GMR
The Original

INTRAMURAL ISTHMIC PREGNANCY FOLLOWING PREVIOUS CESAREAN SECTION AND IN VITRO FERTILIZATION: A CASE REPORT WITH DISCUSSION OF THE MOLECULAR PATHOLOGY OF CESAREAN SCAR IMPLANTATION

Mohammed Malak, MD, MSc*

Department of Obstetrics and Gynecology, School of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
*Corresponding Author:Mohammed Malak, MD, Email: mmmalak@kau.edu.sa | dr.m.malak@gmail.com

ABSTRACT
Intramural pregnancy is among the rarest forms of ectopic implantation, accounting for fewer than 1% of ectopic pregnancies, and is associated with a high risk of uterine rupture and life-threatening hemorrhage when the diagnosis is delayed. The molecular pathology of abnormal implantation at the cesarean scar and lower uterine segment is increasingly being defined and involves altered expression of extracellular matrix remodeling enzymes, dysregulated wound-healing pathways, and changes in endometrial receptivity markers. We report a 35-year-old woman with a previous cesarean section and secondary infertility who conceived following frozen embryo transfer and was diagnosed with an intramural isthmic pregnancy at 7 weeks of gestation. The diagnosis was established by high-resolution transvaginal ultrasonography and confirmed by pelvic magnetic resonance imaging, both of which demonstrated complete myometrial encasement of the gestational sac without communication with the endometrial cavity. A fertility-preserving combined approach was used, comprising laparoscopic excision of the gestational tissue with site-directed local methotrexate injection into the surrounding myometrial bed. The myometrial defect was repaired in two layers and the uterus was preserved. Serial beta-human chorionic gonadotropin titers fell from 38,640 mIU/mL preoperatively to 112 mIU/mL by postoperative day 21. Histopathology confirmed chorionic villi embedded entirely within myometrial smooth muscle fibers, without intervening decidualized endometrium. The case is discussed in the context of recent molecular and gene-expression studies of cesarean scar healing and lower-segment implantation, including data on the connective tissue growth factor (CTGF)–LRP1 axis, matrix metalloproteinase expression, integrin β3 and leukemia inhibitory factor as endometrial receptivity markers, and microRNA dysregulation at the cesarean scar niche.

KEYWORDS: Intramural pregnancy; cesarean scar; gene expression; matrix metalloproteinase; integrin β3; leukemia inhibitory factor; microRNA; in vitro fertilization; fertility preservation.

INTRODUCTION

Intramural pregnancy is a rare and potentially catastrophic form of ectopic implantation in which the gestational sac develops entirely within the uterine myometrium, without communication with the endometrial cavity or the fallopian tubes (Tulandi and Al-Jaroudi, 2004; Marchiole et al., 2004). It represents fewer than 1% of all ectopic pregnancies and is associated with a substantial risk of uterine rupture and life-threatening hemorrhage when the diagnosis is delayed (Memtsa et al., 2013).

Recognized predisposing factors include previous cesarean section, adenomyosis, prior myomectomy or other uterine surgery, instrumented procedures such as dilatation and curettage, and the use of assisted reproductive technology, particularly when embryo transfer is technically difficult (Marchiole et al., 2004; Birch Petersen et al., 2016). Implantation within the isthmic region poses an additional diagnostic challenge, because the imaging appearance overlaps with cesarean scar pregnancy, a degenerating intramural fibroid, or angular pregnancy (Jurkovic et al., 2003). Accurate localization through high-resolution transvaginal ultrasonography, supplemented when necessary by pelvic magnetic resonance imaging (MRI), is therefore essential.

Beyond the anatomical risk factors, there is growing molecular evidence that abnormal implantation in the cesarean scar and lower uterine segment is associated with specific gene-expression changes. Single-cell RNA-sequencing studies of cesarean scar niche tissue have implicated the connective tissue growth factor (CTGF)–low density

lipoprotein receptor-related protein 1 (LRP1) signaling axis in impaired scar healing, with deficient LRP1 expression in distinct fibroblast subpopulations reducing extracellular matrix synthesis (He et al., 2026). Disordered extracellular matrix remodeling, in which matrix metalloproteinases and their inhibitors play central roles, has been highlighted as a critical determinant of scar quality and tissue integrity (Theocharis et al., 2016). Altered endometrial expression of integrin β3 (ITGB3) and leukemia inhibitory factor (LIF), two well-established markers of endometrial receptivity, has been reported in the decidua of cesarean scar pregnancies (Qian et al., 2017). Dysregulation of specific microRNAs, including miR-31-3p, has also been described in cesarean scar-related pathology (Szubert et al., 2022). These observations support the concept that cesarean scar implantation, including intramural variants embedded within or adjacent to the scar, has a definable molecular signature in addition to its mechanical predisposition.

