



Ivane Javakhishvili Tbilisi State University  
Faculty of Medicine

Department of Reproductology  
and Obstetrics-Gynecology

Lela Tandashvili

Neonatal Uterine Bleeding as a precursor  
of adult endometriosis

Thesis

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## Abstract

*Lela Tandashvili\*<sup>1</sup>, Arsen Gvenetadze<sup>1</sup>, Lela Iremadze<sup>1</sup>, Vasilios Tanos<sup>2</sup>*

*Ivane Javakhishvili Tbilisi State University<sup>1</sup>; University of Nicosia, Medical School, and Aretaeio Hospital, Nicosia, Cyprus<sup>2</sup>*

Keywords: Neonatal uterine bleeding; retrograde menstruation;

## Context:

Neonatal uterine bleeding (NUB) is the most neglected type of uterine bleeding. It occurs in approximately 5% of newborns, and is generally considered to be of little clinical significance. Therefore often noticed neonatal uterine bleeding is seldom recorded. Vaginal bleeding in the immediate post-natal period is, similarly to what happens during a menstrual cycle. Progenitor stem cells present in shedding endometrium may have a role in the pathogenesis of early-onset endometriosis through retrograde neonatal uterine bleeding. NUB is not an innocent phenomenon, it may also indicate fetal distress, as its frequency is increased in premature infants, preeclampsia and fetal growth retardation.

In a report (2016) of a workshop of the 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”.

**Study Objective:** 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.

**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.

**Patients:** The frequency of neonatal uterine bleeding was pro-

spectively evaluated among 5 maternity hospitals, in the town of Tbilisi in Georgia between 2016-2018. 6000 female neonates were examined and followed for their first 10 days of life for uterine bleeding. During the same time period, 500 women visited our clinics with histopathological confirmed diagnosis of endometriosis after surgery were interviewed with special questionnaire. These data were compared with controls.

Results: Out of the 500 patients with endometriosis 9 had NUB 1.8%. While out of the 350 patients without endometriosis only 1 had NUB 0.28% ( $p < 0.044$ ). Only 141/6000 neonates 2.35% were diagnosed with NUB. The prevalence of NUB varies considerably between the 2nd and the 7th day postpartum, but peak frequency is on 3 and 4 days. Genetic predisposition for the occurrence of NUB is suspected in our research as 55.6% of women who had NUB as newborns, delivered a baby with NUB themselves. 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 newborns. The pathological course of pregnancy (gestational hypertension, preeclampsia, fetal growth retardation syndrome, etc.) was found to be statistically significantly higher in mothers of newborns who had uterine bleeding ( $P < 0.009$ ).

Conclusion: Vaginal bleeding during newborn first days of life is related with the present condition of the patient diagnosed with endometriosis/adenomyosis. According to our prospective study the risk factor of NUB is gestational age and genetic predisposition for the occurrence of NUB is suspected. The incidence of visible NUB in the area of Tbilisi is 2.35% which conforms the literature.

## Introduction

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 significance. 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 (Puttemans P, et al, 2017).

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” (Rogers PA, et al, 2017).

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 (Giudice LC, Kao LC, 2004). Endometriosis can be asymptomatic, but associated symptoms include pelvic pain, dysmenorrhea, dyspareunia, dyschezia, infertility, ovulation pain, chronic fatigue, heavy menstrual bleeding and intestinal complaints (National Guideline Alliance (UK) 2017). Endometriosis is also considered as a risk factor for ovarian cancer, especially clear cell carcinoma (Ovarian Cancer Association Consortium (OCAC)).

The exact prevalence of endometriosis is unknown but estimates range up to 10% of reproductive-age women, to 25 to 45% of women with painful periods (Sacrez R, et al, 1962) and to 70% of women with chronic pelvic pain (Parasar P, et al, 2017) and 50% of women with endometriosis are infertile (Eskenazi B 1997).

