The impact of uterine immaturity on obstetrical syndromes during adolescence

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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 placentaion. 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. 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.

A similar call for better antenatal and social care for adolescent mothers was made in Europe. Others, however, pointed to biological immaturity in very young mothers as the cause of adverse pregnancy outcome. Frisancho et al studied 412 Peruvian mothers aged between 13 and 15 years. The subjects were studied 412 Peruvian mothers 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. 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, 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...
clinical heterogeneity associated with impaired vascular adaptation of the maternal spiral arteries during the process of endovascular trophoblast invasion, as reviewed in detail elsewhere. 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.

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 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.

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. 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.

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. 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. 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. 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. There is evidence that the corpus grows relatively more than the cervix and that uterine growth continues throughout adolescence and into early adulthood.

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. 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.

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.

Ontogenetic progesterone resistance

Immaturity of the uterus refers not only to suboptimal physical growth but also
to the responsiveness of the organ to steroid hormone signaling. Progesterone resistance is a term widely used to denote blunted progesterone responses in various target tissues, including the uterus, Fallopian tube, and endometriotic implants.19-22

The term, ontogenetic progesterone resistance, refers to the observation that the endometrial stromal compartment is not intrinsically progesterone responsive at birth (Table 2).6,7 During pregnancy, both male and female fetuses are exposed to progressively increasing plasma concentrations of unbound estrogens and progesterone.23,24 Furthermore, total and unbound progesterone levels in the umbilical vein at term are severalfold higher when compared with the maternal circulation.24,25

Following birth, circulating progesterone levels in the neonate drop rapidly and urinary excretion of progesterone metabolites becomes undetectable after the fifth day of life.26 If the endometrium at birth was intrinsically responsive, high circulating progesterone levels during the later stages of pregnancy followed by rapid withdrawal following birth should result in decidualization of the endometrium and menstrual shedding, respectively. However, overt neonatal uterine bleeding is a relatively rare biological phenomenon, affecting approximately 4–5% of newborns.6,7,27 Furthermore, an autopsy study in 169 neonates demonstrated inactive or weakly proliferative endometrium in 68% of term babies, evidence of secretory changes in the glandular compartment in 27%, and decidual transformation and/or menstrual changes in the remaining 5%.28

Intriguingly, the incidence of neonatal uterine bleeding, which is also referred to as pseudomenstruation of the newborn, is lower in preterm babies but higher in postterm babies and following preeclamptic pregnancies.7,29

Ovulatory levels of progesterone have been detected in the saliva or urine of premenarcheal girls without a subsequent withdrawal bleed.16,17 Thus, functional transition of the endometrium to a fully progesterone responsive tissue may already be completed at birth in newborns with neonatal uterine bleeding, but in the majority of girls, this is likely achieved only during adolescence.

Analogous to the perimenopause, the term perimenarche describes the lag period between the menarche and the onset of regular ovulatory menstrual cycles.30 The perimenarchal stage, which reportedly varies between just a few months to 5–7 years,17,30-32 is thought to reflect progressive maturation and increasing robustness of the H-P-O axis, defined by the acquisition of a positive feedback response of the central hypotalamic gonadotropin-releasing hormone pulse generator to estradiol from the growing follicle, leading to an LH surge and ovulation.17,33

The length of perimenarche is strongly influenced by socioeconomic factors and metabolic variables, such as nutritional status and body mass index (BMI).34-36 Hence, disorders that accelerate H-P-O maturation, such as obesity,
are predicted to also increase the risk of adverse pregnancy outcome in young adolescents.

**Transition to progesterone responsiveness**

The onset of regular menstruation signals that the endometrium has acquired the ability to decidualize in response to elevated progesterone levels, a process foremost defined by the transformation of endometrial stromal fibroblasts into specialized epithelioid decidual cells.37 Once decidualized, declining progesterone levels trigger a switch in the secretory repertoire of decidual stromal cells, now characterized by the expression of proinflammatory cytokines, chemokines, and matrix metalloproteinases, which activates a sequence of events leading to tissue breakdown of the superficial endometrial layer, focal bleeding and menstrual shedding.37-40

Based on the clinical and biochemical observations outlined in the previous text, loss of ontogenetic progesterone resistance, whether at birth or during perimenarche, appears to be a stochastic rather than a predetermined process.

