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Uterine dehiscence in term pregnant patients with one previous cesarean delivery: Growth factor immunoexpression and collagen content in the scarred lower uterine segment

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Uterine dehiscence
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Objective: This study aimed at investigating the relationship between the occurrence of uterine dehiscence in term pregnant scarred uteri and the presence of altered biochemical behavior of the scarring process.

Study design: Collagen content and the expression of transforming growth factor–beta and its isoforms transforming growth factor–β1 and transforming growth factor–β3, connective tissue growth factor, basic fibroblast growth factor, vascular endothelial growth factor, platelet-derived growth factor, and tumor necrosis factor–α in myometrium of lower uterine segment were assessed in 19 otherwise healthy term patients with one previous cesarean delivery who were not in labor. We were searching for differences between patients who showed uterine dehiscence (9 cases) and patients who showed a normal-appearing scarred lower uterine segment (10 cases). We also evaluated all these features in lower uterine segment from unscarred uteri of 10 otherwise healthy patients who were not in labor.

Results: In the case of uterine dehiscence, the scarred lower uterine segment showed a higher collagen content, a reduction of pan transforming growth factor–β expression because of a marked decrease or absence of transforming growth factor–β3, a reduction of connective tissue growth factor, an increase in basic fibroblast growth factor and a slight enhancement in vascular endothelial growth factor, platelet-derived growth factor, and tumor necrosis factor–α expression.

Conclusion: These findings contribute to meliorate our knowledge about uterine scar healing and allow us to hypothesize that uterine dehiscence of a scarred uterus may be related to altered biochemical behavior of the scarring process.

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"Once a cesarean always a cesarean": when Cragin[1] made this famous statement in the far 1916, probably he could not imagine the dramatic increase in the rate of cesarean deliveries (CDs) recorded in the last 20 years. Today, the primary cause of CDs is the repeat CD as a consequence of the rare, but higher, possibility of uterine rupture in a CD-scarred uterus.[2-4] Therefore, although any effort to decrease the rate of this operative mode of delivery must regard the elective repeat CDs, we cannot dismiss that uterine rupture of scarred uteri is a major risk of maternal morbidity and neonatal death.[2,4] On the basis of a large number of publications, recent reviews analyzed the safety of vaginal birth after CD (VBAC) and confirmed the relatively low risk of uterine rupture in these cases.[4-6] However, the widespread concern over this obstetric hazard still makes physicians and patients uneasy about attempting trials of labor in women who have had a previous CD.

Wound healing is a complex process, which includes inflammation, angiogenesis, new tissue formation, and tissue remodeling and which finally leads to an at least partial reconstruction of the wounded area.[7] In this cascade of events, evidence revealed a pivotal role of growth factors, step-by-step released from the serum of injured blood vessels and by degranulating platelets, neutrophils, monocytes, lymphocytes, fibroblasts and tissue specific cells.[8] The involvement of transforming growth factor beta (TGF-β) and its isoforms TGF-β1 and -β3, connective tissue growth factor (CTGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and tumor necrosis factor alfa (TNF-α) in the scarring process has been demonstrated.[8-10] A recent review summarized several studies that showed altered growth factor expression in various in vitro and in vivo pathologic scar conditions, such as nonhealing ulcers or hypertrophic scar tissues.[8] Collagen deposition, which is a main step in the scarring process, is under growth factor control also.[8,10]

Today, there are still very few data about pathologic features of CD scars, both in normal and in pathologic conditions.[11,12] Macroscopically, daily clinical practice allows us to appreciate a broad spectrum of lower uterine segment (LUS) thickness in laboring or in nonlaboring patients at the time of a repeat CD. According to scarred LUS appearance categories that were proposed by Cheung et al[13] (modified from those of Michaels et al[14] and Fukuda et al[15]), LUS can range from normal-appearing LUS (practically indistinguishable from an unscarred one) to paper-thin LUS (a thinned LUS but not thin enough to visualize the uterine contents). Sometimes, scarred LUS is interrupted, which results in uterine dehiscence (subperitoneal separation of the uterine scar, with chorioamniotic membrane visible through the peritoneum of the LUS) or, rarely and most often during a trial of VBAC rather than in nonlaboring term pregnant patients, results in uterine rupture (complete separation of the uterine scar, regardless of length, that gives a communication between the uterine and peritoneal cavities).[15,16]

In this study, we evaluated collagen content and TGF-β, -β1, -β3, CTGF, b-FGF, VEGF, PDGF, and TNF-α expression in myometrial smooth muscle cells of scarred LUS from 19 otherwise healthy nonlaboring term patients with one previous CD as we sought differences between patients with uterine dehiscence (9 cases) and patients with a normal-appearing LUS (10 cases). We also evaluated all these features in LUS from unscarred uteri of 10 otherwise healthy nonlaboring term patients. Therefore, in favor of future clinical aims too, we considered the existence of differences in biologic behavior of the scarring process to explain the variable clinical phenotype of LUS in a pregnancy after a CD.

Material and methods

Specimens

Myometrium specimens of LUS that were analyzed in this study were collected during repeat elective CDs from scarred uteri of nonlaboring singleton term otherwise healthy patients from January 2003 to April 2005 (in our Department, we still do not recommend a trial of labor after a CD but support women when they make that choice). All these women had a single previous transverse lower segment CD that had been performed by surgeons of our Department in the last 5 years and at least 1 year before the present intervention. In all cases, at the time of the first CD, the uterine incisions were repaired with resorbable polyglactic acid sutures (Vicryl; Ethicon, Somerville, NJ) by single-layer closure with continuous interlocking sutures through the myometrium followed by closure of the visceral peritoneum with continuous sutures. According to Cheung et al[13] categories, we recruited 9 women with uterine dehiscence (group A) and compared all the evaluated features with specimens obtained from 10 women with a normal-appearing scarred LUS (group B). In total, we evaluated 1210 patients who underwent elective repeat CD for previous CD. We observed an incidence of uterine dehiscence of approximately 0.7%. Myometrium specimens of LUS were also collected during CD from 10 nonlaboring singleton term otherwise healthy pregnant women with unscarred uteri (control group) who underwent CD for fetal indications. Another selection criterion for the inclusion in our study was the absence of uterine contractility that was confirmed by cardiotocographic trace that was performed 2 hours at the most before surgery. All evaluated samples were fixed in formalin and embedded in paraffin. Patient clinical features are given in Table I. Each patient gave informed consent to perform a small biopsy (<5 mm diameter) of