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Pathogenesis of Early-Onset Endometriosis

G. Benagiano¹, C. Gargett², J. J. Brosens³, I. Brosens⁴

Three main theories have been put forward to explain the pathogenesis of endometriosis, that of a retrograde menstrual transplantation, that of an induction of endometrial cells, and that of an in situ development. These hypotheses belong to two main groups: those proposing that implants originate from the endometrium and those advocating an origin from extra-uterine tissues. More recently, the discovery that stem/progenitor cells from bone marrow can differentiate into endometrial cells suggests a novel pathway through which these cells may colonize peritoneal and extra-peritoneal organs and differentiate into ectopic endometrium.

On the other hand, for early-onset endometriosis a different pathogenetic mechanism may be in place. The possibility exists that in neonates endometrial cells and stroma are retrogradely disseminated in the pelvis, thanks to the presence of uterine bleeding, either visible or occult. Since menstrual desquamation causing neonatal bleeding may contain endometrial stem cells, they may in turn be responsible, through a variety of mechanisms, for early onset endometriosis. **J Reproductive Med Endocrinol Online 2015; 12 (4): 227–31.**

Key words: endometriosis, endometrium, adenomyosis, neonatal uterine bleeding

■ Introduction

The first descriptions of what were initially designated as “mucosal invasions of peritoneal organs”, namely the conditions we call today adenomyosis and endometriosis, date back more than a hundred years and by the end of the 19th century they were given a common name, that of “adenomyoma” [1].

In spite of intensive research, even today these two diseases deserve the appellation of “elusive”, utilised by Emge [2] and Bird et al [3] to describe adenomyosis and endometriosis respectively, back in the nineteen sixties and seventies. Elusive, because the exact pathogenetic mechanisms are still incompletely understood and the diagnosis often made after considerable time.

In the early days of the 20th century, researchers concentrated on the histogenesis of adenomyomas. Intriguingly, **C. Rokitansky**, the first to describe a case of what we would identify today as an “adenomyomatous polyp”, immediately recognised the endometrial nature of the epithelial cells found in the lesion. He mentioned that in a number of autopsies of women he found “*fibrous polyps of the uterus*” and that “*among them there are some, in which glandular tubes are found*” [4]; having found them protruding from the endometrium, he correctly identified the “glandular tubules” as of

endometrial nature. Unfortunately, his scientific publication carries the title “*On the neoplasm of uterus glands and uterine and ovarian sarcomas*”, and this seems to have distracted his contemporaries from the significance of his work. Indeed, ignoring Rokitansky’s conclusions, during the second part of the 19th century many pathologists argued that “adenomyomas” were the result of displacement of Wolffian or mesonephric vestiges; the most famous among them was **F. D. von Recklinghausen** [5]. They rejected the possibility that the glands they discovered as invading peritoneal organs were “endometrial” and opted for an embryologic origin.

The first clear description of the morphological and clinical picture of adenomyoma was made by **T. Cullen**. In his book “*Adenomyoma of the Uterus*” [6] he describes an observation made in 1882 and clearly mentions that “*the uterine mucosa was at many points flowing into the diffuse myomatous tissue*”. Cullen’s theory was dismissed for years and it was only during the second decade of the 20th century that it finally gained acceptance [7] and, by 1920, most researches agreed that the epithelial cells and stroma in an adenomyoma were of endometrial nature.

Once, the histogenesis was determined, it remained to clarify the pathogenesis of adenomyomas. This however, would

only be possible once a relationship was found with another condition initially called “*chocolate cysts of the ovary*”, or “*ovarian haematomas*”, the ovarian endometrioma.

The presence of endometrial glands and stroma in an ovary was first mentioned by **W. W. Russel** [8] in 1899 in a premenopausal woman who underwent surgery for a cystic adenocarcinoma of the left ovary. Opening the abdominal cavity, Russel found the right ovary enveloped in adhesion of the posterior face of the broad ligament and at microscopic examination a number of areas were observed that “*were an exact prototype of the uterine glands and interglandular connective tissue*”. In line with the theories of the time, Russel believed that the “tumor” was due to the presence of “*aberrant portions of the Müllerian duct*” in the ovary. A number of additional descriptions of “haematoma of the ovary” and of “chocolate cysts of the ovary” were also published at the beginning of the 20th century [1]. Then, in 1921, **J. Sampson** published the first of his articles on the condition he later named “*endometriosis*”, describing 23 cases of “*ovarian haematomas of endometrial type*” [9]. Initially, he preferred to call the cyst’s epithelium “Müllerian”, because he felt that in some cases the epithelium lining these ovarian ‘haematomas’ or ‘cysts’ may have been derived from the tubal epithelium. Sampson