In USA endometriosis takes leading position with 7.6 million women in a year and even prevails HIV (1.2million), breast cancer (2.8 million), diabetes Type I (1 million). According WHO 2021 endometriosis affects an estimated 190 million women worldwide. According to the data of the National Center for Disease Control, 873 cases of endometriosis were officially diagnosed in Georgia in 2016. These numbers are growing and in 2021 reach 1,314.

According to World Endometrioses Research Foundation in Germany 17.8 billion euro, in Italy 13.2 billion euro, in UK 14.2 billion euro and 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). In the severe form of endometriosis, despite the surgical treatment, recurrence occurs in 62% of cases. More than 100,000 hysterectomies are performed annually in the US due to endometriosis. 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 (Simoens S, et al, 2012).

## Importance of the research

Although endometriosis is known to be a very common gynecologic problem, many studies report that there can be long delays (8-10 years) between onset of symptoms and the diagnosis of endometriosis (Ballweg ML, 2004). Many women with undiagnosed endometriosis present with pelvic pain symptoms including moderate to severe dysmenorrhea. These women are often empirically treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and combination estrogen-progestin contraceptives in either a cyclic or continuous manner. Since many women with endometriosis will have a reduction in their pelvic pain with NSAID and contraceptive treatment, diagnosis of their endometriosis may be delayed until their disease progresses years after their initial presentation. Diagnostic delay allows endometriotic implants to progress toward the more destructive stages of the disease, with an often irreversible impact on the ovarian reserve. It is important to gently alert these women to the possibility that they have undiagnosed endometriosis as the cause of their pain symptoms or infertility.

The reported delay in the diagnosis of endometriosis is much shorter for women who pre-sent with infertility than for women who present with pelvic pain.

Endometriosis was identified around the turn of the 17th century, by Daniel Shroen (Benagiano G, Brosens I, 2011), but its pathogenesis still remain controversial. Pathogenesis can generally be categorized as those proposing that implants originate from uterine endometrium such as retrograde menstruation (Yovich JL, 2020),

Implantation theory (Vinatier D, et al 2001), Lymphatic spread (Halban J, 1924), Iatrogenic (Cubuk A, et al, 2020) and those proposing that implants arise from tissues other than the uterus transformation of peritoneal cells (Iwanoff N, 1898), Mullerian rests theory (Bouquet De Joliniere J, et al, 2020), Inflammation and immune system dysregulation (Rana N, 1996), Vascular endothelial growth factor (McLaren J., et al, 2000), Genetic and epigenetic theory (Borghese B., et al, 2017). 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 hormones. Progenitor stem cells present in shedding endometrium may have a role in the pathogenesis of early-onset endometriosis through retrograde neonatal uterine bleeding (Ballweg ML, 2004). 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 (OBER WB, BERNSTEIN J, 1955). In consequence neonatal menstruation occurs rarely in preterm babies, increases in those born at term and is a relatively frequent event in postmature infants (Simoens S, et al, 2012). Also, regurgitation of endometrial sheddings into the peritoneal cavity is likely to be favored by a functionally blocked cervical canal by thick endocervical mucus. 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 years. Then, during adolescence ectopic endometrial mesenchymal stem cells are presumably activated in response to estrogen actions on niche cells, leading to formation of endometriosis (Bianchi P, et al, 2017).



## Study Objective:

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

If we confirm that NUB is a 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.

## Research tasks:

- Study of the prevalence of uterine bleeding in the population of female newborns in Tbilisi, Georgia
  - Study of the risk factors of neonatal uterine bleeding
  - Study of genetic predisposition to uterine bleeding in newborns
  - Reproductive, antenatal and perinatal anamnesis study in women whose newborns had the phenomenon of uterine bleeding
  - Reproductive, antenatal and perinatal anamnesis study in women whose newborns did not show the phenomenon of uterine bleeding
  - Studying the phenomenon of uterine bleeding in the anamnesis in the group of patients who were histomorphological confirmed to have endometriosis after surgical treatment

- Studying the phenomenon of uterine bleeding in the anamnesis in the group of patients who were histomorphological not confirmed to have endometriosis after surgical treatment
- Comparative analysis of the results of research groups

## Research hypothesis

Neonatal uterine bleeding is a precursor of adult endometriosis.

