Placenta Accreta Spectrum: A Review of Morphological, Histopathological of the Placenta in first-trimester Spontaneous Abortions.

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ABSTRACT

Histopathological examination of products of conception from miscarriages is part of routine clinical practice. The extent of additional clinically relevant information provided by this investigation in the setting of recurrent spontaneous abortion remains uncertain. The included studies indicated that such examination identify hydatid form moles, villous dysmorphic features suggesting fetal aneuploidy, chronic histiocytic intervillitis (CHI) and massive per villous fibrin deposition and impaired trophoblast invasion. However, in most cases, morphological assessment cannot reliably determine the cause of the miscarriage or distinguish recurrent from sporadic miscarriage. Studies reporting on the use of additional immunohistochemically methods do not currently provide additional clinically useful diagnostic or prognostic information. Routine histological examination of products of conception in the setting of recurrent spontaneous abortion can provide important clinical information in a minority of cases.

Keywords: *Abortion; Incomplete abortion; Placenta; Histopathology; Miscarriage.*

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INTRODUCTION

Placenta accreta was first described in 1937 by Irving et al. as failure of separation of the placenta from the uterine wall following delivery of the human fetus leading to the often-used term morbid placental adherence (Irving C. and Hertig A.T., 1937). The condition characterized by invasive placentation, which is associated with catastrophic hemorrhage. Varied terminology has been applied to this condition; however, recent guidelines suggested that placenta accreta spectrum (PAS), which includes accreta, increta, and percreta (defined below), be used going forward (Jauniaux E. and *et al.*, 2018). The condition is unique to human pregnancy with no animal correlate reported in the literature (Chuong E., 2013).

The incidence of PAS has increased substantially from 0.8 per 1000 deliveries in the 1980s to 3 per 1000 deliveries in the past decade, a phenomenon attributed to a rising global caesarean section rate (Higgins M. and *et al.*, 2013). PAS is associated with significant maternal morbidity and mortality, in particular, major obstetric hemorrhage and per partum hysterectomy (Silver R.M. and Barbour K.D., 2015). . Mortality rates of up to 7%

reported to be associated with PAS (Brien J.M. and *et al.*, 1996). The most recent confidential inquiry into maternal mortality in the United Kingdom (MMBRACE-UK, 2017) highlighted the continued high maternal mortality associated with the condition (Knight M. and *et al.*, 2013). The most important antenatal risk factor for PAS is the number of previous caesarean sections. In the presence of low-lying placenta (placenta Previa) and three previous

caesarean sections, a woman would have a 61% risk of PAS. (Bailit J. and *et.al*, 2015). Antenatal diagnosis is a key element to improving maternal and perinatal outcome. Although dedicated ultrasound and MRI having improved antenatal diagnosis, between one half and two thirds of cases remain undiagnosed, resulting in poorer maternal outcomes (Fitzpatrick K. and *et.al*, 2014).

Morphological:

Abortion, miscarriage or loss of the fetus before it is viable, is the most common complication of pregnancy, occurring in 12% - 26% of recognized pregnancies (Breeze C., 2016). These terms are applied to many complications in pregnancy and should be clear on definition. The term "biochemical loss" is applied to abortion after a positive urinary human chorionic gonadotropin (HCG) or a raised serum β -hCG but before ultrasound or histological verification, in other words, abortion before 6 weeks of pregnancy. The term clinical miscarriage refers to pregnancy loss after ultrasound examination or histological evidence has confirmed that an intrauterine pregnancy has existed. Clinical miscarriage (abortion) can be divided into early (before 12 gestational weeks) and late (between 12 to 20 gestational weeks) (Donnelly K and Thompson. R., 2015). Abortion is a common and distressing complication of pregnancy. Recently, progress in immunology and genetics gave us a greater understanding of implantation and maternal-embryo interactions. These gave us a new look into the possible causes of abortion, and opened up new methods for research (Larsen E.,2013). Early pregnancy loss is a physiological phenomenon prevents conception of chromosomally or structurally malformed infants (50%) (Donnelly K and Thompson. R., 2015).The most important antenatal risk factor for PAS is the number of previous caesarean sections. In the presence of low-lying placenta (placenta previa) and three previous caesarean sections, a woman would have a 61% risk of PAS (Bailit, J., *et.al.*, 2015). Antenatal diagnosis is akeyelement to improving maternal and perinatal outcome. Although dedicated ultrasound and MRI having improved antenatal diagnosis, between one half and two thirds of cases remain undiagnosed, resulting in poorer

