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ORIGINAL RESEARCH ARTICLE

Extravillous trophoblast invasion and decidualization in cesarean scar pregnancies

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Abstract

Introduction: The increasing cesarean section rate has led to an increase in the number of subsequent pregnancies resulting in a cesarean scar pregnancy. There appears to be preferential attachment of the blastocyst to the scar site, which may be associated with defective decidua in that region, resulting in abnormal implantation, which can in turn negatively affect the success of the pregnancy. The aim of the current study was to evaluate the extravillous trophoblast, decidua, and myometrium in scar and adjacent non-scar regions of the implantation site of a cesarean scar pregnancy.

Material and Methods: Samples containing a gestational mass were obtained by laparoscopic excision from patients with a cesarean scar pregnancy at 6–11 weeks of gestation as diagnosed by transvaginal or transabdominal ultrasound (n = 8 type II cesarean scar pregnancy). Cesarean scar pregnancy tissues were separated into scar and non-scar regions, and the scar regions were sub-separated into non-implantation and implantation sites. Serial sections were histologically examined after hematoxylin and eosin, Masson's trichrome and immunochemical staining, and changes in the myometrium, extravillous trophoblast, and decidua were evaluated.

Results: In cesarean scar pregnancy, compared with scars not in the implantation site, scars in the implantation site displayed increased fibrosis, and had disrupted myometrium, which was related to varying patterns of E-cadherin expression as a response to extravillous trophoblast invasion. In addition, local decidua was found at the non-scar implantation sites, with multinucleated trophoblast giant cell accumulation and shallow invasion. These features were not evident in the scar implantation sites.

Conclusions: This study emphasizes that the decidua drives multinucleated trophoblast giant cell differentiation, limiting the degree of invasion. Better characterization of this differentiation process may be helpful for better management and avoidance of the consequences of cesarean scar pregnancy.

Abbreviations: CSP, cesarean scar pregnancy; EVT, extravillous trophobast; MTGCs, multinucleated trophoblast giant cells.

The authors Lufen Gao and Hui Chen contributed equally to this study.

KEYWORDS
cesarean scar pregnancy, cesarean section scar, decidua, myometrium, placenta accreta spectrum, trophoblast giant cell

1 | INTRODUCTION

Cesarean scar (CS) pregnancy (CSP) is a potentially life-threatening consequence of a previous CS. In the last decade, China has had one of the highest cesarean section rates in the world.[1] Although generally considered extremely rare, the incidence of CSP is rising in China, partly due to the high CS rate, the rescinding of the 'one child policy', and more effective detection by widespread use of transvaginal ultrasound.[2] Cesarean scar defects are a known complication after cesarean section, and prevalence was up to 84% in a random population of women.[3] The defect may expand and lead to scar dehiscence and result in a CSP.[4] However, little is known about the pathophysiology of the uterine scar defects and their relation to CSP.[5]

When a pregnancy is implanted on a previous cesarean scar, a diagnosis of CSP is established. Histologically, the depth of trophoblast invasion has become a common proxy for the classification of CSP. It can be further subdivided into type I (on the scar) and type II (deep implantation) according to the site of implantation.[6,7] Type I CSP is characterized by implantation on top of a well-healed cesarean scar, whereas type II CSP is a deep implantation within a cesarean scar defect.[7] Resection of gestational contents can be accomplished either through operative hysteroscopy or laparoscopy, and transcervical vacuum suction has been proposed as a minimally invasive treatment option.[8] Extravillous trophoblast cells (EVTs) can invade deeply into the myometrium or beyond the uterine serosa, resulting in placenta accreta spectrum disorders, including accreta, increta, and percreta, which are potentially life-threatening because of associated massive hemorrhage events.[9,10] The pathophysiology of the placenta accreta spectrum is thought to involve excessive trophoblast invasion or/and defective decidua.[11] However, rather than abnormal invasion, the deep implantation of a CSP appears to be due to endometrial/decidual defects under the implantation site.[12-14]

During normal pregnancy, interstitial EVTs invade the uterine wall as far as the inner third of the uterine myometrium, where they fuse to form multinucleated trophoblast giant cells (MTGCs).[15] It has been proposed that EVTs lose their invasive phenotype when they undergo this syncytial-type fusion into MTGCs, although the mechanism of this process is little understood.[14] In the placenta accreta spectrum, the invasion of interstitial EVTs is increased, whereas the number of MTGCs is reduced.[11] In contrast, shallow EVT invasion with increased MTGCs is found in preeclampsia and diabetes mellitus, which may be in response to placental hypoxia.[16]

Although abnormalities in EVT invasion and absence of decidua have been described in CSP,[14] most of what is known today about the pathogenesis of CSP is based on case reports or ultrasound analyses. The aim of the current study was to assess the features of defective scars and their effects on trophoblast cells and decidua in CSP during the first trimester. To better understand the pathophysiology of CSP, we focused on histological differences of trophoblast invasion and decidualization taking place within the scar and adjacent to the scar and compared scar tissue with and without implantation.