The biological drivers of this functional switch in the endometrium are not known, although there are some important clues. First, it is noteworthy that decidualization of the endometrium is not triggered directly by progesterone but initiated approximately 9 days after ovulation. The reason for this lag period is that transcriptional activation of decidual genes is strictly dependent on rising intracellular cyclic adenosine monophosphate levels during the luteal phase of the cycle and induction of decidua-specific transcription factors, such CCAAT-enhancer-binding proteins, Forkhead box protein O1, Homeobox A10, and Homeobox A11.37,41-43

Once the decidual process is initiated, the activated progesterone receptor physically binds decidua-specific transcription factors, thus maintaining and amplifying the expression of differentiation genes, including PRL and IGFBPI. An early event in response to cyclic adenosine monophosphate signaling in endometrial stromal cells is activation of nicotinamide adenine dinucleotide phosphate oxidase-4, triggering a burst in free radical production that kick-starts decidual gene expression.44

Second, in nonmenstruating mammals, decidualization occurs physiologically only upon embryo implantation, although this process can be recapitulated in hormonally primed animals by either scratching of the endometrium or upon exposure of the uterine lumen to an oil drop.45,46 These observations suggest that, under the right endocrine milieu, cellular stress (generated either endogenously or in response to implantation/tissue injury) is the evolutionarily conserved trigger of decidualization. Hence, it is conceivable that intrauterine stress associated with preeclampsia or postmaturity sensitizes the fetal uterus to progesterone-dependent decidualization and menstruation-like bleeding after birth.
Conversely, sustained estrogen-dependent endometrial growth prior to menarche may eventually lead to telomere attrition in a subpopulation of stromal cells, causing replicative exhaustion and senescence. Cellular senescence is characterized by permanent cell cycle exit and secretion of a host of inflammatory mediators, commonly referred to as senescence-associated secretory phenotype. Whether or not estrogen-dependent cellular senescence and senescence-associated secretory phenotype render the perimenarchal endometrium permissive to decidualization remains untested, although it is incontrovertible that rapid estrogen-dependent growth during the proliferative phase is a prerequisite for adequate postovulatory progesterone responses in the endometrium as well as embryo implantation.

**Endometrial stem cells and vascular remodeling**

Cyclic menstruation is thought to be an example of physiological preconditioning that prepares uterine tissue for the vascular remodeling and hyper-inflammation associated with deep hemorrhagic placentaion. In most tissues, injury is a potent cue for activation of resident adult stem and progenitor cells that mediate repair. Not surprisingly, the cycling human endometrium is rich in mesenchymal stem cells (MSCs), which reside in a specialized niche around the spiral arteries in both the basal and superficial layers. Human endometrial MSCs (eMSCs) are multipotent, able to differentiate into various tissue lineages, and form endometrial stroma when injected under the kidney capsule of immunocompromised mice. They are identified by specific cell surface markers, such as Sushi domain-containing 2 (formerly Frizzled-9, STRO-1, 3G5, and α-smooth muscle actin) in placental bed biopsies revealed that DMSCs occupy the vascular niche around non-transformed spiral arteries in the placental bed. Strikingly, they are absent from remodeled vessels, indicating that the vascular niche is either destroyed or replaced by invading trophoblast. Emerging evidence suggests that DMSCs isolated from preeclamptic pregnancies are functionally impaired and more susceptible to apoptosis. Whether dysfunctional DMSCs are a cause or a consequence of preeclampsia is not known, although analysis of their precursors (ie, eMSCs) in cycling endometrium prior to conception could potentially shed light on this issue.

**Maturation of uterine natural killer cells**

Although the fetal endometrium contains some CD45+ leukocytes and CD68+ macrophages, it is devoid of...
CD56<sup>+</sup> natural killer (NK) cells. By contrast, NK cells accumulate in the endometrium during the luteal phase of the cycle along with macrophages, and levels peak by the end of the first trimester of pregnancy.

