MEDAL DE ONOARE

New Perspectives in the Pathways to Preterm Delivery

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The need for new directions in preterm delivery prevention research

Despite significant research efforts, the pathogenesis of preterm delivery (PTD) remains unknown and the human burden of prematurity is growing. Three million infants die every year in the world as the result of being born prematurely.[1] This presentation focuses on PTD and addresses the directions of research aimed at reducing its incidence. We also discuss the evidence base for currently used preventive interventions and in concluding, recommendations will be made.

A myriad of strategies to prevent PTD have been considered along the years. Bed rest, maintenance tocolysis, or antibiotic treatment have proved to be of no benefit.[2-4] Cervical cerclage and progesterone supplementation have recently reemerged, at least in the United States, as preventive therapies in vogue, although their absolute efficacy continues to be debated.[5,6] Based on recent data, the benefit derived from these two interventions is limited to a small proportion of preterm births.

Only with further knowledge of the biology of human parturition will progress be achieved in preventing prematurity. Although the mechanism of normal and abnormal parturition in humans remains an enigma, three types of factors are considered to contribute to spontaneous PTD: social stress, infection/inflammation, and genetics. Social stress has been principally linked to race by United States researchers and the mother's experience of racial discrimination may explain, according to such opinions, the double rate of PTD among black women compared to white women of otherwise similar demographic characteristics. The racial heterogeneity of the US population and the continuous existence of strained racial relationships are advanced as a possible explanation for the high rate of prematurity in the United States (12.4 %) exceeding that reported from other Western countries. The same reasoning however appears to be less successful when applied to the wide diversity in percentage of preterm births among Western European countries with generally homogeneous populations. For instance, the rate of PTD in Austria (11.4 %) is double that in Ireland and Finland (5.5 and 5.6 %, respectively).[7] The rate in Austria, country without much racial diversity, is actually closer to that in the United States than to the rate in Germany (8.9 %).

Infection and/or inflammation have loomed large as possible culprit in the presumed etiology of PTD, especially at earlier gestational ages. It is presumed that early in pregnancy, intrauterine inflammation and/or subclinical infection will develop, subsequently triggering the pathways to PTD. However, pregnant women at risk for PTD have received no benefit from treatment with antibiotics in clinical trials, whether used against bacterial vaginosis, trichomonas, periodontitis, or purely as a prophylactic intervention.[2-4] Furthermore, a recent report at the last Annual Meeting of the Society of Maternal-Fetal Medicine, Chicago, February 2010, noted no relationship between subsequent PTD and inflammation

biomarkers detected in the amniotic fluid in mid second trimester.[8] These findings are intriguing, given that biological factors assessed early in pregnancy, in asymptomatic women, are more likely to be associated with PTD in a predictive rather than a consequential way. At the same meeting, I presented a similar study. Similar in that amniotic fluid samples obtained at 2nd trimester genetic amniocentesis were tested and correlated with subsequent PTD.[9] However, in my study, I tested for thrombin-antithrombin (TAT) complexes. TAT complexes are markers of *in vivo* thrombin activation,[10] and thrombin is a multifunctional serine protease with a proposed central role in the regulation of inflammation, even in relation to PTD.[11] It is well known that inflammatory and coagulation pathways have significant overlap in the causation of disease, particularly in the cardiovascular system.

A prospective cohort of 550 women with singleton non-anomalous pregnancies undergoing second trimester genetic amniocentesis was followed by us to delivery and analyzed as a nested case-control study. Cases of PTD (n=52) were compared with 104 matched, term controls. Amniotic fluid collected at amniocentesis was tested for TAT complexes by enzyme-linked immunoassay. TAT concentrations were significantly higher in women who subsequently delivered preterm (median 115.9 mcg/l, IQR 121.5) than in those who did not (median 62.2 mcg/l, IQR 64.6; P< .001). This difference persisted when 31 spontaneous PTDs (median 100.6 mcg/l, IQR 126.8 vs 61.8 mcg/l, IQR 65.5 in controls; P=.04) and 21 indicated PTDs (median 141.0 mcg/l, IQR 153.9 vs 63.2 mcg/l, IQR 63.6 in controls; P=.004) were analyzed separately. The indicated PTD group included cases with preeclampsia, fetal demise, fetal growth restriction, and placental abruption. Overall, the OR for PTD in the highest TAT quartile relative to the lowest quartile was 4.98 (95% CI, 1.17-22.01; P = .007).[9]