Key message

In cesarean scar pregnancy, multinucleated trophoblast giant cell accumulation occurs in the adjacent local decidua (non-scar) but not in the scar implantation site. This will contribute to the deep invasion observed if a cesarean scar pregnancy is left to develop, putting the mother and baby at risk.

2 | MATERIAL AND METHODS

2.1 | Samples

The CSP specimens containing a gestational mass were obtained from patients who underwent laparotomic wedge excision of the CSP mass at 6–11 weeks of gestation, from January 2019 to December 2021, at the First Affiliated Hospital of Jinan University in Guangzhou, China. All patients were diagnosed based on a previous cesarean delivery and transvaginal ultrasound characteristics, including an empty uterine cavity and cervical canal, a myometrial defect between the sac and the bladder wall, and a gestational sac located at the anterior part of the uterine isthmus,[7,17] using high-resolution ultrasound equipment (Voluson E8 machine; GE Medical Systems). Patients with cervical pregnancy, inevitable miscarriage, and previous CS delivery for an abnormal pregnancy were excluded. In total, eight type II CSP were identified and included in the study.

2.2 | Histopathological examination

The tissues were fixed, embedded in wax, sectioned, and stained with hematoxylin and eosin. Serial sections (5 μm thick) were also prepared for histological staining with Masson's trichrome (Masson) staining to determine the presence of scar tissue.

2.3 | Immunohistochemistry

The primary antibodies used in this study included CK-7 (Maixin, China), Vimentin (CST, USA), and E-cadherin (BD, USA). Briefly,

the tissue sections were first treated in citrate buffer (pH 6.0) and heated in a microwave for antigen retrieval. The sections were then incubated in the presence of the primary antibody overnight at 4°C. Biotinylated goat anti-mouse or anti-rabbit immunoglobulin G was used as the secondary antibody. Streptavidin-peroxidase system (KIT-9901; Elivision plus) and diaminobenzidine tetrahydrochloride substrate (DAB kit; Maxin) kits were used to visualize the staining. As a negative control, the primary antibody was replaced with an isotype control antibody. The average staining intensity was recorded and classified as negative (−), positive (+), and strong positive (++). Five samples were randomly selected from each tissue group, and six fields per sample were photographed at ×400 magnification for assessment.

2.4 | Image acquisition and photography

Human tissues were subjected to hematoxylin and eosin, Masson staining, and immunohistochemical staining and were photographed using an Olympus IX51epi-fluorescence microscope. The images were analyzed using CW4000 FISH Olympus software.

2.5 | Ethics statement

The study was approved retrospectively by the Clinical Trial Ethics Committee of the First Affiliated Hospital (approval No: KYk-2022-006) on April 18, 2022, Jinan University, Guangzhou, China. Written informed consent for using pathological specimens was obtained from each participant.

3 | RESULTS

3.1 | Clinical characteristics

The clinical data and findings of all eight women with CSP are presented in Table S1. The median age was 31.0 years (range 24–38), and gravidity ranged from two to five. The median duration of gestation at diagnosis was 8.2 weeks (range 6–11). The median interval between the current CSP and previous cesarean section was 2.5 years (range 1–7) (Table 1).

3.2 | Comparison of EVT and decidua in implantation sites with and without a scar

The lower uterine segment specimens encompassed implantation sites that included areas of scar and those without (termed non-scar) (Figure 1A,B and Figure S1). Immunohistochemical staining for CK-7 was used to identify EVTs and showed that in regions containing scar tissue the EVTs had invaded deep into the myometrium (Figure 1B). Masson staining showed that the muscular layers were disrupted and thinned out to merge with the fibrous scar (Figure 1C). Furthermore, no decidual tissues were observed in the scar regions of the implantation site, and the trophoblastic villi had adhered directly to the connective tissue of the scar region. Instead, decidual tissue was found in non-scar regions of the implantation site adjacent to the scar site. Where present, the decidua was composed of polygonal, well-delineated cells with a large cytoplasm (Figure 1D,E).

