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Exploring uterine niche: a systemic review on secondary infertility rates, pathophysiological correlations, impact on assisted reproduction technology (ART), and the efficacy of surgical interventions

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Abstract

Background The rising trend of cesarean sections worldwide has resulted in an increased incidence of uterine niches, a cavity formed at the cesarean scar site due to impaired tissue healing. Secondary infertility in women with uterine niches is a hot topic in obstetrics and gynecology. Therefore, the current study aims to untwist the link between secondary infertility and uterine niche, exploring the pathophysiological correlations, effects on assisted reproduction technology, and role of surgical interventions in resuming fertility.

Methodology PubMed, Cochrane Library, Embase, and Science Direct were searched systematically. Rayyan was employed as a semi-automated tool for study selection. Full-text articles in the English language were included. Systematic reviews, meta-analyses, or book chapters were excluded. Newcastle-Ottawa Scale assessed the quality of cohort and case-control studies, while the Cochrane Risk-of-bias tool evaluated randomized controlled trials. Data synthesis followed a thematic analysis.

Results 35 articles from 3301 studies met the inclusion criteria. Among those, 25 were cohort studies, only one was a randomized controlled trial, and the rest had different study designs. The study quality assessment revealed average to good quality. The incidence of secondary infertility in women with uterine niches ranged from 27.37% ($n=95$) to 75% ($n=16$). Decreased residual myometrial thickness, chronic inflammatory changes at the niche site, and fluid accumulation within the niche cavity were identified as leading causes of secondary infertility. The uterine niche adversely affected assisted reproductive outcomes through multiple mechanisms. Various surgical interventions, including hysteroscopy, laparoscopy, or combined surgery, showed differing efficacies in restoring fertility.

Conclusion The study provides valuable insights regarding the association between secondary infertility and uterine niche. However, smaller sample sizes, retrospective nature of study designs, reliance on observational data, and

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heterogeneity of study reporting have limited the ability to arrive at solid conclusions. Therefore, we encourage well-designed prospective studies, including randomized controlled trials, to further explore this trending area.

Register The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD4204526319).

Keywords Uterine niche, Secondary infertility, Assisted reproductive technology, Hysteroscopic niche repair, Laparoscopic niche repair, Prevalence of secondary infertility, Pathophysiology of niche-related infertility.

Introduction

Background

The number of women delivering through the cesarean section has steadily increased, as suggested by recent data from 2010 to 2018, collected from 154 countries, which accounted for 94.5% of global live births. It was shown that 21.1% of women underwent cesarean section for childbirth [1]. Cesarean section rates varied across different geographical regions, with the lowest average of 5% in sub-Saharan Africa and the highest of 42.8% in Latin America and the Caribbean [1]. With the parallel rise of the uterine niche along with the cesarean section rate, concerns regarding their mutual relationship and subsequent long-term maternal morbidity have become an interesting area for discussion [2].

A uterine niche is a reservoir-like cavity in the anterior uterine isthmus where a previous cesarean section scar [3] underwent imperfect or impaired tissue healing [4]. However, the absence of universally accepted diagnostic criteria for a 'uterine niche' seems to be a key obstacle to further scientific evaluation and information sharing. A recent movement to correct this anomaly by experts' agreement by a Delphi process recently produced a definition [5]. After a modified Delphi procedure, the study group concluded that uterine niche should be defined as "an indentation at the site of the cesarean scar with a depth of at least 2 mm" [5]. Poidevin was the first to describe a niche using hysterosalpingography in 1961 as a typical small wedge-shaped morphological abnormality [6]. Other terms used to describe a uterine niche are deficient cesarean scar, diverticulum, pouch, and isthmocele [7]. Diagnosis of a uterine niche is increasingly common, and its reported incidence ranges from 24–84% [8]. Although it seems reasonable to assume that the prevalence of niche is increasing with the rise in cesarean section, pinpointing the exact prevalence is complex due to multiple definitions, differences in diagnostic methods, and study populations [3]. Diagnosis of a uterine niche is typically established through transvaginal ultrasound, which detects an anechoic (lacking echoes) area at the site of the niche. Other diagnostic methods include transvaginal sonohysterography or diagnostic hysteroscopy [8].

While many women may be asymptomatic, the uterine niche has been associated with a range of symptoms, signs, and complications, including post-menstrual spotting, prolonged bleeding, intermittent spotting, pain, midcycle intrauterine fluid accumulation, cesarean scar ectopic pregnancy, bladder dysfunction, obstetric complications in a future pregnancy and scar abscess [4]. The association between niche parameters and clinical symptoms has not been fully elucidated [5]. There is also a growing concern about secondary infertility associated with uterine niche [9], which is being explained through several theoretical mechanisms. It is proposed that the environment for sperm penetration and implantation may be compromised due to the accumulation of intrauterine fluid (buildup of mucous and old menstrual blood) within the niche, secondary to altered uterine contractility stemming from fibrosis [10]. In addition, a physical barrier to embryo transfer and implantation may exist, hindering the successful progression of an embryo [11]. It is also suggested that psychogenic factors may come into play, potentially diminishing the likelihood of a successful pregnancy [11]. Recent research offers substantiating evidence for these theories [10].

A debate is ongoing about the most effective surgical approach and when one should consider repairing a niche for restoring fertility [11]. Surgical niche repair can be performed laparoscopically, hysteroscopically, or combined laparoscopic and hysterescopic surgery [12]. However, no established guidelines specify the preferred technique [13]. Given the growing prevalence of secondary infertility in women who have had a cesarean section, it appears to be of significant clinical importance to determine whether niche impacts the outcomes of ART [2]. It is also crucial to see if intrauterine fluid collection within a niche could negatively affect implantation [14].

Objectives

The current study aims to investigate the link between uterine niche and secondary infertility, establishing a pathophysiological basis, comparing the efficacy of various surgical approaches, and assessing the impact of artificial reproductive techniques.

Materials and methods

Information sources

We retrieved the relevant studies from PubMed, Cochrane Library, Embase, and Science Direct published up to 14/04/2024.

