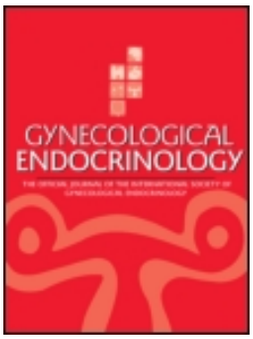

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ENDOMETRIOSIS

Perinatal origin of endometriosis revisited

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Over the years we have become involved in the history of benign reproductive tract disorders, such as adenomyosis and endometriosis and, as a consequence, we have looked at scientific articles published over more than one century ago [1,2]. Unexpectedly, we found that – far from having a purely historical significance – a number of old articles contained information not available in the more recent literature. In particular, an important, but entirely neglected study carried out by Harvard pathologists 60 years ago, detailed the different features of the neonatal endometrium, namely that in 2/3 of the cases, at birth the endometrium is in an indifferent or proliferative phase, with only in a minority of the new-borns showing secretory activity or, even less, decidual or menstrual changes [3]. It seems that in the foetus no glandular development takes place before the 20th week and that signs of secretory activity can be observed starting around the 34th week; then, after birth the endometrium commences to regress and within days it becomes quiescent [4–6]. In view of the high circulating levels of progesterone in foetuses, the conclusion has been reached that at the time of birth there is, in the majority of neonates, a certain degree of progesterone resistance. Acquisition of progesterone responsiveness appears to be dependent on endometrial maturation and relative immaturity may persist in a majority of girls until the menarche and early adolescence [7,8].

On the basis of these and other early observations, we outlined a new theory whereby in foetuses endometrial cells and stroma may be retrogradely disseminated in the pelvis around the time of birth, thanks to the presence in a one-third of new-borns of visible or occult uterine bleeding (NUB) [7]. As our search continued for old articles published in different languages on the presence, frequency and characteristics of NUB, we found additional information and were able to publish a full report on the new theory [8]. In this report, we pointed out that in recent years the study of foetal and neonatal endometrium, as well as that of NUB, have been entirely neglected and that available information only comes from articles published between 50 and 30 years ago. Nevertheless, these early studies produced enough data to grant plausibility to our theory.

At this point, with the help of scientists specifically involved in the study of endometrial stem cells, we have been able to publish a third article further defining our hypothesis [9]. In this paper, we pointed out that the discovery of endometrial stem/progenitor cells (eSPC) caused a revisiting of the pathogenesis of early-onset endometriosis; indeed, eSPC have been identified in menstrual blood, making it plausible to suppose they may also be shed during neonatal overt or occult uterine bleeding. We argued that evidence obtained decades ago showed that, not only the neonatal uterus has a large cervix to corpus ratio, but also the late foetal cervical canal may be functionally blocked with mucus, supporting the concept of a retrograde shedding of fragments of neonatal endometrium, possibly containing eSPC.

Our next step has been to try applying the information we gathered to finding a plausible cause for a particularly puzzling phenomenon: premenarcheal and adolescent endometriosis. The presence of this variant, possessing – among others – characteristic subtle lesions with strong neo-angiogenesis, caused some to argue that in these cases endometriosis may have a pathogenesis that differs from retrograde menstruation [8]. At the same time, given the increased risk of endometriosis in adolescents with cervical outflow obstruction, we have now proposed that early-onset endometriosis may originate from retrograde uterine bleeding soon after birth. Our hypothesis is that stem/progenitor cells present in the endometrium are shed with NUB and that they may have a role in the pathogenesis of early-onset endometriosis through retrograde dissemination.

A recent study [10] showed that endometrial stromal stem cells from women with or without endometriosis differed regarding their morphology, CD-marker expression pattern, proliferation, invasion and adhesion capacities and their ability to express certain immuno-modulatory molecules. The authors suggested the presence of two different endometrial stem cell lines in patients with endometriosis. This finding may support the retrograde and stem cell theories of endometriosis and open new roads of research on the neonatal and adult origin of endometriosis.

Recent investigations have identified two eSPC populations: epithelial and mesenchymal progenitor cells (eEPC and eMSC). Both show a high proliferative potential, are capable of undergoing self-renewal *in vitro*, and *in vivo* are capable of differentiating into mature progeny and of reconstituting tissue [11–13].

There are indications that during the years preceding puberty, shed eSPC, supported by niche cells are also likely to be present in NUB and can survive in the pelvic cavity even in the absence of circulating oestrogens. Indeed, it has been found that eMSC from endometriotic lesions have enhanced properties compared to those in eutopic tissue, showing greater invasiveness and migration ability, as well as the capability to stimulate neo-angiogenesis [14]. Thus, it is plausible to suggest that differences may exist among eSPC and that these anomalies may promote their survival and the ability to quickly implant in the peritoneal/pelvic cavity [15], where they can lay dormant for years [16].

