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Neonatal Uterine Bleeding: An Underestimated Clinical Sign?



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Abstract

Neonatal Uterine Bleeding (NUB), also named neonatal menstruation, is the bleeding that some female newborn show few days after birth. It has always been considered a parapsychological phenomenon, mainly due to the postnatal sudden lowering of maternal hormones levels. In recent years, however, the Literature has raised doubts about the true nature of this clinical sign, giving it a new significance in the evaluation of the health status of the newborn female. Moreover, it has been postulated that its presence could be an indicator of future development of gynecologic chronic pathologies, such as endometriosis. It can be also postulated that some of the genital bleedings reported during childhood and often classified or labeled as 'of unknown origin' could be related to NUB. So, it is expected that in next years this sign will be recorded more accurately in neonatal charts and become a cornerstone in the history of all female patients.

Keywords: Neonatal menstruation; Neonatal Uterine Bleeding; Endometriosis; Preeclampsia; Prematurity; Neonatal distress; Genital Bleeding

Introduction

Neonatal uterine bleeding (NUB) occurs in approximately 5% of newborns and represents, similarly as menstrual bleeding, a progesterone (PG) withdrawal bleeding. While evident NUB is relatively rare, biochemical proofs of vaginal bleeding can be found in 25-61% of neonates, depending on different methods used to detect it. The anatomy of neonatal uterus (large cervix to corpus ratio) and the presence of thick mucus inside the cervical canal are considered predisposing factors for the possibility that a great number of neonatal bleedings are not clinically evident; the concept of retrograde menstruation with shedding of endometrial cells through fallopian tubes into the peritoneum is of paramount importance in the pathogenesis of endometriosis.

Considering that the hormonal environment is the same for all neonates, a particular hormonal sensibility (or insensibility) has to be involved in the pathogenesis of NUB.

A post-mortem study demonstrated in 1955 that the endometrium in newborns presents a spectrum of PG responses, ranging from full or partial resistance in a majority of cases, to full responses in a small minority, which are those who present either occult or overt bleeding [1]. In this study the endometrium at birth was indifferent or proliferative in the majority of cases (65%) and secretory in almost one-third (27%), while only 5 % showed signs of decidualization or menstrual-like shedding (which are PG-dependent changes). It can be argued that if decidual or menstrual

changes are rare in fetal endometrium despite high circulating steroid hormone levels (which drop rapidly after birth), hence acquisition of progesterone responsiveness has to be dependent on endometrial maturation, and relative immaturity may persist in a majority of girls until the menarche and early adolescence. In this respect, the high proportion of dysfunctional uterine bleeding during first years of gynecologic life may represent a confirm to this theory. Progesterone resistance implies a decreased responsiveness of target tissue to bioavailable progesterone, and such an impaired PG response is also seen in the endometrium of women with polycystic ovary syndrome (PCOS) [2,3].

Another classic study published in 1985 [4] clearly demonstrated that NUB, present in a 3,87% of newborns, was almost absent in preterm babies (0,8%), and more frequent in post-term (9.1%) than in at term babies (4.4%). It seems, therefore, that a condition of PG resistance has to be considered physiologic in newborns and that an altered endometrial response to hormonal stimulation could be linked to conditions of fetal distress. Moreover, this PG resistance is likely to persist till the onset of menarche and even beyond, increasing the risk of obstetrical syndromes when pregnancy occurs in early teenage.

In one more of the rare investigations about NUB [5] it has been shown that this it is strongly related to postmaturity/dysmaturity; indeed, NUB was present in 32% of cases with

mild maternal preeclampsia and in 47,5% of cases with severe maternal preeclampsia; it was also present in 14% of cases of fetal growth restriction and in 14,3% of Rhesus or ABO incompatibility. Because fetomaternal 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 triggered by chronic fetal hypoxia during the last trimester of pregnancy. NUB 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.