Search strategy

The search strings included "Niche," "Cicatrix," "Scar," "Isthmocele," "Anechoic," "Pouch," "Wound dehiscence," "Diverticulum," "Uterus," "Uterine disease," "Myometrium," "Endometrium," "Myoendometrium," "Effect," "Impact," "Association," "Related," "Outcome," "Result," and "Influence" which were combined using Boolean expressions "AND", "OR" to form precise search queries. A detailed line-by-line search strategy is given as a supplementary file.

Study selection

The study selection process was conducted following a blinded approach in two steps using the semi-automated tool Rayyan [15], with one author as the reviewer (AJ) and another as the collaborator (TDKM). In the first round, title abstract screening removed duplicates with conflicts resolved by (DMCS); similarly, the second round adopted a similar blinded approach for full-text screening with conflicts resolved by (DMCS). The study selection process followed the PRISMA 2020 flow diagram for updated systematic reviews [16]. The current study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42024526319).

Eligibility criteria

Inclusion criteria:

- Articles with women who are diagnosed with uterine niche or who have had cesarean sections and also diagnosed with secondary infertility.
- Articles describing surgical repair methods and outcomes of uterine niche.
- Articles discussing the pathophysiological basis for secondary infertility associated with uterine niche.
- Articles with incidence of secondary infertility in women with uterine niche.
- Articles explaining assisted reproduction outcomes of women with uterine niche.
- Full-text articles in the English language.
- Randomized Controlled Trials (RCTs), Case-Control Studies, Cross-Sectional Studies, Cohort Studies, or Case Series.

Exclusion criteria:

- Systematic reviews, meta-analyses, or book chapters.

Data extraction

Initial data extraction was conducted by the reviewer (TDKM) and cross-checked by the second (DMCSJ) and third reviewer (SS). Finally, the fourth reviewer (AJ) verified the process for completeness. The conflicts were discussed among reviewers, and the discrepancies were settled. Key study characteristics were extracted and organized into predefined tables concerning outcome measures: incidence of secondary infertility in women with uterine niche, the pathophysiological basis for niche-associated secondary infertility, effects of uterine niche on ART, and surgical correction of uterine niche and subsequent fertility improvement.

Risk of bias and quality assessment

The quality assessment of cohort and case-control studies was conducted using the Newcastle-Ottawa Scale (NOS) [17]. The quality of each RCT was assessed using the Cochrane risk-of-bias (RoB1) tool [18]. However, specific quality assessment tools were unavailable for evaluating Observational Cross-Sectional Studies, Observational and Exploratory Clinical Studies, Retrospective Clinical Studies, Case Series, and Retrospective Cross-Sectional Studies. The risk of bias and quality assessment also employed a similar approach described in 'data extraction,' with conflicts resolved through discussion.

Assessment of the study heterogeneity

Heterogeneity or inter-study variability, referring to differences in underlying study parameters, was evaluated by classifying into three categories (clinical, methodological, and statistical heterogeneity) to improve the applicability of findings in clinical decision-making [19]. Variability in the participants, the types or timing of outcome measures, and intervention characteristics were focused on assessing clinical heterogeneity, while variability in trial designs or execution was focused on assessing methodological heterogeneity. Statistical heterogeneity was assessed by comparing variability in summary treatment effects among trials [19].

Data synthesis

The data synthesis followed a thematic analysis where data regarding primary study outcomes (incidence of secondary infertility, the underlying pathophysiological basis, the impact of uterine niche on ART, and the effectiveness of surgical interventions in restoring fertility) were meticulously extracted and systematically organized into predefined tables. However, a meta-analysis was not conducted due to the qualitative nature of the evidence.

Results

Figure 1 shows the flow diagram for study selection. We identified 3301 studies from four databases. After considering the inclusion and exclusion criteria, 35 studies were selected for the review. We included 25 cohort studies, two case-control studies, one RCT, one observational cross-sectional study, one observational and exploratory clinical study, one retrospective clinical study, one retrospective case series, one prospective case series, one retrospective review, and one retrospective cross-sectional study.