## Scientific novelty of the work

- For the first time, a study was conducted in the Georgian population to determine the correlation between neonatal uterine bleeding and endometriosis in women of reproductive age.
- A survey was conducted for the first time in the Georgian population to determine the prevalence of neonatal uterine bleeding
- Genetic predisposition to neonatal uterine bleeding was established, which was detected in 55.6% of cases ( $p < 0.0001$ )

## The practical value of the work

- As part of the research, neonatologists and midwives received special training, who were provided with relevant information about the importance of uterine bleeding in newborns
- Increased awareness of neonatal uterine bleeding among obstetricians, neonatologists, midwives and patients
- Prepared and printed several thousand information leaflets on neonatal uterine bleeding to be given to patients

## Literature review

First data about neonatal uterine bleeding has been known since the 16th century (Bourgeois, L, 1617). In the 18th century, the publications of the German Catholic priest Albertus Magnus appeared in Western literature, where he described cases of bloody discharge from the womb in newborn girls. In the 19th century, Cullington collected old publications and published a paper on the first reports of the NUB (Cullingworth, C.J, 1876).

The first detailed description of the case of neonatal uterine bleeding in the context in which we consider it today was published in 1822 by Carus (Carus, C.G, 1822).

NUB came again under our attention in the 20th century, after studies reported NUB as one of the pathogenic mechanisms of early-onset endometriosis.

It is proven that the endometrium of a newborn can show

a decidual response, which is a prerequisite for menstruation. Regurgitation of small fragments of the endometrium into the peritoneal cavity is due to the fact that the cervical canal of a mature newborn is functionally blocked by secreted mucus.

Based on the literature, we can assume that visible bleeding from the neonatal uterus occurs in 3-5% of cases, and occult bleeding in 25-60% (Maria C L, 2017). In the case of occult bleeding, it is suggested that the reason of bleeding is not due to fluctuation of mothers' hormones. Prior to the article published in the Journal of Pediatric and Adolescent Gynecology, mothers of newborns with visible uterine bleeding had dramatically increased levels of estrogens, follicle stimulating and luteinizing hormones and decrease progesterone levels, compared to mothers of newborns who had occult uterine bleeding.

Why not all patients develop endometriosis despite retrograde menstruation is a subject of investigation.

There are documented and confirmed cases of endometriosis in premenarcheal girls. In this case, the pathogenesis of endometriosis is different from the retrograde theory proposed by Sampson in 1927.

There are studies in the literature that describe the relationship between neonatal uterine bleeding and feto-maternal conditions: low birth weight, preterm and post term birth, preeclampsia, and endometriosis (Brosens I, et al, 2015).

In 2016, a publication by Ivo Brosen, Giuseppe Benagiano and other authors was published, where NUB is considered as a

phenomenon expressing fetal distress (Brosens I, et al, 2016), They propose maternity hospitals to systematic registration of neonatal menstruation. In the same publication, they emphasize that endometriosis developed at a young age differs from endometriosis in adults in the severity of the course and is characterized by strongly expressed angiogenesis and ovarian endometrioma formation. A contributing factor to all this may be retrograde menstruation during the newborn period.

Since 2017, publications have been published describing the role of endometrial stem cells in the pathogenesis of early-onset endometriosis. Progenitor stem cells present in shedding endometrium through retrograde neonatal uterine bleeding remain on the peritoneum and are activated during puberty under the influence of estrogens. As a result, endometriosis develops (Maria C L, 2017).

