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Review Article

Improved Maternal and Neonatal Outcomes in Advanced Placenta Accrete Spectrum Disorder in Need of Peripartum Hysterectomy after Structured Clinical Guidelines

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Abstract

Introduction The prevalence of Placenta Accreta Spectrum (PAS) disorder, one of the most critical pregnancy complications, increases worldwide. The aim of this study was to compare maternal and neonatal outcomes in cases with advanced PAS in need of Cesarean Section (CS) with Peripartum Hysterectomy (PPHE) before and after altered clinical guidelines.

Material and methods A retrospective cohort study at a regional referral center for PAS in Sweden, including all women in 2008-15 (n = 18) and in 2016-22 (n = 40) with advanced PAS who underwent CS with PPHE, before and after the introduction of new clinical guidelines in 2016.

Results The regional prevalence of advanced PAS in need of CS with PPHE iincreased threefold from 0.7 to 2 per 10 000 deliveries between the study periods. Antepartum diagnosis 67 vs 95% (p=0.05), and planned surgery 44 vs 78% (p=0.02) increased. Perioperative blood loss 3.4 vs 2.0 L (p=0.006), and composite maternal morbidity 83 vs 45% (p=0.02) decreased. The rate of newborns with a low birth weight <2500 g decreased 70 vs 38% (p=0.02), as did signs of asphyxia with a low Apgar score <7 at 5 72 vs 21% (p=0.001), base excess less than -10 mmol/L 27 to 3% and perinatal deaths 11 vs 0% (p=0.03)

Conclusion The implementation of diagnostic 2nd trimester ultrasound for women with predisposing factors, Multidisciplinary Care Team (MCT) planning, taken together with combined uterotonics and fibrinolytic inhibition with tranexamic acid were followed by increased antepartum diagnosis, planned surgery, improved maternal and neonatal outcomes, and shorter hospital stay.

Keywords: Cesarean; Hysterectomy; Placenta accretae spectrum disorder; Ultrasound

Abbreviations: BE(a): Base excess umbilical artery; CS: Cesarean section; FIGO:International Federation of Gynecology and Obstetrics; ICU: Intensive Care Unit; ICD: International Classification of Diseases; NICU: Neonatal Intensive Care Unit; PAS: Placenta Accrete Spectrum; PPHE: Peripartum hysterectomy; WHO: World Health Organization.

Introduction

Reports on Placenta Accretae Spectrum (PAS) disorder, one of the most critical pregnancy complications, have increased globally since the 1950s [1-4]. Severe PAS prevents physiological placental detachment after childbirth, which increases the risk of massive obstetric bleeding. PAS disorder was first described in women with previous manual placental removal or uterine curettage in the 1920 - 30s [1]. The primary predisposing factor today, in line with increasing cesarean section (CS) rates globally, is a placenta previa which covers the internal cervical os, or a low-lying anterior placenta in combination with a prior CS scar [2-7]. Several clinical diagnostic criteria for PAS have been applied, which has resulted in heterogenous study reports. In order to improve the diagnostic accuracy, the International Federation of Gynecology and Obstetrics (FIGO) presented standardized clinical and histological criteria for PAS in 2019 [4]. The histopathological criteria encompass Grade 1 (abnormally adherent placenta accreta), where no decidua is detected and placental trophoblasts attach directly to the superficial myometrium, Grade 2 (abnormally invasive placenta or increta), where trophoblasts invade into the uterine myometrium, and Grade 3 (abnormally invasive placenta or percreta), subdivided into Grade 3a, where invasion is limited to the uterine serosa, Grade 3b, with bladder invasion and Grade 3c, with invasion of other pelvic organs or tissues.

Women with a placenta previa or PAS disorder should be delivered by CS to avoid life-threatening bleeding, and in case of advanced PAS, CS is commonly planned with PPHE. The prevalence of PAS has been estimated according to various diagnostic criteria to 2 - 90 per 10 000 births in different regions of the world [7], The incidence of emergency PPHE in the Nordic countries was 3 - 5 per 10 000 births in 2009 - 12, where four out of 10 were performed because of PAS [7,8]. Advanced PAS disorder should be taken care of at a referral center with Multidisciplinary Care Team (MCT) management to improve clinical outcomes [3-7,9]. The Karolinska University Hospital is a tertiary referral center for high-risk obstetrics including advanced PAS disorders in the Stockholm Region, where approximately one third of the 105 - 110 0000 deliveries per year in Sweden take place [10].

