Incidental uterine perforation during laparoscopy in pregnancy: case report, review of the literature and management proposal

Joan Vilà Casas, Marta Claramonte Nieto, Núria Barbany Freixa, Alberto Rodríguez-Melcón, Bernat Serra Zantop, Pilar Prats Rodríguez

Dexeus Mujer, Departament of Obstetrics, Gynecology and Reproduction, University Hospital Dexeus, Barcelona, Spain

ABSTRACT

Introduction: Laparoscopic surgery can be performed in pregnancy but it is not devoid of risks. Incidental perforation of a pregnant uterus during laparoscopy is a rare complication that requires a quick response and multidisciplinary management due the potential for maternal and fetal morbidity. The aim of this article is to propose an algorithm of action for cases of incidental uterine perforation during laparoscopy in pregnancy.

Methods: The authors present a case report and literature review of previously described cases. Major electronic databases were searched from their inception until July 2020. There was no restriction regarding language. A management proposal and algorithm of action are presented based on data analysis.

Results: A total of 7 cases were reviewed. No entrance technique is free of this risk. Management proposal: if a uterine perforation occurs, the trocar should not be removed initially. Tocolysis, fetal lung maturation, fetal neuroprotection, and prophylactic antibiotic therapy must be considered, depending on the injury and gestational weeks. Conversion to laparotomy is advisable especially if a big trocar perforation, multiple injuries, active bleeding, or significant amniotic leakage occur, or if surgical repair is not feasible by laparoscopy. When stillbirth does not occur during the initial episode, reported fetal survival is high.

Conclusion: Accidental uterine perforation during laparoscopic surgery in pregnancy is a rare complication. We propose a management algorithm for cases of incidental uterine perforation based on the data available.

KEYWORDS

Uterine perforation, appendicitis, laparoscopy, pregnancy, management.

Introduction

Laparotomy and laparoscopy can be performed safely in all pregnancy trimesters [1-12] if anatomical differences are adequately assessed. Acute appendicitis is the most common non-obstetric surgical emergency complicating pregnancy, followed by cholecystitis and ovarian cysts [8,13]. We report a case of incidental uterine perforation during laparoscopic appendicectomy in a 25^{1/7} weeks pregnant patient. The authors performed a review of previously described cases and a data analysis of this uncommon complication. In view of the difficult management and rarity of this complication, the objective of this article is to propose an algorithm of action for cases of incidental uterine perforation in pregnancy.

Case report

We present the case of a 43-year-old primigravida who conceived by *in vitro* fertilization with oocyte donation. She had no previous disease or surgical history. Her initial body mass index was 23. Pregnancy developed normally, with no abnormal clinical or ultrasound findings.

At 251/7 weeks of gestation, the patient presented acute ab-

Article history

Received 10 Sep 2021 - Accepted 2 Dec 2021

Contact

Pilar Prats Rodríguez; pilpra@dexeus.com Department of Obstetrics. Instituto Universitario Dexeus. Barcelona. C/ Sabino Arana 5-19. 08028 Barcelona 932274747.

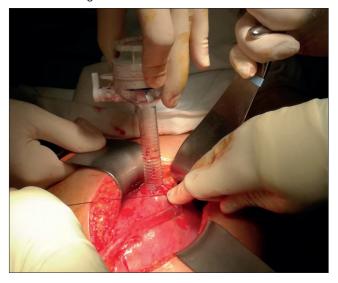
dominal pain located in the right lower quadrant without other accompanying symptoms. She was examined at her local referral hospital and acute obstetric complications were excluded. Three days later the pain worsened. Blood tests showed leukocytosis with neutrophilia and elevated C-reactive protein level. No fever appeared during the emergency stay. Abdominal ultrasound scanning showed a non-compressible blind-ended tubular structure in the right lower abdominal quadrant with a diameter of 11 mm. On the basis of the symptoms, blood test results and ultrasound findings, acute appendicitis was suspected and laparoscopic appendicectomy was indicated. Initial abdominal access with optical entry was performed by a general surgeon with an 11mm optical trocar through an umbilical incision. Intraabdominal CO₂ gas pressure was set to 12 mmHg. The trocar was thought to be correctly positioned inside the abdominal cavity, but fetal parts were visualized within the amniotic sac.

