Placenta Accreta and Placenta Increta: An Approach to Pathogenesis Based on the Trophoblastic Differentiation Pathway

PLACENTA ACCRETA AND PLACENTA INCRETA - AN APPROACH TO PATHOGENESIS BASED ON THE TROPHOBLASTIC DIFFERENTIATION PATHWAY

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Abstract

Morbid adherence remains a puzzling disease. This paper suggests that normal and morbidly adherent placentation may best be viewed in terms of trophoblastic stem cells, and the mutually exclusive branches of the trophoblastic differentiation pathway - villous trophoblast, interstitial and endovascular nonvillous trophoblast (NVT) at the implantation site, and a positional variation in the chorion. Based on hysterectomies for morbid adherence seen over 30 years at a community hospital; analyzed with routine keratin stains, with actin and trichrome stains as indicated, and attempts at sonographic-pathologic correlation; we present selected observations. In true accreta, the site of morbid adherence was to dilated basal plate vessels, infiltrated by endovascular NVT; with scant interstitial NVT, and normal myometrium. It appeared that excess blood flow into the placenta was due to excessively deep keratin-positive endovascular NVT that spread - independently of interstitial NVT - in an angiocentric fashion, in both accreta and increta. Retroplacental abnormalities were due to myometrial destruction by interstitial NVT in increta, sometimes requiring actin stains for detection; and to an admixture of markedly dilated endometrial glands and vessels in true accreta, best appreciated with keratin stains. Variations of depth and extent in increta may be due to variations in myometrial tone, and in the protease-antiprotease balance. Morbidly adherent fetal membranes are described. The role of C-section scars in incretas is addressed.

Introduction

Morbid adherence remains an unsolved puzzle. Standard teaching has been that chorionic villi adhere to normal myometrium in placenta accreta; while villi invade myometrium in placenta increta; but this has been questioned by experts (1-3). Although increased morbid adherence after Cesarean section indicates that decidual deficiency promotes life-threatening myometrial invasion; many doubt that decidual deficiency fully explains morbid adherence (4-9). Although limited myometrial infiltration may be normal (1,9,10), criteria are ill-defined, so myometrial thinning may be needed for diagnosis (1). Sonographic diagnosis can promote Cesarean hysterectomy and save lives; but more work is needed on sonographic-pathologic correlations (6,11,12). There is an increasing trend towards immunohistochemical and molecular study of morbid adherence, but the protease-antiprotease balance in normal vs. abnormal trophoblast is largely unexplored (2,6,13-18)

This article suggests that progress may come from viewing the difference between normal placentation and morbid adherence in terms of stem cell theory; based on the concept of a trophoblastic differentiation pathway. Despite universal belief in stem cell theory, many pathologists are not accustomed to interpreting slides of hysterectomies for morbid adherence using this approach. We will start by explaining our preferred concepts and terminology.

Trophoblastic Stem Cells

The fundamental principle of stem cell theory is that "Normal stem cells arise during development, are present in adult organs as tissue-determined stem cells, and are little changed, if at all, from their embryonic counterparts" (19-21). In placentas, the starting point is the trophoblastic shell; as seen in both early products of conception, and early tubal pregnancies (Figure 1a). We believe that these are the trophoblastic stem cells. These stem cells proliferate tremendously in order to generate both villous and nonvillous trophoblast, which have low proliferative rates; even in exaggerated placental sites (1,10,22).

Although this has been referred to as the cytotrophoblastic shell (9); this terminology is incompatible with stem cell theory. This is because villous cytotrophoblast is a more restricted cell type than stem cells in the trophoblastic shell, which are pluripotential (Figure 1a) and highly proliferative. Figure 1a shows that the trophoblastic shell gives rise to villous trophoblast (VT) in a way that is mutually exclusive with its generation of nonvillous trophoblast (NVT); which includes both interstitial NVT and endovascular NVT (23).

The trophoblastic shell withers away, so as to integrate the VT differentiation pathway, and the bidirectional NVT differentiation pathway on the other side of the early placenta, into a fully developed placental disc. Note that in Figure 1a, both VT and interstitial and endovascular NVT are already present while the trophoblastic shell still dominates. We suggest that the anchoring villi thought by some to play a role in morbid adherence (6,11,24) may represent the final stage in this process of withering away. Ki67 stains support the interpretation that the trophoblastic columns at the tips of anchoring villi are the last conspicuous remnants of

proliferative trophoblastic stem cells (9,10). In our view, stem cell theory suggests that villous trophoblast does not give rise to nonvillous trophoblast; so nonvillous (extravillous) trophoblast between villi and myometrium (2,3,11) may be derived from residual trophoblastic stem cells.

The Trophoblastic Differentiation Pathway

Despite some similarities in cytology and immunostains (2,6), VT and the 2 types of implantation site NVT are not only in mutually exclusive locations (Figure 1a); they are also arranged differently, to mediate different functions, suggesting different patterns of gene activation and protein expression. VT manifests orderly progression from cytotrophoblast to syncytiotrophoblast, so as to regulate transplacental diffusion; which requires intact villous basement membranes.

In striking contrast, it is essential for NVT to destroy basement membranes. Interstitial NVT anchors the placenta to the uterus, largely by attachment to laminin in basement membranes (15). Fully differentiated decidual cells comprise a massive laminin factory (25). To achieve stable anchoring, interstitial NVT uses proteases to break down basement membranes (15-17,26,27), so it can invade deeper. Decidua not only provides a deep anchor (25), but is also a barrier to pathologic myometrial invasion, promoting survival of pregnant women (5,8,10). Although limited myometrial infiltration by interstitial NVT is considered normal (1,9,10); it is not considered normal for interstitial NVT to destroy myometrium.

