Prenatal and Perinatal Management of Preterm Labour

Koucký M.[1], Germanová A.[1,2], Hájek Z.[1], Pařízek A.[1], Kalousová M.[2], Kopecký P.[1]

[1]Charles University in Prague, First Faculty of Medicine and General University Hospital, Department of Gynaecology and Obstetrics, Prague, Czech Republic; [2]Charles University in Prague, First Faculty of Medicine and General University Hospital, Institute of Medical Biochemistry, Prague, Czech Republic

Received March 2, 2009; Accepted October 1, 2009.

Key words: Premature labour – Premature rupture of membranes – Foetal inflammation – Ultrasound cervicometry – Tocolysis – Antibiotics – Thrombophilia – Progesterone

Abstract: New knowledge of the pathophysiology of premature birth enables us to introduce new approaches in prenatal care as well as the management of premature delivery. These apply for the patients with subclinical risk factors, particularly with thrombophilias, chronic infections or other latent chronic infections. The peri- and pre-conceptional dispensarisation of these women might help reduce the development of premature delivery. Secondary prevention with the administration of gestagens is highly important for women with anamnestic or existing risk of premature delivery. During the underlying premature delivery, it is advisable to re-evaluate the significance of the administration of antibiotics and tocolytics as well as timing of corticoid dosage in the induction of foetal lung maturity. Using new diagnostic and therapeutic methods, the aim of present premature delivery management is to prolong the duration of pregnancy to the maximum with the lowest risk of the development of foetal inflammatory response possible and, therefore, with a low risk of long-term handicaps in children.

This study was supported by grant GA UK 71408.

Mailing Address: Michal Koucký, MD., Charles University in Prague, First Faculty of Medicine and General Teaching Hospital, Department of Gynaecology and Obstetrics, Apolinářská 18, 128 00 Prague 2, Czech Republic; e-mail: michalkoucky@seznam.cz

Periconceptional Care for Women with the History of Premature Delivery

Using modern knowledge, we aimed to reduce the risk of premature delivery in the group of women with the history „burdened" with premature delivery or multiple, especially second-trimester abortions. The decisions should be made regarding the principles of evidence based medicine – the base source of information are the data obtained particularly from meta-analyses of studies. Prior to planned conception, a systemic disease, particularly an autoimmune one, should be eliminated in these women. The elimination of orofacial chronic infection – an evidence of the relationship between periodontitis and premature delivery – is important, too [1]. Some pathologies might have a latent course, without apparent clinical symptoms, particularly thyroid gland disorders or anti-phospholipid syndrome, having, however, a demonstrable causal relationship with the risk of prematurity. It is advisable to do examination at a particular specialist, e.g. at an immunologist, internist or endocrinologist. Being aware that even excessive uterine expansion may trigger the complicated cascade resulting in premature delivery, endoscopic examination (hysteroscopy or laparoscopy) is advisable to eliminate hereditary uterine impairments. The exact role of micro-organisms in the pathogenesis (interaction of genes with the environment) has not been explained yet; some works suggest possible relationship between chronic colonisation, particularly by atypical pathogens (ureaplasma, mycoplasma, chlamydia) and premature delivery [2]. Theoretically, adequate preconceptional therapy might reduce the risk; however, there is a lack of reliable data in this field [3].

The chapter on the relationship between thrombophilias and prematurity includes an information on the significance of MTHFR polymorphisms, having been „neglected" until recently. There are more and more works supporting the significance of the necessity of thorough screening of coagulation parameters or miniheparinisation, not only in women with severe thrombophilias (f. V – Leiden mutation, f. II mutation, antiphospholipid syndrome etc.), but also in patients with folic acid metabolism disorders (women with polymorphisms/MTHFR mutations). Besides other pathological conditions, various studies describe the relationship between MTHFR mutation carriage and prematurity [4].

