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Review

Clinical significance of neonatal menstruation

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ABSTRACT

Past studies have clearly shown the existence of a spectrum of endometrial progesterone responses in neonatal endometrium, varying from proliferation to full decidualization with menstrual-like shedding. The bleedings represent, similar to what occurs in adult menstruation, a progesterone withdrawal bleeding. Today, the bleeding is completely neglected and considered an uneventful episode of no clinical significance. Yet clinical studies have linked the risk of bleeding to a series of events indicating fetal distress. The potential link between the progesterone response and major adolescent disorders requires to be investigated by prospective studies.

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Introduction

Neonatal menstrual-like bleeding (NMB) is described in the lay literature as an unusual, but physiological event that deserves no clinical attention; the scientific community seems to agree and consequently NMB is not recorded in clinical birth notes. A search of the electronic databases reveals not a single scientific paper on the phenomenon or its significance published since 1985. On the other hand, its occurrence was reported and discussed extensively in European medical journals in the late 19th century and during the first half of the 20th century. This literature, however, is hard to trace today and in the absence of any recording, prospective studies cannot be performed. Even if recording is started, it will take many decades before results from epidemiological studies will become available.

In this commentary we summarize our research on the potential clinical significance of the bleeding episode described in the English literature as *neonatal uterine bleeding*, or *neonatal menstruation*.

Search strategy and analysis

Our search started with the German, English and French literature published in the early 1970s. An electronic search with different key-words failed to reveal a single publication linked with these subjects. Therefore, we manually, but systematically, searched the literature on the endometrium in the neonate. References listed in these publications were used for a further search of relevant articles and full manuscripts were obtained from different libraries, in particular the Library of the Royal Society of Medicine in London. Ultimately we identified 71 articles including

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case reports, opinion papers and theses or book chapters. For obvious reasons, our search cannot be considered "systematic" in its full meaning, since a manual search is subject to involuntary omission. This step-wise approach led to a series of publications that developed an increasingly more detailed insight. Therefore, the hypothesis we present on a possible relationship between neonatal menstruation, adolescent pregnancy, preeclampsia and endometriosis is probably still incomplete; it should therefore be considered as a clinical opinion. An overview of the initial findings was published in 2013 [1] and the hypothesis on the role of endometrial stem/progenitor cells in the pathogenesis of adolescent endometriosis in 2014 [2].

Neonatal menstrual-like bleeding

As far as we could find, uterine bleeding in the neonate was first described as *vaginal bleeding* by Carus in 1822 in the Zeitschrift für Natür und Heilkunde and as *haemorrhage from the genital organs in the recently born female child*, by Cullingworth in the Liverpool and Manchester Medical and Surgical Journal in 1876.

In a remarkable essay Josef Halban, gynecologist at the Wiedner Hospital in Vienna, stated in 1904 that according to his investigations changes in the fetal organs occurring during pregnancy are almost completely analogous to those of the mother. When the maternal uterus reacts with decidua formation, the weaker fetal uterus reaction leads only to menstrual-like changes. Halban believed that active substances of placental origin caused the changes in the organs and his conclusion was formulated as follows: "*Since eclampsia represents only the highest grade of the intoxication that occurs in normal pregnancies, we need to consequentially conclude for a placental origin of poisoning taking place in eclampsia*". Thus, for the first time an indirect link was claimed between preeclampsia and those events later found to lead to NMB [3]. In the US, neonatal bleeding was mentioned for the first time by Drake in 1907 as "*Vaginal haemorrhage in newborn*" in the Journal of the American Medical Association and subsequently discussed by Emile Novak [4] in his book *Menstruation and its disorders* published in 1922, as a "*non-menstrual genital bleeding in the newborn*".

In 1955 the Harvard pathologists Ober and Bernstein [5] published a large autopsy study of newborns and described a spectrum of endometrial progesterone responses, varying from proliferation to full decidualization and menstrual-like shedding (Table 1). This study clearly indicates that neonatal uterine bleeding represents, similarly as menstrual bleeding, a progesterone withdrawal bleeding. They found that full progesterone response with decidualization and shedding occurred in only some 5% of the neonates, a frequency of endometrial progesterone response in agreement with that reported later by various European studies in the sixties and seventies for the occurrence of visible neonatal menstrual-like bleeding [1].

