The impact of uterine immaturity on obstetrical syndromes during adolescence

Ivo Brosens, MD, PhD; Joanne Muter, PhD; Caroline E. Gargett, PhD; Patrick Puttemans, MD; Giuseppe Benagiano, MD, PhD; Jan J. Brosens, MD, PhD

Pregnant nulliparous adolescents are at increased risk, inversely proportional to their age, of major obstetric syndromes, including preeclampsia, fetal growth restriction, and preterm birth. Emerging evidence indicates that biological immaturity of the uterus accounts for the increased incidence of obstetrical disorders in very young mothers, possibly compounded by sociodemographic factors associated with teenage pregnancy. The endometrium in most newborns is intrinsically resistant to progesterone signaling, and the rate of transition to a fully responsive tissue likely determines pregnancy outcome during adolescence. In addition to ontogenetic progesterone resistance, other factors appear important for the transition of the immature uterus to a functional organ, including estrogen-dependent growth and tissue-specific conditioning of uterine natural killer cells, which plays a critical role in vascular adaptation during pregnancy. The perivascular space around the spiral arteries is rich in endometrial mesenchymal stem-like cells, and dynamic changes in this niche are essential to accommodate endovascular trophoblast invasion and deep placentation. Here we evaluate the intrinsic (uterine-specific) mechanisms that predispose adolescent mothers to the great obstetrical syndromes and discuss the convergence of extrinsic risk factors that may be amenable to intervention.

Key words: adolescent pregnancy, obesity, placentation, polycystic ovary syndrome, preeclampsia, preterm birth, progesterone resistance, stem cells, uterine maturation, uterine natural killer cells

It is often assumed that the increased risks of obstetrical disorders associated with teenage pregnancies are due to social factors and inadequate antenatal care, rather than maternal age per se.[1] In 1990, the National Center for Health Statistics (Atlanta, GA) concluded from a decade-long study (1976–1986) that the risk of both preeclampsia and eclampsia sharply increases in pregnancies in women under the age of 20 years and called for improved antenatal care for teenagers.[2]

A similar call for better antenatal and social care for adolescent mothers was made in Europe.[3] Others, however, pointed to biological immaturity in very young mothers as the cause of adverse pregnancy outcome. Frisancho et al[4] studied 412 Peruvian mothers aged between 13 and 15 years. The subjects were classified as either still growing or growth completed, based on anthropometric measurements of their mothers. They found a significant reduction in birthweight among still-growing adolescents, which they attributed to decreased net availability of nutrients and/or placental insufficiency.

Several large population studies confirmed that pregnancies in young mothers, aged 18 years or younger, carry an increased risk of very low birthweight and preterm birth. Notably, a stratified analysis of 134,088 white girls and women, aged between 13 and 24 years, who delivered singleton, first-born children between 1970 and 1990 in the United States demonstrated that the increased risk of adverse pregnancy outcomes in young women is independent of confounding sociodemographic factors, such as marital status, level of education, and adequacy of antenatal care.[5] Thus, while the deleterious sociodemographic environment associated with teenage pregnancy may compound the risk of adverse outcomes, the primary pathological driver appears to lie in uterine immaturity.

Based on the emerging insights into the life cycle of the human uterus,[6,7] we explore here the potential intrinsic uterine mechanisms that could account for the higher incidence of major obstetrical syndromes in nulliparous teenage pregnancies.

Search strategy and analysis

The present Clinical Opinion is based on a search of the literature via Scopus and PubMed. It was undertaken using the key words of preeclampsia, preterm birth, small for gestational age, low birthweight or fetal growth restriction, and adolescence. In addition, references were examined in published papers on related topics. The search yielded 155 relevant papers.

Epidemiology of the great obstetrical syndromes during adolescence

The expression, great obstetrical syndromes, was coined to describe the

From the Faculty of Medicine, Catholic University of Leuven, Leuven, Belgium (Dr I. Brosens); the Division of Biomedical Sciences, Warwick Medical School, Coventry, United Kingdom (Drs Muter and J. Brosens); the Ritchie Centre, Hudson Institute of Medical Research, Melbourne, and Department of Obstetrics and Gynaecology, Monash University, Victoria, Australia (Dr Gargett); Life Institute for Fertility and Embryology, Leuven, Belgium (Dr Puttemans); Department of Gynecology, Obstetrics, and Urology, Sapienza, University of Rome, Rome, Italy (Dr Benagiano).

