Correlation between Cesarean Scar Niche and Chronic Endometritis: Review Article

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Abstract:

The trend towards an increase in the number of caesarean sections (CS) has led to the fact that many women are more likely to plan a second pregnancy with a caesarean scar niche. According to current data, planning pregnancy with a niche may be associated with a decrease in the likelihood of successful implantation, which is a consequence of the uterine form of secondary infertility. In the context of studying the effect of stagnant contents in the projection of the niche on fertility, it is important to assess the prevalence of chronic endometritis (CE) and use new knowledge to personalize patient management schemes in achieving reproductive goals.

Keywords: Cesarean Scar Niche, Chronic Endometritis, infertility.

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Introduction:

A niche, which is defined as: “an indentation representing myometrial discontinuity at the site of the caesarean scar that communicates with the uterine or cervical cavity”. This niche is detected using contrast-enhanced sonohysterography (SHG) for measurement of myometrial thickness, in which saline fills endometrial cavity and marks the niche scar border rendering it more clear and larger visibility to be measured facilitating assessment of complications and trans-vaginal sonography (TVS) **(1).**

Another definition is: “a triangular anechoic filling defect with a depth of at least 2 mm in the anterior wall of the uterus usually between the uterine body and the cervix immediately under the bladder border” **(2).**

There are other nomenclatures for "niche" such as: diverticulum, pouch and isthmocele, caesarean scar defect (CSD) and deficient caesarean scar **(3).**

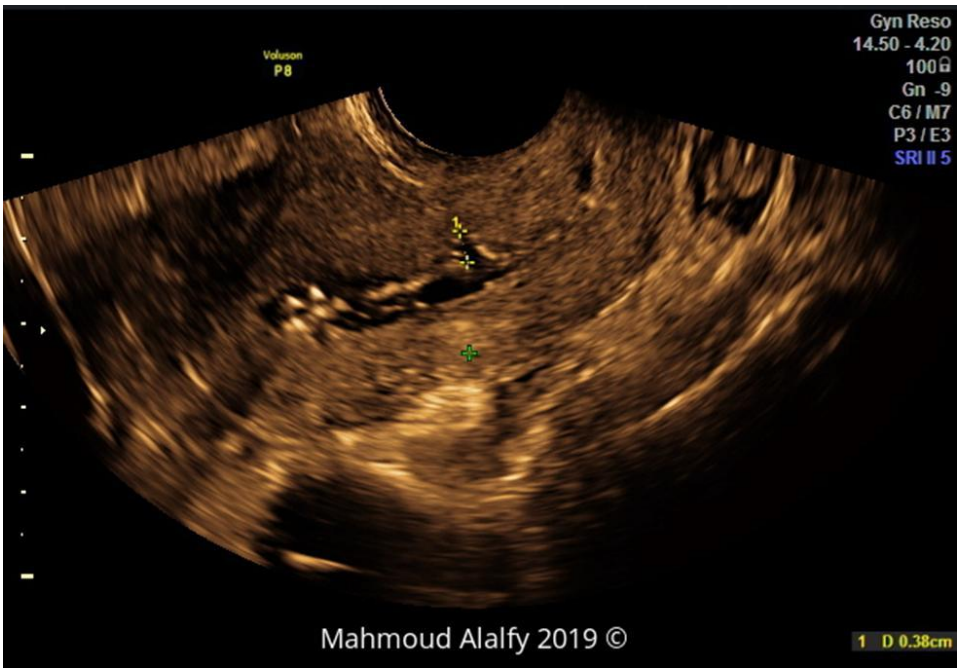

Figure (1): A contrast-enhanced sonohysterography showing a niche scar **(4).**

Various types of niches:

Scars are considered deficient when there is remarkable myometrial thinning on the site. As shown in figure 2, the thinning extent was calculated by ratio between a/b. A severe deficiency occurs when more than 50% of myometrium is lost at the niche scar site (Figure 3) **(3).**

