Neonatal Uterine Bleedings: An Ignored Sign but a Possible Cause of Early-Onset Endometriosis – A Systematic Review

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Keywords

Neonatal uterine bleedings · Endometriosis · Systematic review

Abstract

Objective: Based on the hypothesis that neonatal uterine bleedings (NUB), occurring mostly in the first week after birth, could represent a pathogenetic mechanism for early-onset endometriosis, this systematic review (SR) was undertaken to evaluate the prevalence and screening strategies used to assess and quantify NUB. **Design:** Both a SR and a sample literature search in PubMed and Embase were conducted to gather information on NUB prevalence and screening techniques. This was performed by an information specialist. Only full-text articles regarding the assessment of NUB in neonates in the first 2 weeks after birth were included. No limit on language or publication data was used. **Materials and Methods:** The SR was registered in PROSPERO (CRD42019138121). Data was first assessed for eligibility on title and abstract by 2 blinded review authors. Any disagreements were discussed with a third reviewer if necessary. Subsequently, full-text articles were read and assessed for qual-

ity using the Cochrane Collaboration Handbook. **Results:** Out of 1,988 articles in the systematic search, 10 relevant articles were selected, of which 8 were identified through the systematic search and 2 were found through other sources. The sample search of 4,445 articles did not bring up relevant articles. Results were not comparable due to the heterogeneity of screening techniques, although data showed consensus. The prevalence of visible bleeding ranged from 3.3 to 53.8% and the prevalence of occult bleeding from 25.4 to 96.7%. The occurrence was the highest between the 3rd and 7th day postpartum (PP) and the bleeding lasted for 3–4 days on average. Various screening techniques for detecting NUB were found in the literature, including the use of hemoglobin detection devices (such as Hemastix) in the vaginal vestibulum, comparison of diapers with stains of known volume, colposcopy, and ultrasonography. **Conclusion:** The reported prevalence of NUB varies considerably, with a consistent occurrence between the 3rd and the 7th day PP. Literature to assess NUB is dated. The techniques are poorly described and heterogeneous. Future research should focus on prospective cohort studies in order to attempt to correlate NUB cases to (early-onset) endometriosis.

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Introduction

Early-Onset Endometriosis

Endometriosis is a benign, estrogen-dependent gynecological disease, affecting approximately 6–10% of the female population during the fertile life phase [1]. Symptoms include severe pelvic pain and/or infertility, often leading to a decrease in reported health-related quality of life and an average loss of 10.8 working hours per week, due to ineffectiveness and work absenteeism [2].

Unfortunately, for endometriosis the delay from the onset of symptoms to the diagnosis varies in European countries between 4 and 10 years [2, 3]. In the Netherlands, the median delay has been calculated as 7.4 years [4]. A Brazilian cohort study identified young age at onset of symptoms and pelvic pain as presenting symptom as factors negatively affecting diagnostic delay, since symptoms are often referred to as physiological menstrual complaints at younger age [5].

In recent years, evidence has been accumulating that the condition may affect adolescent and even pre- or perimenarcheal girls. This variant has been coined “early-onset endometriosis” (EOE) [6].

The phenomenon of neonatal bleeding is often observed in girls suffering from uterine obstructive disorders. Evidence for this situation was first discovered in a post-mortem examination of an infant suffering from McKusik-Kaufman syndrome, with an intact vaginal septum and a hemorrhagic endometrial reflux [7]. Nevertheless, Marsh and Laufer [8] discovered endometriotic lesions in 5 premenarcheal girls who presented with chronic pelvic pain, with no evidence of obstructive anomaly.

