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Peripartum Hysterectomy due to Placenta Accreta Spectrum Disorders - Improved Maternal and Neonatal Morbidity after Diagnostic Ultrasound and Multidisciplinary Care

Berglind Arnadottir[1], Sahar Salehi[2], Johan Nordstrom[3] and Ylva Vladic Stjernholm[1]*

[1]*Department of Women's and Children's Health, Obstetric Unit*

[2]*Department of Pelvic Cancer, Theme Cancer*

[3]*Department of Perioperative Medicine and Intensive Care, Karolinska University Hospital and Karolinska Institute, Sweden*

Abstract

Introduction: The increasing Cesarean Section (CS) rate worldwide is followed by increased maternal morbidity due to Placenta Accreta Spectrum (PAS) disorders. The objective was to evaluate the rate of CS with Peripartum Hysterectomy (PPHE) due to advanced PAS disorders during the years 2008-18. Furthermore, we compared the rates of antenatal detection and planned surgery, as well as maternal and neonatal morbidity. between the two periods 2008-15 and 2016-18, before and after the introduction of diagnostic ultrasound in women at increased risk of PAS disorders at 2nd trimester ultrasound and multidisciplinary care in cases of advanced PAS disorders in need of CS with PPHE.

Material and Methods: A retrospective cohort study at a tertiary university hospital in Sweden. All women (n=17) in 2008-15 and (n=19) in 2016-18 who underwent CS with PPHE due to advanced PAS disorders were included.

Results: The rate of CS with PPHE due to advanced PAS disorders increased from 0.7 to 2.2 per 10,000 deliveries during 2008-18. Antenatal detection increased from 70% to 95% (p=0.05) and planned surgery from 53% to 84% (p=0.02) between the two periods 2008-15 and 2016-18. Perioperative blood loss decreased from 6-2 L (p=0.01), erythrocyte transfusion from 12-3 U (p=0.007), and composite maternal morbidity from 88% to 12% (p=0.001). The rate of newborns with birth weight <2500 g decreased from 58% to 21% (p=0.02), Apgar score <7 at 5 min from 58% to 31% (p=0.05) and umbilical artery base excess BE(a) less than -10 mmol/L from 16% to 0% (p=0.05).

Conclusion: The rate of CS with PPHE due to advanced PAS disorders increased three-fold. The introduction of diagnostic ultrasound and multidisciplinary care was followed by increased rates of antenatal detection and planned surgery, and evident improvements in maternal and neonatal morbidity. We suggest diagnostic ultrasound in women at increased risk of PAS disorders and centralized high-risk obstetrics with multidisciplinary care in cases of advanced PAS disorders.

Keywords: Cesarean; Hysterectomy; Placenta Accreta; Ultrasound

Abbreviations

AIP: Abnormally Invasive Placenta; 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

The increasing CS rate worldwide is followed by increased maternal morbidity due to pathological placentation and massive obstetric bleeding [1-3]. A placenta previa which covers the internal cervical os or a low-lying anterior placenta that reaches <2 cm from the internal cervical os in combination with a prior CS are the main risk factors for Placenta Accreta Spectrum (PAS)

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Correspondence:
Ylva Vladic Stjernholm, Department of Women's and Children's Health, Obstetric Unit, Karolinska University Hospital, Solna, SE-171 76 Stockholm, Sweden,
E-mail: ylva.vladic-stjernholm@sll.se