We present a case of intramural isthmic pregnancy diagnosed at 7 weeks of gestation following in vitro fertilization (IVF) in a woman with a previous cesarean section, successfully managed with a combined laparoscopic and local methotrexate approach with complete uterine preservation, and we discuss the case in the context of current molecular knowledge of cesarean scar implantation.

CASE PRESENTATION

A 35-year-old woman presented to the emergency gynecology service at 7 weeks of gestation with mild lower abdominal pain and intermittent vaginal spotting. The pregnancy had been achieved through a hormonally prepared frozen embryo transfer cycle, with single blastocyst transfer, and serial beta-human chorionic gonadotropin (β-hCG) values had risen appropriately during the early gestational period.

Clinical history

The patient had a four-year history of secondary infertility and one previous lower-segment cesarean section. Her gynecologic history included a hysteroscopic adhesiolysis and a documented episode of chronic endometritis, which had been successfully treated prior to this conception. She had also undergone one unsuccessful IVF cycle before the current pregnancy.

Clinical examination

On admission, the patient was hemodynamically stable. Vital signs and examination findings are summarized in Table 1.

Table 1. Findings on initial clinical examination.

Parameter	Finding
Pulse	96 beats per minute
Blood pressure	108/70 mmHg
Temperature	Afebrile
Abdominal examination	Mild suprapubic tenderness; no peritonism
Vaginal examination	Minimal spotting; closed cervical os

Laboratory investigations at presentation are shown in Table 2.

Table 2. Laboratory investigations at presentation.

Investigation	Result
Hemoglobin	11.2 g/dL
Serum β-hCG	38,640 mIU/mL
White blood cell count	Within normal range

Imaging findings

Transvaginal ultrasonography revealed an empty endometrial cavity and a gestational sac measuring 19 mm in maximum diameter, containing a fetal pole with visible cardiac activity. The sac was located within the anterior lower uterine wall at the level of the isthmus and was surrounded by a thin myometrial mantle measuring approximately 3 mm. Color Doppler imaging demonstrated increased peripheral vascularity around the sac. No communication with the endometrial cavity could be identified.

The initial differential diagnosis included cesarean scar pregnancy, intramural pregnancy, and cervico-isthmic ectopic pregnancy (Birch Petersen et al., 2016; Jurkovic et al., 2003). Pelvic MRI was performed to better define the implantation site and confirmed that the gestational sac was completely surrounded by myometrium, implanted within the anterior isthmic wall, without extension into the uterine cavity and with an intact bladder–uterine interface. These features were diagnostic of intramural isthmic pregnancy.

MANAGEMENT

Because fetal cardiac activity was present and the thin overlying myometrium carried a high risk of uterine rupture, a multidisciplinary discussion was convened involving reproductive medicine, minimally invasive gynecologic surgery, and interventional radiology. The patient was counseled on all therapeutic options and expressed a strong preference for fertility preservation. A combined surgical and localized pharmacological approach was therefore selected.

Surgical procedure and local methotrexate administration

Diagnostic laparoscopy demonstrated a vascular, bulging mass at the anterior uterine isthmus with an intact serosal surface and no hemoperitoneum. Diluted vasopressin was infiltrated locally into the surrounding myometrium to minimize intraoperative bleeding. A small transverse myometrial incision was made over the lesion, and the products of conception were carefully evacuated intact.

Following evacuation, methotrexate was administered as a site-directed local injection into the residual myometrial bed surrounding the implantation site, with the aim of ablating any remaining trophoblastic tissue while limiting systemic exposure (Stovall and Ling, 1993). The myometrial defect was then repaired in two layers using delayed absorbable sutures. Estimated intraoperative blood loss was 220 mL, and no hysterectomy was required.

HISTOPATHOLOGICAL FINDINGS

Histopathological examination of the evacuated specimen demonstrated chorionic villi embedded entirely within myometrial smooth muscle fibers, without intervening decidualized endometrium. No tubal tissue was identified. These findings confirmed the diagnosis of intramural ectopic pregnancy.

OUTCOME AND FOLLOW-UP

The postoperative course was uneventful. Serial β-hCG measurements declined progressively in a manner consistent with complete trophoblastic resolution, as shown in Table 3.

Table 3. Postoperative serum β-hCG trend.