To promote fetal growth, the endovascular branch of the NVT differentiation pathway may be induced when NVT encounters arterioles (Figure 1a, lower left, arrow). This implies that pluripotential NVT cells may be present amongst the

interstitial NVT; but no immunohistochemical marker yet exists to identify either pluripotential NVT cells, or residual trophoblastic stem cells in the fully developed placenta. The difficulty of identifying residual stem cells is well recognized in other differentiation pathways (20).

Endovascular NVT binds to vascular basement membranes, invades these vessels, transiently plugs vascular lumens; and transiently replaces the endothelial lining. In striking contrast to interstitial NVT, which does not produce myometrial fibrinoid; endovascular NVT uses proteases to convert spiral artery smooth muscle to fibrinoid, so as to prevent vasospasm that might compromise the fetus. Although destruction of smooth muscle in deeper myometrial arteries can be incomplete, endovascular NVT permits physiologically transformed vessels to massively increase blood flow into the intervillous space (23).

In comparison to interstitial NVT, endovascular NVT not only has a mutually exclusive location (Figure 1a), it also has:

a) different target tissues (vascular smooth muscle and endothelium vs. decidua and myometrium),

b) different functions (vascular remodeling to amplify and redirect blood flow vs. stable anchoring that nonetheless facilitates placental separation); and

c) different normal outcomes (smooth muscle destruction and replacement with fibrinoid, combined with transient replacement of endothelium vs. failure to destroy decidua or produce fibrinoid in the myometrium).

This is strong evidence that endovascular and interstitial NVT are mutually exclusive pathways of trophoblastic differentiation. Our observations will

demonstrate further evidence of mutual exclusivity in morbid adherence.

Lastly, in the fetal membranes, there appears to be a positional variation. Normal chorion is composed of trophoblast that does not invade myometrium, and manifests no endovascular spread. However, NVT in early products of conception can have keratin-positive dendrites that connote their infiltrative nature (Figure 1b). This study does not address NVT in chorionic cysts or placental septa.

Although the term intermediate trophoblast is useful in trophoblastic neoplasia (13,22), it is inadequate to distinguish all these pathways of trophoblastic differentiation. Similarly, the term extravillous trophoblast (EVT) merely connotes a difference in location (2,11). EVT does not distinguish trophoblastic stem cells from either the bidirectional pathway in the placental disc, or trophoblast in normal chorion of the fetal membranes. Although much work remains to be done, this paper demonstrates that viewing morbid adherence in terms of stem cell theory suggests new ideas that merit further study.

MATERIALS AND METHODS

This is neither a review article; a systematic prospective study; nor a retrospective comparison of morbid adherence to "normal controls" (9,10). Its limited ambition is to present evidence that viewing morbid adherence in terms of stem cell theory suggests new ideas that merit future study. It presents selected illustrations, collected from a few dozen cases of morbid adherence examined over 3 decades at a university-affiliated community hospital (about 1-2/year); with routine use of keratin stains (MAK6 or AE1/AE3); actin stains (MSA or SMA) and connective

tissue stains (trichrome, Elastic van Gieson, Kreyberg[1]) (28) as needed; and attempts at sonographic-pathologic correlation. The uteri were generally received fresh, opened, and sliced to facilitate formalin fixation; although emergency cases on nights and weekends were stored in a refrigerator in the operating room, prior to delivery. There are cases diagnosed on sonograms, leading to Cesarean hysterectomy (1,5,7,8); cases with blood loss following attempted placental delivery (24); increatas in Cesarean scar pregnancies from 1st trimester to term (5,7,8); and cases of uterine inversion (1,29), with observations on delivered placentas (2,9). Altogether, the illustrations come from 7 selected cases in the teaching files.

RESULTS

Selected Observations on Morbid Adherence

In a term Cesarean hysterectomy, placental attachment was from the isthmus to upper corpus (Figure 2a); but this was discontinuous. The procedure was done because the sonographer warned that placental delivery might cause hemorrhage (6,11). Because the myometrium was not invaded, this qualifies as a true accreta (1,9,10,24). True accreta (accreta vera) was defined as adhesion without invasion, to distinguish it from placenta increta; as opposed to the continuing clinical practice of lumping accreta vera and increta together as placenta accreta (7,24). All other accretas diagnosed in this series had placental delivery, with hemorrhage leading to postpartum hysterectomy. This case may be unique in the literature, since other

[1] The Kreyberg stain was developed by the author of the WHO "blue book" on lung cancers, L. Kreyberg,(Br J Cancer 1961;25:206-10). It has long been popular in Rochester, NY(Churukian CJ, Schenk E, J Histotechnology, Volume 7, 1984). It has trichrome qualities; since it stains collagen yellow and ground substance blue, while fibrin and muscle are red. It is a very quick, easy, and reproducible stain.

studies reported no term Cesarean hysterectomies for true accreta (9,10). Fetal membranes were normal in this case.

Despite similar sonograms, other term Cesarean hysterectomies showed incretas of the inner third. Although these were also adherent from isthmus to upper corpus, the attachment was continuous (Figure 2b). Degree of myometrial thinning was quite variable, as noted by others (24). In some cases, fetal membranes were so diffusely and firmly adherent that the uterus could be lifted by a clamp on the morbidly adherent fetal membranes (MAFM)(Figure 2c).

In contrast, term Cesarean hysterectomy for Cesarean scar pregnancy could be attached only in the lower uterus, qualifying as partial increta (9,10,24), while penetrating deep into the outer third (Figure 2d). Partial accreta (and increta) have been defined as involving more than one cotyledon, focal accreta (or increta) as involving only 1 cotyledon, and complete accreta (or increta) as involving all cotyledons (24). In contrast to a report of 10 Cesarean scar pregnancies (5), percreta was not universal in Cesarean scar pregnancies. A possible histologic explanation was noted (see below). Fetal membranes could be grossly normal in Cesarean scar pregnancies.

