CORRESPONDENCE

The Prevention, Diagnosis, and Treatment of Premature Labor

by Prof. Dr. med. Ekkehard Schleußner in volume 13/2013

Numerous Errors

In Figure 4 in his review article (1), Schleußner shows a smooth muscle cell in the uterus and signal transduction mechanisms. Unfortunately, there are numerous errors in the accompanying text.

The β-adrenergic receptor in the uterus is the β_2-adrenoceptor. This matters because the pharmacological agents used are β_2-adrenoceptor agonists ([2], page 433).

There are different G proteins. The G protein involved in the signal transduction of the β2-adrenoceptor is the stimulatory G_s protein ([2], page 320).

The represented oxytocin receptors and prostaglandin receptors also act through G proteins—in particular, G_q proteins. Also, for these receptors, phospholipase C as an effector is missing. There is not only one prostaglandin receptor, but it needs to be specified that prostaglandin F2α induces a contraction of the smooth muscle cells through the FP-receptor ([2], page 445).

The receptors are represented by different symbols. The prostaglandin receptor suggests a channel-like structure with one pore and two receptor units. This is erroneous. Prostaglandin receptors are not among the group of the ligand-controlled ion channels but among the group of G-protein-linked receptors. All depicted receptors should have been represented with 7 transmembrane domains ([2], page 64–66).

There is no molecule with the name "inosidol phosphate." The molecule that mobilizes Ca^{2+} from intracellular stores is called inosidol-1,4,5-trisphosphate and originates from the breakdown of phosphatidylinositol-4,5-bisphosphate through phospholipase C ([2], page 64–66).

The soluble guanylyl cyclase as a receptor for NO-pharmacological agents is lacking from the figure. Guanylyl cyclase synthesizes cGMP from GTP. Guanylyl cyclase should have been included in the figure because cAMP-synthesizing adenylyl cyclase is also shown ([2], page 535).

Calcium channel antagonists of the dihydropyridine type, such as nifedipine, inhibit the Ca^{2+} influx through voltage-dependent calcium channels located in the plasma membrane, not the release of calcium from intracellular stores ([2], page 505).

Indomethacine is obsolete because of its high rate of adverse side effects and should be replaced with substances that are better tolerated , such as ibuprofen ([2], page 211–12).

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The author declares that no conflict of interest exists.

Primary Prevention of Premature Labor Was Given Short Shrift

The two most common causes of premature labor are fetoplacental supply disruptions and ascending vaginal infections.

Systematic histological analysis of the placenta in premature babies shows disruptions to maturation and differentiation, as well as discordances and vascular pathologies (associated with reduced endothelial NO production?). Possible causes include suboptimal nutrition of the pregnant woman, which can disrupt placentation and development—for example, subsequent to deficiencies in magnesium, vitamins, and long-chain fatty acids. Magnesium substitution, given as early as possible and continuously throughout the pregnancy, prevents premature labor, neonatal underweight, premature rupture of the amniotic membrane (2), and pre-eclampsia (3, 4): a global indication of the fact that magnesium improves the function of the fetoplacental unit. It is therefore not surprising that for the treatment of premature labor (1), similar substances have been found to be effective as for pre-eclampsia ($MgSO_4$ or nifedipine).

Pathogens from the vagina are (owing to prostaglandin mechanism) a cause for premature cervical maturation (dilation of the internal os to 1 cm, cervical length less than 1 cm, and presence of painful uterine contractions), premature labor, or premature membrane rupture. For the purposes of secondary prevention, measuring the pH in the vagina by using the Saling procedure is useful, as is the often-neglected microscopic examination of a vaginal swab. For the purposes of primary prevention, nutritional status (vitamins) and sufficient magnesium supplementation for the pregnant women are important (2), as has become evident from a reduction in premature membrane rupture (2). Magnesium catalyzes more than 300 enzymatic reactions and contributes to optimizing pregnant

women's immune systems, which is useful in combating pathogens in the vagina.

Long years of the author's own experience, and his own views (further reading at www.magnesium-ges.de) have shown that magnesium supplementation is beneficial for developments in pregnancy and should be given early and continuously. If this has not been done then higher doses of oral magnesium can help save the pregnancy even at the onset of initial symptoms. However, magnesium should not be given simultaneously as oral calcium (which some "prenatals" contain—for example, those of US origin).

