Introduction

Abnormal placentation poses a diagnostic and treatment challenge for all providers caring for pregnant women. As one of the leading causes of postpartum hemorrhage, abnormal placentation involves the attachment of placental villi directly to the myometrium with potentially deeper invasion into the uterine wall or surrounding organs. Surgical procedures that disrupt the integrity of uterus, including cesarean section, hystrotomy and myomectomy, have been implicated as key risk factors for placenta accreta ***(Megier et al., 2000).***

It is critical to make the diagnosis before delivery because preoperative planning can significantly decrease blood loss and avoid substantial morbidity associated with placenta accreta ***(Shih et al., 2002).***

Aggressive management of hemorrhage through the use of uterotonics, fluid resuscitation, blood products, planned hysterectomy, and surgical hemostatic agents can be life-saving for these patients. Conservative management, including the use of uterine and placental preservation and subsequent methotrexate therapy or pelvic artery embolization, may be considered when a focal accreta is suspected; however, surgical management remains the current standard of care ***(Tseng et al., 2006).***

Clinically, the most significant feature of placenta accreta is the abundant uteroplacental neovascularization, which can lead to life-threatening hemorrhage ***(Finberg and Williams, 1992) and (Levine et al., 1997).***

However, its antenatal diagnosis is usually based on characteristic findings on gray-scale ultrasound imaging, such as the loss of subendometrial echolucent zone or the presence of abnormal placental lacunae ***(Comstock et al., 2004).***

Despite the modern advances in imaging techniques, no single diagnostic technique affords complete assurance for the presence or absence of placenta accreta ***(ACOG, 2006).***

The diagnosis is most often made during the third stage of labor or on Cesarean delivery.

The aim of this study was to evaluate the role of 3 Dimensional Multislice view as a new modality in prenatal detection of morbid placentation in cases with placenta previa with history of uterine scar complementary to grayscale and 3 Dimensional power Doppler techniques, and to compare their diagnostic performance based on receiver–operating characteristics (ROC) curve analysis.

Aim of the Work

The aim of this study is to evaluate the potential of the 3 D multislice view of grayscale and power Doppler for prenatal detection of morbid placentation in anterior placenta on scar of previous Cesarean section.

Abnormal Placental Adherence

Abnormal placentation refers to patients with placenta accreta, increta, or percreta.

- Placenta accreta:

Occurs when the placenta becomes abnormally adherent to the uterine wall.On microscopic examination, there is direct attachment of the chorionic villi to the underlying myometrium, rather than the uterine decidua.

- Placenta increta:

occurs when the placenta invades into the myometrium .

- placenta percreta:

Occurs when the placenta penetrates to the uterine serosa or invades into surrounding organs.

In the literature, the term "placenta accreta" may be used to refer to any degree of placental invasion, which is why we prefer the term "abnormal placentation."

Although there are no studies directly comparing outcomes of these conditions, it is commonly understood that surgical morbidity is related to the degree of placental invasion

The incidence of abnormal placentation appears to be increasing.

In a 1977 report, the incidence in the published literature was estimated to be 1 in 7000 deliveries ***(Breen et al., 1977).***

Miller and colleagues reported an incidence of abnormal placentation of 1 in 2510 for a 10-year period at their center ending in 1994 ***(Miller et al., 1997).***

Similarly, Wu and colleagues reported an incidence of 1 in 533 over a 20-year period ending in 2002 ***(Wu et al., 2005).***

These recent estimates are almost certainly influenced by ascertainment bias and the different criteria used to diagnose abnormal placentation.

Miller and colleagues limited their study to histologically confirmed cases of abnormal placentation on cesarean hysterectomy specimen ***(Miller et al., 1997).***

Conversely, the increased incidence reported by Wu and colleagues may be a reflection of the broader definition used in the study, which included:

(1) Clinical diagnosis;

(2) Pathological diagnosis;

(3) Difficult manual piecemeal removal if no separation occurred after 20 minutes, despite active management of the third stage; and

(4) Heavy continued bleeding from the implantation site of a well-contracted uterus after placental removal during cesarean delivery.