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Corresponding author: Ivo Brosens MD, PhD. Ivo.brosens@med.kuleuven.be

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clinical heterogeneity associated with impaired vascular adaptation of the maternal spiral arteries during the process of endovascular trophoblast invasion, as reviewed in detail elsewhere.[8] Great obstetrical syndromes encompass a spectrum of complications of pregnancy, including preeclampsia, small for gestational age, preterm labor, preterm premature rupture of membranes, late spontaneous abortion, and placental abruption. All these disorders are characterized by restricted vascular remodeling in the placental bed and the presence of obstructive lesions in the myometrial segment of the uteroplacental spiral arteries.[8]

Collectively the epidemiological evidence of increased risk of great obstetrical syndromes in adolescent pregnancies is overwhelming. For example, based on analysis of the Swedish Medical Birth Register, Olausson et al[9] demonstrated an inverse correlation between the incidence of very preterm birth (≤32 weeks) and increasing maternal age, declining from 5.9% in very young mothers aged 13−15 years to 2.5%, 1.7%, and 1.1% in women aged 16−17 years, 18−19 years, and 20−24 years, respectively.

Compared with mothers aged 20−24 years, the odds ratios of late fetal death and infant mortality among mothers aged 13−15 years were 2.7 and 2.6, respectively. Again, the adjusted risks declined with increasing age, indicating that neonatal mortality in very young women is largely explained by increased rates of very preterm birth.[9]

Another retrospective cohort study compared pregnancy outcomes in 2930 young (11−15 years) and 11,788 older adolescents (ages 15−19 years) with a control group consisting of 11,830 women aged 20 years or older.[10] Overall, adolescents were significantly more likely to have eclampsia (risk ratio [RR], 2.23; 95% confidence interval [CI], 1.37−3.66) and preterm delivery (RR, 1.12; 95% CI, 1.04−1.21). Compared with control subjects, young mothers in the 11−15 year age group were also significantly more likely to have preeclampsia (RR, 1.33; 95% CI, 1.15−1.54), eclampsia (RR, 3.24; 95% CI, 1.70−6.14), preterm delivery (RR, 1.47; 95% CI, 1.31−1.64), low birthweight (RR, 1.47; 95% CI, 1.31−71.64), and very low birthweight infants (RR, 1.25; 95% CI, 1.01-71.56).

A large registry-based study that linked birth and death certificates with maternal and neonatal hospital discharge records in California over a 5 year period (1992−1997) confirmed that teenage pregnancy is associated with greater neonatal and infant mortality and major neonatal morbidities when compared with pregnancies in the older control women.[11]

These observations were further substantiated in a subsequent nationwide study in the United States, which analyzed linked birth/infant death data sets comprising information on 3,886,364 nulliparous women aged 10−24 years who had singleton live births between 1995 and 2000.[12] The rates of preterm delivery, low and very low birthweight, and neonatal mortality were higher in teenage pregnancies and consistently increased with decreasing maternal age.

Restricting the analysis to white, married, nonsmoking mothers with age-appropriate education and adequate antenatal care did not change the findings, indicating that the risk of adverse outcome is independent of known sociodemographic confounders of teenage pregnancy. More recent studies are summarized in Table 1.

Uterine maturation

Classic anatomical studies have shown that the uterus in the neonate is in many ways an underdeveloped organ that requires progressive maturation before it can accommodate the intense tissue remodeling associated with deep placentation. This is true for the endometrium as well as the whole organ.

Uterine growth

Our knowledge of the steps involved in the transformation of the uterus between birth and menarche, and from menarche into adulthood, is still incomplete. Late in pregnancy there is tremendous growth of both the fetal cervix and vagina.[13] At birth, the length of the cervix is approximately 4 cm, which is 2.0−2.5-times longer than the length of the uterine corpus. However, subsequent involution of the neonatal cervix is more pronounced than in the corpus.

Ultrasound and magnetic resonance imaging studies in healthy girls demonstrated that uterine volume and endometrial thickness increase as puberty progresses.[14,15] In fact, uterine growth in late prepubertal girls (Tanner stage B1) precedes the development of breast tissue and correlates with the number of large ovarian follicles and circulating estradiol levels.[14] There is evidence that the corpus grows relatively more than the cervix and that uterine growth continues throughout adolescence and into early adulthood.[15]

Importantly, marked interindividual variation has been reported in uterine volume and endometrial thickness in postmenarchal girls at various stages of pubertal development. Several lines of evidence indicate that uterine responses to steroid hormones and ovulatory maturation of the hypothalamic-pituitary-ovarian (H-P-O) axis are uncoupled around the menarche (Figure). For example, luteinizing hormone (LH) surges and ovulatory rise in progesterone levels have been documented in some girls before the menarche.[16,17] On the other hand, normal LH surges and estrogen elevation without a significant rise in progesterone levels have also been reported. Furthermore, the duration of the luteal phase, as assessed by urinary concentrations of progesterone metabolites, increases progressively following menarche from 2 to 4 days in length to the 11 to 12 days in adult control subjects.[17]

Taken together, the interindividual variability in uterine growth and maturation of the H-P-O axis may render adolescence a vulnerable period during which pregnancy can occur in an as-yet physically immature uterus. This may lead to uterine overdistention in pregnancy, which is strongly associated with a stress response in both the myometrium and amnion, release of inflammatory mediators, and preterm labor.[18]

Ontogenetic progesterone resistance

Immaturity of the uterus refers not only to suboptimal physical growth but also