

ORIGINAL RESEARCH ARTICLE

Neonatal uterine bleeding as a precursor to endometriosis in adulthood

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Abstract

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/adenomyosis and its real incidence in Tbilisi region a multicenter study has been conducted¹. The frequency of Neonatal uterine bleeding (NUB) was prospectively evaluated among 5 maternity hospitals, in the town of Tbilisi in Georgia between October 1st 2016 until October 1st 2018. During the same time period, 500 women visited our clinics with histopathological confirmed diagnosis of endometriosis after surgery, consented to participate in a survey study of Neonatal Uterine Bleeding were interviewed with special questionnaire. These data were compared with control groups. The incidence of visible NUB in the area of Tbilisi is 2.35%. Retrospective study suggests that there is a link between vaginal bleeding during newborn first days of life with the present condition of the patient diagnosed with endometriosis/adenomyosis. (*Afr J Reprod Health* 2022; 26[8]: 83-88).

Keywords: Neonatal uterine bleeding; retrograde menstruation; pelvic endometriosis; progenitor stem cells

Résumé

Pour étudier l'impact de la survenue de saignements vaginaux pendant les premiers jours de la vie du nouveau-né avec l'état actuel de la patiente diagnostiquée avec une endométriose/adénomyose et son incidence réelle dans la région de Tbilissi, une étude multicentrique a été menée¹. La fréquence des saignements utérins néonataux (NUB) a été évaluée de manière prospective dans 5 maternités de la ville de Tbilissi en Géorgie entre le 1^{er} octobre 2016 et le 1^{er} octobre 2018. Au cours de la même période, 500 femmes ont visité nos cliniques avec un diagnostic confirmé histopathologique d'endométriose. après la chirurgie, a consenti à participer à une étude d'enquête sur les saignements utérins néonataux ont été interrogés avec un questionnaire spécial. Ces données ont été comparées à des groupes témoins. L'incidence des NUB visibles dans la région de Tbilissi est de 2,35 %. Une étude rétrospective suggère qu'il existe un lien entre les saignements vaginaux au cours des premiers jours de vie du nouveau-né et l'état actuel de la patiente diagnostiquée avec une endométriose/adénomyose. (*Afr J Reprod Health* 2022; 26[8]: 83-88).

Mots-clés: Saignement utérin néonatal; menstruations rétrogrades; endométriose pelvienne; cellules souches progénitrices

Introduction

With our research we try to detect a relationship between neonatal uterine bleeding during the first days of life and endometriosis/adenomyosis development later in adolescent or adult life. Neonatal uterine bleeding is the most neglected type of uterine bleeding. It occurs in approximately 5% of newborns, and is generally considered to be of little clinical significance². The real clinical importance of this condition and its consequences still remain unknown, although it has been

attributed to maternal hormonal fluctuation. Therefore often noticed neonatal uterine bleeding is seldom recorded. Evaluated as no impact in newborn health.

In a 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"³.

Endometriosis is characterized by the presence of endometrial-like tissue outside the uterine cavity, which induces a chronic, inflammatory reaction affecting women, mostly during their reproductive years. Endometriosis can be asymptomatic, but associated symptoms include pelvic pain, dysmenorrhea, dyspareunia, dyschezia, infertility, ovulation pain, chronic fatigue, heavy menstrual bleeding and intestinal complaints⁴.

The exact prevalence of endometriosis is unknown but estimates range up to 10% of reproductive-age women, to 50% of infertile women^{5,6}, to 25 to 45% of women with painful periods⁷ and to 70% of women with chronic pelvic pain⁸. Average age at diagnosis is 27. 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 years²⁻⁹. Diagnostic delay allows endometriotic implants to progress toward the more destructive stages of the disease, with an often irreversible impact on the ovarian reserve.

According to World Endometriosis Research Foundation in USA 70.9 billion euro is spent for treatment of endometriosis annual. The economic burden associated with endometriosis is similar to other chronic diseases (diabetes, Crohn's disease, rheumatoid arthritis)¹⁰. 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 burden¹¹.

