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).

Received Aug. 10, 2016; revised May 9, 2017; accepted May 24, 2017.

The authors report no conflict of interest.

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

0002-9378

http://dx.doi.org/10.1016/j.ajog.2017.05.059

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

TABLE 1
Incidence of obstetrical syndromes in nulliparous adolescents

Author	Age groups, y	Number	Preeclampsia, %	Preterm birth, %	IUGR/SGA	Stillbirth/neonatal death, %
Leppalahti et al, 2013 (Finland[b])[94]	13–15	84	7.1[a]	13.1[a]	2.4	2.4
	16–17	1234	2.1	5.5	4.2	0.3
	18–19	5987	3.0	4.9	3.3	0.6
	25–29	**51,142**	**3.0**	**4.8**	**2.5**	**0.4**
Blomberg et al, 2014 (Sweden[c])[95]	<17	2392	1.8	8.9[a]	3.8	0.3
	17–19	29,816	1.9	6.5	3.8	0.3
	25–29	**300,822**	**2.2**	**5.6**	**2.9**	**0.3**
Kaplanoglu et al, 2015 (Turkey[b])[96]	GA <3	101	8.9	21.8[a]	15.3[a]	
	GA >3	132	3.8	13.6	5.3	
	20-35	**202**	**4.0**	**9.4**	**4.0**	
Pergialiotis et al, 2015 (Greece[b])[97]	12–19	244	6.9[a]	27.0	11.5	0.8
	20–34	**1460**	**1.0**	**10.5**	**15.2**	**0.1**
Medhi et al, 2016 (India[c])[98]	15–19	165	11.5[a]	23.6[a]	26.0	5.4
	20–25	**330**	**6.0**	**15.7**	**18.1**	**3.9**

Bold denotes control population.

GA, gynecological age; *IUGR*, intrauterine growth retardation; *SGA*, small for gestational age.

[a] Denotes statistical significance $P < .05$ compared with control group; [b] Denotes retrospective study; [c] Denotes prospective study.

Brosens. Uterine immaturity and obstetrical syndromes. Am J Obstet Gynecol 2017.

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]

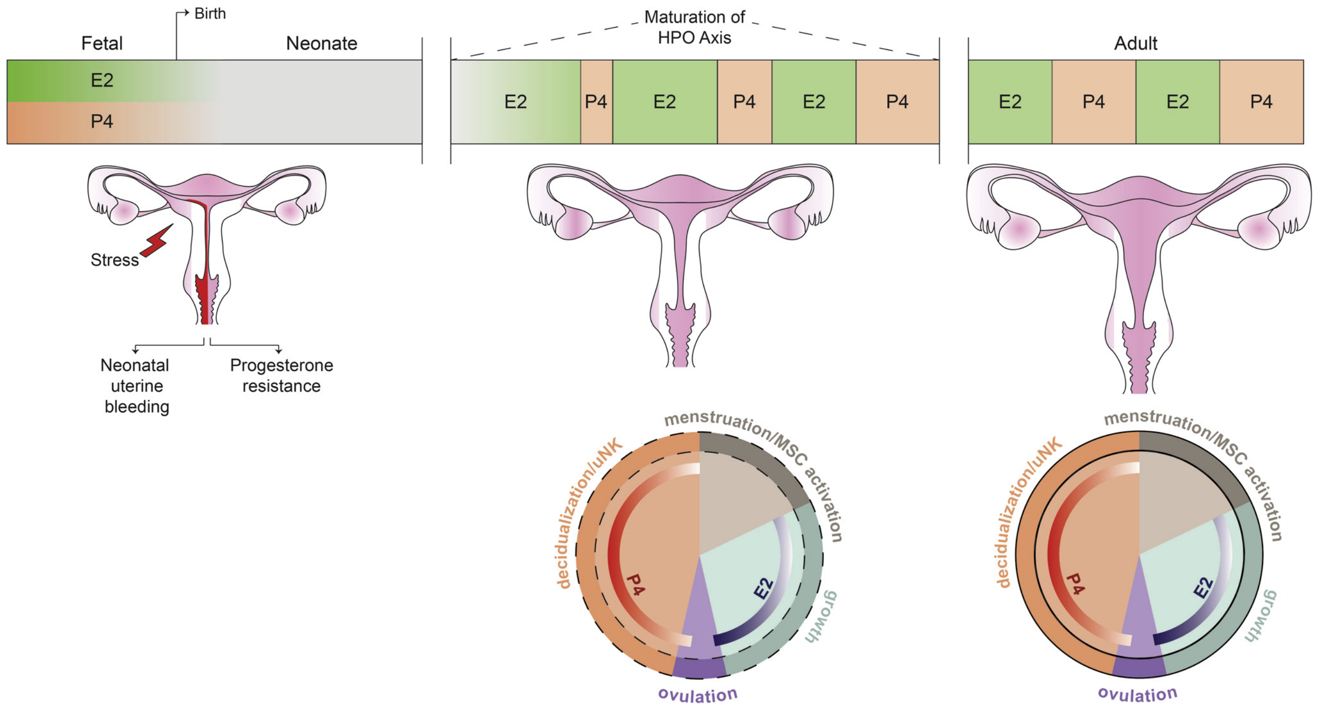
Intriguingly, the incidence of neonatal uterine bleeding, which is also referred to as pseudomenstruation of the newborn, is lower in preterm babies but higher in postterm babies and following preeclamptic pregnancies.[7,29]