Accidental uterine perforation was confirmed and Gynecology and Obstetrics Department staff were called for evaluation. The trocar was left in place. Prophylactic tocolysis (6.75 mg bolus of atosiban, antagonist of the oxytocin receptors), fetal neuroprotection (4.5 g bolus of MgSO₄), a first dose for fetal lung maturation (12 mg of betamethasone), and prophylactic antibiotic therapy following the protocol for premature rupture of the membranes and preterm labor (1g/6h ampicillin and 80mg/8h gentamicin) were administered and an infraumbilical midline laparotomy performed with the trocar still in place (Figure 1). The uterine injury was repaired using a purse-string suture with vicryl 2/0 (polyglactin 910), at the same time removing the trocar (Figure 2). Intra-abdominal inspection revealed inflammation of the appendix with no signs of peritonitis; the appendix was removed without complications. No amniotic fluid leakage was detected. Fetal well-being was verified by ultrasound after surgery. On the first post-operative day, obstetric ultrasound revealed an anterior membrane detachment, normal intra-amniotic fluid, a 7cm column of extra-amniotic fluid with no interposition of fetal parts, posterior placenta, and hypoechoic im-

Figure 1 Uterine perforation with 11mm optical trocar.



Figure 2 Uterine injury being repaired using purse-string suture removing at the same time the trocar.



ages surrounding the umbilical cord suggestive of blood clots (Figure 3). A second dose of betamethasone was administered 24h after the initial one, magnesium sulfate was stopped at 6 hours, and tocolytics and antibiotics were given for 11 days until normalization of the white blood cell count. The patient was discharged on the 19th postoperative day with a normal maternal-fetal follow-up evaluation.

Weekly obstetric follow up was satisfactory until 32^{2/7} weeks. At this gestational age the patient presented with severe oligohydramnios. The patient did not report vaginal leaking and PROM test® proved negative. Intra-abdominal loss of amniotic fluid through the uterine scar was suspected. A new round of two doses of 12mg of betamethasone, 24 hours apart, and antibiotics (ampicillin and gentamicin) were given. The patient remained under close monitoring with the non-stress test and subsequent ultrasound examinations confirmed severe oligohydramnios with an amniotic fluid index of 2.5 centimeters. No clinical or laboratory signs of infection appeared. Contractions appeared on the 4th day (326/7w), and on the basis of the potential risk of uterine rupture at the level of the scar, a C-section was performed through midline laparotomy. At the location of the uterine perforation a decrease in the myometrial layer was objectively identified, as only serosa was observed; there was no amniotic fluid leakage. After birth, this area was strengthened with several stitches. A 1990g male newborn was delivered, with Apgar Score 7/8/8 and normal umbilical cord pH (arterial 7.25 and vein 7.28).

Figure 3 1-Anterior membrane detachment, normal intraamiotic fluid (B), a 4cm column of extraamniotic fluid with no fetal parts interjection (A). Figure 2 Normoinsert posterior placenta and hypoechoic images surrounding the umbilical cord suggestive of clots.



During the immediate postoperative period, the patient presented vomiting and abdominal pain refractory to medical treatment. A CT scan of the abdomen and pelvis was performed showing dilated jejunal loops and suspicion of intestinal sub-occlusion, probably related to the surgical procedure. The case was resolved by medical conservative management and placement of a nasogastric tube.

In the subsequent days, the baby presented respiratory deterioration and was diagnosed with dry lung syndrome and persistence of fetal circulation. Thus, he required 72h of ventilatory support with tracheal intubation, 2 doses of surfactant, caffeine and nitric oxide. Moreover, he needed vasoactive support with dopamine and furosemide to reverse the hemodynamic instability, and parenteral nutrition for the first 5 days. The newborn was discharged on the 31st day, weighing 2,300 g and without signs of hemodynamic or respiratory instability. Follow up at 6 months showed a healthy mother and baby with no sequelae.

Methods

To perform this review, the PubMed, Google Scholar, ScienceDirect, ResearchGate and EMedicine medical databases were searched for articles. The keywords used were "surgery", "pregnancy", "laparoscopy", "appendicitis", "complications", and "uterine perforation". There was no restriction regarding either publication date or language.

Two reviewers (JVC and MCN) independently screened titles and abstracts, assessed the full texts of potentially relevant papers, and extracted the data from the included studies. A third reviewer (PPR) resolved disagreements that could not be resolved by discussion.