Over the years, different theories have been proposed to explain the pathogenesis of EOE, and they can be divided into 2 main hypotheses: the in-situ theory and the transplantation theory. The in-situ theory describes a local origin for endometriosis from (coelomic) metaplasia, embryological remnants or Müllerianosis. The transplantation theory involves the shedding of endometriotic cells through retrograde flux through the Fallopian tubes, leading to an implantation in the peritoneal cavity [9]. However, other factors, such as altered cellular immunity, hematogenous, lymphatic or iatrogenic metastasis, genetic and environmental factors could contribute as well [1]. Although recently novel theories on the origin of endometriosis have been postulated focusing on the deregulation of genes causing aberrant placement of stem cells [10], the most widely accepted pathogenic mechanism for (early-onset) endometriosis is that of retrograde menstruation (the transplantation theory) first proposed by

Sampson [11]. The problem is that Sampson’s theory cannot explain cases of pre- and peri-menarcheal endometriosis, and this is why neonatal uterine bleedings (NUB) have been proposed as a possible source of EOE [12].

Neonatal Uterine Bleedings

There is ample evidence in the literature that menstrual-like bleedings do occur in neonates in the first 2 weeks after birth. In recent years, this condition has been considered “perfectly normal” and due to the massive drop in the level of steroid hormones circulating in the fetus that follows the detachment of the placenta [13]. However, this rapid decrease in steroid hormones occurs in all female neonates, whereas a true NUB is present in only a small fraction of them.

Brosens and Benagiano [14] have hypothesized that, due to the presence of a cervical mucus plug in neonates, NUB could be accompanied by a retrograde flux of endometrial cells, stromal fibroblasts, and possibly also mesenchymal stem/progenitor cells. These may lay dormant until the time of thelarche, when rising estrogen levels may reactivate them and, through a process of neo-angiogenesis, produce early endometriotic lesions [12].

Knowledge Gap

Over the last decades, the phenomenon of NUB has been totally neglected, as shown by the lack of scientific publications dealing with this subject from 1987 to 2013. For this reason, there is a need to explore whether NUB can represent a true cause of EOE, and to achieve this goal, a systematic registration of the presence and prevalence of NUB should be introduced.

Aim of This Systematic Review

The prevalence of NUB is used as primary outcome in this systematic review. Second outcomes include duration of bleeding, peak frequency, quantification (volume of bleeding), and the techniques that could best be used in the assessment and quantification of NUB. This systematic review is registered in PROSPERO (CRD42019138121). We used the methodology as described in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [15].

Methods

Eligibility Criteria

Inclusion criteria are derived from the main research question and comprise: neonates with or without NUB in the first 2 weeks after birth, screening techniques used for the assessment of preva-

Fig. 1. Flow diagram. For the search strategy, a flow diagram was used. It was conducted according to the PRISMA guidelines [15].

lence and quantification of NUB, both visible and occult, assessed by various screening tests, or assessment of decidualization of the neonatal endometrium. Inclusion criteria relate also to other causes of NUB besides the “physiologic” withdrawal bleeding, such as syndromes and diseases. When the data were available, a distinction was made between the prevalence of visible and occult NUB and frequency in neonates born premature, postmature, small-for-gestational-age, of low birth weight, or born after pregnancy complicated by pre-eclampsia or feto-maternal blood group incompatibility.

Exclusion criteria consisted of articles describing only screening techniques for adolescents, since there are different ways in the approach, examination and evaluation of newborn and adolescent females, or articles of which full text was not available.

Information Sources and Literature Search Methods

Systematic searches were performed in the databases PubMed and Embase.com from inception up to the 20th of March 2020 (by I.H. and J.C.F.K.), as represented in the Appendix, available through the online supplementary material (see www.karger.com/doi/10.1159/000512663). The search query included indexed terms and free-text words for “newborn” or “neonate” or “mini-puberty” and “bleeding” or “hemorrhage” and “uterus.” We limited the search to major thesaurus terms and free text words in title or author keywords to limit the number of references retrieved.

We excluded animal studies. No limit on language or publication date was used.

In order to prevent that relevant articles would be left out, a broad sample search was conducted in PubMed alongside the systematic search. The sample intervals were dichotomized in groups of 80 articles per 5 years. If the groups contained articles relevant to the search, 2 review authors (J.D. and I.H.) would deliberate whether it was useful to go over all articles in the sample search. None of the articles screened in the sample search were relevant. Another 2 studies were found using reference lists of background articles. Figure 1 presents the search strategy in a flow diagram.