The objective of this study was to compare maternal and neonatal outcomes between the years 2008 - 15 and 2016 - 22, before and after altered clinical guidelines for PAS in 2016. We hypothesized, that the new guidelines would result in improved clinical outcomes.

Material and Methods

A retrospective single-center cohort study of all women with severe PAS in need of CS with PPHE at the Karolinska University Hospital between Jan 1st 2008 - Dec 31st 2015 (n = 18) as compared to Jan 1st 2016 - Dec 31st 2022 (n = 40), before and after the introduction of structured clinical guidelines for women with predisposing factors for PAS. Data were retrieved from original electronic obstetric records (Obstetrix® Cerner AB, Stockholm, Sweden) by identification of the World Health Organization (WHO) International Classification of Diseases (ICD)-10 codes placenta accreta/percreta O43.2A/B and CS with PPHE O82.2. Classification was made according to the FIGO histologic criteria [4]. Cases with classification according clinical criteria alone and cases that dis not necessitate PPHE were excluded. Some of this material was reported in Arnadottir B, et al. in Clin Surgery 2020.

Ethical approval was obtained from the Swedish Ethics Authority, January 19th 2022, DNr 2021-05018. Since all data were retrieved in retrospect, were anonymized and presented on a group basis only, individual patient consent was not requested by the Ethics Authority.

Clinical Guidelines and Antepartum Care in 2008 - 15

In 2008 - 15, pregnant women in the Stockholm Region with suspected advanced PAS according to routine ultrasonud at 18 - 20 weeks Gestational Age (GA) or emergency ultrasound after vaginal bleeding were planned for CS with arrangements for PPHE at 35 - 38 weeks. Peroperative antibiotic prophylaxis was given at emergency surgery. The operation was performed by an obstetrician and a gynecologic surgical oncologist, mostly in a regular operating theatre, and only occasionally in a hybrid operating theatre. All women received uterotonics with oxytocin injection (Syntocinon®, CD Pharma, Sweden) and less than half of the women received addition of metylergometrine (Methergin®, Novartis, Sweden), prostaglandin F (karboprost, Prostinfenem®, Pfizer AB, Sweden) and fibrinolytic inhibition with tranexamic acid (Cyklokapron® Pfizer, Sweden). The postoperative care was admission to an intensive care unit (ICU) or a high-dependency postoperative unit, analgesia with intravenous and oral opioids, nonsteroidal antiinflammatory drugs (NSAID) and paracetamol, antithrombotic prophylaxis with low molecular weight heparin (LMWH, dalteparin, Fragmin®, Pfizer AB, Sweden) for 1 - 2 weeks and return visit to an obstetrician within 4 - 6 weeks.

Clinical Guidelines and Antepartum Care in 2016 - 22

In 2016 - 22, pregnant women in the Stockholm Region with risk factors for PAS - a placenta previa or a low-lying anterior placenta in combination with a prior CS at routine ultrasound - were planned for diagnostic ultrasound at 24 - 28 weeks´ GA, performed by a fetal-medicine ultrasound specialist. Assessment criteria for PAS were loss of clear zone, intraplacental lacunae, hypervascularity, irregular bladder wall, thinning of the myometrium [11,12]. If signs of PAS were found, Magnetic Resonance Imaging (MRI) and a follw-up ultrasound at 32-34 weeks GA were performed [13,14]. All women were informed about the PAS diagnosis and probability of PPHE. MCT management with an anesthetist, a fetal-medicine ultrasound specialist, an interventional radiologist, a gynecologic surgical oncologist, midwife, neonatologist, obstetrician and a theatre nurse was initiated. Standardized perioperative protocols were initiated and strategies in case of an emergency situation were documented. Planned CS with arrangements for a PPHE was scheduled in a hybrid operative theatre at 34 - 36 weeks´ GA. Timing of surgery was individualized in case of bleeding, uterine contractions or ruptured fetal membranes. All women were admitted to the hospital the day before surgery and antibiotic prophylaxis was given 1-2 hours preoperatively [15,16]. The WHO Surgical Safety Checklist was applied routinely [17]. Large peripheral venous catheters were inserted and monitoring with continuous pulse oximetry, electrocardiography, and invasive blood pressure measurement was initiated. An introducer was inserted in one femoral artery after sterile wash, to allow for embolization of the uterine arteries or balloon catheterization of the aorta. Epidural Analgesia (EDA) was used during the CS. If antepartum diagnosis was made, a midline abdominal wall incision was made, followed by intraoperative ultrasound mapping of the placental demarcation to avoid transplacental incision. The infant was delivered through a corporal uterotomy and the umbilical cord was ligated close to the placenta. All women received oxytocin injection and 4 out of 5 women received combined uterotonics with metylergometrine, prostaglandin F and fibrinolytic inhibition with tranexamic acid. General anesthesia was used during the PPHE leaving the ovaries in situ, performed in by a gynecologic surgical oncologist and an obstetrician. Blood loss was quantified according to standardized routines after separate measurement of amniotic fluid, and weighing of surgical cloths. Intraoperative cell salvage with re-transfusion of leukocyte filtered autologous blood to decrease allogenous transfusion was introduced at our hospital in December 2015 and was used in 2016-22 [18,19]. The postoperative care was admission to a high-dependency postoperative unit for at least 6 h and an ICU if needed, analgesia with EDA for 3 days followed by intravenous and oral analgesia with opiods, NSAID and paracetamol, antithrombotic prophylaxis with LMWH for 6 weeks, mobilization with assistance of a physiotherapist, psychosocial support and return visit to an obstetrician within 4-6 weeks.