The objective of this review was to gather published cases of incidental perforation and to determine the appropriate management of this extremely rare complication. The review included the present paper as well as previous articles describing uterine perforation as a complication of surgery during pregnancy, and the recommendations are based on analysis of this review case series (level of evidence 4, strength of recommendation C).

Results

Seven cases of incidental uterine perforation during laparoscopy in pregnancy are summarized in Table 1.

In summary, no incidental perforation occurred during the first trimester. The most frequent indication for laparoscopic surgery due to maternal pathology was appendicitis. Veress needle and optical entry were the most recurrent techniques for initial abdominal access. In three of the seven cases, conversion to laparotomy was performed to surgically repair the uterine lacerations. There was only one case of stillbirth [14]. All viable pregnancies delivered prematurely except one case.

Table 1 Incidental uterine perforation during laparoscopic surgery in pregnancy. Cases reported in the literature.

	Weeks of gestation	Pathology suspected	Initial abdominal access	Uterine Injury	Support medications	Correction technique	Latency	Gestational age at delivery
Friedman JD, et al. [14]	21 ^{3/7} W	Appendicitis	Veress needle (infraumbilical)	Veress	-	None	0 ^{2/7} w	21 ^{5/7} w (Premature rupture of membranes, stillbirth)
Joumblat N, et al. [15]	19 ^{2/7} w	Appendicitis	Veress needle (supraumbilical)	2 lacerations (Veress + 5mm trocar)	-	Midline laparotomy	13 ^{3/7} w	32 ^{5/7} w (Premature rupture of membranes, C-section)
Mala T, et al. [16]	24 ^{4/7} w	Internal herniation	Optical entry (supraumbilical)	2 lacerations (two 5mm trocars)	Tocolytic, corticosteroids, prophylactic antibiotics and anti-D immunoglobulin	Midline laparotomy	5 ^{3/7} W	30 ^{0/7} w (uterine rupture suspected, C-section)
Vatanchi A, et al. [17]	28 ^{0/7} w	Cholecystitis	Open technique (Hasson) (-)	-	Corticosteroids and prophylactic antibiotics	None	10 ^{0/7} w	38 ^{0/7} w (elective C-section)
Post RJ, et al. [18]	17 ^{6/7} W	Cholecystitis	Veress needle (supraumbilical)	5mm trocar	-	None	12 ^{3/7} w	30 ^{2/7} w (monochorionic- diamniotic twins, C-section due to severe preeclampsia)
	32 ^{1/7} w	Appendicitis	Optical entry (supraumbilical)	5mm trocar	Corticosteroids	None	4 ^{4/7} w	36 ^{5/7} w (Premature rupture of membranes, C-section)
Vilà Casas J, et al.	25 ^{3/7} w	Appendicitis	Optical entry (umbilical)	11mm trocar	Tocolytic, corticosteroids, magnesium sulfate and antibiotics	Midline laparotomy	7 ^{3/7} W	32 ⁶⁷ W (oligohydramnios and uterine rupture suspected, C-section)

Discussion

Incidental uterine perforation during the performance of a laparoscopic intervention in a pregnant woman is a rare complication that requires fast decision-making and a multidisciplinary team to avoid maternal-fetal complications.

Despite obvious limitations in terms of previous data available, as this is a very rare complication, we developed an algorithm of action that may help surgeons and obstetricians in the management of this challenging situation.

It is interesting to point out that uterine perforation has been reported for all laparoscopic abdominal access techniques. All the cases [14-18] including ours experienced premature rupture of the membranes or suspected uterine rupture before 37 weeks and were delivered by C-section except one case of stillbirth. Although the indication for C-section is not specified in all the cases, the potential risk of uterine rupture at the site of the perforation scar has to be considered.

Performing laparoscopy during pregnancy

Laparoscopy versus laparotomy

No surgical approach has proved superior to any other in non-obstetric emergency complications [1.2,4-7,9,11,13,15,18-20]. Laparoscopy should be avoided in cases of maternal hemodynamic instability and multiple previous surgeries [8]. Despite certain discrepancies found in a systematic review [10] dealing with perinatal outcomes such as fetal loss, laparoscopy is considered [8] the preferred approach due to its benefits in terms of postoperative outcomes: less postoperative pain, fewer wound complications and lower risk of thromboembolic events. Both techniques are safe in all trimesters and the decision on which to perform should be based on the skills of the surgeon and the availability of appropriate staff and equipment.