Data Extraction

All studies were blindly selected by 2 review authors (J.D. and I.H.) by title and/or abstract for relevance. We made use of the Rayyan selection tool (rayyan.qcri.org). Full texts of all relevant articles were retrieved and assessed for eligibility.

Data Synthesis

A descriptive, narrative synthesis was carried out in 4 steps by 2 review authors (J.D. and I.H.) using the following protocol:

1. Both reviewers independently developed a description of each study
2. Both reviewers independently considered the relationships within and between studies and created a summary for each

Table 1. Characteristics of the reviewed studies

Source	Study type	Participants				Time of registration	Screening method
		number	preterm	at term	postterm		
Ober and Bernstein [16], 1955	Autopsy cohort study	169	56	113	–	32 weeks GA to 13th day PP	PM histologic examination uterus
Andreoli and Simonetta [19], 1960	Prospective cohort study	30	–	30	–	3rd to 8th day PP	Hemoglobin detection test
Sacrez et al. [24], 1962	Retrospective cohort study	448	331	117	–	Unknown	Unknown
Levy et al. [23], 1964	Retrospective cohort study	Control: 1,207 Risk: 856	584 55	272 –		1st to 7th day PP	Unknown
Pryse-Davies and Dewhurst [18], 1971	Autopsy cohort study	55	55	–	–	Unknown	PM histologic examination uterus
Kaiser and Grassel [20], 1974	Prospective cohort study	75	–	–	–	3rd to 14th day PP	Hemoglobin detection test and spreading labia
		153	–	–	–	3rd to 7th day PP	
Huber [21], 1976	Prospective cohort study	350	–	–	–	1st to 8th day PP	Hemoglobin detection test, spreading labia, vaginal smears, histologic examination
Berić et al. [22], 1985	Retrospective cohort study	2,477	126	2,241	110	1st to 7th day PP	Comparing diaper stains
Nussbaum et al. [25], 1986	Prospective cohort study	31	–	31	–	1st to 7th day PP	Real-time ultrasonography
Söderström et al. [17], 2016	Prospective cohort study	9	–	–	–	5th to 17th day PP	Genital examination and colposcopy

GA, gestational age; PP, postpartum; PM, post-mortem.

exposure and outcome pairing as well as the overarching exposure and outcome pairings. These summaries considered the following:

- a. Confidence in the cumulative evidence
- b. Temporal relationship between exposure and outcome
- c. Exposure-response relationship
- d. Plausibility with reference to the existing literature
- e. Common flaws or gaps needed to be addressed in the future
3. In order to critique the robustness of these syntheses, both reviewers consulted each other. A third reviewer (V.M.) resolved disagreements
4. Reviewers consolidated observations and conclusions into a table of all included studies and a qualitative narrative synthesis

Outcome Reporting

The primary outcome is prevalence of NUB, reported as a percentage. Secondary outcomes include duration of bleeding, reported in days, including the peak frequency day, and quantity of blood loss, reported in volume (mL). The applied screening methods used to detect NUB are reported descriptively. Numerical data are presented as summary statistics.

Results

Characteristics of Included Studies

A total number of 10 articles were selected, of which 8 were recognized via database searching and 2 via other sources. The oldest article included was published in 1955 by Ober and Bernstein [16], and the most recent article was the one by Söderström et al. [17]. All included articles consisted of prospective or retrospective cohort studies. Since most of the articles were written in other languages (German, Spanish, Serbo-Croatian, and Italian), they had to be translated into English first. Characteristics specific for the research question:

- **Participants.** All articles included in the review varied in the number of subjects they included, ranging from 9 to 2,477 neonates. Not all articles made distinctions between the gestational age of the neonates. All characteristics of study participants are listed in Table 1.

