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Review Article

Navigating through the maze of caesarean myomectomy: generating evidence

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ABSTRACT

Management of myomas during pregnancy and labor is a contested subject so far. Currently no recommended national or international guidelines are in place resulting in conflicted opinion and management variation across the globe. Many obstetricians still discourage its practice due to fear of uncontrolled haemorrhage which may lead to unwanted hysterectomy in a reproductive age. However, some researchers have challenged the conventional perspective and argue that caesarean myomectomy (CM) is a safe procedure. The aim of this study is to examine all aspects of CM with an evaluative lens and to weigh its risk-benefit ratio. For this purpose, we conducted a literature review of studies, including those from low-resource countries indexed in scientific databases like PubMed, Google Scholar and Scopus. Most recent articles that reported benefits, complications and different techniques to safely perform caesarean myomectomy with proven benefit for the patient were examined thoroughly so that solid evidence on pros and cons of caesarean myomectomy could be generated. There is a dire need to conduct large sample size studies or randomized controlled trials for the risk-benefit evaluation of CM and to produce evidence-based clinical conclusion.

Keywords: Caesarean section, Caesarean myomectomy, Fibroid, Myomas, Myoma in pregnancy

INTRODUCTION

Uterine myomas, fibroids and leiomyomas are synonymous terms used interchangeably to describe monoclonal, estrogen dependent, benign uterine tumors of reproductive age.[1] Previously called as uterine stones, their existence have been reported by ancient Greeks in 460-375 BC.[2] The term 'fibroid' was first coined by Rokitansky (1860) and Klob (1863) which was later replaced by another term 'myoma' by a German pathologist Virchow who demonstrated that these neoplasms were derived from the smooth muscle cells.[2] Their prevalence range from 20% to 40% in women of reproductive age and exceed 70% if examined at autopsy.[3,4] They are three to nine times higher in Afro-Caribbean than White women or those with a family history of myomas.[4] The incidence rises with the increasing age of a woman but the real frequency in general population is still undefined, as many women remain asymptomatic unless otherwise diagnosed on ultrasonographic scan.[1,2,4] Various growth factors like insulin-like growth factor (IGF), transforming growth factor (TGF), epidermal growth factor (EGF), acidic Fibroblast growth factor (FGF), Heparin binding EGF (HB-EGF), platelet-derived growth factor (PDGF), TGF-a, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), are thought to play some role in the development and proliferation of fibroids.[1,2]

Myomas can be submucosal, sub serosal, intramural, cervical or pedunculated. In about 10% of cases they can present with various symptoms like pelvic pressure, pelvic pain, heavy menstruation, dysmenorrhea, increased urinary frequency and impaired fertility in 1-3% of women.[1-5] The intensity of these symptoms varies according to the location, size and number of fibroids. At times these symptoms can be severe enough to adversely affect the quality of life (QOL) causing substantial morbidity and significant economic and social impact. In United States the estimated annual cost to the healthcare due to myomas range between 5.89 to 34.37 billion dollars of which obstetric outcomes due to myomas in pregnancy contribute for 238 million to 7.76 billion dollars.[6] The estimated cost of economic burden due to fibroids in developing countries remains uncalculated.

MYOMAS IN PREGNANCY

Incidence of uterine myomas in pregnancy varies from 1.6% to 12.6% with higher prevalence in elderly pregnant women or women undergoing in vitro fertilization.[7-11] They are commonly seen in African-American women with an incidence of 18% followed by 8% in white women and 10% in Hispanic women.[10] They are more common in primigravida over 35 years of age due to responsive growth to ovarian steroid hormones, estrogen and progesterone and are rarely seen before puberty.[1,2] On physical examination around 42% of large fibroids (>5 cm) and 12.5% of smaller fibroids can be diagnosed.[12] The gold standard diagnostic criteria to evaluate their size, number, location, relationship with the area of placental insertion and vascularization in pregnant women is gray scale ultrasonography followed by Magnetic resonance imaging in complex and inconclusive cases.[1]

