

Association between etiopathogenesis of morbidly adherent placenta and adenomyosis

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ABSTRACT

The association between etio-pathogenesis of morbidly adherent placenta (MAP) or placenta cretas and adenomyosis has never been described in medical literature. Contrary to the believe that MAP is due to direct invasion of trophoblastic tissues into the adjacent normal myometrium due to prior uterine surgeries, this article describes how pre-existence of adenomyosis acts as a precursor for the development of placenta cretas. It elucidates how prior uterine traumas such as surgeries, repeated child-births and endometritis cause endometrial tissues to invade the myometrium as a result of disruption of decidua basalis. The invaded endometrial tissues cause hyperplasia and hypertrophy of surrounding myometrium to form the clinical entity called adenomyosis. The over-expression of bcl-2 oncogene in the endometrium causes inhibition of apoptosis of endometrial cells removing the barrier of trophoblastic tissues to invade the myometrium to form MAP. This hypothesis is based on the similarity of their clinical perspectives, similar pathological description of the two disease entities and their common molecular components. Both diseases increase with age; more in women older than 35 years and also in those with history of previous endometrial traumas such as surgeries, childbirth and endometritis. Both diseases also share common pathological factors and molecular components due to absence of deciduas basalis and over-expression of bcl-2 oncoprotein gene, inhibition of cell apoptosis and failure to find genetic abnormalities such as mutations of K-ras, P53 or LOH. An on-going study looking at uterine specimens from cesarean hysterectomies and pelvic MRI evaluation of patients with retained placentas to prove that pre-existing adenomyosis may be a precursor to the development of morbidly adherent placenta is near to conclusion.

Keywords: Morbidly Adherent Placenta (Placenta Accretes); Adenomyosis, Association; Epidemiology; Etio-Pathogenesis and Clinical Perspective

1. INTRODUCTION

Adenomyosis is a disorder characterized by the presence of islets within the myometrium that consist of both epithelial and stroma elements of endometrial tissues. It was first described by Rokitansky in 1860 and then clearly defined by Von Reckinghausen in 1896 [1,2]. In 1991, Sathganarayana divided adenomyosis into 3 categories depending on the location of the lesion; basal, deep and surface layers. The minimum myometrial invasion required for diagnosis has been debated, but a depth of 2.5 mm or half a low-power field (LPF) from the endomyometrial border has been universally accepted in most assessments [3-6]. Any site may be involved, but the posterior wall is affected the most [7,8].

Morbidly adherent placenta is globally referred to as placenta cretas and it is defined as the abnormal adherence either in whole or in part of the placenta to the underlying uterine wall. It occurs when a defect of the decidua basalis results in abnormally invasive placenta implantation. Risk factors include placenta previa, previous cesarean section, advanced maternal age, multiparity and previous uterine curettage. It is classified into 2 broad categories according to depth of myometrial invasion and amount of placenta involvement. A partial or total absence of the deciduas basalis and imperfect development of the fibrinoid layer (Nitabuch layer) results in chorionic villi adherent to superficial myometrium—placenta accreta, or chorionic villi involving myometrium—placenta increta and chorionic villi penetrating full thickness myometrium and involving the serosa—placenta percreta. Classification based on the amount of placental involvement are: focal adherence—when part of the cotyledon is involved, partial adherence—when more than one of the cotyledon is involved and total adherence when whole placenta is involved.

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2. EPIDEMIOLOGY

2.1. Epidemiology of Adenomyosis

Accurate determination of the prevalence of adenomyosis is difficult because the diagnosis can reliably be made with certainty by microscopic examination of extirpated uterus. It has been estimated to affect 20% of women, however, it was found in approximately 65% of women in one study of meticulous histopathological analysis of multiple myometrial sections [9]. Adenomyosis most often co-exists with other organic pelvic pathologies such as leiomyoma, endometriosis and pelvic inflammatory disease. The co-existence of adenomyosis and leiomyoma has been reported in up to 60% of cases studied. Black women have been reported to have a higher incidence of leiomyomas than Adenomyosis [10]. Adenomyosis is usually found in women 35 - 50 years of age who are multiparous and present with abnormal uterine bleeding, usually hypermenorrhea and secondary dysmenorrhea [11].