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disorders where the placental trophoblasts invade the decidua basalis (placenta accreta), the uterine myometrium (placenta increta), or through the myometrium reaching the uterine serosa and sometimes into adjacent organs such as the urinary bladder, parametrial tissues, intestine or abdominal wall (placenta percreta) [1-5]. This prevents physiological placental detachment from the uterine myometrium after birth and may lead to massive blood loss. Other risk factors are advanced maternal age, smoking, other uterine surgery, uterine anomalies, and intrauterine scar tissue (Asherman's syndrome) [1,4-6]. The clinical grading system of PAS disorders introduced by the International Federation of Gynecology and Obstetrics (FIGO) also includes cases of adhesive placentas that do not grow invasively [7]. The rate of PAS disorders has been estimated to 2-90 per 10,000 births globally [1,4,7-9]. The incidence of emergency PPHE in the Nordic countries was 3-5 per 10,000 births in 2009-12, of which 43% were carried out because of placenta accreta [4-5]. In women with a placenta previa or placenta accreta, delivery by CS is mandatory to avoid life-threatening bleeding. In women with advanced PAS disorders, CS is commonly accompanied by PPHE. It has been suggested, that women with advanced PAS disorders should be delivered at a tertiary hospital [1,7-9]. The Karolinska University Hospital is a tertiary hospital for high-risk obstetrics including advanced PAS disorders. Diagnostic ultrasound carried out by a fetal-medicine ultrasound specialist was introduced at our hospital in 2016 for routine follow-up of women at increased risk of PAS disorders at 2nd trimester ultrasound [7,8]. If signs of advanced PAS were found, multidisciplinary care was initiated.

The objective of this study was to evaluate the rate of CS with PPHE due to advanced PAS disorders at our hospital between the years 2008-18. Furthermore, we compared the rates of antenatal detection and planned surgery, the perioperative morbidity among these women and the early neonatal morbidity among their newborns between the two periods 2008-15 and 2016-18 before and after the introduction of diagnostic ultrasound and multidisciplinary care. Our hypothesis was that the rates of antenatal detection and planned surgery would increase, and that this might be associated with improved maternal and neonatal morbidity.

Material and Methods

Patients

This retrospective cohort study included all women who underwent CS with PPHE due to advanced PAS disorders at the Karolinska University Hospital between January 1st 2008 to December 31st 2018. Cases of focal PAS disorders that were clinically diagnosed at delivery or CS and did not necessitate PPHE were not included. 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 O43.2A/B placenta accreta/percreta and O82.2 CS with PPHE. Ethical approval was obtained from the Regional Ethics Board for Medical Sciences in Stockholm, Sweden April 9th 2015, Ref 2014/255-31. Since all data were anonymized and presented on a group basis only, individual patient consent was not requested.

Antenatal care in 2008-15

In 2008-15, all pregnant women in the Stockholm Region with antenatally suspected advanced PAS disorders according to routine 2nd trimester ultrasound, later planned ultrasound for other reasons, or emergency ultrasound carried out because of bleeding or abdominal pain were planned for CS with arrangements for PPHE at 35-38 gestational weeks. Perioperative antibiotic prophylaxis was given at emergency, but not planned operations. The CS with PPHE was performed by an obstetrician and a gynecologic surgical oncologist, mostly in a regular operative room, only occasionally in a hybrid operative room. All women received oxytocin injection (Syntocinon®, CD Pharma, Sweden) and less than half of the women received methylergometrine (Methergin®, Novartis, Sweden), prostaglandin F (karboprost, Prostinfenem®, Pfizer AB, Sweden) and fibrinolytic inhibition with tranexamic acid (Cyklokapron® Pfizer, Sweden). The postoperative care included admission to an Intensive Care Unit (ICU) or a high-dependency postoperative unit, analgesia with intravenous and oral opioids, Non-Steroid Anti-inflammatory 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 after 4-6 weeks.