2020 Stefan Gordts and others published a paper that identified gestational age as a risk factor for NUB (Gordts, S, et al, 2020). According to the conducted research, NUB was observed in 0.78% of cases in premature newborns, and in 9.10% of post term newborns. The difference was statistically significant.

In 2022, a retrospective cohort study (Ogawa K, et al, 2022) was published, in which 807 female newborns born in 2013-2017 participated. Out of 807 newborns, only 25 were diagnosed with NUB, which was 3.1%. Risk factors of NUB were also identified: gestational age and mother's age. The longer the gestational age (>39-40 weeks) and the younger the mother, the more cases of NUB were observed. These data were statistically significant.

## 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.

### Patients:

#### 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 1<sup>st</sup> 2016 until October 1<sup>st</sup> 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 10<sup>th</sup> 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.

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, dyspareunia, 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, dyspareunia, 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 (control group), 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:

1. St. George's Med School, Nicosia University and Aretaeio Hospital (Cyprus)

2. LIFE Expert Centre, Service de Gynécologie-Obstétrique CHR de la Citadelle and Ziekenhuis Oost-Limburg a.v. (Belgium)

3. 1st Dept Obstetrics and Gynecology Aristotle University of Thessaloniki (Greece)

4. University of Federico II, S.I.S.Me.R. srl (Italy)

5. IVI Valencia (Spain)

6. Maribor University Hospital (Slovenia)

7. Chinese University of Hong Kong (China)

8. Hôpital NATECIA and Chirurgie Gynécologique (France)

9. University Hospital of Obstetrics and Gynecology Elena Doamna (Romania)

10. Reproductive Clinic of Zurab Sabakhtarashvili (Georgia)

11. Malinov Clinic (Bulgaria)

It is registered in ISRTN, reference number: ISRCTN60023255.

Ethical issues: Patients included in the study were fully informed about the purpose of the survey and their use. The questionnaire was filled only after informed consent. The patient could refuse to participate in the survey and use the data in the study at any time without any penalty. Confidentiality of the data is protected and used only within the scope of the study. Since the study involved only a survey based on a structured questionnaire, the patients involved in the study did not receive even minimal potential harm within the scope of the study. The research was conducted without any bias or discrimination, the selection of participants was based on objective criteria only. Participants had the opportunity to ask any questions about the study. Consent is confirmed by the signatures of the independent local ethical commission of the clinics involved in the study.

#### Main outcomes:

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 uterine bleeding. Only 141/6000 neonates 2.35% were diagnosed with visible NUB (Illustration 1).

### Prevalence of NUB in Tbilisi Area from 6000 randomly selected mothers

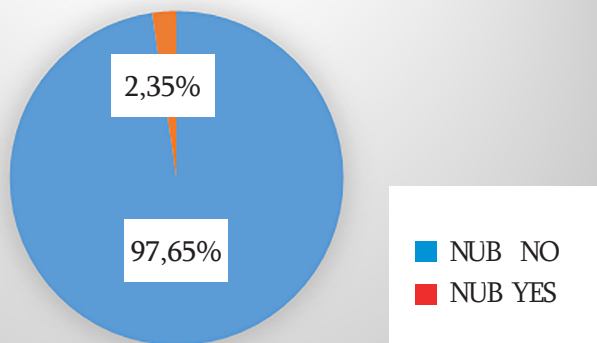


Illustration 1

Parity and number of children were higher in the control group-neonates born without uterine bleeding ( $P<0.001$ ). Mother's polycystic ovarian syndrome cases were higher in "neonatal uterine bleeding yes" group. The prevalence of endometriosis in women who experience painful periods is recognized in 45-70%. According to our prospective study 66.4% of mothers of neonates with uterine bleeding had dysmenorrhea ( $P<0.000$ ). Based on this theory we can suggest that mothers of neonates with uterine bleeding have a statistically significant increased risk for having endometriosis. All differences were statistically significant.