Safety during laparoscopic intervention in a pregnant woman

There follow several points and recommendations to prevent complications when performing laparoscopic surgery in pregnancy:

- Patient's position: women should be placed in left lateral decubitus and Trendelenburg position to minimize compression of the vena cava and improve the surgical view [8].
- Initial abdominal port placement: this should be performed safely and effectively, according to the surgeon's experience and the uterine height. It is mandatory to place the main trocar in the supraumbilical area at least 6 centimeters above the uterine fundus or consider other locations such as Palmer or subxiphoid area [8].
- Entrance technique: both open (Hasson) and closed (Veress needle or optical entry) techniques have been safely and effectively used [8].
- Ultrasound-guided Veress needle and trocar placement has been described in the literature [3] as an additional safeguard to avoid uterine injury and should be used in our opinion.

- Use of transcervical instruments to manipulate the uterus is prohibited in pregnant patients.
- CO₂ insufflation: a 10-15 mmHg pressure level is safe in the pregnant patient⁸. According to some studies [21,22], gasless laparoscopic surgery, as an alternative to the conventional technique, may be a reliable option in selected cases.
- Fetal monitoring: the fetal heartbeat should be checked prior to and after surgery. There is no evidence of utility of prophylactic tocolytics unless signs of preterm labor appear [8]. Treatment to promote fetal lung maturation must be based on obstetric indications.
- Location: it is recommended to perform laparoscopic surgery in pregnant women in a third-level hospital with highly specialized staff and technical equipment, such as adult and neonatal intensive care units, especially in gestations >23 weeks [23].

Management

If an incidental perforation of a gravid uterus occurs during laparoscopic surgery, the response has to be fast and multidisciplinary. In all the cases described in the literature incidental fetoscopy was confirmed by the identification of fetal parts within the amniotic sac once the laparoscope was inserted. Table 2 summarizes our management proposal in the case of incidental uterine perforation during laparoscopic surgery.

Initially, trocars should not be removed, in order to avoid amniotic fluid leakage and uterine bleeding. This is especially important with big (≥ 10mm) or multiple trocar perforations. If a single small perforation is objectively identified, the trocar could be carefully removed under direct view as done in fetoscopy, and usually no repair is needed [18]. Due to the absence of articles describing laparoscopic repair of incidental perforation lesions, we recommend conversion to laparotomy, especially in cases of big trocar (>10mm) perforation, multiple injuries and active bleeding.

If surgical repair is required (due to the extension or bleeding of the uterine lesion), even though in our case we performed a purse-string suture, the subsequent evaluation taking into account the evolution of the case has led us to recommend the use of another suture technique: one simple deep interrupted stitch with absorbable suture at each side of the incision and after extraction of the trocar another simple deep interrupted stitch between the first two, to correctly close the perforation. Additional full-thickness sutures can be necessary depending on the size of the uterine injury. In fetoscopic fetal surgery this type of suture is performed to close the trocar access and ensure membrane attachment, so we consider it to be a more appropriate type of suture [24,25]. After that, it is important to check that there is no amniotic fluid leakage.

A peritoneal fluid sample should be taken to grow cultures in cases of incidental uterine perforation during laparoscopy performed due to a suspected abdominal infection.

Intraoperative ultrasound is advised in order to evaluate the fetal heart rate and possible fetal or placental injuries related to the accident.

Tocolytic drugs must be considered especially when surgical repair is performed between 24^{1/7} and 34^{6/7} weeks of gesta-

Incidental uterine perforation suspected (visualization of fetal parts within the amniotic sac) Gynaecology/Obstetrics Evaluation Intraoperative ultrasound to evaluate the fetus and placenta Trocar < 10mm Trocar > 10mm and/or Multiple injuries and/or Trocar can be removed Active bleeding and/or carefully under direct view. Significant amniotic leakage If no complications, expectant management. Do not remove the trocar/s. Conversion to laparotomy (infraumbilical midline laparotomy). Simple interrupted stich at each side of the trocar. After removing the trocar another simple interrupted stich between the two prior stiches Check for absence of amniotic fluid leakage or active bleeding. $< 24^{1/7} w$ 24^{1/7}- 34^{6/7}w $> 34^{6/7}$ w Prophylactic antibiotics. Prophylactic antibiotics. Prophylactic antibiotics.

