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The Rate Of Placenta Accreta And Previous Exposure To Uterine Surgery

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Abstract

THE RATE OF PLACENTA ACCRETA AND PREVIOUS EXPOSURE TO UTERINE SURGERY

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Placenta accreta is a disorder of abnormal placentation that causes significant maternal morbidity and mortality, and whose incidence is rising in the US. Accreta is thought to be linked closely to endometrial disruption introduced by exposure to uterine surgery; its connection to cesarean delivery is well-established, however, there is a poorer understanding of the contribution made by other forms of uterine surgery, and by relatively subjective indications for which women with placenta accreta may have initially received a cesarean delivery. The aims of the study were to quantify the rate of placenta accreta at YNHH, the rate of exposure to various uterine surgeries prior to the accreta pregnancy, and the rate of subjective indication for primary cesarean delivery amongst all patients with placenta accreta from 1995-2011. Among the 72,845 births during the study period, 249 cases of placenta accreta were identified via query of pathology records, including 122 focal accreta, 63 accreta vera, 23 increta and 14 percreta.

Twenty-seven cases were excluded due to lost chart, multiple accreta in a single patient, and absence of baseline birth data for Jan 1995 - June 1996; a total of 100 cases of non-focal accreta were included in the final analysis. Non-focal accreta is increasing over the study period; the rate was 1.4 cases per 1,000 births; it increased on average 12% per 3-year period over the course of the study (95% CI -1.6% to 28.5%). Among all births, women with placenta accreta and a prior index cesarean delivery increased significantly over the study period, with a mean increase of 21.9% per 3-year period (95% CI1.4% to 46.6%), while those with placenta accreta and other index uterine surgery increased by 71.1% per 3-year period (95% CI 10.4% to 165%). Over this 15 year period, the cumulative increase in risk of having placenta accreta in the setting of prior cesarean delivery was 2.69 (95% CI 1.07 – 6.8) while the cumulative increase in risk for having placenta accreta in the setting of prior other uterine surgery was 14.66 (95% CI 1.64 – 131). There was no significant difference in rate of placenta accreta with prior index cesarean delivery for subjective or objective indication. Placenta accreta in the setting of prior uterine surgery is increasing over time. Larger studies are needed to further elucidate the increasing role of prior uterine surgery on the development of placenta accreta in the population.

Acknowledgements

Many thanks go to the many people who have contributed significantly through the course of this project. Brian West, MD, Director of Anatomic Pathology at Yale-New Haven Hospital, has been a tireless, insightful, enthusiastic partner in exploring the vagaries of pathologic diagnosis of placenta accreta, along with Linda Hager, his very capable and pleasant assistant. The planning and feedback for the project was so enriched by the engagement, patience and creativity of Divya Patel, PhD and other members of the Comparative Effectiveness Working Group. Daniel Bercik, research assistant, and his advisor Chris Pettker, MD provided deeply valued feedback and assistance in data collection and discussion of the project. Lisbet Lundsberg has provided wonderful feedback and a keen eye throughout the project, as well as being delightful to work with. Most of all, Dr. Jessica Illuzzi's vision, dedication to positively shaping the field of obstetrics & gynecology through incisive research, guidance and friendship has been a highlight and a privilege.

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Introduction

Overview

Placenta accreta is a disorder of abnormal placentation that causes significant maternal morbidity and mortality, and whose incidence is rising in the US.(1,2,3,4) In placenta accreta, placental villi invade beyond their usual implantation in the decidua basalis into or through the myometrium. This impairs a major physiologic mechanism to control postpartum bleeding, leading to high rates of hemorrhage and increased maternal and perinatal morbidity and mortality. Women with placenta accreta face a range of complications, including acute respiratory distress syndrome, disseminated coagulation, transfusion-related complications, injury to ureters, bladder or bowel, emergency hysterectomy and death.(1) In the setting of severe hemorrhage, hysterectomy may be necessary as a lifesaving intervention; despite aggressive surgical intervention, maternal death rates in placenta accreta have been reported as high as 7%.(5)

The incidence of placenta accreta has risen significantly compared with rates in the 1950s,(6) recent estimates place it at 1 per 533 deliveries to 1 per 2510 deliveries.(6,7) Cesarean delivery has been identified as a significant factor leading to the increase in accreta rates, attributed to uterine wall disruption and resulting uterine scar.(6,7,8,9,10) Other types of uterine instrumentation that disrupt the endometrium are also viewed as potential contributors, though their role is less clearly defined(1,10,11,12) As patterns of cesarean delivery and other uterine surgery change, it is important to examine their potential contribution to the rate of placenta accreta.(3) In the United States, the cesarean delivery rate increased to 32.9% in 2009, compared with 5% in 1970 and 25% in 1989.(10)

As rates of cesarean delivery increase, a recent study at one tertiary care center showed that the majority of indications for primary cesarean from 2003-2009 were done for indications that can be considered subject to varied interpretation by different clinicians. These more subjective indications include non-reassuring fetal heart tracing, labor arrest disorders and suspected macrosomia.(13) Elective cesarean per maternal request can also be considered subjective, or without objective medical indication. Over time, the use of other uterine procedures, including myomectomy, has also shifted. To date, there has not been an effort to examine the rate of exposure to previous uterine surgery among patients with placenta accreta, in order to better understand the indications that may underlie the increasing rates of placenta accreta.

Incidence

Rates of placenta accreta are estimated to have increased significantly compared with rates in the 1950s.(6) Recent estimates place the incidence at 1 per 533 deliveries to 1 per 2510 deliveries,(6,7,14) in comparison with rates from the 1930s-1950s of 1:30,000 births.(15) Estimates of the incidence of placenta accreta vary widely, due to variations in diagnostic criteria and study population; nevertheless, there is consistent demonstration in the literature that the rate has increased substantially over time.

Pathogenesis

The placenta is a remarkable organ, constantly undergoing change throughout its relatively brief existence. Upon implantation of an embryo, the endometrium becomes known as the decidua, and forms the maternal portion of the placenta. The decidua develops into several layers: the decidua compactus is the most superficial to the uterine cavity. Beneath it is the stratum spongiosum, below this is the stratum compactum or dedicua basalis.(16,17) This barrier layer interacts with invading trophoblastic cells, and

lies adjacent to the underlying myometrium, with an intervening fibrinoid layer known as Nitabuch's layer.(18) At parturition, the decidua sloughs off at the decidua basalis, and the maternal spiral arteries that penetrate the decidua at right angles to fill the intervillous space are compressed by uterine contraction and spasm to achieve hemostasis.

Placenta accreta is a relative newcomer to obstetric pathology. It was first documented in 1937 by Irving & Hertig, who described it as "the abnormal adherence, either in whole or in part, of the afterbirth to the underlying uterine wall," which they attributed to a deficiency or absence of the decidua basalis.(19) There are three types of placenta accreta: *placenta accreta vera* (more often termed just *placenta accreta)* denotes placental attachment directly onto the myometrium without intervening decidua basalis, *increta* indicates invasion into the myometrium, *percreta* denotes penetration through the myometrium into or beyond the serosa, which may include involvement of nearby organs, including bladder or bowel.(Fig. 1) The term *placenta accreta* can be used as an overarching term that includes all degrees of pathological placental invasion.

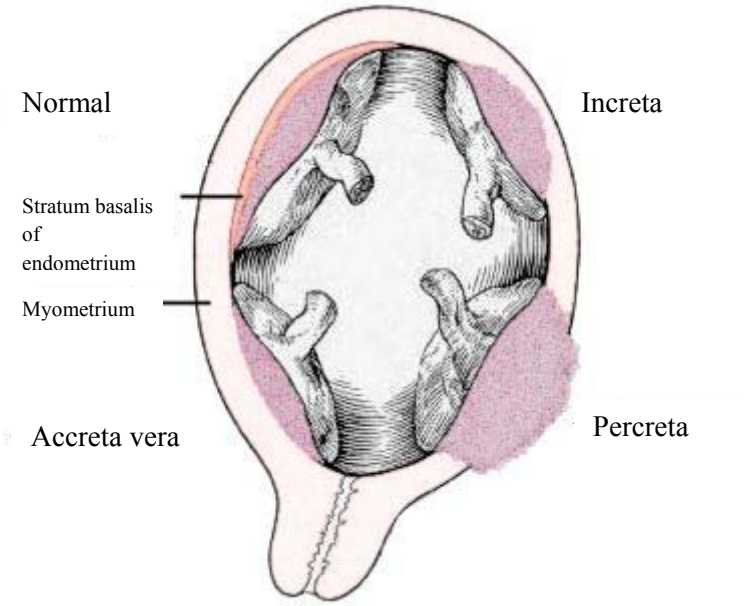


Fig. 1. Types of placenta accreta by degree of invasion.

Placenta accreta can also be categorized according to the surface area of the placenta that is abnormally adherent, as focal, partial or total.(16) The designation of focal accreta is useful to denote a small area of abnormal placentation, as small as one cotyledon.(20,21), however the clinical significance of this finding is less clear.

The key pathologic finding associated with placenta accreta is the absence or deficiency of the decidual plate, with the finding of placental villi embedded directly onto myometrium, often described in histopathology as the presence of *basal plate myometrial fibers*.(16) More recently, accreta has also been found to include abnormally invasive extravillous trophoblast, underlining the importance of the balance between decidua and trophoblastic invasion.(22) Uterine surgery or procedures that disrupt the endometrium are assumed to increase risk of accreta through their potential disruption of decidualization, and possible creation of scar tissue.(21) There are several, likely overlapping, theories advanced to explain the etiology of placenta accreta. The first

theory is that a deficiency or absence of decidua prevents its usual role in preventing excessive trophoblast invasion into the myometrium.(23,24) There is also evidence that deficient vascularization and resulting negative oxygen tension in scarred areas of the uterus leads trophoblastic cells to invade more deeply to establish adequate blood supply.(5) Finally, the oldest theory posits that trophoblastic tissue itself is abnormally invasive.(16,26) The fact that placenta accreta was first recognized less than 100 years ago suggests a significant iatrogenic component.(27)

Risk Factors

Although the etiology of placenta accreta is still a topic of debate, the risk factors for placenta accreta are better understood. According to one study, approximately 95% of women diagnosed with placenta accreta have identifiable risk factors.(10) The most common presentation of placenta accreta is a woman with one or more previous cesarean deliveries and current placenta previa. There is robust evidence that the risk of placenta accreta also increases significantly with repeated cesarean deliveries.(29,31,32,33) A prospective observational cohort study of 30,132 women with cesarean delivery without labor taking place in four academic centers between 1999-2002 scrutinized number of placenta accreta by number of previous cesarean deliveries. The study identified cases of accreta via histopathology, or via clinical diagnosis in cases where hysterectomy was not performed. Specific criteria for clinical diagnosis were not enumerated. They found that risk of accreta in women with *placenta previa* rises from 3% in the setting of one previous cesarean delivery, to 11%, 40%, 61% and 67% with two, three, four and five or more previous cesarean deliveries, respectively, a trend that is mirrored at a lower rate in patients without placenta previa, as well.(8) Compared with a first vaginal birth, women with a first birth by cesarean have 1.9 times higher odds (CI 1.3-2.8) of placenta accreta

in the subsequent pregnancy.(12) Having two or more cesarean deliveries is associated with an odds ratio of 8.6 (95% CI 3.54-21.08) for development of placenta accreta in the subsequent pregnancy.(7) In view of the strength of this association, the increasing rate of cesarean delivery is agreed to be one of the most significant factors contributing to placenta accreta.(8,9,11)

