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REVIEW

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Neonatal menstruation explains epidemiological links between fetomaternal conditions and adolescent endometriosis

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ABSTRACT

Background: Different fetomaternal conditions may influence the risk of endometriosis during adolescence and in adult life; here we focus on the hormonal maturation of the fetal endometrium in the final stages of pregnancy and on the theory that neonatal menstruation should be considered, similar to cyclic menstruation in the adult, as a risk factor for adolescent endometriosis.

Methods: The literature on neonatal menstruation and associated factors was systematically searched, and 19 relevant articles, published in different languages between 1950 and 1984, were retrieved. After closer scrutiny, 11 publications were selected as relevant.

Results: At birth, the neonatal endometrium displays different degrees of progesterone resistance, varying from a complete absence of progesterone responses, to secretory activity, decidualization and menstrual-like shedding. A temporal relationship exists between endometrial maturation and the incidence of neonatal menstruation, supporting the hypothesis that vaginal bleeding at birth is triggered by progesterone withdrawal. Neonatal menstruation occurs rarely in preterm babies, increases in those born at term and is a relatively frequent event in postmature infants. Analysis of archival clinical studies indicates that being born postterm or to a preeclamptic mother increases the risk of neonatal menstruation. Low birthweight may also enhance the likelihood of neonatal menstruation, whereas prematurity could be protective, although the available data are inconclusive.

Conclusions: The available data suggest that fetomaternal risk factors associated with neonatal menstruation could also potentially be useful in identifying women at risk of endometriosis. However, archival clinical studies have important limitations, including lack of accurate dating of pregnancy, therefore necessitating prospective studies and systematic registration of neonatal menstruation.

Keywords: Endometriosis, Low birth weight, Neonatal menstruation, Postmaturity, Preeclampsia, Prematurity

Introduction

Increasing experimental evidence suggests that exposure to environmental pollutants during the early stages of development can disrupt endocrine and reproductive functions, thereby increasing the risk of endometriosis later in life. We have recently reviewed the potential link between in utero conditions or exposures and endometriosis and found that conclusive evidence is as yet lacking (1). At the same time, data have been accumulating supporting the hypothesis that – over and above toxic compounds – the risk of endometriosis can be influenced by a number of other factors, including dietary habits (2-6).

Following the emerging evidence that different in utero conditions, whether hormonal, nutritional or those caused by pregnancy complications, may influence the risk of endometriosis, we focused our attention on the hormonal responsiveness of the neonatal endometrium. To this end, we elaborated a new theory to explain premenarcheal and early-onset endometriosis based on the observation that endometrium exhibits different degrees of progesterone resistance at birth (7). Indeed, the neonatal endometrium can display a number of cellular responses, varying from full progesterone resistance, to secretory activity in the glandular compartment and, in approximately 3%-5% of cases, changes akin to those

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seen prior and during menstruation in adults (8, 9). Thus, like menstruation during reproductive years, neonatal uterine bleeding is triggered by partial shedding of the endometrium in response to withdrawal of placental progesterone; hence the term *neonatal menstruation.* An integral part of this theory is the conjecture that retrograde transplantation of endometrial stem/progenitor cells in response to neonatal menstruation plays a critical role in the pathogenesis of early-onset endometriosis (10).

It seems therefore that the origin of endometriosis, at least in premenarcheal and adolescent girls, may be linked to the presence or absence of physiological neonatal menstruation. It has been argued that the likelihood of retrograde bleeding is particularly high at birth because of the structure of the neonatal cervical canal, which is twice as long as the uterine corpus and functionally blocked by thick endocervical mucus (11-13). Indeed, a unique case report described the presence of epithelial deposits of endometrial origin on the serosal surface of the sigmoid colon in a newborn (14).

Clinical and scientific interest in neonatal menstruation has been largely confined to 1960s and 1970s, and relevant studies were reported mainly in the French and German literature (15-19). Intriguingly, although there are no original studies on neonatal uterine bleeding in the more recent medical literature, a lively discussion on this topic can be found on the internet. For instance, the WebMD site explains clearly:

> Your newborn girl's genitals have been exposed to many hormones in the uterus. Among other things, these hormones may have made the outside of the vagina ("labia majora" and the "clitoris") a little swollen and prominent and caused a thick, milky discharge in the vagina. Most dramatically, at 2 or 3 days of age, your daughter may have a little bit of bleeding from her vagina. This is perfectly normal – it is caused by the withdrawal of the hormones she was exposed to in the womb. It will be her first and last menstrual period for another decade or so (20).