The reciprocal relationship between myomas and pregnancy remains controversial as they may effect each other but the effect of fibroids on pregnancy is more discussed in literature. Selective apoptosis of small lesions during postpartum uterine remodelling and ischemia during parturition are some suggestive theories given in literature.[13] Approximately 30 to 40% myomas grow during early pregnancy, 7.8% will shrink up to 10% in third trimester and only a few continue to grow after puerperal regression.[12,13] There is a mean increase of 12% in fibroid volume and a few increase by 25% under the effect of increased estrogen levels but so far prediction of exact growth rate is impossible.[10,12] Adverse obstetric complications are reported in 10%-40% of cases like spontaneous miscarriage, labor dystocia, intrauterine growth restriction, preterm labor, placental abruption, Placenta Previa, fetal malpresentation and postpartum haemorrhage.[4,8-10,12,14]

Management controversy and complications of myomas

Management of uterine myomas during pregnancy is still disputed despite several studies that have been conducted with an aim to disentangle this clinical dilemma. It is a daunting challenge for many obstetricians due to variation in knowledge, skills, facilities and resources across different geographical regions. For last few years there has been a growing interest in the management of myomas during pregnancy due to stunning advances in medical and surgical modalities for fibroid management. Several medical and surgical options are available to treat myomas, but the preferred choice of treatment in symptomatic pregnant women remains conservative. However; in cases where medical treatment fails and acute symptoms are non-responsive for more than 72 hours, surgery is recommended.[10] Recent studies also reveal that pregnancy outcome is better in cases where surgery is performed during the second trimester, by a high volume gynecologist and preferably in a well-equipped tertiary care institute with blood bank facilities.

Historically, the first myomectomy was done by Amussat for submucosal fibroids, followed by first scientific report on myomectomy by Dr. Washington Atlee published in 1845 in the American Journal of the Medical science.[15] The first cesarean myomectomy was reported by a British surgeon, Bonney in 1913 when he removed six myomas with largest of a melon size in a 30 years old primipara.[15] Following this surgery Bonney further reported three vaginal deliveries in subsequent pregnancies of the same woman. However, it was not appreciated until recently after the publication of various articles in favor of cesarean myomectomy. In modern obstetrics, the first case series of 13 incidental cesarean myomectomies was published in 1989 by Burton et al, who endorsed their safety and feasibility.

Nevertheless, researchers strongly opposed their recommendation, and despite major scientific progression and surgical innovations in last decade, its recommendation stays questionable and discouraged in the textbooks of obstetrics and gynaecology. The main aim of this review is to examine all aspects of cesarean myomectomy with a wide-angle lens and generate evidence that may help to postulate guidelines for caesarean myomectomy in future.

Myoma in pregnancy can be uneventful in majority of the cases but it can cause various complications in 10%-30% of women depending upon the trimester of pregnancy. Risk of complications is also increased with submucosal, retro placental, large and multiple fibroids.[4,12] In early pregnancy, chances of spontaneous miscarriage are 8% with single fibroid and 23.6% with multiple fibroids. Early miscarriage and abdominal pain are common when fibroid is located in the body than in lower segment and with intramural or submucosal fibroid.[10,12,16] There is 60% chance of vaginal bleeding if placenta is implanted close to the myoma.[12] Fetal mal-presentation (OR 2.9; 95% CI, 2.6-3.2), intrauterine growth restriction in 10%, preterm labor (OR 1.5; 95% CI, 1.3-1.7), premature rupture of membranes, placental abruption, labor dystocia, obstructed labor, cesarean delivery (OR 3.7;

95% CI, 3.5-3.9), postpartum hemorrhage and hysterectomy can also occur in late pregnancy or during labor and delivery.[12] Most of these complications are caused by retro-placental fibroids and fibroids >5 cm in size.[4] Premature labor can occur in women who experience intractable pain and inflammation due to "red degeneration".[12,14,17]

Obstetric concerns are considerably raised when myomas are complicated with secondary changes like necrosis, red degeneration (necrobiosis), torsion, impaction and hemorrhage leading to unbearable pain. Approximately 5-21% of women are hospitalized during pregnancy for pain control.[15] In extreme cases rare complications like pyomyoma, uterine axial torsion, uterine incarceration and fibroid rupture can also occur.[4] The exact mechanism by which they exert obstetric complications in pregnancy is not completely understood.[8,12]