The prevalence of NUB varies considerably between the 2nd and the 7th day postpartum, but peak frequency is on 3 and 4 days (Illustration 6). It lasted 1-4 days and did not need any medical intervention.

In addition neonatal uterine bleeding occurred in 0.7% of preterm, in 88.6% at term, and in 10.7% of post-term female newborns. 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 newborns (Illustration 2).

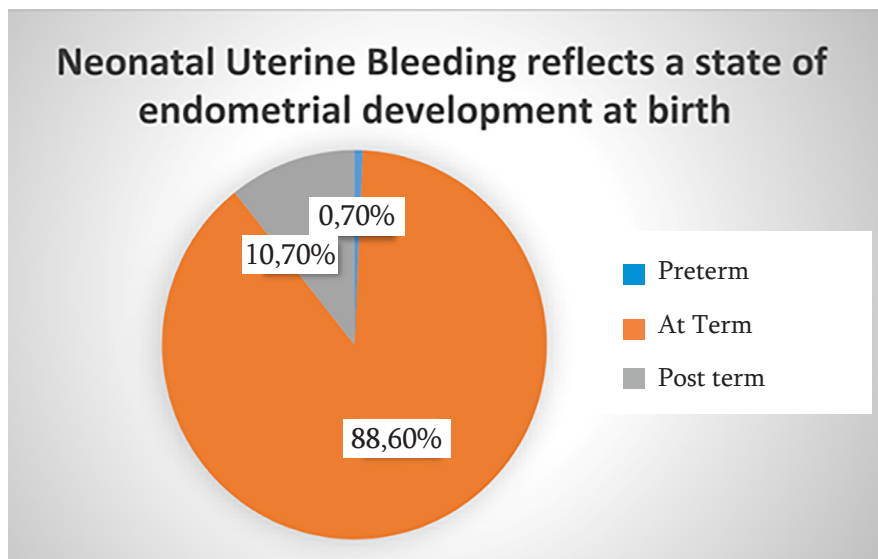


Illustration 2

The pathological course of pregnancy (gestational hypertension, preeclampsia, risk of premature birth, fetal growth retardation, gestational diabetes, hypothyroidism, obesity, pyelonephritis) was statistically significantly higher in the group «neonatal uterine bleeding yes» ( $P < 0.009$ ). The number of caesarean sections was statistically significantly higher in the group «Neonatal uterine bleeding No» ( $P < 0.022$ ).

There was no statistically significant difference between the duration of labor (<12 hours and >12 hours). No statistically significant differences between variables: demography, smoking, alcohol, BMI, mother's age. The number of births and children was statistically significantly higher in the control group: «neonatal uterine bleeding no» ( $P < 0.001$ ).

According to our retrospective study out of the 500 patients with endometriosis 9 had NUB 1.8% as reported by their mothers (Illustration 3). While out of the 350 patients without endometriosis only 1 had NUB 0.28% ( $p < 0.044$ ) (Illustration 4) .