3.3 | Comparison of the scar tissue in implantation and non-implantation sites

In each sample from patients with CSP, we investigated the scar within the implantation site (designated as within 5 mm of the gestational mass) and the non-implantation site (designated as 10 mm beyond the gestational mass) (Figure 2A). In the non-implantation sites, the uterine scar contained a number of microvessels and fibroblasts. The smooth muscle cells were arranged regularly in bundles or whorls in the myometrium (Figure 2B). CK-7 staining showed that the non-implantation sites contained no EVTs (Figure 2C). The myometrium showed weak immunopositivity for E-cadherin (Figure 2D).

In the implantation sites, the placental villi were close to the dehiscent scar without an intervening decidual layer. EVTs had invaded the scar tissue, and the underlying myometrium was disrupted

TABLE 1 Clinical characteristics of cesarean scar pregnancy

Case	Age (years)	Gravidity and parity	Gestational (weeks)	Fetal heart beat	Pre-treatment hCG level (IU/l)	CS (*n*)	Time since the latest CS (years)
1	38	G3P2	10 W^{5+}	−	N/K	2	3
2	29	G5P1	8 W^{4+}	+	27037	1	1
3	24	G2P1	6 W	+	23610	1	1
4	38	G5P2	6 W^{5+}	+	42846	2	5
5	37	G2P1	8 W	−	68273	1	6
6	33	G3P1	8 W^{3+}	−	163641	1	5
7	28	G4P1	8 W^{6+}	−	214499	1	2
8	29	G5P2	6 W^{5+}	+	196281	2	1

Abbreviations: CS, cesarean section; G, gravidity; hCG, human chorionic gonadotropin; N/K, not known; P, parity; W, week.

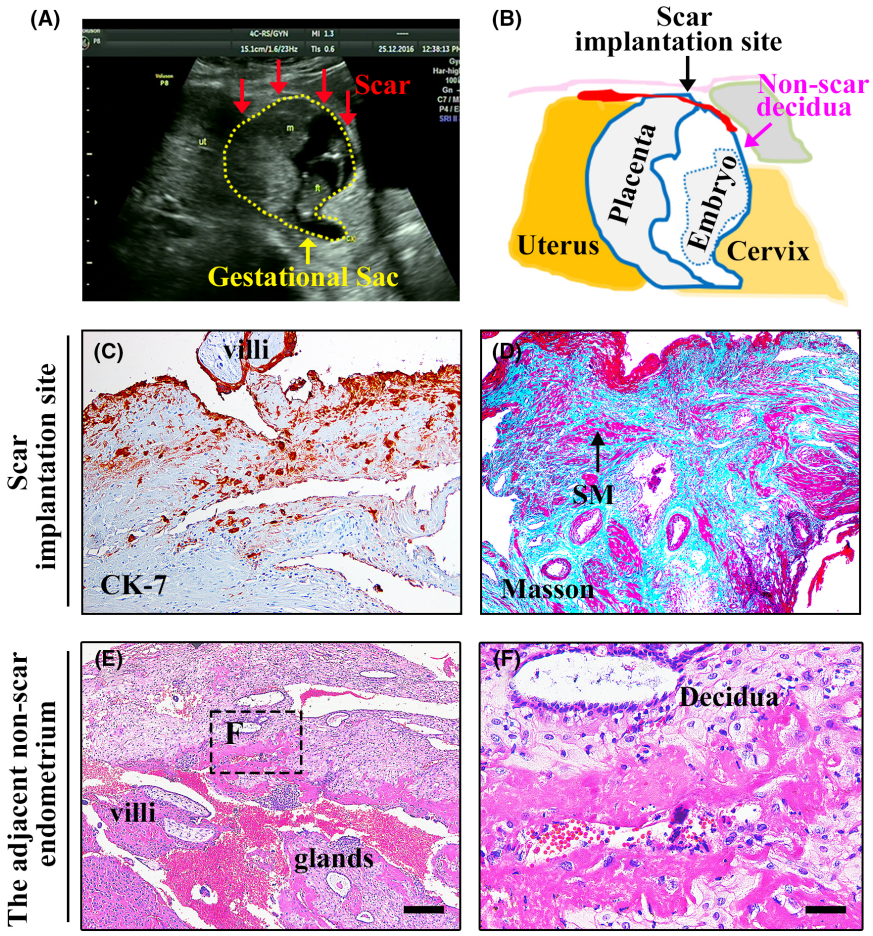

FIGURE 1 Extravillous trophobast cell (EVT) invasion and decidua in cesarean scar pregnancy (CSP). An example of the ultrasound characteristics and the appearance of a CSP at 11 weeks' gestation (A). A schematic diagram illustrating the relative position of scar and the adjacent non-scar decidua at the implantation sites (B). EVT invasion was tracked by immunohistochemical staining (CK-7) in a scar implantation site (C). Consecutive serial section of Masson staining showing the smooth muscle (SM) and fibrinoid deposits in a scar implantation site (D). Decidua reaction in the adjacent non-scared endometrium (E). (F) A magnified image of the framed region in E, which shows the decidua cells. Scar bars = 500 μm in (C)–(E), 50 μm in (F).