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 hypothalamic 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,

FIGURE
Uterine maturation from birth to adulthood



Brosens. Uterine immaturity and obstetrical syndromes. Am J Obstet Gynecol 2017.

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 *IGFBP1*. 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.

TABLE 2
Estrogen and progesterone responses in the fetal endometrium

Months	Fetal endometrium	Fetal ovaries	
4.5	Virtual uterine cavity		Estrogenic phase
5	Proliferative endometrium Gland formation Angiogenesis		
7.5	Basal vacuoles		
8	Stromal edema Hyperemia Convoluted glands Aprocrine secretion	Follicles	Luteal phase
8.5	Glycogen accumulation		
9	Occasional decidualization	No corpus luteum	

Estrogen responses in the fetal endometrium are followed by partial progesterone responses late in pregnancy, reflecting increased responsiveness to steroid hormones of placental origin, rather than from fetal ovaries as initially assumed. Adapted from Rosa.[99]

Brosens. Uterine immaturity and obstetrical syndromes. Am J Obstet Gynecol 2017.

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.[47,48] 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.[49,50]

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 hemochorial placentation.[51] In most tissues, injury is a potent cue for activation of resident adult stem and progenitor cells that mediate repair.[52]

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.[39,53-55] 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.[56] They are identified by specific cell surface markers, such as Sushi domain-containing 2 (formerly W5C5) or coexpression of CD146 and platelet-derived growth factor receptor beta.[54,56,57]

Transcriptomic analysis demonstrated that eMSCs first give rise to a more committed but still clonogenic population of cells before differentiating into mature stromal fibroblasts.[58] Importantly, different subpopulations of stromal cells are likely responsible for spatial organization of the decidual response. For example, secretome analysis of cultured Sushi domain-containing 2–positive cells revealed that these cells produce a range of chemokines upon decidualization that may direct invading cytotrophoblast to the spiral arteries in pregnancy.[59]

In light of these novel findings, it is reasonable to assume that uterine maturation not only may be a matter of adequate estrogen-dependent growth and loss of ontogenetic progesterone resistance but also requires menstrual programming of eMSCs and homeostatic balancing of different stromal subpopulations.