In uterine inversion with placental delivery, there was no gross increta at the dome implantation site, but morbidly adherent retained membranes in the mid-corpus were so tightly bound that the uterus could be lifted off the dissecting table with a clamp on the retained membranes (Figure 2e).

Pathology of True Placenta Accreta in a Cesarean Hysterectomy

The site of morbid adherence was dilated basal plate vessels in the decidua. This explained the discontinuous morbid adherence, and validated the sonographic warning that placental delivery might lead to hemorrhage. Furthermore, vascular wall smooth muscle might well have been seen on the maternal surface of the delivered placenta (30). These basal plate vessels had markedly irregular walls; shown on the actin stain to vary from thick to thin to moth-eaten to almost totally destroyed (Figure 3a). There was more preservation of smooth muscle than in normally transformed spiral arterioles. Keratin stain showed conspicuous endovascular NVT in these basal plate vessels, with markedly dilated subjacent endometrial glands (Figure 3b). Both actin (Figure 3c) and keratin stains showed intravascular villi in these vessels. When basal plate vessels with abnormal smooth muscle and intravascular villi were seen in other delivered placentas, this was reported as raising the question of occult accreta.

Although the decidua above these vessels looked like normal implantation sites, the lower endometrium lacked conspicuous decidualized stromal cells and interstitial NVT. Instead, there was a spongy zone (Figure 3d), correlating with the retroplacental abnormality seen on ultrasound. Keratin stain showed that some spaces were markedly dilated endometrial glands, while others were markedly dilated vessels (Figure 3e). These anomalies distinguished this true accreta from implantation sites in hysterectomies for uterine atony.

Routine keratin stain showed that the dilated vessels in the spongy zone were supplied by abnormally deep vessels involved by endovascular NVT. Actin

stain showed these spongy zone vessels had intact smooth muscle. No spongy zone vessels had the fibrinoid that is considered "physiological" (9). Keratin stain with a Kreyberg counterstain showed irregularity of the endomyometrial junction; which had markedly dilated endometrial glands; and essentially normal myometrium (Figure 3f). Even if one might describe this true accreta as partly deficient in decidual cells, it did not predispose to myometrial infiltration by interstitial NVT.

Selected Observations on Sonographic-Pathologic Correlation of Chaotic Intraplacental Blood Flow (Venous Lakes).

Sonograms of true accreta or increta show abnormal intraplacental blood flow, sometimes referred to as chaotic, or as "venous lakes" (6,11,31). This correlated with excessively deep endovascular NVT in larger vessels, best seen with keratin stains (Figure 4a). In both true accreta and inner third increta, endovascular NVT went deeper than interstitial NVT, and deeper than seen in normal implantation. These larger deeper vessels were demonstrated in other accreta cases with a trichrome stain (Figure 4b), showing hyalinized vessels lacking intact muscle. These larger deeper abnormal vessels tend to be dilated, as noted by others (9), presumably reflecting excess blood flow into the placenta.

In this study, keratin stains did not always demonstrate endovascular NVT in cases of morbid adherence. Endovascular NVT was not seen in dome implantation associated with uterine inversion; or in sections of morbidly adherent membranes. In a term deep increta invading the CS scar, there was insufficient myometrium deep to the scar to detect endovascular NVT. In a 1st trimester Cesarean scar pregnancy with increta (Figure 4c), detected on a sonogram, the keratin stain was negative for

endovascular NVT (Figure 4d). The thin layer of keratin positive trophoblast on the surface was not placenta membranacea, which is composed of well developed villi in an intervillous space. There was no intervillous space, just sparse villi in a flat sheet of trophoblast, consistent with withering away of the trophoblastic shell, as compared to Figure 1a. Dilated vessels were seen in the C-section scar (Figure 4c), and deep to both the scar and implantation site were large parametrial arteries; providing a possible explanation for increased blood flow.

Selected Observations on the Retroplacental Zone of Placenta Increta

Retroplacental myometrial pathology was always present in placenta increta, as seen by others (9); although it was sometimes necessary to do actin stains for detection or confirmation. In a term increta of the inner third, the retroplacental zone showed conspicuous degeneration, edema, and mild chronic inflammation of inner myometrium (Figure 5a). At first glance, this might resemble autolysis; where tissue breakdown is mediated by tissue enzymes. This similarity should not be surprising if myometrium is being destroyed by placental proteases in increta. However, specimens had been processed so as to prevent autolysis; and in contrast to autolysis, nuclei were generally well preserved; with notable chronic inflammation, as seen by others (9).

Myofibers infiltrated by interstitial NVT were small, ragged, and irregular, as compared to normal gestational hypertrophy of myometrial cells. In this and other incretas (Figure 5b) and percretas, intravascular chorionic villi were seen in the myometrium. Figure 5b also demonstrates small, degenerated myofibers in the basal plate. Inflamed degenerated retroplacental myometrium in a 1st trimester

laparoscopic hysterectomy for sonographic placenta accreta in a Cesarean scar pregnancy at 6 weeks; was best seen with an actin stain (Figure 5c). In marked contrast was a huge hypocellular zone in a term Cesarean scar pregnancy with deep increta; with only a few scattered NVT and shrunken myofibers adjacent to a CS scar infiltrated by interstitial NVT (Figure 5d).

The CS scar infiltration was in a zone of massive globular elastosis (Figure 5e)(28). The pale staining zone of elastosis in the trichrome stain was dark black on the Elastic van Gieson stain (28). Keratin stain confirmed that the cells in the elastosis were interstitial NVT. We have seen massive globular elastosis in unstable C-section scars that ruptured, and it is common both in postablation scars and the outer wall scars that were formerly diagnosed as fibrosis uteri (28). This elastosis may possibly have resisted protease digestion, allaying progression to percreta (5). Globular elastosis was also seen in the 1st trimester C-section scar in Figure 3c.