Neonatal menstrual-like bleeding as a sign of fetal distress

With regard to birth weight, it is noteworthy that in the autopsy study of Ober and Bernstein, the neonates with decidual endometrium were delivered between 35 and 41 weeks gestation and had a birth weight below 3 kg. In the group with menstrual shedding, birth occurred between 37 and 40 weeks gestation and the birth weight varied between 2400 and 3280 g. During the same period, pediatricians at the Maternity and Paediatrics Clinic of Strasbourg, France, tried to study the repercussion of typical preeclampsia on the neonate [6], defined as mild by the presence of two of the three symptoms (hypertension, albuminuria and edema) and severe by the presence of all three symptoms. They excluded all pregnancies with history of chronic hypertension, nephropathy and other disorders and reported on repercussions of pure preeclampsia on the neonate including effects on birth weight, mortality, morbidity, icterus and the occurrence of NMB, called "*crise génitale du nouveau-né*". They reported a frequent association between low birth weight and neonatal menstruation, but as pediatricians they could not make a distinction in their study between prematurity and fetal growth retardation. The association between maternal or pregnancy factors and neonatal menstruation is tabulated in Table 2. Preeclampsia in mild and even more in severe forms was significantly associated with NMB. Postmaturity, defined by the criteria of Clifford which include postnatal symptoms of anoxic injury to the respiratory and nervous systems and skin symptoms was also associated with increased risk of neonatal menstrual-like bleeding. The Strasbourg group also found an increased risk of NMB in association with ABO or Rhesus blood group incompatibility at term.

Table 1
Classification of changes seen in endometria of 169 neonatal infants (adapted from Ober and Bernstein [5]).

Endometrium	Newborns
Proliferative	116 (68%)
Secretory	45 (27%)
Decidual or menstrual	8 (5%)

Table 2
Presence of adverse clinical conditions and neonatal uterine bleeding (Levy et al. [6]).

Clinical condition	Newborns	Neonatal bleeding
Control group	1.207	57 (4.7%)
Preeclampsia	65	27 (41.5%)*
Mild	25	8 (32%)
Severe	40	19 (47.5%)
Postmaturity	13	7 (54%)
Rhesus isoimmunization (full term)	49	7 (14.2%)

* $p < 0.001$.

A large study of neonatal menstrual-like bleeding was performed by the Department of Obstetrics and Gynaecology at the University of Novi Sad, then part of the former Yugoslavia. All neonates from January 1 till December 31, 1979 were controlled for the presence of visible uterine bleeding [7]. Of the total of 2477 female newborn infants, 126 were premature, 2241 at term and 110 postmature. The incidence of visible uterine bleeding was respectively 0.78%, 3.79% and 9.10%. The study confirmed that postmaturity is a significant cause of neonatal menstruation.

The association of neonatal menstrual-like bleeding with disorders including preeclampsia, low birth weight, postmaturity or dysmaturity and fetal anemia caused by blood group isoimmunization suggests that NMB is related to the presence of fetal distress caused by placentation disorders or fetal anemia during the last months of pregnancy.

Neonatal menstruation may be linked with early onset endometriosis

Drawing on the old and new literature on neonatal menstrual-like endometrial bleeding, the hypothesis has been presented that endometrial stem/progenitor cells may be present in NMB and they may be causally linked to early-onset endometriosis [1,2]. This new theory offers an explanation for the occurrence of endometriosis in the pre-menarcheal girl and the presence of severe endometriosis, including ovarian endometriomas, in adolescent girls [1].

In recent years epidemiological studies have been performed to explore the possibility of a link between in utero events and the

risk of endometriosis. The case-control study by Borghese et al. [8] included 743 women less than 42 years old operated for benign gynecological conditions. The study group included 358 patients with histologically proven endometriosis and a control group of 375 patients without endometriosis, as surgically checked. They found that patients with birth weight ≤2500 g had a higher risk of endometriosis and observed a "dose-effect" for the risk according to birth weight and for an increased risk of developing deep infiltrating endometriosis. The findings are in line with the epidemiological study by Missmer et al. [9] who documented an increased risk of endometriosis for lower birth weight with a relative risk of 1.2 (95% CI 1.0–1.8, $p < 0.01$).