Antenatal care in 2016-18

In 2016-18, all pregnant women in the Stockholm Region at high risk of PAS disorders - a placenta previa or a low-lying anterior placenta in combination with a prior CS - at 2nd trimester ultrasound were planned for diagnostic ultrasound at 24-28 weeks carried out by a fetal-medicine ultrasound specialist who assessed signs of PAS disorders - loss of clear zone, intraplacental lacunae, hypervascularity, irregular bladder wall, thinning of the myometrium [10,11]. If signs of advanced PAS disorders were found, Magnetic Resonance Imaging (MRI) was performed and multidisciplinary care with standardized perioperative protocols were initiated. The multidisciplinary team included an anesthetist, fetal-medicine ultrasound specialist, interventional radiologist, gynecologic surgical oncologist, midwife, theatre nurse, neonatologist and an obstetrician. Clinical strategies in case of emergency situations were documented. All women were informed about the probability of PPHE. Planned CS with arrangements for PPHE was scheduled in a hybrid operative room at 34-36 weeks. These women were admitted to the antenatal ward in the evening prior to the planned operation and antibiotic prophylaxis was given 1-2 h before the operation [12]. Timing of surgery was individualized in cases of bleeding, uterine contractions or preterm, Prelabor Rupture of Fetal Membranes (pPROM). The WHO checklist for safe surgery was used [13]. Large peripheral venous catheters were inserted and monitoring with continuous pulse oximetry, electrocardiography, and invasive blood pressure measurement was initiated. After sterile wash of the abdomen and groins an introducer was inserted in one femoral artery to allow for embolization of the uterine arteries or balloon catheterization of the aorta. Epidural Analgesia (EDA) was used during the cesarean part of the operation. When an advanced PAS disorder was detected antenatally, a midline abdominal wall incision was made followed by intraoperative ultrasound mapping of the placental attachment site to avoid transplacental incision and massive bleeding. 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 methylergometrine, prostaglandin F and tranexamic acid. Thereafter the operation proceeded with general anesthesia and a PPHE leaving the ovaries *in situ*, performed by a gynecologic surgical oncologist and an obstetrician. The perioperative blood loss was quantified according to standardized routines after separate measurement of the amniotic fluid volume. Intraoperative cell salvage technique with re-transfusion of leukocyte filtered autologous blood to decrease

allogenous transfusion was introduced in December 2015 and was used in the latter period 2016-18 [14]. The postoperative care was admission to a high-dependency postoperative unit for at least 6 h and ICU care if needed, analgesia with EDA for 3-5 days followed by intravenous and oral analgesia with opiods, NSAID and paracetamol, antithrombotic prophylaxis with LMWH for 6 weeks, mobilization with help from a physiotherapist, psychosocial support and return visit to an obstetrician after 4-6 weeks.

Outcomes

We evaluated the rate of CS with PPHE due to advanced PAS disorders at our hospital during the years 2008-18. Furthermore, we compared the rates of antenatal *vs.* emergency perioperative detection and planned *vs.* emergency surgery, maternal perioperative morbidity and early neonatal morbidity between the periods 2008-15 and 2016-18, before and after the introduction of diagnostic ultrasound in women at increased risk of PAS disorders at 2nd trimester ultrasound and multidisciplinary care in cases of advanced PAS disorders in need of CS with PPHE. Maternal perioperative morbidity was bleeding and composite morbidity. Composite morbidity was ICU care for >24 h, transfusion of ≥ 4 U of packed red cells, coagulopathy (platelet count ≤ 100 × 10^9/mL, prothrombin complex/international normalized ratio ≥ 1.2, or fibrinogen ≤ 2 g/L), ureteral injury, re-operation, intraabdominal infection, hospital readmission within 6 weeks, or death [9]. The early neonatal morbidity was low birth weight <2500 g, signs of neonatal asphyxia with Apgar score <7 at 5 min or umbilical artery Base Excess (BE) less than -10 mmol/L, Neonatal Intensive Care Unit (NICU) admission, intrauterine fetal death or early neonatal death ≤ 7 days.

