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NEONATAL UTERINE BLEEDING AS A BIOMARKER FOR REPRODUCTIVE DISORDERS DURING ADOLESCENCE: A WORLDWIDE CALL FOR SYSTEMATIC REGISTRATION BY NURSE MIDWIFE

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Abstract

Neonatal uterine bleeding (NUB) occurs in approximately 5% of newborns, and is generally considered to be of little clinical significance. However, the real clinical importance of this condition and its long-term implications remain to be determined. The reason why NUB is rare despite high circulating levels of progesterone can be attributed to a progesterone resistance present in a majority of neonates. Recent work indicates that NUB represents a significant biomarker for events that can occur later-on during adolescence. Indeed, clinical studies have shown that "neonatal menstruation" constitutes a sign of fetal distress during late pregnancy, reflecting a stage of endometrium development that may subsequently have an impact on the reproductive life of the adolescent and the young adult. Via retrograde flow, NUB can cause endometrial stem/progenitor cells to arrive into the pelvic cavity and survive there, dormant underneath the peritoneal surface, until menarche activates them. Indeed, there is both clinical and

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epidemiological evidence of a link between NUB and adolescent endometriosis. In addition, if progesterone resistance persists till the onset of menarche, in case of an early teen pregnancy, it can result in a disorder of deep placentation. Therefore, we propose that NUB should be carefully recorded so that prospective studies can examine its links with reproductive disorders in adolescence and beyond.

Clinical series published in the sixties, seventies, and eighties have documented that uterine bleeding in the neonatal period occurs in approximately 5% of newborns[1]. Today, the phenomenon of neonatal uterine bleeding (NUB) is considered of little clinical importance and essentially remains ignored by neonatologists. The lack of interest in its occurrence and significance is reflected *inter alia* by the internet site *WebMD* describing it as follows: "*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*"[2]. Despite this neglect, NUB has recently been the subject of re-evaluation[3–8]. Intriguingly, neonatal bleeding has been extensively described in the European literature for almost two centuries[9] and, more than a century ago, it was labelled as "*neonatal menstruation*"[10].

Although the functional significance of progesterone withdrawal in the neonatal period is not fully understood, we have provided persuasive evidence that NUB should not be ignored, but actually may represent an important biomarker for reproductive events that can occur during adolescence[3–8].

The concentration of progesterone in the fetal circulation increases dramatically to levels much higher than those found in the maternal circulation[11] (Table 1). Yet, after birth, a genuine and visible menstrual bleeding – as a consequence of a physiological progesterone withdrawal – occurs only in a minority of female newborns. We have proposed that this is due to a developmental form of progesterone resistance, a concept that is supported by classic studies of pathology[12,13]. This progesterone resistance is defined as the decreased responsiveness of target tissues like the endometrium to ever increasing levels of bioavailable progesterone[14], hence explaining the absence of any neonatal uterine bleeding in a majority of neonates.

Clinical studies suggest that neonatal uterine bleeding (or neonatal menstruation) may represent a sign of fetal distress during late pregnancy. Indeed, a study reported by Levy et al. demonstrated that bleeding is significantly more frequent in the presence of preeclampsia, fetal growth restriction, and in conditions such as Rhesus alloimmunization[1]. Subsequently, a study performed by Beric et al., encompassing all neonates born at a hospital in Serbia during the year 1979, found that NUB occurred in 0.8% of preterm, in 3.8% at term, and in a significantly higher proportion (9.1%) of post-term female newborns[15]. These findings suggest that NUB reflects a state of endometrial development at birth that may subsequently have an impact on the reproductive life of the adolescent and the young adult. (Table 2).

We propose that the occurrence of NUB represents a predisposing risk factor for early-onset pelvic endometriosis during adolescence. The thick mucus plug inside the long neonatal

endocervical canal filters the visible or occult vaginal bleeding occurring between the 3rd and the 5th day of life, predisposing to retrograde endometrial shedding into the pelvic cavity[16]. Under these circumstances, well-differentiated endometrial cells, as well as endometrial stem/progenitor cells, may enter the pelvic cavity via this retrograde menstruation; unlike the differentiated cells, stem cells may survive in an inactive or dormant state underneath the peritoneal surface, until menarche. When circulating estrogen levels increase, stimulation of these cells leads to the early growth of ectopic, clonal endometriotic cell nests, and angiogenesis[6]. This process may commence even prior to menarche.

To date, no direct evidence for the role of endometrial stem/progenitor cells in the pathogenesis of endometriosis has been reported, but clinical observations supporting a link between NUB and adolescent endometriosis have been documented by the occurrence of pelvic endometriosis in a newborn[17] and in pre-menarcheal females[18]. Epidemiological evidence also supports this hypothesis, because of the low risk of endometriosis in females born preterm[19] and the higher risk in females with a low birth weight[20].