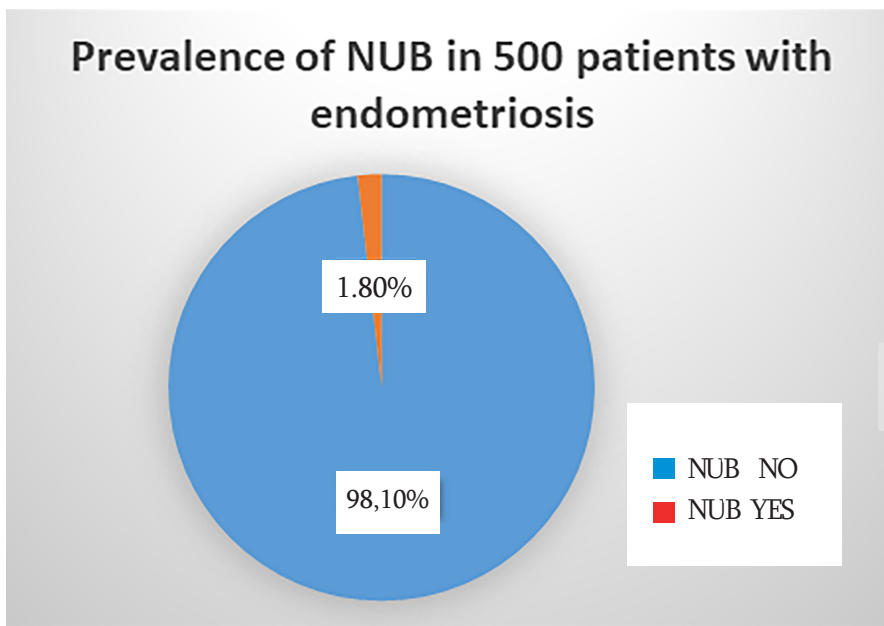


Illustration 3

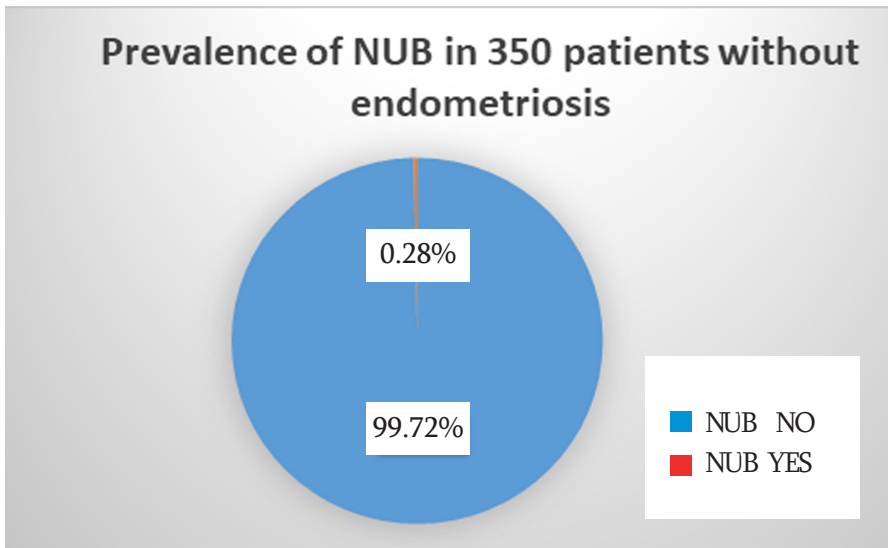


Illustration 4

The number of pregnancies ( $P < 0.006$ ) and births ( $P < 0.007$ ) is statistically significantly higher in the control group. Dysmenorrhea ( $P < 0.000$ ), dyspareunia ( $P < 0.000$ ), dysuria ( $P < 0.004$ ) and dyschezia ( $P < 0.001$ ) were statistically significantly higher in the group of endometriosis patients.

It is well established that pathogenesis of endometriosis combines genetic factor. Familial tendency of endometriosis is detected in patients' first-degree relatives. 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 ( $p < 0.0001$ ) (Illustration 5).