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quickly developed a theory whereby the ovary would act as an incubator in the development of pelvic implantation of adenomas of the endometrial type [10]. Finally, in 1927, Sampson detailed his theory that the rupture of the endometrial cyst was the cause of peritoneal endometriosis [11], whereas several authors proposed the opposite mechanism, namely that endometriotic lesions on the peritoneum moving to the cortex invaded the ovary, or that endometrial cells arrived inside the ovary via lymphatic vessels [12]. It was only in 1957 that **P. E. Hughesdon** demonstrated histologically in ovaries with chocolate cysts *in situ* that in 90% of the cases the wall of the cyst originated from invaginated ovarian cortex, but was frequently modified by cortical fibrosis and smooth muscle metaplasia of the inner cortex obscuring the presence of follicles in the deeper layers [13]. In the meantime, **O. Frankl** had developed his theory that adenomyomas growing within the uterine wall were a distinct entity which he named “adenomyosis” [14].

At this stage, endometriosis and adenomyosis became known as different nosological entities with allegedly a different pathogenesis and, for decades to come, the two were considered independent diseases.

■ Adult Endometriosis

Over the years, Sampson's theory of a retrograde menstrual origin of endometriosis [11] gained acceptance and is today the most widely accepted hypothesis for its existence. Nonetheless, the presence of various forms of endometriosis (peritoneal superficial, deep, ovarian and extra-peritoneal) have led some to believe that they constitute separate nosological entities [15] and therefore that their pathogenesis may present different connotations.

In 1980, Simpson et al [16] and Malinak et al [17] were the first to explore genetic and familial aspects of endometriosis and found that female siblings of subjects with histologically proven endometriosis are almost 7-times more likely to develop the disease than women without a family history of endometriosis. To explain their findings they opted for a polygenic/multifactorial aetiology and concluded that an apparently healthy woman

with an affected first-degree relative would have a 7% chance of developing endometriosis. Aberrant gene expression in endometriosis is not confined to the ectopic lesions but is also apparent in the eutopic endometrium [18–20]. In this respect, it is more and more evident that the characteristics of the endometrium play a key role in the complex sequence of events leading to the adherence of nests of endometrial cells and stroma to the peritoneum, its acquisition of a blood supply and ultimately its survival.

Recently, Burney and Giudice [21] expressed the opinion that theories regarding the pathogenesis of endometriosis can be reduced to two main groups: those proposing that implants originate from the endometrium and those advocating an origin from extra-uterine tissues. This is indeed the prevailing view of this enigmatic disease today.

Some 10 years ago, Nap et al [22] reviewing the subject concluded that 3 theories on the pathogenesis of endometriosis seem the most acceptable: the retrograde transplantation, the induction and the *in situ* development theories.

The Retrograde Menstruation Theory

As mentioned, today the most widely accepted hypothesis for the genesis of endometriosis is that presented by Sampson in 1927, i. e. peritoneal endometriosis is caused by retrograde dissemination and implantation of endometrial tissue fragments into the peritoneal cavity at the time of menstruation [11]. Years later Sampson [23] presented a complete version of his theory, specifying that in women with patent tubes, fragments of endometrial tissue are retrogradely transported into the peritoneal cavity where, under facilitating conditions, they are able to adhere to peritoneal mesothelial cells and establish a blood supply that enables them to survive and proliferate. A number of observations support the reflux theory, from the distribution of the lesions in the abdominal cavity, to the *in vitro* proven viability of shed menstrual endometrium, to animal experiments in which a forced increase in retrograde shedding increases the chance of developing endometriosis [22].

It has been pointed out that menstrual reflux, while a pre-condition for its occur-

rence, is not *per se* sufficient to cause endometriosis: indeed, retrograde menstruation seems to occur in the vast majority of women [24], whereas only a minority of them develop the disease. One of the proposed explanations for this discrepancy is that natural immunity is altered in women with endometriosis; this decrease in a vital defence mechanism can cause an impairment of the physiologic clearing ability of the peritoneum to remove endometrial fragments shed in retrograde menstruation [25, 26].