Selected Observations on Uterine Inversion

Examination of the dome implantation site - in a case where a term uterine inversion was surgically corrected, with no subsequent bleeding - showed absent decidua, despite the lack of a known predisposing factor (Figure 6a). Although subjacent muscle fibers were shrunken and degenerated, consistent with inner third increta (Figure 6b), the interstitial NVT was indistinguishable from normal myometrial infiltration (1), and endovascular NVT was not observed.

This, and delivered placentas in other cases, had myofibers on the maternal surface. There were also small irregular spindle cells inside the basal plate, with isolated NVT cells and spindle cells in basal plate fibrinoid. Actin stain showed

degenerated muscle both on the maternal surface and higher up in the basal plate (Figure 6c). Report of this finding led to a postpartum ultrasound, which reported retained cornual placenta, but no accreta (31). Retained cornual placenta led to a delayed postpartum hysterectomy, for fear of cornual perforation.

During the hysterectomy 5 days later, the cervix unexpectedly fell apart in the surgeon's hands, with massive blood loss. No percreta of cervix was seen by the surgeon, but only 1 mm separated the placenta from the outside of the cervix. On pathologic examination, there was deep increta in both the cornu and the cervix. There were many involuted and obliterated placental site blood vessels in the myometrium; and there were also dilated thrombosed subinvoluted vessels (1).

In another term inversion, there was continued bleeding after placental delivery, despite surgical correction of the inversion; requiring immediate postpartum hysterectomy. There was hemorrhagic necrosis of superficial dome myometrium, consistent with early venous infarction, due to grossly obvious myometrial venous thrombosis; secondary to the inversion. Lines of Zahn were seen in the thrombi. Deeper dome myometrium was markedly edematous (29). This case had morbidly adherent retained fetal membranes, but no gross increta. Despite microscopic implantation in endocervix , there was no increta in the cervix.

Selected Observations on Pathology of Morbidly Adherent Fetal Membranes

Sections of morbidly adherent fetal membranes (MAFM) included both decidua and myometrium. In a term inner third increta with diffusely attached MAFM, there was an undulating chorion, with variable distance between chorion and myometrium, and a heterogeneous decidual matrix (Figure 7a). Unlike sections

of normal membranes, fibrinoid was focally prominent in the decidua (Figure 7b). The keratin stain showed alternating zones of infiltrative and noninfiltrative chorionic NVT, but no endovascular NVT (Figure 7c). An infiltrative pattern on the left in Figure 7c corresponds to an area on the left with prominent fibrinoid in Figure 7a. The lower decidua had dilated endometrial glands, which are not seen in normal membranes. When dilated endometrial glands have been seen in fetal membranes from a delivered placenta, basal plate myofibers were looked for and found on the maternal surface of the placenta; suggesting that this can be a sign of clinically occult morbid adherence.

In a case of uterine inversion with no gross increta, but with retained MAFM after placental delivery, the keratin stain showed less undulation of the chorion, and markedly dilated endometrial glands (Figure 7d), as compared to Figure 7c. At high magnification, a raggedly irregular infiltrative pattern of chorionc NVT was reminiscent of protease-mediated stromal invasion in cancers (32)(Figure 7e). Actin stain in this case showed focal muscle destruction under MAFM (Figure 7f). Infiltrative interstitial NVT was seen at this site; but there was no endovascular NVT.

DISCUSSION

The Role of Villous Trophoblast in Morbid Adherence

Standard teaching about morbid adherence is that chorionic villi adhere to or invade the myometrium, but some experts have taken tentative steps away from this dogma (1-3,9,11). Kraus, Redline, Gersell et al noted in the AFIP Fascicle that: "In placenta accreta, it is a common misperception that well vascularized villi must

directly abut smooth muscle"(3). Stanek and Drummond used actin and keratin stains to demonstrate that "between the myometrium and chorionic villi there are only the extravillous trophoblasts and Rohr fibrinoid, but no decidua" (2). An article on ultrasound and MRI by Benirschke et al illustrated accreta with the comment: "Note that the extravillous trophoblast is adherent directly to myometrium…"(11); and this was also observed by Khong and Robertson (9). An open break with prevailing dogma in the former paper was avoided by the statement that defective decidua allows "anchoring villi to penetrate myometrium" (9,11,15). However, current evidence suggests to us that the trophoblastic columns at the tips of anchoring villi (9,10) are highly proliferative residual trophoblastic stem cells, remnants of the withering trophoblastic shell.

We assert that routine keratin stains in hysterectomies for morbid adherence always demonstrate nonvillous trophoblast at the invading front. Based on our view that NVT derives from pluripotential, highly proliferative trophoblastic stem cells, as a mutually exclusive branch of the trophoblastic differentiation pathway; we suggest that morbid adherence is a disease of nonvillous trophoblast. .

Pathogenesis of True Placenta Accreta

The pathologic analysis of true accreta in a term Caesarian hysterectomy in this report may be unique in the literature (9,10,24). Postpartum hysterectomies after placental delivery (9,10) may be suboptimal for demonstrating the dilated basal plate vessels, spongy zone, and essentially normal myometrium with little or no interstitial NVT seen in this case. We suggest that limited understanding of the

pathogenesis of true accreta may often lead to classification of early increta as true accretas. There are 2 criteria for recognizing an early increta: 1) actin-positive shriveled myofibers may be located in the basal plate between the maternal surface and the villi; 2) shriveled retroplacental myofibers may be easily overlooked without an actin stain; leading to classification of some early incretas as true accretas (Figures 5b,c). Myometrium should be normal in true accretas (1).

