DOI: https://doi.org/10.17816/aog631927

Uterine scar after caesarean section: principles of healing and evaluation criteria

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ABSTRACT

Caesarean delivery results in the formation of a uterine scar. Inadequate scar healing and subsequent formation of an incompetent uterine scar tissue are common complications that may lead to the abnormal uterine bleeding, painful menstrual periods, and secondary infertility. In pregnant women, an incompetent scar may cause life-threatening complications, such as uterine rupture at any gestational age or placenta increta at the scar level.

Given the potential dangers of uterine scars, numerous recent studies have focused on identifying risk factors and understanding the pathophysiology of incompetent scar formation, as well as developing diagnostic methods. Early diagnosis is essential in maintaining women's health and well-being and preventing complications in subsequent pregnancies. Unfortunately, there is currently neither exact understanding of the pathophysiological mechanism of uterine scar formation, nor unambiguous guidelines on some aspects of its diagnosis after caesarean section.

Keywords: caesarean section; uterine scar; niche; ultrasound diagnostics.

To cite this article:
Gulyaeva MA, Zhilkina AA, Bokieva DS, Panina OB. Uterine scar after caesarean section: principles of healing and evaluation criteria. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):395–405. DOI: https://doi.org/10.17816/aog631927

Received: 13.05.2024 **Accepted:** 09.08.2024 **Published online:** 12.12.2024

DOI: https://doi.org/10.17816/aog631927

Рубец на матке после операции кесарева сечения: принципы заживления, критерии оценки

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АННОТАЦИЯ

Последствием операции кесарева сечения является образование рубца на матке. Неадекватное заживление рубцов и последующее формирование несостоятельности рубцовой ткани на матке являются распространёнными осложнениями, которые могут проявляться в виде аномальных маточных кровотечений, болезненных менструаций и вторичного бесплодия. У беременных наличие рубцового дефекта может быть ассоциировано с потенциально опасными для жизни осложнениями, например, разрывом матки на любом сроке гестации или врастанием плаценты в рубец.

В связи с потенциальными опасными последствиями, связанными с наличием рубца на матке, в последние годы проведены многочисленные исследования, изучающие факторы риска и патофизиологические основы образования рубцового дефекта на матке, а также исследования, направленные на изучение методов диагностики. Ранняя диагностика необходима для поддержания здоровья и благополучия женщины, а также для предотвращения развития осложнений в следующих беременностях. К сожалению, в настоящее время нет чёткого понимания патофизиологического механизма образования рубца на матке, а также однозначных рекомендаций по некоторым аспектам его диагностики после кесарева сечения.

Ключевые слова: кесарево сечение; рубец на матке; ниша; ультразвуковая диагностика.

Как цитировать:
Гуляева М.А., Жилкина А.А., Бокиева Д.С., Панина О.Б. Рубец на матке после операции кесарева сечения: принципы заживления, критерии оценки // Архив акушерства и гинекологии им. В.Ф. Снегирёва. 2024. Т. 11, № 4. С. 395–405. DOI: https://doi.org/10.17816/aog631927

Рукопись получена: 13.05.2024 **Рукопись одобрена:** 09.08.2024 **Опубликована online:** 12.12.2024

DOI: https://doi.org/10.17816/aog631927

剖宫产术后子宫瘢痕：愈合原则及评估标准

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摘要

剖宫产术后子宫瘢痕的形成是常见后果之一。不完全的瘢痕愈合及其引发的子宫瘢痕功能不全是常见并发症，表现为异常子宫出血、痛经以及继发性不孕。在孕妇中，瘢痕缺损可能导致潜在的危及生命的并发症，例如妊娠期间任何阶段的子宫破裂或胎盘植入瘢痕组织。

鉴于子宫瘢痕相关并发症的潜在风险，近年来已开展大量研究，旨在探讨瘢痕缺损的风险因素和病理生理机制，同时改进诊断方法。早期诊断对子宫瘢痕相关疾病的预防、女性健康的维护以及未来妊娠并发症的避免至关重要。然而，目前对子宫瘢痕形成的病理生理机制的理解尚不全面，且剖宫产术后瘢痕诊断的某些方面缺乏统一的指南和标准。

关键词：剖宫产；子宫瘢痕；瘢痕缺损；超声诊断。

引用本文:
Gulyaeva MA, Zhilkina AA, Bokieva DS, Panina OB. 剖宫产术后子宫瘢痕：愈合原则及评估标准. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):395–405. DOI: https://doi.org/10.17816/aog631927