# Patients with Endometriosis and NUB themselves delivered babies with NUB

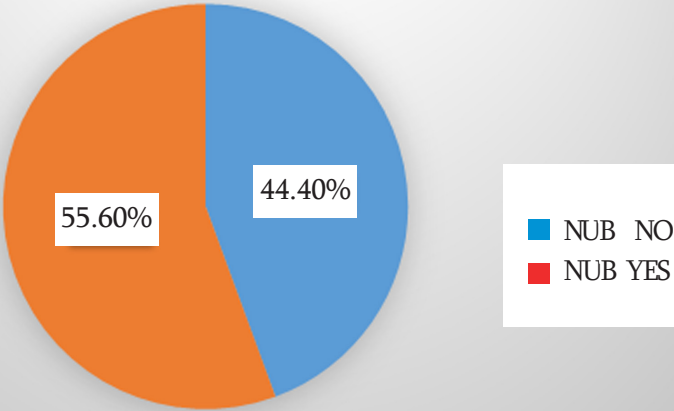


Illustration 5

## NUB Exposure by days

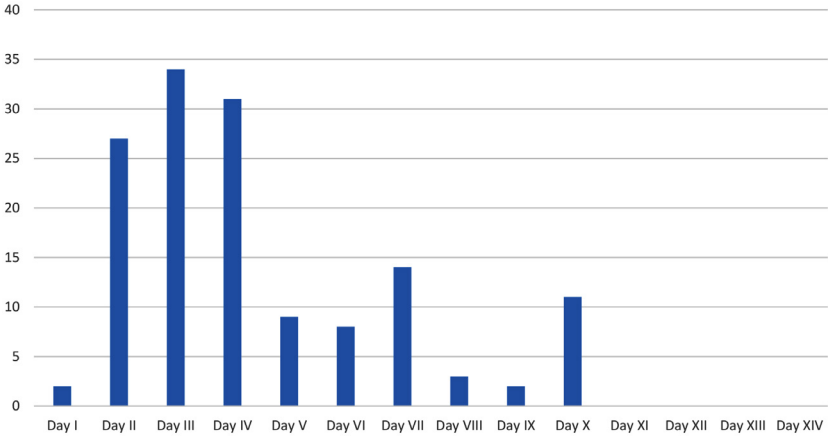


Illustration 6

## Conclusions:

- Vaginal bleeding during newborn first days of life is related with the present condition of the patient diagnosed with endometriosis/adenomyosis
- The incidence of visible NUB in the area of Tbilisi is 2.35%
- Gestational age is a risk factor for neonatal uterine bleeding
- Neonatal uterine bleeding may indicate fetal distress, as its number is statistically significantly higher in newborns whose mothers had an abnormal course of pregnancy
- Neonatal uterine bleeding usually does not need any medical intervention

## Recommendations

- Mothers of newborns with uterine bleeding should be given appropriate information about endometriosis and related reproductive potential
- We encourage the systematic registration of neonatal uterine bleeding in maternity services. Only systematic recording of the presence or absence of neonatal uterine bleeding will allow the approval of our hypothesis.



## Bibliography

Bibliography includes 178 sources

List of scientific works on the topic of thesis:

- Lela Tandashvili, Arsen Gvenetadze, Vasilios Tanos: „Neonatal Uterine Bleeding as a precursor in adult endometriosis” (18 months of experience); Translational and Clinical Medicine-Georgian Medical Journal, Vol 4, No2 (2019);
- Lela Tandashvili, Arsen Gvenetadze, Lela Iremadze, Vasilios Tanos: „Neonatal Uterine Bleeding as a precursor to endometriosis in adulthood”; African Journal of Reproductive Health August 2022; 26 (8):88;
- Lela Tandashvili, Arsen Gvenetadze, Vasilios Tanos: „Neonatal Uterine Bleeding as a precursor in adult endometriosis”; Experimental and Clinical MEDICINE 2018, N5;

## Research reports

- TSU Faculty of Medicine Colloquiums (2017; 2023)
- 27-th European Society for Gynecological Endoscopy, 2018 Vienna, Austria.

Poster-presentation: „Neonatal Uterine Bleeding as a precursor in adult endometriosis” (18 months of experience)

- 2018 International Medical School-Conference, Bakuriani, Georgia

Oral presentation: „Modern aspects in treatment of ovarian endometrioma”

- 2018 conference dedicated to the 100th anniversary of TSU - Human reproduction and assisted reproductive technologies; Oral presentation: «Neonatal uterine bleeding as a precursor to adult endometriosis, (18 months of experience)»

- 19-th World Congress on Human Reproduction 2023, Venice, Italy

Oral presentation: „Neonatal Uterine Bleeding as a precursor of adult endometriosis”