Placenta previa is also independently associated with placenta accreta, particularly when the placenta is overlying a previous uterine scar. Abnormal placentation is often found in association with placenta previa. Accreta is now seen in 9.3% of women with placenta previa.(7) Other risk factors include advanced maternal age, multiparity, Asherman syndrome, leiomyomata, radiation exposure, uterine anomalies, hypertension and smoking.(1,6,7,11,29,30)

Given their disruption of the endometrium, it is likely that other forms of uterine surgery, such as myomectomy, endometrial ablation, septum resection, and lysis of adhesions also contribute to risk of placenta accreta; however, comparably little has been done to investigate this association, aside from case reports.(34,35) Fibroids contribute to infertility, and prevalence in the United States may be as high as 13% however, no direct causal relationship between fibroids and infertility has been established.(36) Treatment is tailored to the reproductive wishes of the patient, and treatment regimens are shifting over time, including an effort to study medical therapies; however, myomectomy, endometrial ablation and other surgical interventions are also still frequently used,(37) with ongoing debate as to the effectiveness of abdominal versus laparoscopic or robotic approaches for myomectomy.(38) There is relatively little data available as to rate of myomectomy over time or outcomes of subsequent pregnancies.(39)

Diagnosis

Diagnostic imaging

There are three modes of diagnosis for placenta accreta: pre-natal imaging, intrapartum clinical findings, and histopathology from a placental or uterine specimen. A fourth mode of diagnosis is in development: immunohistochemical markers that could help predict presence and/or severity of placenta accreta. (1,21)

Prenatal diagnosis of placenta accreta mainly takes place via ultrasound, usually during the second or third trimester. Criteria for sonographic diagnosis of placenta accreta include a range of associated findings, including loss of the normal hypoechoic retroplacental zone; presence of multiple vascular lacunae within the placenta; blood vessels or placenta bridging the uterine-placental margin, myometrial-bladder interface or crossing the uterine serosa; retroplacental myometrial thickness of <1mm; and presence of numerous coherent vessels visualized with 3-dimensional power Doppler in basal view.(1) Across four studies, sonographic diagnosis of placenta accreta has been associated with a sensitivity of 77.0 – 93.0% and specificity of 71.0 – 96.8%, with a PPV of 65.0 – 87.5% and NPV of 92.0 – 98.0%.(40,41,42,43) Ultrasound is particularly useful for ruling out accreta, given its high negative predictive value.(40) In women with low-lying placenta or placenta previa in setting of previous uterine instrumentation, it is particularly important to be vigilant in screening for placenta accreta.

MRI can also be used in evaluation of placenta accreta, though evidence on its utility is mixed. It may be particularly useful in cases of posterior placenta(44) or where patient habitus limits sonography and also has the advantage that it is not operator dependent. An analysis in 2007 showed that three MRI findings were associated with abnormal

placentation: abnormal uterine bulging, heterogenous signal intensity, and presence of dark intraplacental bands on T2-weighted images.(45) One study evaluated ultrasound and MRI diagnosis of placenta accreta in a cohort of 453 women with placenta previa, previous cesarean delivery and low-lying anterior placenta, or previous myomectomy; it found ultrasound to accurately predict placenta accreta in 30 of 39 women and appropriately rule out accreta in 398 of 414 women (sensitivity 77%, specificity 96%).(42) In the same study, among 42 cases with inconclusive or suspicious findings on ultrasound, MRI was a useful adjunct: it accurately predicted placenta accreta in 23 of 26 cases, and correctly ruled out placenta accreta in 14 cases (sensitivity 88%, specificity 100%).(42) Given its increased expense and comparable sensitivity and specificity to ultrasound, MRI is perhaps most often useful as a second stage of evaluation in cases where ultrasound findings are inconclusive.

The extent of myometrial invasion noted on ultrasound reflects the type of accreta, particularly denoted by presence of blood vessels or placenta traversing the myometrium or crossing the serosa. Lower degrees of invasion are more difficult to appreciate, and there is no data on diagnosis of focal accreta via ultrasound or MRI, though positive identification would likely be limited to cases with invasion that disrupts macroscopic architecture.

Clinical Diagnosis

The second mode of diagnosis is intrapartum clinical diagnosis, based on presence of hemorrhage or retained placenta without a clear plane of separation. In cases of clinical suspicion, submission of the placenta for pathologic evaluation is warranted. A 2006 study by Silver and colleagues, which established accreta risk relative to number of

previous cesarean, used both pathologic diagnosis in cases where hysterectomy was performed, and clinical findings of adherent placenta with difficult removal, in cases where hysterectomy was not performed.(8) The authors recognize that a possible limitation of the study was the use of a clinical definition for accreta; however, for their study, histologic diagnosis was only available when hysterectomy was performed. An alternative reason for inclusion of clinical diagnostic criteria is among populations where access to sonography is limited.(32)

Several other studies have used a mix of clinical and pathologic criteria. For instance, Gielchinsky et al 2002 used the definition below, which was subsequently replicated in another study: (28)

> (1) Difficult manual, piecemeal removal of the placenta, that was performed if no evidence of placental separation was noticed at least 20 min after parturition, and despite of active management of the third stage of labour (i.e. administration of intravenous oxytocin, transabdominal manual massage of the uterus, drainage of blood from the placenta, and firm-controlled traction of the umbilical cord); OR
> (2) sonographic evidence of retained placental fragments requiring curettage after vaginal delivery; OR
> (3) heavy bleeding from implantation site after removing the placenta during conservatively managed caesarean section, with excision of part of the uterine wall and the attached placenta, or over-sewing the bleeding defects; OR
> (4) histologic confirmation of a hysterectomy specimen.(29)

Histopathological Diagnosis

The third mode of diagnosis is via histopathology, which relies on demonstrating the presence of basal plate myometrial fibers, or direct apposition of trophoblastic tissue onto the underlying myometrium, without intervening decidual tissue.(16) The diagnosis can be made on hysterectomy specimen, but also on placenta or placenta with uterine biopsy,

if myometrial fibers are found to be present either immediately adjacent to placental villi or with only an intervening fibrin layer.(18,20)

Comparison of modes of diagnosis

There are pros and cons of the three diagnostic modalities for accreta: they have different functions and operate at different times during the pregnancy and peripartum periods. Their varying use in previous research makes comparison across studies difficult. Prenatal diagnosis via ultrasound usually occurs during the second and third trimesters, though it has been documented in the first trimester. Antenatal diagnosis provides the opportunity for delivery planning, which is an important way to reduce intrapartum hemorrhage and improve outcomes. Intrapartum clinical diagnosis is made within the acute management setting, where the diagnosis of accreta is secondary to effective assessment of the evolving problem and adept management. Clinical severity is also the major factor used in evaluating the impact of placenta accreta, and can be important in distinguishing between symptomatic non-focal accreta and asymptomatic cases of focal accreta. (20,21)

Finally, postpartum pathologic diagnosis occurs on either placental or hysterectomy specimen and provides the most objective basis for diagnosis; however, it is also subject to uncertainty, particularly in relation to focal placenta accreta. Focal placenta accreta is often less clinically severe, and may even be clinically silent, making its relevance unclear. In contrast, some argue that any case of retained placenta or manual removal of placenta represents a minor case of abnormally adherent placenta.(16,21,47) One study compared placentas with basal plate myometrial fibers on histopathology but no clinical findings of accreta (so-called 'occult placenta accreta') with placentas from similar

deliveries without basal plate myometrial fibers.(48) They found that the occult placenta accreta cases had a significantly higher level of extravillous trophoblast, signaling that although they were not symptomatic, they had evidence of the same pathology underlying overt placenta accreta.(25) Thus, on one hand some argue that focal placenta accreta is not relevant because it often does not have clinical findings of placenta accreta; alternatively, if there is a shared pathology, it may help advance our understanding of accreta.

VARIATION IN DIAGNOSTIC CRITERIA ACROSS ACCRETA RESEARCH STUDIES

One of the reasons for varying estimates of incidence of placenta accreta is that studies have used differing diagnostic criteria over time, with a contrast between those that rely strictly on histopathologic diagnosis, usually from hysterectomy specimen, and those that accept both clinical and pathologic evidence.

The degree of overlap between clinical suspicion and pathologic diagnosis can be problematic. In one retrospective review of cases of accreta between 1985 and 1994, clinical suspicion of placenta accreta was found to correctly identify only 48% of cases. The remaining 62 of 127 hysterectomy cases with operative diagnosis of accreta were found on pathology to not meet criteria for placenta accreta.(6) One solution to this has been to rely on only on pathological diagnosis rather than using clinical criteria; in many cases, only hysterectomy specimens have been examined, although placenta accreta can be diagnosed on placental specimens, as well.(49)

Outcomes of Placenta Accreta

Developing an accurate understanding of the prevalence, risk factors, and options for prevention and management of placenta accreta is of the utmost importance, given its particular impact on maternal health.

Women with placenta accreta face a range of sequelae, including not only hemorrhage, but also blood transfusion with associated complications, injury to local organs, amniotic fluid embolism, postoperative infection, thromboembolism, multi-organ failure and death.(1) One case series of 76 patients with accreta found that blood transfusion was required in 80% of deliveries, and that 40% of cases required transfusion of 4 units or more of packed red blood cells.(10) Average blood loss at time of delivery can be 3000-5000mL, and may exceed 10L.(50,51)

In the setting of severe hemorrhage, hysterectomy may be necessary to prevent maternal death. Placenta accreta is now the leading cause of peripartum hysterectomy in the developed world.(2,52) One retrospective cohort study of all deliveries occurring in three hospitals in Dublin, Ireland from 1966-2005 found that the rate of peripartum hysterectomy due to placenta accreta increased from 5.4% during 1966-1975, to 46.5% from 1996-2005, an increase of more than 700%, representing a major shift in the profile of indications for peripartum hysterectomy.(52) Even with aggressive surgical intervention, maternal death rates in placenta accreta have been reported as high as 7%.(5) Placenta accreta also poses a threat to the infant, mostly due to preterm birth due to vaginal bleeding or electively to avoid hemorrhage. A survey of 109 cases of placenta percreta occurring among patients of members of the Society of Perinatal Obstetricians over a three-year period found a perinatal mortality rate of 9%.(5)

Public Health Impact

The impact of placenta accreta on public health is also significant. A recent decision analysis sought to forecast the effect of rising primary cesarean section rates on annual incidence of previa and accreta. The study reported that if primary and repeat cesarean rates continue their recent rate of rise, by 2020 the cesarean delivery rate will be 56.2%, and there will be an additional 6,236 previas, 4,504 accreta, and 130 maternal deaths annually.(4) Of interest, the study also found that the rise in rates of placenta accreta trails the rise in cesarean rate by an estimated six years. The findings were consistent with another model predicting that for every 5% increase in the elective primary CS rate, will come up to 32 more maternal deaths, 24,000 more surgical complications, and between $750 million and $1.7 billion in healthcare expenditures.(53)

This concerning data must be considered in light of recent deterioration of maternal mortality in the United States. From 1998 to 2004, maternal mortality rate in the United States rose from 10 per 100,000 to 14 per 100,000 live births.(50) Although the reason for this rise is unclear, the increase in rates of placenta accreta is thought to make a significant contribution.(6,7,9,40)

Management

It is important to consider both prevention and management so as to minimize the impact of rising rates of placenta accreta. Optimizing management is receiving a great deal of attention in the literature. Broad themes include the importance of prenatal diagnosis to facilitate delivery planning and the crucial role of multidisciplinary care teams. Given the likelihood of massive hemorrhage and need for cesarean hysterectomy, and possibility of other complications, pre-delivery planning is essential in cases of suspected placenta accreta. Scheduled cesarean delivery with a multidisciplinary team and

measures in place to anticipate possible accreta has been associated with reduced morbidity, reduced blood loss, and improved outcomes.(1,10,40)

Prevention? A closer look at uterine surgery

Despite our best efforts to optimize management, it is also crucial to focus attention on ways to avert placenta accreta. With the strong association between previous cesarean delivery and placenta accreta, and the significant increase in cesarean delivery rates over the past several decades, cesarean delivery rates are an important target. Modern cesearean delivery came about in 1926 with the advent of a new surgical approach; this, coupled with improved use of uterotonics, aseptic technique, and other advances led to far improved survival rates after cesarean. The rate of cesarean delivery in the US rose from 5% in 1970 to 25% in 1989 to 32.9% in 2009, or an increase of over 600%.(3) The rate of vaginal birth after previous cesarean delivery (VBAC) has decreased significantly. As the VBAC rate declines, for every woman who has a primary cesarean delivery, her likelihood of having a subsequent cesarean delivery increases, and of developing placenta accreta.