In pregnancy, the decidua also harbors maternal mesenchymal stem cells (DMSCs) with multilineage differentiation potential similar to other MSCs in terms of morphology, cell-surface antigen expression, and gene expression patterns.[60] Multilabel immunofluorescence analysis of specific MSC markers (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.[61] 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.[62] 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+ natural killer (NK) cells.[63] 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.[64-66]

Uterine NK cells have low cytotoxicity, at least in pregnancy, and are functionally and phenotypically distinct from their counterparts in peripheral blood.[67] By secreting a wide variety of chemokines, cytokines, and angiogenic factors, uterine NK cells are thought to effect spiral artery remodeling.[68,69] Furthermore, specific combinatory 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.[70,71]

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.[72] Furthermore, coculture with decidual stromal cells converts CD34+ 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.[73]

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.[74] 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 overnourishment reduces trophoblast proliferation, impairs angiogenesis, and attenuates uteroplacental blood flow, resulting in premature birth of a hypoxic, growth-restricted fetus with a small placenta.[75] 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[76] 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.[77]

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.[78] 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.[79]

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 $\geq$40 kg/m^2) when compared with nonobese women aged 20–24 years.[80] The association between obesity and preeclampsia in nulliparous teenage pregnancy has been substantiated in other studies.[81-84]

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,[85] 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).[86]

The increased risk of preterm birth in PCOS women was also observed in a recent population-based study from Western Australia,[87] 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[88] and with impaired endovascular trophoblast invasion at the end of the first trimester of pregnancy.[89] 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.[36] Similarly, polycystic ovary morphology on ultrasound may be an incidental finding in healthy adolescents and not associated with metabolic or ovulatory abnormalities.[90] 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.[36]

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 preconditioning of the uterine vasculature.[91]

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 ontogenetic 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,[92] 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.[93] 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

1. Block RW, Saltzman S, Block SA. Teenage pregnancy. Adv Pediatr 1981;28:75-98.

2. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979—1986. Am J Obstet Gynecol 1990;163:460-5.

3. Orvos H, Nyirati I, Hajdu J, Pal A, Nyari T, Kovacs L. Is adolescent pregnancy associated with adverse perinatal outcome? J Perinat Med 1999;27:199-203.

4. Frisancho AR, Matos J, Bollettino LA. Influence of growth status and placental function on birth weight of infants born to young still-growing teenagers. Am J Clin Nutr 1984;40:801-7.

5. Fraser AM, Brockert JE, Ward RH. Association of young maternal age with adverse reproductive outcomes. N Engl J Med 1995;332:1113-7.

6. Brosens I, Benagiano G, Brosens JJ. The potential perinatal origin of placentation disorders in the young primigravida. Am J Obstet Gynecol 2015;212:580-5.

7. Brosens I, Curcic A, Vejnovic T, Gargett CE, Brosens JJ, Benagiano G. The perinatal origins of major reproductive disorders in the adolescent: research avenues. Placenta 2015;36:341-4.

8. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol 2011;204:193-201.

9. Olausson PO, Cnattingius S, Haglund B. Teenage pregnancies and risk of late fetal death and infant mortality. Br J Obstet Gynaecol 1999;106:116-21.

10. Eure CR, Lindsay MK, Graves WL. Risk of adverse pregnancy outcomes in young adolescent parturients in an inner-city hospital. Am J Obstet Gynecol 2002;186:918-20.

11. Gilbert W, Jandial D, Field N, Bigelow P, Danielsen B. Birth outcomes in teenage pregnancies. J Matern Fetal Neonatal Med 2004;16:265-70.

12. Chen XK, Wen SW, Fleming N, Demissie K, Rhoads GG, Walker M. Teenage pregnancy and adverse birth outcomes: a large population based retrospective cohort study. Int J Epidemiol 2007;36:368-73.

13. Fluhmann CF. The developmental anatomy of the cervix uteri. Obstet Gynecol 1960;15:62-9.

14. Hagen CP, Mouritsen A, Mieritz MG, et al. Uterine volume and endometrial thickness in healthy girls evaluated by ultrasound (3-dimensional) and magnetic resonance imaging. Fertil Steril 2015;104:452-9.e2.

15. Holm K, Laursen EM, Brocks V, Muller J. Pubertal maturation of the internal genitalia: an ultrasound evaluation of 166 healthy girls. Ultrasound Obstet Gynecol 1995;6:175-81.

