Human Reproduction, Vol.28, No.11 pp. 2893–2897, 2013
Advanced Access publication on September 17, 2013 doi:10.1093/humrep/det359

human reproduction

OPINION *Reproductive endocrinology*

Neonatal uterine bleeding as antecedent of pelvic endometriosis

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Submitted on May 29, 2013; resubmitted on August 1, 2013; accepted on August 14, 2013

ABSTRACT: We elaborate on a new theory to explain pelvic endometriosis, including endometriosis in premenarcheal girls, based on the finding that the neonatal endometrium can display secretory activity immediately after birth and, in some cases, changes analogous to those seen at menstruation in adults. The neonatal uterus is therefore capable of shedding its endometrium. Indeed, occult vaginal bleeding occurs in a majority of neonates, although overt bleeding is estimated to occur in only 5% of neonates. This may be due to functional plugging of the endocervical canal in the neonate, which in turn would promote retrograde flux of endometrial cells contained in menstrual debris. Ectopic endometrial implantation in a newborn with hydrometrocolpos has been documented. These data, coupled with the observation of a significantly increased risk of endometriosis in adolescents with cervical outflow obstruction and patent Fallopian tubes, indicate that endometriosis, especially in children and young adolescents, may originate from retrograde uterine bleeding soon after birth.

Key words: neonatal uterine bleeding / retrograde menstruation / fetal uterus / cervical obstruction / pelvic endometriosis

Introduction

Endometriosis was identified more than a hundred years ago, but its pathogenesis is still debated. Recently Maruyama and Yoshimura (2012) summarized the various hypotheses being considered at present; beside classic retrograde menstruation, these include lymphatic and vascular metastasis, iatrogenic direct implantation, coelomic metaplasia, embryonic rest and mesenchymal cell differentiation or induction. In addition, the persistence of a form of embryonic endometriosis, described by Signorile *et al.* (2012), may be involved. Finally, over the last decade, a possible role of endometrial stem/progenitor cells has been investigated and discussed (Gargett and Masuda, 2010).

In this context, a particularly puzzling phenomenon is early-onset endometriosis. Indeed, the presence of endometriosis, albeit with characteristics of predominantly subtle lesions, has been documented soon after menarche and even in pre-menarcheal girls. It has been argued that in these cases the lesions may have a pathogenesis that differs from retrograde menstruation (Brosens *et al.*, 2013a).

In a brief conceptual paper (Brosens and Benagiano, 2013), we outlined a new theory based on the extrapolation that endometrial stem cells may become disseminated in the pelvis at the time of neonatal uterine bleeding (NUB). These neonatal endometrial stem cells may in turn be responsible, through a variety of mechanisms, for early-onset endometriosis. Here we wish to detail the evidence supporting this hypothesis. NUB has been entirely neglected over the last few decades. Only indirect evidence of its cause and prevalence is available, mostly from papers published between 50 and 30 years ago. As such, the quality of the data reflects research practices of that time and these studies cannot be considered conclusive. Nevertheless, we hold the opinion that enough data exist to warrant further research aimed at substantiating, or rejecting altogether, our theory.

In addition, we wish to elaborate on the defining features of NUB in comparison with menstrual bleeding and to highlight evidence that implicates NUB in the pathogenesis of endometriosis.

Methods

The literature was searched via Scopus and PubMed for the following key words: 'neonate', 'newborn', 'infant' in combination with either 'endometrium', 'uterine bleeding', 'endometriosis', 'ultrasound' and 'vaginoscopy'. In addition, references were examined in published papers on related topics. The literature search included medical articles published in French, German and English.

The female neonatal reproductive tract

The endometrium in the fetus, newborn and infant

In their classical study, Ober and Bernstein (1955) from Harvard University described the post-mortem findings of uteri and ovaries from 169 newborn infants. In a majority of cases (65%), the endometrium was

found to be in an indifferent or proliferative phase. Secretory activity and decidual changes were recorded in 27 and 5% of cases, respectively. Menstrual changes were observed in five babies, all of whom had died within 3 days after birth. In these cases, the uterus was described as containing clotted blood in the endometrial cavity. On microscopy, the coagulum was composed of red blood cells, a rather prominent fibrin component, and cellular detritus in which sloughed endometrial structures were occasionally identifiable. Because of the lack of histological evidence of fetal ovarian activity, the authors concluded that endometrial changes must have been secondary to a placental endocrine stimulus. In other words, they believed that the fetus could become sufficiently exposed to placental progesterone to produce secretory and decidual uterine changes which precede menstrual shedding.