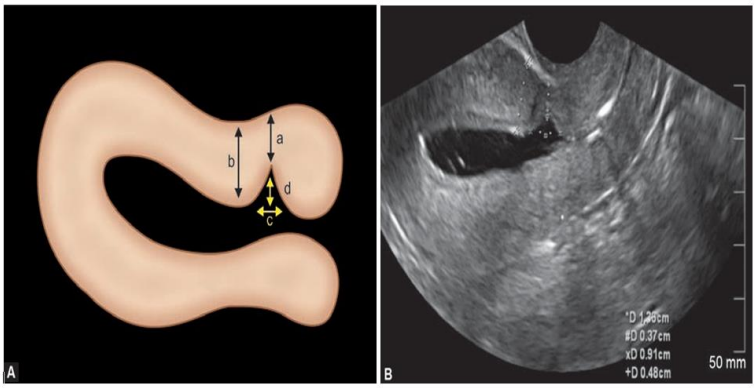

Figure (2): Schematic diagram illustrating measurements of thickness of the residual myometrium over the defect (a), total intact myometrium (b), width (c), and depth (d) of the cesarean scar defect

(CSD).The thickness of the residual myometrium is measured between the tip of the niche and serosal surface of the uterus (a) and the thickness of the normal myometrium adjacent to the defect (b) should be recorded. The width of the niche also can be measured by a straight superimposed line adjoining two apposition edge of scar over the niche (c). The depth of the niche is measured between the upper tips of the niche to midpoint of this line (d) **(3).**

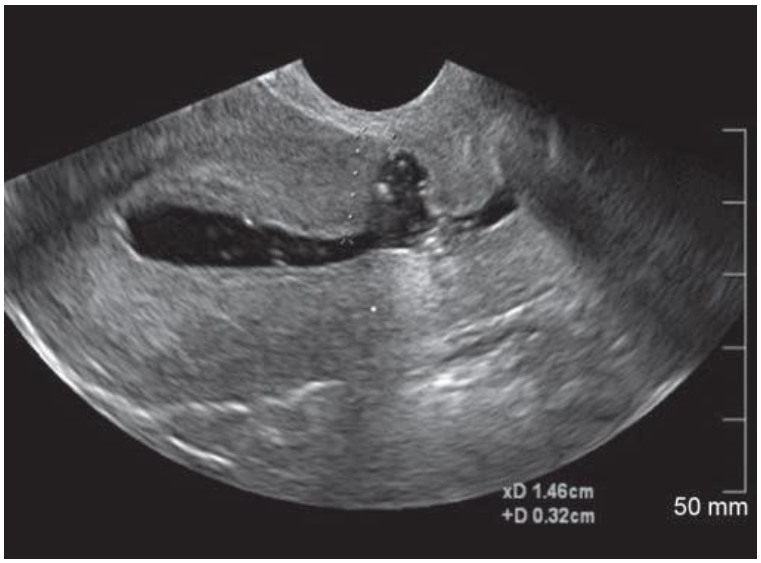

Figure (3): Severe cesarean scar deficiency, more than 50% of myometrium at the scar level was lost **(2)**

The niche can be mistaken for other scars of other pathologies or other normal findings as prominent cervical glands, post myomectomy diverticulum, synechiae, and focal adenomyosis **(5).**

Prevalence

Caesarean niche appears to be a fairly common finding dependent on the imaging modality used, time after caesarean or during pregnancy, phase of menstrual cycle and diagnostic expertise for detection. The actual incidence reported in the literature is therefore varied, with no clear consensus on its true or clinically relevant incidence **(6).**

Nevertheless, a reported prevalence of 24–70% using transvaginal ultrasonography (TVS) and 56–84% using contrast-enhanced sonohysterography suggests formation of a caesarean niche is a common postoperative event. The same authors recommend sonohysterography as the gold standard, while questioning any overzealous attempts at diagnosing smaller defects without a clear understanding of their clinical significance **(7).**

Interestingly, there was no change in the prevalence of niche over time when a 3-mm threshold was used and indeed, with more time, there was a significant reduction in the thickness of both residual myometrium and adjacent myometrium. These findings are of unclear functional significance, but may represent myometrial scar weakness and deserve further study **(8)**.