Endometriosis was identified around the turn of the 19th century¹², but its pathogenesis still remain controversial. Vaginal bleeding in the immediate post-natal period is, similarly to what happens during a menstrual cycle, due to endometrial shedding consequent by withdrawal of circulating steroid hormones¹³. Progenitor stem cells present in shedding endometrium may have a role in the pathogenesis of early-onset endometriosis through retrograde neonatal uterine bleeding¹⁴. At the end of pregnancy the fetal endometrium is transformed into a secretory layer that is desquamated after birth, as manifested by overt vaginal bleeding in most neonates. In consequence neonatal menstruation occurs rarely in preterm babies, increases in those born at term and is a relatively frequent event in postmature infants¹⁵. Also, regurgitation of endometrial sheddings into the peritoneal cavity is likely to be

favoured by a functionally blocked cervical canal by thick endocervical mucus¹⁵⁻¹⁶. Endometrial stem/progenitor cells and their supporting niche cells must be able to survive in the pelvic cavity in the absence of steroid hormones for many years¹⁷. Then, during adolescence ectopic endometrial mesenchymal stem cells are presumably activated in response to estrogen actions on niche cells, leading to formation of endometriosis.

If we detect that NUB is precursor of endometriosis we can avoid diagnostic delay and irreversible impact on reproductive potential of young women. In consequences improve quality of women's life and avoid socio-economic burden.

Methods

A prospective questionnaire-based survey and retrospective case-control study was done. Adjusted odds ratios and 95% confidence intervals were calculated using a Chi-Square Tests. Means of two groups were compared with T test.

Prospective study for neonatal uterine bleeding (NUB)

The frequency of Neonatal uterine bleeding was prospectively evaluated among 5 maternity hospitals, in the town of Tbilisi, Georgia between October 1st 2016 until October 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 these two years study period, 14142 deliveries were registered. Male newborns 6919 deliveries, stillbirth, newborns from surrogate mothers, newborns admitted in intensive care unit, and mothers refused participating in a survey study or could not reach by phone, were excluded from the study. Overall, 6000 deliveries with female newborns were evaluated in this study.

The author LT visited regularly, all 5 hospitals' delivery and newborn units, and registries confirming the number of female deliveries and reported newborns with NUB. Mothers of neonates were interviewed with a

structured questionnaire investigated the following: the age of the woman, nationality, BMI, gravity, parity, type of conception, primary and secondary infertility, PCOD, family and medicine history, history about endometriosis and adenomyosis, pregnancy course, and way of delivery, if any symptoms of dysmenorrhea, dysparheunia, dyschezia, dysuria, smoking, alcohol, newborn birth weight, NUB onset date and time. The clinical status of mothers, their contact address and phone numbers and newborn health status were also registered and archived in an excel file.

Collected data were compared with control groups. Results from group “neonatal uterine bleeding yes”-141 patients, were compared with control group “neonatal uterine bleeding No”. Control group included neonates born in the same maternity hospitals, on the same day, without uterine bleeding-141 patient.

Retrospective case-control study

To evaluate the impact of NUB on endometriosis manifestation a concomitant study on women with established endometriosis was performed. During the same time-period, 500 women visited our clinics with histopathological confirmed diagnosis of endometriosis after surgery due to infertility or pelvic pain, consented to participate in a survey study of Neonatal Uterine Bleeding were interviewed with the same special questionnaire. These data were compared with control groups.

The announcement of NUB is traumatic to the mother and she will remember it for life. It is an unexpected and rare phenomenon. The mother discusses it with the doctors and nurses and it is impossible such an event to pass and forget it. Only patients that their mothers firmly remembered their daughters as newborns able to report about neonatal uterine bleeding status were included in the study. The structured questionnaire investigated the following: the age of the woman, nationality, BMI, gravity, parity, type of conception, infertility, PCOD, family and medicine history, history about endometriosis and adenomyosis, pregnancy course, and way of delivery, if any symptoms of dysmenorrhea, dysparheunia, dyschezia, dysuria,

newborn birth weight, NUB onset date and time. Questionnaires were answered by direct communication during a visit in the clinic or by phone.

