

## Editorial

# Risk factors for preterm birth and new approaches to its early diagnosis

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This issue of the *Journal of Perinatal Medicine* has a number of articles providing important insights into the causes, diagnosis and management of preterm birth (PTB). Szymusik and colleagues report on their case control study comparing PTB rates amongst patients complaining of first trimester vaginal bleeding (FTB) vs. controls without first or second trimester bleeding [1]. As others have found, FTB was associated with higher rates of subsequent PTB with an odds ratio (OR) of 2.11 (95% confidence interval [CI]: 1.43–3.10). However, the authors also evaluated this association in the various categories of PTB severity. Thus, they noted that the link between FTB and PTB was strongest amongst those with moderate (32–33 weeks), very (28–31 weeks) and extremely (<28 weeks) preterm births compared with those having late (34–37 weeks) PTBs. These findings are consistent with those of Lykke et al., who interrogated a large Danish pregnancy registry and observed that FTB was most strongly associated with PTB at 28–31 weeks' gestation (OR 2.98; 95% CI: 2.50–3.54) [2]. While the study by Szymusik et al. was underpowered to ascertain whether FTB was more strongly associated with spontaneous PTB vs. indicated PTB, the study by Lykke and colleagues noted that the occurrence of FTB also increased the risk of subsequent preterm premature rupture of the membranes (PPROM) (OR 1.18; 95% CI: 1.01–1.37), placental abruption (OR 1.48; 95% CI: 1.30–1.68), and severe preeclampsia (OR 1.25; 95% CI: 1.09–1.43), suggesting that FTB is a marker for a primary defect in placentation linked to both spontaneous and indicated prematurity [2]. In support of this contention, Salafia and colleagues demonstrated that decidual hemosiderin was far more commonly present amongst patients with PTB at <32 weeks (196/462; 43%) compared to term birth (1/108; 0.8%) ( $P < 0.00001$ ) and that amongst the former patients, decidual hemosiderin was found in 60% of patients with preterm preeclampsia (45/76), 38% with PPRM (72/192) and 36% with preterm labor and intact membranes (58/161) ( $P < 0.003$ ) [3]. Since clinically evident FTB was commonly associated

with decidual hemosiderin, decidual hemorrhage (i.e. abruption) is likely the most common cause of FTB.

While the precise etiology of the aberrant placentation associated with these abnormal pregnancy outcomes remains a mystery, decidual hemorrhage (abruption) can trigger substantial local thrombin generation due to the presence of abundant decidual cell tissue factor, the primary initiator of clotting [4]. In the first trimester, decidual thrombin production has been associated with increased expression of soluble fms-like tyrosine kinase-1 (sFlt-1) and monocyte-recruiting chemokines, factors known to contribute to the shallow extravillous trophoblast invasion and impaired spiral artery remodeling linked to preeclampsia, abruption, stillbirth, fetal growth restriction and many cases of spontaneous PTB [4]. Later in pregnancy decidual cell-derived thrombin can bind to its receptor to inhibit decidual cell progesterone receptor expression and increased production of matrix metalloproteinases and cytokines strongly linked to PTB [5–7]. Thus, while FTB may be a marker for abnormal placentation and a risk factor for adverse pregnancy outcomes, it may also play a direct role in the genesis of such adverse outcomes. Interestingly, obesity has also been linked to these adverse pregnancy outcomes and Szymusik and colleagues found that the combination of obesity and FTB was associated with an extraordinary 7-fold increased risk of PTB (OR 7.47; 95% CI: 1.18–59.8).

Smoking has long been associated with PTB and other adverse pregnancy outcomes, but there is little information available about discrete risks conferred by the level of maternal smoking. In this issue of the *Journal*, Mei-Dan and associates report the results of a population-based cohort study of over 20,000 women delivering between 2001 and 2007 in Montreal, Canada, in which they compare pregnancy outcomes in active smokers vs. non-smokers and then assess the dose-response relationship between self-reported smoking levels and adverse pregnancy outcomes [8]. As expected, smokers had a substantially greater prevalence of PTB than non-smokers (22.2% vs. 12.4%, OR 2.0; 95% CI: 1.8–2.3). Moreover, the risk of PTB increased with the number of cigarettes smoked per day (19.8% for those smoking <5/day, 22.3% for those smoking 5–10/day, and 24.6% for those smoking >10/day). Not surprisingly, birth

weight also decreased with increasing levels of smoking, and stillbirth was also more common among smokers (1.4% vs. 0.3%, OR 4.2; 95% CI: 2.6–6.8). The authors noted that despite having similar BMIs and the fact that smokers were younger than non-smokers ( $29.3 \pm 6.3$  years vs.  $31.5 \pm 5.1$  years;  $P < 0.05$ ), smokers had higher rates of pre-gestational hypertension (2.1% vs. 1.3%, OR 1.6; 95% CI: 1.1–2.4) and hypertensive disorders of pregnancy (6.6% vs. 4.2%, OR 1.6; 95% CI: 1.3–2.0). This latter finding is in contrast to older studies reporting an inverse relationship between smoking and preeclampsia [9] but, as was the case with FTB, suggests a more global effect of smoking on placentation.