maternal outcomes (Fitzpatrick K., *et.al.*, 2014). This is supported by studies, assessed fetal morphology prior to evacuation. In these studies, fetal malformations represented 85% of cases, while three quarters of fetuses had abnormal karyotype. On the other hand, the importance of the immune system in abortion, is evident in genetic studies, showing that genetic biomarkers are important for immunologic dysregulation in pregnancy (Gerdtts C.,2013). It is well known, that thyroid dysfunction and thyroid autoimmunity are associated with abortion. For example, patients who are euthyroid with thyroid antibodies or in thyroid antibody negative patients with high level of thyroid stimulating hormone (TSH). Added to that, it is well known that, hypothyroidism is highest among fertile women (Say L., 2014). In addition, the age of both parents has a significant role as the risk of an adverse pregnancy outcome increased if the parents are 35 years old or older and it is 50% higher if the mother is 42 years of age. On top of that, acquired or congenital uterine malformations are a well-known cause of recurrent pregnancy loss. In addition, factors such as ethnic origin, psychological state of the mother, feelings of stress, use of non-steroidal anti-inflammatory drugs, have also been associated with significantly higher rates of miscarriage (Ramasamy R., 2016). In the other hand, life style factors may cause or increase incidence of abortion. These factors include alcohol consumption, smoking, very low body mass index (BMI) and obesity. Finally, a number of infections linked to miscarriage. Specifically, 15% of early miscarriages and 66% of late miscarriages have been attributed to infections (Vaiman D.,2015). If a woman is having abortion, she will probably have vaginal bleeding, abdominal pain, and cramping. Bleeding may be only slight spotting, or it can be quite severe. Pain and cramping occur in the lower abdomen. They may occur on only one side, both sides, or in the middle. The pain can also go into the lower back, buttocks, and genitals. The woman may no longer have signs of pregnancy such as nausea or breast swelling/tenderness if she has experienced an abortion (Jungheim E., 2012). Abortion divided into medical and surgical. Medical abortion brought about by medication taken to induce it, either as single pill or a series of pills. Medical

abortion, depending on the stage of gestation and the medical products used, has a success rate of 75 - 95%, with about 2 - 4% of failed abortions requiring surgical abortion. On the other hand surgical abortion, means using a surgical technique to remove the content of the uterus and all its parts (Larsen E., 2013). Medically, abortion divided into 7 types. First type is threatened abortion, where clinical symptoms of abortion occurred, but pregnancy products remained in uterus. This commonly happens in early pregnancy, were symptoms including, vaginal bleeding (bright red to brown) for a few days or weeks. Abdominal pain may happen. On examination: cervix closed, the amniotic sac has not broken, the size of the uterus consistent with the time of pregnancy (Breeze C., 2016). The second type is inevitable abortion this refers to pregnancy that cannot be sustained. Vaginal bleeding is more and may last for longer time, blood clots, and lower abdominal pain intermittently, or amniotic fluid outflow. On examination: cervix opened, amniotic sac prominent or may be broken, and embryonic tissue may be felt in the cervical canal, or out of the cervix (Pineles B., 2014). Next type is the fetus and part of placenta discharge, and part or the entire placenta retained in the uterine cavity, which called the incomplete abortion. If abortion occurred before 8 weeks of pregnancy, sometimes, fetus and placenta can be discharged simultaneously. While, 8 to 12 weeks of pregnancy, the product is not easy to discharge completely. Because of this residual tissue within the uterine cavity, uterus cannot contract well, resulting in vaginal bleeding for long time with the possibility of intrauterine infection (Larsen E., 2013). On examination: cervix open, and sometimes the embryonic tissue felt in the cervix. The uterus is less than the number of normal pregnancy days. The fourth type is complete abortion, were fetal and placental tissue completely discharged with vaginal bleeding and abdominal pain stopping. It often occurred before 8 weeks of gestation (Giakoumelou S., 2016). On examination: the cervix is closed and the uterus is almost normal size. The fifth type is missed abortion, were fetal death occurred and remains in the uterus. The exact cause is not clear, may be related to the levels of estrogen and progesterone and the sensitivity of uterus. On the other hand,