REVIEW OF LITERATURE

To conduct a literature review, studies published in peer reviewed medical journals were searched in following electronic scientific databases: MEDLINE, PubMed, Cochrane Library, Scopus, Google Scholar, Pak Medinet, ClinicalTrials.gov and science.gov. The key terms searched for literature review in different combinations were 'cesar', 'cesarean', 'caesarean', caesarean, 'C-section', "myomectomy", "leiomyoma", "fibroid", "pregnancy", "myoma", "myomectomy" with Boolean terms "or" "and". Relevant case series, cohort studies, case-control studies, reviews and comparative studies published in English language were identified. Articles that showed changes in haemoglobin level, estimated blood loss, duration of surgery, and frequency of blood transfusion, need for hysterectomy and any post-operative complication like fever or relaprotomy were included. Studies that described different techniques to control inevitable blood loss were also included. References from all the studies that met inclusion criteria were manually searched to widen the search results and to avoid any duplication by same authors. Case reports and animal studies were excluded. We initially aimed to conduct a systematic review and meta-analysis by using PRISMA guidelines but due to huge clinical and methodological diversity among studies from both developed and developing countries a narrative review was conducted on fifteen studies that were included.

RESULTS

Fifteen observational studies were selected to assess immediate outcomes in women with and without caesarean myomectomy that are given in Table 1.

In a retrospective cohort study by Dedes et al, 48 women underwent CM out of 162 pregnant women with myomas and rest had cesarean only (CO).[17] Overall there was no adverse outcome like hysterectomy or blood transfusion CM group. There was no significant difference in estimated blood loss (p=0.78), change in hemoglobin (p=0.60), operating time (p=0.13) or use of uterotonics (p=0.51). However, there was more blood loss and increased operation time in patients who underwent CM due to multiple myomas or myomas >5 cm in size.

Akbas et al, conducted a retrospective cohort study to compare a group of 63 women who had caesarean myomectomy (CM) with 63 pregnant women who had caesarean only (CO).[18] They selected women with only intramural fibroids for homogeneity. There was no significant difference in both groups in respect of length of hospital stay (p=0.16), post-operative haemoglobin levels (p=0.333), incidence of haemorrhage (p=0.187) and blood transfusion (p=0.64). The only statistically significant finding was duration of operation (p<0.001) and mean change in haemoglobin (p=0.01) between both groups. They affirmed that intramural myomectomy during caesarean is safe and can be performed without any major complications.

Alternatively, Rai and Mishra, performed a prospective cohort study of 15 patients with different types of myomas including intramural myomas 33.3%, subserosal 26.6%, pedunculated 20%, submucosal 6.6% and myomas on different sites 26.6%.[19] Stepwise devascularization was done in 3 patients without any massive haemorrhage and blood transfusion. None of the patients had postoperative fever, operating time was 15 minutes more than a normal CS with additional 1.5 days hospital stay in patients with CM. Similarly, Valson et al, performed CM in women with different types of subserosal, intramural and sub mucosal myomas that are less than 5 cm.[20] Only three patients had blood transfusion but exact reason for transfusion was not given. There was no postpartum hemorrhage, wound site infection or postoperative pyrexia in any of the operated woman. However, duration of surgery in CM was 45 mins prolonged than routine cesarean section.

Mangla et al, did a comparative study of CM with abdominal myomectomy on 33 women of similar characteristics in each group.[13] Blood loss and change in hemoglobin between two groups were not statistically significant and no complication was encountered. Ozcan et al, retrospectively reviewed 306 patients with leiomyoma.[8] There were 82 women who underwent CM and 224 women with myomas had caesarean only (CO). They observed a significant difference in hospital stay (p=0.006) and operation duration (p<0.05) in both groups but no significant difference in the mean postoperative Hb. Another comparative retrospective study conducted by Topcu et al, examined 76 women with myomas in CM group and 60 women with myomas in cesarean only (CO) group.[16] Both groups had comparable features of maternal age, gestational age, parity and mean diameter of myomas. They observed that mean duration of operation was significantly longer in the CM group in contrast to CO group (p=0.032). Difference between both groups in context of intra-operative bleeding, variation in

hemoglobin after surgery, postoperative fever and duration of hospital stay were not statistically significant (p >0.05). Kwon et al, showed the safety of caesarean myomectomy in a retrospective cohort study.[9] They compared 96 women with fibroids who had caesarean delivery without myomectomy and 65 women who had caesarean myomectomy. Women in both groups had same gestational age and neonatal weight at the time of surgery. No difference was observed between postoperative fever, transfusion, hemoglobin or hospitalization days of both groups. However, the duration of operation was significantly longer in caesarean myomectomy group as compare to caesarean without myomectomy group (91.9 versus 60 minutes, p=0.02).