(Figure 2E,F). These EVTs were mononuclear and irregularly shaped, and the majority formed a stellate shape, as shown clearly by E-cadherin+ staining (Figure 2F1). In the deeper myometrium that was not invaded by EVTs, there was strong E-cadherin immunostaining (Figure 2G2). In contrast, the more superficial myometrium that was invaded by EVTs was negative for E-cadherin (Figure 2G1), suggesting that functional E-cadherin in the myometrium may be down-regulated as EVT migrate and invade this tissue. The expression of E-cadherin in smooth muscle cells of the myometrium in the scar tissue in non-implantation and implantation (superficial and deep) sites are summarized in Table S1.

3.4 | Local decidua and MTGC accumulation in the non-scar implantation sites

It has been suggested that the decidua is lacking at the beginning of gestation during CSP[9,14]; therefore, we investigated whether non-scar decidua (adjacent to the scar implantation site) was involved in a compensatory mechanism to support placental development.

CK7-positive immunostaining was restricted to trophoblast and glandular cells. The invasive EVTs were more densely located in the myometrium than in the decidua (Figure 3A). The decidual cells were distinguished by vimentin immunoreactivity (Figure 3B). Masson staining showed that the dense (bright blue stain) collagen network was the predominant tissue component, with interstitial EVTs interspersed within the network, discernible by the dark blue stain of their nuclei. Smooth muscle cells were disrupted, the preserved cells were stained red and lined with CK^+ interstitial EVT, and the lost cells were replaced with collagen networks, which enclosed the decidual cells. The loss of smooth muscle at the decidual–myometrium junction was very noticeable (Figure 3C).

EVTs appeared to congregate within the myometrium and even within the serosa, in confluent sheet or clump patterns (Figure 4A–D). The scatted MTGCs were multinucleate and very irregular in shape, and the nuclei were darkly stained in fibrin deposits and were always denser around the endometrial glands than around the spiral arteries in the decidua (Figure 4E–J). In the deeper portions of the myometrium, remodeled vessels were seen in the myometrium, where the smooth muscle cells were almost lost, as well as in the serosa (Figure 4K). In particular, the presence of MTGCs was correlated with the occurrence of the maternal blood pools and were thus outlined by red blood cells (Figure 4E, I and K).

4 | DISCUSSION

In CSP, the risk of deep implantation depends on the presence of a niche in an existing CS scar.[7,18] However, evidence as to whether a surgical repair of scar dehiscence can prevent CSP remains