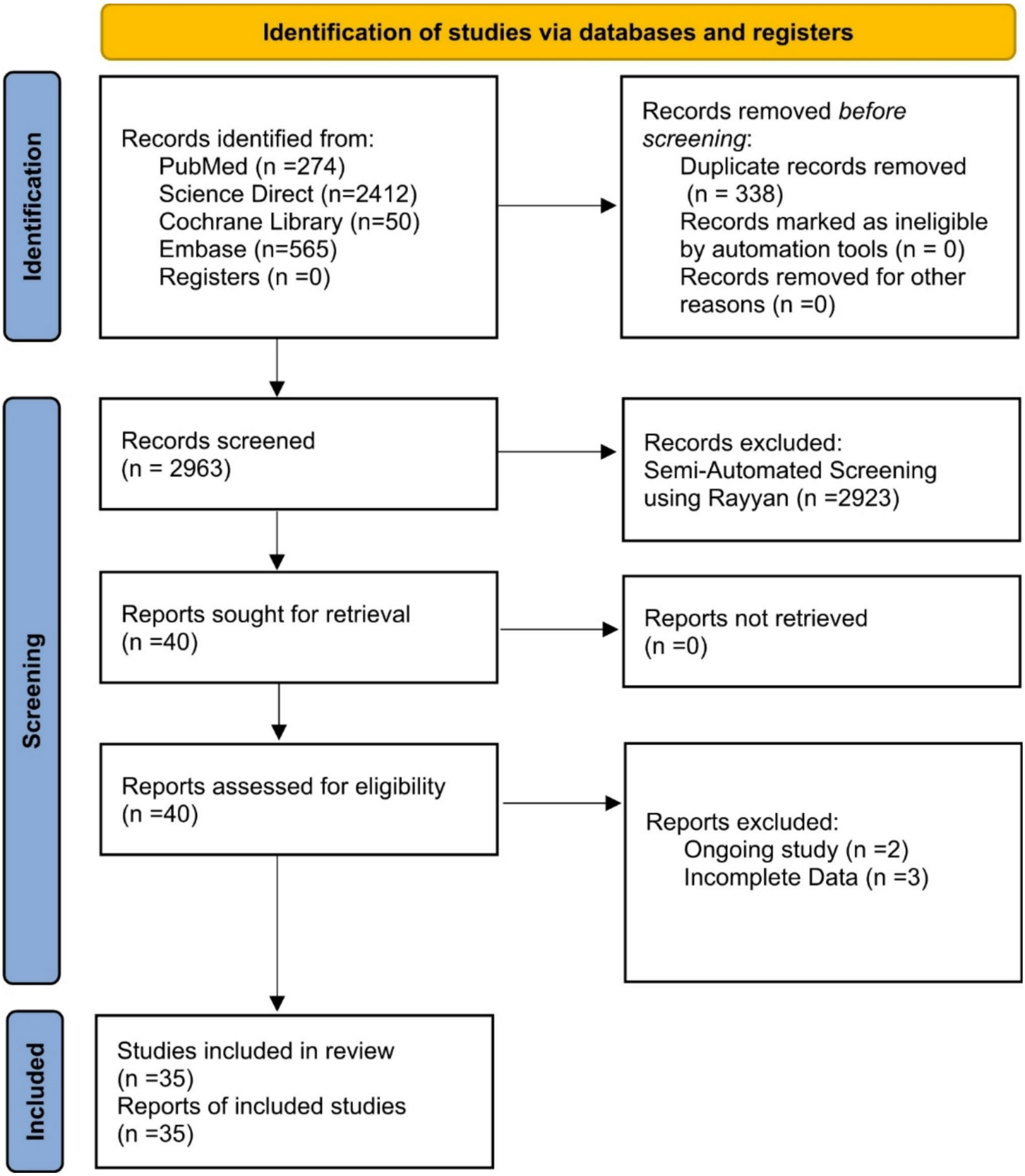

Fig. 1 PRISMA 2020 flow diagram for study selection

Risk of bias and quality assessment

The quality assessment of the included studies was conducted using the NOS for cohort and case-control studies and the RoB1 for RCTs. The NOS scores for cohort studies varied, with some studies scoring as low as 2 out of 9 (e.g., Sonmezer 2022, Etman 2022) due to limitations in cohort representativeness, comparability, and follow-up, while others achieved higher scores of 6 out of 9 (e.g., Diao 2021, Yao 2022, Zhang D 2018, Higuchi 2021) by demonstrating adequate follow-up, better exposure ascertainment, and well-defined study groups. Studies such as Mensi 2023, Gubbini 2008, Cohen 2020, Chuqing 2023, Schepker 2014, Shapira 2019, Tanimura 2015, and Zhang X 2016 scored 5 out of 9, indicating moderate quality with some methodological limitations. Other studies, including Zhang 2022, Tsuji 2020, Calzolari 2019, Safarowska 2021, and Piriyev 2022, received a score of 4 out of 9, while Enderle 2020 and Bingqing 2018 scored 3 out of 9. The case-control studies, Cohen 2023 and Nobuta 2022, each received a total score of 6 out of 9, reflecting good study quality, though challenges in comparability and representativeness of cases were noted. The RoB1 assessment of the only RCT, Abdou 2018, indicated a moderate risk of bias, with a high risk noted explicitly in the blinding of participants and personnel, potentially influencing study outcomes.

Furthermore, seven studies—Almarzuki 2022 (observational cross-sectional study), Lawrenz 2019 (observational and exploratory clinical study), AbdullGaffar 2022 (retrospective review), Istvan 2017 (retrospective clinical study), Beilei 2021 (retrospective cohort study), Mohr-Sasson 2023 (retrospective cross-sectional study), and Zhang D 2018 (retrospective case series)—employed diverse methodologies that were not assessable using a standardized quality assessment tool. Despite this, their methodological rigor was carefully reviewed before inclusion to ensure validity and reliability. (Annexure 1: Detailed study quality assessment).

Study heterogeneity

The studies showed methodological heterogeneity across a wide range of trial designs, with a majority of cohort studies (71.43%, $n=25$). Even the studies with similar designs differed in risk of bias and quality assessment, further enhancing the methodological heterogeneity. The studies used different niche definitions, different durations of secondary infertility, and different numbers of participants, creating clinical heterogeneity. Cohen 2023, Yao 2021, Zhang 2022, Abdou 2018, Chuqing 2023 and Shapira 2019 defined uterine niche as an anechoic area at the site of the cesarean scar with a depth ≥ 2 mm, aligning with Delphi consensus 2018 [5]. In contrast, Lawrenz 2019 used 1 mm uterine scar depth as the cut-off measurement. Although the rest of the studies appreciated various uterine niche parameters, they did not define them. All the studies used the standard secondary infertility definition [20–25]. However, the duration of secondary infertility varied across the studies. Schepker 2014 and Abdou 2018 used participants with secondary infertility for more than two years, while Lorenz 2019 used participants with one year of secondary infertility, and Gubbini 2008 used participants with 3–8 years of secondary infertility. However, the remaining studies did not report the duration of secondary infertility. The studies, Diao 2021, Mensi 2023, Yao 2021, Zhang 2022, Beilei 2021, Higuchi 2021, Nobuta 2022, Almarzuki 2022, Etman 2022, Abdou 2018, Chuqing 2023, Gubbini 2011, Istvan 2017, Schepker 2014, Szafarowska 2021 and Tanimura 2015 excluded other factors (tubal obstruction, scarred uterus, uterine malformations) contributing to secondary infertility and described uterine niche as the sole identifiable etiology. However, the rest of the studies reported incomplete data investigating the other contributory factors for secondary infertility. The study participants ranged from 8 (Cohen 2017) to 2449 (Yao 2022). Only 31.43% ($n=11$) of the studies had participants above 100, while only 5.7% ($n=2$) had participants above 1000. The studies lacked uniform statistical measures for reporting the outcomes, creating significant statistical heterogeneity.