收到: 13.05.2024 **接受:** 09.08.2024 **发布日期:** 12.12.2024

BACKGROUND

Caesarean section (CS), which was avoided just over a century ago due to alarming maternal mortality rates, is now the most common surgical procedure. In the Russian Federation in 2020, there were 423,000 CS births, or one in every three births [1]. From 1990 to 2014, the rate of CS surgery increased by an average of 12.4% (from 6.7% to 19.1%), according to a trend analysis of data from 121 countries. The annualized growth rate is 4.4% [2] despite attempts at vaginal delivery after previous CS [2]. In the Russian Federation, the prevalence of CS was 29.2% in 2017 and 30.1% in 2018 [1]. It is natural to ask what complications can develop after CS and how to diagnose them.

Inadequate uterine healing followed by caesarean scar dehiscence is a common complication of CS. In recent years, several published studies have shown that a caesarean scar defect increases the risk of hemorrhage, placenta previa, and placenta accreta [3]. A history of CS is also a risk factor for uterine rupture, which is associated with adverse maternal and perinatal outcomes [4, 5]. Although CS is a safe procedure, clinicians have reported an increasing number of complications over the past two decades [2, 6]. In 1999 Thurmond et al. first suggested [7] that these symptoms might be related to caesarean scar. In a later prospective cohort study, van der Voet et al. showed that the prevalence of caesarean scar dehiscence after the first CS in a group of 263 women was 49.6% when assessed by transvaginal ultrasound examination and 64.5% when assessed by sonohysterography at 6–12 weeks [8].

Rotas et al. reported a consecutive pregnancy after the first CS in approximately 52% of cases [9, 10]. Pregnancy outcome depended on the caesarean scar status.

In addition, caesarean section scar can be a reason for infertility [11]. Ohashi et al. showed that the number of subsequent childbirths (regardless of delivery mode) was 2% lower in the CS group than in the vaginal delivery group [11].

Despite a large number of studies on caesarean scar defects, only in 2019 the European society proposed an internationally accepted definition of a caesarean scar dehiscence as an anatomical defect of the anterior uterine body wall in the scar area with a thinning of the myometrium by at least 2 mm [12]. However, the criteria for caesarean scar dehiscence are still controversial [13].

The exact prevalence of caesarean scar defect is unknown, ranging from 19.7% to 100.0% [12], and seems to depend on the definition used, study design, risk factors, and diagnostic modality.

These data highlight the importance of the diagnosis and management of patients with caesarean scar, as well as the evaluation of the principles of uterine tissue healing and the factors of caesarean scar dehiscence.

PATHOPHYSIOLOGY OF THE CAESAREAN SCAR

The wound-healing process involves inflammation, proliferation, and remodeling of injured tissue to form scar tissue [5]. This process relies on a complex and extensive interaction of growth factors and cytokines that regulate the synthesis of various cell types [5].

Most authors believe that the lower uterine myometrium is healed by caesarean scar formation, but the size and residual thickness of the myometrium varies greatly depending on the exact location of the scar [14].

Uterine incision during CS leads to excessive fibroblast activation and continuous collagen secretion [5]. Excessive collagen deposition prevents proliferation, differentiation, and migration of native uterine cells and induces the myometrial scar formation [15]. Hyperproliferation is often induced by the dysregulation of growth factors and cytokines during the remodeling process, leading to the scar tissue formation.

Roeder et al. evaluated histopathology of iatrogenic trauma (CS) to the myometrium as an initial approach to assessing changes in human uterine tissue healing [14]. Histology of lower uterine myometrial scars showed not only the expected fibrous scar tissue, but also the affected myofibril structure manifested by the arrangement of myometrial smooth muscle cells perpendicular to the surface of the endometrium, elastosis, tissue edema, and inflammation [14]. Small fibroids, myometrial hyperplasia, keloid-like scars, and adenomyosis were also observed, which may be markers of impaired uterine tissue healing.

In vivo studies show that heterogeneous myometrial remodeling after surgery depends on both phenotype and genotype [16, 17]. Buhimschi et al. studied myometrial healing post-caesarean delivery using two mouse strains with different wound healing and collagen remodeling characteristics: MRL/MpJ(+/+) as a “high-healer” phenotype and C57Bl/6 as a “low-healer” phenotype [16]. Histologically, significant differences in wound healing were reported between the two mouse strains, suggesting that differences in regenerative capacity result in histological, mitotic, and functional differences in the biomechanical properties of scarred myometrium after CS.