For the assumed pathophysiological mechanism, see the chapter on the role of uteroplacental ischaemia in premature delivery pathogenesis (previous author's article "Pathophysiology of preterm labour" published in *Prague Medical Report* 10(1): 13–24). The administration of 4-tetrahydrofolate – metafoline represents a proper way of the primary prevention of premature delivery in pregnant MTHFR carriers. Metafoline is available in the formulation containing folic acid [5, 6]. It is recommended to monitor pregnant women with thrombophilias in cooperation with a haematologist, not only due to a possible risk of thromboembolia. Regular monitoring of coagulation parameters, supplementation with metafoline and/or folic acid in MTHFR carriers and, as the case may be, administration of miniheparin, is a rational way of the secondary prophylaxis of premature delivery, intrauterine

restriction (IUGR), pre-eclampsia and other potential pathological conditions. However, there has been a lack of extent studies with miniheparin so far, particularly of placebo controlled ones.

Prenatal Care about Women with Anamnestic and/or Existing Risk of Premature Delivery

Pregnant women with the chronic disease potentially related to premature delivery should be monitored in cooperation with proper specialists. Stabilization of the disease increases the likelihood of bearing the full term. Thrombophilic women are monitored by haematologists; see above. Prenatal care takes place similarly as in physiological pregnancy. Based on the results of the study with gestagens, we can administrate them from the beginning of the second trimester to 36th week of the pregnancy. Pregnant women apply themselves micronised progesterone in the form of vaginal tablets. Optimal dosage has not been established yet; the recommended doses are 2–4 tablets per day. Dodd's meta-analysis suggests significant reduction of premature delivery in women with prematurity in the history and in the pregnant with asymptomatic cervical incompetence (based on ultrasound cervicometry). However, no reduction of the risk has been observed in women with symptoms of immediate premature delivery (frequent contractions) in multiple pregnancy [7].

A number of past as well as recent works are focused on the relationship between bacterial colonisation and premature delivery [8]. An important role is played by gene interaction with the environment; see chapter on the infection and premature delivery (previous author's article "Pathophysiology of preterm labour" published in *Prague Medical Report* 10(1): 13–24). None of the studies including their meta-analysis has shown a reliable evidence of the assumed reduction of premature delivery risk by the treatment of asymptomatic bacterial colonisation [9]. From this point of view, there is no clinical significance of cultivation screening in asymptomatic women [10]. The use of antibiotics is related to a potential risk; it is therefore necessary to take it into consideration when prescribing them. King and Flenady´s work, focused on the administration of antibiotics in the pregnant women with threatening premature delivery without the signs of clinical infection, suggested the conclusion that routine administration of antibiotics does not improve the prognosis of prematurely delivered newborns [11]. Long-term (7 years so far) follow-up in ORACLE II study has shown more frequent incidence of various functional impairments in these newborns [12]. In short-term follow-up, it can only be expected a benefit for the mother, i.e. reduction of the incidence of puerperal endometritis [13]. Repeated administration of antibiotics during pregnancy is connected with a risk of the development of resistant neonatal sepsis [14].

There is only agreement in the matter of vaginal/cervical infection (particularly ureaplasma, mycoplasma and group B streptococcus) in the pregnant with clinical (haemorrhage, frequent contractions, discomfort due to outpouring, cervical