Anti-D immunoglobulin

 Magnesium sulfate (< 316/7 w) for fetal neuroprotection.

(Maternal Rh-).

Betamethasone (fetal lung maturation) Tocolytic drugs (atosiban)

Consider:

Table 2 Algorithm of action in the event of incidental uterine perforation during laparoscopy in pregnancy

tion. Betamethasone under $34^{6/7}$ weeks for fetal lung maturation and magnesium sulfate under $31^{6/7}$ weeks for fetal neuroprotection must be considered in cases of suspected imminent preterm delivery. Prophylactic antibiotics are recommended especially if the laparoscopy was indicated for inflammatory or infectious pathology. Anti-D immunoglobulin in maternal Rh-negative cases is indicated.

Anti-D immunoglobulin

(Maternal Rh-).

Discharge is to be considered once maternal and fetal well-being is confirmed. Given the lack of evidence on this situation, and despite the fact that we performed weekly clinical

and ultrasound checks, it may be possible to follow up these patients after a week and thereafter every 2-4 weeks as has been suggested in a postoperative protocol in open fetal surgery [26]. It is essential to ensure that the patient is well informed about alarm signals, and fast accessibility to the hospital must be guaranteed as the incidence of complications and preterm delivery is high. Despite this, unless fetal loss or death occurs during the initial episode, fetal survival is high. Neonatal complications are those associated with prematurity, although long-term outcomes cannot be elucidated.

Anti-D immunoglobulin

(Maternal Rh-).

Strengths and limitations

The strength of this study is that it provides suggestions on how to manage incidental perforation of the uterus during pregnancy, based on a systematic review, albeit one limited by the low number of published cases.

Limitations of this work are that the evidence is based on a very low number of cases and that there is no report on longterm follow up of neonates. A publication bias is suspected, with cases probably underreported.

Conclusions

Incidental uterine perforation during laparoscopy in pregnancy is a rare complication, probably underreported. No entrance technique is free of this risk.

On the basis of the available evidence and previous reported cases, our group has developed suggestions on how to manage and prevent this situation.

Ultrasound can be useful to guide Veress needle and trocar placement, in order to avoid uterine injury. If a uterine perforation occurs, initially the trocar should not be removed, to avoid uncontrolled fluid leakage. Prophylactic tocolysis, fetal lung maturation, fetal neuroprotection and prophylactic antibiotic therapy must be considered depending on the clinical situation. Conversion to laparotomy should be considered indicated in some situations, i.e., in the case of a big trocar perforation, multiple injuries or active bleeding. If fetal demise does not happen during the initial episode, reported fetal survival is high.

The major risk after this complication is prematurity <37 weeks, mainly due to preterm rupture of the membranes.

We consider that a clear management algorithm in cases of accidental uterine perforation during laparoscopy in pregnancy may help surgeons to manage this rare complication and possibly improve maternal-fetal outcomes.

References

- Conron RW, Abbruzzi K, Cochrane SO, Sarno AJ, Cochrane PJ. Laparoscopic procedures in pregnancy. Am Surg. 1999;65:259-63.
- Estadella J, Español P, Grandal B, Gine M, Parra J. Laparoscopy during pregnancy: case report and key points to improve laparoscopic management. Eur J Obstet Gynecol Reprod Biol. 2017;217:83-8.
- Affleck DG, Handrahan DL, Egger MJ, Price RR. The laparoscopic management of appendicitis and cholelithiasis during pregnancy. Am J Surg. 1999;178(6):523-9.
- Andreoli M, Servakov M, Meyers P, Mann WJ Jr. Laparoscopic surgery during pregnancy. J Am Assoc Gynecol Laparosc. 1999;6:229-33.
- Lee SH, Lee JY, Choi YY, Lee JG. Laparoscopic appendectomy versus open appendectomy for suspected appendicitis during pregnancy: a systematic review and updated meta-analysis. BMC Surg. 2019:19:41.
- Cox TC, Huntington CR, Blair LJ, et al. Laparoscopic appendectomy and cholecystectomy versus open: a study in 1999 pregnant patients. Surg Endosc. 2016;30:593-602.
- Lyass S, Pikarsky A, Eisenberg VH, Elchalal U, Schenker JG, Reissman P. Is laparoscopic appendectomy safe in pregnant women? Surg Endosc. 2001;15:377-9.
- 8. Pearl JP, Price RR, Tonkin AE, Richardson WS, Stefanidis D. SAG-