Irrespective of its origin, in clinical practice the delay in diagnosing endometriosis in adolescents remains a critical issue, particularly in view of the observation that the earlier dysmenorrhea appears, the longer is the delay in diagnosis. This delay, together with the different origin, can explain the severity of endometriosis affecting some adolescents, especially the form affecting the ovaries with the formation of endometriomas [1]. For this reason, finding a simple, non-invasive tool for screening the presence of endometriosis in the adolescent is mandatory. In the absence of any registration of neonatal menstrual-like bleeding, the feto-maternal factors affecting the presence of NMB can be used for investigation. Recently, Riazi et al. [10] explored the literature on clinical manifestations of endometriosis with the aim of developing a tool for an early and accurate detection of pelvic endometriosis in adult women. Whether or not such a tool is developed, the question still remains to which extent circumstances associated with neonatal menstrual-like bleeding can be used as a sign or symptom for suspecting endometriosis of neonatal origin. While there is a strong relationship between preeclampsia and NMB, the history of maternal preeclampsia is likely to be a potential marker of endometriosis and improve its early diagnosis in the adolescent with dysmenorrhea or a suspected ovarian cyst.

Wolff et al. [11] performed a matched cohort study involving 473 women undergoing laparoscopy/laparotomy, and an age and residence matched population cohort comprising 127 women undergoing pelvic magnetic resonance imaging. They found that in utero exposures were not statistically associated with the odds of an endometriosis diagnosis. Reduced odds were observed for preterm birth (OR = 0.41; 95% CI 0.18–0.94). They concluded that endometriosis remains an elusive disease to diagnose and to study at the population level. The findings could be explained by the rare occurrence of neonatal menstrual-like bleeding in preterm newborns [7]. It can be hypothesized that clinical conditions such as history of preeclampsia, low birth weight (<2500 g) and postmaturity are signs indirectly related to the development of endometriosis in adolescents.

Absence of neonatal bleeding

Based on post-mortem studies by Ober and Bernstein [5] the endometrium at birth is not secretory but proliferative in two-third of neonates. The progesterone resistance is likely to persist till the menarche and during the early years of adolescence. In case of pregnancy during the first years after menarche the persistence of a degree of progesterone resistance may compromise deep placentation and account for the increased risk of major obstetrical syndromes, including preeclampsia, fetal growth retardation and preterm birth [13]. The concept of "ontogenetic progesterone resistance" infers that the human uterus may start out as a relatively immature organ that acquires progressively the competence for deep placentation during the first years after menarche [14].

Conclusions

A review of the old literature on NMB reveals that the phenomenon is unlikely to be an insignificant clinical event for several reasons:

First, available evidence clearly indicates that neonatal bleeding is a menstruation characterized by progesterone withdrawal. Because feto-maternal factors influencing its frequency (fetal growth restriction, preeclampsia) are characterized by a reduced blood supply to the placenta, it seems that the decidualization process in the neonate is elicited by chronic fetal hypoxia during the last trimester of pregnancy. NMB can therefore be used as a marker of intrauterine distress and, as a sign of fetal distress the bleeding requires to be registered in medical notes of all newborns.

Secondly, NMB may represent a sign of increased risk of developing endometriosis during adolescence and, in turn that this form may be more frequently progressive, as shown by several studies [12]. Registration of NMB will allow prospective studies aimed at validating the application to newborns of the menstrual regurgitation theory.

Thirdly, there is a need to revive scientific interest in the neonatal menstrual-like bleeding; an event that possibly plays a role, among others, in the transgenerational evolution of major reproductive disorders and adolescent endometriosis.

Although the vaginal hemorrhage in the newborn has been called physiological and is described in the lay literature as a bleeding of no concern, the old literature, and in particular French, German and Serbian pediatricians have demonstrated that the bleeding occurs in neonates when they were exposed to fetal distress in late pregnancy.

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