More recently, it has been found that naturally-occurring endometrial stem cells (ESCs) play a role in the cyclic regeneration of the endometrium [27]. These ESCs can also have an important role in the pathogenesis of endometriosis, since they have been found in menstrual blood [28].

In summary, whereas “there is virtually no other scientific evidence supporting alternate mechanisms of development of endometriosis” [29], there are still many questions that require an answer before Sampson's theory can be fully accepted.

The Induction (or Coelomic Metaplasia) Theory

The oldest theory, dating back more than a century, to explain “epithelial invasions of peritoneal organs” involved a mechanism called “coelomic metaplasia”, namely the transformation of peritoneal mesothelial tissue into epithelial glands and stroma. However, the endometrial nature of these epithelial nests was not initially recognised [30] and, as a consequence of the work of Cullen [31], the metaplasia theory was all but abandoned until the nineteen fifties when it was resurrected by Levander and Normann [32] and, a decade later by Merrill [33]. According to this hypothesis, endometriosis may develop through a series of metaplastic changes induced by the release of cellular factors from degenerating menstrual endometrium.

In 1999, Ohtake et al [34] developed an *in vitro* experimental model for ovarian endometriosis employing a three-dimensional culture of human ovarian surface epithelial cells in collagen gel. Using this system, they obtained evidence that when both ovarian surface epithelium and ovarian stromal cells are co-cultured with oestradiol, endometrial-like nests

can develop through a process of metaplasia. In these co-culture experiments ovarian surface epithelial and endometrial stromal cells formed an epithelial structure with lumen, surrounded by stromal cells. Immunoreactivity for cytokeratin and epithelial membrane antigen was detected in the glandular cells and cilia were identified on the cell surface by electron microscopy. Importantly, none of these structures were detected in the absence of oestradiol.

While *in vitro* models support the induction theory, direct evidence of the formation of endometrial cells and stroma as a consequence of a metaplastic process is as yet lacking [22].

The In-situ Development Theory

This hypothesis involves the growth of endometrial cells and stroma from multipotent cells and embryonic remnants and was first presented by Ferguson et al who proposed that the peritoneal lining contains undifferentiated cells that can differentiate into endometrial cells under certain circumstances [35].

It has been invoked to explain cases of peritoneal endometriosis occurring before menarche, in women who have never menstruated, and in postmenopausal women. It has also been invoked to explain extra-peritoneal cases, such as the lesions found in right-sided thoracic organs and in castrated men treated with oestrogens [36]. The theoretical basis of this hypothesis has been put forward by Fujii [37] who believes that a shared embryologic origin exists for coelomic epithelium-related tissues and Müllerian-derived epithelia of the adult. Thus, tissues derived from the coelomic epithelial and mesenchymal cells have the potential to differentiate into Müllerian-type epithelium and stroma and this mechanism can be involved in the pathogenesis of endometriosis.

New Theories

The discovery that stem/progenitor cells from bone marrow can differentiate into endometrial cells suggests a novel pathway for the development of ectopic endometriotic implants. In a remarkable experiment, Taylor [38] obtained proof that endometrial cells can be derived from bone marrow cells, studying female allogenic bone marrow transplant recipients receiving a graft under conditions

allowing identification of the donated cells. This investigation demonstrated the presence of donor-derived endometrial cells in endometrial biopsies of the recipients, suggesting that bone marrow-derived cells can differentiate into human uterine endometrium.

■ Early-Onset Endometriosis

Initially, endometriosis was considered a disease of adult women; however, taking a life cycle's approach [39], it became clear that its presence had been described in foetuses in the posterior pelvic cavity [40], in girls before menarche [41], and during adolescence on the pelvic organs, including the ovaries [42, 43].

It seems logical that this intraperitoneal variant in young adolescents possessing in a majority of instances characteristic subtle superficial lesions with strong neo-angiogenesis, but also manifesting it with ovarian endometriomas, may have a pathogenesis that differs from cyclic retrograde menstruation. For this reason, we became interested in the pathogenesis of this early form and decided to investigate whether they may draw their origin from a totally neglected, but well proven endometrial bleeding, that occurring at birth in some neonates.

To our surprise, over the last 30 years, we found only one report dealing with Neonatal Uterine Bleeding (NUB) published in a Yugoslavian Journal and not mentioned in any of the most widely consulted data bases [44]. By contrast, earlier publications exist on foetal and neonatal endometrium. Specifically, in the nineteen seventies French and German investigators described NUB in great detail [45–49].