Cesarean delivery is the most common surgical procedure undergone by women in the United States. The National Center for Health Statistics estimated that 15% of inpatient surgeries that took place in the United States in 2001 were cesarean deliveries, or approximately one million of a total of seven million surgeries.(53) This estimate underscores the significant implications that cesarean delivery rates have for healthcare utilization more broadly.

Although cesarean delivery is ubiquitous, it is important to be cognizant of both the short- and long-term complications. The risk of complications increases with multiple

cesareans. One study found that women with three or more planned cesarean deliveries had significantly higher incidence of excessive blood loss (7.9% versus 3.3%; P <.005), difficult delivery of the neonate (5.1% versus 0.2%; P < .001), and dense adhesions (46.1% versus 25.6%; P <.001) compared with a group after second cesarean.(50) They also reported that risk of major complication (uterine rupture, hysterectomy, re-laparotomy, bladder or bowel injury, thromboembolism, or excessive blood loss) was also significantly higher in the repeat cesarean group(8.7% versus 4.3%, P = .013), and increased with the delivery index number: 4.3%,7.5%, and 12.5% for second, third, and fourth or more cesarean delivery, respectively (P for trend = .004).(55)

Reasons for increasing rate of cesarean delivery

The reasons for the increase in cesarean rate continue to be a subject of debate. Possible explanations include increased maternal age, worse maternal health, increased rates of obesity, maternal preference, provider convenience, and avoidance of legal liability. With regard to age, Northern Europe has had a similar demographic shift toward increased maternal age at childbirth without such an increase in cesarean rate.(53) Also, within the United States cesarean delivery rates have increased across all age groups.(53) Alternative explanations include patient and provider preference/convenience, avoidance of legal liability, and malpractice awards; for a small portion of cesarean deliveries, they may be attributed to a decrease in clinical skills for and change in attitudes toward operative delivery.(2,3,4,13)

It is certainly the case that there is a crucial role for cesarean delivery. In West Africa, for example, there is a threshold relationship between the maternal mortality ratio and cesarean rate: countries or regions with maternal mortality ratios above 450 per 100,000

typically exhibit CD rates below 1%.(56) The World Health Organization set a target rate for cesarean delivery of 15%, estimating that 12-15% of deliveries will have a condition needing intervention, including cesarean.(56) On the opposite end of the spectrum, the WHO points out that cesarean rates above 15% are accompanied by increased risk to both mother and baby. Indeed, while cesarean rates in the United States have increased over recent decades, maternal and neonatal outcomes have not improved.(13)

In light of concern over high cesarean rates, a few recent studies have sought to elucidate the clinical situations and indications that precipitate cesarean delivery, including those marked by variability in clinical thresholds to intervene by cesarean delivery. A recent study investigated the indications for primary cesarean delivery at Yale-New Haven Hospital over a seven year period, 2003-2009.(13) They found that the rate of cesarean delivery increased from 26.0% to 36.5% over that time, equivalent to an increase of 73%; the rate of repeat cesarean also increased, from 9.8% in 2003 to 14.8% in 2009. The VBAC rate during the study period dropped from 17.8% to 7.8%. The study reported that 68% of the increase in primary cesarean rate could be attributed to more subjective indications, including non-reassuring fetal heart tracing (32%), labor arrest disorders (including arrest of dilation and arrest of descent; 18%), suspected macrosomia (10%) and elective per maternal request (8%).(See Fig 2; 13) The study also reported that rates of cesarean delivery for multiple gestation and preeclampsia increased at rates 200% and 87% higher, respectively, than would be predicted based on population increases in multiple gestation and preeclampsia.(11)

Of note, Although rates of cesarean for non-reassuring fetal heart rate have increased over time, neonatal outcomes have not improved.(52) Several recent studies have suggested that exercising increased patience in the setting of active phase arrest of labor could lead to successful vaginal delivery in 33 to 61% of cases.(53)

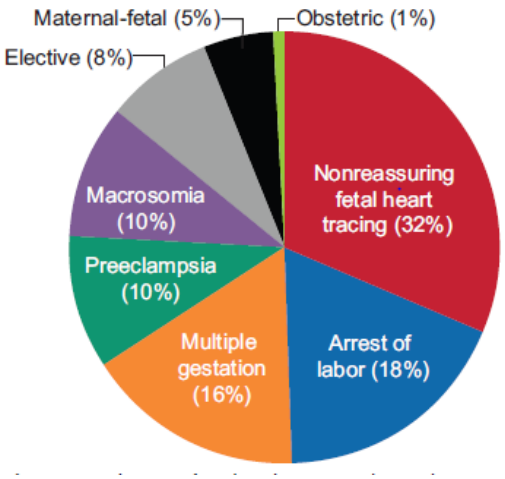


Fig. 2. Indication for primary cesarean deliveries at Yale-New Haven Hospital, 2003-2009. Adapted from Barber et al 2011.(13)

SUMMARY

Placenta accreta is a growing threat to maternal health, due at least in part to rising rates of cesarean delivery, with contributions from other uterine surgeries as well. As antenatal diagnosis and peripartum management improve, secondary prevention of poor outcomes among women with placenta accreta is more effective. Better provider preparation and provision of multi-disciplinary peripartum care have been shown to improve outcomes, but will not help turn the tide of this growing problem. It is important to seek better understanding of potential modifiable risk factors that may aid in primary prevention. Among these, recent evidence that a majority of primary cesarean deliveries at one tertiary care center occurred due to a subjective indication suggests that a

proportion of these interventions could have been averted without compromising maternal or fetal health, thereby reducing the number of women who cross that threshold of increased risk for subsequent accreta. Rates of myomectomy and other surgical fertility-enhancing management of fibroids have also changed over time. Building a clearer picture of the rates of and indications for previous uterine surgery may help us not only better understand and manage this formidable challenge, but also eventually prevent its further growth.

Statement of purpose, specific hypothesis, and specific aims of the thesis

Because placenta accreta is associated with significant maternal and perinatal morbidity and mortality, it is important to establish the rate of placenta accreta, and profile the risk factors contributing to placenta accreta over time. To date, there are no documented efforts to examine the indications for index uterine surgery in women with placenta accreta.

In this study, we will retrospectively determine the rate of placenta accreta at Yale-New Haven Hospital from 1996 to 2011 and the indications for index uterine surgery in these patients, in order to meet three aims:

Aim 1: To determine the rate of placenta accreta at Yale-New Haven Hospital over the period of 1996 to 2011.

Aim2: To determine the rate of previous uterine surgery exposure among patients with placenta accreta.

Aim 3: To determine the rate of index cesarean deliveries due to subjective indications in patients with placenta accreta.

Analysis will include a retrospective examination of indication for primary uterine surgery by year of accreta diagnosis, including calculating change in rates of placenta accreta associated with a given indication over time, based on number of all births at YNHH in a given year. We will also analyze indication for index uterine surgery, and plan to calculate proportion of uterine surgeries due to each indication, to compare for

change in proportion over time. Finally, the analysis will include presence of other risk factors, including number of cesarean deliveries or other uterine surgeries, maternal age, and comparison of outcomes by risk exposure. Results from this study will inform a future extension of the project, to incorporate a control group for comparison.

Establishing whether the rate of placenta accreta is increasing at Yale-New Haven Hospital, whether the profile of patient outcomes has shifted over time, and gaining a better understanding of the indications for which women are receiving first exposure to uterine surgery will demonstrate the degree to which cesarean section versus other uterine surgery is the index exposure in this group of patients with placenta accretaAmong cesarean deliveries, documenting the rate of more subjective indications and the change in this rate over time may provide evidence that at least a proportion of placenta accreta have the potential to be safely averted. It may also help emphasize the need for further research on management of more subjective indications for cesarean delivery, including non-reassuring fetal heart tracing, suspected macrosomia, and labor arrest disorders, to optimize both maternal and neonatal outcomes.

We hypothesize that rate of placenta accreta has increased over the study duration, and that a majority of patients will have previous uterine surgery exposure. Of those with previous uterine surgery exposure, we anticipate that a significant proportion will have received their index exposure to cesarean delivery for subjective indications, including non-reassuring fetal heart tracing, arrest of labor, suspected macrosomia and elective per maternal request.

METHODS

The group of patients with histopathologic diagnosis of placenta accreta at Yale-New Haven Hospital from January 1995 to December 2011 was generated via query of the database maintained by the Department of Surgical Pathology. Query of all pathology reports that include text of 'accreta', 'acreta', 'percreta' or 'increta' from January 1995 to December 2011 returned a total of 249 cases with a diagnosis of abnormal placentation.

Data on all births at Yale-New Haven Hospital were available for July 1996 through December 2011, based on obstetric department records kept monthly by an obstetric department nurse administrator. This data formed the basis for analysis in the recent investigation of indication for cesarean delivery at Yale-New Haven Hospital,(13) improving our ability to compare findings between these two studies. Hence, we decided to exclude cases of accreta occurring between January 1995 and June 1996 (n=22) from analysis of accreta trends, rather than augment with a different source of data for baseline birth rate.

For purposes of evaluating diagnostic consistency, cases of placenta accreta were also identified via query of International Classification of Disease-9 (ICD-9) codes from hospital billing records. ICD-9 codes 666.0 or 667.0 designate retained placenta with and without hemorrhage, including primary or secondary diagnosis of placenta accreta with and without hemorrhage. This query generated a list of 802 cases from n October 1995 (earliest available date) to December 2011.

Comparison of the pathology-confirmed and ICD-9-based patient pools to examine diagnostic methods revealed significant discrepancy. Of the 249 cases of placenta

accreta diagnosed by histopathology, which is often taken to be the gold standard for diagnosis of placenta accreta, 173 (69.5%) were not captured in the ICD-9 code query. A sample of cases from the ICD-9 query (20 randomly selected, 20 selected for clinical features consistent with placenta accreta) were reviewed for pathology findings, and did not return any additional cases of pathology-confirmed placenta accreta. In addition, review of 82 randomly selected cases of the ICD-9 query revealed 17 cases (20.7%) that were consistent with placenta accreta by pathology. There were numerous cases of mild retained placenta as well as normal deliveries that lacked a clear indication for their coding. This data translates to a sensitivity of 31% and specificity of 99% for the identification of cases of placenta accreta by ICD-9 code compared with actual cases identified by histopathology (positive predictive value 9% and negative predictive value 99%). In this sample, with a prevalence of placenta accreta of 0.34%, the high specificity and high negative predictive value are essentially meaningless, and the low sensitivity and low positive predictive value reflect the inadequacy of using ICD-9 code to capture cases of placenta accreta. These findings demonstrated that at our institution, ICD-9 code query cannot be relied upon to return all cases of placenta accreta; therefore clinical diagnosis through ICD9 code query was excluded as a means to establish this group of patients. Thus, in this study we opted to restrict case inclusion to confirmed histopathologic diagnosis. A total of 100 cases of non-focal accreta were included in the final analysis. These cases were compared to the 122 cases of focal accreta in the descriptive results.