Table 1: Type of studies and short-term outcomes in women with and without caesarean myomectomy.

Authors of publication	Type of study	Setting	Change in hemoglobin levels	Duration of surgery	Incidence of hemorrhage	Duration of hospital stay	Post-operative fever
Akbas et al	Retrospective cohort study	Training and Research hospital Istanbul	p=0.01	p<0.001	p=0.187	p=0.16	N/A
Rai and Mishra	Prospective cohort study	MGM hospital and Research centre, Patna, India	7.5%	50 minutes	20%	5.6 days	N/A
Valson et al	Prospective cohort study	DM WIMS Medical College and hospital, Kerala, India	N/A	75 minutes	NS	N/A	NS
Dedes et al	Retrospective cohort study	University Hospital Zurich	p=0.60	p=0.13	p=0.78	N/A	NS
Peker and Demir	Retrospective case control study	OBGYN Clinic Place Not given	p>0.05	NS	NS	p >0.05	NS
Basaranoglu et al	Retrospective comparative study	Obstetrics and Gynecology Clinic Turkey	p=0.050	N/A	N/A	N/A	N/A
Sparic R	Retrospective case control study	Teaching hospital Serbia	N/A	p<0.0001	N/A	N/A	N/A
Ozcan et al	Retrospective case-control study	Tepecik Research and Training Hospital, Izmir, Turkey	NS	p<0.001	NS	NS	N/A
Akkurt et al	Retrospective cohort study	Single tertiary OBGYN hospital	NS	p<0.005	NS	NS	N/A
Topcu et al	Retrospective	Women Health education and Research Centre, Ankara	p=0.087	p=0.032	p=0.749	p=0.359	p= 0.299
Tinelli et al	Prospective case control study	University affiliated hospitals, Italy	NS	<0.05	NS	<0.05	NS
Kumar, Patil and Sa	Retrospective Case control study	Teaching Hospital, Karnataka	p=0.271	0.005	p=0.323	p=0.183	NS
Kwon et al	Retrospective cohort study	Hallym University Kangam Sacred Heart Hospital, Korea	p=0.51	p=0.02	p=0.19	p=0.13	p=0.66
Simsek et al	Retrospective case-control study	Inonu Univeristy Hospital, Turkey	p=0.01	p<0.01	NS	p<0.05	NS
Hassiakos et al	Retrospective case-control study	University of Athens Hospital, Greece	NS	p<0.05	NS	p<0.05	NS

NS: Non significant, NA: Not available.

Sultana et al, conducted a cohort study on 96 women with myomas and observed that there is no difference in blood loss and hospital stay between women who had CO and those who had CM.[21] Only duration of surgery was prolonged in women who underwent cesarean myomectomy. Similar results were found by Machado et al, in a retrospective study of 8 patients with 7 anterior lower segment fibroids and one posterior lower segment fibroid.[22] No significant post-operative morbidity was found other than stepwise devascularization in one case who went into PPH after 3200 ml blood loss due to large myoma (10x12 cm). Extra 15 minutes were added to the normal duration of each surgery and one day extra for hospitalization. Average blood loss was 1.5 L in 5 cases.

Ehigiegba et al, suggested a high dose of intravenous oxytocin after the delivery of the baby in an attempt to reduce the transfusion rate.[23] Only 20% in 25 CM cases had blood transfusion in women with anterior myomas. The only significant difference was duration of operation (p=0.02) while there was no difference in preoperative, postoperative or mean changes in haemoglobin (p=0.51), duration of hospital stays (p=0.13), transfusion (p=0.19) and postoperative fever (p=0.66). They concluded that caesarean myomectomy is a safe procedure even in large myomas.

A case-controlled study conducted by Brown et al, compared the effect of diluted oxytocin injection in pseudo capsule of intramural and subserosal myomas of 16 women undergoing CM in contrast to 16 women undergoing routine CS.[24] There was no difference in mean blood loss, hemoglobin levels, length of hospital stay, and febrile illness and transfusion rate in both groups. Characteristics of myomas, location and their sizes given in different studies are listed in Table 2.