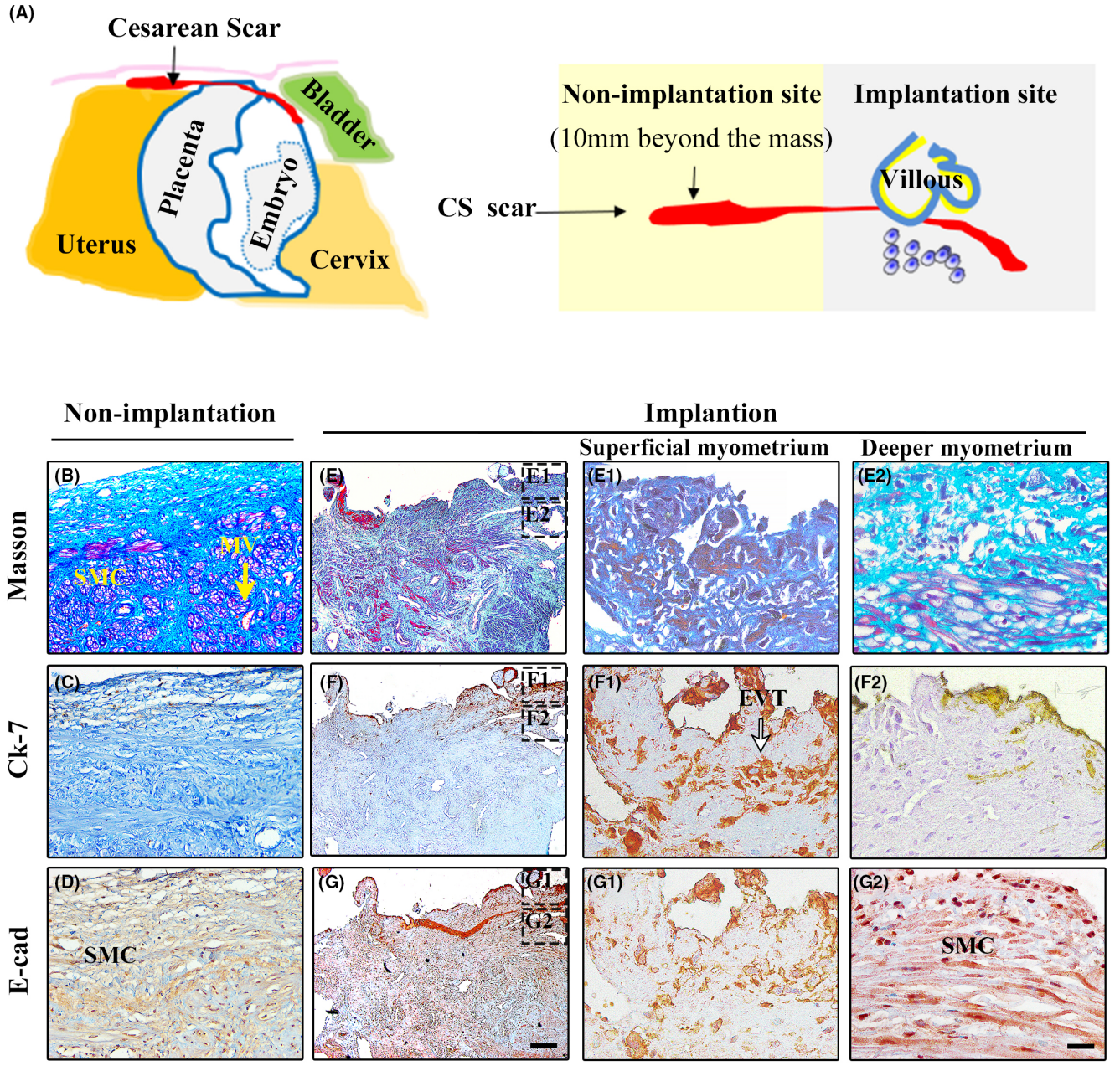

FIGURE 2 Defective cesarian scar at the implantation site. A schematic diagram illustrating the relative position of non-implantation scar adjacent to the implantation scar (A). Consecutive serial sections that were stained serially using Masson staining (B and E) and immunohistochemical staining for CK-7 (C and F) and E-cadherin (D and G). (E1–E2), (F1–F2), and (G1–G2) are magnified images of the framed regions in E, F, and G that show the smooth muscle, extravillous trophobast cells (EVT), and E-cadherin-positive cells in the non-implantation and implantation scar sites, respectively. Scar bars = 50 μm in (B–G), 50 μm in (E1–G2).

insufficient.[19] The pathophysiology of abnormal placentation in CS scars is poorly understood. In this study, we found that the defective appearance of scar tissue at the implantation sites was associated with the discontinuation and degeneration of the myometrium, accompanied by increased fibrosis, which differed from the adjacent non-implantation scar tissues.

Blastocyst implantation involves key steps, including apposition, attachment, and invasion. In vitro, trophoblasts have a stronger propensity for attaching to the exposed extracellular matrix than to endometrial epithelial cells.[20,21] Moreover, multiple CS deliveries likely leads to higher rates of implantation into a scar region of the uterus because of the increased scar surface.[22] Similar to Seow et al.,[23] we found that the chorionic villi and trophoblast cells were inside the dense and fibrotic myometrium in cases of CSP. These findings suggest a preferential adhesion and invasion of the scar regions rather than those with underlying decidua.

Adhesion molecules are known to play a role in the apposition and attachment of the blastocyst. E-cadherin has been detected in both blastocyst and uterine epithelium, which is thought to provide migration guidance for implanting blastocysts.[24] Over