In the presence of NUB, tubal reflux into the peritoneal cavity of endometrial stem/progenitor cells may also occur. There, given the right environment, these cells can survive and become activated at the time of thelarche, causing the specific phenotype of early-onset endometriosis. It is not inconceivable that endometrial progenitor cells seeded in the pelvis soon after birth remain quiescent until rising estrogen production that precedes the menarche stimulates angiogenesis and promotes the formation of hemorrhagic endometriotic lesions. It can be then argued that the earlier the menarche takes place in the life cycle, the higher the risk may be of aggressive endometriotic disease because of seeding of less committed and more multipotent endometrial stem/progenitor cells. Whether or not NUB in turn is associated with early menarche, possibly reflecting increased steroid hormone responsiveness of the endometrium, is not known. In fact, it is not unreasonable to assume that neonatal eMSCs (endometrial mesenchymal stem cells) and endometrial epithelial progenitor cells are longer lived, less committed, and more multipotent than their adult counterparts.

The epidemiologic finding that being born preterm (but not being born small for gestational age, at term) provides protection against endometriosis [6] should be further investigated, since the data from a unique cohort from Novi Sad (Serbia) [4] indicate that in prematurely born babies there is a very low incidence of NUB (and so we should expect a reduced risk of endometriosis later in life). On the other hand, higher risk of endometriosis in females with a low birth weight (LBW) has also been described [7]. Among patients with LBW, the risk is almost two-times higher to develop deep infiltrating endometriosis. This association could reflect common signaling pathways between endometriosis and fetal growth regulation (supposed epigenetic origin of endometriosis), but there is also the possibility of a role played by placental insufficiency on the development of the neonate's pelvis and the occurrence of neonatal uterine bleeding that could have consequences on the risk of severe endometriosis. Since PG withdrawal bleeding after preterm birth is rarely followed by uterine bleeding, it can be postulated that in the absence of NUB early-onset endometriosis may not occur or may be less aggressive.

At least, the same girls who presented NUB at birth may be the same with pre/peri pubertal uterine bleeding without cause (almost 25% in a recent review [8]): a lesser resistance to PG can be, during late infancy and adolescence, a predisposing

sensitizing factor predisposing to endometrial bleeding in presence of transitory or exogenous estrogenic stimuli. Moreover, during thelarche rising estrogen production by girl's ovaries can stimulate the proliferation of endometrial stem/progenitor cells establishing the ectopic endometrial invasion that characterizes endometriosis.

Discussion

It has been postulated [9] that the development of a form of progesterone-resistance is needed to explain the absence of NUB in the majority of neonates, protecting them from bleeding when the hormonal levels lower after birth. In fact, bleedings are significantly more frequent when preeclampsia, fetal growth restriction, Rhesus isoimmunization are complicating the last weeks of pregnancy, indicating a defective development of such resistance. The presence of neonatal evident or hidden NUB it has also been related to early onset of endometriosis due to tubal reflux.

Endometriosis, once considered a chronic pathology of reproductive age, it has also been described in a newborn with genital obstruction [10] and in premenarcheal girls [11,12]. Accumulating evidence indicates that adolescent endometriosis is common and often severe. Marsh and Laufer in 2005 [12] stated that cases of premenarcheal endometriosis are evidence of coelomic metaplasia or of Mullerian embryonic rests, being impossible to explain these cases by the menstrual regurgitation theory by Sampson (1927), but Ebert in 2009 [11] suggested that even pre-menarcheal endometriosis may be explained by retrograde bleeding due to early uterine activity.

Neonatal uterine bleeding and endometrial stem/progenitor cells may play a critical role in the development of early-onset endometriosis and explain the severity of endometriosis in the adolescent. Withdrawal from the maternal environment of high estrogen and progesterone concentrations at full-term birth may affect the secretory neonatal endometrium by producing menstruation-like changes. As stated above, prematurity seems to decrease the risk of endometriosis in adulthood. This finding would be in agreement with the likely absence of neonatal uterine bleeding in preterm neonates when no secretory changes have occurred. In contrast, in full-term pregnancies, the neonatal uterine structure with a cervical canal twice the length of the corpus with thick mucus may favor retrograde menstruation. This may be even more pronounced if utero-placental insufficiency, reflected by LBW, has hampered the normal development of pelvic vessels and connective tissue, explaining why LBW seems to positively influence the development of severe endometriosis.