Clinical Outcomes

We quantified the prevalence of CS with PPHE for advanced PAS per 10 000 births in the region, the proportions of antepartum diagnosis and planned surgery, early maternal and neonatal outcomes, length of ICU care and hospital stay.

Maternal Outcome: Early maternal outcome was perioperative blood loss during surgery and the following 24 hours, and composite morbidity within 42 days, according to the WHO definition of the postpartum period. Composite morbidity was ICU care for >24 h, transfusion of ≥4 U of erythrocytes, coagulopathy (platelet count ≤100 x 10^9/mL, prothrombin complex/international normalized ratio ≥1.2, or fibrinogen ≤2 g/L), ureteral injury, re-operation, intraabdominal infection, hospital readmission or death within 42 days (9).

Neonatal Outcome: Early neonatal outcome was low Birth Weight (BW) <2500 g, signs of asphyxia with Apgar score <7 at 5 min, and umbilical artery Base Excess (BE) less than -10 mmol/L, Neonatal Intensive Care Unit (NICU) admission, intrauterine death or neonatal death within 28 days.

Statistical Methods

Based on clinical observations in 2008 - 15, we assumed that antepartum diagnosis and rate of planned surgery would increase from 50 to 90%. If so, a sample size of (n = 17) in each group would be required when aiming at a significance level of 5% and 80% power. A two-tailed p-value <0.05 was considered significant. Continuous data were analyzed with Mann Whitney U-test and General Linear Model when appropriate, and categorical data with Chi^2-test or Fisher´s exact test when appropriate or with Kruskal Wallis´test. Continuous data were presented as mean ± Standard Deviation (SD) when normally distributed or median ± range if not, and categorical data as numbers and percentages.

Results

The total CS rate in Sweden increased from 17.1% in 2008 to 19.1% in 2022, and the Stockholm Region CS rate increased from 20.4% to 21.9% between these years (10). The prevalence of CS with PPHE due to advanced PAS in the Stockholm Region increased threefold from 0.7 to 2.0 per 10 000 deliveries between the study periods 2008 - 15 and 2016 - 22. (Figure 1). Antepartum diagnosis increased from 67 to 95 % (p=0.05), and planned surgery from 44 to 78% (p=0.02) (Table 1).