Another careful examination of the early stages of endometrial development was carried out by Huber *et al.* (1971). This study encompassed 82 uterine samples obtained from fetuses, infants and children. It demonstrated the absence of glandular development in the endometrium prior to the 20th gestational week. Cellular differentiation of glands and stroma started gradually thereafter. Secretory changes in the endometrium became apparent only from 34 weeks of pregnancy onwards. Peak secretory activity occurred at birth and was characterized by the presence of tall cylindrical epithelial cells with clear cytoplasm and visible glycogen and mucin in the lumen. Regression of the endometrium commenced soon after birth. By the second week of extra-uterine life, the endometrium no longer showed glandular activity and glycogen was absent. Again, this time line suggested that endometrial regression after birth is a direct consequence of withdrawal of placental estrogens and progesterone. Other studies have also reported disintegration of partially secretory glandular structures and areas of pre-decidualized stromal cells in the endometrium 5 days after birth (Kaiser and Grässel, 1974; Kaiser *et al.*, 1974). From the time of disintegration and regression, and throughout infancy and early childhood, the endometrium was reported to consist of a thin, atrophic, epithelial layer and scant stroma.

Karyometric investigations of endometrial glands in the fetal uterine corpus showed that nuclei increase in size with gestation. This marker of cellular activity plateaued at term and immediately after delivery (Tietze *et al.* 1970). By the 22nd day of life, the endometrium is inactive again and this continues until age 7 when increased variability in nuclear size is observed, reflecting a cellular responsiveness to weak hormonal signals. In addition, Hiersche and Meinen (1971) found that the nuclei of stromal cells also enlarge during fetal life, reaching a maximum in the last month of pregnancy. After birth, the nuclei reduce in size over ~1 year. From this age onwards and until the 7th year of life, no changes in nuclear size were observed. Then, in the stage preceding menarche between the age of 8 and 11, the stromal cell nuclei enlarged again.

The distribution of various leukocyte populations has also been investigated in the endometrium of 20 uteri obtained between 17 weeks of gestation and 5 years of life (Kammerer *et al.*, 2003). $CD45^+$ (lymphocyte common antigen) and $CD68^+$ (monocytes/macrophages) cells were significantly higher in the neonatal compared with fetal endometrium. $CD14^+$ monocytes represented the largest leukocyte subpopulation in the endometrium both ante- and post-natally. Natural killer cells ($CD56^+$) and HLA-DR^+ antigen-presenting cells were absent from fetal endometrium. There were no differences in the density of $CD3^+$ T cells between the two groups, whereas $CD4^+$ T helper cells were found only in fetal endometrium. Thus, the endometrial leukocyte population of fetuses and very young children differs from that seen in adult women. The appearance of natural killer cells and HLA-DR^+ cells in the endometrium seems to be a post-natal event, which may be induced by changes in hormone levels and/or the adaptation of the local immune system to a changing ecology.

Table I Prevalence of overt and occult NUB.

Clinical presentation	Incidence (%)	References
Visible	4.7	Levy *et al.* (1964)
	5.3	Kaiser and Grässel (1974)
	3.3	Huber and Zechmann (1974)
Occult[a]	61.3	Kaiser and Grässel (1974)
	25.4	Huber and Zechmann (1974)

[a]Based on blood detection test.

Uterine bleeding in the neonate

NUB is the most neglected type of uterine bleeding. Although often noticed, NUB is seldom recorded or investigated. As outlined above, vaginal bleeding in the immediate post-natal period is, similarly to what happens during a menstrual cycle, due to endometrial shedding triggered by withdrawal of circulating steroid hormones.