excessive treatment to threatened abortion may be another reason. Next is the sixth type, which is recurrent abortion. This consist of three consecutive or more abortions (Pineles B., 2014). The incidence is 1 - 5% of all pregnancies, but accounts for 15% of all abortions. Lastly, infected abortion which abortion combined with the infection of reproductive system. (Gerdtz C., 2013). Up to 50% or more of all pregnancies will spontaneously abort, with the majority of these pregnancy losses occurring in the first trimester. First-trimester spontaneous abortions are often due to genetic or chromosomal anomalies. Spontaneous losses in the second trimester are less common. However, it known that many of them are associated with an ascending infection and/or acute chorioamnionitis. Although chorioamnionitis characterized in the older literature, a Medline search revealed only two large studies in the recent English-language literature evaluating clinical, histological and microbiological aspects of second-trimester pregnancy loss. Those studies reported rates of chorioamnionitis of 39.3% and 58.2%, respectively (Gaillard DA, *et.al.*, 1993). The University Hospital in Newark, New Jersey serves an inner-city population, and therefore ascending infection would probably be a common cause of second trimester abortion in this population. In this study, we sought to identify associated risk factors and evaluate the utility of histological stains for microorganisms, which used on these specimens. Common risk factors for pregnancy loss include increasing maternal age, medical conditions, medication and/or substance use, and environmental exposures. Increasing age-Extremes of age increase the risk of pregnancy loss, with age >35 years being the most significant risk factor because of the strong association with fetal chromosomal abnormalities (Nybo Andersen A.M. *et.al.*, 2000). In a national prospective cohort study of over 421,000 pregnancies, the risk of miscarriage (after excluding induced abortions) was lowest (10 percent) in women age 25 to 29 years and rose to a high of 57 percent for women age ≥ 45 years (Magnus MC *et.al.*, 2019). The early pregnancy loss (EPL) rates by other subgroups were 17 percent for women <20 years, 11 percent for women 20 to 24 years, 11 percent for women 30 to 34 years,

17 percent for women 35 to 39 years, and 33 percent for women 40 to 44 years. While the impact of increasing paternal age is somewhat less clear, EPL risk does appear to rise with increasing paternal age. (Slama R. , *et.al.* , 2005). These issues presented in detail separately. Prior pregnancy loss appears to increase the risk of subsequent pregnancy loss, independent of maternal age. In the above prospective cohort study of over 421,000 pregnancies, after adjusting for maternal age, the risk of miscarriage increased among women whose prior pregnancy ended in a miscarriage adjusted odds ratios (OR) of miscarriage for one prior miscarriage: 1.54, 95% CI 1.48-1.60; two prior miscarriages: 2.21, 95% CI 2.03-2.41; three prior miscarriages: 3.97, 95% CI 3.29-4.78) . (Magnus MC *et.al.*, 2019). In addition, at least one study has reported that women who experienced pregnancy loss were more likely to have a mother who also had a history of pregnancy loss, which suggests a potentially inheritable component (Woolner A. *et.al.*, 2020). Maternal medical conditions — various causes of maternal morbidity, such as endocrinopathies and metabolic disorders including obesity, are also associated with EPL. These considered modifiable risk factors, as well-controlled maternal conditions are far less likely to result in EPL. While any medical condition that negatively influences maternal health can have potential reproductive consequences, some of the more common conditions that increase the risk of EPL discussed below. Infection - Overall, approximately 15 percent of EPL is associated with an infectious etiology (Frazier T. *et.al.*, 2018). Parvovirus B19 infection in pregnancy has a nearly 8 percent cumulative incidence of loss, and the risk of loss is 5.6 times higher with infection in the first trimester as compared with the second trimester (Xiong Y. ,*et.al.* ,2019). Untreated syphilis leads to a 21 percent increased risk of fetal loss and stillbirth (Gomez G. *et.al.*, 2013). Maternal cytomegalovirus (CMV) infection has 2.5-increased odds of EPL as compared with non-infection (Rasti S. *et.al.*, 2016). However, maternal infection with HIV or toxoplasmosis does not appear to be associated with an increased risk of EPL (Ghasemi F. *et.al.* , 2015; Wedi C. *et.al.* , 2016). Diabetes – The effects of type 1 and type 2 diabetes on early