(Wu et al., 2005)

Pathophysiology of Abnormal Placentation

Abnormalities in the process of trophoblast invasion may result in abnormal placentation. Both the embryonic trophoblast and maternal deciduas produce corticotrophin-relasing hormone (CRH), which promotes implantation. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), which is expressed in extravillous tropho-blasts (EVTs) of normal human placenta, may also function in trophoblast/endometrial interactions ***(Bamberger et al., 2006)***.

Locally produced CRH plays a role in trophoblast invasion, primarily by regulating CEACAM1 expression. CRH inhibits trophoblast invasion by decreasing the expression of CEACAM1 through CRHR1, an effect that might be involved in the pathophysiology of clinical conditions, such as preeclampsia and placenta accreta ***(Bamberger et al., 2006)***.

The complex development process of implantation involves a series of steps leading to an effective cross-talk between invasive trophoblast cells and the maternal endometrium. This dynamic process requires a precisely coordinated development of a hormonally primed adhesive endometrium and a blastocyst competent to implant. The trophoblast undergoes a number of

distinct interactions with the underlying endometrial surface initiated by apposition, which involves close proximity between trophoblast and endometrial epithelium, followed by attachment, and concluded by invasion of trophoblast into the decidualized stroma ***(Bamberger et al., 2006)***.

The hypothalamic neuropeptide corticotrophin-releasing hormone (CRH) is produced in several organs of the female reproductive system, including the endometrial glands, decidualized stroma, and trophoblast. In addition, the gene encoding the CRH receptor type 1 (CRHR1) is expressed in human endometrial and myometrial cells, indicating a local effect of uterine CRH. Indeed, locally produced CRH promotes implantation and maintenance of early pregnancy ***(Bamberger et al., 2006)***.

The trophoblast is the first tissue to differentiate in the mammalian conceptus, and its normal development and specific properties are crucial for both implantation and further survival of the embryo. Furthermore, the placenta is unique in its ability to proliferate and invade another tissue in a controlled manner. It is not surprising that similarities exist between trophoblast invasion and the invasion of cancer cells. The endometrium restricts trophoblast invasion, whereas the latter is highly invasive when it implants in ectopic sites, such as the peritoneum. Thus, trophoblast invasion is a very interesting model for the study of molecular mechanisms involved in these processes ***(Bamberger et al., 2006)***.

Starting with the initial contact, which is made between the trophoblast and the apical plasma membrane of the endometrial surface epithelial cells, through the invasion of the deciduas and the invasion of decidual vessels with gradual colonization of the arterial wall of the spiral arteries, cellular contacts mediated by cell adhesion molecules are essential. Cell adhesion molecules are important mediators of tissue architecture and cellular polarity and have also been shown to modulate proliferation and differentiation processes ***(Bamberger et al., 2006)***.

The pathogenesis of placenta accreta has been well-characterized microscopically (e.g., poor decidualization with intramyometrial infiltration of the villous tissues) and macroscopically (e.g., prominent uteroplacental neo-vascularizaiton in the region of interest) ***(Tseng et al., 2004)***.

Placental development requires the synergistic effect of angiogenic growth factors and their receptors. Among them, both Tie-1 (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains) and Tie-2 (tunica internal endothelial cell kinase) receptors have been regarded as specific vascular endothelial markers. However, in humans, their expression is not only limited to the vascular endothelium but also the palcenta; furthermore, their expression is altered in the villous trophoblasts of affected women with recurrent abortion. Therefore, Tie-1 and Tie-2 might be key players in implantation ***(Partanen and Dumont, 1999)***.

Immunohistochemical expression of Tie-2 in the syncytiotrophoblast complicated by placenta accreta was significantly reduced. Ang-2 immunoreactivity in the syncytiotrophoblast of placental villi showed a higher expression in placenta accreta specimens ***(Wulff et al., 2003)***.