Our literature search revealed that only one French and two German groups have carried out systematic studies of vaginal bleeding in the neonate (Table I). In the French literature, the phenomenon was described as '*Crise génitale du nouveau-né*' (Levy *et al.*, 1964). The study included observations of metrorrhagia in new borns conducted at the Strasbourg Maternity Hospital and Paediatrics Department. Over a period of 12 months, this group recorded 57 cases (4.7%) with macroscopic bleeding out of a total of 1207 new borns. Kaiser and Grässel (1974) examined daily vaginal secretions for visible or occult bleeding in 75 newborn girls during the first 14 post-natal days. Overt bleeding occurred in 4 babies (5.3%) and a haemoglobin-positive reaction was present in 46 (61.3%). Vaginal bleeding in most cases started 3–7 days after birth and lasted on average 3.2 days. The authors concluded that whereas visible bleeding is relatively rare in newborn girls, occult bleeding is a frequent event. Another study evaluated 350 new borns and found visible bleeding in 3.3% of the cases (Huber, 1976). Furthermore, erythrocytes were observed in only two cytological preparations on Days 6 and 7. However, a blood detection test (Heglostix) was positive in 25.4% of neonates. The bleeding appeared always in the first week with the highest frequency on the fifth day after birth. Taken together, these observational studies indicate that NUB commences 3–5 days after birth. It is overt in ~3–5% of neonates. However, the incidence of occult vaginal bleeding is estimated to range between 25 and 60% (Table I).

There are no data showing that NUB is associated with the presence of blood in the peritoneal cavity of female neonates. However, in 1981 Blumenkrantz *et al.* observed blood in the peritoneal dialysis catheter of adult women with severe renal failure prior to menstruation. The same phenomenon was also observed in three pre-menarcheal girls who reached menarche while undergoing peritoneal dialysis (Turner and Coulthard, 1995). In these young girls, a 'cyclical blood staining of peritoneal dialysis fluid' was observed 'prior to any vaginal bleeding'.

By extension, it is not only plausible, but likely, that vaginal bleeding is preceded by retrograde bleeding in the neonate.

Functional obstruction of the fetal and neonatal cervical canal

During the third trimester of pregnancy, the uterine cervix undergoes tremendous growth along with the vagina but not along the uterine corpus. At birth, the length of the vagina is estimated to be 4 cm. According to Fluhmann (1960), the length of the cervix in the newborn is between 2 and 2.5 times that of the uterine corpus. In a vaginoscopic study, Terruhn (1980a) found that ectropion of the uterine cervix is a physiological phenomenon at birth as well as during puberty.

By the 14th week of pregnancy, the fetal urethra, vagina, uterus and Fallopian tubes have a defined lumen, which can be identified by intravaginal injection of rapidly setting liquid silicon (Terruhn, 1980b). However, after 26 weeks of gestation, the cervical canal is no longer patent, presumably because of plugging of lumen by secretions of the cervical epithelium that lines the canal.

A case of neonatal endometriosis

Arcellana *et al.* (1997) published a case report of endometriosis in a neonate, which was associated with hydrometrocolpos and McKusick-Kaufman syndrome, a rare genetic syndrome that causes vaginal agenesis or stenosis. The 4800 g baby died 8 h after Caesarean section for obstructed labour and was found to have a large pelvic cyst. Aspiration of the cyst showed yellowish cloudy fluid. Post-mortem examination revealed spillage of genital tract secretions into the peritoneal cavity through the open ends of the Fallopian tubes. Endometrial epithelial fragments were embedded within fibrinous adhesions around the ovaries and upper uterus, some with haemorrhage. Interestingly, a biopsy from a lesion on the serosa of the sigmoid colon demonstrated implantation of endometrial epithelium.

Exploration of NUB

Vaginal exploration

Various methods have been used to explore vaginal bleeding and the lower genital tract in female neonates and young children. Kaiser and Grässel (1974) examined the incidence of NUB by gently spreading the labia, so that no harm is done. Terruhn (1979) used a vaginoscope to assess the cervix in 1850 girls, ranging from newborns (n = 124) to adolescents. The vaginoscope varied in length from 6.5 to 11 cm and in diameter from 9.5 to 13 mm (Huber and Zechmann, 1974). Sharma *et al.* (2004) investigated vulvovaginitis and vaginal discharge in prepubertal girls. Samples were obtained with the 'catheter within a catheter' technique (Pokorny and Stormer, 1987). The two catheters are obtained by cutting with a sterile technique 4 inches from the distal end of a No. 12 bladder catheter and 4.5 inches from the proximal (hub end) of an intravenous butterfly catheter. The butterfly tubing is inserted inside the bladder catheter and a small syringe with 1 ml normal saline solution is attached to the hub of the 'butterfly' tubing to flush and aspirate the secretions (Fig. 1).