Having identified 2 novel intrauterine variables that may influence the risk of endometriosis later in life – i.e., the degree of neonatal endometrial progesterone responsiveness and the incidence of retrograde bleeding soon after birth – we reexamined the available literature in search of fetomaternal factors relevant to both neonatal menstruation and endometriosis.

Search strategy and analysis

To develop our hypothesis on the neonatal origins of endometriosis, we started with the more recent literature (1980-2014) and identified a single study on neonatal menstruation, published in 1985 in the *Yugoslav Journal of Gynecology and Perinatology,* a medical journal from the former Yugoslavia (18). In addition, in our attempt to identify putative fetomaternal markers of endometriosis, we searched for *neonatal endometrium*, or *endometrium in the neonate* in combination with *preeclampsia* or *adolescent pregnancy*; however, among the 33,971 publications on *preeclampsia* and 78,736 publications on *adolescent pregnancy*, not a single publication linked these subjects. Therefore, we manually but systematically searched the literature on neonatal menstruation between 1950 and 1984 in the Library of the Royal Society of Medicine in London. The references listed in these publications were then used for a further search of relevant articles. We identified 19 articles and, after scrutiny of the data, retained 11 publications relevant to our hypothesis. For obvious reasons, our search cannot be considered "systematic" in its full meaning, since a manual search is subject to involuntary omission. Another drawback of our approach is that a comprehensive understanding of the possible impact of neonatal menstruation on reproductive events later in life emerged progressively as we were able to obtain and analyze the full text of these old publications. This step-wise approach led to a series of publications that developed an increasingly more detailed theory (8, 9, 10, 21). Therefore, the hypothesis we present here on a possible relationship between neonatal menstruation, preeclampsia, adolescent pregnancy and endometriosis is probably still incomplete, and should therefore be considered as a clinical opinion. Methodologically, the incidence of neonatal menstruation in various clinical cohorts was compared using either the chi-square or Fisher's exact test with a p value <0.05 considered significant.

The first menstruation

The criterion used to determine the incidence of neonatal menstruation in most studies is based on the presence of visible vaginal bleeding starting a few days after birth and lasting for several days (Tab. I). We identified 5 informative studies, encompassing 5,163 babies. The overall incidence of overt menstruation was very consistent across studies, ranging from 3.0% to 5.2% (median 3.9%); which is entirely commensurate with the frequency of full progesterone responsiveness of the neonatal endometrium when defined on histological evidence of decidual transformation of the stroma or menstruation-like

TABLE I - Incidence of overt and occult neonatal menstruation

	Newborns (no.)	NUB cases (no.)	Incidence
Overt			
Rosa et al (1955) (19)	976	29	3%
Lévy et al (1964) (15)	1,207	57	4.7%
Kaiser et al (1974) (16)	153	8	5.2%
Huber et al (1976) (17)	350	12	3.4%
Berić et al (1985) (18)	2,477	96	3.9%
Occult			
Rosa et al (1955) (19)*	50	13	26%
Kaiser et al (1974) (16)†	153	93	61%
Huber et al (1976) (17)‡	350	89	24%

NUB = Neonatal uterine bleeding.
*Detection method: cytology.
†Detection method: hemoglobin.
‡Detection method: perox-ortho-toluidine.

tissue breakdown. Three studies also reported the incidence of occult uterine bleeding, defined as "the presence of blood detected by cytology or biochemical tests" in the absence of visible vaginal bleeding (Tab. I). By contrast to overt uterine bleeding, the reported incidence of occult uterine bleeding varied widely, from 25% to 61%, which likely reflects the sensitivity of different methods used in these studies. Neonatal menstruation is a transient phenomenon that is typically detectable between postpartum days 3 and 7.