More study of true accretas in Cesarean hysterectomies is needed, but several points bear emphasis:

1) Morbid adherence of this true accreta occurred in the endometrium. The risk of massive hemorrhage, and discontinuous attachment on gross exam, reflected morbid adherence to strikingly dilated basal plate vessels with keratin-positive endovascular NVT and degenerated vascular smooth muscle. Deficient endovascular NVT effects in accreta have been seen by others (9,10). True accreta is among the diseases of endovascular NVT (23,33).
2) As per standard teaching (1), this true accreta had normal myometrium; despite morbid adherence, and sonographic recognition of both an abnormal retroplacental zone and blood lakes in the placenta (6,11). Interstitial NVT appeared less than normal, with little or no myometrial infiltration.
3) The retroplacental zone seen on ultrasound in true accreta was composed of admixed markedly dilated endometrial glands and vessels. Dilated endometrial glands are characteristic of implantation sites (23,34,35). This may reflect NVT-induced secretion of glycogen-rich fluid to nourish the early embryo. In true accreta, endometrial glands are markedly dilated.

4) Intravascular chorionic villi in the basal plate are currently considered normal (1). However, they were observed in this true accreta in vessels with abnormal smooth muscle architecture; in superficial myometrium of inner third increta; and in deep myometrium of percreta. Further study of intravascular villi in the basal plate, in relation to normal vs. abnormal vascular smooth muscle, appears to be warranted.

Role of Endovascular NVT in the Pathogenesis of Sonographic Blood Lakes

Chaotic intraplacental blood flow, also known as blood lakes or venous lakes, is characteristic of both true accreta and increta on ultrasound (6,11,31). These blood lakes are inside the placenta. Transformation of endometrial and inner third myometrial arteries by endovascular NVT is the generally accepted mechanism of adaptation to support normal intraplacental blood flow; although deeper vessels can be involved to a lesser degree, with some residual intact smooth muscle (23). Keratin stains in hysterectomies for morbid adherence suggest that larger deeper vessels are transformed by endovascular NVT, leading to the excessive intraplacental blood flow seen on ultrasound. This has been seen by others in increta (9,10), but it appears that routine keratin stains may be needed to detect deep endovascular NVT in true accreta. Dilated vessels in the basal plate and spongy zone may reflect resistance of the intervillous space to increased blood flow.

The increased blood flow due to deep vessel involvement by endovascular NVT may possibly explain intravascular villi in the basal plate and myometrium, if villi are “carried along” in the increased venous drainage from the intervillous space.

Their presence in inner myometrium in early increta and deep myometrium in percreta may not reflect significantly greater displacement from intravascular villi in the basal plate, if myometrium is driven up towards the placenta by myometrial tone (see below). Alternatively, intravascular villi may be developmental anomalies that occur as the trophoblastic shell withers away. It is our subjective impression that intravascular villi are seen more in term placentas than earlier placentas, suggesting that they are an acquired anomaly.

Discordance between depth of endovascular NVT and interstitial NVT is common in increta, and has been seen by others (9,10); and measurements have shown significantly greater penetration than normal depth of endovascular NVT (10). These deep vessels are often dilated, as noted by others (9). We suggest that endovascular NVT is a mutually exclusive branch of the NVT that can spread deeper (more obvious with routine keratin stains) because it spreads along blood vessels in an angiocentric fashion. A similar mechanism of spread has been observed during prenatal nevogenesis, where the favored descriptive term was angiotropic spread (22,36). Further work is needed to explore if there are different proteases and/or protease inhibitors in endovascular NVT. It is known that proteases unique to the placenta appeared during evolution (26), and that proteases and their inhibitors are very heterogeneous (18,27).

The present report suggests that endovascular NVT may not be induced in all morbid adherence. In a 1st trimester Cesarean scar pregnancy, with no endovascular NVT on the keratin stain; increased blood flow through the scar was suggested by

vascular ectasia, possibly deriving from large parametrial arteries near the C-section site. This may be an alternative explanation for blood lakes in the placenta. In addition, endovascular NVT was not seen in dome implantation associated with uterine inversion, or in morbidly adherent fetal membranes.

Pathogenesis of Sonographic Retroplacental Zones in Placenta Increta

Despite literature since 2000 on occult placenta accreta and "early placenta accreta"; most recent attention has focused on increta or percreta (2,6,7,12,13). Occult accreta was defined as basal plate myofibers in association with deficient decidua in delivered placentas (2). In marked contrast, "early placenta accreta" was defined from a clinical perspective as a 2nd trimester placenta with "no myometrium between the placenta and the serosa or bladder" - histologically, these were cases of increta or percreta (7).

Hysterectomies done for increta always show retroplacental myometrial degeneration, edema, and mild chronic inflammation, explaining abnormal retroplacental zones on sonograms. Myometritis and hyaline degeneration have been observed by others (9), but shriveled myofibers are more easily recognized by actin and trichrome stains; as illustrated in this paper. These may be underdiagnosed on routine H&E stains. Shriveled myofibers were also seen in the basal plate in incretas. They can also be seen in postablation scars and C-section scars (28). Shriveled myofibers may help diagnose incretas, both in cases without sonograms (e.g., inversion cases) and in first trimester incretas; where actin stains may be necessary (2). Although NVT may infiltrate myometrium in normal

implantation, myometrial cells should be normal in the absence of increta (1).

Enhanced placental protease activity in IS NVT (15,16) is the likely cause of myometrial degeneration; which could be due to a deficiency of protease inhibitors and/or other decidual factors (14,17,18). This idea is supported by comparison to protease-mediated lung diseases:

1. When bacteria secrete proteases to generate nutrients (37), bacterial proliferation can lead to massive tissue destruction in lung abscesses. However, proliferation of interstitial NVT in morbid adherence is minimal (< 1mm, and <twice normal) (2,10,13); and to date there is no evidence to associate exaggerated placental sites with morbid adherence (1,13,22).
2. Neutrophil serine proteases can overwhelm antiproteases in cystic fibrosis, leading to potentially fatal chronic lung infections (38). There is no evidence of a role for neutrophils in morbid adherence.
3. Serine proteases in alveolar macrophages lead to premature emphysema in young smokers with alpha-1-antitrypsin deficiency (A1ATD)(18). This mechanism remains unexplored in morbid adherence, despite the fact that smoking is a risk factor for accreta (39).