Table 2. An overview on the prevalence of NUB (occult and/or visible), including prevalence of NUB for different subgroups, and the quantity of NUB

Source	Prevalence of NUB		Quantity of NUB in percentage or volume	
	visible, %	occult, %		
Ober and Bernstein [16], 1955	3.0	–		
Andreoli and Simonetta [19], 1960	33.3	96.7	Sparse Mild Distinct	10.0% 26.7% 60.0%
Sacrez et al. [24], 1962				
Preterm	6.9	–		
At-term	18.8			
HD/PE	61.5			
Levy et al. [23], 1964				
Control	4.7	–		
At term + postterm	13.9			
Preterm (+SGA)	6.2			
FMBI	14.3			
PE	14.5			
Postterm	53.8			
Pryse-Davies and Dewhurst [18], 1971	3.6			
Kaiser and Grässel [20], 1974	5.3	61.3	Visible Occult	3.0–5.0% 25.0–38.0%
Huber [21], 1976	3.3	25.4		
Berić et al. [22], 1985	3.9	–	Mean	2.4 mL
Preterm	0.8			3.0 mL
At-term	3.8			2.2 mL
Postterm	9.1			3.0 mL
Nussbaum et al. [25], 1986	–	23.0		
HD, hypertensive disorders; PE, pre-eclampsia; SGA, small for gestational age; FMBI, feto-maternal blood group incompatibility.				

- *Primary outcome.* All articles provided data on prevalence of NUB (in %), but not all made the distinction between occult and visible NUB. Prevalence of NUB is outlined in Table 2.
- *Secondary outcomes.* Registration times varied between 32 weeks gestational age until the 14th day postpartum (PP). Some articles reported onset and duration of bleeding (in days PP), described in Figures 2 and 3, whereas some reported a peak frequency of bleeding (in days PP), and some quantified bleeding using different techniques (in volume or by scoring the amount of bleeding using a –/+ score system) and are described in Table 2.
- *Screening methods.* Screening for NUB was conducted using various methods which are described for each study separately in Table 1.

Outcomes

Post-Mortem Cohort Studies

The first study included in the analysis, by Ober and Bernstein [16], consists of a postmortem histologic analysis of the endometria of 169 neonates. In this study, the endometrium was classified as “proliferative,” “secretory,” and “decidualized.” In 8 cases (5%), the endometrial layer showed full progesterational changes, and in 5 cases (3%), menstrual-like changes were reported. Ober and Bernstein [16] attributed the presence of clotted blood in the uterine cavity in these cases to hormonal changes in

Fig. 2. Onset time of NUB. Three studies reported on the onset time of NUB. The percentage of neonates showing NUB was compared to the day of onset of NUB. The results on onset time of Lévy et al. [23] were left out of this graph because they only gave a range wherein bleeding occurred, from day 3 to day 6.

Fig. 3. Duration of NUB. Only 2 studies provided a detailed and complete overview on the duration of NUB, presented as a percentage of neonates showing NUB. The results on duration of Berić et al. [22] and Lévy et al. [23] were left out of this graph because they only gave an average duration of bleeding, being 2 days on average for both studies.

the neonate. The study described 61 cases of hyperemia and petechial hemorrhages among the neonates with both proliferative and secretory endometria. However, these findings were considered to be the result of perinatal asphyxia, stasis of the body post-mortem or as an effect of stasis ante-mortem. Thus, the overall prevalence of visible NUB was 3.0%.

A similar post-mortem analysis of neonatal uteri was conducted by Pryse-Davies and Dewhurst [18], who observed histologic changes in 55 neonatal uteri. In 31 cases (56.3%), secretory changes were present, resembling the adult endometria in the menstrual cycle. These were described as “vacuolation.” Nonetheless, full shedding of the endometrium, accompanied by bleeding into the uterine cavity was present in only 2 cases (3.6%). Because both studies [16, 18] were postmortem histologic examinations of neonatal uteruses, information on the duration of bleeding and peak frequency, as well as quantity of bleeding, is lacking.