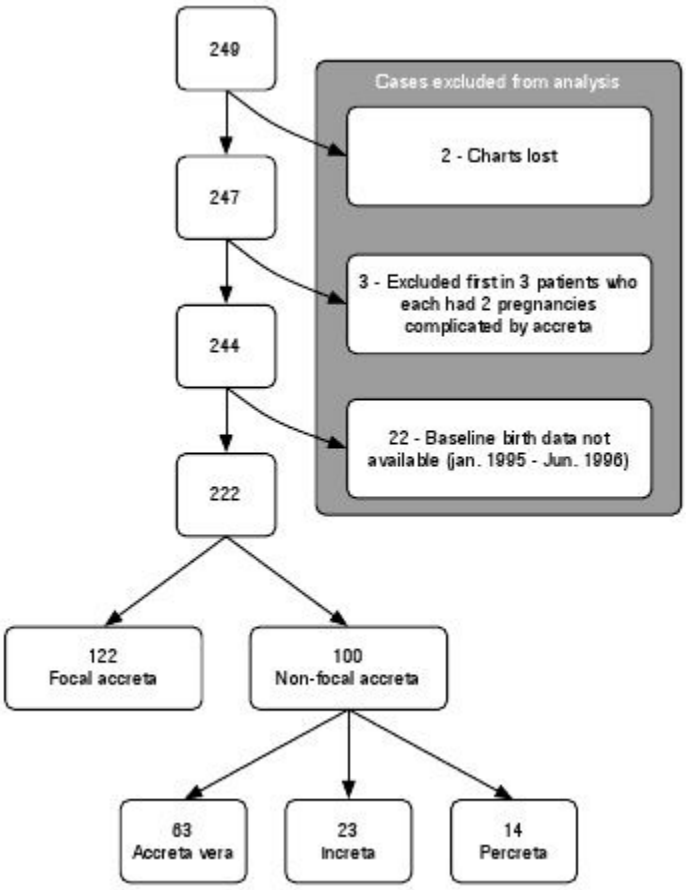


Fig. 3. Cases of placenta accreta diagnosed by pathology at Yale-New Haven Hospital, 1995-2011.

Of the 249 cases of placenta accreta diagnosed via histopathology, cases were divided between focal accreta, accreta vera, increta and percreta.(Fig. 3) In this paper, *placenta accreta* will be used as the general term for all types of placenta accreta, while the specific type of abnormal placentation will be designated *focal placenta accreta, placenta accreta vera, increta or percreta;* the latter three types will collectively be referred to as *non-focal accreta.* Two cases were excluded from the analysis because the patient chart had been lost. There were three patients who each had two cases of diagnosed accreta. For these patients, the second instance of accreta was included in study analysis, and first was excluded. Of the 244 remaining patients with placenta accreta, 22 cases that

occurred from January 1995 through June 1996 were excluded from analysis because birth data was not available for that time period. A total of 122 cases of focal placenta accreta and 100 cases of non-focal accreta were used in the current analysis. Non-focal accreta cases consisted of: 63 cases of placenta accreta vera, 23 cases of placenta increta and 14 cases of placenta percreta. The 122 cases of focal placenta accreta were analyzed separately for patient characteristics and outcomes, because of varying sensitivity in diagnosis of focal accreta. The Yale University Human Investigations Committee approved this protocol.

Each patient chart was reviewed to determine obstetric history, indication for all previous cesarean deliveries, and maternal and perinatal care and outcomes for the accreta pregnancy. All index cesarean deliveries were categorized as one of the following indications, based on the classification used by Barber et al: non-reassuring fetal heart tracing; labor arrest disorders (arrest of dilation or descent, including failed vacuum or failed forceps); suspected macrosomia; elective per maternal request; malpresentation; multiple gestation; preeclampsia, ecclampsia (including eclampsia and HELLP cases); other maternal or fetal indications; and other obstetric indications.(13) Suspected macrosomia was defined by the provider based on either an ultrasound-derived estimated fetal weight or a clinical estimated fetal weight. General practice has been a threshold of 5,000g in non-diabetic patients, and 4,500g in diabetic patients. Elective indication was defined as elective per maternal request, in absence of medical indication. Malpresentation represents breech presentation, face presentation, transverse lie, and unstable lie. Preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelets syndrome are represented in a distinct category because of their higher

frequency. Other maternal indications are defined as other maternal conditions predating the pregnancy that could complicate delivery (e.g., maternal malignancy, maternal human immunodeficiency virus). Fetal indications include antenatal problems preceding the intrapartum period (e.g., fetal anomalies and intrauterine growth restriction). Other obstetric indications include conditions brought about by the presence of the current intrauterine pregnancy (e.g., placental abruption, accreta, previa, and cord prolapse). Indications designated as 'subjective' included: non-reassuring fetal heart tracing, labor arrest disorders, suspected macrosomia and elective by maternal request. There were five patients for whom the indication for index cesarean delivery was unavailable. In cases where more than one indication for cesarean delivery was present, the indication that most directly caused the plan of care to shift to cesarean delivery was used.

Based on convention at YNHH, pregnancies recorded in the patient chart as 'TAB' were assumed to have a dilation & curettage (D&C) unless otherwise specified. All dilation & curettage procedures were counted as part of the total number of uterine surgeries, with the exception of a curettage done as part of a more extensive uterine surgery, in which case it was accounted for as part of that surgery. In several cases, the type of abortion in a patient's obstetric history was not specified. Such cases are included in the total number of abortions, but not categorized as spontaneous or induced. For pregnancy terminations recorded as occurring during the first trimester, the gestational age was recorded as 12 weeks. 'Full term' pregnancies were recorded as occurring at a gestational age of 40 weeks.

For the 16 patients (focal accreta, n=12; accreta, n= 4) whose estimated blood loss during the accreta delivery was listed as 'normal,' a volume was assigned based on average

values reported in the literature: 300mL for vaginal birth,[1] and 600mL for Cesarean delivery.[2] Estimated blood loss was not noted for 23 patients, which were excluded from analysis of blood loss. In case of autologous blood transfusion, 1 unit was assumed to be ~220mL to calculate units of autologous blood when volume was reported in mL.

Tobacco use was analyzed by any previous smoking (yes/no) and smoking during accreta pregnancy (yes/no). Availability of data on quantity of tobacco use was insufficient to stratify by intensity of use. Second-hand smoke exposure was not counted as smoking exposure. Medication use and presence of co-morbidities were recorded primarily as a proxy for maternal health status.

For the study, Daniel Bercik performed chart review on 20% of the cases. Regression analysis was performed by Jessica Illuzzi, MD, MS.

Demographic characteristics, including age, gravidity, parity, race, obstetric history, and maternal and perinatal outcomes of mothers with and without previous exposure to uterine surgery were compared. Rates of placenta accreta were calculated annually as the number of cases of placenta accreta per 1,000 births, and stratified by focal and non-focal accreta cases. Because several accreta pregnancies ended in fetal demise, rates were calculated based on data for all births, rather than live births. Patient categorical characteristics were compared using chi-square analysis, except where small number of observations necessitated use of Fisher's exact test. Continuous variables (e.g. estimated blood loss) were analyzed using t-test for focal/non-focal and ANOVA for comparison of

[1] Average estimated blood loss (EBL) for vaginal delivery: 287mL, based on findings of 2 studies cited in Begley et al 2011, and consistent with other published estimates.(55)
[2] Average EBL for cesarean delivery: 592 +/- 222mL as estimated by obstetricians, in audit of 126 patients delivered by cesarean.(56)

accreta vera, increta and percreta. Logistic regression was done to analyze the primary outcome of rate of placenta accreta by primary exposure variable of indication for cesarean delivery (e.g. objective versus subjective), using time period as the predictive variable. Indications for index uterine surgery were analyzed by logistic regression and cumulative annualized relative risk increase (e.g. odds ratio compounded annually over the duration of the study period; shows the increase in risk for a patient over the duration of the study period). Statistical analysis was performed using SAS 9.2.

Results

Patient characteristics

Comparison between focal and non-focal accreta

Characteristics of patients with focal and non-focal accreta as well as among those with placenta accreta, increta and percreta are compared in Table 1. Comparing the 100 patients with non-focal accreta with the 122 cases of focal accreta, there was a significant difference in age and gravidity;there were no significant differences in race/ethnicity, parity average number of previous cesearean deliveries, and rate of concurrent placenta previa.(Table 1) Grand multiparous women (with ≥ 5 previous births of > 20 weeks gestation) made up 3% of cases. (Data not shown) Overall rate of co-morbidities appear to be higher among focal accreta versus no-focal accreta (p=0.04), including hysterectomy ICU admission, rate of transfusion, estimated blood loss, units of red blood cells transfused, and duration of hospital stay after delivery. There was one woman with increta who did not undergo hysterectomy. She was a 37-year old G6P1132 who had a previous histologically-confirmed placenta accreta vera in her third pregnancy, which was followed by myometrial resection and repair of the area of the accreta; at the time of the increta pregnancy, she had had a total of three previous cesarean deliveries, one previous curettage, and two previous myomectomies. In the increta pregnancy, she had 1L of blood loss, and underwent wedge resection of placenta and adjacent large uterine window on anterior wall. She had no complications and did not need blood transfusion.