Features of neonatal endometrium were carefully detailed some sixty years ago by two Harvard pathologists [50] who described the different features of neonatal endometrium at birth as an indifferent or proliferative phase in some 2/3 of the cases. They recorded secretory activity and decidual changes in 27% and 5% of cases, respectively. Changes of the type observed at menstruation in adults were observed in 5 out of a total of 169 newborn infants, all of whom had died within 3 days after birth. Observed features in the five babies included the presence of clotted blood in the endometrial cavity;

in the coagulum, sloughed endometrial structures were occasionally identifiable.

The development of the endometrium during foetal life was carefully investigated more than 40 years ago by Huber et al [51] who documented that no glandular development occurs before the 20th week, whereas signs of secretory activity can be observed in some foetuses beginning around the 34th week. After birth the endometrium starts a process of regression and at one week becomes quiescent.

There is now unequivocal evidence that the neonatal endometrium can mount a decidual response in 5% of the neonates, a prerequisite for menstrual shedding. It is also established that overt vaginal bleeding occurs in 3–5% of the neonates and that in an unspecified larger number of new-born bleeding is occult. Regurgitation of sloughed endometrial fragments into the peritoneal cavity is likely promoted in the neonate by the thick endocervical mucus in the relatively long cervical canal [52].

At this stage we outlined a theory to explain early-onset endometriosis based on the possibility that in some foetuses and neonates endometrial cells and stroma may be retrogradely disseminated in the pelvis around the time of birth, thanks to the presence of uterine bleeding, either visible or occult [53]. This preliminary communication was followed by a full report detailing the new theory [54] and by a further article in which we discussed the possibility that menstrual debris present in NUB may contain endometrial stem cells. These neonatal ESCs may in turn be responsible, through a variety of mechanisms, for early onset endometriosis [55].

Today there is evidence that ESCs have the ability of establishing endometriotic implants [56] and several experiments support the hypothesis of their involvement in the development of the disease [57]. Following this line of thinking, we hypothesised that ESCs are shed into the pelvic cavity in concomitance with NUB. We further postulated that during the neonatal and pre-pubertal period ESCs can survive in the pelvic cavity even in the absence of circulating oestrogens, thanks to the support of niche cells, also shed during neonatal uterine bleeding. Then, at the time of thelarche, under

the influence of rising oestrogen levels, ESCs can proliferate and – in specific cases – establish nests of ectopic endometrial cells and stroma [55].

In support of our theory, two populations of ESCs have been recently identified: epithelial and mesenchymal progenitor cells (eEPCs and eMSCs). Both show a high proliferative potential, are capable of undergoing self-renewal *in vitro* and are capable of differentiating into mature progeny and of reconstituting tissue *in vivo* [58–60]. There is evidence that eMSCs from endometriotic lesions show greater invasiveness and migration ability, as well as the capability to stimulate neo-angiogenesis compared to those in eutopic tissue [61]. These properties in turn may promote ESCs survival and the ability to quickly implant in the peritoneal/pelvic cavity [62], where they can lay dormant for years [63].

Attractive as it may sound, before the new theory can be accepted it will require clinical and experimental confirmation. To this aim, we have suggested several lines of investigations [64].

■ Conclusions

If proven true, the new hypothesis will have practical consequences also outside its possible role in early-onset endometriosis. NUB occurs rarely in pre-term babies, increases in those at term and is frequent in post-mature infants. If a temporal relationship could be established between endometrial maturation and NUB, its occurrence might be taken as a reflection of the maturity of progesterone response in the endometrium. Pre-eclampsia, particularly if severe, low for gestational age birth weight, and foeto-maternal blood incompatibility seem to represent factors increasing the frequency of NUB [47]. For this reason, a series of new foeto-maternal markers can be envisaged to evaluate the risk of endometriosis in adolescents and young women [65].

Finally, it has been shown that the occurrence of major obstetric syndromes can be caused by impaired placental bed spiral artery remodelling [66]; these are prevalent in teenage pregnancies and include pre-eclampsia, foetal growth restriction and spontaneous preterm labour [67]. It can be argued that, if the partial

progesterone resistance observed in newborn foetuses and babies can persist into adolescent years, this phenomenon may impair physiological deep placentation in case of pregnancy [66]. Thus, understanding the mechanisms of functional maturation of the uterus during the early reproductive years may yield novel insights into the major obstetric syndromes [68].

■ Conflict of Interest

All authors declare no conflict of interest.

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