Prospective Cohort Studies

Three studies examined NUB using a hemoglobin or color test. Andreoli and Simonetta [19] designed their own cotton sterile pad, soaked in 50 mL glacial acetic acid, benzene, and 15 mL oxygen peroxide, so that a color change to blue would appear when hemoglobin was present in the vaginal vestibulum of 30 neonates. They reported a prevalence of occult bleeding in 29 cases (96.7%), and a prevalence of visible bleeding in 10 cases (33.3%). They used a quantification score (– absence of discoloration, + sparse stains of discoloration, ++ mild stains of discoloration, +++ distinct discoloration) and observed that NUB was sparse in 3 cases (10%), mild in 8 cases (26.7%), and distinct in 18 cases (60%). They reported the highest frequency of bleeding between the 5th and the 6th day. The bleedings lasted for 3 or 4 days on average.

Kaiser and Grässel [20] made use of Hemastix (based on peroxide-o-toluidine-reaction) to detect hemoglobin in the neonatal vaginal vestibulum. With this procedure, they examined 2 groups of neonates, one group consisting of 75 neonates who were followed from the 3rd day after birth until the 14th day, and one group consisting of 153 neonates that were only analyzed from the 3rd until the 7th day after birth. In the first group, they found a prevalence of visible bleeding in 4 cases (4.72%) and a prevalence of occult bleeding in 50 cases (61.3%). The frequency of bleeding was highest on the 7th and 8th day after birth (41%). They quantified NUB by assessing the intensity of the discoloration (sparse: light blue, positive: blue, strongly positive: dark blue) and found the peak fre-

quency between the 6th and 9th day, ranging from 25 to 38%. Mean duration of NUB was 3.2 days.

The same Hemastix method was used in a larger study by Huber [21], consisting of 350 neonates. In this study, a prevalence of occult bleeding was reported in 25.4% and a prevalence of visible bleeding in 3.3%. NUB was most frequent on day 5. Huber also analyzed 108 vaginal smears in these neonates and found erythrocytes in only 2 cases. Histologic examination of the neonatal uteri did not show a full menstrual-like transformation of the endometrium. However, it did reveal hyperemia and erythrocytes in the uterine cavity in 20% of the cases.

A more recent study by Söderström et al. [17] investigated the causes of vaginal bleeding in premenarcheal girls. Among their subjects, 10 neonates were included, in whom the NUB was found to be the cause of the vaginal blood loss in 9 cases; for 1 neonate, the etiology of bleeding remained unknown. The bleeding lasted no longer than a week in all but one case, in which the bleeding ceased within 24 h. Because the neonates were preselected due to their vaginal bleeding, this study does not provide information on the prevalence of NUB.

Retrospective Cohort Studies

The largest study of this type, by Berić et al. [22] included 2,477 neonates. They analyzed the volume of the blood stains in the diapers of the neonates by comparing these with test diapers. These test diapers contained stains of colored fluid, the volume of which was known. By comparing the neonate’s diapers and the test diapers, they could quantify the blood stains. Berić et al. [22] reported a prevalence of visible bleeding in 3.87% of the cases. Among postmature neonates, a significantly higher prevalence of bleeding was found (9.09%, $p < 0.05$). Furthermore, they reported a mean time of onset of NUB of 4.3 days, a mean duration of bleeding of 2.3 days, and a mean amount of blood loss of 2.4 mL.

A large retrospective case-control study by Lévy et al. [23] reported on the occurrence of visible bleeding in neonates in the first week after birth. They divided their subjects into a control group of 1,207 neonates and a risk-group, consisting of 856 neonates. Neonates in the control group were born healthy and admitted to the neonatal unit without medical indication. In this group, a prevalence of visible NUB of 4.7% was found. Although the neonates were classified as healthy, in 7 cases pregnancy had been complicated by preeclampsia (PE), defined according to the following 3 characteristics: arterial hypertension, albuminuria, edema, leading to a preeclamptic crisis. Out of these 7 cases, 2 neonates had NUB.