pregnancy can be extreme, even resulting in lethal fetal anomalies or pregnancy loss. Euglycemia in the preconception and preconception time periods brings this risk back to baseline Obesity – Obesity is more strongly and consistently associated with pregnancy loss than either type 1 or type 2 diabetes. A 2008 meta-analysis of 16 studies demonstrated that a body mass index greater than 25 was associated with nearly 70 percent-increased odds of EPL after spontaneous or assisted conception (OR 1.67, 95% CI 1.25-2.25). (Metwally M. *et.al.*, 2008). Thyroid disease – Both hyper- and hypothyroidism have been associated with increased risk of pregnancy loss, with some studies reporting a doubling of risk of pregnancy loss (Maraka S. *et.al.* , 2016). These topics are covered in detail elsewhere Stress – Both acute and chronic stress can increase the risk of pregnancy loss (Ding *et.al.*, 2017). Stress is multifactorial and can be difficult to separate out from other risks. Chronic stress can lead to increased cortisol levels, decreased immunity, and may increase susceptibility to infection and other maternal conditions, all of which can then increase the risk of pregnancy loss (Frazier T *et.al.*, 2018). If a person has an otherwise stable life, a short period of stress, such as a busy time at work or acute illness in a loved one, is unlikely to have a major impact. However, racial/ethnic, financial or other disparities, risk of violence, significant periods of housing or food insecurity in the past or present, or other long-term life stressors can negatively affect health in many ways, including increasing the risk of EPL (Frazier T. *et.al.*, 2018). Inherited thrombophilia's – The effect of heritable thrombophilia's on EPL risk is unclear as the body of evidence conflicts. The available data covered in detail elsewhere. Pregnancy with intrauterine device (IUD) in place – While IUDs are some of the most effective contraceptive methods, device failures do occur. Though pregnancy with an IUD in place is relatively rare, for those patients who choose to continue their pregnancies, the risk of EPL appears to be higher for women who elect to leave the IUD in place rather than have it removed (Ozgu-Erdinc A. *et.al.*, 2014). These issues presented in detail in a related topic. Medication and substance use — Information regarding the impact of specific drugs on the risk of miscarriage is available at

the US National Library of Medicine Toned toxicology data network site. The role of medication and substance use on EPL risk is challenging to assess as the impact varies by agent, dose, and timing of exposure. Numerous therapeutic medications considered teratogenic in pregnancy, and some teratogenic effects result in an increased risk of EPL. Alternately, medications may be associated with EPL even in the absence of teratogenicity. As an example of the complicated nature of medication and EPL risk, the nonsteroidal anti-inflammatory drugs (NSAIDs) aspirin and indomethacin are used for specific obstetric indications (preeclampsia prevention and treatment of acute preterm labor) while other NSAIDs, including ibuprofen and diclofenac, may increase EPL risk (Ferber J. *et.al.*, 2018). Substance use during pregnancy confounded with other factors that lead to poor health status and increased risk of EPL, and thus it is difficult to assess the independent impact of the drug(s) in epidemiologic studies. In general, smoking, caffeine, and alcohol consumption appear to increase the risk of pregnancy loss in a dose-related fashion (Sundermann A. *et.al.*, 2019). Some studies have reported increased risks with exposure to cocaine or methamphetamines (Ness R. *et.al.*, 1999). Marijuana use in pregnancy does not appear to increase the risk of pregnancy loss, although it does negatively impact neonatal development (Conner S. *et.al.*, 2016). Environmental factors and exposures — Exposure to toxins and pollutants and other environmental factors may increase the risk of EPL by causing cell death, altering growth of normal tissues, or interfering with normal cellular differentiation or other processes. Exposure to ionizing radiation is associated with EPL, while excessive lead, arsenic, and air pollution exposure appear to increase the risk. Some of these avoided, but many exposures occur where one lives or works and may not be avoidable. Lower socioeconomic status is associated with increased environmental exposures, as this can result in less agency in determining where one lives and works. The role of environmental exposure and specific agents discussed in more detail in related topics. Race and ethnicity - Studies have consistently reported an increased risk of EPL in women of color compared with white women (Oliver-

Williams CT and Steer PJ. 2015). However, this difference more likely reflects the impact of the cumulative stressors of social determinants of health and unavoidable occupational and/or environmental exposure to potential toxins than a true biological difference Subchorionic hematoma — Subchorionic hemorrhage or hematoma is associated with increased risk of EPL, particularly when it amounts to 25 percent or more of the volume of the gestational sac (image 1 and image 2) (Pearlstone M and Baxi L. 1993). In a meta-analysis of seven comparative studies, women with sub chorionic hematoma had double the odds of EPL compared with women without (18 versus 9 percent, OR 2.18, 95% CI 1.29-3.68) (Tuuli M. *et.al.*, 2011). Location of the hematoma also appears to impact outcome, with worse outcomes reported for retro placental versus marginal hematomas. Data on the impact of hematoma size and outcome are inconclusive (Oliver-Williams C. and Steer P., 2015).

