors for VPTD, present before pregnancy, are shown in Table 2 and those in pregnancy are shown in Table

3. Slovenia, with a well established NPIS and with around 18,000 deliveries per year is very appropriate as a perinatal model.

Specific screening tests should be based on pathophysiologic mechanisms.

## **MECHANISMS OF PRETERM DELIVERY**

Lockwood explains four processes that lead to common pathway of PTD. Extracellular matrix changes, which is visible as ripening of the cervix. Fetus also has a role in the initiation of labour.<sup>13-16</sup>

The first process, evident by stress and anxiety, is more often found in young primiparas with genetic predisposition.<sup>17-19</sup> Stress of the fetus also leads to elevated levels of corticotropin releasing hormone (CRH), the mediator of stress. Changes in ACTH, prostaglandins, oxytocin receptors, matrix metallo-proteinases, interleukin-8, cyclooxygenase-2, DHEAS, placental estrogens and fetal adrenal enlargement follow. The latter, in connection with preterm delivery, was found already in 1971, before the era of ultrasound (US).<sup>20</sup> Later Turan prospectively measured fetal adrenals in women with preterm labor.<sup>21</sup> In women that finally delivered preterm, fetal adrenals were enlarged. The incidence of PTD is higher in *Homo sapiens* than in other mammals; reasons for that being upright walk, narrower pelvis, bigger brain, speech, and social connections.<sup>1</sup> The incidence of PTD is higher in lower social classes, undernourished and pathologically overweight (ITM > 35kg/m<sup>2</sup>).<sup>3,16,22-24</sup>

Specific markers for the first process are CRH and salivary estriol but they did not prove themselves as predictors of preterm delivery.<sup>25-27</sup> The levels of CRH are consistent with psychological tests regarding stress.<sup>28</sup> In Slovenia, the EUROPOP research showed that the level of stress is the highest in employed women, who do no housework.<sup>29</sup> The explanation was that they are afraid of becoming unemployed if they use their sick leave when feeling sick, so they just rest at home after work.

The second process is deciduo-chorio-amnionitis as the result of systemic infection, which is the cause of more than 50 % of EPTD.<sup>30</sup> Periodontal disease might lead to PTD.<sup>31</sup> Bacterial vaginosis (BV), diagnosed before 16 w.p., is significantly connected with PTD; BV helps development of pathological organisms.<sup>32-42</sup>

With proteomic profile the intra-amniotic infection was proved.<sup>43</sup> Maternal and fetal inflammatory responses are changed, leading to preterm labour when there is genetic predisposition; because of that, there might be specific treatment in the future.<sup>44, 45</sup> There is ongoing research to find genes for term as well as

for PTD.<sup>46</sup> Maternal immune reaction is more often seen in male fetuses.<sup>47</sup> Infection also influences fetal hypothalamic-pituitary-adrenal axis.<sup>48</sup> Conisation is a high risk factor for PTD.<sup>49</sup> As with induced abortions, related to EPTD, infectious or mechanical causes may be involved.<sup>50</sup>

C reactive protein (CRP) and pro-inflammatory cytokines are not sensitive enough as markers; pentraxin 3 (PTX3) might be more useful. CRP is produced in liver in response to IL-6, and PTX3 is produced in different cells in response to IL-1, tumor necrosis factor, and bacterial products.<sup>51</sup> The population, where PTD evolves after this process, is usually young, from a minority and usually poor.

The third process is related to abruption of placenta. Retroplacental haematoma is found in a third of PTD and in less than one percent of term deliveries. The causes are primary or secondary thrombophilias, hypertension, cocaine abuse, trauma and others.

Sclerosis of myometrial arteries is found in 11 % of 18 years old women and in 83 % after 39 years of age.<sup>52</sup> The elevation of blood pressure is higher in women, who deliver before 34 w.p.<sup>53</sup> Elevated homocysteine level is a risk factor for arterial diseases and venous thrombosis; in pregnant women, apoptosis of the trophoblast is induced, human chorionic gonadotropin production is decreased and problems with placentation might follow.<sup>54</sup> Homocysteine induces human myometrial contractions.<sup>55</sup> Changes of genes, coding the folate metabolism, elevate the risk for preterm delivery.<sup>56</sup>

The marker of the third process is thrombin-antithrombin complex.<sup>57</sup> In the third group are older, educated multiparas.