The wide variety of alleles with highly variable phenotypes in protease inhibitor deficiency (18) might help to explain some of the wide variation in depth of penetration by interstitial NVT in increta (9,10,24). This wide variation accounted for skepticism of the decidual barrier concept in the past (9); since it was

not clear why every increta did not go all the way through the wall. Species variations in the interstitial NVT protease-antiprotease balance may also explain why thinner decidua in other species is not associated with deep myometrial invasion (9).

Also unexplained to date is the pathogenesis of partial vs. complete increta. Previous studies have confirmed our observation that previa creta often is not restricted to the C-section site of decidual deficiency (9,10,24). Protease inhibitor deficiency as a cofactor may explain involvement of the upper uterus in these cases.

It appears unlikely that increased interstitial NVT proliferation or invasion explains deeper incretas (10). Interstitial NVT usually does not "look" more invasive in incretas, as compared to "normal" infiltration (1). Indeed, the most ragged, irregular NVT we have encountered, resembling stromal invasion in cancers (32), has been infiltrative chorionic NVT in morbidly adherent fetal membranes. There is, in fact, reason to question that increta moves deeper in the wall as the myometrium beneath it disappears. The reverse is more likely, in our view.

It is often said, perhaps nonchalantly, that increta "eats" its way through the wall; but we suggest that this analogy to eating may be the literal truth. We point out that during true eating, swallowing occurs, with partly digested material moving away from the site of "ingestion". In morbid adherence due to increta, this implies that partly digested muscle fibers may end up in the basal plate, between the maternal surface and the villi; as observed in this study. This implies that some clinically occult cases with myofibers inside the basal plate may actually be early incretas.

Rather than the interstitial NVT moving down, we suggest that the myometrium may be moving up. This may be driven by myometrial tone, with the greatest pressure exerted by the larger, more parallel myofibers of the outer third (40-43). Since myometrium is a complex and heterogeneous muscular tissue (42) that can contract in various directions, uneven myometrial tone may at least partly explain the variable degree of myometrial destruction in increta s.

Similar considerations may explain why normal placental separation can occur despite myometrial infiltration by interstitial NVT (1). We suggest that "normal myometrial infiltration" may leave the involved myometrium sufficiently strong to resist shear stress, as the placenta is cleaved from the uterus (10). In contrast, degenerated myometrium in "occult cretas" may be too weak to resist shear stress, so that some myofibers come out with the delivered placenta; leading to suspicion of placenta creta on placental examination (2).

Pathogenesis of Uterine Inversion

Morbid adherence in the dome, causing uterine inversion, has received little attention (29). Although percreta of the dome was seen when this was the site of Cesarean section incision (24), we and others have not seen deep increta and percreta in the dome (29). Inversion cases were not diagnosed by sonograms, but microscopic retroplacental myometrial degeneration was seen; consistent with early increta s. The degree of myometrial NVT infiltration was within the spectrum of what is considered "normal" in other locations (1). We suggest that this can be explained in terms of basic dome biology.

The dome, cornus, and tubes derive from the upper Mullerian ducts (43).

Although cornus do not decidualize, decidua is seen in Fallopian tube segments resected at the time of delivery. However, this decidua is not generally observed in ectopic tubal pregnancies; supporting the suggestion that decidual deficiency can – to some extent – be the result of placental invasion and destruction (9,14). The lack of decidua at the dome implantation site in uterine inversion raises the question of inherent decidual deficiency. This needs study.

Although deficient dome decidualization might promote myometrial infiltration at implantation sites, it is suggested that the dome may have special defenses to pathologic myometrial invasion (deep increta and percreta). This is based on the observation that dome myometrium is both unique and essential to successful labor and delivery. Dome myometrium has a unique set of muscle bundles that contract so as to pull the cornus towards each other (28), which may help the dome provide downward pressure during uterine contraction. Perhaps the protease-antiprotease balance (15-18,27) is modified in the dome, to preserve and protect this vital function. More study is needed.

Two other aspects of dome biology merit further investigation. First is the observation that during development, hypoxia in utero may cause large fibrous scars in the dome (43). Such scars might negate effective dome contraction, leading to myometrial exhaustion. A search for dome scars in cases of uterine atony (29) should be on the to-do list of obstetric research.

Secondly, the shear stress that allows placental separation from decidua (10) needs further analysis in uterine inversion with dome implantation. When the dome

functions properly, it provides the downward force necessary to promote placental separation from myometrium, despite "normal" myometrial infiltration by interstitial NVT in the corpus. However, when implantation is in the dome, insufficient shear stress may be generated to disrupt what would otherwise be considered "normal" myometrial infiltration; so that attempted placental delivery results in uterine inversion.

Lastly, we note that uterine inversion due to dome implantation can coexist with endocervical implantation. This can range from incidental microscopic involvement to advanced increta with impending percreta. This wide phenotypic variation might be partly explained by a wide range of protease inhibitor deficiencies (18); with the fetus (placenta) providing protease variations, and the mother providing protease inhibitor variations. This needs more study.

Pathogenesis of Morbidly Adherent Fetal Membranes (MAFM)

The pathogenesis of MAFM is previously unexplored. Some might question whether diffusely adherent fetal membranes may reflect failure of labor to induce membrane separation in Cesarean hysterectomy; but we disagree because MAFM can be so tightly adherent that a pregnant uterus could be lifted off the dissecting table with a clamp on the membranes. We doubt that diffusely adherent fetal membranes in a Cesarean hysterectomy reflect failure of labor, since retained membranes in a postpartum hysterectomy looked more infiltrative and more deeply adherent. We note that a previous case of increta was illustrated as showing adherent myometrium to fetal membranes (9), but that retrospective study had no details

about gross pathology. We have seen over a dozen cases of MAFM, although they have not been systematically analysed other than to note that MAFM is usually associated with placental adherence in the upper corpus, dome, and/or cornu.