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Thyroid Function as a Possible Cause

Professor Schleußner concludes with some degree of resignation in his CME article that currently no measures exist to reduce the preterm birth rate. In the context of medical therapeutic freedom new drugs could be used off-label in order to reduce prematurity; but, even more importantly, a pressing need exists for high-quality research in this area of obstetrics.

This is not entirely correct. My experiences over the past 12 years have shown that optimizing maternal thyroid function during pregnancy can substantially lower the rate of preterm birth in multiparous women with singleton pregnancies, to below 3% (versus 6.7% in the perinatal statistics for Baden–Württemberg in 2006).

Each pregnancy increases maternal thyroid function substantially. For the fetus, maternal free serum thyroxine (fT4) is of crucial importance as it promotes the development of the fetal brain. A maternal fT4 concentration in the high normal reference range is optimal. In the presence of iodine deficiency or thyroid antibodies, the thyroid produces primarily triiodothyronine (T3) and not the inactive prohormone thyroxine, in order to maintain maternal euthyroidism throughout the pregnancy. The resultant maternal hypothyroxinemia may impair the development of the fetal brain.

Hypothyroxinemia can be corrected by using L-thyroxine and iodide. This benefits the development of the fetal brain, and lowers the rate of preterm birth in multiparous women with singleton pregnancies drastically.

In 2010, the data were presented at the Congress of the German Society for Gynecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V., DGGG) in Munich and published in 2011 (www.ncbi.nlm.nih.gov/pubmed/22203918)

Since the 2010 publication, nothing much has changed in the rate of preterm birth in spite of an increase in the number of cases. Much evidence suggests a physiological association between maternal hypothyroxinemia and preterm birth. I am quite happy to provide the original data to Professor Schleußner for inspection.

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Dr Torremante has received honoraria for preparing scientific advanced training events from Schering Bayer and Dr Pfleger. Furthermore, he has received author fees from Hexal.

Administration of Vitamin D

In recent years, several studies have shown, for example (1), that administration of vitamin D at a dosage of 4000 IU during pregnancy halves preterm labor rates. This result applied to women from all ethnic backgrounds (African-American, Hispanic, Caucasian white). It is simply frustrating that no one in Germany is paying any attention to these insights, which meet the highest quality criteria and are not supported by the pharmaceutical industry. Since vitamin D is a non-patentable, cheap natural substance, it provides very little incentive for further research or even implementation to the gigantic industry behind preterm birth, with its financial interests. I can only

advise anyone who has gained the relevant advanced training certificate to read the study listed in the reference list (which can be downloaded from the internet as a pdf)—the surprise will be enormous. In my opinion, this should become mandatory reading on the topic for students and doctors.

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Previous Induced Terminations

Regarding the aspect of prevention, which is of crucial importance in a scenario of the risk of preterm birth, a relevant and proved association was not mentioned: induced terminations of pregnancies also lead to a higher rate of premature labor and a higher rate of neonates with a low birth weight (1, 2). This is medically plausible since the trauma to the cervix (as the uterus's attachment and closure mechanism) causes lasting damage. The article mentions as a risk factor "a history of obstetrical problems (previous preterm births or late miscarriages)," but does not mention previous terminations. It is regrettable that this contributing cause of a large number of preterm births (1, 2) was not considered in the primary prevention, because from a medical perspective, this would mean that the large number of preterm babies would be reduced permanently—a favorable outcome for babies from current and subsequent pregnancies.

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The Coagulation Status Should Be Determined

Ekkehard Schleußner in his article explains the problem clearly. In spite of this fact, however, we wish to add several comments on the topic of cerebral intraventricular hemorrhage. Unfortunately, cerebral hemorrhage occurs in more than 70% of neonates weighing 500–750g and 15% in those weighing 1500–2000g. Some 10–15% of surviving, very small preterm babies will have lifelong disabilities (1). In order to investigate the incidence of cerebral hemorrhage, 11 887 neonates were sonographically examined on the 3rd to 10th day of life in the years 1985–94. 303 babies (2.5%) had intraventricular or periventricular bleeds (2).