	Focal accreta (n=122)	Non-focal accreta [A] (n=100)	p	Accreta vera (n=63)	Increta (n=23)	Percreta (n=14)	p
Age	32.1 {6.3}	33.9 {5.2}	0.023	33.3 {4.7}	36.2 {4.3}	33.1 {7.5}	0.060
Race			0.107				0.383
Black	29 (23)	14 (14)		10 (16)	2 (9)	2 (14)	
Hispanic	15 (12)	10 (10)		5 (8)	3 (13)	2 (14)	
White	69 (57)	72 (72)		46 (73)	18 (78)	8 (57)	
Other [B]	9 (7)	4 (4)		2 (3)	0 (0)	2 (14)	
Smoking							
Ever	25 (20)	14 (14)	0.206	7 (11)	3 (13)	4 (29)	0.260
Current	18 (15)	7 (7)	0.069	1 (2)	2 (9)	4 (29)	0.003
Obstetrical history							
Gravidity	3 (2-4)	3 (2-5)	0.005	3 (2-4)	4 (2-5)	5.5 (4-7)	0.001
Parity	1 (0-1)	1 (0-2)	0.0003	1 (0-2)	1 (1-2)	2 (1-3)	0.316
Uterine surgery							
Cesarean deliveries (#)	0.27 {0.55}	1.05 {1.13}	<0.0001	0.78 {1.02}	1.22 {1.0}	2.00 {1.3}	0.001
Curettage (#)	0.75 {1.12}	0.93 (1.91}	0.397	0.7 {1.06}	0.78 {1.0}	2.21 {4.34}	0.024
Other uterine surgery (#) [C]	0.1 {0.42}	0.25 {0.6}	0.042	0.26 {0.66}	0.32 {0.57}	0.07 {0.27}	0.461
Multiple gestation	22 (18)	6 (6)	0.007	5 (8)	0 (0)	1 (7)	0.459
IVF (during accreta pregnancy)	13 (10)	10 (10)	0.873	7 (11)	2 (9)	1 (7)	1.000
Placenta previa	13 (10)	45 (45)	<0.0001	22 (35)	13 (57)	10 (71)	0.021
Comorbidities [D]	88 (72)	59 (59)	0.040	34 (59)	14 (61)	11 (79)	0.234
Preeclampsia or hypertension [E]	36 (30)	17 (17)	0.030	8 (17)	5 (22)	4 (29)	0.241
DM	21 (17)	14 (14)	0.513	7 (14)	2 (9)	5 (36)	0.077
Obesity	9 (7)	7 (7)	0.914	4 (7)	2 (9)	1 (7)	0.859
Medications	40 (33)	25 (25)	0.205	11 (25)	8 (35)	6 (43)	0.065
Age >= 35 years	49 (40)	44 (44)	0.564	24 (44)	16 (70)	4 (29)	0.015
Substance abuse	7 (6)	6 (6)	0.934	2 (6)	2 (9)	2 (14)	0.105
Asthma	12 (10)	9 (9)	0.832	3 (9)	4 (17)	2 (14)	0.108
Asherman's syndrome	2 (2)	4 (4)	0.413	4 (4)	0 (0)	0 (0)	0.607
Outcomes							
Maternal							
Hysterectomy	7 (6)	68 (68)	<0.0001	34 (54)	22 (96)	14 (100)	0.0004
Multiple cases of accreta	0 (0)	3 (3.0)	0.090	2 (3)	1 (4)	0 (0)	1.000
ICU admission	7 (6)	42 (42)	<0.0001	19 (30)	12 (52)	11 (79)	0.002
Transfused	18 (15)	61 (61)	<0.0001	29 (46)	19 (83)	13 (93)	0.0003
Estimated blood loss (L)	0.9 {0.9}	3.6 {5.2}	<0.0001	2.5 {4.3}	4.6 {6.3}	6.9 {5.4}	0.007
Units of pRBCs transfused	4.1 {3.0}	10.2 {7.4}	<0.0001	8.9 {6.4}	9.7 {8.6}	13.9 {6.8}	0.125
Duration of hospital stay after delivery (days)	4.6 {2.2}	7.0 {7.4}	0.002	6.1 {5.2}	6.7 {3.6}	11.9 {15.3}	0.028
Perinatal							
Gestational age	36.7 {5.0}	34.8 {7.2}	0.006	34.8 {5.9}	33.1 {6.0}	27.8 {11.0}	0.004
Gender							
F	70 (59.8)	42 (47.2)	0.071	27 (47.4)	8 (36.4)	7 (70.)	0.210
Baby to NICU	53 (43.4)	36 (36.)	0.260	21 (33.3)	11 (47.8)	4 (28.6)	0.382
Intrauterine fetal demise	2 (1.6)	4 (4.0)	0.413	4 (6.4)	0 (0)	0 (0)	0.152
Baby weight (g)	2624 {925}	2641 {752}	0.899	2866 {617}	2406 {617}	2103 {965}	0.008

Data presented as n(%) for discrete variables, mean {SD} for continuous variables, median (inter-quartile range) for gravidity and parity. Chi-square test used except where n was too small; Fisher's Exact test was then used instead.

[A] Includes accreta, increta and percreta

[B] Includes American Indian, Asian and Other.

[C] Includes myomectomy, septum resection, lysis of uterine adhesions, endometrial ablation and polypectomy

[D] Recorded primarily as a proxy for maternal health status.

[E] Any previous diagnosis of preeclampsia, ecclampsia or hemolysis, elevated live enzymes, low platelets syndrome, or hypertension.

[F] Excluded from data collection were: nifedipine, prometrium, 17-OHP, prenatal vitamins, iron, albuterol, and common non-prescription medications that are approved in pregnancy (e.g. acetaminophen).

Table 1. Patient characteristics by type of placenta accreta.

Comparison between accreta vera, increta and percreta

Between types of accreta, there was no significant difference in average age or parity at accreta delivery. There was a significant difference among rate of smoking during the accreta pregnancy, gravidity, number of previous cesarean deliveries, and placenta previa. Maternal outcomes were significantly more severe among percreta cases in comparison with accreta vera cases in regard to: hysterectomy (92.9% versus 54%; p = 0.0004); ICU admission (78.6% versus 30.2%; p = 0.002); transfusion (92.9% versus 46.0%; p = 0.0003); estimated blood loss (6.94 L versus 2.47 L; p = 0.007) and duration of hospital stay after delivery (11.9 days versus 6.1 days; p = 0.028). Outcome among neonates also differed significantly between types of accreta.

Description of accreta trends, with focal accreta included

From July 1996 to December 2011, a total of 72,845 births occurred at Yale-New Haven Hospital (including still births). During that time, there were a total of 222 patients with placenta accreta diagnosed by histopathology, which is a rate of 3.05 cases per 1,000 births.(Table 2) This total includes 122 cases of focal placenta accreta (1.67 per 1,000 births), 63 cases of placenta accreta vera (0.86 per 1,000 births), 23 cases of placenta increta (0.32 per 1,000 births), and 14 cases of placenta percreta (0.19 per 1,000 births). To reduce the influence of annual variation, analysis was done by 3-year periods, with the exception of 3.5-year period from July 1996 – December 1999.

Year[A]	All births[B]	Focal accreta	Non-focal accreta[C]	Accreta vera	Increta	Percreta	All accreta[D]
1996-1999[E]	17,244	3 (.17)	17 (.99)	13 (.75)	3 (.17)	1 (.06)	20 (1.16)
2000-2002	14,164	17 (1.2)	20 (1.41)	17 (1.2)	2 (.14)	1 (.07)	37 (2.61)
2003-2005	14,353	33 (2.3)	19 (1.32)	10 (.7)	7 (.49)	2 (.14)	52 (3.62)
2006-2008	13,864	62 (4.47)	21 (1.51)	15 (1.08)	3 (.22)	3 (.22)	83 (5.99)
2009-2011	13,220	7 (.53)	23 (1.74)	8 (.61)	8 (.61)	7 (.53)	30 (2.27)
Total	72,845	122 (1.67)	100 (1.37)	63 (.86)	23 (.32)	14 (.19)	222 (3.05)

[A] Of accreta delivery

[B] Live and still births

[C] Denotes accreta, increta and percreta.

[D] Focal and non-focal accreta.

[E] Time period includes July 1996-Dec 2011. The other four time periods are each three calendar years.

Data presented as n (rate per 1,000 births)

Table 2. Rates of histologically-diagnosed placenta accreta by type

Over this time period, the rate of placenta accreta including all cases varied considerably, from a nadir of 1.16 in per 1,000 births in 1996-1999 to a peak of 5.99 per 1,000 births in 2006-2008, with a subsequent sharp decline to 2.27 per 1,000 births in 2009-2011. (Fig.4)

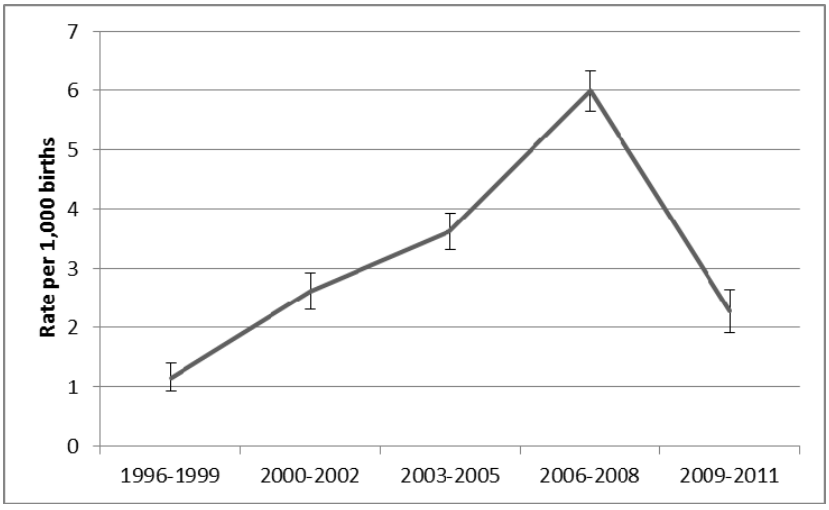


Fig. 4. Rate of all cases of placenta accreta, per 1,000 births. Error bars reflect standard error of the mean.

It would be surprising for the rate of placenta accreta to have a precipitous drop to less than half of its previous rate from one 3-year period to the next. The potential influences on this trend are more apparent when the cases are divided by type of accreta: a similar pattern is noted in cases of focal placenta accreta: rising from 0.17 per 1000 births in 1996-1999 to 4.47 per 1,000 births in 2006-2008, followed by a decline to a rate of 0.53 per 1,000 births in 2009-2011. (Fig. 5)

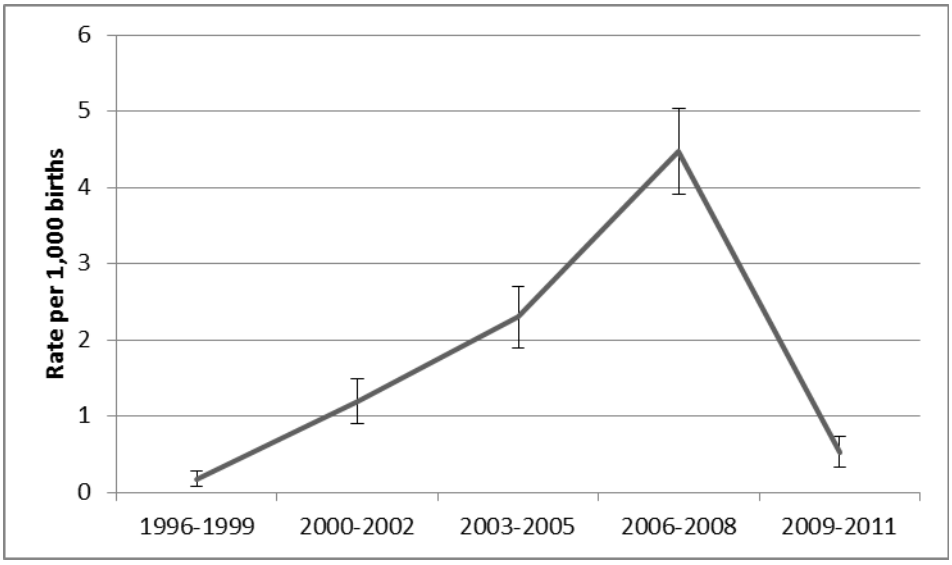


Fig. 5. Rate of focal placenta accreta, per 1,000 births. Error bars represent standard error of the mean.