- **Clinical Presentation**

Though most women may remain asymptomatic, post-caesarean niche has been linked to following symptoms:

Post-menstrual Spotting

It is defined as ≥ 2 days of intermenstrual spotting, or ≥ 2 days of brownish discharge after the end of menstruation if bleeding duration exceeds 7 days (discharge is considered normal if bleeding duration is < 7 days). This is the most predominant symptom seen in 30–55% women at 6–12 months post-caesarean due to collected menstrual blood. The anterior edge of niche obstructs flow of menstrual blood, besides, poor contractility of surrounding fibrosed muscle retains it which is then discharged gradually. When observed prospectively after 1 year of caesarean, post-menstrual spotting was found in 20% women with isthmocele compared to 8.3% women without isthmocele, with 3.34 OR for large defects **(9)**.

Prolonged Bleeding

Impaired menstrual drainage results in prolonged flow. Since not yet specified, it may be described as AUB-N as per FIGO-PALMCOEIN nomenclature of abnormal uterine bleeding (AUB) **(10)**.

Intermittent Spotting

In situ blood formation in the niche, evidenced by free erythrocytes in scar, leads to intermenstrual spotting **(11)**.

Pain

Women with niche may present with dysmenorrhea (40–50%), chronic pelvic pain (35%), dyspareunia (18%) or suprapubic pain. Pain could be due to abnormal myocontraction to empty niche contents **(12)**.

Midcycle Intrauterine Fluid Accumulation

It may be due to excess mucus formation by retained blood in approximately 45% women **(13)**.

Caesarean Scar Ectopic Pregnancy

Pregnancy may implant in the niche with risk of rupture **(12)**.

Secondary Infertility

Probable mechanisms might be chronic inflammation by residual blood or peri-ovulatory fluid accumulation interfering with sperm penetration, fertilization and implantation. A large niche may interfere with conception similar to hydrosalpinx **(11)**.

Problems in IVF

Difficult embryo transfer is encountered in 20% women with niche undergoing IVF, due to a distorted anatomy, especially in a retroflexed uterus. Also, chances of unsuccessful IVF are higher in presence of uterine niche **(14)**.

Bladder Dysfunction

Local accumulation of fluid and scarring were postulated to cause dysfunction due to proximity of niche to the bladder; however, prospective studies did not support this **(14)**.

Obstetric Complications in Future Pregnancy

There is increased risk of scar ectopic, placenta accreta, scar dehiscence and uterine rupture **(15)**.

Scar Abscess

Though rare, it has been reported even up to 6 years after caesarean, due to residual blood and mucus that gets infected **(16).**

- **Risk factors**

Factors that were associated with niche development were divided into four domains: (i) factors related to uterine closure technique, (ii) factors related to development of the lower uterine segment or level of the uterine incision, (iii) factors possibly related to wound healing and (iv) miscellaneous **(17).**

- **Ischemia and Mal-Apposition Hypothesis for CS Niche**

A leading hypothesis that ischemic necrosis of some of the myometrium in the uterine incision edges (due to very tight and/or locking suturing) is a more important cause of development of CD defect. The subject of ischemic impairment has received hardly any attention in the past. Defective/ inappropriate apposition of myometrial layers in the form of interposing excessive decidua and inclusion of very wide bites of adjoining normal myometrium also makes a contribution **(18).**

- **Non-closure of deeper myometrial layers**

This does not seem an important cause. In Netherlands, in most of the cohort studies, 95% of the cases had a single layer closure without peritoneal closure and in only half of the cases, non-inclusion or avoiding of substantial endometrium/ decidua was practiced **(19)**, but CD niches do occur.

- **Mal-alignment versus ischemia of myometrium**

More importantly, most of the discussion about the hypotheses of CD niche formation in past seems to be focussed on deficient alignment (apposition) of myometrial tissue, but there has been hardly any attention paid to ischemia of tissues or preservation of vascularity of the myometrial edges sutured together. This is particularly surprising given that a number of published case reports of uterine scar dehiscence in the puerperium with massive late PPH predominantly show ischemic necrosis of the uterine scar (hence devascularization) in most cases **(20)**.