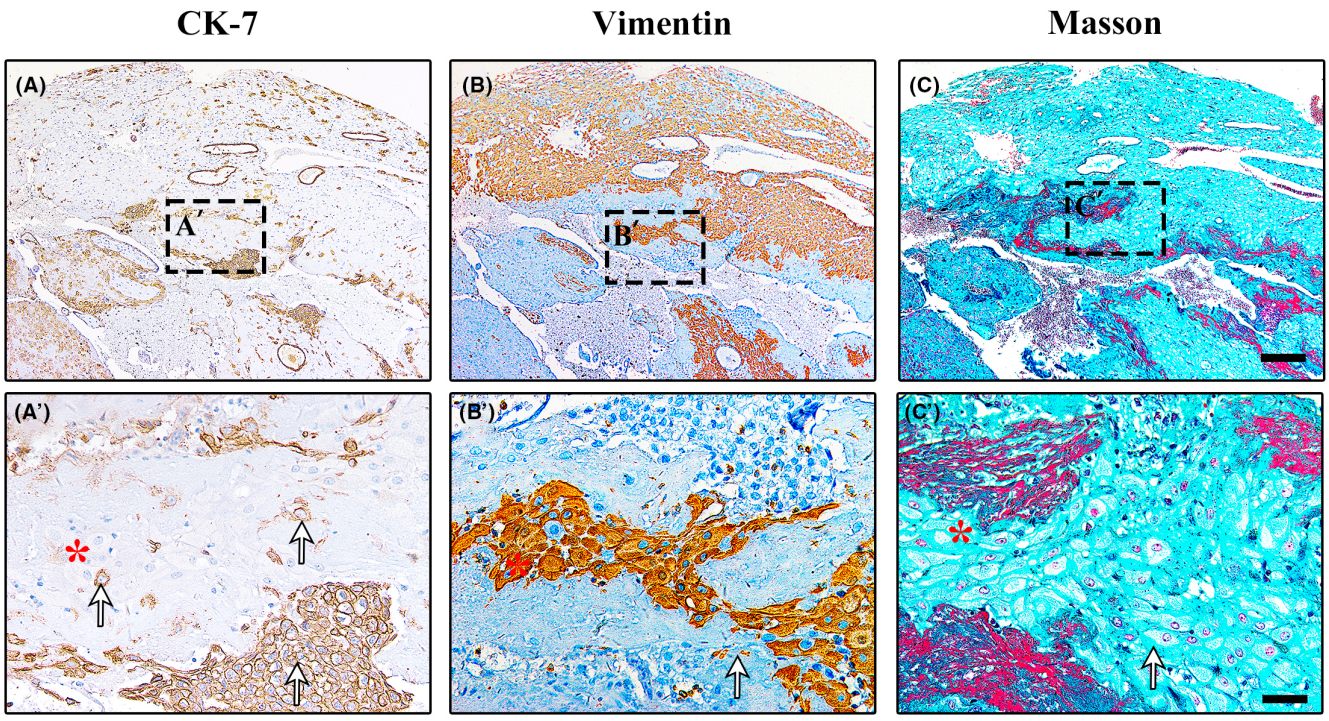

FIGURE 3 Local decidua at a non-scar implantation site. Immmunostaining for (A) CK-7 and (B) vimentin, and (C) Masson staining. Asterisks indicate the decidua cells; white arrowheads indicate the extravillous trophobast. Scar bars = 500 μm in (A–C), 50 μm in (A′–C′).