One possible contributor to this trend is suggested by the pattern of diagnosis of focal placenta accreta by two particular pathologists: among 18 pathologists who diagnosed accreta over the study period, 84% of cases were diagnosed by two pediatric pathologists with expertise in the placenta, with a rise in diagnosed focal placenta accreta cases of two to three-fold between 2005-2009. The possible influence of interpathologist variability on diagnosis rates is further underscored by the fact that the decline in rate of focal accreta diagnosis occurred at the time of their departure from Yale-New Haven Hospital

to other institutions. The decline in rate of focal accreta diagnosis roughly corresponds to the timing of their two departures in 2008 and 2009, as indicated below on the graph of focal accreta diagnosis by year.(Fig. 6) Both of the pathologists had been present prior to this increase, and attribute it to an increase in emphasis on diagnosis of focal accreta in the literature and pathology conferences. (Personal communication with Miguel Reyes Mugica MD and Brian West MD, March 7, 2012). The diagnosis pattern at our institution suggests that there are varying thresholds for the diagnosis of focal accreta among some pathologists. Studies have shown that pathologists without specialization in placental pathology have a high rate of underdiagnosis.(61)

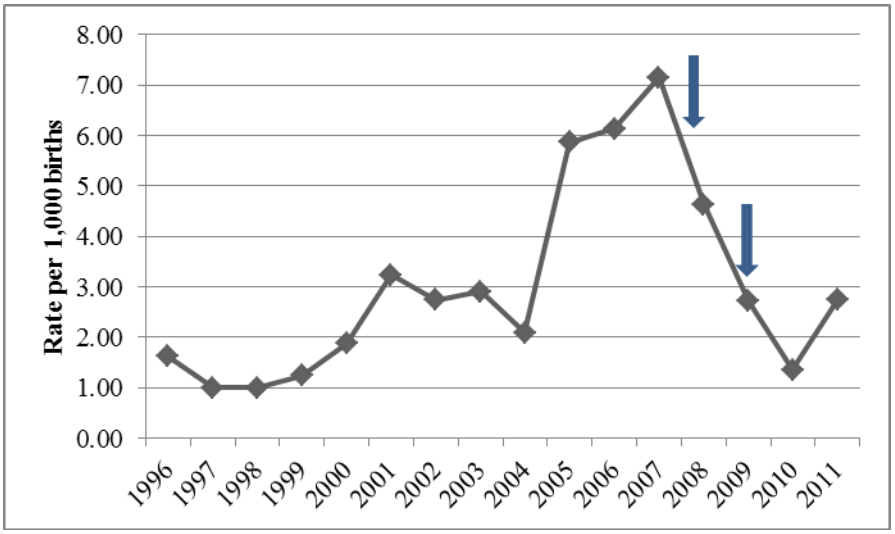


Fig. 6. Rate of focal placenta accreta by year. Arrowheads depict the timing of departure of the two pathologists responsible for 84% of diagnoses of focal placenta accreta across the study time period. Pathologist 1 departed in mid-2007, and pathologist 2 departed in late 2008.

The presence of this correlation suggests that the sensitivity of diagnosis for focal accreta at Yale-New Haven Hospital may have fluctuated over time.. Although there are likely other influences also underpinning the fluctuations in rate of focal accreta over the study period, we felt this fluctuation warranted separation of data for focal placenta accreta

from data for accreta vera, increta and percreta. Thus, the focal accreta cases were analyzed separately and excluded from analysis of trends in rate of incidence and exposure to previous uterine surgery.

Exposure to uterine surgery among non-focal accreta cases

Among patients with non-focal accreta, there was a significant difference between rate of exposure to index uterine surgery ($p = 0.039$); see Table 3. Among women with accreta vera, 42.9% had cesarean delivery as their index exposure, 20.6% had D&C, 12.7% had other uterine surgery (including myomectomy, septum resection, lysis of adhesions, endometrial ablation and polypectomy), and 23.8% had no previous uterine surgery exposure. Index surgeries among women with increta were cesarean delivery in 65.2% of women, D&C among 13%, other uterine surgery among 17.4% and no uterine surgery among 4.4%. Among women with percreta, index surgery was cesarean delivery in 85.7%, D&C in 7.1%, other uterine surgery in 7.1%; there were no women with percreta who did not have a previous uterine surgery exposure. Specific previous uterine surgery varied significantly by type of non-focal accreta ($p = 0.042$). Sixty-four percent of women with percreta cases had been exposed to more than one type of uterine surgery (e.g. had a history of cesarean delivery, D&C and/or other uterine surgery), in contrast to 47.8% of women with increta and 22.2% of women with accreta vera ($p = 0.042$). On average, women with accreta vera had 1.73 previous uterine surgeries (of any type; SD 1.53); women with increta had an average of 2.0 previous uterine surgeries (SD 1.4), and women with percreta had an average of 4.36 previous uterine surgeries (SD 4.33; $p = 0.0003$).

	Accreta vera (n=63)	Increta (n=23)	Percreta (n=14)	p
Index uterine surgery type				0.039
Cesarean delivery	27 (43)	15 (65)	12 (86)	
D&C	13 (21)	3 (13)	1 (7)	
Other [A]	8 (13)	4 (17)	1 (7)	
None	15 (24)	1 (4)	0 (0)	
Previous types of uterine surgery				0.042
Cesarean delivery only	17 (27)	7 (30)	3 (21)	
Curettage only	13 (21)	3 (13)	2 (14)	
Other uterine surgery only	15 (24)	1 (4)	0 (0)	
>1 type of uterine surgery [A,B]	14 (22)	11 (48)	9 (64)	
None	15 (24)	1 (4)	0 (0)	
Total number of previous uterine surgeries	1.73 {1.53}	2 {1.4}	4.36 {4.33}	0.0003

Data presented as n(%) for discrete variables or mean {SD] for continuous variables. Chi-square used except where n was too small; Fisher's Exact test was then used.

[A] Includes myomectomy, septum resection, lysis of uterine adhesions, endometrial ablation and polypectomy

[B] More than one of: CS, D&C/curettage or other uterine surgery.

Table 3. Patient characteristics: exposure to uterine surgery among non-focal accreta cases.

TREND IN NON-FOCAL ACCRETA RATE

The overall rate of non-focal placenta accreta at Yale-New Haven Hospital between July 1996 and December 2011 was 1.37 per 1,000 births.(Table 2) The rate of all non-focal cases increased from 0.99 per 1,000 births to 1.74 per 1,000 births, with an average increase of 12.4% per 3-year period (95% CI -1.6 – 28.5%). (Table 4, Fig. 7)

Year[A]	1996-1999[B]	2000-2002	2003-2005	2006-2008	2009-2011	Mean 3-year Period Increase [%(95% CI)]	Cumulative Risk (95% CI)	p value
Type of placenta accreta								
Focal	0.17	1.20	2.30	4.47	0.53	31.6% (16.1 - 49.2%)	3.95 (2.11 - 7.4)	<.0001
Non-focal accreta[C]	0.99	1.41	1.32	1.51	1.74	12.4% (-1.6 - 28.5%)	1.79 (0.92 - 3.5)	0.0854
Accreta vera	0.75	1.20	0.70	1.08	0.61	-3.2% (-18.1 - 14.4%)	0.85 (0.37 - 2.0)	0.7046
Increta	0.17	0.14	0.49	0.22	0.61	33.0% (-0.3 - 78.3%)	4.16 (0.99 - 18.0)	0.0526
Percreta	0.06	0.07	0.14	0.22	0.53	81.9% (17.3 - 182%)	19.9 (2.22 - 179)	0.0075
All placenta accreta[D]	1.16	2.61	3.62	5.99	2.27	22.4% (11.8 - 34.1%)	2.75 (1.75 - 4.3)	<.001

[A] Of accreta delivery
[B] Time period includes July 1996-Dec 2011. The other four time periods are each three calendar years.
[C] Includes accreta, increta and percreta
[D] Includes focal and non-focal accreta

Table 4. Change in rate of non-focal placenta accreta over time, per 1,000 births

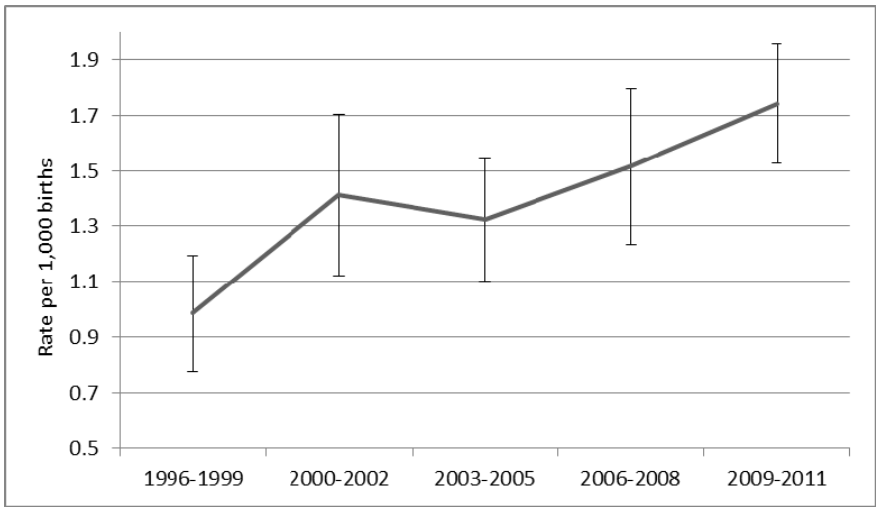


Fig. 7. Rate of non-focal accreta, per 1,000 births. Error bars represent standard error of the mean.

The rate of placenta accreta vera did not change significantly, with a slight decrease of -3.2% per 3-year period (95% CI -18.1% – 14.4%), whereas the rate of placenta increta increased from 0.17 to 0.61 per 1,000 births, or 33.0% per 3-year period (95% CI -0.3% – 78.3%).(Fig. 8) The cumulative risk of placenta accreta vera over this time period was 0.85 (95% CI 0.37 – 2.0); for increta, it was 4.16 (95% CI 0.99 – 18.0). The rate of

placenta percreta increased from 0.06 to 0.53 per 1,000 births, or 81.9% per 3-year period (95% CI 17.3% – 182%), for a cumulative risk of 2.75 (95% CI 1.75 – 4.3) over the study period.

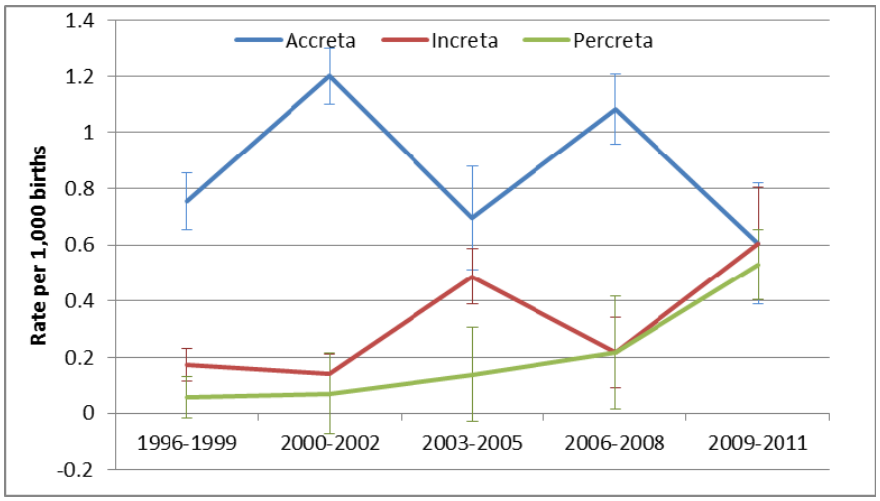


Fig. 8. Rate of non-focal placenta accreta by type, per 1,000 births. Error bars represent standard error of the mean.