Ultrasound exploration

The neonatal or infantile uterus is described as prominent under ultrasound examination (Garel *et al.*, 2001). The cervix is larger than the fundus (the fundus-to-cervix ratio is ~1:2), the uterine length is ~3.5 cm and the maximal thickness is ~1.4 cm; the endometrial lining is often echogenic. Some fluid can be seen within the endometrial cavity. Arguably, the relatively long cervix, often 'plugged' by sticky cervical secretions, is likely to promote retrograde menstruation in the neonate. A similar association between stenosis of the external cervical os and endometriosis has been described in a case series of young women suffering chronic pelvic pain (Barbieri, 1998).

Perspective

Outflow tract anomalies and endometriosis

It is well documented that the risk of adolescent endometriosis increases significantly in the presence of Müllerian anomalies, especially those associated with outflow tract obstruction (Sanfilippo *et al.*, 1986). This is not surprising as outflow obstructions, whether caused by cervical mucus or not, increase the probability of retrograde bleeding. Indeed, the reported incidence of adolescent endometriosis in teenagers with genital tract anomalies varies between 11 and 40% (Dovey and Sanfilippo, 2010). To explore this association further, Olive and Henderson (1987) recorded the presence or absence of endometriosis, tubal patency, haematocolpos or haematometra and outflow obstruction in 64 women with Müllerian anomalies at the time of abdominal surgery. Endometriosis was present in 10 of 13 women with functioning endometrium, patent tubes and outflow obstruction, but in only 16 of 43 women with no obstruction (77 versus 37%, $P < 0.01$). Yang *et al.* (2012) reported that genital tract malformation is associated with much earlier onset and more severe stages of endometriosis, often with involvement of the ovaries.

Endometriosis and infertility are arguably the most prominent late-stage consequences of cervical occlusion. Early diagnosis and treatment of outflow obstruction might preserve fertility by reducing the risk of

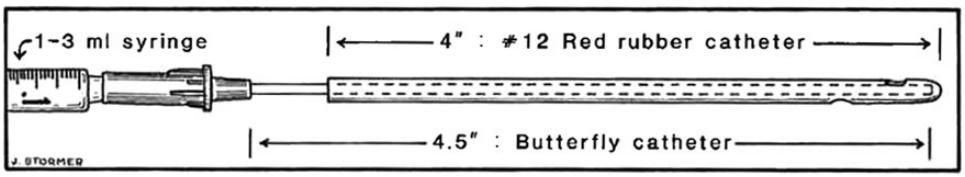

Figure 1 Pokorny's technique of 'catheter within a catheter' for obtaining vaginal specimens in the neonate (reprinted from Pokorny and Stormer (1987), with kind permission from Elsevier).

haematometra and haematosalpinx formation, leading to the development of pelvic endometriosis (Joki-Erkkila and Heinonen, 2003). Indeed, a pre-menarcheal gynecological examination to exclude the presence of congenital abnormalities of the lower genital tract, such as a transverse vaginal septum, has been advocated for the prevention of endometriosis (Deligeoroglou *et al.*, 2012). This suggestion is further supported by an experimental model in baboons, in which partial cervical occlusion by supracervical ligation produces endometriosis within 3 months of the procedure (D'Hooghe *et al.*, 1994). In addition, the observation, first reported by Meigs (1953), that pregnancy during the early reproductive years reduces the risk of subsequent endometriosis has also been explained by the simple fact that a vaginal delivery produces cervical dilatation (Brosens and Brosens, 2000).

Pre-menarcheal versus adolescent endometriosis

There are documented cases of endometriosis in pre-menarcheal girls (Marsh and Laufer, 2005). It has been assumed that in these cases the pathogenesis must differ from post-menarcheal endometriosis as it cannot be explained by the menstrual regurgitation theory, first proposed by Sampson (1927). Marsh and Laufer (2005) stated that these cases of pre-menarcheal endometriosis are evidence of coelomic metaplasia or the presence of Müllerian embryonic rests. On the other hand, Ebert *et al.* (2009) suggested that even pre-menarcheal endometriosis may be explained by retrograde bleeding due to early uterine activity, although other origins could not be excluded. On the basis of what is stated above, we suggest that NUB is a major contributing factor in early-onset endometriosis.