2.2. Epidemiology of Morbidly Adherent Placenta

Morbidly adherent placenta (MAP) was first reported by Plater in a case of a noble woman; Galla who was delivered on March 25 in the year 88 AD [12]. The placenta was retained and she died. Upon autopsy, the placenta was found to be firmly adherent to the uterine wall above the internal Os. The incidence ranges between 1:2500 to 1:110 [13-15]. The increasing incidence of morbidly adherent placenta is linked to the rising cesarean section rate. This is suggested to result from the consequences of failure of reconstitution of the endometrium/decidua basalis after repair of a cesarean incision. Histopathology of the placental bed usually shows that the trophoblasts invade the myometrium without intervening deciduas [16].

3. ETIO-PATHOGENESIS

Adenomyosis has been variously described by different experts as “elusive disease” or “*déjà vu*” disease based on the little knowledge of its pathogenesis. However, the universal agreement is that it is associated with accentuation of the myometrial muscle pattern, multiparity, and endometrial hyperplasia. Common proposed etiologies are hereditary, hormonal influences, trauma, viral transmission, and chronic postpartum endometritis. Some authors suggest that the myometrium is vulnerable to invasion by endometrial hyperplasia. Other authors postulate that the myometrium is vulnerable to invasion by endometrial glands because of the absence of a basal membrane—decidua basalis [17]. A retrospective study by Panganamamula *et al.* found a link between prior uterine surgery and adenomyosis. The hypothesis is that

there is a disruption of the junction of the endometrium and myometrium by any surgical intervention. This results in the endometrial glands growing into the uterine muscle leading to the development of Adenomyosis [18]. However, there is a strong suggestion that adenomyosis does not originate from the basal endometrium based on the variation of cell death repressor activity, bcl-2 gene expression and proliferative marker, ki-67 expression as compared with eutopic Endometrium [19]. Other theories proposed are: invasive tissue growth, developmental origins and uterine inflammation related to childbirth. Risk factors include uterine surgeries such as previous cesarean section, dilatation and curettage, myomectomy, and childbirth.

The ectopic endometrial tissue appears to induce hypertrophy and hyperplasia of the surrounding myometrium, which results in a diffusely enlarged uterus called “globular enlargement”. A focal occurrence of adenomyosis can result to nodules; called “adenomyoma” which clinically resemble leiomyoma. The uterus generally does not exceed the size of a pregnant uterus at 12 weeks of gestation.

4. THE LINK BETWEEN THE ETIOLOGY OF MORBIDLY ADHERENT PLACENTA AND ADENOMYOSIS

The hypothesis of an association between adenomyosis and future development of second or third trimester retained placenta and morbidly adherent placenta such as placenta accretas can be viewed at three different levels: Clinical, pathological and molecular perspective.

4.1. Clinical Perspective

Age and prior uterine surgeries such as cesarean section are independent risk factors for placenta previa—placenta accreta as well as Adenomyosis [11,20]. The incidence of both disease entities are increased in women older than 35 years and history of previous uterine surgeries. Disruption of endomyometrial junction by any surgical intervention allows in-growth of endometrial tissue into the myometrium and this creates a pathway for trophoblasts to invade the myometrium during placentation. The association between etiology of morbidly adherent placenta and adenomyosis is based on the hypothesis that pre-existing adenomyosis heralds the development of placenta accretas. Our hypothesis is proposing that patients with suspected adenomyosis based upon its clinical, radiological and hysteroscopy features are more likely to develop placenta accretas. The clinical symptoms of adenomyosis include but not limited to dysmenorrhea, menorrhagia, metrorrhagia, dyspareunia and/or dyschezia. Global shape uterus, hypoechoic or slightly heterogeneous appearance on trans-