Statistical methods

Based on clinical observations in the period 2008-15, we assumed that antenatal detection would increase and that planned surgery would increase from 10% to 50% between the periods 2008-15 and 2016-18. If so, a sample size of (n=17) in each period would be needed 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 using Mann Whitney U-test and General Linear Model when appropriate, and categorical data with Chi^2-test or Fisher's exact test when appropriate. 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

Approximately 29,000 deliveries out of the 112,000 deliveries in Sweden take place in the Stockholm Region each year [15]. The CS rate in the Stockholm Region was comparable 20.9% to 21.1% between the two periods 2008-15 and 2016-18. About 8000 deliveries take place at the Karolinska University Hospital each year, and the hospital CS rate was 19% to 22% during the two periods. Referrals of women with advanced PAS disorders from other hospitals to the Karolinska University Hospital was comparable 35% (n=6/17) *vs.* 37% (n=7/19) between the two periods (p=0.95). The rate of CS with PPHE due to advanced PAS disorders at our hospital increased three-fold from 0.7-2.2 per 10,000 deliveries in the Stockholm region 2008-18. We identified n=17 women in the period 2008-15 who underwent CS with PPHE due to advanced PAS disorder, of whom 12% (n=2/17) had twin pregnancies. The corresponding sample size in 2016-18 was n=19, all (n=19/19) singleton pregnancies. Of these (n=17+19=36) women 92% (n=33/36) had a placenta previa which was anterior in 86% (n=31/36) and posterior in 5% (n=2/36). One woman (3%) had an anterior low-lying placenta and only 5% (n=2/36) had a placenta attached in the uterine corpus.

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].

Variable	2008-15 n=17	2016-18 n=19	p value
Age, years (mean ± SD)	34 ± 4	37 ± 6	0.16[1]
BMI, kg/m² (mean ± SD)	26 ± 4	25 ± 5	0.73[1]
Parity, n (median ± range)	2 (0-4)	2 (0-5)	0.49[1]
Previous CS, n (median ± range)	1 (0-4)	2 (0-3)	0.47[1]
Pregnancy, n (%)			
Singleton	15 (88)	19 (100)	0.13[2]
Twin	2 (12)	0	
Antepartum symptoms, n (%)	13 (77)	11 (58)	0.45[2]
Bleeding	13 (77)	8 (42)	
Preterm uterine contractions	2 (12)	4 (21)	
pPROM	2 (10)	1 (5)	
Antenatal detection, n (%)	12 (70)	18 (95)	0.05[2]
Planned CS with PPHE, n (%)	9 (53)	16 (84)	0.02[2]
Angiographic intervention, n (%)	6 (35)	2 (11)	0.08[2]
Operation time, min (mean ± SD)	156 ± 96	124 ± 41	0.47[1]
Blood loss, mL (mean ± SD)	6347 ± 6016	2232 ± 1194	0.01[1]
Erythrocyte transfusion, U (mean ± SD)	12 ± 14	3 ± 3	0.007[1]
Erythrocyte transfusion >4 U, n (%)	11 (65)	5 (26)	0.008[2]
Coagulopathy, n (%)	10 (59)	2 (10)	0.001[2]
Composite morbidity, n (%)	15 (88)	4 (12)	0.001[2]
Histopathology, n (%)			
Accreta	7 (41)	3 (16)	
Increta	6 (35)	9 (47)	
Percreta	4 (24)	7 (37)	
Postoperative care (median ± range)			
ICU, h	45 (0-216)	0	0.006[1]
High-dependency care unit, h	46 (2-192)	29 (4-65)	0.57[1]
Hospital stay, days (median ± range)	9 (2-24)	7 (3-9)	0.14[1]

Abbreviations: BMI: Body Mass Index; CS: Cesarean Section; ICU: Intensive Care Unit; PAS: Placenta Accrete Spectrum; PPHE: Peripartum Hysterectomy; pPROM: preterm Prelabor Rupture of Fetal Membranes