The incidence of secondary infertility in women with uterine niche

The incidence of secondary infertility in women with uterine niches has been explored in different studies, providing insights into this intricate relationship. Cohen 2017, Enderle 2020, Gubbini 2008, Calzolari 2019, Szafarowska 2021, Karampelas 2021, Donnez 2021, Chuqing 2013, Schepker 2014, Shapira 2019, Sonmezer 2022, and Etman 2022 which explored the above relationship revealed secondary fertility rates as 50%($n=8$), 55.56%($n=18$), 34.62%($n=26$), 45.71%($n=35$), 51.76%($n=85$), 38.71%($n=31$), 47.37%($n=38$), 33.13%($n=166$), 46.15%($n=13$), 27.37%($n=95$), 75%($n=16$), 62%($n=50$) respectively [8, 26–36]. Tables 1 and 2 summarize the key study findings.

Table 1 Prevalence of uterine niche in women with secondary infertility

Study	Design	*n*	Fertility status/ Prevalence of infertility
Sonmezer 2022 [28]	Prospective cohort study	16	Among the 16 patients experiencing secondary infertility, excluding four with advanced maternal age as a causative factor, the remaining 12 patients were found to have Isthmocele as the sole identified factor.
Etman 2022 [8]	Prospective cohort study	50	Out of the 50 women who experienced secondary infertility after at least one cesarean section, 31 of them, or 62%, were found to have uterine niches.
Almarzuki 2022 [37]	Observational cross-sectional study	100	Out of 100 women who had both uterine niche and secondary infertility, 25 had experienced infertility for a minimum of 1 year, 31 for at least two years, and 44 for a minimum of 3 years. However, no correlation was observed between the anatomical characteristics of the uterine niche and this group's secondary infertility duration.

Table 2 Impact of uterine niche on ART

Study	Design	*n*	Artificial reproduction technique	Result
Zhang 2022 [38]	Retrospective cohort study	1122	In vitro fertilized frozen-thawed embryo transfer	The clinical pregnancy and live birth rates were decreased in the CSD group compared with the VD and CD groups.
Lawrenz 2019 [14]	Observational and exploratory clinical study (No strict cohort design)	495	Frozen embryo transfer	No significant differences in the reproductive outcome after FET were found between the patients with and without an Isthmocele when ICF was excluded before the embryo transfer procedure.
Mensi 2023 [2]	Retrospective cohort study	114	IVF	The clinical pregnancy rate and live birth rate were significantly lower among women with CSD.
Diao 2021 [39]	Retrospective cohort study	834	IVF/ICSI	The live birth rate and mean implantation rate in the CSD group were significantly lower than those in the VD and CD groups.
Yao 2022 [40]	Retrospective cohort study	2449	IVF/ICSI	Compared with women without niches, women with niches had a reduced live birth rate and implantation rate.
Cohen 2023 [41]	Retrospective case-control study	86	Embryo transfer	Patients undergoing fertility treatments, whether diagnosed with a uterine niche before conception or not, exhibited similar live birth rates.

CSD– Cesarean scar defect, VD– Vaginal delivery, CD– Cesarean delivery, FET– Frozen embryo transfer, ICF– Intracavity fluid, IVF– In vitro fertilization, ICSI– Intracytoplasmic sperm injection

The pathophysiological basis for the association between uterine niche and fertility

Ten studies, incorporating five retrospective cohort studies [13, 20–23], one retrospective cross-sectional study [24], one retrospective case-control study [25], one retrospective review [42], and two prospective observational studies [14, 36], examined pathophysiological mechanisms contributing to secondary infertility linked with the uterine niche. Four studies [36, 22–24] reported an association with decreased residual myometrial thickness (RMT) at the niche, while three studies [20, 21, 25] proposed the role of inflammation in altering the uterine microenvironment. Another three studies [13, 14, 42] highlighted the impact of intracavity fluid accumulation within the uterine niche, resulting in implantation failure. Table 3 summarizes the key study findings.

Mohr-Sasson 2023 discovered that secondary infertility was associated with an RMT of less than 2.5 mm ($p = 0.001$) [24]. Piriyev 2022 demonstrated an increase in mean pre-operative myometrial thickness from 2 mm to 8.7 mm (myometrial thickness increase by 335%) through laparoscopic niche correction as a preventive measure for patients with fertility desire [22]. Donnez 2017 documented a rise in RMT from 1.4 ± 0.76 mm to 9.6 ± 1.8 mm following laparoscopic niche repair reinforcing the myometrium [36]. Tsuji 2020. observed a significant post-operative RMT difference between pregnant and non-pregnant groups [4.9 (3.4–6.6) mm vs. 2.3 (2.1–4.4) mm, respectively; $p = 0.02$)] [23].

Tanimura 2015 underscored that infertility arises from the entry of bloody fluid or bleeding from the niche into the uterine cavity, negatively impacting implantation [13]. through embryotoxicity, disturbance of cytokine expression, and potential mechanical hindrance reducing endometrial receptivity, exacerbated by uterine retroflection. Lawrenz 2019 proposed that poor contractility in fibrotic tissue surrounding the niche leads to fluid accumulation, with more prior cesarean section procedures deepening the niche. AbdullGaffar 2022 emphasized an altered isthmocervical canal environment with endocervical, endometrial, and isthmic mucosa and thickened fibromuscular stromal edges [42].

Nobuta 2022 identified CD138-positive cells and elevated proinflammatory cytokines, TNF-α, and IL-1β in niche patients [25]. Higuchi 2021 revealed a chronic inflammatory nature marked by altered expression of inflammatory markers and the absence of endometrium in the uterine niche, further complicated by adenomyosis [20]. Beilei 2021 showed severe pelvic adhesions, altered tubal patency, and increased inflammatory factors in women with uterine niches, establishing a role for chronic inflammation in secondary infertility [21].