This also raises a possibility whether lesser degrees of scar dehiscence (smaller complete or large incomplete defects particularly following repeat cesareans) could be the cause of very rare cases of late (4 - 6 weeks) heavy PPH, such cases going undiagnosed or unreported. It is proposed that in addition to good apposition of the myometrial layers, it is equally important to prevent devascularization of the apposed edges; and aims to increase the awareness in this regard. The current commonly practiced technique in the UK (by peer imitation) generally involves quite tight first suture layer including entire thickness of myometrium and substantial decidua **(17).**

1. **Development of lower uterine segment or scar location**

It was originally proposed by Vervoort et al as the first hypothesis. It is unclear whether they intend it to be the leading or most important hypothesis. They propose that the thick mucoid brown discharge and a frequent finding in large niches of mucus accumulation and formation of large retention cysts supports this particular hypothesis **(19)**.

Although it is an interesting observation, this hypothesis seems to lack broader base from direct practice observation and consideration of actual techniques of placing the cesarean uterine incision **(21)**

2. Formation of adhesions hindering wound healing after CS

The third factor is related to the adhesion formation between the CD scar and the abdominal wall. When there are adhesions, the scar tissue may be retracted approximating the uterine scar to the abdominal wall leading to adhesions causing the formation of the niche that could be aggravated by gravity in retroflexed uteri **(20)**.

Factors as multiple CSs, inadequate haemostasis, inflammation due to infection, tissue ischaemia, tissue devascularisation and tissue manipulation can cause formation of adhesions **(20)**.

In case of non- closure of the peritoneum, especially in the presence of a non-sutured bladder flap, the risk of adhesion between the bladder and the uterus is increased **(22).**

The usage of adhesion barriers as sodium hyaluronate-carboxycellulose or Interceed has been suggested to decrease the risk of adhesions but more studies with larger sample size are needed **(23)**.

3. Wound healing:

A few factors like genetic predisposition, obesity, preeclampsia/ hypertension, etc. have been suggested. However, there is little evidence to suggest that some patients could be more prone to form uterine scar defects. Any such influence would be very minor and mostly irremediable any way **(19).**

Moreover, it would not be possible to design good quality studies including enough number of subjects to confirm or rule out these patient factors. Hence, this will remain simply a hypothesis of no practical importance mentioned here just to comment on the theoretical etiological list. It would be important to concentrate research efforts and limited resources on the important factor of uterine incision closure techniques **(19)**.

Complications of caesarean scar defect (CSD):

1. Abnormal Uterine Bleeding:

This bleeding is due to the weak myometrial contractility around scar where the defect functions as reservoir. Another explanation is the congestion of the endometrial fold and small polyps limited to the scar **(24).**

2. Risk of Uterine Rupture:

There is a relationship linking the thinning of lower uterine segment measured near delivery and the risk of uterine rupture at birth. In one of the studies, when the lower uterine segment was thinner than 3.5 mm at 37 weeks of pregnancy, uterine rupture risk becomes higher **(24).**