Maternal data are shown in Table 1. Demographic data were comparable between the two periods 2008-15 and 2016-18. Antenatal detection of advanced PAS disorders increased from 70% (n=12/17) in the earlier period to 95% (n=18/19) in the latter (p=0.05), and planned surgery from 53% (n=9/17) in the earlier period to 84% (n=16/19) in the latter (p=0.02). More than half of the women 77% (n=13/17) in the earlier period and 58% (n=11/19) in the latter (p=0.45) received antenatal care due to bleeding, uterine contractions or pPROM. Some women 12% (n=2/17) in the earlier period and 21% (n=4/19) in the latter had no previous CS. Unfortunately, we did not obtain any information about other uterine surgery. The mean gestational age at CS with PPHE was 33+0 weeks and 34+6 weeks respectively (p=0.13). In the earlier period 24% (n=4/17) of women had an emergency PPHE carried out at a second operative session between 2 h and 2 weeks after CS, whereas all women (n=19/19) in the latter period underwent a CS with PPHE at the same operative

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].

Variable	2008-15 n=19	2016-18 n=19	p value
Gestational age, weeks + days (mean ± SD)	33+0 ± 25	34+6 ± 21	0.13[1]
Birth weight <2500 g, n (%)	11 (58)	4 (21)	0.02[2]
Apgar score <7 at 5 min, n (%)	11 (58)	6 (31)	0.05[2]
BE(a) less than -10 mmol/L, n (%)	3 (16)	0	0.05[2]
NICU admission, n (%)	13 (68)	12 (63)	0.81[2]
Intrauterine or early neonatal death, n (%)	2 (10)	0	0.12[2]

Abbreviations: BE(a): Base Excess umbilical artery; NICU: Neonatal Intensive Care Unit

session. Angiographic intervention with coiling of the uterine arteries and occasionally balloon catheterization of the aorta tended to decrease from 35% (n=6/17) in the earlier period to 11% (n=2/19) in the latter (p=0.08). Perioperative blood loss decreased from 6 to 2 L (p=0.01), erythrocyte transfusion from 12 to 3 U of packed red cells (p=0.007), coagulopathy from 59% (n=10/17) to 10% (n=4/19) between the two periods (p=0.001). The use of cell salvage technique increased from 12% (n=2/17) to 47% (n=9/19) between the two periods (p=0.02), and the re-transfused 200-400 mL of autologous blood was included in the total bleeding volume. Complications in the earlier period included 3 relaparotomies due to intraabdominal bleeding, one pelvic abscess and one emergency thrombectomy after femoral artery occlusion. Complications in the latter group included one ureteral injury and one pelvic abscess. The length of ICU care decreased from 45h to 0 h (p=0.006), whereas the length of high-dependency postoperative care 46 h to 29 h (p=0.57) and total hospital stay 9 to 7 days (p=0.14) were unchanged. There were no maternal deaths. Neonatal data are shown in Table 2. The rate of newborns with a low birth weight <2500 g decreased from 58% (n=11/19) in the earlier period to 21% (n=4/19) in the latter (p=0.02). Signs of neonatal asphyxia Apgar score <7 at 5 min decreased from 58% (n=11/19) in the earlier period to 31% (n=6/19) in the latter (p=0.05) and BE(a) less than -10 mmol/L from 16% (n=3/19) in the earlier period to 0% (n=0/19) in the latter (p=0.05). The rate of NICU admission was unchanged 68% (n=13/19) and 63% (n=12/19) respectively (p=0.81). There was one intrauterine fetal death and one early neonatal death due to massive blood loss in combination with prematurity 10% (n=2/19) in the earlier period and none (n=0/19) in the latter (p=0.12).