Histopathological:

Placenta accrete spectrum (PAS) is a condition of abnormal placental invasion encompassing placenta accreta, increta, and percreta and is a major cause of severe maternal morbidity and mortality (Burton G., 2017). PAS refers to a spectrum of abnormal placental adherence ranging from the subclinical (often-microscopic) finding of adherent myometrium fibres within the basal plate to a dramatic presentation of placenta percreta, where there is placental invasion through the uterus and the serosa into the peritoneal cavity or bladder. Traditionally, PAS thought to occur because of a localized uterine injury (e.g., previous caesarean section) which can result in locally defective decasualization/scarring and abnormal placental adherence in a subsequent pregnancy. Although typically attributed to previous caesarean delivery, even small disruptions to the lining of the uterus can result in subsequent placenta accrete (Dannheim K., *et.al.*, 2016). While interactions between the maternal-fetal interfaces may also play a role in the pathogenesis of placenta accreta, this is beyond the scope of this article, and a number of studies describing the pathology of PAS in detail have been published (Collins S., 2018). Abnormal adherence of the placenta to the myometrium is

established in very early pregnancy and can be subdivided into placenta accreta (where chorionic villi directly implant on to the myometrium), placenta increta (where chorionic villi invade into the myometrium), and placenta percreta (where chorionic villi invade through the myometrium and may involve surrounding structures). Placenta accreta is the most common component of PAS and accounts for 75% of cases. Mild forms of PAS may present as retained placenta that may require manual removal. When PAS is identified, the placentas are more often affected by chronic basal inflammation, changes of maternal vascular perfusion, and retro membranous and sub chorionic/intervillous hemorrhage (Ernst L., *et.al.*, 2017).

Figure 1: Histopathology of placenta accreta syndrome. (a) High-power picture of decidualized endometrium because of pregnancy. Stromal cells are large, pale, and polygonal. (b) Low-power image of decidualized endometrium on the surface with underlying congested myometrium blood vessels and myometrium. (c) Low-power image of PAS showing chorionic villi in direct contact with myometrium (no intervening decidua). (d) Chorionic villus with polar trophoblast invading myometrium muscle. (e) No adherent area of the same placenta where decidua between villi (bottom right) and myometrium (top left). (f) PAS—chorionic villi in direct contact with muscle; a multinucleated extra villous trophoblast is seen in the top right.

The diagnosis of a PAS based on histopathologic examination and characterized by an absence of decidua and chorionic villi

directly adjacent to myometrium fibres (Figure 1). Although not visible macroscopically, microscopic examination of the placenta may confirm the presence of (placental) basal plate myometrium fibres (Figure 1); although this finding can be seen in normal pregnancies, their presence is thought to indicate abnormal placental separation. Perhaps more importantly, basal plate myometrium fibres are associated with an increased risk of a morbidly adherent placenta in a subsequent placenta/pregnancy (Miller E., *et.al.*, 2016). This review highlights the paucity of data addressing the clinical value of routine histopathological examination of products of conception in cases of recurrent spontaneous abortion, a common and clinically significant problem. Presently available data indicate that a small subgroup of women with recurrent Spontaneous abortion may show evidence of CHI or massive per villous fibrin deposition, both of which are histopathological diagnoses which may influence future reproductive management but which affect only around 1 in 200 to 1 in 2000 pregnancies, respectively (Jacques and Qureshi, 1993 ; Katzman and Genest, 2002). With no reliable data on their prevalence in the setting of miscarriage specifically. An additional minority will miscarry due to hydatid form mole, which is of major clinical significance because the patient requires both surveillance for the detection of persistent gestational trophoblastic neoplasia and may also be at risk for recurrent mole in future pregnancies. Rarely, recurrent pregnancy losses may be due to familial hydatid form mole syndrome in which there are recurrent, usually complete, hydatid form moles of parental rather than androgenetic origin, which is probably a consequence of dysregulation of imprinting (Fisher, *et. al.*, 2004). A further subgroup, most notably those with APL syndrome, may demonstrate abnormalities of trophoblastic invasion indicating the possible mechanism of the loss. However, this information may not alter further management because the APL status is usually determined on clinical screening as part of the assessment for recurrent spontaneous abortion. The remainder of patients, the majority, may simply have intrauterine products of conception confirmed. In these cases, the products may be further morphologically classified to suggest