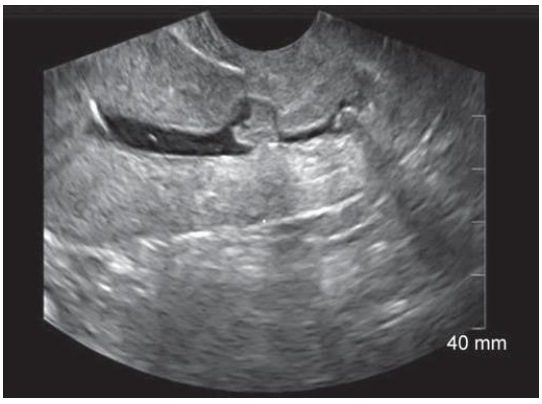

Figure (4): Severe cesarean scar defect **(24).**

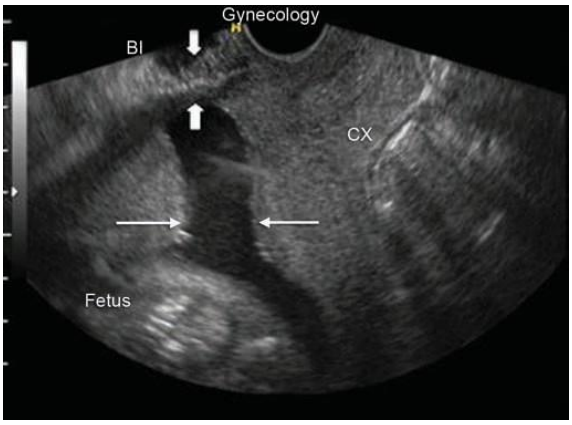

Figure (5): Transvaginal ultrasound of a pregnant (24 weeks) demonstrated a fenestration within a uterine scar (large arrows). Thinning of the myometrium over the CD scar defect (small arrows) **(24).**

3. Cesarean Scar Pregnancy (CSP)

Where the gestation sac is surrounded completely by the myometrium and the scar fibrous tissue is separate from the endometrial cavity **(25)**.

CSP is first diagnosed with ultrasound, the majority are diagnosed using transvaginal US **(26)**. In this case, which is rare, ectopic pregnancy occurs. There are two types of CSP, one that may develop into normal pregnancy with risk of hemorrhage at delivery (when the embryo develops more towards the uterine cavity), while the other type is dangerous and should be aborted, which develops outwards towards the abdominal cavity and the urinary bladder which should be discovered early **(3)**.

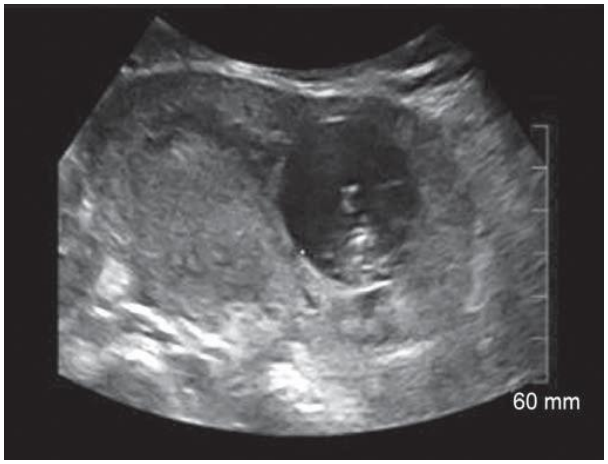

Figure (6): Transvaginal ultrasound examination shows a gestational sac (10 weeks) in the expected location of cesarean scar **(6).**

Correlation between Cesarean scar niche and chronic endometritis:

Wei, et al. (27) conducted a large case–control study regarding the relationship between CSDs and CE which can provide reliable evidence for clinical decisions. In this study, **Wei L et al. (27)** used propensity score matching to match the data of infertile women with and without a CSD, and a total of 501 cases were matched successfully. A total of 28.8% of patients with a CSD were diagnosed with CE, which is a relatively high frequency. Moreover, the frequency of CE in the control group was 20.54%. Generally, the prevalence of CE ranges from 8% to 72% **(28).** We assumed that this may be related to the patients selected. All the women involved in this study were infertile. Only one difference existed among the successfully matched patients (whether they had a CSD), and the differences in all other covariates were eliminated. It can be assumed that these women were randomized into the CSD and control groups. After correcting for all confounding factors, a logistic regression analysis still showed that a CSD remained an independent risk factor for CE (OR, 1.571; 95% CI, 1.021–2.418; p

= 0.040). Additionally, these findings were consistent throughout the sensitivity analyses, which increases the credibility of this study **(27).**

A CSD, described for the first time as an "isthmocele" by Morris in 1995, was considered to be a risk factor for inflammation in the uterine cavity. In a study by **Morris et al. (29)** pathological changes in the CSD were reported for a series of 51 hysterectomy cases. The changes involved moderate to marked lymphocytic infiltration and capillary dilatation **(28).**