Postoperative day	Serum β-hCG (mIU/mL)
Day 1	21,400
Day 7	4,220
Day 21	112

Follow-up transvaginal ultrasonography at six weeks demonstrated a well-healed myometrial scar with no residual trophoblastic tissue and preserved uterine anatomy. Normal menstruation resumed approximately two months postoperatively. The patient was counseled to defer further conception for at least 12 months to allow adequate myometrial healing, and to plan for elective cesarean delivery in any subsequent pregnancy because of the residual risk of uterine rupture at the previous implantation site.

DISCUSSION

Intramural pregnancy remains one of the most hazardous variants of ectopic implantation, with a strong tendency toward delayed diagnosis and a historically high rate of emergency hysterectomy (Tulandi and Al-Jaroudi, 2004; Memtsa et al., 2013). The proposed mechanism involves implantation through microscopic myometrial defects or sinus tracts created by prior uterine trauma, including cesarean section, myomectomy, curettage, or hysteroscopic procedures (Marchiole et al., 2004). The present case demonstrates the convergence of two important risk factors: previous cesarean delivery and assisted reproductive technology.

Molecular and gene-expression context of cesarean scar implantation

While intramural pregnancy has historically been described in purely anatomical and surgical terms, a growing body of molecular and gene-expression data is reshaping our understanding of why implantation may localize to, or invade

through, the cesarean scar and adjacent isthmic myometrium. Recent single-cell RNA-sequencing of cesarean scar niche tissue, adjacent myometrium, and well-healed scar controls has identified disordered wound-healing programs centered on the connective tissue growth factor (CTGF)–low density lipoprotein receptor-related protein 1 (LRP1) signaling axis (He et al., 2026). In that study, LRP1 deficiency was demonstrated in a specific fibroblast subpopulation within niche tissue and was associated with impaired extracellular matrix synthesis through reduced activation of ERK and WNT signaling. Donnez et al. (2017) likewise emphasized substantial deposition of collagen fibers at the niche site compared with adjacent myometrium, and broader work on extracellular matrix biology has underscored the role of matrix metalloproteinases and their inhibitors in maintaining matrix homeostasis (Theocharis et al., 2016). Taken together, these observations describe a focal area of structurally abnormal, fibrotic, and poorly contractile myometrium that may be more permissive of trophoblastic invasion.

At the level of the endometrium overlying or adjacent to the cesarean scar, altered expression of canonical implantation-receptivity markers has been documented. Qian et al. (2017) reported increased decidual expression of integrin β3 (ITGB3) and leukemia inhibitory factor (LIF) in cesarean scar pregnancies compared with normotopic pregnancies, suggesting that focal upregulation of receptivity-associated gene products at the scar may contribute to preferential implantation in this abnormal location. Dysregulation of specific microRNAs has also been reported in cesarean scar pathology; miR-31-3p, in particular, shows the highest expression in cesarean scar endometriosis and is implicated in the regulation of epithelial–mesenchymal transition and matrix remodeling pathways relevant to abnormal implantation (Szubert et al., 2022).

In our case, the gestational sac was embedded entirely within the anterior isthmic myometrium, with no communication with the endometrial cavity and without recognizable decidual tissue at histology. This pattern is consistent with implantation through a microscopic myometrial defect created by the previous cesarean — a process that current molecular data suggest is facilitated by a combination of CTGF–LRP1-driven abnormal scar healing, matrix-metalloproteinase-mediated extracellular matrix remodeling, focal upregulation of receptivity markers such as ITGB3 and LIF, and microRNA-level dysregulation of epithelial–mesenchymal programs (He et al., 2026; Qian et al., 2017; Szubert et al., 2022). The case therefore exemplifies, at the clinical level, a pathology whose molecular substrate is increasingly being defined at the gene-expression level.

Clinical lessons

Several clinically important points emerge from this case. First, pregnancies achieved through IVF warrant meticulous early ultrasound localization, even when β-hCG kinetics and the presence of fetal cardiac activity appear reassuring; neither finding excludes an abnormal implantation site. Second, the radiological distinction between cesarean scar pregnancy and intramural isthmic pregnancy can be challenging because both are intimately related to the lower uterine segment. In our case, pelvic MRI added decisive value by clearly demonstrating circumferential myometrial encasement of the gestational sac and the absence of communication with the endometrial cavity, criteria considered essential for the intramural diagnosis (Memtsa et al., 2013).

Third, when diagnosis is established prior to uterine rupture, fertility-preserving management is feasible. Conservative options described in the literature include systemic methotrexate, ultrasound- or laparoscopy-guided local methotrexate injection, uterine artery embolization, hysteroscopic resection, laparoscopic excision, and combined regimens (Birch Petersen et al., 2016; Memtsa et al., 2013). Site-directed intralesional methotrexate is particularly attractive because it maximizes the tissue concentration of the cytotoxic agent at the trophoblastic interface while limiting systemic absorption (Stovall and Ling, 1993). With the increasing global use of assisted reproductive technology and rising cesarean delivery rates, atypical implantation patterns are likely to be encountered more frequently, and progress in understanding their molecular basis may eventually allow identification of women at highest risk before pregnancy is attempted.