Association between exposure to index uterine surgery and risk of non-focal accreta

Among women with non-focal accreta, index exposure to uterine surgery was cesarean delivery for 54 (54%) patients, dilation & curettage for 17 (17%) patients, and other uterine surgery for 13 (13%) patients.(Table 5) Other uterine surgery includes myomectomy, septum resection, lysis of uterine adhesions, endometrial ablation and polypectomy. There were 16 patients for whom there was no known exposure to uterine surgery. This analysis was not completed for the cases of focal accreta, due to the variable sensitivity of diagnosis over the study period (see methods, above).

Year[A]	Non-focal accreta	CS	OUS	D&C	No uterine surgery
1996-1999 B	17 (0.99)	7 (0.41)	2 (0.12)	4 (0.23)	4 (0.23)
2000-2002	20 (1.41)	8 (0.56)	1 (0.07)	6 (0.42)	5 (0.35)
2003-2005	19 (1.32)	14 (0.98)	1 (0.07)	2 (0.14)	2 (0.14)
2006-2008	21 (1.51)	12 (0.87)	1 (0.07)	3 (0.22)	5 (0.36)
2009-2011	23 (1.74)	13 (0.98)	8 (0.61)	2 (0.15)	0 (0.00)
Total	100 (1.37)	54 (0.74)	13 (0.18)	17 (0.23)	16 (0.22)

[A] Of accreta delivery

[B] Time period includes July 1996-Dec 2011. The other four time periods are each three calendar years.

CS - cesarean section; OUS - other uterine surgery (myomectomy, endometrial ablation, septum resection; excluding cesarean and curettage); D&C - D&C or other curettage

Data presented as n (rate per 1,000 births)

Table 5. Non-focal accreta by index exposure to uterine surgery: n (rate per 1,000 births)

Over the study period, the rate of placenta accreta with cesarean delivery as index uterine surgery among all births increased from 0.41 per 1,000 births to 0.65 per 1,000 births; the proportion of women with placenta accreta and D&C as index exposure decreased from 0.23 per 1,000 births to 0.15 per 1,000 births.(Table 5) Rate of accreta and other uterine surgery (OUS) as index exposure changed over time from 0.12 per 1,000 births in 1996-1999 to 0.07 per 1,000 births in 2000-2008, to 0.61 per 1,000 births in 2009-2011. Rate of non-focal placenta accreta and previous uterine surgery exposure declined from 0.23 per 1,000 births to 0 per 1,000 births.

Among women with non-focal placenta accreta, index uterine surgery exposure was cesarean delivery for 54 patients; 27 (50%) of these patients underwent surgery for a subjective indication (Table 6, Fig. 9). Nineteen (35%) of these patients had an objective

indication for primary cesarean delivery. Subjective indications included non-reassuring fetal heart tracing, labor arrest disorder, suspected macrosomia and elective per maternal request in absence of medical indication. Another 5 (9%) of patients had an unknown indication for primary cesarean, and 3 (6%) of patients had preeclampsia listed as the indication for uterine surgery.

Year[A]	All CS [B]	Subjective [C]	Objective [D]	Unknown [E]	PEC [F]
1996-1999 [G]	7 (0.41)	5 (0.29)	1 (0.06)	1 (0.06)	0 (0.)
2000-2002	8 (0.56)	3 (0.21)	4 (0.28)	0 (0.)	1 (0.07)
2003-2005	14 (0.98)	7 (0.49)	5 (0.35)	2 (0.14)	0 (0.)
2006-2008	12 (0.87)	7 (0.5)	4 (0.29)	0 (0.)	1 (0.07)
2009-2011	13 (0.98)	5 (0.38)	5 (0.38)	2 (0.15)	1 (0.08)
Total	54 (0.74)	27 (0.37)	19 (0.26)	5 (0.07)	3 (0.04)

[A] Of accreta delivery

[B] Sum of subjective, objective, unknown and preeclampsia cases.

[C] Includes non-reassuring fetal heart tracing, labor arrest disorder, suspected macrosomia, and elective per maternal request (with no medical indication).

[D] Includes malpresentation, multiple gestation, maternal/fetal and obstetric indications.

[E] Includes cases with indication cited as unknown.

[F] Preeclampisa is not an indication for cesarean delivery, but often no other reason is cited in records.

[G] Time period includes July 1996-Dec 2011. The other four time periods are each three calendar years.

CS - cesarean section; PEC - preeclampsia

Table 6. Cases of non-focal accreta with cesarean section as index uterine surgery exposure, by indication for index primary cesarean: n (rate per 1,000 births)

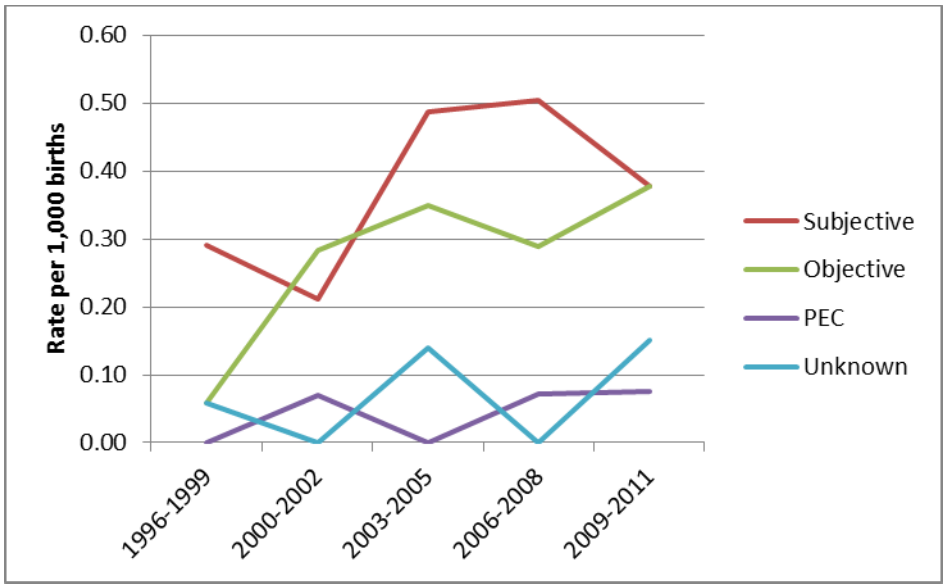
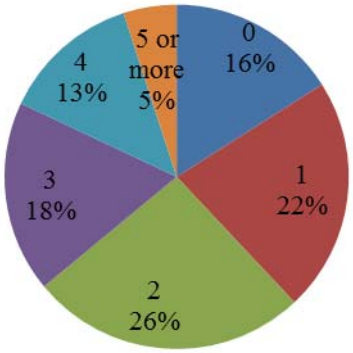


Fig. 9. Rate of accreta among women with cesarean section as index uterine surgery exposure, by indication for cesarean.

The data can also be considered based on rate of accreta associated with cumulative exposure to uterine surgery (e.g. all uterine surgeries prior to accreta pregnancy) either total number of exposures (with all exposures taken as equal), or by type of exposure (e.g. cesarean only, uterine surgery & curettage, etc). The overview of this data is depicted in Fig. 10A-B. Based on total number, 22% had one known uterine surgery; 26% of cases had 2 previous uterine surgeries, 18% had 3 and 18% had 4 or greater. Of course, 16% of women still had no prior uterine surgery exposure. Based on type of uterine surgery exposure (but not taking into account frequency), for 18% of women, curettage was their only known surgical exposure; for 27% of women it was cesarean delivery alone (1 or more); 5% of women had another uterine surgery as their only surgical exposure. Twenty-two percent of patients had at least one of each cesarean and curettage; 5% of patients had all three types of uterine surgery exposure.



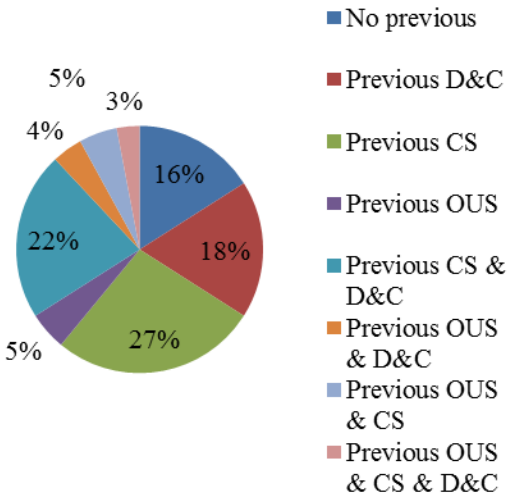


Fig. 10A. **Fig. 10B.**

Fig. 10A-B. Cumulative exposure to previous uterine surgery. A. By total number of previous uterine surgeries, including cesarean section, curettage and other uterine surgeries. B. By types of uterine surgery.

Among the four categories of exposure to previous uterine surgery, there was a significant increase over the study period in the likelihood of cesarean delivery and other uterine surgery as types of index exposure to uterine surgery among women with non-focal placenta accreta.(Table 7) The rate of cesarean delivery as the index uterine surgery increased by 21.9% per 3-year period (95% CI 1.4% - 46.6%). This translated to a cumulative risk of 2.69 (95% CI 1.07 – 6.8), meaning that among all births over the duration of the study, women were 2.69 times more likely to have an accreta in the setting of a prior index cesarean delivery at the end of the study period (2009-2011) compared to the beginning (1996-1999). For other uterine surgery, the average increase over each 3-year interval was 71.1% per 3-year period (95% CI 10.4% - 165%), with a cumulative risk of 14.66 (95% CI 1.64 - 131). The rates of curettage and for no previous exposure to uterine surgery did not change significantly. There was no significant change in the rate of non-focal placenta accreta associated with any of the indications for

cesarean delivery: subjective, objective or unknown, though the rates of each increased slightly. Subjective indication increased slightly, at 13.2% per 3-year period (95% CI -12.4% - 46.4%), objective indication increased by 30.4% per 3-year period (95% CI -5.1% - 79.1%). Preeclampsia was included as a separate category; although it is not an absolute indication for cesarean delivery, it is often noted as such with no other data available.

Year[A]	1996-1999[B]	2000-2002	2003-2005	2006-2008	2009-2011	Mean 3-year Period Increase [%(95% CI)]	Cumulative Risk (95% CI)	p value
Index uterine surgery exposure								
Cesarean delivery	0.41	0.56	0.98	0.87	0.98	21.9% (1.4 - 46.6%)	2.69 (1.07 - 6.8)	0.0352
Curettage	0.23	0.42	0.14	0.22	0.15	-12.8% (-37.0 - 20.8%)	0.50 (0.10 - 2.6)	0.4110
Other uterine surgery[C]	0.12	0.07	0.07	0.07	0.61	71.1% (10.4 - 165%)	14.66 (1.64 - 131)	0.0163
No uterine surgery	0.23	0.35	0.14	0.36	0.00	-16.4% (-40.5 - 17.3%)	0.41 0.07 - 2.2)	0.2993
Indications for cesarean delivery								
Subjective[D]	0.29	0.21	0.49	0.50	0.38	13.2% (-12.4 - 46.4%)	1.86 (0.52 - 6.7)	0.3433
Objective[E]	0.06	0.28	0.35	0.29	0.38	30.4% (-5.1 - 79.1%)	3.77 (0.77 - 18.4)	0.1014
Preeclampsia[F]	0.00	0.07	0.00	0.07	0.08	49.0% (-36.0 - 247%)	7.34 (0.11 - 501)	0.3549
Unknown indication[G]	0.06	0.00	0.14	0.00	0.15	27.5% (-31.0 - 136%)	3.37 (0.16 - 72.4)	0.4385

[A] Of accreta delivery
[B] Time period includes July 1996-Dec 2011. The other four time periods are each three calendar years.
[C] Includes myomectomy, septum resection, lysis of uterine adhesions, endometrial ablation and polypectomy
[D] Includes non-reassuring fetal heart tracing, labor arrest disorder, suspected macrosomia, and elective
[E] Includes malpresentation, multiple gestation, maternal/fetal and obstetric indications.
[F] Preeclampisa is not an indication for cesarean delivery, but often no other reason is cited in records.
[G] Includes cases with indication cited as unknown.