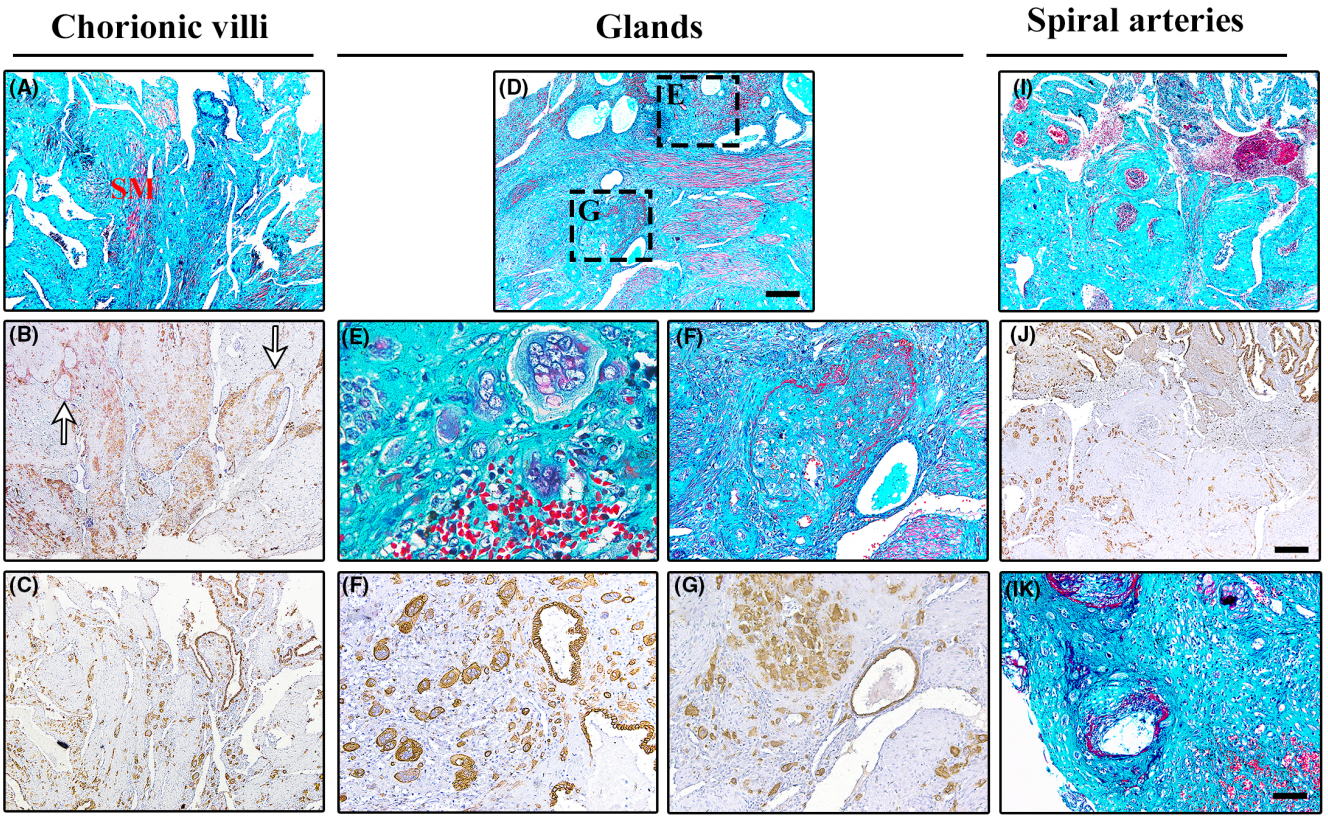

FIGURE 4 Multinucleate trophoblast giant cell (MTGC) accumulation at the non-scar implantation site. Chorionic villi implanting into myometrium, with extravillous trophobast embedded in fibrinoid deposit (A) with invasion throughout the thickness of myometrium as clumps (B) or sheets (C). Morphology of MTGC (E). MTGC around the endometrial glands with hemorrhage (D and E) as scattered (F) or bundles (G and H). MTGC around the spiral arteries undergoing vascular remodeling within the myometrium (I and J). The incomplete remodeling spiral arteries within the serosa (K). Scar bars = 500 μm in (A–D), 50 μm in (E–H), 500 μm in (I–J), and 50 μm in (K).

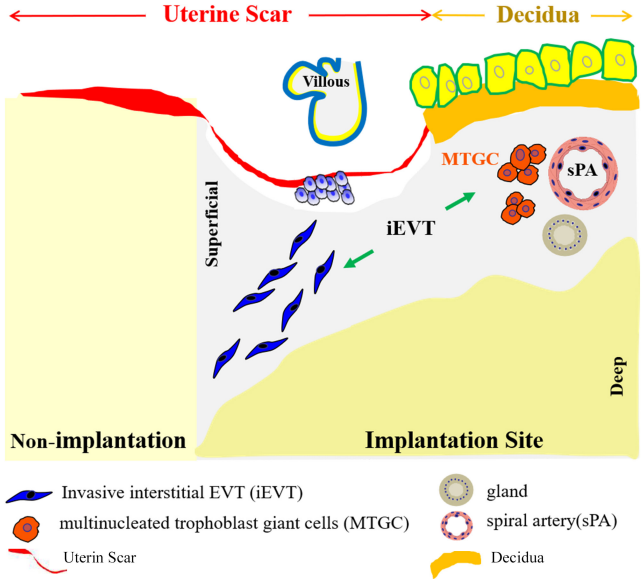

FIGURE 5 Schematic diagram illustrating the invasion and transformation of extravillous trophoblast cells (EVT) with and without scar during a cesarean scar pregnancy.