Higuchi A et al. (30) also reported that some chronic inflammatory markers, such as CD138, were observed in the CSD area **(30).** These findings suggest the presence of chronic inflammation in the CSD area. We assumed that chronic inflammation in the CSD area may cause further changes in the uterine environment, as they are interconnected. A study by **Yang et al. (31)** analyzed 16S recombinant DNA (rDNA) of endometrium flora in the CSD population and noted that there was a similar pattern in the interrupted microbial flora at each level in infertile women that received a CS. Moreover, compared with the controls, there was a lower lactobacillus-dominating percentage in the CS group. This change could be a sign of chronic endometritis **(31).**

Researchers have reported a lower pregnancy rate in patients who previously underwent a CS delivery compared with patients who previously delivered vaginally after ART **(32)**. Although the CSD area is located at the cervical uterine junction, this is far away from where we would assume the implantation to occur. A high prevalence of CE in women with a CSD may be one of the causes of this situation. Although patients with CE may not have any clinical symptoms, there has been much research conducted that shows the relationship between CE, infertility, and implantation failure **(33-35)**.

A large amount of research suggests that standardized antibiotics are effective at clearing CE and improving the reproductive prognosis of patients. This study suggests that conducting a hysteroscopy and endometrial biopsy in infertile women with a CSD as early as possible might be beneficial **(36).**

References:

1. Jenabi, E., Khazaei, S., Bashirian, S., Aghababaei, S., & Matinnia, N. (2020). Reasons for elective cesarean section on maternal request: a systematic review. The Journal of Maternal-Fetal & Neonatal Medicine, 33(22), 3867-3872.
2. Veef, E., & Van de Velde, M. (2022). Post-cesarean section analgesia. Best Practice & Research Clinical Anaesthesiology, 36(1), 83-88.

3. Eleje, G. U., Ugwu, E. O., Enebe, J. T., Okoro, C. C., Okpala, B. C., Ezeora, N. C., ... & Ikechebelu, J. I. (2022). Cesarean section rate and outcomes during and before the first wave of COVID-19 pandemic. SAGE Open Medicine, 10, 20503121221085453.
4. Alalfy M, Elgazzar A, Fares T, Nagy O, Ellithy A, Lasheen Y, Kamel A, Soliman M, Hassan A, Samy A, Taher AM (2019): Effect of subcutaneous tissue closure technique in cesarean section on postoperative wound complications in obese Egyptian women. The Journal of Maternal-Fetal & Neonatal Medicine; 32(15): 2452-9.
5. Hordeaux, J., Hinderer, C., Buza, E. L., Louboutin, J. P., Jahan, T., Bell, P., ... & Wilson, J. M. (2019). Safe and sustained expression of human iduronidase after intrathecal administration of adeno-associated virus serotype 9 in infant rhesus monkeys. Human Gene Therapy, 30(8), 957-966.
6. Jordans, I. P. M., De Leeuw, R. A., Stegwee, S. I., Amso, N. N., Barri-Soldevila, P. N., Van Den Bosch, T., ... & Huirne, J. A. F. (2019). Sonographic examination of uterine niche in non-pregnant women: a modified Delphi procedure. Ultrasound in Obstetrics & Gynecology, 53(1), 107-115.
7. Venumadhav, T., Zackay, B., Roulet, J., Dai, L., & Zaldarriaga, M. (2019). New search pipeline for compact binary mergers: Results for binary black holes in the first observing run of Advanced LIGO. Physical Review D, 100(2), 023011.
8. van der Voet LF, Jordans I, Brölmann H, Veersema S, Huirne J (2018): Changes in the Uterine Scar during the First Year after a Caesarean Section: A Prospective Longitudinal Study. Gynecologic and obstetric investigation, 83(2), 164–170.
9. Meuleman, S. K., Min, N., Hehenkamp, W. J. K., Uiterweer, E. P., Huirne, J. A. F., & de Leeuw, R. A. (2023). The definition, diagnosis, and symptoms of the uterine niche–a systematic review. Best Practice & Research Clinical Obstetrics & Gynaecology, 102390.
10. Stegwee, S. I., Beij, A., de Leeuw, R. A., Mokkink, L. B., van der Voet, L. F., & Huirne, J. A. (2020). Niche-related outcomes after caesarean section and quality of life: a focus group study and review of literature. Quality of Life Research, 29, 1013-1025.
11. Wang, Y., He, X., Tian, Y., Xie, L., Mol, B., Huirne, J., & Jian, Z. (2023). P-751 Comparing levonorgestrel intrauterine system versus hysteroscopic niche resection in women with