The fourth process is over-distension of the uterus because of multiple pregnancies, polyhydramnion, or relative over-distension because of uterine anomalies or operations of the cervix.<sup>49</sup> IL-8, prostaglandins and COX-2 mediate the process.<sup>27</sup>

The risk for PTD and other obstetrical complications increases in infertile women regardless of medical (non) intervention, and after ART also.<sup>58,59</sup>

Markers for all four processes are fetal fibronectin and cervical length.<sup>60-65</sup> Combination of cervical assessment in combination with pHIGFBP-1 at 30 weeks had the steepest ROC curve (area under the curve = 0.93; 95% CI, 0.88-0.98, P < 0.001).<sup>66</sup> Inflammation, abruption and over-distension all end in short cervix. Light-induced fluorescence is a method that measures the ripeness of the cervix; together with electrohysterography (EHG) it is a good predictor of successful induction of labor.<sup>67</sup> The use of EHG as a predictor of PTD is still in research area.<sup>68-70</sup>

$\beta$ -human chorionic gonadotropin,  $\alpha$ -fetoprotein, inhibin, activin, relaxin and others were also evaluated as markers.<sup>71</sup> The goal of our study RP P3-0124 is to find pregnant women at high risk for PTD and use all proven managements to prolong pregnancy over 28 w.p. if this does not harm the woman or fetus. The study was approved by State Ethical Committee (No 90/11/05). PTD is being studied in Slovenia for more than three decades.<sup>72-77</sup>

Most of women that deliver preterm, do not have risk factors written in Tables 2 and 3. What is as important, we can not influence these factors (except perhaps smoking habits). So to improve prediction and management various tests – compatible with mechanisms of PTD - are added. Entering the study, women fill in the *Prediction model for preterm delivery risk estimation*, the well being questionnaire and the questionnaire regarding social quality of life. Smears for detecting BV (we use Nugent and Amsel scoring) and pathogenic bacteria are taken. Cervical length is measured in 22<sup>nd</sup> to 24<sup>th</sup> w.p.<sup>78,79</sup>

In the case the cervix is shorter than 25 mm, EHG is performed and repeated in 32<sup>nd</sup> to 34<sup>th</sup> w.p. After delivery, the data on pregnancy, delivery and neonate are completed.

## **MANAGEMENT OF THE HIGH RISK GROUP FOR PRETERM DELIVERY**

In most of the literature it is stated that preterm delivery can not be prevented.<sup>80</sup> This is certainly true if we take 37 w.p. as a limit. But, as survival over 32 w.p. is almost 100%, our aim is to achieve 32 or at least 28 w.p. As preterm labor (and delivery) have many causes, it is important to lower or remove as many as possible.

### **Management early in the process of preterm labor**

Pregnant women must have prenatal care. It sounds too simple: but sometimes everything is done that the woman conceives; when she does, prenatal care just seems to be “not scientific enough” and they forget about it.

#### **Progesterone**

With use of 250mg 17- $\alpha$ -hydroxy-progesterone caproate per week the incidence of VPTD was 11.4% in treated group and 19.6% in control group of women who previously had PTD.<sup>81</sup> In the group of high risk women that was given vaginal suppositories with 100 mg progesterone per day the incidence of PTD under 34 w.p. was 2.7% vs 18,5% in the control group.<sup>82</sup>

In the group of women with cervical length less than

15 mm in midgestation 200 mg of vaginal progesterone from 24 to 34 w.p. PTD before 34 w.p. was less frequent (19.2%) than in the placebo group (34.4%).<sup>83</sup>

### **Management of women with chronic diseases**

These women represent the majority of those who have iatrogenic PTD. The percentage of iatrogenic PTD is rising all over the developed world, especially VPTD. Because of increasing age at parturition, there are more pregnant women with diabetes mellitus and patients with hypertensive diseases of pregnancy.<sup>84</sup>

There are patients with systemic lupus erythematoses, transplanted kidneys, heart diseases, respiratory diseases and others. Team approach is used for best results for the mother and the baby.