incompetence) and laboratory (CRP elevation, immature/total index in blood cell differential count – the ratio of mature and immature forms of neutrophilic granulocytes) symptoms of an immediate risk of premature delivery. Regarding the most frequent infectious agents assumed, macrolide antibiotics represent an optimal choice [15]. Using macrolides, the maximum benefit for the foetus/newborn is seen before 30th week of the pregnancy. Ureaplasma and mycoplasma might cause atypical pneumonia in immature lungs. In the next weeks, potential risks from the administration of antibiotics prevail the benefit, see above. Macrolide antibiotics exert bacteriostatic, not bactericid, effects; there is a risk of the development of antibiotic resistance after repeated administration [16]. After group B streptococcus has been cultivated in birth canal, it is advisable to apply penicillin G. The route of administration of both macrolides and penicillin G is parenteral. Macrolides are replaced by the combination of ampicilline and gentamycine in the occurrence of clinical signs of intraamnial inflammation and the mother's temperature exceeding 38 °C, maternal and/or foetal tachycardia; the combinations of clindamycine and gentamycine or azithromycine and gentamycine are used in the allergy to penicillin. Their administration is connected particularly with a benefit for the mother, see above. The tactic of using various tocolytics in premature delivery has been changed recently. Tocolytics are agents applied with the aim to prevent premature uterine contractions. The use of oxytocine receptor antagonists (atosiban, barusiban) is a modern way of tocolysis. They do not exert systemic adverse effects in the mother as well as foetus, related to the use of betamimetics [17]. There is a lack of reliable evidence of the efficacy of magnesium sulphate (tablets as well as parenteral form) in tocolysis [18]. The use of corticosteroids represents an important part of premature delivery management. Corticosteroids used by the mother induce the formation of order II pneumocyte surfactant in foetal lungs. Thus, the incidence of newborn mortality, RDS (respiratory distress syndrome) and IVH (intraventricular haemorrhage) is reduced. The incidence of newborn mortality and RDS is therefore reduced. One series of corticosteroids includes administration of betamethasone or dexamethasone in two doses in a 24-hour interval or in four doses in 12-hour intervals. Until recently, repeating the series has been considered risky due to potential intrusion of myelinisation of white matter fibres (animal study). The meta-analysis of Cochrane Library from 2007 shows that multiple doses of corticosteroids reduce the occurrence and severity of neonatal pulmonary complications with no increase in the risk of other infectious complications in newborns and mothers. This short-term benefit supports the possibility of multiple dosages of corticosteroids in patients at a high risk of premature delivery. Some studies however describe the reduced delivery weight and head perimeter. There has been no adequate evidence of long-term benefit and potential risk of multiple administrations of corticosteroids for the newborn's further development. Thus, there is a need of adequate timing of one series at immediate threat of premature delivery [19].

Management of Pregnancy with Premature Rupture of Membranes – PROM

Premature rupture of membranes is the most severe form of premature delivery. Premature delivery with contractions and intact membranes is – in terms of the management – a reversible process; PROM represents an irreversible one. We suppose both the presence of micro-organisms as a usual trigger factor and the possibility of secondary intraamniotic infection after the rupture of membranes. Both situations are connected with a risk of the development of unfavourable neonatal disorders (pneumonia, sepsis, intraventricular haemorrhage, etc.).

In patients with PROM, it is necessary to eliminate intraamnial infection/inflammation at the admission to the delivery room. However, a complete clinical picture of intraamnial infection (the mother's temperature over 38 °C, maternal and foetal tachycardia, increased uterine tonus, outpouring of malodorous amniotic fluid, etc.) is not seen very often in our conditions. We have an opportunity to see the pregnant and women who are about to give birth before the development of the clinical picture. At present, the diagnosis of intraamnial infection is based on biochemical, haematological, cardiotocographic, ultrasound, microbiological and clinical examination (see the clinical picture). Microbiological examination includes cultivation of a sample from birth canal (complete examination of aerobic and anaerobic micro-organisms including ureaplasms, mycoplasms and chlamydias). Cardiotocographic examination might suggest the presence of infection if foetal tachycardia occurs, particularly if it is connected with the disappearance of accelerations and decrease in oscillations. Besides checking the fetal position, ultrasound examination has a "monitoring" significance in the abovementioned expecting procedure. Evaluation of amniotic fluid amount, foetal motor activity and respiratory motions is significant in terms of the transmutation of amniotic fluid between the lungs and gastrointestinal tract and „outer" foetal environment. Amniotic fluid represents significant stimulation medium of the development of foetal lungs. Thus, keeping the continuity of the exchange of pulmonary and amniotic fluids is highly important. The most used haematological and biochemical examinations include blood count (white blood cell count) and CRP, respectively. There was carried out a number of studies evaluating sensitivity of these tests in the prediction of intraamnial infection. The sensitivity of blood count as well as CRP varied from 33% to 100% with higher CRP levels in the studies. It has been known that leukocyte levels are modified by administration of corticoids (corticoids reduce the adherence of neutrophilic granulocytes in the vascular wall, stimulating the release of neutrophilic granulocytes into the vascular bed). White blood cell differential count can be assessed, too. More specific information is provided by immature/total index. It is an immature/total granulocyte number ratio, enabling the differentiation between inflammation and blood count alteration caused by corticoids. The disadvantage of the abovementioned examinations is, however, obvious: these

are serum biochemical markers and refer to the mother's condition, not to the foetus [20].