postmenstrual spotting related to a niche in the uterine caesarean scar. Human Reproduction, 38(Supplement_1), dead093-054.

12. Kulshrestha V, Agarwal N, Kachhawa G. Post-caesarean Niche (Isthmocele) in Uterine Scar: An Update. J Obstet Gynaecol India. 2020 Dec;70(6):440-446.
13. Verest, A., Borwski, E., Cadron, I., Van Calenbergh, S., & Vanspauwen, R. (2019). Intrauterine device (IUD) migration in cesarean delivery scar: What to do with the niche?. Facts, Views & Vision in Obgyn, 11(3), 251.
14. Armstrong, F., Mulligan, K., Dermott, R. M., Bartels, H. C., Carroll, S., Robson, M., ... & Brennan, D. J. (2023). Cesarean scar niche: An evolving concern in clinical practice. International Journal of Gynecology & Obstetrics, 161(2), 356-366.
15. Vissers, J., Hehenkamp, W., Lambalk, C. B., & Huirne, J. A. (2020). Post-Caesarean section niche-related impaired fertility: hypothetical mechanisms. Human Reproduction, 35(7), 1484-1494.
16. de Luget, C. D., Becchis, E., Fernandez, H., Donnez, O., & Quarello, E. (2022). Can uterine niche be prevented?. Journal of Gynecology Obstetrics and Human Reproduction, 51(3), 102299.
17. Bjorklund, J., Wiberg-Itzel, E., & Wallstrom, T. (2022). Is there an increased risk of cesarean section in obese women after induction of labor? A retrospective cohort study. PLoS One, 17(2), e0263685.
18. Sholapurkar SL (2018): Etiology of Cesarean Uterine Scar Defect (Niche): Detailed Critical Analysis of Hypotheses and Prevention Strategies and Peritoneal Closure Debate. Journal of clinical medicine research, 10(3), 166–173.
19. Vervoort AJ, Uittenbogaard LB, Hehenkamp WJ, Brölmann HA, Mol BW, Huirne JA (2015): Why do niches develop in Caesarean uterine scars? Hypotheses on the aetiology of niche development. Human reproduction (Oxford, England), 30(12), 2695–2702.
20. Olm, M. R., Crits-Christoph, A., Bouma-Gregson, K., Firek, B. A., Morowitz, M. J., & Banfield, J. F. (2021). inStrain profiles population microdiversity from metagenomic data and sensitively detects shared microbial strains. Nature Biotechnology, 39(6), 727-736.
21. Nahar, Z., Sohan, M., Hossain, M. J., & Islam, M. R. (2022). Unnecessary Cesarean Section Delivery causes risk to both mother and baby: a commentary on pregnancy complications

and women's Health. INQUIRY: The Journal of Health Care Organization, Provision, and Financing, 59, 00469580221116004.