Impact of uterine niche on ART

Six studies—comprising four retrospective cohort studies [2, 38–40], one retrospective case-control study [41], and one prospective observational study [14], investigated the impact of uterine niche on ART. Table 2 summarizes the key study findings.

Zhang 2022 [38] reported on 1122 In Vitro-Fertilation Frozen Embryo transfer (IVF-FET) patients in the Single Embryo Transfer (SET) group ($n = 409$), including 55 niche cases of a Double Embryo Transfer (DET) group ($n = 713$) comprising 74 niche cases. Lower clinical pregnancy and live birth rates were evident in the niche group compared to previous cesarean delivery (without niche) and vaginal delivery groups only in the DET group ($P < 0.001$.

Table 3 The pathophysiological basis for the association between uterine niche and fertility

Aetiology	Study	Design	*n*
The altered environment and anatomy of the isthmocervical canal.	AbdullGaffar 2022 [42]	Retrospective review	22
Embryo implantation failure- associated with chronic endometritis, endometriosis, and chronic inflammation in the uterine cavity.	Nobuta 2022 [25]	Retrospective case-control study	201
The absence of endometrium, the presence of adenomyosis, and chronic inflammation in CSD contribute to secondary infertility due to CSS.	Higuchi 2021 [20]	Retrospective cohort study	84
Embryo transfer success can be compromised when there is an Isthmocele and Intracavity fluid.	Lawrenz 2019 [14]	Observational and exploratory clinical study (No strict cohort design)	495
Correlation analysis showed that the levels of inflammatory factors (tumor necrosis factor-a, interleukin-1b, interleukin-6), the size of uterine scar diverticulum, and the myometrial thickness at uterine scar were significantly correlated with subsequent infertility ($r=0.307$, 0.083, 0.147, 0.405, 0.291, $P<0.05$).	Beilei 2021 [21]	Retrospective cohort study	60
An RMT < 2.5 mm was associated with secondary infertility.	Mohr-Sasson 2023 [24]	Retrospective cross-sectional study	282
Surgical correction of Isthmocele increases RMT, resulting in improved fertility.	Piriyev 2022 [22]	Retrospective cohort study	28
	Donnez 2017 [36]	Prospective case series	38
	Tsuji 2020 [23]	Retrospective cohort study	38
Infertility associated with PCSD, cesarean scar syndrome, is caused by the retention of bloody fluid in the uterine cavity and scarring. When the bloody fluid flows into the uterine cavity, it may cause implantation failure.	Tanimura 2015 [13]	Retrospective cohort study	22

RMT– Residual myometrial thickness, PCSD– Post cesarean scar defect

Lawrenz 2019 [14], involving 103 FETs, revealed that excluding intracavitary fluid before the procedure mitigated the impact of niche on reproductive success.

Mensi 2023 [2], with 114 women with a history of cesarean section, found that niche significantly decreased reproductive outcomes during IVF cycles. Among those, 67% of women ($n=76$) had a niche, and none opted for surgical intervention. The clinical pregnancy rate was 43% in the niche group compared to 71% in the control group ($P=0.006$). The live birth rate was 33% in the niche group and 55% in the control group ($P=0.027$).

In Diao 2021 [39], the niche group ($n=74$) exhibited significantly lower live birth rates following IVF compared to both the vaginal ($n=401$) and cesarean delivery ($n=359$) groups, with a marked difference of 21.6% in the niche group versus 36.4% in the vaginal delivery group (adjusted OR 0.50 [0.27–0.90]). Moreover, the mean implantation rate in the niche group was notably decreased compared to the vaginal delivery group. [(0.35 ± 0.41 versus 0.25 ± 0.39) (adjusted OR 0.90 {0.81–0.99}].

Yao 2021 [40], involving 2515 women with previous cesarean sections and 7.12% of those with a uterine niche ($n=179$) revealed that women without a uterine niche had significantly higher live birth rate (31.51% vs. 18.99%, aOR: 0.51, 95% CI: 0.34–0.77) and implantation rates (36.95% vs. 25.87%, aOR: 0.53, 95% CI: 0.38–0.76) compared to those with a niche.

Cohen 2023 [41], with 86 patients experiencing secondary infertility and a history of cesarean delivery, found no difference in clinical pregnancy rate, implantation rate, live birth rate, and preterm delivery rate in those with a uterine niche ($n=56$) and control group ($n=30$).

Efficacy of surgical interventions in restoring fertility through uterine niche repair

Various studies have delved into a spectrum of surgical treatment modalities encompassing hysteroscopic niche repair, laparoscopic niche repair, laparoscopic combined with hysteroscopic repair, vaginal repair, and repair through laparotomy, aimed at addressing secondary infertility in women with a uterine niche. Table 4 shows the key study findings.

Eleven studies [9, 12, 23, 26, 29–31, 33, 35, 44, 45] focused on hysteroscopic niche repair. Cohen 2017 [26], with 8 participants experiencing secondary infertility, repeated hysteroscopic niche resection was undertaken after the failure of the first hysteroscopy or niche recurrence, revealing no significant differences in fertility and obstetric outcomes between the initial and subsequent surgeries. Gubbini 2008 [44], with nine women having secondary infertility, conducted hysteroscopic correction of niche, resulting in seven out of nine women (77.77%) achieving pregnancy between 12 and 23 months of follow-up. Similarly, in a study by Gubbini 2011 [33], all 41 secondary subfertile women who underwent hysteroscopic niche correction achieved spontaneous pregnancies between 12 and 24 months post-surgery. Abdou 2018 [12], a randomized non-blinded trial involving 56 secondary infertile women, explored hysteroscopic resection

Table 4 Surgical approaches and their success rates in restoring fertility through uterine niche repair