16. Gray SH, Ebe LK, Feldman HA, et al. Salivary progesterone levels before menarche: a prospective study of adolescent girls. J Clin Endocrinol Metab 2010;95:3507-11.

17. Zhang K, Pollack S, Ghods A, et al. Onset of ovulation after menarche in girls: a longitudinal study. J Clin Endocrinol Metab 2008;93:1186-94.

18. Adams Waldorf KM, Singh N, Mohan AR, et al. Uterine overdistention induces preterm labor mediated by inflammation: observations in pregnant women and nonhuman primates. Am J Obstet Gynecol 2015;213:830.e1-19.

19. Al-Sabbagh M, Lam EW, Brosens JJ. Mechanisms of endometrial progesterone resistance. Mol Cell Endocrinol 2012;358:208-15.

20. Attia GR, Zeitoun K, Edwards D, Johns A, Carr BR, Bulun SE. Progesterone receptor isoform A but not B is expressed in endometriosis. J Clin Endocrinol Metab 2000;85:2897-902.

21. Burney RO, Talbi S, Hamilton AE, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. Endocrinology 2007;148:3814-26.

22. Wang C, Mavrogianis PA, Fazleabas AT. Endometriosis is associated with progesterone resistance in the baboon (*Papio anubis*) oviduct: evidence based on the localization of oviductal glycoprotein 1 (OVGP1). Biol Reprod 2009;80:272-8.
23. Tulchinsky D, Hobel CJ, Yeager E, Marshall JR. Plama estradiol, estriol, and progesterone in human pregnancy. II. Clinical applications in Rh-isoimmunization disease. Am J Obstet Gynecol 1972;113:766-70.
24. Tulchinsky D, Okada DM. Hormones in human pregnancy. IV. Plasma progesterone. Am J Obstet Gynecol 1975;121:293-9.
25. Hill M, Parizek A, Jirasek JE, et al. Is maternal progesterone actually independent of the fetal steroids? Physiol Res 2010;59:211-24.
26. Ferris B, Green OC. Pregnanediol excretion by newly born infants. Am J Dis Child 1968;115:693-7.
27. Brosens I, Brosens J, Benagiano G. Neonatal uterine bleeding as antecedent of pelvic endometriosis. Hum Reprod 2013;28:2893-7.
28. Ober WB, Bernstein J. Observations on the endometrium and ovary in the newborn. Pediatrics 1955;16:445-60.
29. Levy JM, Rosenthal R, Dellenbach P, Pequenot JP. [Genital crisis in the newborn. repercussion of certain maternal or pregnancy factors on the frequency of neonatal metrorrhagia]. Arch Fr Pediatr 1964;21:819-27.
30. Metcalf MG, Skidmore DS, Lowry GF, Mackenzie JA. Incidence of ovulation in the years after the menarche. J Endocrinol 1983;97:213-9.
31. Metcalf MG. Incidence of ovulation from the menarche to the menopause: observations of 622 New Zealand women. N Z Med J 1983;96:645-8.
32. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil 1967;12:77-126.
33. Bourguignon JP, Hoyoux C, Reuter A, Franchimont P. Urinary excretion of immunoreactive luteinizing hormone-releasing hormone-like material and gonadotropins at different stages of life. J Clin Endocrinol Metab 1979;48:78-84.
34. Elizondo-Montemayor L, Hernandez-Escobar C, Lara-Torre E, Nieblas B, Gomez-Carmona M. Gynecologic and obstetric consequences of obesity in adolescent girls. J Pediatr Adolesc Gynecol 2017;30:156-68.
35. Jasik CB, Lustig RH. Adolescent obesity and puberty: the "perfect storm". Ann N Y Acad Sci 2008;1135:265-79.
36. Welt CK, Carmina E. Clinical review: lifecycle of polycystic ovary syndrome (PCOS): from in utero to menopause. J Clin Endocrinol Metab 2013;98:4629-38.
37. Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. Endocr Rev 2014;35:851-905.
38. Brosens JJ, Gellersen B. Death or survival—progesterone-dependent cell fate decisions in the human endometrial stroma. J Mol Endocrinol 2006;36:389-98.
39. Evans J, Salamonsen LA, Winship A, et al. Fertile ground: human endometrial programming and lessons in health and disease. Nat Rev Endocrinol 2016;12:654-67.
40. Maybin JA, Critchley HO. Menstrual physiology: implications for endometrial pathology and beyond. Hum Reprod Update 2015;21:748-61.
41. Brosens JJ, Hayashi N, White JO. Progesterone receptor regulates decidual prolactin expression in differentiating human endometrial stromal cells. Endocrinology 1999;140:4809-20.
42. Lynch VJ, Leclerc RD, May G, Wagner GP. Transposon-mediated rewiring of gene regulatory networks contributed to the evolution of pregnancy in mammals. Nat Genet 2011;43:1154-9.
43. Nnamani MC, Ganguly S, Erkenbrack EM, et al. A derived allosteric switch underlies the evolution of conditional cooperativity between HOXA11 and FOXO1. Cell Rep 2016;15:2097-108.