Uterine wound healing process involves many cells: endothelial cells, neutrophils, monocytes/macrophages, lymphocytes, fibroblasts, myometrial cells as well a stem cell population found in the myometrium, myoSP (side population of myometrial cells) [17]. Lofrumento et al. showed that a higher ratio of transforming growth factor isoforms β1 and β3 (TGF-β1/β3) reduced scarring and fibrosis. Impaired expression of connective tissue growth factor (CTGF) may be a factor of abnormal caesarean scars of the lower uterine segment and caesarean scar dehiscence [17]. Basic fibroblast growth factor (bFGF) deficiency results in decreased collagen deposition at the wound site and thicker scars. In addition, changes in the expression of tumor necrosis factor alpha

DOI: https://doi.org/10.17816/aog631927

(TNF-α), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) in myometrial smooth muscle cells were observed with cervical dilation. This change is thought to be involved in the healing process.

Monavarian et al. provided an update on strategies for scar-free wound healing, considering the role of various cell types, growth factors, cytokines, and extracellular components [18]. In scar-free wound healing, interleukin-6 (IL-6) levels were decreased, while interleukin-10 (IL-10) and epidermal growth factor (EGF) levels were increased. TGF-β3 expression was significantly increased and TGF-β1 expression was decreased, which further clarified the mechanism of scar-free wound healing.

An interesting study by Yao et al. found that stem cell-derived exosomes (Exo) derived from bone marrow mesenchymal stem cells (BMSCs) could promote endometrial repair via the TGF-β1/Smad signaling pathway [19]. TGF-β was also shown to increase the proliferative capacity of endometrial and muscle cells, promote microvascular regeneration, and restore the ability of the endometrium to implant and support the development of embryos to a viable stage through the transplantation of bone marrow-derived mesenchymal stem cell (BM-MSC) constructs. Further study of TGF-β, its downstream signaling, and the role of signals may provide new therapeutic targets to reduce the incidence of caesarean scar dehiscence [5].

Connective tissue growth factor (CTGF) was also shown to stimulate adhesion of certain cell types, including human vascular endothelial cells, lung epithelial cells, and fibroblasts [5]. The CTGF-mediated adhesion is induced by phosphorylation of focal adhesion kinase protein when CTGF binds to various cell surface molecules, including fibrinoconnectin, cell surface proteoglycans, and integrins, resulting in increased focal adhesion [5]. In addition, CTGF can stimulate the production of TGF-β and vascular endothelial growth factor (VEGF) [5, 20]. Pollio et al. confirmed that CTGF may be the cause of abnormal scar formation in the lower uterine segment after caesarean delivery, as well as the cause of uterine rupture through changes in granulation tissue development and angiogenesis [20]. In another study, Sun et al. concluded that regulation of CTGF could improve granulation tissue growth and angiogenesis, and ultimately improve scarring [5].

Based on preclinical studies, IL-10 was proposed as an alternative for scar healing [5]. When comparing skin and soft tissue defects in IL-10 knockout mice and wild-type controls, IL-10 was found to promote wound healing and reduce scarring by inhibiting the inflammatory response. King et al. found that IL-10 could prevent scar formation by inhibiting the synthesis of IL-6, IL-8, and TGF-β [21]. However, there were some negative findings: higher serum IL-10 levels were also associated with endometriosis [22]. Based on these results, it is reasonable to believe that uterine incision healing and scar formation may be improved by regulating IL-10 levels. However, several factors need to be considered [5].

Wound healing is a complex, highly controlled process that requires coordinated activity of cellular factors involved. Changes at any stage can disrupt the healing process.

PATIENT-RELATED FACTORS IN TISSUE HEALING

Tissue healing is a complex biological process that depends on many factors, including patient-related factors that affect the rate and outcome of healing, such as genetic predisposition, obesity, pre-eclampsia, medical conditions such as arterial hypertension [12, 23].

In the study by Vervoort et al., the majority of patients evaluated for laparoscopic repair of large scar defects had a retroverted uterus [23]. This is supported by two studies that reported a higher incidence of caesarean scar dehiscence in women with a retroverted uterus, although the study design in these cases did not include determination of uterine position prior to CS [24]. The question what came first remains unresolved: the retroverted uterus causing inadequate scar healing or the scar causing the retroverted uterus. One possible hypothesis to explain this finding was related to incomplete wound healing caused by the retroverted uterus position affecting vascular perfusion [23], although other data [12] challenged this hypothesis.