Study	Design	*n*	Fertility status before surgery or intervention	Surgery/Intervention	Fertility status after surgery or intervention
Cohen 2017 [20]	Retrospective cohort study	8	Four women with secondary infertility	Repeated hysteroscopic niche resection following failure of first hysteroscopy or recurrence of niche.	There were no significant differences regarding fertility and obstetric outcomes between the first and second surgeries.
Enderle 2020 [34]	Retrospective cohort study	18	Ten women with secondary infertility	Isthmocele surgery by hysteroscopy, vaginal way, or laparotomy.	Six conceived (6/10,60%), resulting in five miscarriages and three live births. Isthmocele surgery is effective for infertility regardless of the surgical route.
Bingqing 2018 [43]	Retrospective cohort study	82	N/D	Laparoscopic combined with hysteroscopic repair	The surgery improved pregnancy rates, but no statistically significant difference was observed between the two surgical techniques.
Gubbini 2008 [44]	Prospective cohort study	26	Nine women with secondary infertility	Resectoscopic correction of the Isthmocele.	Seven of 9 women with secondary infertility became pregnant.
Gubbini 2011 [33]	Prospective cohort study	41	41 women with secondary infertility	Operative hysteroscopy	All 41 women became pregnant spontaneously between 12 and 24 months after surgery.
Abdou 2018 [12]	Randomized non-blinded trial	56	56 women with secondary infertility	Hysteroscopic resection of uterine niche	The clinical pregnancy rate was significantly higher ($p=0.001$) in the group of women who had hysteroscopic surgery when compared with the expectant management group (75% vs. 32.1% respectively)
Cohen 2020 [9]	Retrospective cohort study	39	Thirty-two women attempted and failed to conceive spontaneously, and seven women underwent IVF treatment and failed.	Hysteroscopic niche resection	One year after the hysteroscopic resection, 18 women conceived (14 spontaneously and four following IVF), leading to a cumulative pregnancy rate of 46.15%. Among the women who failed to conceive after at least two IVF cycles before the hysteroscopic resection, 42.8% conceived following surgery (three women out of seven)
Tsuji 2022 [45]	Retrospective cohort study	70	70 women with secondary infertility	Hysteroscopic niche resection	Among the 70 women, 49 women (70%) became pregnant after hysteresopic surgery.
Calzolari 2019 [29]	Retrospective cohort study	35	16 women with secondary infertility	Operative hysteroscopy	9/16 women (56%) became pregnant within 12 months of isthmoplasty.
Istvan 2017 [46]	Retrospective clinical study (No traditional design as cohort)	15	15 women with secondary infertility	Hysteroscopy-guided laparoscopic isthmoplasty	80% ($n=12/15$) became pregnant within 24 months of the treatment.
Szafarowska 2021 [31]	Prospective cohort study	85	44 women with secondary infertility	Operative hysteroscopy	52% ($n=13/25$) of women who underwent operative hysteroscopy and became pregnant compared to 26% ($n=5/19$) of women who underwent diagnostic hysteroscopy, but the result is not statistically significant.
Karampelas 2021 [32]	Retrospective case series	31	12 women with secondary infertility	Laparoscopic niche repair	The success rate for surgery to improve secondary infertility is 83.3%, with 10 out of 12 cases showing improvement.
Piriyev 2022 [22]	Retrospective cohort study	28	28 women with fertility desire have Isthmocele	Prophylactic laparoscopic niche repair	Laparoscopic correction of the Isthmocele increased myometrial thickness from 2 mm to 8.7 mm (average values). This represents an increase in myometrial thickness of 335%.
Donnez 2017 [36]	Prospective case series	38	18 women with secondary infertility	Laparoscopic niche repair	Among the 18 women with infertility, eight (44%) became pregnant and delivered healthy babies by cesarean section at 38–39 weeks of gestation.
Chuqing 2023 [35]	Retrospective cohort study	166	55 women with secondary infertility	Hysteroscopic niche resection	There was a significantly higher live birth rate ($p=0.04$) and pregnancy rate ($p=0.01$) in the HNR group compared to the expectant management group.
Tsuji 2020 [23]	Retrospective cohort study	38	38 women with secondary infertility	Hysteroscopic niche resection	Twenty-seven women (71%) became pregnant (pregnant group), while 11 (29%) did not (non-pregnant group).

Table 4 (continued)

Study	Design	*n*	Fertility status before surgery or intervention	Surgery/Intervention	Fertility status after surgery or intervention
Schepker 2014 [27]	Retrospective cohort study	13	Six women with secondary infertility	A microsurgical uterus reconstruction was performed by mini-laparotomy.	Post-operatively, three women (60%) became pregnant naturally. One no longer wished to become pregnant, and another patient planned to become pregnant by assisted reproductive therapy.
Shapira 2019 [30]	Retrospective cohort study	95	26 women with secondary infertility	Hysteroscopic niche resection	Of the 26 women who had infertility, 19 attempted to conceive spontaneously after CSD excision. Ten women (52.6%) conceived, and nine delivered at least once (47.36%).
Tanimura 2015 [13]	Retrospective cohort study	22	22 women with secondary infertility	Hysteroscopic repair/ Laparoscopic and hysteroscopic repair	Fourteen of the 22 women (63.6%) who were followed up for ≥ one year after surgery achieved pregnancy. RMT ≥ 2.5 mm with the straight uterus or uterus ante flexion underwent hysteroscopic repair, while RMT ≤ 2.5 mm with uterus retroflection underwent combined laparoscopic and hysteroscopic repair. Pregnancies occurred in all four women (100%) who underwent hysteroscopic surgery and in 10 of the 18 women (55.6%) who underwent laparoscopic surgery.
Zhang X 2016 [47]	Prospective cohort study	142	32 women with fertility desire	Laparoscopic niche repair	All 32 women who desired fertility underwent laparoscopy; 12 (37.5%) became pregnant after this procedure.
Zhang D 2018 [48]	Retrospective cohort study	67	43 women with fertility desire	Transvaginal repair/Laparoscopic repair	Conception rates for the two groups (Transvaginal repair/ Laparoscopic repair) were similar among women who desired fertility.