- ES guidelines for the use of laparoscopy during pregnancy. Surg Endosc. 2017;31:3767-82.
- Rollins MD, Chan KJ, Price RR. Laparoscopy for appendicitis and cholelithiasis during pregnancy: a new standard of care. Surg Endosc. 2004;18:237-41.
- Walsh CA, Tang T, Walsh SR. Laparoscopic versus open appendicectomy in pregnancy: a systematic review. Int J Surg. 2008;6:339-44.
- Walker HGM, Al Samaraee A, Mills SJ, Kalbassi MR. Laparoscopic appendicectomy in pregnancy: a systematic review of the published evidence. Int J Surg. 2014;12:1235-41.
- Wilasrusmee C, Sukrat B, McEvoy M, Attia J, Thakkinstian A. Systematic review and meta-analysis of safety of laparoscopic versus open appendicectomy for suspected appendicitis in pregnancy. Br J Surg. 2012;99:1470-8.
- Augustin G, Majerovic M. Non-obstetrical acute abdomen during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2007;131:4-12.
- Friedman JD, Ramsey PS, Ramin KD, Berry C. Pneumoamnion and pregnancy loss after second-trimester laparoscopic surgery. Obstet Gynecol. 2002;99:512-3.
- Joumblat N, Grubbs B, Chmait RH. Incidental fetoscopy during laparoscopy in pregnancy: management of perforation of the gravid uterus. Surg Laparosc Endosc Percutan Tech. 2012;22:e76-8.
- Mala T, Harsem NK, Røstad S, Mathisen LC, Jacobsen AF. Perforation of the pregnant uterus during laparoscopy for suspected internal herniation after gastric bypass. Case Rep Obstet Gynecol. 2014;2014:720181.
- Vatanchi A, Pourali L, Jafari M. A uterine perforation during laparoscopic cholecystectomy: case report. Tehran Univ Med J. 2018;76:148-5.
- Post RJ, Friedrich E, Amaya KE, Chmait RH. Inadvertent perforation of a gravid uterus during laparoscopy. JSLS. 2019;23:e2019.00026.
- Prodromidou A, Machairas N, Kostakis ID, et al. Outcomes after open and laparoscopic appendectomy during pregnancy: a meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2018;225:40-50.
- Kilpatrick CC, Monga M. Approach to the acute abdomen in pregnancy. Obstet Gynecol Clin North Am. 2007;34:389-402, x.
- Sesti F, Pietropolli A, Sesti FF, Piccione E. Gasless laparoscopic surgery during pregnancy: evaluation of its role and usefulness. Eur J
 Obstet Gynecol Reprod Biol. 2013;170:8-12.
- D'Ercole C, Cravello L, Guyon F, Montgolfier RD, Boubli L, Blanc B. Gasless laparoscopic gynecologic surgery. Eur J Obstet Gynecol Reprod Biol. 1996;66:137-9.
- Newton E. Surgical Problems in Pregnancy. Glob. Libr. Women's Med. ISSN 1756-2228. 2008.
- Kabagambe SK, Jensen GW, Chen YJ, Vanover MA, Farmer DL.
 Fetal surgery for myelomeningocele: a systematic review and meta-analysis of outcomes in fetoscopic versus open repair. Fetal Diagn Ther. 2018;43:161-74.
- Ochsenbein-Kölble N, Brandt S, Bode P. Clinical and histologic evaluation of the hysterotomy site and fetal membranes after open fetal surgery for fetal spina bifida repair. Fetal Diagn Ther. 2019;45:248-55.
- Sacco A, Ushakov F, Thompson D, et al. Fetal surgery for open spina bifida. Obstet Gynaecol. 2019;21:271-82.

Statement of ethics: The protocol was approved by the Dexeus Institutional Review Board for Human Investigation and the Ethics Committee. Informed consent was obtained from all the patients and the reported investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in

Acknowledgments: Under the auspices of the Càtedra d'Investigació en Obstetrícia i Ginecologia de la Universitat Autònoma de Barcelona.

Disclosure statement: The authors have no conflicts of interest to declare. Funding sources: The authors received no specific funding for this work.