Our data showed that amniotic fluid TAT levels in the second trimester are significantly higher in women destined to deliver preterm compared with those who deliver at term. In our cohort we found a distinct difference in the pattern of intra-amniotic thrombin generation between women destined to deliver at term and those who deliver preterm, regardless of the type of PTD (spontaneous or indicated). Although pathogenic pathways leading to spontaneous or indicated PTD may be different, we hypothesize that at least initially, early in pregnancy, they may share common pathways, including thrombin generation. This is in keeping with the findings of other researchers who have reported a crossover recurrence between spontaneous and indicated PTD, suggesting that there is considerable etiologic overlap between the two conditions.[12] Furthermore, it has been postulated that PTD, preeclampsia, and intrauterine growth restriction may all have in common abnormal placental development with placental insufficiency.[13] These conditions may be different clinical manifestations of a common early etiological pathway.

Spontaneous PTD is the final pathway by which a number of different causes and contributors may act. PTD may even be a complex genetic disorder characterized by genetic susceptibility and interactions with environmental factors.[14] Examples of complex genetic diseases include cardiovascular disease, type 2 diabetes, obesity, and autism. These diseases tend to run in families but not clearly along monogenic or mendelian patterns of inheritance. Rather, familial clusters may be seen. Similarly, familial patterns of PTD and an individual recurrence pattern in parturition timing suggest the existence of a genetic contribution in the pathogenesis of spontaneous PTD.[15,16]

Genomewide association studies have lead to important discoveries with practical applicability in heart disease, diabetes, and stroke.[17] To date, the associations between polymorphisms in candidate genes and the risk of PTD have been modest at best, but such research directions may prove more fruitful in the future. If research is to have an impact on PTD, progressive thinking is necessary, with investigators from diverse disciplines working together and sharing intellectual perspectives with a

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mutual appreciation for the complexity of PTD. In order to advance the study of human parturition to exciting new frontiers, a more in depth exploration of molecular or genetic mechanisms is necessary rather than revisiting obsolete, simplistic interventions such as cerclage placement or even pessary use as recently proposed.[18]

Current risk prediction for PTD is based on obstetrical history, ultrasound assessment of cervical length and sometimes fetal fibronectin determination in cervico-vaginal secretions. However, it is unclear what to do with women found to be at risk, and successful interventions directed at risk modification and promotion of a successful pregnancy remain to be discovered. Unfortunately, over the last decades, very little progress has actually been made and we continue to borrow on past ideas, as in the case of progesterone and cerclage.

Recent perspectives on progesterone supplementation

Progesterone has been used in obstetrics for more than 40 years, but 2 studies in 2003 rekindled the interest in it. Da Fonseca et al from Brazil randomized 157 women with various risk factors for PTD to either placebo or vaginal progesterone suppositories, observing a significant reduction in PTD with progesterone.[19] However, data were not analyzed according to intention to treat and arbitrary, a posteriori exclusions occurred, such as in the case of women with premature preterm rupture of membranes, a common pathway to PTD. If those women were included, the outcome difference wouldn't have been significant anymore. The study of Meis et al, published in the same year and conducted in the United States, included 463 women with history of PTD, randomized to placebo or weekly injections of 17 alpha-hydroxyprogesterone caproate (17-OHPC).[20] A significant reduction in PTD, necrotizing enterocolitis, and intraventricular hemorrhage was noted, but neonatal mortality remained unchanged.