44. Al-Sabbagh M, Fusi L, Higham J, et al. NADPH oxidase-derived reactive oxygen species mediate decidualization of human endometrial stromal cells in response to cyclic AMP signaling. Endocrinology 2011;152:730-40.
45. Finn CA, Pope M. Vascular and cellular changes in the decidualized endometrium of the ovariectomized mouse following cessation of hormone treatment: a possible model for menstruation. J Endocrinol 1984;100:295-300.
46. Rudolph M, Docke WD, Muller A, et al. Induction of overt menstruation in intact mice. PLoS One 2012;7:e32922.
47. Acosta JC, Banito A, Wuestefeld T, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat Cell Biol 2013;15:978-90.
48. Salama R, Sadaie M, Hoare M, Narita M. Cellular senescence and its effector programs. Genes Dev 2014;28:99-114.
49. Kasius A, Smit JG, Torrance HL, et al. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. Hum Reprod Update 2014;20:530-41.
50. Yuan X, Saravelos SH, Wang Q, Xu Y, Li TC, Zhou C. Endometrial thickness as a predictor of pregnancy outcomes in 10787 fresh IVF-ICSI cycles. Reprod Biomed Online 2016;33:197-205.
51. Brosens JJ, Parker MG, McIndoe A, Pijnenborg R, Brosens IA. A role for menstruation in preconditioning the uterus for successful pregnancy. Am J Obstet Gynecol 2009;200:615.e1-6.
52. Rafii S, Butler JM, Ding BS. Angiocrine functions of organ-specific endothelial cells. Nature 2016;529:316-25.
53. Gargett CE, Schwab KE, Brosens JJ, Puttemans P, Benagiano G, Brosens I. Potential role of endometrial stem/progenitor cells in the pathogenesis of early-onset endometriosis. Mol Hum Reprod 2014;20:591-8.
54. Gargett CE, Schwab KE, Deane JA. Endometrial stem/progenitor cells: the first 10 years. Hum Reprod Update 2016;22:137-63.
55. Mutlu L, Hufnagel D, Taylor HS. The endometrium as a source of mesenchymal stem cells for regenerative medicine. Biol Reprod 2015;92:138.
56. Masuda H, Anwar SS, Buhring HJ, Rao JR, Gargett CE. A novel marker of human endometrial mesenchymal stem-like cells. Cell Transplant 2012;21:2201-14.
57. Schwab KE, Gargett CE. Co-expression of two perivascular cell markers isolates mesenchymal stem-like cells from human endometrium. Hum Reprod 2007;22:2903-11.
58. Barragan F, Irwin JC, Balayan S, et al. Human endometrial fibroblasts derived from mesenchymal progenitors inherit progesterone resistance and acquire an inflammatory phenotype in the endometrial niche in endometriosis. Biol Reprod 2016;94:118.
59. Murakami K, Lee YH, Lucas ES, et al. Decidualization induces a secretome switch in perivascular niche cells of the human endometrium. Endocrinology 2014;155:4542-53.
60. Fukuchi Y, Nakajima H, Sugiyama D, Hirose I, Kitamura T, Tsuji K. Human placenta-derived cells have mesenchymal stem/progenitor cell potential. Stem Cells 2004;22:649-58.
61. Kusuma GD, Manuelpillai U, Abumaree MH, Pertile MD, Brennecke SP, Kalionis B. Mesenchymal stem cells reside in a vascular niche in the decidua basalis and are absent in remodelled spiral arterioles. Placenta 2015;36:312-21.
62. Ji L, Zhang L, Li Y, et al. MiR-136 contributes to pre-eclampsia through its effects on apoptosis and angiogenesis of mesenchymal stem cells. Placenta 2017;50:102-9.
63. Kammerer U, Rieger L, Kapp M, Dietl J, Ruck P. Immunocompetent cells in the endometrium of fetuses and children. Hum Reprod 2003;18:969-75.
64. Hanna J, Goldman-Wohl D, Hamani Y, et al. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med 2006;12:1065-74.
65. Koopman LA, Kopcow HD, Rybalov B, et al. Human decidual natural killer cells are a unique NK cell subset with immunomodulatory potential. J Exp Med 2003;198:1201-12.
66. Russell P, Sacks G, Tremellen K, Gee A. The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure. III: further observations and reference ranges. Pathology 2013;45:393-401.
67. Sharkey AM, Xiong S, Kennedy PR, et al. Tissue-specific education of decidual NK cells. J Immunol 2015;195:3026-32.
68. Lash GE, Otun HA, Innes BA, et al. Regulation of extravillous trophoblast invasion by uterine natural killer cells is dependent on gestational age. Hum Reprod 2010;25:1137-45.
69. Robson A, Harris LK, Innes BA, et al. Uterine natural killer cells initiate spiral artery remodeling in human pregnancy. FASEB J 2012;26:4876-85.