Uterine NK cells have low cytotoxicity, at least in pregnancy, and are functionally and phenotypically distinct from their counterparts in peripheral blood. By secreting a wide variety of chemokines, cytokines, and angiogenic factors, uterine NK cells are thought to effect spiral artery remodeling. Furthermore, specific combinatorial interactions between killer immunoglobulin-like receptors expressed on the surface of uterine NK cells and HLA-C ligands on trophoblast have been shown to increase or decrease the risk of preeclampsia.

Increasing evidence indicates that cyclic decidualization plays a pivotal role in instructing uterine NK cells, meaning that decidual cues bestow specialist functions on these immune cells. For example, conditioned medium from decidual cells supplemented with IL-15 and stem cell factor was sufficient to convert peripheral blood NK cells into a phenotype that resembles decidual NK cells. Furthermore, coculture with decidual stromal cells converts CD34<sup>+</sup> hematopoietic precursors into phenotypic uterine-like NK cells.

Another study reported that a combination of hypoxia, transforming growth factor beta 1, and a DNA demethylating agent attenuates the cytotoxicity of peripheral NK cells, increases the expression of vascular endothelial growth factor, and bestows an ability on these cells to promote invasion of human trophoblast cell lines.

Interestingly, when injected into immunocompromised pregnant mice, these induced uterine-like NK cells migrate to the uterus and reduce the uterine artery resistance index, indicative of improved perfusion. These observations illustrate the plasticity of NK cells to adapt to a tissue-specific environment. Whether or not the decidua in pregnant teenagers contains sufficient NK cells is not known; however, it seems likely that incomplete cyclic programming of NK cells in an as-yet-immature uterus contributes to incomplete vascular remodeling in adolescent pregnancies.

**Placental studies**

In pregnant adolescent sheep, accelerated maternal growth induced by over-nourishment reduces trophoblast proliferation, impairs angiogenesis, and attenuates uteroplacental blood flow, resulting in premature birth of a hypoxic, growth-restricted fetus with a small placenta. By contrast, relative underfeeding prevents maternal growth during pregnancy and reduces fetal growth in late pregnancy only modestly without impacting on placental development.

These animal experiments suggested that growing teenagers may be particularly at risk of placental disorders and adverse pregnancy outcome. However, placental analyses from growing and nongrowing teenagers do not support this notion. For example, using detailed morphometric analyses, Hayward et al found no differences in placental weight or composition between growing and nongrowing teenagers. However, the birthweight/placental weight ratio was higher in growing teenagers, suggesting more efficient placental nutrient transport.

In a follow-up study, the same team demonstrated that expression of genes encoding for amino acid transporters (system A) was intrinsically lower in placentas from teenagers when compared with adults. However, the activity of system A transporters was higher in placentas from growing compared with nongrowing teenagers. These observations are broadly in line with an earlier study demonstrating that the villous/capillary surface area in placentas from adolescent mothers does not correlate with either maternal chronological age or bone age. However, this study did find an inverse correlation between the placental villous/capillary surface and gynecological age, further suggesting that uterine immaturity is the primary driver of placental dysfunction during adolescence. Unfortunately, there are as yet no studies that have examined the impact of gynecological age on spiral artery remodeling in placental bed biopsies.

**Extrinsic risk factors**

**Obesity**

The detrimental impact of obesity on pregnancy outcome is profound. A population-based analysis of 120 million deliveries in the United States pointed strongly to the ongoing obesity pandemic as the reason for the increasing rates of severe preeclampsia between 1980 and 2010.

Another population-based study reported that the risk of preeclampsia and eclampsia increases significantly with increasing BMI and decreasing age. The risk increased almost 4 times in extremely obese teenagers (BMI ≥40 kg/m<sup>2</sup>) when compared with nonobese women aged 20—24 years. The association between obesity and preeclampsia in nulliparous teenage pregnancy has been substantiated in other studies.

Intriguingly, some but not all studies also found that obesity lowers the risk of preterm birth during adolescence. One possible explanation is that the increased estrogen production associated with excess fat stores, combined with lower circulating levels of sex hormone-binding globulin, not only brings forward puberty (thelarche, pubarche, and menarche) but also accelerates uterine growth and maturation. On the other hand, BMI correlates inversely with the abundance of eMSCs in the niche around the spiral arteries, suggesting that preexisting uterine vascular pathology, combined with metabolic perturbations during pregnancy, predispose obese adolescents to preeclampsia.