possible fetal aneuploidy or estimate the timing of intrauterine death using previously suggested histopathological classifications (Rushton, 1978), but both of these issues can be more reliably determined by other means, karyotyping and serial sonography, respectively. Additionally, there are practical issues that make specific interpretation of such routine histopathological samples problematic, including the limited and fragmented nature of the tissues, and the difficulty in determining which events, if any, are primary etiological factors and are simply consequences of the pregnancy failure (Jauniaux and Burton, 2005). At present, therefore, routine histopathological examination of products of conception in patients with recurrent spontaneous abortion only rarely provides significant additional specific information in determining the cause of the recurrent loss or influencing future management. Several studies have attempted to supplement routine morphological examination with immunohistochemically markers of infiltrating cells, usually leukocyte subpopulations; however, at present, these have no direct implications for clinical practice. In addition, further studies have used specialist research techniques not applicable to routine practice, such as the detection of auto-antibodies to adhesion molecules which may interfere with anchoring villi formation (Aplin *et al.*, 1998). Testing sera from recurrent spontaneous abortion patients in trophoblast adhesion assays (Bulla, *et al.*, 1999). In vitro detection of

persistent NK cell expression of CD56 and reduced expression of trophoblast HLA-G in recurrent spontaneous abortion (Emmer, *et al.*, 2002). However, these data are inconsistent and, until further studies have been undertaken, are unlikely to affect clinical management. There is now a growing body of evidence, based on pathological data, that many miscarriages may be associated with impaired early trophoblastic invasion, premature intervillous space blood flow, fragmentation of the trophoblastic shell and subsequent oxidative damage (Khong *et al.*, 1987; Michel *et al.*, 1990; Jauniaux and Burton, 2005), although not all studies support these findings (Ball *et al.*, 2006). However, despite these general findings, there remains poor correlation between specific histological features and the etiology of the miscarriage (Jauniaux and Burton, 2005), and recurrent spontaneous abortion cannot be reliably distinguished from sporadic losses on this basis. Furthermore, the identification of many such pathological features requires placental bed biopsies, an additional sampling technique not used as part of routine therapeutic uterine evacuation. Although implantation site fragments may be present in routinely evacuated material and can provide some information regarding trophoblastic invasion, extrapolation of events deeper in the placental bed from superficial decadal fragments may be misleading (Sebire *et al.*, 2002; Ball *et al.*, 2006).

placentation remains elusive (Lawrence J.B. and *et.al.*, 1999). . With further supporting data from larger study populations, it may be possible for biomarkers to be combined with sonographic and MRI imaging to screen for PAS antenatally in a model similar to that used for aneuploidy screening. The benefit of this remains unknown until more prospective data are available (Oztas E. and *et.al.*, 2016). Areas for future research may include those biomarkers in use at preclinical/investigational level in the investigation of aneuploidy and disorders of placentation such as preeclampsia. Optimal timing of marker sampling for suspected cases of PAS also warrants further investigation. Future Work. Our understanding of the underlying molecular biology of PAS is limited. The current evidence supports the theory that

CONCLUSION

In summary, a limited number of studies that have contributed too understanding of the molecular biology of PAS; however, it does bear many similarities to cancer biology. Chronic basal inflammation combined with a failure of normal placental apoptosis appear to partially explain the underlying biology of invasive placentation with associated angiogenesis. Further studies needed fully understand these processes. A number of potential serum biomarkers have been investigated in PAS. They have shown variable reliability and variability of measurement depending on gestational age at sampling. At present, a sensitive serum biomarker for invasive

PAS occurs due to a failure of a normal decidua to form, which may form an invasive niche similar to the metastatic niche seen in cancer biology. This may result from a deficient endometrium, such as in the presence of a uterine scar, or where there is no normal endometrium to transform into decidua, such as in a tubal ectopic pregnancy (Craven C. and *et.al*, 2002). A number of studies have shown that tubal ectopic pregnancy results in immunologically normal and hormonally active trophoblast cells (Vassiliadou N. and Bulmer J., 1998). Therefore, tubal ectopic pregnancies

may offer a model to gain more insight into the molecular processes underlying invasive placentation. Furthermore, additional research needed that compares uterine specimens of PAS to those with a uterine scar and no evidence of PAS. An improved understanding of this biology may allow us to implement novel preventative strategies in the future leading to a reduction in this profoundly morbid condition.

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