Compared with the approach to premature delivery with contractions, the basic difference in the approach is administration of antibiotics immediately after a patient with PROM is admitted to the delivery room. Multicentric, randomised ORACLE I study evaluated the relationship of administration of antibiotics (amoxiclav + clavulanate and erythromycine in monotherapy or combination) and neonatal morbidity and mortality in patients with PROM. The results were rather surprising. Compared with placebo, amoxiclav + clavulanate as well as those combined with erythromycine did not bring any benefit. On one hand, their administration helped prolong the pregnancy in patients with PROM; on the other hand, the incidence of necrotising enterocolitis was relatively high in prematurely delivered newborns. The administration of erythromycine itself also resulted in pregnancy prolongation, with additional effects of the reduction of surfactant therapy of newborns, reduction of oxygen supplying after 28th day of the life and reduction of the incidence of neonatal infectious complications, including reduction of the incidence of positive haemocultures [21].

Thus, macrolide antibiotics are considered optimal. However, the results of the study should not be overestimated; geographical specificities must be taken into consideration. Protocols on antibiotic administration differ in particular regions all over the world. In fact, the therapy always starts with empirical administration of an antibiotic based on the cultivation from birth canal; the therapy should be adjusted on the base of sensitivity test. The issue of an optimal antibiotic remains open, too.

Azithromycine is used in our conditions as a first choice antibiotic. If there is no sign of intraamniotic infection/inflammation (see bellow), we dose it for five days i.v, once a day. Each case is considered strictly individually. Like in patients with intact membranes, in clinical signs of infection, i.e. the mother's temperature exceeding 38 °C, tachycardia in the mother and/or foetus or outpouring of malodorous amniotic fluid, a parenteral combination of ampicillin + gentamycine is used or, in penicillin allergy, ampicillin is replaced by clindamycine, as established by the guidelines of Czech Society of Gynaecology and Obstetrics. The next management depends on the pregnancy week in which premature rupture of membranes occurred. There are two different approaches to the care: An expecting one – preferred in PROM occurring before the completed 28th week of the pregnancy, and an active one – applied after the mentioned week. The active one is based on the assumption that "planning" the delivery helps keep the low incidence of perinatal morbidity and mortality after a certain degree of lung development was achieved. Potential infectious/inflammatory risks connected with PROM should be taken into consideration. Besides antibiotics, active management includes tocolytics, too; they are used during the time of corticoid application in this case. The pregnancy is discontinued after the completion of corticoid therapy,

regarding the conditions given; first, tocolytics are withdrawn, then, the delivery is induced in a patient with favourable vaginal finding and longitudinal position of the child's head or elective Caesarean section is done in a patient with a finding inadequate for delivery induction or position of the foetus other than the abovementioned one. For tocolytic procedures and induction of lung maturity, see the previous chapter. The expectation approach regards the fact that if PROM does not occur before the completed 28th week, the postnatal care is limited particularly by the level of lung maturity. The admission of the patient should be followed by administration of antibiotics and tocolytics and dynamic monitoring of inflammatory markers, ultrasound examination, amniotic fluid amount analysis, respiratory and general motions of the foetus. If clinical and laboratory signs do not suggest active infectious/inflammatory response of the mother and/or foetus, it is possible to continue the pregnancy even after the withdrawal of the antibiotics. These are usually applied for 5–8 days, depending on their type. The timing of pulmonary maturity induction by corticosteroids is individual. If allowed by the clinical condition, their application should be delayed until the decision on planned discontinuation of the pregnancy, when the expecting approach is used. When the expecting approach is used in patients with PROM, the type and duration of tocolytic therapy is controversial. Vague information (lack of extent studies) on the effects of tocolysis on immature newborn suggests shortening of the tocolytic therapy; this applied particularly for betamimetics. Even after the withdrawal of antibiotics, and tocolytics and discontinuation of corticoid therapy, the expecting approach is connected with the necessity of vaginal monitoring (cultivation from birth canal) and monitoring of inflammatory markers and ultrasound parameters; see above.