Polycystic Ovary Syndrome (PCOS) is a disease affecting 4-18% of women in reproductive years, and it is mainly characterized by hyperandrogenism, chronic oligo/anovulation, polycystic ovaries, insulin resistance and type 2 diabetes mellitus [13]. Young women with PCOS-induced endometrial hyperplasia are more likely than non-PCOS women to develop endometrial carcinoma. PG-resistance implies a decreased responsiveness of target tissue

to bioavailable PG, and such an impaired PG response is seen in the endometrium of women with PCOS.

In the Literature, PG resistance generally refers to women who suffer from endometriosis (an E2-dependent disease that alters a subset of PG-regulated genes and pathways in the endometrium). Gene expression analysis of PCOS endometrium reveals PG resistance and candidate susceptibility genes in women with PCOS, but the molecular mechanisms underlying endometrial PG resistance or sensitivity in these patients are not completely understood. Moreover, it has been postulated a 'potential' role of menstrual shedding on the genesis of the increased incidence of obstetric and/or neonatal complications observed in women with PCOS. Only few and sparse data with strong clinical evidence are available in the Literature regarding the role of other potential cofactors (than anovulation) as cause of infertility in PCOS. All scientific societies are in agreement that women with PCOS cannot be definitively considered at increased risk of spontaneous abortion because scientific data on the relationship of PCOS and abortion are still weak, but preliminary data coming from 'Pregnancy in PCOS I trial' report better reproductive outcomes in patients who did not have progesterone-induced endometrial shedding.

In endometriosis the main basic event in the pathogenesis is well recognized and consist in the altered expression of estrogen and progesterone receptors in endometriotic tissue [14]. In addition to estrogen dependence, several evidences support a profile of PG resistance in the pathogenesis the disease: it has been demonstrated an overall reduction of PG receptors expression relative to eutopic endometrium and absence of one sub-type (B) of PG receptors.

Conclusion

NUB has been defined as 'the most neglected form of uterine bleeding' [15]. After a thorough Literature review Puttemans et al. [9] reported that in the past only one French and two German groups have systematically studied this phenomenon: taken together, their observational studies indicate that NUB commences 3-5 days after birth and is overt in 3-5% of neonates, but occult vaginal bleeding is estimated to range between 25 and 60%.

Despite a growing attention toward this clinical sign in recent years, it is possible at the moment only to formulate hypotheses linking this paraphysiologic phenomenon to gynecologic health:

- 1) Clinical studies have linked the risk of bleeding to a series of events indicating fetal distress. Besides more perspective studies are needed to confirm these data, actual knowledge about this topic is limited by the difficulty to obtain information about NUB.
- 2) Early-onset endometriosis may be caused by menstruation-like bleeding in the neonate, leading to tubal reflux and ectopic implantation of endometrial stem/progenitor cells.

- 3) Persistence of partial progesterone resistance in adolescent girls may compromise deep placentation and account for the increased risk of major obstetrical syndromes, including preeclampsia, fetal growth retardation and preterm birth.

- 4) Even other clinical manifestations, such as dysfunctional uterine bleeding in adolescence and PCOS, could be related to prenatal e neonatal effects of PG at endometrial level, conferring it a sort of imprinting for the future.

The concept of prenatal and neonatal origins of common reproductive disorders it is emerging in modern research, and a clinical sign like NUB cannot be ignored or not recorded in this perspective. In the gynecologic field this awareness has come to attention in recent years, but since the clinical onset of bleeding is often soon after the discharge, neonatologists and pediatricians play an important role in this direction and must be informed about future development of clinical research about this topic.

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