**Polycystic ovary syndrome (PCOS)**

A meta-analysis of 15 studies, involving 720 women with PCOS and 4505 control subjects, demonstrated that PCOS increases significantly the risk of developing gestational diabetes (odds ratio [OR], 2.94; 95% CI, 1.70—5.08), pregnancy-induced hypertension (OR, 3.67; 95% CI, 1.98—6.81), preeclampsia (OR, 3.47; 95% CI, 1.95—6.17), and preterm birth (OR, 1.75; 95% CI, 1.16—2.62).

The increased risk of preterm birth in PCOS women was also observed in a
recent population-based study from Western Australia, which further highlighted the profound negative impact of maternal PCOS on the subsequent health of their offspring. Experimental studies have shown that PCOS is associated with impaired decidualization of endometrial stromal cells and with impaired endovascular trophoblast invasion at the end of the first trimester of pregnancy. However, to the best of our knowledge, the impact of PCOS on pregnancy outcome in adolescent mothers has not yet been studied.

This is not surprising because the clinical signs and symptoms that characterize PCOS, such as menstrual irregularities, are obscured during puberty and adolescence. Similarly, polycystic ovary morphology on ultrasound may be an incidental finding in healthy adolescents and not associated with metabolic or ovulatory abnormalities. Furthermore, the onset of menarche in girls with PCOS is much more variable than in control subjects, ranging from early menarche at or before the age of 9 years to primary amenorrhea, defined by the absence of menarche by the age of 16 years or 4 years after the onset of telarche.

While the differential impact of PCOS-associated obesity, hyperandrogenemia, and metabolic syndromes may account for the variable timing of activation of the H-P-O axis during adolescence, the same confounding factors may also affect uterine function and pregnancy outcome in different ways. Furthermore, we have previously argued that clomiphene citrate treatment to induce menstruations should be considered in women with anovulatory PCOS prior to a planned pregnancy to compensate for the lack of menstrual preconditining of the uterine vasculature.

**Perspective**

During adolescence, the immature uterus is transformed into an organ with unrivalled regenerative capacity. Notwithstanding the overwhelming epidemiological evidence of increased risk of great obstetrical syndromes in pregnancies in very young mothers, surprisingly little is known about the biological events that imbues the uterus with the necessary plasticity to accommodate a deeply invading placenta. Prolonged estrogen-dependent growth prior to the menarche and loss of onotogenic progesterone resistance followed by iterative cycles of tissue breakdown and repair appear essential for tissue-specific expansion and programming of resident stem and immune cell populations involved in vascular adaptations during pregnancy. As highlighted by others, gynecological rather than chronological age is the better proxy for uterine immaturity, and this should be taken in account in future epidemiological studies.

The vascular pathologist and placental bed pioneer William Robertson noted 50 years ago that arteriosclerosis occurs to a greater extent and at a lower level of hypertension in the placental bed than would be expected in other organs. This applies equally to adolescent first-time mothers as a combination of obesity and young gynecological age strongly predisposes for preeclampsia. Hence, we echo the plea of many others for improved nutritional, lifestyle, and reproductive health education for teenage girls, especially as interventions during pregnancy in this group may fail to mitigate the deleterious effects of uterine immaturity.

**REFERENCES**


## Glossary

- **Adolescents**: young people aged 10–19 years.
- **Low birthweight (LBW)**: birthweight <2500 g.
- **Obstetrical syndromes**: the expression, great obstetrical syndromes, was coined to indicate clinical heterogeneity associated with impaired remodeling of uterine spiral arteries during pregnancy.
- **Small for gestational age (SGA)**: weight below the 10th percentile for the gestational age.
- **Progesterone resistance**: attenuated responsiveness of target tissues/cells to bioavailable progesterone.
- **Tanner’s classification**: classification of the timing and sequence of changes in secondary sexual characteristics.
- **Teenagers**: young people aged between 13 and 19 years.
- **Very low birthweight**: birthweight <1500 g.