### **Management of infections**

In Cochrane database there is a statement, that therapy for asymptomatic bacteriuria lowers the possibility of pyelonephritis, but does not lower the incidence of PTD.<sup>85</sup> Treatment of periodontal disease decreases the incidence of PTD.<sup>86,87</sup> Hauth found that treatment of BV in high risk group decreased the incidence of PTD.<sup>88</sup> Kekki included 5432 pregnant women into prospective, randomised, double blind, placebo controlled research.<sup>33</sup> There was no difference in the incidence of PTD between women, treated for BV, and those who were given placebo, but women, where BV relapsed, delivered preterm 7 times more often. Hoyme and Saling introduced a programme of self determination of vaginal pH.<sup>34</sup> If it was over 4.7, women were instructed to visit gynaecologist. When BV was present, they were treated locally, when not they were only given *Lactobacillus acidophilus* medication. The percentage of VPTD among more than 16000 pregnant women was 0.99% in research and 1.58% in the control group. Nishijima gave *Lactobacillus Johnsonii* per os with similar results.<sup>35,36</sup> Ugwumadu also gave oral treatment to BV positive women in their prospective placebo controlled study of 485 pregnant women; the incidence of PTD was decreased.<sup>89</sup> Kiss found that treatment of asymptomatic vaginal infection in the research group of 4429 women decreased PTD.<sup>37</sup> After they were criticised because of expenses, they also provided financial analysis.<sup>38</sup> As a basis they took financial burden of preterm neonate with 1.900 g birth weight and care for the child until its sixth year; it was estimated to be 60,262 Eur. This was compared to expenses of the screening program including expenses for medicines.

With 50 % of reduction of PTD 11 000 000 Eur per year would be saved in Vienna only; expenses for the screening program together with drugs represented

only 7% of this money.

On the other side, there are reports, that giving bactericidal metronidazol increases risk for PTD.<sup>40</sup>

There are reports that vaginal douching 6 months before pregnancy decreases the risk for PTD for 63%; douching in pregnancy, however, increases the risk for 64%.<sup>90</sup>

Liu showed in mice that TL4 receptor antagonist, induced by *Fusobacterium nucleatum*, in 50 % prevents the death of the fetus because of inflammation.<sup>91</sup>

The summary can be that as early as possible in pregnancy – at least in the beginning of the second trimester – pathogenic organisms should be removed from vagina before the inflammatory process is triggered. Treatment later or treatment with metronidazol may harm because toxic products may trigger new cascades. It is for this reason that the results of studies are controversial.

### **Cerclage**

There is no clear cut answer.<sup>92</sup> In a well known study in 47123 pregnant women cervix length was measured. If it was less than 15 mm, women were randomized into the group with cerclage (253) or no cerclage. There were 22% of VPTD in the research and 26% in the control group. There was no statistical significance (RR 0,84; 95% CI 0,54-1,31), which does not mean there was no clinical significance. The main author later demonstrated, that besides cervix length the obstetrical history is also important.<sup>8</sup>

In women with high risk for PTD (previous preterm delivery, cervical trauma, diethylstilboestrol exposure, uterine anomalies) and cervix length under 25mm before 27 w.p., the incidence of PTD before 34 w.p. decreased after cerclage.<sup>93</sup> Cerclage may also be the cause of complications.<sup>94</sup>

### **Omega-3 fatty acids**

In women with PTD in their history, the incidence of PTD under 34 w.p. decreased for 68% with use of omega-3 fat acids.<sup>95</sup>

### **Psychological support, social support, proper nutrition**

*Tender loving care* (TLC) is efficient in management of recurrent miscarriage.<sup>96</sup> Mamelle showed that psychological support decreases the incidence of PTD in women with high risk for PTD.<sup>97,98</sup> BMI below 20kg/m<sup>2</sup>, standing at work for more than 2 hours per day, and stress were shown to be socio-economic and psycho-social risk factors for PTD. It is advisable to increase BMI over 20kg/m<sup>2</sup> or decrease below 35kg/m<sup>2</sup>, change working conditions and give support in

acute emotional problems.<sup>99</sup> PTD is more common in the lowest social class, so it was expected that social and psychological support would decrease the incidence, which was proven.<sup>22,100</sup> Regarding the difference in the incidence of PTD in Europe and U.S.A. Meis states, that in latter there is no real social support.<sup>3</sup>