The presence of functional Tie-2 receptor in tropho-blast cells demonstrates a specific role for angiopoietins as regulators of trophoblast behavior in placental development. The interactions between Tie-2 and its ligands (Ang-1 and Ang-2) are involved in the well-prepared endometrium, trophoblast invasion, and remodeling of the maternal vasculature during the peri-implantation stage ***(Rowe et al., 2003)***.

Thus, the increased in placental Ang-2 level would result in an overall destabilization of uterine vasculature and then enhance the neovascularized phenomenon found in palcenta accreta ***(Dunk et al., 2000)***.

In placentation, the Ang-1/Tie-2 pathway could promote trophoblast growth, act as a potent chemotactic factor for trophoblasts, and maintain fetoplacental vascular development and stabilization; furthermore, the Ang-2/ Tie-2 pathway could stimulate an increase in trophoblast DNA synthesis and the release of nitrous oxide, and remodel the maternal vasculature. In a variety of invasive, highly vascular malignancies ***(Wulff et al., 2003)***.

In conclusion, it has preliminary findings of increased Ang-2 expression as well as reduction of a special receptor for

the ligand, Tie-2, in placentas from pregnancies complicated by placenta accreta. This report demonstrates that life-threatening uteroplacental neovascularization typical of placenta accreta may be correlated with these molecular changes. In addition, that it was acknowledge that decidual defect is still a major contributing factor for the formation of placenta accreta; however, differential expression of Tie-2 and Ang-2 may play an additive or synergistic role ***(Wulff et al., 2003)***.

Human embryo implantation and placentation relay on a series of complex interactions between the trophoblast and the different components of the maternal deciduas. During these morphogenetic processes, trophoblast cells undergo remarkable differentiation allowing them to participatie in distinct functions. Early in the process of placentation, the formation of free-floating villi and anchoring villi directs the differentiation of the trophoblasts along 2 main pathways, namely, the villous and the extravillous one. Although villous trophoblasts display features of a polarized epithelial cell layer, extra-villous trophoblasts lose their polarization and behave like mesenchymal cells invading the deciduas ***(Kliman and Feinberg, 1990)***.

The pathways involved in the regulation of tropho-blast invasion and migration may be very complex and cAMP may be involved at various steps. Importantly, cAMP was previously found to inhibit trophoblast invasion ***(Kliman and Feinberg, 1990)***.

Placenta Accreta:

Placenta accreta is a placenta that implants too deeply and too firmly into the uterine wall. Similarly, placenta increta and percreta are placentas that imbed themselves even more deeply, into uterine muscle or through the entire thickness of the uterine wall, sometimes extending into nearby structures such as the bladder. These disorders, which occur in about 1 in 2500 deliveries, are most common in women with placenta previa and in those who have had a previous c-section or other uterine surgery. Like placenta previa, these disorders often cause vaginal bleeding in the third trimester and frequently result in the birth of a premature baby ***(ACOG, 2002)***.

The incidence of placenta accreta should increase steadily over the next century as the number of Cesarean sections and maternal age at delivery increase. There is a need for reliable antenatal diagnosis since placenta accreta encountered unexpectedly can lead to catastrophic blood loss, multiple complications such as catastrophic blood loss, multiple complications such as adult respiratory distress syndrome, Sheehan's syndrome, renal failure, and even death. If these pregnancies can be identified before delivery, the site and time of delivery, as well as the surgical approach, can be planned ahead and blood loss minimized ***(Anath et al., 1999)***.

- **Risk factors for placenta accreta:**

Placenta accreta occurs when there is a defect of the deciduas basalis, resulting in abnormally invasive implantation of the palcenta ***(ACOG, 2002)***. Risk factors for accreta include placneta previa, maternal age over 35 years, grand-multiparity, previous curettage, previous myomectomy, previous uterine surgery, submucous myoma endometrial ablation, Asherman's syndrome and hystoscopic surgeries ***(Gielchinsky et al., 2002)***.

Placenta accreta is associated with 7% mortality rate, as well as intraoperative and postoperative morbidity caused by massive blood transfusions, infection, and adjacent organ damage ***(Wax et al., 2000)***.