The neonates in the risk group were hospitalized due to pregnancy-related complications, such as pre-eclampsia (divided in diagnosed PE or possible PE if only 2 of the above-mentioned symptoms were present), prematurity or postmaturity. In this group, the prevalence of NUB was increased, when compared to the control group, for at term combined with postterm neonates (13.9%). Unfortunately, when comparing prevalence with the control group, researchers did not make a distinction between neonates at term and postterm. Prevalence of NUB was also increased for prematurely born infants (6.16%), though a distinction between “true prematurity” and “small-for-gestational-age” neonates was not made. Additionally, prevalence of NUB was increased in the presence of fetomaternal blood group incompatibility (14.3%). Prevalence of NUB significantly increased for neonates born from mothers with PE (41.5%, $p < 0.001$); for the mild form of PE, prevalence was 32%, and it rose to 47.5% in the severe form. Finally, in postmature neonates a significantly higher prevalence of 53.8% ($p < 0.001$) was found. They reported an onset of NUB most frequently seen between the 3rd and 6th day PP, with a mean duration of 3 days.

Another study by Sacrez et al. [24] explored the appearance of NUB after pregnancies complicated by PE. The first group of subjects consisted of 331 preterm neonates, of which 23 (6.9%) had macroscopically visible NUB. Of these 23 neonates, 11 (47.8%) were born after a pregnancy complicated by PE and 3 (13.0%) after a pregnancy complicated by “signs of PE.” The second group of subjects consisted of 117 at-term neonates, of whom 22 (18.8%) had macroscopically visible NUB. Of these neonates, 11 (9.4%) were born after pregnancy complicated by PE, and in this group, 6 (54.4%) had NUB. The 2 neonates born from a mother with “signs of PE” both had NUB (100%), providing an overall prevalence of NUB in hypertensive disorders of 61.5% (8/13). They compared these results to the onset of neonatal icterus, to investigate whether what they called a “hormonal imbalance” could be an explanation of the bleedings. However, they did not find a correlation. On the contrary, the prevalence of icterus was lower in neonates born after pregnancies complicated by PE. At the same time, the prevalence of NUB was higher in neonates born after pregnancies complicated by PE, when compared to neonates born after uncomplicated pregnancies. Unfortunately, information on duration of NUB and the registration method was not included.

Finally, Nussbaum et al. [25] used ultrasonography to evaluate the neonatal uterus at birth. They observed in 7

out of 31 neonates a small amount of fluid in the uterine cavity. They were not able to determine whether this fluid consisted of mucous secretions or blood, although it was concluded that in either event, its presence was related to maternal hormonal changes.

Discussion

The literature describing the phenomenon of NUB can be dated back to 1822 [26], and NUB has been described in detail by various authors during the second half of the 19th century and up to 2016. In an early review of the subject published in 1876, Cullingworth [27] mentions a series of publications dating back to the middle of the 17th century, allegedly mentioning the occurrence of menstruation in the early days of female life; whether they include NUB is unclear.

Prevalence of NUB

The overall prevalence of visible NUB as found in the literature search ranged from 3 to 53.8%, and the prevalence of occult NUB ranged from 23 to 96.7%. Due to the broad ranges, in order to reach meaningful conclusions, the quality of the studies should be taken into account.

Ober and Bernstein [16] mentioned menstrual changes in 5 cases (3%) of at-term neonates. The prevalence found in the other postmortem histological study by Pryse-Davies and Dewhurst [18] was similar (3.6%). They concluded that vacuolation (secretory endometrium), which also accounted for the 2 cases of NUB, increases with maturity and is more frequently seen after 36 weeks of gestation.

The study by Andreoli and Simonetta [19] indicated an extreme rate of 96.7% in the prevalence of occult bleeding. However, the relatively small sample size ($n = 30$) prevents firm conclusions; these results, at variance from all other studies, may have been due to coincidence, especially because the authors did not provide any information on patient selection. At any rate, it is rather interesting that the whole group consisted of full-term, healthy neonates born from an uncomplicated (physiological) pregnancy. In addition, as the exact location of the cotton sterile pad was not reported, positive reactions due to bleedings of the gastro-intestinal or urinary tract (false-positive tests) cannot be ruled out; therefore, the reliability of the high prevalence of occult bleeding as described by Andreoli and Simonetta [19] is questionable.