Table 2: Characteristics of myomas.

Articles	Subserosal	Pedunculated	Intramural	Submucosal	Multiple sites	<5 cm	>5cm and <6cm	>6cm >10
Akbas et al	N/A	N/A	100%	N/A	N/A	39.7%	60.3%	N/A
Rai and Mishra	26.6%	20%	33.3%	6.6%	26.6%	N/A	N/A	N/A
Valson et al	50%	Nil	41.6%	8.3%	Nil	75%	25	N/A
Dedes et al	29.2%	70.8%	N/A	N/A	N/A	91.7%	9.3%	N/A
Mangla et al	72.7%	N/A	27.3%	N/A	N/A	N/A	N/A	N/A
Basaranoglu et al	78.6%	11.9%	7.1%	2.4%	N/A	57.1%	30.9%	11.9%
Sparic, R	40.1%	8.8%	10.7%	N/A	40.1%	N/A	N/A	N/A
Ozcan et al	43.1%	1.3%	50.3%	5.2%	N/A	62.1%	22.5%	15.4%
Akkurt et al	39.6%	8.8%	10.9%	8.8%	40.5%	24%	44%	32%
Topcu et al	24%	N/A	68.3%	8.82%	N/A	20.6%	46.3%	33.1
Sparic, Guido and Tinelli	40.2%	8.8%	10.78%	N/A	40.2%	N/A	N/A	N/A
Tinelli et al	70.5%	8.8%	20.5%	N/A	17.6%	-------	11.7%	88.3%
Kumar, Patil and Sa et al	81%	N/A	16.2%	2.7%	N/A	37.8%	37.8%	24.3%
Kwon et al	33.8%	0%	60%	3.1%	3.1%	50%	50%	N/A
Mu et al	80%	0%	12%	2%	6%	N/A	N/A	N/A
Desai et al	34%	04%	48%	07%	07% cervical	N/A	N/A	N/A

Techniques of Caesarean myomectomy

Different techniques of caesarean myomectomy have been demonstrated in literature and 'Myoma pseudocapsule sparing' is a largely reported method. Its main advantage is preservation of healthy myometrial tissue which is said to have neuro-transmitters and neuropeptides that enhances myometrial healing after the surgery. Tinelli et al, carried out a prospective case-control study on 68 patients who had intracapsular CM, compared to 72 controls with myomas who underwent CO.[25] Majority of women had subserous myomas (n=48), 14 had intramural, 6 had pedunculated and 12 had multiple site myomas (17.6%). Myomas were approached by linear incision over uterine serosa either by scalpel or low wattage monopolar electro-scalpel. After reaching

the surface of myoma, edges were freed and myoma was hooked to extract from its capsule. Hemostasis was secured by a low wattage coagulation of the pseudocapsule vessels followed by 10 IU of intravenous oxytocin infusion and normal saline infusion for 12-24 hours after myoma enucleation. There was no difference in preoperative and postoperative hemoglobin values, mean change in hemoglobin values, incidence of intraoperative hemorrhage, frequency of blood transfusion and postoperative fever between the groups. Only duration of operation and hospitalization were prolonged in the CM group ($p>0.05$).

Lee and Cho, suggested a purse-string suture during caesarean after observing good results in 31 patients with subserosal (76%) and intramural myomas (24%).[26] The authors reported favorable outcomes in terms of surgery duration without late hemorrhages, uterine ruptures in subsequent pregnancies and reduced blood loss by collapsing the blood vessels. Nonetheless, this technique is not recommended for myomas that are submucosal, intra-ligamentary, deep intramural and those near the tubes.

Alternative technique presented by Incebyik et al, was a combination of tourniquet, electrosurgery and oxytocin infusion.[27] They applied tourniquet through a window on the broad ligaments at the cervico-isthmic level and removed it after suturing the uterus. Myoma dissection was performed using electrocautery; intravenous oxytocin was administered postoperatively to facilitate uterine contraction and blood was transfused in 2 out of 16 patients.

Desai et al, performed selective uterine devascularization to reduce blood loss during myomectomy by bilaterally ligating both ovarian vessels and ascending uterine arteries before excising the myoma.[28] They also ligated descending uterine arteries in patients where myomas were located near lower uterine segment. Conventional surgical technique was used to excise myomas and no immediate morbidity was observed. Mean blood loss was 430±97.5 ml and only one patient required blood transfusion while incidence of postpartum sepsis was 4%.