Decades ago more information was given to pregnant women regarding proper nutrition; at that time people were poor and could not afford quality food. Today many women are on strange diets, some even take drugs for losing weight. Inappropriate nutrition can have dire consequences in next generations.<sup>23</sup>

### **Corticosteroids when fibronectin is positive**

Specificity of fetal fibronectin as marker of all pathogenetic processes of preterm delivery is high; positive predictive values is more than 50 %.<sup>61</sup> Some authors suggest that all pregnant women, pregnant over 23 w.p. and with positive fibronectin, should be given corticosteroids for fetal lung maturation.<sup>13</sup> Progesterone efficiency was also proven in high risk patients.

In our research, if women score below a certain cut-off point, they are offered psychological and social support. There are algorithms for management if pathogenic bacteria, BV or short cervix are discovered.

### **Management late in the process of preterm labor**

#### **Corticosteroids**

Repeated doses influence fetal growth and behavioural changes. At 30 years of age of those, who were given steroids when *in utero*, also had changed response to glucose tolerance test.<sup>101</sup>

#### **Tocolysis**

Tocolysis does not prevent PTD but prolong pregnancy for a few days.<sup>102</sup> Many drugs are used, but only  $\beta$ -mimetics and atosiban are registered for tocolysis.<sup>103,104</sup> All other drugs are used “*off-label*”. Drugs that are used have unwanted side effects.<sup>105,106</sup> There are data in the Cochrane database that magnesium sulphate is not efficient as tocolytic and that perinatal mortality is higher with its use; nevertheless it is still being used.<sup>107-109</sup> On the basis of retrospective study decreased incidence of cerebral palsy was hypothesised.<sup>110</sup> Mittendorf and Pryde calculated that because of magnesium sulphate use 1900 additional neonates die in U.S.A.; and may be 400 less have cerebral palsy.<sup>109</sup>

In the future it might be proven that adding low doses of magnesium sulphate to tocolytics decreases the incidence of cerebral palsy.<sup>104,109,111</sup> Atosiban has, compared to  $\beta$ -mimetics, less side effects.<sup>112</sup> Exogenous donors of NO do calm myometrium but at the same time provoke cervical ripening.<sup>113</sup>

### Prevention and early diagnosis of fetal anomalies

Primary prevention and early diagnosis of lethal malformations or chromosomopathies can decrease the PTD rate.<sup>114</sup>

## DISCUSSION

There is absolute agreement that preterm birth is a major public health issue. It may well be proven in the future, that in fact there are two diseases: preterm labor and delivery before 32 (according to some authors 34) w.p. and preterm labor and delivery from 32 (34) to 37 w.p. It is the VPTD, i.e. before 32 w.p., that is most important to prevent.

VPTD may be divided into spontaneous and iatrogenic. The unwanted result, i.e. a preterm neonate with immediate need for intensive therapy and long term handicap, is the same, however the management is different. This is the reason we discuss VPTD as an entity, even if authors do not agree.<sup>115</sup> In the future, when genetic and other causes are found, the definitions will be different.

The multitude of different prediction schemes shows that none is perfect. Some risk factors are not valid for all populations; that was partly explained by genetic differences. There is no agreement in the literature what primary and what secondary predictors are.<sup>115,116</sup> Some authors define primary predictors as those from medical history: conisation, previous preterm delivery, pathological signs from the current pregnancy (bleeding, e.g.) and pathological results of additional tests (BV, positive fibronectin, short cervix).<sup>116</sup> Others define as primary predictors only those from medical history, all the others as secondary.<sup>115</sup> The fact is we can not change the factors from medical history (conisation, diabetes mellitus, previous preterm delivery etc). The same is true for pathological events in pregnancy (bleeding, e.g.).

These are the basic predictors for individual women with high risk for preterm delivery; these women represent minority of those who do deliver preterm. In Slovenia, according to the *Prediction model for preterm delivery risk estimation*, each of these factors was given a score.