Microscopic study of MAFM suggests that morbid adherence can be limited to the upper decidua, or can have superficial myometrial infiltration with subjacent myometrial degeneration detected on actin stains. The lower decidua can have dilated endometrial glands, which is more striking in association with retained membranes. Keratin stains demonstrate a more infiltrative phenotype in retained membranes, as compared to diffusely adherent MAFM in Cesarean hysterectomies. There is heterogeneity of the decidual matrix, with more prominent fibrinoid at sites of more infiltrative chorionic NVT. In our experience, dilated endometrial glands and decidual fibrinoid in sections of fetal membranes may merit actin stains to evaluate for basal plate myofibers and/or subchorionic myometrial degeneration.

Proteases in Morbid Adherence

It is generally accepted that placental proteases mediate both anchoring of the placenta by interstitial NVT and destruction of vascular wall smooth muscle by endovascular NVT. Further study of placental proteases may lead to better understanding of both trophoblastic differentiation and morbid adherence. There is no inherent reason to expect that the trophoblastic shell has proteases that can break down basement membranes, unless they are blocked by antiproteases (16,17, 27). While interstitial NVT does have such proteases (15,16), it would seem that

589 such proteases must be either absent or blocked by antiproteases in VT, since
590 regulation of transplacental diffusion requires intact basement membranes.

591 It will go a long way to confirming our hypothesis that the trophoblastic
592 columns at the tips of anchoring villi are remnants of trophoblastic stem cells if they
593 are found to have the same protease-antiprotease phenotype as the trophoblastic
594 shell. It is already known that Ki67 stains distinguish VT and NVT from
595 trophoblastic columns in anchoring villi (10).

596 Endovascular NVT proteases that destroy smooth muscle in spiral arterioles
597 may differ from interstitial NVT proteases which destroy basement membranes.
598 Endovascular NVT proteases appear to be abnormal in true accreta (9,10). The same
599 may be true in increta (9,10). This may reflect variation in the protease-antiprotease
600 balance in endovascular NVT in morbid adherence. Paradoxically, endovascular NVT
601 goes deeper in both true accreta and increta (9,10). Depth of angiocentric spread
602 may be independent from degree of vascular smooth muscle destruction; since
603 depth of angiocentric spread is greater than normal (10), but replacement of
604 vascular smooth muscle by fibrinoid is less than normal.

605 Although infiltration of inner myometrium by interstitial NVT is considered
606 normal; destruction of myometrium by the proteases of interstitial NVT is evidence
607 of placenta increta; including clinically occult early incretas. We suggest that
608 variation in the protease-antiprotease balance (16-18,27) may distinguish the
609 interstitial NVT of increta from normal interstitial NVT.

610 Infiltrative chorionic NVT has a different morphology than noninfiltrative
611 chorionic NVT. Variation in the protease-antiprotease balance would be an expected

612 correlation with this finding. Since chorionic NVT does not normally infiltrate
613 myometrium; and since morbid adherence of fetal membranes can occur in the
614 decidua, without myometrial destruction; we suggest that protease-antiprotease
615 variations in chorionic NVT may differ from those in other NVT.

616 **Uterine Scars and Morbid Adherence**

617 It has recently been suggested that increta and percreta may gain access to
618 the deep uterine wall via uterine scars (10). This was based in part on analysis of
619 the data showing only a limited amount of proliferation and invasion by interstitial
620 NVT; a viewpoint with which we agree. The authors only observed 3 uterine scars in
621 their series of 38 cases, but 11 additional cases were located at the site of the prior
622 C-section incision. Although a previous series with 18 hysterectomies (9) reported
623 no detectable uterine scars, the possibility of limited sampling of C-section scars
624 applies to both series (9,10). However, ACOG Practice Bulletin 115 emphasizes that
625 not all CS scars are an obstacle to vaginal delivery (44), so the mere history of prior
626 C-section does not constitute evidence of the kinds of altered wound healing seen in
627 our previous work (28). A recent study emphasized that stretching of C-section
628 scars and isthmic myometrium can lead to a thin wall in hysterectomies for morbid
629 adherence (45), interfering with distinction of true accreta from increta; and
630 sometimes requiring trichrome stains to distinguish increta from percreta. This
631 study emphasized intravascular villi in myometrium as a criterion for increta. Based
632 on our experience with morbid adherence, and our histopathologic analysis of
633 uterine scars in hysterectomies for pain or bleeding (28); we endorse further
634 histologic evaluation of the relationship of uterine scars to morbid adherence (10).

It is not uncommon for cases of previa with suspected accreta to lack pathologic confirmation of accreta (11, 39, 46). In such cases, myofiber disarray and globular elastosis, consistent with abnormal wound healing in the isthmus, may preclude the contraction required to achieve isthmic hemostasis (28). Although loss of landmarks validates obstetric use of the term "lower uterine segment" (43); the pathologist can distinguish muscular-walled isthmus from fibrous-walled endocervix in postpartum hysterectomies. The research on C-section scars should include cases of previa with suspected accreta that is not confirmed on pathologic examination (28,39,46).

Some uterine scars may retard progression of myometrial destruction. Unstable scars with globular elastosis (28, 46) may be obstacles to protease-mediated destruction; since some proteases are less active against elastic tissue (18). We have noted association of a markedly hyopcellular retroplacental zone (Figure 5d) in myometrium in deep increta of a term Cesarean scar pregnancy with interstitial NVT infiltration of the adjacent C-section scar with massive globular elastosis. Elastotic outer corpus scars previously reported as fibrosis uteri, and the newly described pattern of inner corpus globular elastosis in hysterectomies done for pelvic pain; should also be scrutinized for relationship to increta. (28,47).