In addition, it is important to consider factors that are known to affect wound healing and are reliably associated with a higher incidence of caesarean scar dehiscence. These factors include diabetes mellitus, body mass index (BMI), smoking, and maternal age [12].

Herstad et al. showed that the number of operative deliveries and the risk of maternal complications increased with increasing maternal age [25].

The prevalence of medical conditions (hypertension, diabetes mellitus) is increasing every year [26]. A meta-analysis by Martin et al. found a significant association between diabetes mellitus and surgical wound infection in different types of interventions [26]. In patients with diabetes mellitus, there was a clear association between impaired wound healing and excessive neutrophil extracellular traps (NETs) produced by neutrophils infiltrating the wound tissue [27]. NETs are composed of DNA coated with citrullinated histones and antimicrobial peptides released by neutrophils with higher expression of peptidyl arginine deiminase type-4 (PADI4) and calcium [27]. Their physiological role is to rapidly and non-specifically bind and neutralize pathogens [27]. Hyperglycemia is thought to increase the already elevated baseline level of NETosis in patients with diabetes mellitus, thereby exacerbating its adverse effects and potentially interfering with caesarean scar healing.

Patients with the above diseases depend on daily medications for their treatment. Stuermer et al. investigated the effects of various antihypertensive agents on wound healing [28]. Antihypertensive agents are shown to affect keratinocytes and fibroblasts. Angiotensin-converting enzyme

inhibitors and thiazide diuretics delayed wound healing in 3D organotypic models; beta-receptor blockers seem to improve wound healing to a small extent just like calcium channel blockers [28].

Objective evidence shows that obesity is associated with some postoperative complications. In wound healing, these factors include adipose tissue anatomy, circulatory failure, altered cellular composition, altered immune mediators, and nutritional deficiencies [29].

In obesity, an increase in adipose tissue can lead to hypoxia that can trigger inflammation, fibrosis, and insulin resistance [29, 30]. In addition to the overexpression of collagen VI (col6), obesity is associated with increased expression of 11f3-hydroxysteroid dehydrogenase type 1 (11f3HSD1) [30]. Due to the impaired adipose tissue angiogenesis, hypoxia and hypoxia-inducible factor 1-alpha (HIF1α) levels increase [31], which induces local inflammation and fibrosis by activating lysyl oxidase (LOX) to cross-link collagen I and III [29, 31]. Therefore, overexpression of these factors impairs wound healing by suppressing angiogenesis, a process essential for repairing the wound vasculature, and promotes the progression of hypoxia and fibrosis in obesity. Other proposed mechanisms of microcirculatory impairment by excessive adiposity include reduced nitric oxide availability, leading to decreased vascular density and impaired blood flow, and long-term elevation of blood free fatty acid levels due to increased adipose mass, which impairs capillary filling [30].

Smoking significantly alters neutrophil functions such as chemotaxis, phagocytosis, and inflammatory response [32]. Aspera-Werz et al. evaluated the effect of smoking on wound healing and tissue infection as major complications in smokers [32]. Pathogen defense mechanisms are altered in smokers due to higher neutrophil levels than in non-smokers, while higher PADI4 expression is associated with higher complication rates.

Taken together, these data support the multifactorial nature of caesarean scar dehiscence, likely due to a combination of surgical, anatomical (inadequate blood supply and retroverted uterus), and patient-related factors.

HYPOTHESES ON THE MECHANISMS OF CAESAREAN SCAR DEHISCENCE

The odds ratio for caesarean scar dehiscence in women with a history of CS is approximately 2.0, and the CS rate in the general population is approximately 35% [33]. Tang et al. found statistically significant risk factors for development of caesarean scar defect in women with and without CS, including uterine position, age at time of CS, duration of CS, stage of labor when CS was performed, suturing technique, intraoperative blood loss (p <0.01 in all cases). There were no significant differences between the two groups in terms of age, number of CSs, and type of anesthesia (p > 0.05).

Bij de Vaate et al. identified three main groups of risk factors for caesarean scar dehiscence: those related to the formation of the lower uterine segment/level of uterine incision, those related to the uterine closure technique, and those related to wound healing [16]. The authors also identify a fourth group of factors that include medical conditions, smoking, age, BMI, parity, multifetal gestation, time of CS, burdened obstetric and gynecologic history.