Interestingly, Huber [21] and Kaiser and Grässel [20] used a similar method for detecting bleedings, the hemo-

globin detection device (Hemastix), but found a much different prevalence of occult NUB (25.4 and 61.3% respectively). It should be stressed that the sample size in Huber's study ($n = 350$) was larger than the sample size in Kaiser and Grassel's study ($n = 75$). Nevertheless, in Kaiser and Grassel's study, which consisted of 2 groups of neonates, researchers calculated prevalence with the results derived from the group consisting of 75 neonates. This group was tested for vaginal bleedings for 14 days PP. Additionally, they tested another group of 153 neonates in the first 7 days PP. If they would have combined these results with the other group of 153 neonates, the prevalence would have been lower (varying from 9 up to 36%), and therefore more similar to Huber's findings (25.4%).

It is important to stress that NUB frequency varied according to several factors. The largest ever investigation, conducted by Berić et al. [22] showed a significantly higher prevalence of visible NUB among post-term neonates (9.09%), and a higher prevalence in postmaturity (53.8%) was found in the study by Lévy et al. [23] as well. Unfortunately, Lévy et al. [23] did not mention what technique was used to assess the presence of bleeding, making any conclusion on the quality of the study problematic. However, the hypothesis that postmaturity seems to positively affect the frequency of NUB seems to have merit. Other interesting findings by Lévy et al. [23] were that neonates with a low birth weight, and neonates born after a complicated pregnancy due to PE or feto-maternal blood group incompatibility seemed to have a higher prevalence of NUB. In this respect, a recent investigation by Wolff et al. [28] (the ENDO-study), who performed laparoscopy/laparotomy or magnetic resonance imaging to diagnose 600 women for endometriosis, as part of the anamnesis, assessed the presence of in utero exposure risk. They found a significantly decreased adjusted odds ratio for preterm birth in the group of subjects that underwent laparoscopy or laparotomy (0.41; 95% CI 0.18–0.94). Such lower prevalence of endometriosis for women with a preterm birth corresponds to findings of Berić et al. [22] of a lower prevalence of NUB (0.79%) in neonates born prematurely. The reason they provided for this low prevalence was that the uterus of preterm neonates is subjected to maternal hormones to a lesser extent than that of at-term neonates. Additionally, Pryse-Davies and Dewhurst [18] concluded that vacuolation (secretory endometrium) increases with maturity and is more frequently seen after 36 weeks of gestation. The theory of "ontogenetic progesterone resistance" could explain differences in prevalence of NUB among neonates [29]. It is believed

that full progesterone response may lead to NUB and therefore could cause (early-onset) endometriosis. It is hypothesized that the endometrium becomes more responsive to progesterone towards the end of pregnancy and therefore the prevalence of NUB would be higher in postmature neonates [30].

Finally, Lévy et al. [23] observed a higher prevalence of NUB among the preterm neonates (6.16%) than in their control population (4.72%). Unfortunately, they defined "preterm neonates" as those with a birth weight inferior to 2,500 g, without distinguishing between neonates born prematurely and those born small-for-gestational-age. This makes interpretation of their findings difficult.

Onset, Duration, and Quantity of NUB

The time of onset of NUB, as derived from the literature, is mostly placed between the 3rd and 4th day after birth and recordings of bleedings after 8 days are sparse. In addition, cases reporting bleeding beyond the first week could be due to pathological events [19, 20]. Berić et al. [22] reported that bleedings beyond 7 days after birth and with a total blood loss of more than 5 mL (described as *metrorrhagia neonatorum prolongata*), could be a sign of vaginal or cervical malignant tumors, or genital tract injuries after delivery. Other authors did not discuss the background or etiology of the amount of bleeding. Since authors did not use the same method and used different volume units, information on the quantity of bleeding remains limited.