In this regard, it is important to stress that premenarcheal disease has both peculiar as well as classic features of peritoneal endometriosis. The distribution of the lesions in the pelvis is identical to adolescent endometriosis. The implants consist of clear and red vesicles or foci with extensive neo-angiogenesis and even ovarian endometriomas have been found (Brosens *et al.*, 2013a). In a series of five cases not associated with obstructive abnormalities of the reproductive tract, the clear and red endometriotic lesions were characterized by chronic inflammation, vascular proliferation, areas of granulation tissue, haemosiderin deposits and fibro-connective tissue focally lined by mesothelium and macrophage proliferation (Marsh and Laufer, 2005). A few additional cases have now been reported. One involved a 9-year old pre-menarcheal girl who was found to have superficial clear and red endometriotic lesions at laparoscopy (Ebert *et al.*, 2009). The lesions contained small glands, prominent stroma and pigment-carrying macrophages. Another case involved an 11-year old adolescent who underwent emergency surgery for a left ovarian cyst (Gogacz *et al.*, 2012). This cyst contained endometrial epithelium, stroma and haemosiderin-laden macrophages, but no glandular structures.

Reviews of studies published since 2002 on endometriosis in symptomatic adolescents have shown that the disease is frequently severe, as defined by the r-AFS classification, and often involves extensive adhesions and even ovarian endometriomas (Yang *et al.* 2012; Brosens *et al.*, 2013b).

A new direction in endometriosis research

Our hypothesis is based on the assumption that significant retrograde menstruation takes place in some neonates and that viable endometrial cells can reach the abdominal cavity and implant (Nap *et al.*, 2004). While this concept seems to be supported by several clinical and histological studies, incontrovertible evidence that links NUB to the development of endometriosis is, as yet, lacking. Arguably, this is a challenging direction for endometriosis research. Yet, several approaches can be envisaged that may provide insight into the role of NUB in the pathogenesis of endometriosis. For example, it would be informative to obtain flushes from the pouch of Douglas for cytology when laparotomy or laparoscopy is indicated in the neonate. Immunohistochemistry and scanning electron microscopy are valuable tools to search for microlesions in peritoneal biopsies (Vasquez *et al.*, 1984). In the presence of a functional outflow obstruction, as hypothesized, it is reasonable to speculate that a mild haematometra precedes retrograde bleeding. Transabdominal ultrasound and 3D power Doppler ultrasound could be used to search for evidence of endometrial bleeding and transient accumulation of fluid in the neonate uterus in the 1st week after birth. If so, it is important to determine if this fluid is haemorrhagic in nature, as reported in neonates with reproductive tract obstruction (Garel *et al.*, 2001). Molecular phenotyping can be used to characterize the cellular fraction in aspirates and to examine the expression of stem cell markers. Furthermore, the migratory, invasive and differentiation potential of these cells could be assessed in primary cultures or appropriate animal models.

Conclusion

NUB is a neglected phenomenon both in terms of clinical and basic research. Yet existing data, albeit scant, support the hypothesis that retrograde bleeding in the neonate lies at the roots of pelvic endometriosis, thus extending Sampson's theory (Sampson, 1927) to include the pathogenesis of pre-menarcheal and adolescent disease. There is unequivocal evidence that the neonatal endometrium can mount a decidual response (Ober and Bernstein, 1955), a prerequisite for menstrual shedding. It is also established that discrete, and occasionally overt, vaginal bleeding occurs in a majority of neonates. Regurgitation of sloughed endometrial fragments into the peritoneal cavity is likely promoted by functional obstruction of the endocervical canal at term, although this requires further confirmation. Apart from renewing the interest in the clinical significance of NUB, the challenge now is to identify and characterize the cells in the neonatal uterus that may give rise to pelvic endometriosis.

Authors' roles

All three authors contributed equally to this article.

Funding

No funding was obtained for this work.

Conflict of interest

The authors report no conflict of interest.

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