70. Hiby SE, Apps R, Sharkey AM, et al. Maternal activating KIRs protect against human reproductive failure mediated by fetal HLA-C2. J Clin Invest 2010;120:4102-10.

71. Hiby SE, Walker JJ, O'Shaughnessy KM, et al. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. J Exp Med 2004;200:957-65.

72. Keskin DB, Allan DS, Rybalov B, et al. TGF beta promotes conversion of CD16+ peripheral blood NK cells into CD16- NK cells with similarities to decidual NK cells. Proc Natl Acad Sci USA 2007;104:3378-83.

73. Vacca P, Vitale C, Montaldo E, et al. CD34+ hematopoietic precursors are present in human decidua and differentiate into natural killer cells upon interaction with stromal cells. Proc Natl Acad Sci USA 2011;108:2402-7.

74. Cavalli RC, Cerdeira AS, Pernicone E, et al. Induced human decidual NK-like cells improve utero-placental perfusion in mice. PLoS One 2016:e0164353.

75. Wallace JM, Luther JS, Milne JS, et al. Nutritional modulation of adolescent pregnancy outcome—a review. Placenta 2006;27(Suppl A):S61-8.

76. Hayward CE, Greenwood SL, Sibley CP, Baker PN, Jones RL. Effect of young maternal age and skeletal growth on placental growth and development. Placenta 2011;32:990-8.

77. Hayward CE, Greenwood SL, Sibley CP, Baker PN, Challis JR, Jones RL. Effect of maternal age and growth on placental nutrient transport: potential mechanisms for teenagers' predisposition to small-for-gestational-age birth? Am J Physiol Endocrinol Metab 2012;302:E233-42.

78. Stevens-Simon C, McAnarney ER. Skeletal maturity and growth of adolescent mothers: relationship to pregnancy outcome. J Adolesc Health 1993;14:428-32.

79. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980–2010: age-period-cohort analysis. BMJ 2013;347:f6564.

80. Aliyu MH, Luke S, Kristensen S, Alio AP, Salihu HM. Joint effect of obesity and teenage pregnancy on the risk of preeclampsia: a population-based study. J Adolesc Health 2010;46:77-82.