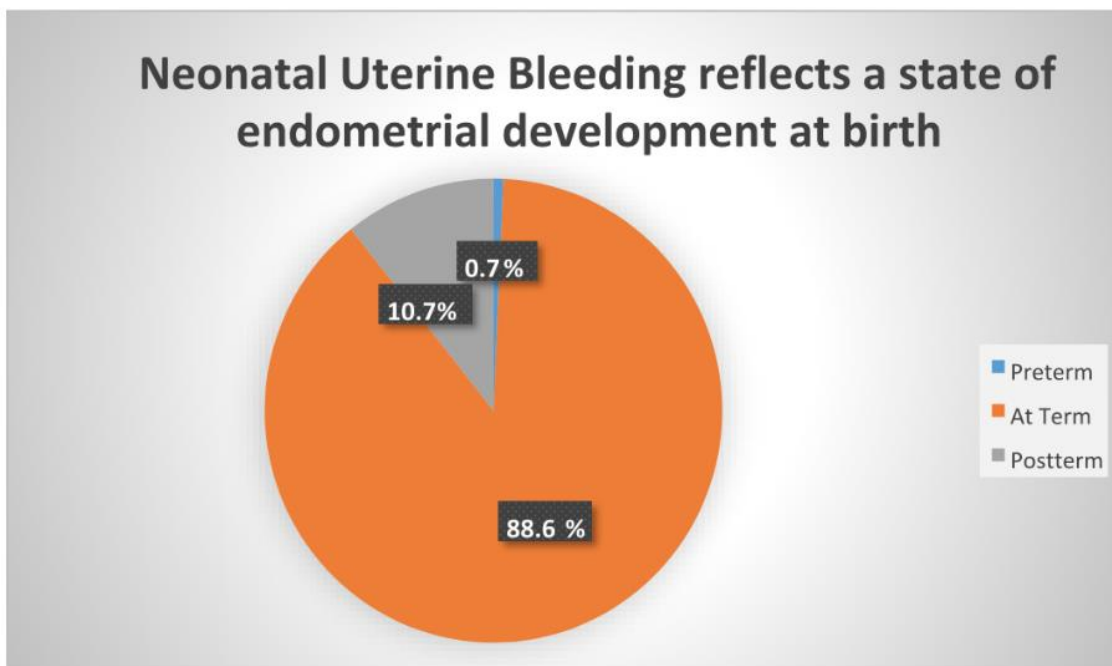
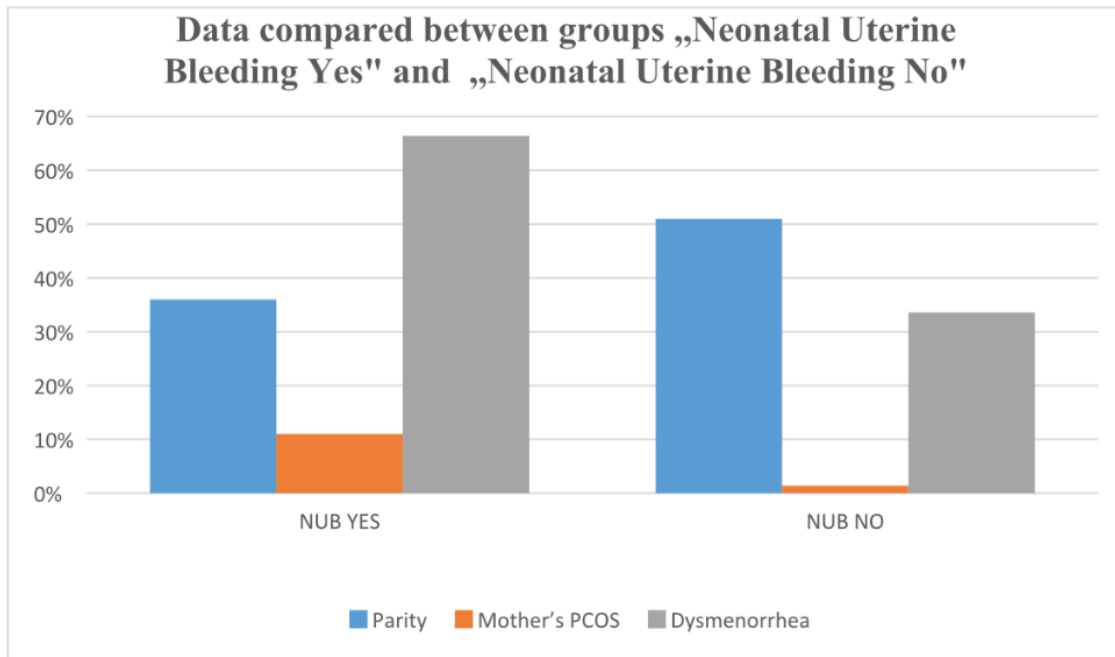
Also, to investigate the incidence of neonatal uterine bleeding in patients without endometriosis, we have investigated 350 women visited our clinics with histopathological not confirmed diagnosis of endometriosis after surgery due to infertility or pelvic pain, consented to participate in our survey study. These 350 patients visited our clinics had the same complains: infertility or pelvic pain, but different diagnosis. They were operated due to leiomyoma, dermoid cyst, paratubal cyst, hydrosalpinx, follicular cyst. Research was a part of multicenter study which was held in 2016-2018 in 11 different countries: Cyprus, Belgium, Greece, Italy, Spain, Slovenia, China, France, Romania, Bulgaria, Georgia and is registered in ISRTN, reference number: ISRCTN60023255..