Another case-control study of 72 patients with myomas was performed by Lin et al.[29] There were 36 women in each group and both groups had women with similar mean age, parity, gestational age and size, position and location of dominant myoma. Bilateral uterine arteries were occluded by bilateral uterine artery ligation with silks followed by myomectomy and injection of diluted vasopressin (1:60) into the myometrium and myoma tissues in case group (UAO+CM). Subsequently intravenous oxytocin infusion was given in both groups after the delivery of baby and placenta.

Kaymak et al, performed myoma dissection with electrocautery in 40 CM cases and compared their results to 80 CS cases with myomas.[30] The incidence of hemorrhage, postoperative fever, number of transfusions, and postoperative hemoglobin values were not considerably different except duration of surgery and length of hospitalization that were longer in the CM group.

Kwawukume, has also advocated the similar technique of applying tourniquet around uterine arteries and ovarian vessels to reduce the risk of intrapartum haemorrhage.[31] Use of electrosurgery and vasopressin injection into the incision site of myoma have also shown positive results of minimal blood loss during CS.[31-33] A study of 22 myomectomies with large myomas (>5 cm) during caesarean was directed by Ortac et al.[34] They used electrocautery or argon beam coagulator to remove myomas with minimum blood loss without using any vasoconstrictive agent. Mean size of removed myomas was 95±46 (range, 50-190 mm) with mean intra operative blood loss of 324±131.1 ml and mean operative time of 41.6±8.0 min. (25-60 mm). No major complication like hysterectomy or any perinatal death was seen.

DISCUSSION

Generating Evidence: Is Caesarean myomectomy a safe bet?

Possible complications of cesarean myomectomy reported in aforementioned studies include perioperative hemorrhage leading to arterial embolization, ligation, blood transfusion, reoperation or hysterectomy, obstetric intensive care unit admissions and massive hemorrhage leading to disseminated intravascular coagulopathy (DIC) after the surgery. Seffah had reported a maternal mortality after a re-laparotomy and hysterectomy due to intractable hemorrhage followed by DIC after CM but complete details of the procedure and patients who underwent CM, were not given therefore the results cannot be generalized.[35] In modern days, autologous blood transfusion during CM is suggested to overcome the hazards of blood loss during surgery and risks of heterologous blood transfusions but this modern facility is expensive and not generally available in majority settings thus making it a limited choice.[36]

Nonetheless, there are social and economic perks of caesarean myomectomy over interval myomectomy.[36] For instance, two operations can be done in one abdominal incision, under one anesthesia and by the same surgeon. This saves, re-hospitalization, money and time of both the patient and the surgeon; thus, making it cost effective and time-saving by avoidance of relaprotomy and wastage of hospital resources. Additionally, the incision given at the time of caesarean is smaller as compare to the one given at the time of laparotomy for myomectomy hence making it aesthetically more favorable. Moreover, it provides symptom relief, decreased chances of myoma related complications in future and increased chances of spontaneous vaginal

delivery in subsequent pregnancy, provided there is appropriate birth spacing.[35]

Strengths and limitations includes various points. Every effort was made to include recent studies conducted in both high- and low-income countries so that experience of surgeons from resource limited settings can also be included. However, due to large heterogeneity in sample size, methodology, settings, and limited information on study results a systematic review or Meta-analysis could not be performed. Our study also lacked inclusion of randomized controlled trials that are paramount in providing robust evidence. Additionally, many queries related to number, position, size of myomas, associated risk during CM and level of competence of a surgeon and settings remain unanswered.

Taking stock of all the available evidence, myomectomy of a single myoma during Caesarean can be considered a feasible and safe option only in experienced hands and favourable settings. However, due to scarcity of robust data, decision for evidence-based management should be considered on case to case basis. The procedure is recommended in selected patients by high volume surgeons, in well-resourced settings with the facility of blood banks, intensive care units and in symptomatic patients where it is unavoidable to assist safe delivery of the fetus. Further research in multi-centres with large sample size, multivariate analysis and prospective randomized controlled trials are required to draw evidence-based clinical conclusion.

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