HNR– Hysterescopic niche resection

of the uterine niche, revealing a significantly higher ($p = 0.001$) clinical pregnancy rate (75% vs. 32.1%) compared to expectant management. Cohen 2020 [9], with 39 secondary infertile women, focused on hysteroscopic niche resection of 21 women experiencing unsuccessful attempts with spontaneous conception and 18 women with failed IVF treatment, resulting 18 women (46.15%) conceived one year later (15 spontaneous and three IVF). Tsuji 2022 [45], with 70 secondary infertile women, investigated hysteroscopic niche resection, resulting in a 70% pregnancy rate. Calzolari 2019 [29], with 16 secondary infertile women, explored operative hysteroscopy, resulting in 9 out of 16 women (56%) achieving pregnancy within 12 months of niche repair. Szafarowska 2021 [31], with 44 participants having secondary infertility, focused on operative hysteroscopy, indicating a 52% (13/25) pregnancy rate in women who underwent the procedure compared to 26% (5/19) who underwent diagnostic hysteroscopy. However, the result was not statistically significant. Chuqing 2023 [35], with 55 women having secondary infertility, examined hysteroscopic niche resection, reporting a significantly higher live birth rate ($p = 0.04$) and pregnancy rate ($p = 0.01$) in the hysteroscopic niche resection group compared to the expectant management group. Tsuji 2020 [23], with 38 secondary infertile women, concentrated on hysteroscopic niche resection, revealing a 71% pregnancy rate, while 11 participants (29%) did not conceive. In Shapira 2019 [30], among the 26 women with infertility, 19 attempted spontaneous conception after niche excision, with ten women (52.6%) conceiving and nine delivering at least once (47.36%).

Four studies [22, 32, 36, 33, 44] focused on laparoscopic niche repair. Karampelas 2021 [32] reported an 83.3% success rate for improving secondary infertility, with 10 out of 12 cases achieving pregnancy. Piriyev 2022 [22], with 28 women desiring fertility, demonstrated a 335% increase in myometrial thickness after prophylactic laparoscopic niche repair. In Donnez 2017 [36], among 18 women with secondary infertility, 44% became pregnant and delivered healthy babies following laparoscopic niche repair. Zhang X 2016 [47], with 32 women desiring fertility, revealed a 37.5% pregnancy rate after the procedure. Schepker 2014 [27], with six women with secondary infertility, performed microsurgical uterus reconstruction through mini-laparotomy, resulting in a 60% natural pregnancy rate post-operatively.

Five studies [13, 34, 43, 46, 48] employed multiple or combined surgical methods for niche repair. Enderle 2020 [34], with ten women having secondary infertility, explored niche repair by hysteroscopy, vaginal way, vs. laparotomy concluding niche repair is effective for infertility, irrespective of the surgical route. Zhang D 2018 [48], with 43 women desiring fertility, examined transvaginal vs. laparoscopic niche repair, revealing similar conception rates. Bingqing 2018 [43], with 28 women desiring pregnancy, explored laparoscopy combined with hysteroscopic repair vs. hysteroscopy alone for niche repair, showing an improvement in pregnancy rates. However, no statistically significant difference was observed between the two surgical techniques. Istvan

2017 [46], with 15 secondary infertile women, investigated hysteroscopy-guided laparoscopic niche repair vs. hysteroscopic repair alone, resulting in an 80% pregnancy rate within 24 months of treatment. Tanimura 2015 [13], 22 infertile women, explored hysteroscopic vs. laparoscopic niche repair. Fourteen out of 22 women (63.6%) achieved pregnancy during the follow-up period, with pregnancies occurring in all four women (100%) who underwent hysteroscopy and in 10 of the 18 women (55.6%) who underwent laparoscopy.

Discussion

The studies revealed significant clinical, methodological, and statistical heterogeneity, adulterating the findings' validity and reliability, making it difficult to apply directly in clinical decision-making. However, as the secondary infertility associated with the uterine niche is an evolving area, the current study findings will give directions for further exploration as an eye-opener. The key impediment seems to be the lack of a universal definition for a uterine niche, making the study populations heterogeneous.

The incidence of secondary infertility

The incidence of secondary infertility in women with uterine niches ranged from 27.37% ($n = 95$) to 75% ($n = 16$). These values may not represent actual figures due to significant study heterogeneity. However, by analyzing the secondary infertility rates, we infer that women with a uterine niche are likely to experience a higher rate of secondary infertility.

The pathophysiological basis for infertility

Decreased RMT, inflammatory changes, and intracavity fluid altering uterine microenvironment are the key study findings suggesting a pathophysiological basis for secondary infertility in women with uterine niches. The muscular density of the residual myometrium covering the niche was relatively low, and it mainly contained fibrotic tissue, leading to poor contractility and fluid accumulation [36]. However, none of the studies had explored the role of prophylactic uterine niche correction in asymptomatic patients for improving fertility and obstetric outcomes. Histological evaluation revealed CD138 plasma cells in the resected specimens of the uterine niche. Intracavity fluid analysis revealed inflammatory factors like TNFα, IL-1β, and IL-6 [21]. These findings support the idea that some patients with uterine niches cannot be pregnant even if the intracavity fluid is aspirated, as the infiltrated inflammatory plasma cells are not removed through fluid aspiration [25]. The intracavity fluid causes infertility by impairing the quality of cervical mucosa, impairing sperm penetration, embryotoxicity, reducing endometrial receptivity through altered expression of cytokine cascade, cytotoxicity of iron in the blood, and acting as a mechanical barrier for implantation [13, 24, 36]. Iatrogenic adenomyotic tissue was also noted in resected niche specimens, further exacerbating the hostile intrauterine environment [20, 22]. Higher rates of obstructed fallopian tubes were also found in women with uterine niches, which may be due to trapped intracavity fluid [21]. The histological evaluation further revealed disorganized neovascularization at fibromuscular stromal edges of the uterine niche [42], which may explain the possible mechanism behind the re-accumulation of blood within the niche following aspiration and cleansing, suggesting bleeding is coming from the niche itself instead of trapping menstrual blood [13]. Intracavity fluid retention was not found following hysteroscopic niche resection despite a persisting cavity [13]. Intracavity fluid production positively correlates with the depth and circumference of the uterine niche and the distance from the niche to the external os [14]. These findings are inconsistent with the menstrual blood trapping theory The exact mechanisms for intracavity fluid accumulation are yet to be fully understood and will need further research. It is also possible that changed uterine environment, presence of intrauterine fluid may alter the microbiome and result in an unsuitable and toxic intrauterine environment for the implantation of embryo. And we could not find single study describing and comparing the microbuome in a uterine niche.