In the future genes, defining high risk for preterm

delivery, will be determined.<sup>117</sup> Preterm delivery is also an inherited disease.<sup>118</sup> Genes can not be changed; expression of genes may be influenced by environment. Epigenetic influences are very important.<sup>23</sup> For the time being, the prediction on the basis of cervical length and obstetric history is the most promising.<sup>8</sup>

It was only in France that temporary decrease in PTD rate was achieved in seventies and eighties of the previous century.<sup>2</sup> Early prenatal care was offered to all pregnant women, information was spread regarding life style in pregnancy, risk factors, and early signs of preterm labor, sick leave and maternity leave were offered. In 1972, there were 2.4% of PTD under 34 w.p. and only 0.9% in 1988. In that year there were 4.9% PTD altogether, but ten years later, in 1998, there were already 6.27%, the increase being mostly because of iatrogenic PTD and PTD in immigrants.

In U.S.A. the effort to decrease PTD did not succeed; Meis commented that it was so because there was no media support and no governmental policy regarding maternity leave existed.<sup>3</sup>

We can put risk factors/signs in two broad categories: those we can not and those that we could influence; in the latter group, we could intervene before pregnancy, early in the process of PTD or late in the process of PTD.

Some risk factors we can not influence (examples in the brackets):

- Facts from medical history (e.g. previous preterm delivery);

- Positive results of tests (e.g. short cervix).

Some risk factors we could partially influence (possible intervention in the brackets):

a. Before pregnancy:

- Ignorance (education);

- Congenital uterine anomalies (correct);

- Unplanned pregnancies (plan);

- BMI under 20kg/m<sup>2</sup> or over 35kg/m<sup>2</sup> (change);

- Smoking (stop);

b. Early in the process of labor:

- Women with high risk (progesterone);

- BV or pathogenic bacteria (treat properly);

- Psychological stress (support);

- Socio-economic problems (social support);

- Short cervix (progesterone, cerclage);

- Maternal disease (treat accordingly, prevent complications);

c. Late in the process of labor when delivery is imminent:

- Pulmonary immaturity (corticosteroids);

- Infection/ inflammation (antibiotics);

- Contractions (tocolysis, *in utero* transport to a center with NICU).

In the future, some more risk factors will move into the group where prevention is possible. At the moment an example is operative correction of uterine anomalies.<sup>119</sup>

The area of primary prevention is very interesting from the psychological view also. Since 1991 it is well known that folic acid prevents more than 70% of neural tube defects when taken properly from conception until the 8 w.p. Women with metabolic syndrome and epilepsy, who have elevated risk for NTD, should take ten times larger dose, i.e. 4000 µg of folic acid per day.

All women without contraception should take folic acid; even those, who think they do not want a baby. It is well known they change their minds when they become pregnant. It is an extremely depressing truth that all over the world only a minority of women takes folic acid properly.

Not taking folic acid some call the biggest defeat of public health endeavours. As if taking folic acid is an advice too simple and too cheap to follow!<sup>120</sup> It is to be hoped that regarding PTD the attitude will be different..

As interesting is comparison of screening for trisomy 21 (T21) and screening for PTD. Screening for T21 was first done on the basis of maternal age, triple test, nuchal translucency, double test, quadruple test, integrated test etc. Pregnant women definitely know about that screening much more than about screening for preterm delivery. The incidence of T21 depends on the population's average age; in a very "old" population it is around 2/1000. The incidence of EPTD is 5/1000 in Slovenia, and of VPTD 11/1000. It is true that all preterm neonates do not have long term handicap. It is to be seen if different combinations of the same test would predict different complications.<sup>121, 122</sup> At the end, with genomics, proteomics and pharmacogenomics, the prediction and management will be specific.<sup>123</sup>

## CONCLUSIONS

### **Prolongation of pregnancy is possible**

In women with high risk for PTD, also after ART, and short cervix, progesterone should be given from midgestation to 34 w.p.

Cerclage may be indicated in high risk women with short cervix.

As soon as possible – at least at the beginning of second trimester – abnormal vaginal flora is to be discovered and treated. Later treatment or treatment with metronidazol can harm

Free prenatal care, paid sick leave, psychological and social support, proper nutrition and other state

based interventions are very important.

When preterm delivery is imminent, tocolysis, administration of corticosteroids (once), and *in utero* transport to a centre with NICU decrease neonatal morbidity and mortality.

Before planned pregnancy some interventions (correction of uterine anomalies, achievement of proper BMI etc) can lead to better results regarding VPTD.

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