At present, there is an evidence of the presence of the foetal inflammatory response (FIRS) in some patients, even in the absence of maternal inflammatory response in premature delivery/PROM [22]. This is the fact which most complicates the expecting approach in PROM – particularly in situations when amniotic fluid is pouring out in the periviable period, i.e. before are at 24th week of the pregnancy. Experimentally, it is possible to do the diagnostics of foetal inflammation – FIRS – by cordocentesis and interleukin-6 levels analysis in umbilical blood. The presence of FIRS is connected with higher incidence of neonatal morbidity and mortality. The discontinuation of the expecting procedure should be considered in elevated interleukin-6 levels in umbilical blood, suggesting the evidence of FIRS. It is an invasive method connected with a risk of complications, not being used in our conditions. As mentioned above, there is a non-invasive method of intraamnial (foetal?) inflammation monitoring by semi-quantitative MMP-8 analysis (see the chapter on infection and premature delivery – previous author's article "Pathophysiology of preterm labour" published in *Prague Medical Report* 10(1): 13–24). This procedure of intraamnial inflammation assessment is waiting for being used in clinical practice; it has not been known so far to what extent it will be used

in the expecting approach and if it will reduce the risk of the development of neonatal complications.

The decision on the discontinuation of the expecting procedure and delivery management depends on dynamic evaluation of the clinical condition as well as laboratory, cardiotocographic and ultrasound examinations.

Conclusion

In the past years, the use of recent scientific information has helped to improve results of diagnostic and therapeutic care for pregnant women and newborns. Premature delivery is considered a serious social-economical problem. The underlying pathogenetic base of the premature delivery is inflammation. This process refers to both the mother and the foetus. Foetal inflammatory response (FIRS) – might take place without the maternal response – being connected with significantly higher perinatal morbidity. FIRS is characterised by defined laboratory, histological and clinical criteria. The inflammation process is triggered faster than the infection; other significant causes, particularly gestagen metabolic and functional disorders and a role of uteroplacental ischaemia have been studied. At present no effective primary prevention of premature delivery exists. The use of new information on the above mentioned potential trigger mechanisms enables screening of pregnant women at the high risk who might be offered an adequate solution, based on present knowledge. The use of gestagens in women with prematurity in the history or symptomatic cervical incompetence seems to be an efficacious way of secondary prevention of premature delivery. Intensive research of new inflammatory markers has been carried out with the aim of early identification of the group of women at high risk of premature delivery and foetal inflammation. The procedures and duration of the administration of tocolytics, antibiotics and corticoids, particularly in women with PROM in the periviable period, have been constantly re-evaluated with the aim to reduce perinatal morbidity and mortality as well as a risk of long-term handicaps.

References

1. JEFFCOAT M. K., GEURS N. C., REDDY M. S., GOLDENBERG R. L., HAUTH J. C.: Current evidence regarding periodontal disease as a risk factor in preterm birth. *Ann. Periodontol.* 6: 183–188, 2001.
2. ROMERO R., CHAIWORAPONGSA T., KUIVANIEMI H.: Bacterial vaginosis, the inflammatory response and the risk of preterm birth: A Role for genetic epidemiology in the prevention of preterm birth. *Am. J. Obstet. Gynecol.* 190: 1509–1519, 2004.
3. TITA A. T., CLIVER S. P., GOEPFERT A. R., CONNER M., GOLDENBERG R. L., HAUTH J. C., ANDREWS W. W.: Clinical trial of interconceptional antibiotics to prevent preterm birth: Subgroup analyses and possible adverse antibiotic-microbial interaction. *Am. J. Obstet. Gynecol.* 197: 367.e1–6, 2007.
4. ENGEL S. M., OLSHAN A. F., SIEGA-RIZ A. M., SAVITZ D. A., CHANOCK S. J.: Polymorphisms in folate metabolizing genes and risk for spontaneous preterm and small-for-gestational age birth. *Am. J. Obstet. Gynecol.* 195: 1231.e1–11, 2006.