This issue of the Journal also contains two important studies related to the detection of patients at risk for PTB. Hadži-Lega and colleagues examined the relationship between sonographic cervical length (CL) measurements, determination of cervico-vaginal fluid fetal fibronectin (fFN) and phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1), as well as measurements of cervico-vaginal and serum inflammatory cytokine levels (i.e. interleukin-2 receptor [IL-2R], IL-6, and tumor necrosis factor-alpha [TNF $\alpha$ ]) in the prediction of PTB [10]. They assessed the relative accuracy of these endpoints for predicting PTB within 14 days in 58 patients with symptoms of preterm labor. Of 36 patients delivering within 14 days, 27 (75%) had a positive fFN (sensitivity) while 15 of 22 (68%) patients remaining undelivered had a negative fFN (specificity). The positive and negative likelihood ratios for fFN were 2.46 and 0.37, respectively, with an area under the ROC curve (AUC) of 0.716 and OR for predicting PTB of 6.43; 95%CI: 1.99–20.76. Measurement of fFN proved the most effective single predictor of PTB. The optimal cutoff for CL determination of 22 mm yielded a sensitivity of only 30.6%, specificity of 36.4%, positive and negative likelihood ratios of 2.54 and 0.42, respectively (AUC of 0.716; OR 3.5). The optimal cutoff for cervico-vaginal IL-6 of 1305 pg/mL produced a sensitivity of 69.4%, specificity of 68.2%, positive and negative likelihood ratios of 2.18 and 0.45, respectively (AUC of 0.759; OR 3.87). A positive cervico-vaginal phIGFBP-1 produced a sensitivity of 33.3%, specificity of 63.6%, positive and negative likelihood ratios of 1.83 and 0.52, respectively (AUC of 0.652; OR 3.5). The optimal cutoff of serum IL-2R was 385 pg/mL which produced a sensitivity of 69.4%, specificity of 68.2%, positive and negative likelihood ratios of 2.18 and 0.45, respectively (AUC of 0.688; OR 4.87). Cervico-vaginal TNF $\alpha$  and serum levels of the other cytokines were not discriminatory. The closest correlation with CL was cervico-vaginal IL-6 ( $R = -0.38$ ;  $P < 0.05$ ). Thus, it is interesting, and rather disconcerting, that nearly 25 years after its discovery, fFN remains

the optimal biochemical marker of PTB [11]. Moreover, the combination of CL and fFN enhance the utility of either test used alone [12] and recent studies suggest that the combination of CL and quantitative fFN determinations adds additional predictive accuracy [13].

In the same issue, von Schöning and colleagues conducted a small prospective cohort study among 64 patients with preterm labor at 23–34 weeks to determine whether cervical sonoelastography improved prediction of PTB compared with CL measurement and fFN [14]. The former is a measure of cervical elasticity and consists of the ratio of nondeformable cervical tissue to the total region of interest. They found that CL was nondiscriminatory, and while only 25 patients delivered prematurely, a cervical sonoelastography cut-off of 9.1% predicted PTB with a sensitivity of 72.7%, specificity of 73%, respectively. By contrast, fFN had a sensitivity of 36% and a specificity of 95%. While these results are very preliminary, cervical sonoelastography holds promise as a novel predictor of PTB. It will be interesting to see whether, like CL determinations, cervical sonoelastography can be combined with quantitative fFN to further improve diagnostic accuracy.

The current issue of the Journal also reports on an animal model of the neuroprotective effects of magnesium sulfate (MgSO<sub>4</sub>) in preterm infants suggesting that this agent's benefits appear maximal in inflammation-induced PTB [15]. Another study reports that maternal serum concentrations of magnesium are lower following MgSO<sub>4</sub> infusion in mothers with twins compared with singleton gestations which may help account for the lesser neuroprotective effects of this agent in multiple gestations [16]. Finally, Justus and colleagues examine the full gamut of alternatives to corticosteroids for enhancing lung maturity and present these agents' risk benefit data in either animal studies or human clinical trials [17]. Taken together, the current issue of the *Journal of Perinatal Medicine* contains rich offerings for clinicians and clinical researchers interested in reducing the perinatal morbidity and mortality attendant preterm birth.

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