22. Opiyo, N., Torloni, M. R., Robson, M., Ladfors, L., Gholbzouri, K., Kacerauskiene, J., ... & Betrán, A. P. (2022). WHO's Robson platform for data-sharing on caesarean section rates. Bulletin of the World Health Organization, 100(5), 352.
23. Feng, J., Kang, Y., Chen, G., Zhang, Y., Li, Y., Li, Y., & He, H. (2022). Spontaneous complete uterine rupture with protrusion of foetal limbs at the third trimester following laparoscopic cornuostomy: a case report. Medicine, 101(8).
24. Bossung, V., Lupatsii, M., Dashdorj, L., Tassiello, O., Jonassen, S., Pagel, J., ... & Härtel, C. (2022). Timing of antimicrobial prophylaxis for cesarean section is critical for gut microbiome development in term born infants. Gut Microbes, 14(1), 2038855.
25. Dahlquist, K., Stuart, A., & Källén, K. (2022). Planned cesarean section vs planned vaginal delivery among women without formal medical indication for planned cesarean section: A retrospective cohort study of maternal short-term complications. Acta Obstetricia et Gynecologica Scandinavica, 101(9), 1026-1032.
26. Fitzpatrick, K. E., Abdel-Fattah, M., Hemelaar, J., Kurinczuk, J. J., & Quigley, M. A. (2022). Planned mode of birth after previous cesarean section and risk of undergoing pelvic floor surgery: A Scottish population-based record linkage cohort study. PLoS Medicine, 19(11), e1004119.
27. Wei, L., Xu, C., Zhao, Y., & Zhang, C. (2022). Higher Prevalence of Chronic Endometritis in Women with Cesarean Scar Defect: A Retrospective Study Using Propensity Score Matching. Journal of Personalized Medicine, 13(1), 39.
28. Kimura, F.; Takebayashi, A.; Ishida, M.; Nakamura, A.; Kitazawa, J.; Morimune, A.; Hirata, K.; Takahashi, A.; Tsuji, S.; Takashima, A.; et al. Review: Chronic endometritis and its effect on reproduction. J. Obstet. Gynaecol. Res. 2019, 45, 951–960.
29. Morris H. Surgical pathology of the lower uterine segment caesarean section scar: is the scar a source of clinical symptoms? Int J Gynecol Pathol 1995; 14:16–20.
30. Higuchi, A.; Tsuji, S.; Nobuta, Y.; Nakamura, A.; Katsura, D.; Amano, T.; Kimura, F.; Tanimura, S.; Murakami, T. Histopathological evaluation of cesarean scar defect in women with cesarean scar syndrome. Reprod. Med. Biol. 2021, 21, e12431.

31. Yang, X.; Pan, X.; Cai, M.; Zhang, B.; Liang, X.; Liu, G. Microbial Flora Changes in Cesarean Section Uterus and Its Possible Correlation With Inflammation. Front. Med. 2021, 8, 651938. [
32. Gurol-Urganci, I.; Bou-Antoun, S.; Lim, C.; Cromwell, D.; Mahmood, T.; Templeton, A.; Van Der Meulen, J. Impact of Caesarean section on subsequent fertility: A systematic review and meta-analysis. Hum. Reprod. 2013, 28, 1943–1952.
33. Li, Y.; Xu, S.; Yu, S.; Huang, C.; Lin, S.; Chen,W.; Mo, M.; Lian, R.; Diao, L.; Ding, L.; et al. Diagnosis of chronic endometritis: How many CD138 + cells/HPF in endometrial stroma affect pregnancy outcome of infertile women? Am. J. Reprod. Immunol. 2020, 85.
34. Martingano, D.; Renson, A.; Rogoff, S.; Singh, S.; Nasir, M.K.; Kim, J.; Carey, J. Daily gentamicin using ideal body weight demonstrates lower risk of postpartum endometritis and increased chance of successful outcome compared with traditional 8-hour dosing for the treatment of intrapartum chorioamnionitis. J. Matern. Neonatal Med. 2018, 32, 3204–3208.
35. Song, D.; Feng, X.; Zhang, Q.; Xia, E.; Xiao, Y.; Xie, W.; Li, T.C. Prevalence and confounders of chronic endometritis in premenopausal women with abnormal bleeding or reproductive failure. Reprod. Biomed. Online 2018, 36, 78–83
36. Vitagliano A, Saccardi C, Noventa M, Di Spiezio Sardo A, Saccone G, Cicinelli E, Pizzi S, Andrisani A, Litta PS. Effects of chronic endometritis therapy on in vitro fertilization outcome in women with repeated implantation failure: a systematic review and meta-analysis. Fertil Steril. 2018;110:103–12.e1.