5. BUKOWSKI R., MALONE F., PORTER F.: Preconceptional folate prevents preterm delivery. *Am. J. Obstet. Gynecol.* 197(Suppl. 1): S3, 2007.
6. OZBEK A. N., ATAC B. F. B., VERDI B. H.: Relationship between small-for-gestational age births and maternal thrombophilic mutations. *Thromb. Res.* 12: 175–178, 2007.
7. DODD J. M., FLENADY V. J., CINCOTTA R., CROWTHER C. A.: Progesterone for the prevention of preterm birth: a systematic review. *Obstet. Gynecol.* 112: 127–134, 2008.
8. GOLDENBERG R. L., HAUTH J. C., ANDREWS W. W.: Intrauterine infection and preterm delivery. *N. Engl. J. Med.* 342: 1500–1507, 2000.
9. CAREY J. C., YAFFE S. J., CATZ C.: The vaginal infections and prematurity study: an overview. *Clin. Obstet. Gynecol*. 36: 809–820, 1993.
10. SIMCOX R., SIN W. T., SEED P. T., BRILEY A., SHENNAN A. H.: Prophylactic antibiotics for the prevention of preterm birth in women at risk: a meta-analysis. *Aust. N. Z. J. Obstet. Gynaecol.* 47: 368–377, 2007.
11. KING J., FLENADY V., MURRAY L.: Prophylactic antibiotics for inhibiting preterm labour with intact membranes. *Cochrane Database Syst. Rev*. (issue 4) DOI: 10.1002/14651858. CD000246, 2002.
12. KENYON S., PIKE K., JONES D.: Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet* 372: 1276–1278, 2008.
13. KENYON S. L., TAYLOR D. J., TARNOW-MORDI W.; ORACLE COLLABORATIVE GROUP: Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. ORACLE Collaborative Group. *Lancet* 357: 989–994, 2001.
14. MERCER B. M., CARR T. L., BEAZLEY D. D.: Antibiotic use in pregnancy and drug-resistant infant sepsis. *Am. J. Obstet. Gynecol*. 181: 816–821, 1999.
15. RAYNES-GREENOW C. H., ROBERTS C. L., BELL J. C., PEAT B., GILBERT G. L.: Antibiotics for ureaplasma in the vagina in pregnancy. *Cochrane Database Syst. Rev*. (issue 1) DOI: 10.1002/14651858. CD003767.pub2, 2004.
16. SCHELONKA R. L., WAITES K. B.: Ureaplasma infection and neonatal lung disease. *Semin. Perinatol.* 31: 2–9, 2007.
17. DE HEUS R., MULDER E. J., DERKS J. B., VISSER G. H.: Acute tocolysis for uterine activity reduction in term labor a review. *Obstet. Gynecol. Surv.* 63: 383–388, 2008.
18. KAM K. Y., LAMONT R. F.: Developments in the pharmacotherapeutical management of spontaneous preterm labor. *Expert Opin. Pharmacother.* 9: 1153–1168, 2008.
19. CROWTHER C. A., HARDING J. E.: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. *Cochrane Database Syst. Rev*. (issue 3) DOI: 10.1002/14651858. CD003935.pub2, 2007.
20. ASRAT T.: Intra-amniotic infection in patients with preterm prelabor rupture of membranes. Pathohysiology, detection, and management. *Clin. Perinatol.* 28: 736–739, 2001.
21. KENYON S. L., TAYLOR D. J., TARNOW-MORDI W.; ORACLE COLLABORATIVE GROUP: Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. ORACLE Collaborative Group. *Lancet* 357: 979–988, 2001.
22. GOMEZ R., ROMERO R., GHEZZI F.: The Fetal inflammatory response syndrome (FIRS). *Am. J. Obstet. Gynecol*. 179: 194–198, 1998.