After four more years, in 2007, the largest to date randomized study of progesterone supplementation for prevention of PTD was published by O'Brien et al.[21] In this multinational study, 659 women with history of PTD were randomized to placebo or vaginal progesterone gel, without any reduction in PTD rate as result of treatment. However, in a very limited subanalysis of 46 women with short cervix, there was suggestion of progesterone effect in reduction of PTD before 32 w.[22] The authors speculated that the indiscriminate practice of progesterone administration to all women with history of PTD was unadvisable, proposing instead an objective assessment of cervical length first, to better target the intervention to those women more likely to benefit. The same idea was supported by a study conducted by the Fetal Medicine Foundation in England in which 250 asymptomatic women with a short cervix (< 15 mm) were randomized to either placebo or vaginal progesterone capsules with a 44% reduction in PTD before 34 w with progesterone, however without any improvement in perinatal morbidity and mortality.[23] Interestingly, the beneficial effect of progesterone was present even in women without history of PTD.

These randomized trials have used different progestin formulations and routes of administration, making the interpretation of the results more difficult. Indeed, a recent study in rats suggested that the action of progestins in delaying delivery depends on formulation and route of administration.[24] There is still considerable uncertainty regarding the progesterone effect on PTD and the uncertainty is further compounded by the unclear mechanism of action. Additionally, without demonstrated reduction in neonatal mortality, any benefit remains questionable. Consequently, the rates of progesterone usage for this indication are strikingly different all over the world: 74% of practitioners in the US prescribe progesterone,[25] compared to only 5% in Australia and New Zealand.[26] Fortunately, as of 2008 there

were 20 different registered randomized controlled trials of progesterone all over the world, and we can expect more conclusive statements to come.

Recent perspectives on cervical cerclage

Cervical cerclage was devised more than 50 years ago and the original indication included both historical and contemporaneus factors.[27,28] The appropriate candidate had to have a history of 2nd trimester losses presenting as painless dilatation in the absence of infection, ruptured membranes or fetal demise, as well as asymptomatic cervical changes in current pregnancy. By now however, cerclages are being considered for all kind of unproved indications, even without a history of prior losses, or without cervical changes in the index pregnancy, to the effect that presently, in the United States, 1% of all pregnancies will undergo cerclage placement.[29]

According to an older British study from 1993, an elective cerclage (ie cerclage placed in the absence of contemporaneus cervical changes) is justified only in women with a history of 3 or more second trimester losses or PTD's.[30] Although this conclusion has frequently been presented in the literature as the result of a large randomized trial, the observation was in fact generated by a secondary analysis. Furthermore, included in the secondary analysis were women who only had 3rd trimester PTD's even at 36 weeks, raising doubts about the categorization of such cases as cervical insufficiency. However, what is cervical insufficiency? The entire concept gained a new perspective when recently, cervical changes early in pregnancy were considered part of a continuum that can precede either preterm or term spontaneous labor. Cervical shortening early in pregnancy was no longer linked to an innate or acquired cervical weakness, but viewed as an early asymptomatic phase in the path to PTD in case of an acceleration of the normal process. As a result of this new paradigm, cerclage started to be performed based only on current cervical changes in 2nd trimester, even without a history of prior losses. The authors of a recent study in a mouse model noted however significant differences in the molecular mechanism of cervical remodeling in preterm birth versus normal term ripening and proposed that PTD should not be regarded as the result of an acceleration of the normal pathway.[31]

Taken together, current data do not support cerclage placement based only on the finding of a short cervix. A meta-analysis of 4 randomized cerclage trials in women with short cervix, found cerclage to be beneficial only in those women with a history of PTD.[32] On the other hand, history of PTD alone is not sufficient. For the cerclage to be beneficial, the cervix in the current pregnancy has to be significantly shortened on ultrasound, at least according to the most recent randomized clinical trial of cerclage.[33] In this study that randomized 300 women with short cervix on ultrasound and history of PTD, benefit with cerclage was noticeable only in those women with sonographic cervical length of less than 15 mm.