Limitations

A search through other sources, cross-referencing, for example, had to be carried out as the systematic search through the available electronic databases was not able to find all the relevant articles. Since most of the included studies were old, data was not registered as strictly as currently is usual and almost none of the articles tested the significance levels. In addition, there was limited information regarding the effect of complications that the mothers encountered before or during the appearance of NUB. Methods applied to assess NUB were heterogeneous. Therefore, the data could not be pooled for this review.

As stated in the introduction, the linking of EOE with NUB is just one of the theories for (early-onset) endometriosis, and further research is necessary to fully clarify the pathogenesis of all variants of the disease. For example, this theory cannot explain the rare cases of endometriotic lesions in males [31], a finding that instead supports the theory of an in situ origin of the endometriotic lesions, coined "coelomic metaplasia" [32].

Conclusion

In conclusion, NUB is not very often visible, with larger studies indicating a prevalence between 3.0 and 5.0%, although occult bleedings occur more frequently, with larger studies indicating a prevalence between 25.4 and 61.3%. The onset of NUB is reported from the 3rd until the 7–8th day after birth; and in the second week after birth, the occurrence is very rare and often due to pathological events. The duration of NUB varies between 3 and 4 days. Techniques found in the literature to assess NUB are heterogeneous.

Future Research Possibilities

The first step in conducting future research find an association between the occurrence of NUB and EOE, would be to set up an epidemiological investigation aimed at determining the prevalence of endometriosis in a cohort of neonatal bleeders in comparison to controls. Such a trial would have to last some 20 years. A separate set of investigations could ascertain the existence of a neonatal retrograde flux and examine the type of cells that are shed into the peritoneal cavity. In this respect, Laganà et al. [9] provided a detailed overview of all chemical alterations that could lead to migration, adhesion, proliferation and induction of angiogenesis of endometrial stem cells, mostly regulated by differences in the extracellular matrix, local production of estrogen and a local inflammatory reaction, and a lesser apoptotic response due to, among others, a lower cytotoxicity levels of macrophages. Unfortunately, this knowledge is based on studies conducted in fertile women, and information on the neonatal situation is lacking.

Nevertheless, these findings support the theory of a transplantation of endometriotic stem cells via retrograde flux, with a possible activation and stimulation of endometriotic cells later on. Under these circumstances, it will be useful to investigate the occurrence of a neonatal retrograde flux and the presence and role of a mucus plug in neonates, which could improve the chance of retrograde bleeding.

Other future research options could be directed at defining the pathologies leading to an increased prevalence of NUB in neonates with risk factors, such postmaturity, or pregnancies complicated by PE, or feto-maternal blood group incompatibility.

Interestingly, Vejnović et al. [33] published an abstract mentioning that they traced a group of women from the 1985 Berić et al. [22] cohort. They managed to identify 20% of the bleeders and only 2.5% of the non-bleeders

and examined them for signs of endometriosis, such as dysmenorrhea, severity of pain, chronic pain, infertility, visibly diagnosed endometriosis through laparotomy or laparoscopy and stage of endometriosis in both groups. In these preliminary results, they found an increased risk of developing endometriosis for the women with NUB in their medical history [33]. However, these data are limited by the very small number of non-bleeders and should therefore be considered with caution until more information is available on the group of non-bleeders.

Due to the lack of up-to-date information on the prevalence of NUB, we advise neonatologists, nurse-midwives, and maternity nurses to systematically register the prevalence of NUB in neonates in the first 2 weeks after birth, utilizing one of the previously stated registration methods. Additionally, we advise to brainstorm with professionals for new (ethically approved) registration methods, finding an opportunity to register a retrograde bleeding in neonates as well.

Statement of Ethics

The paper is exempt from Ethical Committee approval since this systematic review merely includes a literature search, and no study with live subjects has been conducted.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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