- **Etiology of abnormal placentation:**

Although the risk factors for abnormal placentation are well established, the precise etiology of this condition is largely unknown. In normal pregnancy, the chorionic villi implant into the spongiosus layer of the uterine decidua. There is a natural cleavage plane superior to the decidua basalis which allows prompt placental separation after delivery, caused by the shearing action between the contracting myometrium and the placenta. Myometrial contraction after delivery constricts the vascular supply to the placental bed, and hemostasis is achieved postpartum. Aberrations at any of these steps likely contribute to defective implantation, failure of placental separation, and subsequent hemorrhage.

Historically, abnormal placentation has been attributed to an absence or deficiency of Nitabuch's layer. Raissa Nitabuch was a German physician who studied the vascular supply to the placenta. The concept of Nitabuch's layer is based on observations from her doctoral thesis at the University of Bern in 1887. 12. Nitabuch R: Beitrage zur Kenntniss der menschlichen Placenta. Bern, Stampfli'sche Buchdruckerei, 1887 Nitabuch examined a single gravid uterus of approximately 6 months gestational age with the placenta in situ. She described the presence of a dark line located proximal to the basal plate underlying most of the placenta, which appeared to be a largely extracellular or "fibrinoid" layer. Nitabuch postulated that this was the border that separated the chorion from the deeper decidua. It was later implied from her work that this border effectively limited trophoblast invasion ***(Pijnenborg et al., 2008).***

More recently, the concept of Nitabuch's layer having a functional role and contributing to the pathology of abnormal placentation has been refuted. Pijnenborg's work on placental implantation has led to the discovery that trophoblasts normally invade through the endometrium to the inner third of the myometrium ***(Pijnenborg, 1998).***

Two subgroups of extravillous cytotrophoblast invade the uterine wall: the interstitial trophoblast invades the myometrial tissue, and the endovascular trophoblast remodels the maternal spiral arteries. This tightly regulated process peaks between 9

weeks and 12 weeks of pregnancy and appears to be an important event in normal pregnancies ***(Clark et al., 1985).***

A deficiency of decidualization may contribute to the development of abnormal placentation. There is an increased incidence of abnormal placentation in pregnancies with placenta previa, even in the absence of other risk factors ***(Silver et al., 2006).***

In comparison to the rest of the uterine cavity, the lower uterine segment proximal to the cervical canal contains relatively less decidualized tissue ***(Khong, 2008).***

Similarly, cesarean delivery, uterine curettage or hysteroscopic surgery, myomectomy, endometrial ablation, and uterine artery embolization may result in localized decidual defects and consequently abnormal placentation.

The risk of abnormal placentation in patients with previous cesarean delivery and an anterior or central placenta previa is increased four fold over those patients with a posterior previa, which may be related to combined effects on decidualization in the region of the prior scar ***(Miller et al., 1997).***

Abnormal placentation may also result from abnormal or excessive trophoblast invasion. The primary invasive trophoblastic cell type is mononuclear; these cells later fuse to form multinuclear giant cells. It is believed that the multinucleated giant cells represent the terminally differentiated

stage of extravillous trophoblast, with low invasive potential ***(Pijnenborg, 1998).***

There is a paucity of giant cells at the placental–myometrial junction in cases of abnormal placentation, suggesting either an intrinsic abnormality in these trophoblasts or a defect in other regulating factors ***(Khong and Robertson, 1987).***

In an alternative hypothesis, localized differences in oxygen tension within uterine scarring may contribute to the development of abnormal placentation. The human embryo develops in a relatively hypoxic environment, and in vitro work suggests that difference in oxygen tension determines whether cytotrophoblast cells proliferate or invade ***(Genbacey et al., 1997).***

Embryos may preferentially implant into areas of uterine scarring and deficient decidua because of the relative deficiency of blood flow and oxygen tension. Abnormal vascular remodeling may also contribute to abnormal placentation. A recent study by Tantbirojin and colleagues demonstrated that cases of abnormal placentation had a decreased proportion of normally remodeled vessels (in which the full circumference of the vessel is replaced with endovascular trophoblast), with many vessels displaying partial vascular changes ***(Tantbirojin et al., 2008).***