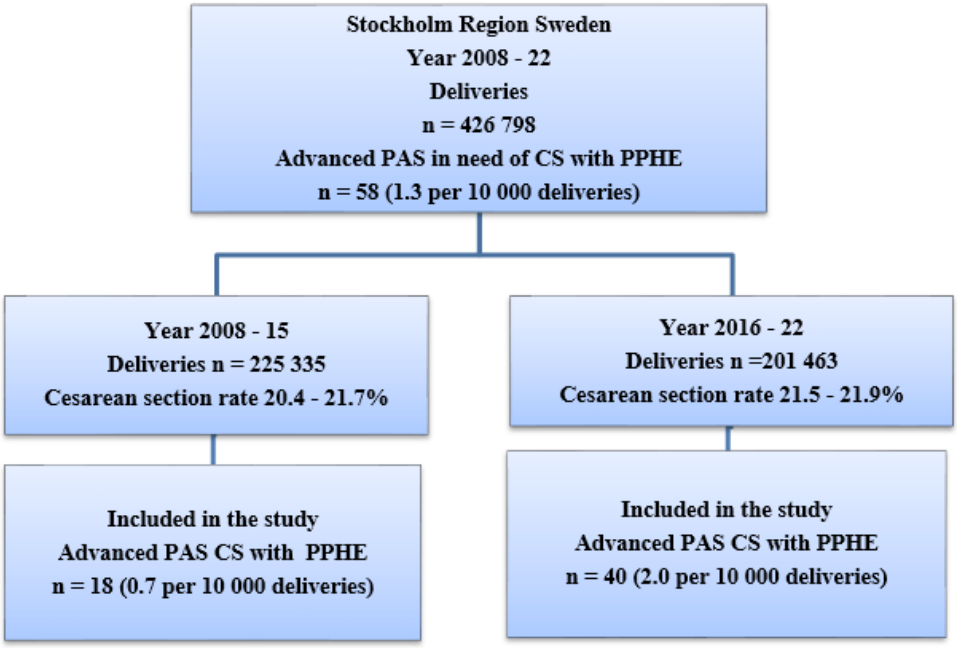

Figure 1: Regional prevalence of women with advanced Placenta accrete spectrum (PAS) in need of peripartum hysterectomy (PPHE) in 2008 – 15 as compared to 2016 – 22.

In 2022, 29 206 deliveries took place in the Stockholm Region, which was 28% of the 103 840 deliveries in Sweden.

Source: Swedish Board of Health and Welfare, Medical Birth Register (10).

Variable	**2008-15**	**2016-22**	**p value**
	n = 18	**n = 40**	**2 sided exact**
Age, years (median ± IQR)	34 (32-37)	36 (31-46)	0.33[1]
BMI kg/m^2 (median ± IQR)	25 (23-28)	25 (23-29)	0.77[1]
Parity, n (median ± IQR)	1 (1-2)	1 (1-3)	0.35[1]
Previous CS, n (%)	116 (89)	35 (88)	0.98[2]
Previous CS, n (median ± IQR)	1 (1-2)	1 (1-2)	0.21[1]
Previous D&C, n (%)	6 (33)	15 (38)	0.24[2]
Placenta previa n (%)	14 (78)	33 (82)	0.68[2]
Antepartum symptoms, n (%)			0.83[3]
Bleeding	14 (78)	21 (53)	
Preterm uterine contractions	2 (12)	3 (8)	
pPROM	0	2 (5)	
None	4 (22)	14 (35)	
Antepartum diagnosis, n (%)	12 (67)	38 (95)	0.05[2]
Planned surgery, n (%)	8 (44)	31 (78)	0.02[2]

Angiographic intervention, n (%)	8 (45)	2 (5)	0.004[2]
Bleeding, mL (median ± IQR)	3450 (2000-9000)	1972 (1500-3550)	0.006[1]
Transfusion			
Erythrocytre concentrate, U (median ± IQR)	8 (2-14)	2 (0-6)	0.004[1]
Erythrocyte concentrate >4 U, n (%)	12 (67)	13 (33)	0.02[2]
Coagulopathy, n (%)	11 (61)	6 (15)	0.001[2]
Composite morbidity, n (%)	15 (83)	18 (45)	0.02[1]
Histologic classification FIGO, n (%)			
Grade 1 Accreta	5 (28)	5 (12)	0.59[3]
Grade 2 Increta	8 (44)	21 (53)	
Grade 3a Percreta limited to uterine serosa	5 (28)	10 (25)	
Grade 3b With bladder invasion	0	3 (8)	
Grade 3c With invasion other organs/tissues	0	1 (2)	
Postoperative ICU and high-dependency care, h (median ± IQR)	28 (23-50)	12 (5-28)	0.004[1]
Hospital stay, days (median ± IQR)	8 (7-10)	6 (5-8)	0.04[1]

Abbreviations: BMI: Body Mass Index; D&C: Dilation and Curettage; ICU: Intensive Care Unit; PPROM: Preterm Prelabor Rupture of Fetal Membranes (pPROM).

