Endometriosis and obstetric syndromes: early diagnosis must become a priority

If and how endometriosis impact on obstetric outcome are two questions that have generated considerable debate in recent years—with limited cohort and large population studies often arriving at different answers. A new population-based study from Glavind and colleagues (1) seems to settle the "if" question. Analysis of 82,793 singleton pregnancies in 55,829 women in the Aarhus Birth Cohort in Denmark provides further evidence that a diagnosis of endometriosis is a significant risk factor of preterm birth and preeclampsia. Stratification of the data indicated that assisted reproductive technology (ART) does not compound the risk of adverse pregnancy outcome in patients with endometriosis. A common drawback of population-based studies, however, is the lack of granularity of potential confounding factors, such as the type and severity of endometriosis, coexistence of adenomyosis, and impact of treatment. A strength of the new study is that data retrieval were based on linkage of various databases, including the Danish National Pathology Registry and Data Banks. For example, the association between endometriosis and obstetric syndromes was stronger when the analysis was confined to pregnancies in subjects with histologically verified endometriosis, which instills further confidence in the findings. Although not surprising, the recorded incidence of adenomyosis in women with endometriosis was low (14.7%), reflecting the continued neglect of this disorder despite increasingly accurate diagnostic imaging tools, such as magnetic resonance imaging (MRI) and three-dimensional ultrasound. Adenomyosis is caused by smooth muscle hyperplasia and disorganization in the inner myometrium, also termed the uterine junctional zone. Important, this zone forms the placental bed in pregnancy and failure of trophoblast-mediated remodeling of the junctional zone spiral arteries underpins the spectrum of obstetric syndromes, ranging from preterm labor to small for gestational age and preeclampsia (2).

The overall incidence of endometriosis in this study, diagnosed either *before* or *after* pregnancy, was 2.2%, again reflecting that the disease likely remains undiagnosed in most women. Twenty years ago it was shown that the delay in diagnosis of endometriosis in the United States and United Kingdom amounted to 11 and 7 years, respectively. More recent studies from Norway, the Netherlands, Germany, and Austria confirmed that, despite the availability of modern diagnostic technologies, no real progress has been made in accelerating the diagnosis of early-stage endometriosis. Important, when Glavind et al. (1) restricted their analysis to women diagnosed with endometriosis *before* pregnancy, the risk estimates were higher. This observation raises the possibility that early-stage endometriosis is a stronger risk factor for obstetric syndromes than late-stage disease. Recent studies have shown that the presentation of endometriosis in very young women differs from that in adults (3). Early-onset endometriosis is characterized by the presence of profoundly angiogenic peritoneal lesions and occasionally endometrioma formation. Deep endometriosis appears very rarely and sclerosis of the ovarian cortex within endometriomas is all but absent (3). It is well established that obstetric syndromes, including preeclampsia, are more prevalent and more severe in adolescent girls and young women. Yet the diagnosis of early-onset endometriosis appears particularly cumbersome. Of 1,065 women aged $\leq$19 years included in the study, only 10 had a diagnosis of endometriosis (0.9%). The frequency of diagnosis, which does not necessarily reflect the incidence of disease, increased with age, reaching 2.6% in those aged $\geq$35 years. And herein lies the real obstacle. Without an accurate, noninvasive tool to diagnose endometriosis, especially early-onset disease, the true impact on pregnancy outcome cannot be accurately quantified.

Neonatal uterine bleeding (NUB) was recently proposed to be a potential low-cost clinical biomarker for endometriosis (3). Neonatal uterine bleeding, which is triggered by the rapid decrease in circulating P levels in the first few days after birth, affects only 4%–5% of newborn girls. Histologic studies have provided evidence that NUB is caused by premature P sensitivity of the endometrial stroma, leading to decidualization of the endometrium late in pregnancy, and menstruation-like shedding soon after birth. Instead of a clinically irrelevant phenomenon, NUB is thought to lead to seeding and implantation of naïve endometrial stem cells into the pelvic cavity (4). These progenitor cells may be dormant until the onset of menarche. Increasing estrogen (E) levels then stimulates growth and angiogenesis of these early lesions. The presence of inflammatory and highly vascularized endometrial lesions during adolescence may adversely impact on the uterus, including its stem cell populations. Clearly, the hypothesis that NUB is a predictive marker of early-onset endometriosis needs validating in prospective studies. However, at the very least, the presence or absence NUB stratifies newborns on the basis of the intrinsic uterine responses to hormonal stimulation (and withdrawal), which arguably may determine the tissue responses in a future pregnancy (5). As cost implications are minimal, failure to routinely record this putative biomarker seems increasingly unacceptable.

The findings of Glavind and colleagues (1) reinforce the need for better and earlier diagnosis of endometriosis. A concerted effort is needed to steer research away from the current fixation with, and naval gazing of, ectopic lesions, which likely represent the terminal phenotype of a disease that started much earlier. A focus on the origins of endometriosis, whether at birth or at menarche, holds the potential to prevent disease progression and, important, mitigate the adverse effects of the disease on the health of mothers and their babies.

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