Fetomaternal determinants of neonatal menstruation

Low birthweight

Lévy et al (15) investigated the incidence of neonatal menstruation in 3 groups of neonates. The first cohort consisted of 1,207 female neonates born at the Maternité de Strasbourg between the 12th of February 1961 and 12th of February 1962. The incidence of neonatal menstruation in this control group from the maternity hospital was 4.7% (57/1,207). The frequency of neonatal menstruation was also examined in 2 study groups, consisting of newborns admitted to the neonatal unit. The first study group included 584 so-called premature newborns, defined by a low birthweight (<2,500 g), admitted to the neonatal unit over a 69-month period, starting on the 1st of January 1957. The second study group involved 272 term or postterm babies admitted over a 32-month period. Interestingly, the incidence of neonatal menstruation in the low birthweight group was 6.2% (36/584), higher than the control group, although not significantly so ($p = 0.22$). Unfortunately, gestation length was not recorded in this study, rendering it impossible to separate premature from small-for-gestational-age newborns. By contrast, the incidence of neonatal menstruation in the second study group was 14% (38/272), significantly higher when compared with the control group ($p<0.0001$). Two tentative conclusions can be drawn from this study. First, the data on birthweight and the risk of menstruation are inconclusive and require further investigation. Second, the data also suggest that pregnancy disorders that impact neonatal well-being may increase the risk of neonatal menstruation.

Prematurity and postmaturity

A study by Berić et al (18) included all female babies born at the Department of Obstetrics and Gynaecology in Novi Sad, Serbia, throughout 1979. The incidence of visible vaginal bleeding in term babies was 3.9% (96/2,241). In preterm newborns, the incidence was 0.8% (1/126) and in postterm 9.1% (10/110). Statistical analysis of this data confirmed that the incidence of neonatal menstruation was significantly different between preterm and postterm babies ($p = 0.004$) and between term and postterm babies ($p = 0.009$). By contrast, the difference between preterm and term babies did not reach statistical significance ($p>0.05$). In an earlier study, Rosa et al (19) reported 3 cases of menstruation in 206 girls born before 36 weeks of gestation (1.5%) compared with 23 cases in 770 term babies (3%; $p = 0.24$). The authors also stated that these 3 preterm babies were almost mature as their birthweights were between 2,750 and 2,900 g. As mentioned above, the study of Lévy et al (15) defined *term* and *preterm* on the basis of birthweight and not on length of gestation. Nevertheless, the authors also recorded menstruation in 7 out of 13 (54%) newborns with clinical evidence of postmaturity, as defined by the criteria of Clifford and Reid (22). Taken together, these observations demonstrate that postmaturity is a strong risk factor for neonatal menstruation. Prematurity is likely protective, although the evidence is inconclusive. In any case, the incidence of menstruation illustrates the temporal relationship between endometrial maturation in late gestation and the incidence of uterine bleeding at birth; further supporting the notion that neonatal uterine bleeding, like adult menstruation, is caused by withdrawal of progesterone actions on a responsive endometrium.

Preeclampsia

In the study of Lévy et al (15), 65 babies were born to mothers with preeclampsia. Preeclampsia was defined as severe, in the presence of hypertension, albuminuria and edema, and as mild, in the presence 2 of 2 symptoms. The incidence of menstruation associated with mild preeclampsia was 32% (8/25) and with severe preeclampsia 47.5% (19/40). Thus the overall incidence of neonatal uterine bleeding in babies born to preeclamptic mothers, irrespective of the severity, was 42% (27/65), which is significantly higher than the overall incidence in the control or either study group ($p<0.001$).

Fetomaternal blood incompatibility

A well-defined subgroup in the study of Lévy and colleagues (15) consisted of 49 females at term or postterm babies admitted to the neonatal unit because of Rhesus or ABO incompatibility. This subgroup is of interest as hemolysis and increased hematopoiesis could theoretically increase mobilization and trafficking of bone marrow–derived progenitor cells to the uterus, which has been proposed as one possible explanation for increased progesterone responsiveness of the endometrium at term (23). However, the incidence of neonatal menstruation in this subgroup was 14.3% (7/49), which is greater than in the control group, but not significantly different from the overall incidence of in the term/postterm study group ($p>0.05$).