Table 1: Maternal data. Statistical methods: Mann Whitney U-test and General Linear Model when appropriate[1]; Chi[2]-test and Fisher´s exact test when appropriate[2], Kruskal-Wallis test[3]

Maternal outcomes are shown in Table 1. Demographic data were comparable. A majority 89 vs 88% had a previous CS, and 33 vs 38% had a previous dilation and curettage (D & C). A majority 78 vs 82% had a placenta previa, and a majority 89 vs 92% (16/18 vs 37/40) had a ventral placenta. More than half of the women in both study periods had antepartum symptoms, bleeding in 78 vs 53%, uterine contractions in 12 vs 8% and pPROM in 0 vs 2%. Emergency PPHE was performed in a second séance between 2 hours and 2 weeks after CS in 28% (5/18) women in the earlier period and none in the latter. Most women 78 (14/18) vs 98% (39/40) underwent a total PPHE with extirpation of the uterine cervix. The need of angiographic intervention with coiling of the uterine arteries or aortic balloon decreased from 45 to 5% (p=0.004). Median peroperative blood loss decreased from 3.4 to 2.0 L (p=0.006), and transfusion of >4 U of erythrocyte concentrate decreased from 67 to 33% (p = 0.02). The re-transfused 200-400 mL of autologous blood using cell salvage was included in the total bleeding volume. The median operation time 135 (98 - 180) vs 154 (115 - 184) did not differ (p=0.40) (data not shown). Maternal composite morbidity decreased from 83 to 45% (p=0.02). Complications in the earlier period were three re-laparotomies because of intraabdominal bleeding, one pelvic abscess and one emergency thrombectomy after femoral artery occlusion. Complications in latter period were two ureteral injuries, one pelvic abscess and one re-laparotomy for intestine injury. There were no maternal deaths. The length of ICU and high-dependency postoperative care decreased from 28 to 12 days (p=0.004) and total hospital stay from 8 to 6 days (p=0.04).

Neonatal outcomes are shown in Table 2. Median GA at delivery was 33+5 vs 35+3 weeks (p=0.09). The proportion of newborns with a low BW <2500 g decreased from 70 to 38% (p=0.02). Signs of asphyxia Apgar score <7 at 5 min decreased from 72 to 21% (p=0.001) and BE(a) less than -10 mmol/L decreased from 27 to 3% (p=0.05). There was one intrauterine fetal death and one early neonatal death within 7 days because of massive antepartum bleeding in combination with prematurity 11% in the earlier period and none in the latter (p=0.03). NICU admission was needed in 89 vs 53% (p=0.07).

Variable	2008 - 15 n = 20 (%)	2016 - 22 n = 42 (%)	p value 2 sided exact
GA at birth, weeks + days (median ± IQR)	33+5 (29-35)	35+3 (33-36)	0.09[1]
Birth weight <2500 g, n (%)	14 (70)	16 (38)	0.02[2]
Apgar score <7 at 5 min, n (%)	13 (72)	9 (21)	0.001[2]
BE(a) less than –10 mmol/L, n (%)	3 (27) n = 11	1 (3) n = 36	0.05[2]
Intrauterine or neonatal death < 28 d, n (%)	2 (11)	0	0.03[2]
NICU admission, n (%)	16 (89)	23 (53)	0.07[2]

Abbreviations: BE(a): Base excess umbilical artery; GA: Gestational Age; NICU: Neonatal Intensive Care Unit.

Table 2: Neonatal data. Statistical methods: Mann Whitney U-test and general Linear Model when approproate[1]; Chi[2]-test and Fisher´s exact test when appropriate[2].

Discussion

We have compared the prevalence of histologically classified advanced PAS in need of CS with PPHE, the proportions of antepartum diagnosis and planned surgery, early maternal and neonatal outcomes, length of postoperative ICU care and hospital stay at a regional referral center for PAS in Sweden between 2008 - 15 and 2016 - 22, before and after the introduction of structured clinical guidelines for women with predisposing factors for PAS.