Results

During the 24 months of study period 6000 female neonates from randomly selected mothers were examined and followed for their first 10 days of life for Neonatal Uterine Bleeding. Only 141/6000 neonates 2.35% were diagnosed with visible NUB. Parity and number of children were higher in the control group-neonates born without uterine bleeding. Mother's polycystic ovarian syndrome cases were higher in “neonatal uterine bleeding yes” group. Also 66.4% of mothers of neonates with uterine bleeding had dysmenorrhea. All differences were statistically significant (chart 1).

In addition, neonatal uterine bleeding occurred mostly at term female newborns (chart 2). No statistically significant differences between variables: demography, smoking, alcohol, BMI, mother's age.

Out of the 500 patients with endometriosis 9 had NUB 1.8% as reported by their mothers. While out of the 350 patients without endometriosis only 1 had NUB 0.28% ($p < 0.044$). Also 55.6% of women who had NUB as newborns, delivered a baby with NUB themselves. Whereas, none of the women born without NUB, delivered NUB babies ($p < 0.0001$).



Discussion

The incidence of visible NUB in the area of Tbilisi is 2.35%. Based on knowledge that NUB is not very often visible and occult bleedings occur more frequently, with larger studies indicating a prevalence between 25.4 and 61.3%¹⁴⁻¹⁸, we can suppose that the real incidence is higher. The prevalence of NUB varies considerably between the

2nd and the 7th day postpartum, but peak frequency is on 3 and 4 days.

It is well established that pathogenesis of endometriosis combines genetic factor. Familial tendency of endometriosis is detected in patients' first-degree relatives¹⁹. Genetic predisposition for the occurrence of NUB is also suspected in our research as 55.6% of women who had NUB as newborns, delivered a baby with NUB themselves.

The prevalence of endometriosis in women who experience painful periods is recognized in ≈70%²⁰. According to our prospective study 66.4% of mothers of neonates with uterine bleeding had dysmenorrhea. Based on this theory we can suggest that mothers of neonates with uterine bleeding have a statistically significant increased risk for having endometriosis.

According to our survey study we support theory that neonatal uterine bleeding reflects a state of endometrial development at birth as it occurred mostly at term and in post-term female newborns²¹.

Conclusion

According to our prospective study the incidence of visible NUB in the area of Tbilisi is conform the literature. The retrospective study suggests that vaginal bleeding during newborn first days of life is related with the present condition of the patient diagnosed with endometriosis/adenomyosis, although genetic factor cannot be excluded and number of patients is too low. We encourage the systematic registration of neonatal uterine bleeding in maternity services as a potential precursor of adult endometriosis. Only systematic recording of the presence or absence of neonatal uterine bleeding will allow the approval of our hypothesis.

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Author's contribution

Lela Tandashvili-corresponding author, collected and analysed data and prepared the manuscript

Arsen Gvenetadze- analysed data, made design

Lela Iremadze- analysed data, made design

Vasilios Tanos- analysed data, made design, prepared the manuscript.

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