vaginal sonogram and MRI features of widening of the junctional zone of 12 mm or greater increase the risk of future development of placenta accretas in pregnancy. The presence of irregular endometrium, endometrial defects, hypervascularization, strawberry pattern or cystic hemorrhagic lesions which are hysteroscopic characteristics of possible adenomyosis are also proposed in this hypothesis as risk factors for the development of placenta accretas. Adenomyosis and placenta accretas share common other risk factors such as multiparity, endometritis and previous uterine surgeries such as dilatation and curettage, myomectomy and cesarean section. Any condition that leads to disruption of the endometrium can alter decidualization and placentation during pregnancy which can lead to invagination of placenta tissues.

4.2. Pathological and Molecular Perspectives

The apparent similarity between the etio-pathogenesis of morbidly adherent placenta and adenomyosis is based on the common pathological factors such as absence of decidua basalis and over expression of bcl-2 in both disease entities. There is a possibility that the invading endometrial tissues leaves the decidua basalis devoid of normal endometrium covering leading to invasion of corresponding myometrium by immortal endometrial tissues due to over-expression of the bcl-2 oncoprotein gene, an inhibitor of cell apoptosis. The pathogenesis of placenta accretas is multi-dimensional involving increased but incomplete trophoblast invasion in a background of absent decidua. Placenta accretas result from primary deficiency of decidua, abnormal maternal vascular remodeling and excessive trophoblastic invasion of the myometrium [21].

4.3. The Role of Bcl-2 Oncoprotein Gene in the Etiology of Morbidly Adherent Placenta and Adenomyosis

Morbidly adherent placenta is associated with retention of a piece or the whole placenta tissue resulting in uterine sub-involution and delayed secondary postpartum hemorrhage. Increase bcl-2 oncoprotein is associated with inhibition of apoptosis and prolonged cell survival. It is seen mostly in sub-involuting placenta bed as compared with involuted bed. The expression of bcl-2 gene is associated with sub-involution of the utero-placental arteries which inhibit complete resolution of pregnancy induced changes [22]. There is also a decrease cellular apoptosis in adenomyosis and ectopic endometrium due to high bcl-2 gene expression in ectopic endometrium tissues. In a study by Ueki et al, occurrence of adenomyosis was correlated to bcl-2 expression regulated by estrogen and estrogen receptor rather than genetic mutation [23]. Constant expression of bcl-2 with estrogen receptor (ER) and hyper-estrogenic metabolic states promote invagination

and spreading of adenomyosis into the myometrium. This hypothesis is also anchored on the failure to find genetic abnormalities such as mutations of K-ras, P53 or LOH [23].

5. CONCLUSION

Any patient with retained placental tissues following delivery should be evaluated for prior history of symptoms, radiologic or hysteroscopic features of adenomyosis. Till date, transvaginal sonogram and magnetic resonance imaging are the mainstay of pre-operative diagnosis of adenomyosis with sensitivity of 68% and 70% and specificity of 65% and 86% respectively [24]. When available, they should be utilized without hesitation. Other diagnostic approaches are pre-operative biopsy, hysterosalpingography and hysteroscopy. The definitive treatment and diagnosis of adenomyosis is hysterectomy and pathological examination of extirpated uterus. However, conservative management such as norethindrone acetate, levonorgestrel impregnated IUD (mirena), estrogen, danazol, GnRH agonists, resection of lesions, hysteroscopic endometrial ablation, uterine artery embolization (UAE) and magnetic resonance guided focused ultrasound surgery (MRgFUS) can be employed [24,25]. Our hypothesis suggesting an association between etiopathogenesis of placenta accretas and pre-existing adenomyosis may be factual rather than a mere proposition. Fertility preserving management of adenomyosis may play a great role in reducing the incidence of placenta accretas. More research study to explore temporal association between the etiology of MAP and adenomyosis is under way. The result of our on-going study on this topic will finalize whether this association is true or not.

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