Discussion

We have evaluated the rate of CS with PPHE due to advanced PAS disorders at a tertiary university hospital in Sweden during the years 2008-18. Furthermore, we compared the rates of antenatal detection and planned surgery, perioperative maternal morbidity among these women and early neonatal morbidity among their newborns before and after the introduction of diagnostic ultrasound in women at increased risk of PAS disorders at 2nd trimester ultrasound and multidisciplinary care in cases of advanced PAS disorders in need of CS with PPHE. Our results demonstrated that the incidence of CS with PPHE due to advanced PAS disorders increased three-fold during the years 2008-18. The introduction of diagnostic ultrasound and multidisciplinary care was followed by a clear increase in antenatal detection and planned surgery, and evident improvements in maternal perioperative morbidity and early neonatal morbidity. Despite the three-fold increase in CS with PPHE due to advanced PAS disorders, the incidence 2.2 per 10,000 deliveries in the Stockholm Region in 2016-18 was low compared to previous reports [5,7-9]. This could partly be explained by the fact that only advanced PAS disorders were included in our study, whereas others have included a broader spectrum of PAS disorders. The rising incidence of advanced PAS disorders could be a consequence of increased rates of CS [15] and referrals of women with suspected PAS disorders to our hospital. However, the rates of CS in the Stockholm Region and referrals from other hospitals were comparable between the two periods. Unfortunately, we did not obtain any information about other uterine surgery among the women in the study groups. The introduction of diagnostic ultrasound and multidisciplinary care was followed by increased antenatal detection 70% to 95% and planned surgery 53% to 84%. In contrast, only 30% of cases of advanced PAS disorders were diagnosed antenatally in the Nordic countries in 2009-12 [4]. Despite the standardized ultrasound criteria for PAS diagnostics, the interpretation of the ultrasound investigation is highly individual. The sensitivity of ultrasound diagnostics of PAS disorder has been reported to range between 53% to 74% and the specificity between 70% to 94% [16]. 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+0-35+6 weeks [7]. The present findings confirmed that antenatal detection of advanced PAS disorders and planned CS with PPHE, rather than emergency situations are associated with reduced maternal morbidity. In addition, the present results showed that delivery of women with advanced PAS disorders in a tertiary hospital with multidisciplinary care is associated with improved maternal and neonatal morbidity [1,9,11]. The perioperative blood loss 2 L in the latter period 2016-18 was lower than the recently reported 3-6 L at CS with PPHE because of advanced PAS disorders [4-5,17]. The routine use of fibrinolytic inhibition treatment with tranexamic acid in the latter period might have contributed to the lower blood loss in this group [18]. Our results supported the use of uterotonics, which were given during the CS part of the operation without delaying the decision for PPHE. A conservative approach with attempts to avoid a PPHE was chosen in one out of four women 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 at the same operative session. Conservative management leaving the placenta in utero after CS with no further surgery except later curettage is associated with severe maternal morbidity such as bleeding, sepsis and urgent hysterectomy according to several studies [7-8,19]. Additional chemotherapy treatment with methotrexate to promote placental involution is not recommended, since the term placenta lacks mitotic activity [8,19]. Conservative surgery with partial resection of the PAS part of the uterine wall only has also been described [20]. The rate of NICU admission was unchanged despite the decreased rates of neonates with a low birth weight and signs of asphyxia between the two periods studied. This was probably due to the preterm gestational age at delivery, which tended to increase between the two periods, but still involved the birth of a late preterm neonate in need of NICU admission.

Strengths of this study included its population-based setting with centralized high-risk obstetrics to one hospital. Moreover, all data were collected from original obstetric records. Limitations were the retrospective observational design and the limited sample size, although the sample size was adequate according to a power analysis.

The use of cell salvage technique could have been a confounder when quantifying blood loss. We don't consider this to be a confounder, since the re-transfused autologous blood was included in the total bleeding volume.

In conclusion, the present results demonstrated that the incidence of CS with PPHE due to advanced PAS disorders increased three-fold over the years 2008-18 reaching a rate of 2.2 per 10 000 deliveries in 2016-18. The introduction of diagnostic ultrasound and multidisciplinary care was followed by clear increases in antenatal detection and planned surgery, and evident improvements in maternal and neonatal morbidity. We suggest routine diagnostic ultrasound in women at high risk of PAS disorders, and centralized high-risk obstetrics with multidisciplinary care in cases of advanced PAS disorders.

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Key Message

Diagnostic ultrasound in women at increased risk of placenta accreta spectrum disorders and multidisciplinary care increased antenatal detection and planned surgery and improved maternal and neonatal morbidity.

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