The study found that the most important risk factor was prematurity, but the duration of gestation, birth weight, and body length correlated inversely. Furthermore, a correlation exists between pediatric infections passed by the mother and twin pregnancies (2). A possible coagulation disorder was not investigated. Schleußner mentions the problem of cerebral hemorrhage after administration of magnesium sulfate and glucocorticoids (reduction of cerebral intraventricular hemorrhage), magnesium sulfate combined with fenoterol (the highest rate of cerebral intraventricular hemorrhage altogether), and when using calcium antagonists (reduction of cerebral intraventricular hemorrhage). The causes of cerebral hemorrhage are the subject of controversy, whereas coagulation disorders hardly find any mention. In preterm babies, plasmatic coagulation becomes subject to a tendency to hemorrhage, and neonatal alloimmune thrombocytopenia (NAIT) may be present (3). Both should be considered on obstetric medicine, in order to prevent, or at least ameliorate, cerebral hemorrhage.

In preterm babies, the recommendation is to determine as rapidly as possible the thrombocyte count and coagulation status, in order to alleviate postnatal hemorrhage by early administration of thrombocytes or clotting factors. This should be followed by a diagnostic evaluation of the causes by measuring thrombocyte antibodies.

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In Reply:

My thanks go to Professor Seifert for his corrections to the very simplified Figure 4 in my article, whose intention was by no means to represent intracellular signaling mechanisms in an exact and exhaustive fashion. A detailed explanation of the pharmacological context was not the focus of the review, and neither would it have been possible within the prescribed scope of the article. Extending and simplifying a figure taken from Simhan et al. 2007 (1) led to the inconsistencies described by Seifert, and I welcome their rectification. With regard to using ibuprofen for the purpose of tocolysis, however, I feel the need to object, since no clinical data exist in support of such a measure and since I clearly pointed out the contraindications to using indomethacin.

Dr Kiworr rightly points out the importance of induced terminations as a risk factor, which was subsumed in the review article under "a history of obstetrical problems," but was not mentioned explicitly. A recent meta-analysis established a significantly increased risk of preterm birth (odds ratio 1.36; 95% confidence interval 1.24 to 1.50), which increases further after further terminations (2).

The other readers' letters deal with supplementation of trace elements and hormones that were not considered in the review article, which was based on current evidence. Conradt mentions the possible benefits of magnesium substitution, which is not the same as high-dose magnesium tocolysis. Although several working groups reported encouraging outcomes in the 1980s, a Cochrane meta-analysis of seven studies concluded that because of the limited study quality, a benefit cannot be confirmed with any certainty (3). More recent review articles have found a potential benefit in pregnant women with malnutrition or a poor diet—for example, women of a low socioeconomic status or US African-American women (4).

Torremante reported his own very interesting results from a non-randomized retrospective observational study (5). However, before general recommendations can be deduced from this, the data require confirmation in further studies.

Contrary to what Dr Daumann in his letter expresses, there is no financially strong industry behind preterm birth. One indication for this is the fact that most effective tocolytic drugs are used off-label. The study he cited did not report any differences between the study groups in terms of age at birth, birth weight, and referral rates to neonatal wards. A recent publication by the same authors did not find halved rates of preterm birth, but the authors themselves wrote: "Evidence of risk reduction in infection, preterm labor, and preterm birth was suggestive … ." A Cochrane meta-analysis from 2011, of vitamin D substitution during pregnancy, does not make any recommendations because of a scarcity of study data (6).

The letter from Professor Kiesewetter, PD Dr Radtke, und Dr Schmidt from the Haemostaseologicum center recommends rapid determination of the neonate's thrombocyte count and coagulation status, in order to prevent neonatal cerebral hemorrhage. A thrombocyte count is included among the standard first examination of preterm babies. A detailed diagnostic evaluation of the coagulation status is not done by default but on an indication-related basis, because it requires a larger blood sample and because neonatal alloimmune thrombocytopenia is an extremely rare event.

In sum, the correspondence illustrates that the prevention and therapy of preterm birth has been an unsolved problem in obstetric medicine for decades, and no easy solution exists.

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