CONCLUSION

Intramural isthmic pregnancy is a rare but potentially life-threatening form of ectopic pregnancy that demands a high index of clinical suspicion, particularly in women with prior uterine surgery undergoing IVF. Early diagnosis through transvaginal ultrasonography, with MRI as an adjunct in equivocal cases, allows timely conservative management before uterine rupture occurs. A combined approach of minimally invasive laparoscopic excision and site-directed local methotrexate injection achieved complete resolution and uterine preservation in the present case. The case is well placed within a rapidly evolving molecular framework of cesarean scar implantation, in which gene-expression studies of the CTGF–LRP1 axis, matrix metalloproteinases, endometrial receptivity markers, and microRNA networks are increasingly defining the biological substrate of abnormal implantation.

ACKNOWLEDGEMENTS
The author thanks the multidisciplinary teams of the Departments of Obstetrics and Gynecology, Reproductive Medicine, and Radiology for their contribution to the clinical care of the patient described in this report.

CONFLICT OF INTEREST
The author declares no conflicts of interest relevant to the content of this article.

SOURCE OF FUNDING
This case report received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ETHICAL APPROVAL AND CONSENT
Written informed consent was obtained from the patient for the anonymized publication of her clinical details and imaging. The report was conducted in accordance with the principles of the Declaration of Helsinki (2013) and with the approval of the institutional research ethics committee.

REFERENCES
1. Birch Petersen K, Hoffmann E, Rifbjerg Larsen C, Svarre Nielsen H (2016). Cesarean scar pregnancy: a systematic review of treatment studies. Fertil Steril 105(4): 958–967. doi: 10.1016/j.fertnstert.2015.12.130.
2. Donnez O, Donnez J, Orellana R, Dolmans MM (2017). Gynecological and obstetrical outcomes after laparoscopic repair of a cesarean scar defect in a series of 38 women. Fertil Steril 107(1): 289–296.e2. doi: 10.1016/j.fertnstert.2016.09.033.
3. He C, Ge S, Xia W, Wang Y, Yan L, Sun J, Yan L, Zhu Q, Zhao X, Zhang J (2026). Role of CTGF–LRP1 in impaired healing of cesarean section incisions. Nat Commun 17(1): 3278. doi: 10.1038/s41467-026-69747-9.
4. Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ (2003). First-trimester diagnosis and management of pregnancies implanted into the lower uterine segment Cesarean section scar. Ultrasound Obstet Gynecol 21(3): 220–227. doi: 10.1002/uog.56.
5. Marchiole P, Gorlero F, De Caro G, Podestà M, Valenzano M (2004). Intramural pregnancy embedded in a previous Cesarean section scar treated conservatively. Ultrasound Obstet Gynecol 23(3): 307–309. doi: 10.1002/uog.981.
6. Memtsa M, Jamil A, Sebire N, Jauniaux E, Jurkovic D (2013). Diagnosis and management of intramural ectopic pregnancy. Ultrasound Obstet Gynecol 42(3): 359–362. doi: 10.1002/uog.12437.
7. Qian ZD, Weng Y, Wang CF, Huang LL, Zhu XM (2017). Research on the expression of integrin β3 and leukaemia inhibitory factor in the decidua of women with cesarean scar pregnancy. BMC Pregnancy Childbirth 17(1): 84. doi: 10.1186/s12884-017-1270-3.
8. Stovall TG, Ling FW (1993). Single-dose methotrexate: an expanded clinical trial. Am J Obstet Gynecol 168(6 Pt 1): 1759–1765. doi: 10.1016/0002-9378(93)90687-e.
9. Szubert M, Nowak-Glück A, Domańska-Senderowska D, Szymańska B, Sowa P, Rycerz A, Wilczyński JR (2022). miR-31-3p has the highest expression in cesarean scar endometriosis. Int J Mol Sci 23(9): 4660. doi: 10.3390/ijms23094660.
10. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK (2016). Extracellular matrix structure. Adv Drug Deliv Rev 97: 4–27. doi: 10.1016/j.addr.2015.11.001.
11. Tulandi T, Al-Jaroudi D (2004). Interstitial pregnancy: results generated from the Society of Reproductive Surgeons Registry. Obstet Gynecol 103(1): 47–50. doi: 10.1097/01.AOG.0000109218.24211.79.