Neonatal uterine bleeding as a precursor in adult endometriosis

18 months of experience

Tandashvili L.¹ Gvenetadze A.¹ Tanos V.²

Abstract

Background: Endometriosis predominantly as subtle lesions, has been documented soon after menarche and even in pre-menarcheval girls, may have a pathogenesis that differs from retrograde menstruation. It is postulated that progenitor stem cells present in shedding endometrium may have a role in the pathogenesis of early-onset endometriosis through retrograde neonatal uterine bleeding.

Aim: To investigate the impact of the occurrence of vaginal bleeding during newborn first days of life with the present condition of the patient diagnosed with endometriosis /endometrioma / adenomyosis. Also, with our study we investigate the real incidence of neonatal uterine bleeding in Tbilisi region. The study is ongoing, but we would like to share our 18 months results.

Methods: The frequency of Neonatal uterine bleeding was prospectively evaluated among 4 maternity hospitals, in the town of Tbilisi, Georgia between October 1st 2016 until April 1st 2018. Midwives, nurses and pediatricians following these neonates were informed and participated in the study registering any neonatal uterine bleeding events and informing the study chief investigator. In addition, all neonatal uterine bleeding cases were followed by telephone direct communication with the mothers’ newborns during the 10th post-partum day for verification of absence or presence of neonatal uterine bleeding. During the same time period, 192 women age from 17 to 55 visited our clinics with histopathological confirmed diagnosis of endometriosis after laparoscopy, laparotomy or vaginal surgery due to infertility or pelvic pain, consented to participate in a survey study of neonatal uterine bleeding were observed. Only patients that their mothers firmly remembered their daughters as newborns able to report about neonatal uterine bleeding status were included in the study. A structured questionnaire regarding the age, type of conception, family and medicine history, history about endometriosis and adenomyosis, etc. were reported in details by both study groups.

Results: During the 18 months of study period 3188 female neonates were examined and followed for their first 10 days of life for neonatal uterine bleeding. Only 43/3188 neonates 1.3% were diagnosed with neonatal uterine bleeding. Out of the 192 patients with endometriosis only 2 had neonatal uterine bleeding 1% as reported by their mothers.

Conclusion: The incidence of neonatal uterine bleeding in the area of Tbilisi is 1-1.3%. According to our retrospective analysis, vaginal bleeding during newborn first days of life is 1% related with the present condition of the patient diagnosed with endometriosis /endometrioma / adenomyosis. (TCM-GMJ November 2019; 4(2):P4-P6).

Keywords: Neonatal uterine bleeding; Retrograde menstruation; Fetal uterus; Pelvic endometriosis;

Introduction

Neonatal uterine bleeding (NUB) has been a neglected phenomenon for many years. It has been brought back under our attention by the research work of Prof. Ivo Brosens (1) who spotted some old publications describing the presence of neonatal uterine bleeding mostly in the French and German literature. Incidence of visible bleeding was reported between 3.3 -5.3 % while occult bleeding was detected in 25.4 – 65.3% of the female neonates. Neonatal uterine bleeding is not an innocent phenomenon, but is probably also a sign of fetal distress as the frequency is reported to be increased in cases of postmaturity, pre-eclampsia and fetal growth retardation. So the impact in later life could be important (2).

In a recent report (2016) of a workshop of the World Endometriosis Society (WES) and World Endometriosis Research Foundation (WERF) one of the new recommendations is the registration of NUB: "the systematic registration of neonatal menstruation should be encouraged in maternity services as a potential biomarker of early-onset endometriosis".

Neonatal uterine bleeding is the most neglected type of uterine bleeding. Although often noticed, neonatal uterine bleeding is seldom recorded or investigated. 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.

The neonatal uterus has a large cervix to corpus ratio, which is functionally blocked with mucous. It is hypothesized that stem/progenitor cells present in shedding endometrium may have a role in the pathogenesis of early-onset endometriosis through retrograde neonatal uterine bleeding.