Finally, endometriosis in the adolescent has a different phenotype than in the adult[21] and is characterized by strong angiogenesis, bleeding, and endometrioma formation[22]. For all these reasons, “neonatal menstruation” (or neonatal uterine bleeding) can be considered as a predisposing factor for early-onset endometriosis[4–6]. However, in contrast to cyclic menstruation, proof that NUB is a cause of early-onset endometriosis can only be obtained by prospective studies once the phenomenon of NUB is systematically recorded in clinical notes. It must be stressed that the diagnosis of endometriosis in adolescents remains a challenge and is almost inevitably delayed for several reasons and sometimes for a very long period of time. This diagnostic delay is consequential, because it allows endometriotic implants to progress toward the more destructive stages of the disease, with an often irreversible impact on the reproductive potential and the ovarian reserve of these young women. Surgical treatment at that late stage is also more likely to have an additional negative impact on reproductive success. A survey conducted by the Endometriosis Association reported that the average time between the onset of pain and the final diagnosis of endometriosis is 9.3 years[23] (see also: www.endometriosisassn.org). The authors consider this to be a potentially actionable target to reduce the burden of this disease.

When the endometrium shows resistance to the action of progesterone at birth, not only will the female newborn not show any sign of either visible or occult neonatal bleeding, but this resistance is likely to persist till the onset of menarche and even beyond. In cases of early teen pregnancy, such a condition may affect the normal process of placentation and result in a disorder of deep placentation. A recent epidemiological study conducted in Finland demonstrated that the risk of preeclampsia and preterm delivery is significantly elevated in 13–15 year-old pregnant teenagers and is lower if the female becomes pregnant at the age of 16–17[24]. The improved endometrial progesterone response after a period of normal menstruations can be explained by menstrual preconditioning[25] or ‘priming’ of the human uterus. In response to dynamic remodeling events, triggered by true ovulatory cycles and monthly menstruations and some miscarriages, the relatively immature uterus gradually

acquires competence of deep placentation, and is eventually capable of supporting normal ongoing pregnancies[26] with term deliveries.

In conclusion, the progesterone response in the neonatal endometrium exhibits a spectrum of biological maturity, varying from an absent to a full response. This will result in menstrual-like bleeding at birth in a small minority of cases, whereas in the majority of newborn girls, progesterone-resistance may persist till the onset of menarche. The presence or absence of NUB can have consequences: on one hand, tubal reflux and pelvic seeding of endometrial stem/progenitor cells in the neonate can increase the risk of early-onset endometriosis. Alternatively, persisting biological immaturity until adolescence may result in defective deep placentation in the event of a very early pregnancy, increasing the odds of major obstetrical disorders, such as preeclampsia, low birth weight, or spontaneous preterm labor[27].

The challenge today is to test the hypothesis that NUB is a biomarker for subsequent reproductive disorders. This requires the conduct of prospective studies aimed at ascertaining whether the progesterone response of the neonatal endometrium is a key factor for reproductive health in the adolescent[8]. The observation of the "*little bleeding from the vagina*" described in the lay press as perfectly normal, may indeed be "normal," but it does not seem to be "*unimportant,*" or without consequences. For these reasons, its presence should be recorded carefully, and the hypothesis that this is an endometrial marker of fetal distress explored. Only systematic recording of the presence or absence of NUB will allow the prospective examination of this hypothesis. We encourage the creation of an international registry for neonatal uterine bleeding, coupled with links in adolescence and first pregnancy, to determine whether this simple sign can identify patients at risk for adverse reproductive outcomes. This is also one of this year's new research priorities for endometriosis from the WES/WERF Consortium, i.e., a global consortium of investigators in endometriosis[28].

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Table 1

Total and unbound plasma progesterone concentrations in maternal and fetal plasma (11)

Sources of plasma samples	Total* ng/ml	Unbound*	
		%	ng/ml
Luteal phase (n=5)	17 ± 3	4.83 ± 0.1	0.82 ± 0.14
Term pregnancy (n=10)	160 ± 10	5.02 ± 0.1	8.03 ±0.50
Umbilical vein at term (n=10)	788 ± 30	7.01 ± 0.2	55.20 ± 2.10

*Means ± S.E.

Table 2

Endometrial shedding in the neonate and reproductive outcome

ENDOMETRIUM DEVELOPMENT	
At birth	
NORMAL PREGNANCY	**FETAL DISTRESS**
Progesterone resistant	Progesterone responsive
No bleeding	Neonatal menstruation
At menarche	
Persistence of progesterone resistance	Menstrual preconditioning
Defective deep placentation	
Risk of endometriosis	
Risk of preeclampsia	Normal pregnancy

During pregnancy, the fetal endometrium remains progesterone-resistant except when fetal distress causes decidualisation and menstruation at birth.

During infancy, the endometrium remains progesterone-resistant, but the onset of ovarian activity causes shedding and preconditions the endometrium for progesterone response and normal menstruation.

In the absence of adequate preconditioning, very young girls are exposed to defective deep placentation and the risk of preeclampsia.