81. Baker AM, Haeri S. Estimating risk factors for development of preeclampsia in teen mothers. Arch Gynecol Obstet 2012;286:1093-6.

82. Haeri S, Guichard I, Baker AM, Saddlemire S, Boggess KA. The effect of teenage maternal obesity on perinatal outcomes. Obstet Gynecol 2009;113:300-4.

83. Kansu-Celik H, Kisa Karakaya B, Guzel AI, Tasci Y, Erkaya S. To evaluate the effect of pre-pregnancy body mass index on maternal and perinatal outcomes among adolescent pregnant women. J Matern Fetal Neonatal Med 2016:1-13.

84. Wang LF, Zhou H, Zhang Y, Wang Y. [Relationship between pre-pregnancy body mass index and preterm birth]. Beijing Da Xue Xue Bao 2016;48:414-7.

85. Murakami K, Bhandari H, Lucas ES, et al. Deficiency in clonogenic endometrial mesenchymal stem cells in obese women with reproductive failure—a pilot study. PLoS One 2013:e82582.

86. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 2006;12:673-83.

87. Doherty DA, Newnham JP, Bower C, Hart R. Implications of polycystic ovary syndrome for pregnancy and for the health of offspring. Obstet Gynecol 2015;125:1397-406.

88. Piltonen TT, Chen JC, Khatun M, et al. Endometrial stromal fibroblasts from women with polycystic ovary syndrome have impaired progesterone-mediated decidualization, aberrant cytokine profiles and promote enhanced immune cell migration in vitro. Hum Reprod 2015;30:1203-15.

89. Palomba S, Russo T, Falbo A, et al. Decidual endovascular trophoblast invasion in women with polycystic ovary syndrome: an experimental case-control study. J Clin Endocrinol Metab 2012;97:2441-9.

90. Codner E, Villarroel C, Eyzaguirre FC, et al. Polycystic ovarian morphology in post-menarchal adolescents. Fertil Steril 2011;95:702-6. e1-2.

91. Brosens I, Benagiano G. Menstrual preconditioning for the prevention of major obstetrical syndromes in polycystic ovary syndrome. Am J Obstet Gynecol 2015;213:488-93.

92. Gibbs CM, Wendt A, Peters S, Hogue CJ. The impact of early age at first childbirth on maternal and infant health. Paediatr Perinat Epidemiol 2012;26(Suppl 1):259-84.

93. Robertson WB, Brosens I, Dixon HG. The pathological response of the vessels of the placental bed to hypertensive pregnancy. J Pathol Bacteriol 1967;93:581-92.

94. Leppalahti S, Gissler M, Mentula M, Heikinheimo O. Is teenage pregnancy an obstetric risk in a welfare society? A population-based study in Finland, from 2006 to 2011. BMJ Open 2013;3:e003225.

95. Blomberg M, Birch Tyrberg R, Kjolhede P. Impact of maternal age on obstetric and neonatal outcome with emphasis on primiparous adolescents and older women: a Swedish Medical Birth Register Study. BMJ Open 2014;4:e005840.

96. Kaplanoglu M, Bulbul M, Konca C, Kaplanoglu D, Tabak MS, Ata B. Gynecologic age is an important risk factor for obstetric and perinatal outcomes in adolescent pregnancies. Women Birth 2015;28:e119-23.

97. Pergialiotis V, Vlachos DE, Gkioka E, Tsotra K, Papantoniou N, Vlachos GD. Teenage pregnancy antenatal and perinatal morbidity: results from a tertiary centre in Greece. J Obstet Gynaecol 2015;35:595-9.

98. Medhi R, Das B, Das A, Ahmed M, Bawri S, Rai S. Adverse obstetrical and perinatal outcome in adolescent mothers associated with first birth: a hospital-based case-control study in a tertiary care hospital in North-East India. Adolesc Health Med Ther 2016;7:37-42.

99. Rosa P. Endocrinolgie sexuelle du foetus humain [Sexual endocrinology of the human fetus]. Paris: Masson and Cie; 1955.

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.