expression of E-cadherin in a nonreceptive endometrial cell line significantly enhanced its receptivity to BeWo cell attachment in vitro.[25] Although E-cadherin seems to be best characterized for the formation of adhesion junctions in epithelial cells, smooth muscle cells also need intact intercellular mechanical adhesion. Without this adhesion, muscle bundles would disintegrate if simultaneous excitation occurred.[26] It has been reported that E-cadherin is evenly distributed across the uterine myometrium.[27] Here, we described an intrinsic difference in E-cadherin expression in the myometrium in scars in implantation sites and non-implantation sites. The hypothesis of our study was that a different presentation of E-cadherin, a potent adhesion molecule, at the scar implantation site could reveal a pattern for CSP. E-cadherin is strongly expressed in the myometrium at the implantation site, similar to that seen in the uterine epithelium of a normal pregnancy[28]; we thus suggest that the E-cadherin expression of myometrium tissues gives rise to the advancement of the developing blastocyst in the deficient scar. Furthermore, we observed a marked reduction in E-cadherin expression in myometrium tissues with trophoblast invasion in the superficial site compared with those without trophoblast invasion in the deep site, which exhibited a normal cohesive pattern. This finding is in accordance with previous reports showing that downregulation of E-cadherin was necessary for trophoblast invasion through decreased cell–cell adhesion.[28]

CSP is a precursor to placenta accreta spectrum, with the two conditions representing a continuum of the same disease, with CSP being diagnosed in early pregnancy and placenta accreta spectrum later in pregnancy.[29] The development of placenta accreta spectrum outside the CS site represents trophoblastic conversion of myometrium.[24] In the current study, it was demonstrated that trophoblast invasion and adhesion may also be reversely influenced by paracrine effects of E-cadherin derived from the myometrium. Thus, CSP resulting from a heterotopic presentation of E-cadherin represents trophoblastic conversion of the deficient scar and the adjacent myometrium.

The development of CSP is linked to a previous CS scar, leading to preferential attachment of the blastocyst and to decidual defects.[9,14] However, some live CSPs could continue into the second trimester and are likely to have a close to normal uterine pregnancy.[24] If the scar only occupies a small section of the implantation site, it is possible that the rest of the implantation site displays normal decidualization and is able to provide some histotrophic nutrition, even if the corresponding glandular secretions are unlikely to reach the scar gestational sac.[30,31] Although we found an absence of decidua and structured myometrium underneath the scar implantation region, we raise the possibility that the adjacent endometrium is another source of histotrophic nutrition for the developing placenta during CSP.

MTGCs are the final form of the invading EVTs, which lose their invasive properties as they differentiate into MTGCs.[32] MTGCs are restricted to the decidual–myometrial border in normal pregnancy. MTGCs were not found in the decidua in normal pregnancies but were seen in most patients with placenta accreta spectrum.[33] Possible functions for MTGCs are the production of proteases, hormones, and angiogenic factors, which are required for the continuation of a pregnancy.[32,34] The prevalence of MTGCs may result in disturbed migration into the arterial wall, and – as a consequence – spiral artery remodeling is lacking.[35] We observed an absence of MTGCs at the scar implantation site but a significant accumulation of MTGCs in local decidua (which was adjacent to the deficient scar). This could partly be because MTGC differentiation in the decidua appears to be similar to that in placenta percreta but differs from that in the adjacent scar. In normal pregnancy, the signals produced by the epithelial cells are essential for establishing fetal–maternal communication. Thus, the trophoblast is exposed to and influenced by the different paracrine effects of the deficient scar or the decidua, which may in turn alter the degree of trophoblast differentiation.

Our results also suggest that MTGCs are involved in the remodeling of the glands and spiral arteries, with MTGC accumulation and shallow invasion in the non-scar region and excessive trophoblast invasion and MTGC deficiency in the scar region. In fact, endometrial glands are an important source of nutrients and provide a range of growth factors for the developing placenta, and the pathophysiological roots in abnormal trophoblast differentiation may be due primarily to deficient decidualization.[36] The effects of local decidua may help explain why patients with CSPs that progress to term are predisposed to spontaneous miscarriage and placenta accreta spectrum disorders. Furthermore, the transformation of interstitial EVTs in local decidua is favored and required for the continuation of a CSP.

5 | CONCLUSION

The development of a CSP depends on a defective CS scar, which – due to deficient decidualization – leads to preferential attachment of

the blastocyst to the scar tissue. A defective scar is associated with increased fibrosis and disrupted myometrium, as observed through varying patterns of E-cadherin expression as a response to trophoblast invasion. In addition, local decidua was found in the non-scar implantation sites, with MTGC accumulation and shallow invasion. Thus, it would seem reasonable to assume that defective scar and the adjacent non-scar decidua are coordinated in the pathophysiology of CSP (Figure 5).

AUTHOR CONTRIBUTIONS

JL, HC, and FL performed the experiments; LG and MW contributed the materials; GEL analyzed the data and edited the manuscript; PL conceived and provided financial support for the study and wrote the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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