Evidence-based practical recommendations

As seen so far, the role of progesterone is far from conclusive, and the efficacy of cerclage is at best limited in the prevention of PTD. However, these are the only interventions currently available to those women and clinicians who may prefer intervention over no intervention when faced with the major risk of PTD. A few practical guiding points can be made based on current accumulated evidence:

Both progesterone supplementation and cerclage placement are ineffective in multiple pregnancies. This fact has been confirmed in many randomized studies, irrespective of the formulation used or population included.[32,34-37] Many reports over the years have indicated a lack of benefit with cerclage in multiple pregnancies and actually suggested the possibility of harm. The 2005 metaanalysis by

The Dakshineswar Kali Temple, is a Hindu temple located in Dakshineswar near Kolkata. Situated on the eastern bank of the Hooghly River, the presiding deity of the temple is Bhavatarini, an aspect of Kali, literally meaning, 'She who takes Her devotees across the ocean of existence'.The temple was built by Rani Rashmoni, a philanthropist and a devotee of Kali in 1855. The temple is famous for its association with Sri. Ramakrishna

Berghella et al indicated that cerclage placement in twins may double the rate of PTD and may increase neonatal mortality.[32]

In women with suspected cervical insufficiency, the risk may be more precisely established with sonographic cervical surveillance starting at 16 weeks. Waiting for cervical changes to occur, even in women with highly suggestive history for cervical insufficiency, the window of therapeutic opportunity is not going to be missed, based on data from several randomized trials.[38,39] The advantage with serial ultrasounds instead of electively placing a cerclage is that women who don't need intervention may be identified avoiding unnecessary surgical risks. When the cervix is less than 20 mm and fetal fibronectin is negative (only after 20 weeks), cerclage may be considered. We are not recommending a prescriptive cutoff of 15 mm as it may be inferred from the findings of the Owen randomized trial,[33], because women with too short a cervix may have a high rate of subclinical intraamniotic inflammation. They may have already entered the irreversible phase of parturition with activation of the inflammatory cascade, and cerclage would not be effective or even advisable.[40] A recent study demonstrated that in midtrimester, a fourth of cases with cervical length less than 15 mm have intraamniotic inflammation (defined by metalloproteinase concentration, a better predictor of inflammation/infection than IL-6) and even culture-proven infection in 4% of cases.[41] Choosing a higher threshold, such as 20 to 25 mm, may increase the false-positive rate of ultrasound surveillance, exposing women to a heightened risk of unnecessary intervention.[39] Furthermore, the risk of spontaneous early PTD increases only from 1.1% at a cervical length of 25 mm to 4.0% with a cervical length of 15 mm (compared with 78% risk when the cervix is 5 mm) suggesting that the risk acuity is not so marked with progressive cervical shortening between 25 and 20 mm.[42]

When the short cervix is an incidental finding (no history of PTD), or the cervix is only minimally shortened and/or fetal fibronectin is positive, progesterone supplementation may be considered. Consistent with the findings of a randomized comparison of cerclage vs progesterone in 79 women with short cervix on ultrasound, cerclage is superior to progesterone only in women with cervical length less than 15 mm.[43]

There is emerging evidence that only women with short cervix in the absence of infection/inflammation may benefit from cerclage.[44,45] Fetal fibronectin in the cervico-vaginal secretions after 20 weeks gestation is a genital marker for inflammation and identifies a subgroup of women with short cervix who would not benefit from cerclage placement. Similar caution should be exercised when cervical sludge, an inflammatory exudate is identified by ultrasound in proximity to the internal os.

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Konark: The Sun Temple, built in the thirteenth century, was conceived as a gigantic chariot of the Sun God, Surya, with twelve pairs of exquisitely ornamented wheels pulled by seven horses. Majestic in conception, this temple is indeed one of the most sublime monuments of India, famous as much for its imposing dimensions and faultless proportions as for the harmonious integration of architectural grandeur with plastic allegiance. Its fine tracories and scrollwork, as well as the beautiful and natural cut of animal and human figures, give it a superiority over other temples. It is in Orissa.