Table 7. Rate of non-focal placenta accreta associated with index uterine surgery and indication for index cesarean delivery.

CHARACTERISTICS OF WOMEN WITH NO PRIOR UTERINE SURGERY

Of the 16 women with placenta accreta who had no known previous uterine surgery exposure, there were no smokers or women with history of preeclampsia. The average

gravidity was 2.0 and parity was 0.8. In nine of these women (56%), a potential risk factor could be identified: three women had a documented abortion, but method was undocumented; four patients were of advanced maternal age (age ≥ 35 years); one patient had a history of Hodgkin's lymphoma with radiation therapy; one patient had transfusion-dependent thrombotic thrombocytopenic purpura, with weekly or biweekly plasmapheresis throughout her pregnancy, which ended in fetal demise.

Discussion

Analysis of pathology-confirmed placenta accreta from a major academic medical center reveals an increasing rate of non-focal placenta accreta over the past 15 years (OR 1.12, 95% CI 0.98 - 1.29). The increasing rate is consistent with other literature, and with statistical modeling that predicts an ongoing increase in rate of placenta accreta in parallel with the trend of the cesarean section rate. This change is driven by an increase in increta (OR 1.33, 95% CI 0.98 – 1.17) and particularly percreta (OR 1.82 95% CI 1.17 – 2.82). A woman with placenta accreta was 19.9 times more likely to have percreta if she presented in 2009-2011 compared with a woman in 1996-1999.

With the increased rate of the more invasive degrees of accreta, there is also an increase in severity of clinical presentation and outcomes. Women with percreta had significantly more several clinical outcomes as gauged by rate of hysterectomy, ICU admission, blood transfusion, estimated blood loss and duration of hospital stay compared with women with placenta accreta. Through the course of this study, there has been an increasing awareness reflected in the literature of the need to optimize management of placenta accreta, including through planned early cesarean delivery and use of multi-disciplinary teams, to minimize morbidity and mortality.(5,10,50) Although this study does not evaluate management patterns, it is clear that placenta accreta continues to pose a challenging clinical management scenario. In our case series, there was one maternal death (1%) among the cases of non-focal placenta accreta in a mutigravida with antenatally-diagnosed placenta percreta. In our study, women with percreta all had three or more previous uterine surgery exposures. It is difficult to quantify the degree of endometrial disruption that occurs by type of uterine surgery; however, in light of the rate

of rise of the percreta rate, it is worth taking an inclusive view of uterine instrumentation in evaluating risk of placenta percreta – particularly including myomectomy, endometrial ablation, and other invasive procedures, as well as curettage.

In this study, there was a significant increase in rate of accreta associated with exposure to cesarean delivery as the index uterine surgery. This is not surprising, as the cesarean delivery rate continues to climb. At Yale-New Haven Hospital, the cesarean rate increased from approximately 20 to over 35% between 1996 and 2009, an increase of 75%.(13) There was a significant change in the rate of primary cesarean exposure for subjective indications over this time period; however, the rate of placenta accreta with a prior index cesarean for subjective indications did not increase significantly. However, if more than 60% of the increase in the primary cesarean delivery rate is due to more subjective indications suggests, it suggests that, theoretically, with the benefit of improved tools to guide acute obstetric management, we can safely reduce the cesarean rate.

Ways to reduce the cesarean rate are under debate. Thorough patient counseling of the risks and benefits of primary cesarean and also of trial of labor after cesarean – particularly for women who desire three or more children – is crucial. One author also suggests setting reimbursement levels for successful VBAC to the same level as that of elective repeat cesarean deliveries, to prevent any financial incentive for cesarean.(3) A recent Cochrane review evaluated the effectiveness and safety of non-clinical interventions for reducing unnecessary cesarean sections.(63) Strategies that show promise include provider directed efforts, including implementing guidelines with mandatory second opinion,(64) mandatory second opinion and peer review feedback at

department meetings(65), guideline implementation with support from local opinion leaders,(66) and maternal-directed of prenatal education, support programs, computer patient decision-aids, and intensive group therapy, though evidence for their effectiveness is less strong to date.(63)

Case identification for cases of placenta accreta was found to be more reliable via histopathologic diagnosis compared with ICD-9 code query. In our study, ICD-9 code had a 9% positive predictive value for histopathologic diagnosis of placenta accreta. Of greatest importance, 69.5% of pathology-confirmed accreta cases were falsely negative for placenta accreta according to ICD-9 code. Use of ICD-9 code to identify placenta accreta should be avoided in future investigations. A better strategy would be to use histopathologic diagnosis, and also to consider establishment of a placenta accreta case registry to enable broader analysis of this relatively rare pathology.

In addition, there is evidence that the rate of focal placenta accreta has been as high as 5.20 per 1,000 births, but also that sensitivity of diagnosis has varied considerably between pathologists and degrees of awareness of the problem of milder placenta accreta. In the case of focal placenta accreta, increase in diagnosis over the middle part of the study period likely reflected in part an increase in awareness associated with the publication of several studies highlighting focal accreta. (Personal communication with Miguel Reyes Mugica MD and Brian West MD, March 7, 2012) Across all types of accreta, improved diagnostic capabilities through antenatal ultrasound may account for part of the increase in antenatal diagnosis over the past several decades. However, standards for histopathologic diagnosis of accreta vera, increta and percreta have not changed significantly, and it is less likely that the increase in incidence of pathology-

confirmed accreta is attributable to improved clinician awareness or increased diagnostic testing.

Placenta accreta is usually considered to be a clinically candid disease, with striking presentation and outcomes; our true understanding is hindered by a surprising diagnostic gray area. All agree that a difficult placental delivery and/or massive hemorrhage with placental or uterine histopathological evidence of basal plate myometrial fibers constitutes placenta accreta. However, the appropriate characterization of both incidental pathological diagnosis of accreta without typical clinical signs and clinically severe cases that are diagnosed by solely clinical findings (e.g. are just diagnosed clinically), remain a source of relatively unfocused debate. This is particularly concerning, in view of the evidence that diagnosis of pathology in placenta specimens has considerable interoperator variability.(55)

Though generally agreed to be increasing, there remains significant variation among published estimates of the rate of placenta accreta. In addition to differences between populations, this is due to variation in diagnostic criteria employed – in particular, clinical versus histopathologic from hysterectomy specimen versus histopathologic from placental specimen. Both in relation to pathologic diagnosis and in general, a standard set of criteria for diagnosis of placenta accreta would benefit our efforts to better understand the patterns of incidence and permit improved comparison between studies. One of the strengths of this paper was inclusion of all pathology-defined cases identified in both hysterectomy and placental specimens, unlike most previous studies, which more often limit pathology specimens to hysterectomy. Although use of stringent inclusion criteria is important, including only cases in which hysterectomy was performed biases

our understanding of placenta accreta by failing to consider potentially less clinically severe, but nevertheless relevant cases of placenta, including cases in which hysterectomy was a near-miss. In this study, hysterectomy rate averaged 68% across all non-focal accreta, and exceeded 96% for both placenta increta and percreta. However, instead of restricting to hysterectomy cases, it is arguably more important to include criteria that will capture the near-miss cases where conservative management may have succeeded, in order to gain insight into optimization of management and to have a more accurate estimate of the extent of this disease. This paper thus may contribute to the working definition of placenta accreta and the development of standard diagnostic criteria.

There are a number of limitations to this study. First, by including only pathology-confirmed cases of placenta accreta, we may have excluded cases that were clinically significant but in which the placenta was not submitted for pathological examination, or in which the specimen was insufficient to make a diagnosis, and thus possibly underestimated the rate of placenta accreta. This possible underestimate is increased by excluding cases of focal placenta accreta. Nevertheless, comparing the rates with those found by other recent studies using combined clinical and histopathological diagnosis, our findings are consistent. Moreover, you would expect broader inclusion criteria to result in greater sensitivity of diagnosis and thus higher estimated rates.

The small sample size was a limitation of this study. The sample size was further reduced by our decision to restrict analysis to non-focal accreta; however, the variation in sensitivity of diagnosis of focal accreta would have introduced unacceptable uncertainty into our analysis. In the future, extension of a larger project to draw from a broader

population, including non-tertiary care facilities, would be an improvement. By stratification of accreta into degree of invasiveness (accreta vera, increta, percreta), it enabled comparison within our case series, to better define the trends between these groups. This is particularly relevant, given that our study also found a higher rate of antenatal diagnosis among cases of placenta percreta compared with increta and accreta(data not shown), which implies better ability of the clinical team to prepare to optimize delivery. Despite the small size of our case series, the ability to stratify by type of accreta and review trends in incidence within these strata is provides an important insight into patterns of placenta accreta at our institution. Moreover, our demonstration of the variation in the focal accreta rate based on variation in pathological diagnosis is relevant for future studies.

A second potential limitation is our baseline assumptions. For instance, by assigning a standard value for 'normal' estimated blood loss (300mL for vaginal birth, 600mL for cesarean delivery), we may have distorted the actual pattern of blood loss among accreta deliveries.

Larger studies of placenta accreta are needed. In a future case-control study, it would be interesting to include analysis of degree of anemia (by hemoglobin/hematocrit), and use of medications such as nifedipine and other tocolytics, antihypertensives and iron as exposures to correlate with the outcome of placenta accreta. Each of these might influence accreta risk by lowering oxygen carrying capacity or blood pressure. Randomized controlled trials are necessary. However, even before that, establishing use of accreta tracking systems would be useful to following trends. For instance, at Yale-New Haven Hospital, a research RN in the labor & birth department records all deliveries

by mode of delivery and indication, and whether delivered by private, university or high-risk provider, which provides a powerful tool for analysis. In a future study, it would also be useful to seek to compare the rates of antenatal/ultrasound, clinical and pathological diagnosis in order to help establish the best diagnostic methods for identifying accreta and related types, in order to prevent misclassification of cases and better understand etiology and strategies for prevention.

In conclusion, over the last 15 years, the rate of non-focal accreta has increased, paralleled by an increase in proportion of more severe degrees of invasion and more severe clinical presentation and outcomes. As antenatal diagnosis and peripartum management improve, secondary prevention will likely become more effective. Better provider preparation and provision of multi-disciplinary peripartum care has been shown to improve outcomes, but will not help turn the tide of this growing problem. It is important to seek better understanding of potential modifiable risk factors that may aid in primary prevention, including exposure to uterine surgery, and to balance the short-term indications that support uterine surgery with the desire to prevent women from unnecessarily crossing that gateway to increased risk of complications. Central to this effort will be patient education, including strategic discussion about number of desired pregnancies and long-term risks. Rates of myomectomy and other uterine procedures have also increased over time. A clearer picture of the rates of placenta accreta associated with various uterine surgeries and their contributions to current increases in placenta accreta is essential, so we can seek to divert childbearing women currently headed down the potentially risky path of multiple uterine surgeries, and joining the ranks

of women with greatly increased risk for placenta accreta and the severe outcomes it forebodes.

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