Vervoort A et al. suggested that factors of caesarean scar dehiscence should be divided into only in two instead of four groups: surgery-related factors and patient-related factors [23].

CAESAREAN SCAR: CURRENT DIAGNOSTIC CRITERIA

The literature describes several diagnostic modalities, including two- and three-dimensional transvaginal ultrasound examination with or without saline/gel contrast enhancement as the main diagnostic modality [12]. The use of magnetic resonance imaging (MRI) [12], computed tomography [6], hysteroscopy, and sonohysterography [23] is also described.

It should be noted that the maximum thickness of a caesarean section scar predicting a higher risk of scar rupture has not been established [3].

Jordans et al. used a modified Delphi procedure to provide updated guidelines for ultrasound evaluation of scar defects [34]. Most experts agreed that caesarean scar dehiscence should be defined as a depression at the site of the caesarean scar of at least 2 mm in depth [34]. In addition, it is also recommended to identify a complex caesarean scar with additional defects.

The study identified clinically relevant parameters such as length, depth and thickness at the scar apex (residual myometrial thickness, RMT), adjacent myometrial thickness (AMT) and width, the distance from the defect to the vesicovaginal fold (VV) (an artificial triangular fold between the bladder, vagina, and cervix that is visualized by placing the transvaginal probe in the anterior vaginal fornix), and the distance from the scar defect to the external cervical os [34]. It was decided to measure length, depth and RMT in the sagittal plane. The transverse plane was deemed adequate for quantifying the width of the scar defect and identifying branches. Repeated depth and RMT measurements using this plane were not recommended. Length, depth, and width should be measured in the plane where these parameters are largest. RMT should be measured in the sagittal plane where the scar defect has the lowest RMT. Therefore, for simple scars, all measurements can be performed in one plane, while complex scars may require multiple planes [34].

It should be noted that Osser et al. previously showed that RMT and the RMT/AMT ratio were the ultrasound criteria that best differentiated defects classified as hysterotomy scar dehiscence by an ultrasound examiner in women after a first CS [35]. Optimal RMT for predicting large defects after first CS was reported to be less than 2.5 mm.

DOI: https://doi.org/10.17816/aog631927

Verberkt et al. noted that Doppler ultrasound is not mandatory for standard scar measurements; however, it may be a useful tool for differential diagnosis [36].

The use of MRI to diagnose scar dehiscence is an emerging area of both clinical and research interest. Although there are currently no guidelines for its use, the advantages of MRI in pelvic evaluation include lower interobserver variability and higher soft tissue contrast enhancement compared to ultrasound and [37]. Nair et al. showed that T2-weighted MRI images better assessed RMT [6]. Donnez et al. compared the histological features of the scar with preoperative MRI findings [37]. Histological RMT measurements were comparable to preoperative MRI findings: 1.40±0.77 mm vs. 1.4±0.7 mm [37].

Tang et al. compared 147 scar defects assessed by MRI; the mean depth and length were significantly greater than those measured by ultrasound [33].

CONCLUSION

Uterine incision healing is a complex process involving many steps. In recent years, significant progress has been achieved in understanding the molecular mechanisms involved. Special attention is paid to the involvement of TGF-β, CTGF, bFGF, PDGF, VEGF, IL-6 and IL-10 in the etiology of wound healing and the interaction between these growth factors and cytokines that collectively regulate different steps of healing. However, there are still unknown molecular mechanisms of uterine incision healing that require further investigation, as caesarean scar dehiscence is a common complication associated with several adverse scenarios, including increased risk of bleeding, placenta previa and placenta accreta, chronic pelvic pain, dyspareunia, dysmenorrhea, and postmenstrual bleeding.

Early diagnosis is necessary to maintain a woman's health and well-being and to prevent complications in subsequent pregnancies, highlighting the important role of high-quality diagnosis and adequate caesarean scar evaluation criteria, which unfortunately are not available today. A structured approach to assessing the caesarean scar defect in daily clinical practice will reduce and prevent some complications and adjust the management strategy for patients with a caesarean scar.

ADDITIONAL INFO

Acknowledgements. The authors are grateful to the staff of the perinatal center of the State Budgetary Healthcare Institution Vorokhobov City Clinical Hospital No. 67 (Moscow).

Authors' contributions. M.A. Gulyaeva, A.A. Zhilkina performed literature review, collected and analyzed literature sources, prepared and wrote the text, and edited the manuscript; D.S. Bokieva, O.B. Panina developed the concept of the literature review, edited the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work).

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.

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