Discussion

The role of the in utero environment in the pathogenesis of endometriosis is an emerging but controversial topic. Epidemiological studies have largely focused on adult endometriosis and the mothers' lifestyle during the index pregnancy. We recently highlighted that neonatal menstruation, a physiological but entirely neglected phenomenon, not only extends Sampson's theory on the origins of endometriosis but could potentially explain early-onset endometriosis. In this study, we investigated the putative fetomaternal risk factors of neonatal menstruation to determine the overlap, if any, with those implicated in endometriosis. This exercise has important limitations especially as all informative clinical studies predate the introduction of ultrasound and fetal growth charts in clinical practice. Moreover, several putative risk

factors, such as low birthweight and prematurity, are interdependent but their relative importance cannot be ascertained from the available data.

Nevertheless, our exercise yielded a number of intriguing observations relevant to our understanding of pelvic endometriosis and confirmed by recent epidemiological studies (Tab. II). For example, the Nurses' Health Study II reported a linear increase in the incidence rate of laparoscopically confirmed endometriosis with decreasing birthweight. This observation was not corroborated by the more recent Endometriosis, Natural History, Disease, Outcome (ENDO) Study (24). However, this study reported that preterm birth decreases the odds of finding endometriosis at the time of surgery. This finding caused some consternation at the time of publication, as there was no obvious explanation. However, the equivocal data on birthweight and the protection conferred by preterm birth are in keeping with the incidence of neonatal menstruation reported many decades ago. Intriguingly, while several recent studies have tried to assess the impact of endometriosis on obstetrical disorders, including preeclampsia (25), there are to our knowledge no studies that have examined the link between preeclampsia and the risk of the child developing endometriosis in adulthood or beyond.

The current interest in in utero exposures and risk of endometriosis is predicated on the early origins of health and disease hypothesis, first proposed by David Barker in 1990 (26). This hypothesis posits that maternal signals or exposures may permanently reprogram the developing fetus in a manner that determines the likelihood of developing disease later in life. In the context of endometriosis, the data are ambiguous and inconclusive, reflecting the inherent biases associated with retrospective transgenerational studies. Furthermore, reprogramming of fetal organs is widely speculated to involve an epigenetic mechanism, although a validated pathway has yet to emerge. Arguably, neonatal menstruation and pelvic seeding of endometrial progenitor cells constitute a compelling and direct mechanism that could link in utero events to the risk of endometriosis, especially early-onset disease.

Finally, the fact that neonatal menstruation is related to progesterone sensitivity and represents a risk factor for endometriosis later in life, whereas endometriosis has been linked to progesterone resistance, may be seen as a paradox. In this respect, it has been argued that the term *progesterone resistance* within the context of endometriosis is a misnomer since endometriotic cells, especially stromal cells, are also resistant to other signals, such as cyclic AMP or hCG (27). Hence, it is far from clear whether "progesterone resistance" in the context of endometriosis is related or comparable to the fetal situation.

The challenge now is to test this hypothesis prospectively, which could be easily achieved if the presence or absence of neonatal uterine bleeding is systematically recorded as a putative clinical marker of future reproductive health. In this respect, agreement should be sought on how to determine the presence of vaginal blood in the neonate. Clearly this is easy in the event of *overt* bleeding but more cumbersome if occult bleeding is included since – as shown in the Table I – different methods have different sensitivities. Furthermore, it remains to be established if occult bleeding reflects focal disintegration of the neonatal endometrium that is otherwise still largely resistant to progesterone withdrawal.

TABLE II - Fetomaternal conditions linked with endometriosis, as confirmed by epidemiological studies

Fetomaternal condition	Epidemiological confirmation
Neonatal menstruation is very rare in preterm newborns (Berić et al, 1985 (18))	The ENDO study found that, *for an unknown reason*, endometriosis is rare in preterm born women (Wolff et al, 2013 (23))
Low birth weight (<2,500 g)* is associated with increased frequency of neonatal menstruation (Lévy et al, 1964 (15))	Low birth weight (<2,500 g)* is independently associated with the risk of deep endometriosis in adults (Borghese et al, 2015 (24))

*Includes both premature and small-for-gestational-age newborns.

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