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a
chronic, inflammatory reaction affecting women, mostly during their reproductive years. Endometriosis can be asymptomatic, but associated symptoms include abdominal pain, painful periods, dyspareunia, dyschezia, infertility, ovulation pain, cyclical or perimenstrual symptoms with or without abnormal bleeding and chronic fatigue.

The exact prevalence of endometriosis is unknown but estimates range from two to 10% of women of reproductive age, to 50% of infertile women (3, 4) and to 87% of women with chronic pelvic pain. Average age at diagnosis is 27, but endometriosis also occurs among adolescents.

According to World Endometriosis Research Foundation in USA 70.9 billion euro is spent for treatment of endometriosis annual. As such, endometriosis not only has a significant impact on the lives of millions of women and their families, but also is associated with an enormous socioeconomic burden.

Endometriosis was identified more than a hundred years ago, but its pathogenesis is still debated. Recently Maruyama and Yoshimura (5) 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. (6), may be involved. Finally, over the last decade, a possible role of endometrial stem/progenitor cells has been investigated and discussed. 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 (7).

Only one French and two German groups have carried out systematic studies of vaginal bleeding in the neonate. In the French literature, the phenomenon was described as ‘Crisé génitale du nouveau-né’ (8). The study included observations of metrorrhagia in newborns 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 newborns. Kaiser and Grässel 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 newborns 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 (Hegloóstix) 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% (9).

In their classical study, Ober and Bernstein (10) 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. The fetus could become sufficiently exposed to placental progesterone to produce secretory and decidual uterine changes which precede menstrual shedding.

There are documented cases of endometriosis in premenarcheal (11). 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 in 1927 (12). In 2005 Marsh and Laufer stated that these cases of premenarcheal endometriosis are evidence of coelomic metaplasia or the presence of Mullerian embryonic rests. On the other hand, Ebert et al. suggested that even premenarcheal endometriosis may be explained by retrograde bleeding due to early uterine activity, although other origins could not be excluded.

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 (13).

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 been reported. One involved a 9-year old pre-menarcheal girl who was found to have superficial clear and red endometriotic lesions at laparoscopy (14). 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 (15). 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 and often in-
volves extensive adhesions and even ovarian endometriomas (1,16).

Methods

Study design: Prospective study and Retrospective study

Study eligible patients: All patients visited our clinics due to infertility or pelvic pain between October 1st 2016 until April 1st 2018, have histopathological confirmed endometriosis/adenomyosis after laparoscopic, laparotomy or vaginal surgery and willing to participate to the study, are included in the study.

Survey: We have included in our study 4 maternity hospitals, in the town of Tbilisi, Georgia to evaluate the real incidence of neonatal uterine bleeding in this region. We have trained pediatricians and nurses in maternity hospitals. Pediatricians call to the study chief investigator and inform about neonatal uterine bleeding cases. The chief investigator usually goes there and fill special questionnaire. Mothers of newborns in these maternity hospitals are informed to call pediatrician from our maternity hospitals, if they have any problem during first 10 days included neonatal uterine bleeding. Also, we call to every mother of girl newborn, for verification of absence or presence of neonatal uterine bleeding during the 10th post-partum day. We have excluded stillbirth. After we have information of 100 patients, we discuss existing results.

Results

During the 18 month of study period 3188 female neonates were examined and followed for their first 10 days of life for neonatal uterine bleeding. Only 43/3188 neonates 1.3% were diagnosed with neonatal uterine bleeding. Out of the 192 patients with endometriosis only 2 had neonatal uterine bleeding 1% as reported by their mothers.

Conclusion

The incidence of neonatal uterine bleeding in the area of Tbilisi is 1-1.3%. According to our retrospective analysis, vaginal bleeding during newborn first days of life is 1% related with the present condition of the patient diagnosed with endometriosis / endometrioma / adenomyosis.

References