Conclusion

In normal placentas, the VT differentiation pathway appears to be mutually exclusive with the NVT differentiation pathway; and it appears that the interstitial and endovascular branches of the NVT pathway are also mutually exclusive. Selected observations on morbid adherence further suggest mutual exclusivity in

658 the branches of the trophoblastic differentiation pathway. Stem cell theory and the
659 concept of a trophoblastic differentiation pathway may help to better understand
660 morbid adherence in true accreta, increta, morbidly adherent fetal membranes, and
661 clinically occult cretas that are risk factors affecting future patient management.
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LEGENDS FOR ILLUSTRATIONS

Figure 1 – Trophoblastic differentiation Pathway

Figure 1a – Keratin stain of tubal pregnancy. The primitive trophoblastic shell gives rise to villous trophoblast and nonvillous trophoblast (NVT) on opposite sides of the shell. Interstitial NVT predominates, but endovascular NVT can be seen plugging the lumen of vessels in the lower left (arrow). A similar pattern has been seen in intrauterine products of conception.

Figure 1b – Keratin stain, products of conception. Interstitial NVT in myometrium (note spindle cells in background) has dispersed ”starfish cells” with keratin-positive dendrites that connote their infiltrative nature.

Figure 2 – Morbid Adherence

Figure 2a (left)– Morbidly adherent true placenta accreta extends to upper corpus, in a discontinuous fashion. Freshly sliced.

Figure 2b (right) – Morbidly adherent placenta increta irregularly invades and thins inner third of wall, from lower uterus to upper corpus, with continuous attachment.

Figure 2c - Morbidly adherent fetal membranes (MAFM) allow uterus to be lifted up off dissection table with a clamp attached to MAFM.

Figure 2d– Placenta of Cesarean scar pregnancy at term was attached only in lower uterus.

Figure 2e– Uterine inversion case had retained MAFM (arrow) after placental delivery, and uterus could be lifted up with a clamp on the retained membranes.

Figure 3 True Accreta

Figure 3a– Actin stain shows highly abnormal smooth muscle in huge basal plate vessels.

Figure 3b– Keratin stain of abnormal basal plate vessels showed endovascular NVT.

Figure 3c– Actin stain shows intravascular villi in abnormal basal plate vessels.

Figure 3d – True accreta has spongy retroplacental zone in lower endometrium. Kreyberg stain.

Figure 3e - Keratin stain with alcian blue counterstain shows dilated vessels and dilated endometrial glands in spongy zone.

Figure 3f – Keratin stain with Kreyberg counterstain shows irregular endomyometrial junction, with essentially normal myometrium.

Figure 4 – Blood Lakes

Figure 4a – Term inner third increta has angiocentric endovascular NVT going deeper than interstitial NVT, involving larger deeper dilated vessels than usual. Keratin stain.

Figure 4b – Deep large dilated vessel with endovascular NVT was clearly apparent on the trichrome stain, in a case classified as accreta after placental delivery led to hemorrhage. Clearcut myometrial thinning at lower uterine implantation site was not obvious (1), and myometrial infiltration by interstitial NVT appeared “normal” on H&E (1).

Figure 4c -Vascular ectasia (arrow) in C-section scar next to 1st trimester inner third increta. Trichrome stain.

Figure 4d – This 1st trimester increta had no endovascular NVT on keratin stain. The villi on the surface (arrow) appear to be anchoring villi, appearing as the trophoblast shell withers away. An insert shows a few of the anchoring villi at high magnification.

Figure 5 – Retroplacental Zone in Placenta Increta

Figure 5a – Retroplacental myometrial pathology of term inner third increta, correlating with sonogram superficially resembles autolysis, but nuclear detail is well preserved.

Figure 5b - Intravascular chorionic villi were often seen in retroplacental degenerated myometrium in incretas. Note shriveled myofibers in basal plate. Actin stain.

Figure 5c – 1st trimester Cesarean scar pregnancy had placenta increta of inner third, with retroplacental inflamed degenerated myometrium, correlating with sonogram. Actin stain

Figure 5d – Extremely hypocellular retroplacental myometrium was adjacent to C-section scar in term increta of lower uterus, with only a few NVT and a few shriveled myofibers.

Figure 5e - Trichrome stain of term deep increta (same case as Figure 5d) shows shriveled myofibers, normal myofibers (upper right), and infiltration of interstitial NVT into pale-staining massive globular elastosis of CS scar.

Figure 6 - Uterine Inversion

Figure 6a – Implant site in dome lacks decidua, with shriveled muscle in retroplacental zone.

Figure 6b - Interstitial NVT infiltrates shriveled retroplacental myometrium of dome. The NVT was indistinguishable from that seen in "normal" myometrial infiltration (1).

Figure 6c – Actin stain of delivered placenta in this case of uterine inversion was positive for myofibers both on the maternal surface, and higher up in the basal plate.

Figure 7 Morbidly Adherent Fetal Membranes

Figure 7a - Undulating chorion and heterogeneous decidua of diffusely attached MAFM.

Figure 7b – Fibrinoid in decidua under MAFM.

Figure 7c – Keratin stain of diffusely attached MAFM shows alternating zones of infiltrative vs. noninfiltrative chorionic NVT. Deep decidua has dilated endometrial glands.

Figure 7d – Keratin stain of retained MAFM in postpartum hysterectomy after uterine inversion shows less undulation, more infiltration, marked dilation of endometrial glands.

Figure 7e – Raggedly infiltrative chorionic NVT in retained MAFM "looks invasive" on keratin stain.

Figure 7f – Actin stain shows retrochorionic myometrial degeneration under retained membranes.