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According to our theory, during thelarche, rising oestrogen production by the girl's ovaries can stimulate the proliferation of endometrial stem/progenitor cells establishing the ectopic endometrial invasion that characterises endometriosis.

At this stage of our hypothesis, the first priority is to design and implement studies aimed at proving or disproving the new theory, because – if proven – this new pathogenetic mechanism will have a number of practical applications.

Several lines of investigations can be envisaged [17].

First, using the technique of ''catheter within a catheter'' [18], it should be feasible to collect samples from neonates with signs of vaginal bleeding, a vital piece of information, since – to this day - there are no data on cellular constituents of NUB. In other words, as mentioned above, it is not known whether viable endometrial cells, including eSPC are present in vaginal fluid after filtering through the mucus of the long cervical canal.

Second, the existence of the postulated neonatal tubal reflux, with its consequent ''seeding'' of endometrial cells in the pelvic cavity should be established and an attempt should be made to isolate eSPC presumably present in it. Clearly, this constitutes an awkward goal to achieve, but if proven would do more than any other study to prove the new theory.

Third, the epidemiologic finding that being born preterm (but not being born small for gestational age, at term) provides protection against endometriosis [19], should be further investigated, since the data from a unique cohort from the Serbian city of Novi Sad [20] indicate that in prematurely born babies there is a very low incidence of neonatal uterine bleeding. Could this indicate a reduced risk of endometriosis later in life?

Finally and most important in view of recent findings, could be the demonstration of the presence of stem cells with different stromal and epithelial characteristics in neonatal and adult endometrium.

If a link can be established between the occurrence of NUB and the development of early-onset endometriosis, these data will have clinical implications: Indeed, if it could be proven that the reactivation of dormant neonatal eMSC at the time of telarche and menarche is at the origin of early-onset endometriosis in predisposed subjects, then the question can be raised whether in these subjects subsequent menstruations may, on a regular basis, seed additional eMSCs (this time adult ones), contributing to the generation of periodic waves of endometriotic lesions, thereby making endometriosis in this subset of young subjects a chronic disease [21]. The opposite may also be the case, namely that adult eMSC may lack the ability to establish ectopic lesions due to their different origin. The best way to investigate these two opposing scenarios is to compare neonatal and adult eMSC, a very challenging endeavour.

There is, however a much simpler approach, that of detailing the presence or absence of NUB in neonatal records; this simple measure will go a long way to create the possibility of prospective studies to prove, albeit in a number of years and probably a century after Sampson's 1927 publication of the menstrual hypothesis [22], whether there is a concordance between the frequency of NUB and the incidence of endometriosis in the adolescent population and whether this is due to the neonatal endometrial shedding containing eSPC.

Endometriosis in the adolescent girl has become in recent years a challenging issue, since – besides the severe pain it inflicts – it may affect her future fertility. For this reason, elucidating features of early-onset disease, with the ensuing ability to distinguish transient forms of peritoneal endometriosis from the more severe variants that include the presence of an endometrioma, have today become an important goal. Indeed there is evidence that, although the pain may start soon after menarche or even before the onset of menstruations, a firm laparoscopic diagnosis is too often postponed by several years. Under such circumstances, appropriate surgical treatment may be delayed till a time when in specific cases any attempt to eliminate the disease will affect ovarian reserve and severely compromise the young woman's ability to bear child. Several factors may play a role, but one important reason is likely to be the delay in diagnosis. Therefore, there is a need to quickly identify severe cases through transvaginal ultrasound and/or magnetic resonance imaging [23]. Having done that, the use of transvaginal access with less invasive needle endoscopy is recommended for a definitive diagnosis and immediate treatment before severe lesions have developed.

It has been argued that, since there is no strong evidence in the literature that in a majority of instances juvenile endometriosis is progressive, biomarkers may do more harm than good by precipitating unnecessary surgery. This may be true in many cases of ''transient'', superficial disease; however, the situation is different in the event of ovarian endometriosis (even in the presence of a small cyst) and there is increasing evidence that in the presence of severe dysmenorrhea in girls this type of condition may not be so rare. According to the information we gathered in a previous article and to recent studies of endometriosis in adolescents ovarian endometriomas may not be so rare [23].

We hope that our new theory on the possible cause of early-onset endometriosis will help selecting adolescents at higher risk and if there is the presence of NUB in the history of these girls, this may become an ''indication'' that they deserve special attention.

In conclusion, the new theory being shaped in these days may help explain how Sampson's theory of retrograde menstruation [22] could be applied also to early-onset endometriosis. In addition, it may also help identifying adolescents who may have only a transient form of superficial endometriosis, from those with severe endometriosis including endometriomas, a condition that can represent a most serious obstacle to their future fertility.

All these are good reasons to make a call for registration of uterine bleeding in neonatal notes.

Declaration of interest

The authors declare no conflict of interest.

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