Our results showed, that the regional prevalence of advanced PAS in need of CS with PPHE increased three-fold from 0.7 to 2.0 per 10 000 births. The new guidelines introducing diagnostic ultrasound at 24 - 28 weeks´ GA for women with risk factors for PAS at routine ultrasound, in combination with diagnostic MRI and repeat ultrasound at 32 - 34 weeks´ GA, were followed by improved antepartum diagnosis in 95% and planned surgery in 78%. These clinical practices, in combination with MCT management, routine use of combined uterotonics, fibrinolytic inhibition with tranexamic acid, and intraoperative cell salvage when needed, were followed by reduced perioperative blood loss, need of transfusion, evidently improved early maternal outcome within the first 42 days, evidently improved early neonatal outcome within the first 28 days, shorter ICU care and hospital stay.

A majority of women, 9 out of 10 in both groups had a previous CS and a ventral placenta, 8 out of 10 had a placenta previa, and 3 - 4 out of 10 had undergone a previous D&C. Among the total of 11 women with no placenta previa, 10 had a medical history of a previous D&C, manual placental removal, intrauterine adenomyosis operation or peripartum uterine infection. These results were in line with recent reports on uterine surgery such as D&C, In vitro Fertilization (IVF) treatment, myomectomy or intrauterine adhesions (Asherman´s syndrome) as predisposing factors for PAS [20].

In contrast to our results, 29% of cases of advanced PAS were diagnosed antepartum in the Nordic countries in 2009 - 12 [7], whereas 86% were diagnosed antepartum at a Swedish referral center for PAS.in 2016 - 20 [21]. With standardized diagnostic criteria, the sensitivity of ultrasound and MRI have been reported to be 80 - 90%, and higher when used by a trained specialist [3,4,6,11-14]. According to the FIGO Guidelines for asymptomatic women with suspected PAS, ultrasound investigations are recommended at 18 - 20 weeks, 28 - 30 weeks and 32 - 34 weeks, and CS with preparations for PPHE is recommended between 34+0 and 35+6 weeks´ GA [22].

The perioperative blood loss 2 L in the latter period was lower than previously reported 3 - 6 L at CS with PPHE [7,8]. This result followed after the higher proportion of antepartum diagnosis and planned surgery, and also after routine administration of combined uterotonics and fibrinolytic inhibition with tranexamic acid. Routine use of combined uterotonics has been questioned, but is recommended at operative delivery in recent reports [23,24]. Also, routine administration of fibrinolytic inhibition with tranexamic acid at operative delivery has been debated, but recommended in recent studies [25,26]. The reduced need of angiographic intervention with coiling of the uterine arteries or application of an aortic balloon to 5% was of value, since these interventions are associated with risk of complications [27].

A conservative approach with attempts to avoid a PPHE was chosen in 5/18 (28%) situations in the earlier period, and none in the latter. Our results showed, that this strategy was associated with higher maternal and neonatal morbidity than performing CS and PPHE in the same séance. Conservative management leaving the placenta in utero after CS with no further surgery except later

curettage has been associated with severe maternal morbidity such as bleeding, sepsis and urgent hysterectomy according to some studies [3-6]. Conservative surgery with partial resection of the PAS part of the uterine wall only in selected cases has been described [28]. This study did not investigate the prevalence of late maternal or neonatal complications. All women in the latter period were offered psychosocial support antepartum before and after childbirth. It is important to offer structured psychosocial support for women with advanced PAS in need of CS with PPHE, since the prevalence of psychosocial suffering and Post Traumatic Stress disorder (PTSD) increases this group of women [3,29,30]. The neonatal outcome was evidently improved, with decreased prevalence of a low BW < 2500 g, and reduced signs of neonatal asphyxia. The unchanged rate of NICU admission was probably a result of GA at delivery, which tended to increase, but still involved the birth of a late preterm neonate in need of NICU care. Strengths of this study were its population-based setting with centralized high-risk obstetrics to one hospital, and that all data were collected from original obstetric records. Limitations were the retrospective observational design and the limited sample size, although it was adequate according to a power analysis.

In conclusion, our results showed an increased prevalence of advanced PAS in need of CS with PPHE at a regional referral center in Sweden, reaching 2.0 per 10 000 deliveries in 2016 - 22. The introduction of structured clinical guidelines with diagnostic ultrasound in women at high risk, in combination with diagnostic MRI and MCT management, was followed by increased antepartum diagnosis and planned surgery. These clinical practices, in combination with routine use of combined uterotonics and fibriolytic inhibition with tranexamic acid, were followed by reduced blood loss, evidently improved early maternal and neonatal outcomes, shorter ICU care and hospital stay.

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