Impact on ART

It is possible that placing an embryo in an optimal position in embryo transfer is more challenging in the presence of a uterine niche. There was a scarcity of studies comparing operators' difficulty performing embryo transfers in the presence of a uterine niche. Zhang 2022 discussed the effects of uterine niche on single vs. double embryo transfer, revealing significantly lower clinical pregnancy and live birth rates only in the double embryo transfer group. However, exact pathophysiological explanations are not presented justifying the observations. No information is given regarding RMT and intracavity fluid accumulation [38].

Lawrenz 2019 found no significant differences between niche and control groups when intracavity fluid was absent in frozen embryo transfer success rates. They did not remove the intracavity fluid mechanically but conducted embryo transfer when intracavity fluid was absent. Not assessing the embryo transfer outcomes when intracavity fluid is present is one of the key limitations of the study, making it hard to conclude the role of intracavity fluid on ART. Moreover, the study was not primarily designed to look for causes of intracavity fluid accumulation during ovarian stimulation or to evaluate reproductive outcomes [14].

Mensi 2023 showed that a uterine niche significantly reduced clinical pregnancy and live birth rate compared to the control group. No surgical interventions were done for niche repair. They failed to identify any sonographic characteristics defining the IVF failure. The presence of intracavity fluid was 2.63% among the women with uterine niche ($n = 76$), hampering its clinical utility for discriminating the harmful effects of intracavity fluid on ART [2]. Low prevalence may be due to the time selected for testing after menstruation and before ovulation.

Diao 2021 found that implantation and live birth rates were significantly lower in the niche group compared to the control in younger females (≤ 35 years). The endometrial thickness in the niche group was significantly lower on the trigger day. However, these findings were not observed in women ≥ 35 years old. The possible explanation could be that the profound impact of age on IVF pregnancy outcomes exceeds that of uterine defects. They also compared these outcomes, subgrouping the niche group ($n = 74$) as a group with intracavity fluid ($n = 25$) and a group without intracavity fluid ($n = 49$), showing that fluid in the niche had no added detrimental effects on implantation [39]. In Yao 2022, those with a uterine niche ($n = 179$) had significantly lower live birth and implantation rates than those without a niche ($n = 2336$). In addition, it was also found to have significantly higher rates of early miscarriages in the niche group, which may be secondary to implantation close to or across a niche [40]. Disproportionate sample sizes make it hard to arrive at conclusions.

Cohen 2023 showed no statistical differences in clinical pregnancy, implantation, live birth, and preterm delivery rates in women with ($n = 30$) or without a uterine niche ($n = 30$). Moreover, there were no cases of cesarean scar pregnancy [41]. These findings are more controversial than those described in previous studies. Thus, various studies have highlighted differing results showing how a uterine niche can interfere with ART.

Efficacy of surgical interventions

Uterine niche resection through surgical techniques removing the entire scar tissue until myometrium is reached may enable thickening of the residual myometrium, normal endometrium development, and synchronization with the surrounding endometrial lining. Histological assessment of resected niche specimens reflected unsynchronized endometrial tissue development inside and outside the defect, resulting in an irregular bleed that hampers the accurate timing of the procedure concerning the menstrual cycle of each individual [30].

Hysteroscopic niche resection

Eleven studies investigated hysteroscopic niche resection with overall favorable outcomes in improving secondary infertility. Cohen 2017, a study with a relatively smaller sample size ($n = 8$), found that repeated hysteroscopic niche resections did not improve secondary infertility. The interval from first to second surgery ranged from 4 months to five years [26]. It needs to be re-investigated with a larger sample size regarding the timing between first and second surgeries, allowing an adequate time to assess pregnancy outcomes. In addition, it is also possible that a second surgery causes a greater tendency for complications due to remaining thinner myometrium following repeated resections.

Gubbini 2011 did not advise the participants to refrain from attempting to get pregnant for a specific period following hysteroscopic niche repair [33], while Tsuji 2022 allowed them to conceive two months after surgery [45]. None of the participants in each study had uterine rupture or cesarean scar pregnancy. Minimal duration from hysteroscopy to pregnancy is an important area for further discussion.

Abdou 2018, the only RCT included in the study, found that the clinical pregnancy rate is higher in hysteroscopic niche repair than in expectant management. A relatively smaller sample size ($n = 50$), unavailability of trial registration information, average quality according to RoB1, and a follow-up period of only a year diluted the practical applicability of its conclusions. However, conducting all surgeries by the same person and study primarily designed to assess pregnancy outcomes added more scientific validity, minimizing the risk of bias. None of the study participants had a uterine rupture. However, no information was reported regarding cesarean scar pregnancy and placenta previa [12].

Various studies have introduced different minimal RMT cut-off values for hysteroscopic niche repair, considering the risk of uterine perforation. Abdou 2018, Cohen 2020, Szafarowska 2021, and Chuqing 2023 proposed minimal cut-off RMTs as 3 mm, 2 mm, 2.5 mm, and 2.5 mm, respectively, referring to the literature [9, 12, 31, 35]. None of these studies reported cases of intraoperative uterine perforation. However, Tsuji 2020 conducted hysteroscopic niche resection even with an RMT of 1.3 mm without any uterine perforation [23]. Therefore, minimal RMT for hysteroscopic niche repair needs to be re-evaluated instead of merely moving with traditional figures mentioned in the literature.

Tsuji 2020 found a significant difference in pre-operative and two months post-operative RMT in pregnant and non-pregnant groups ($P < 0.001$) following hysteroscopic niche repair [23]. Baseline RMT differences between the two groups made it harder to appreciate the contribution of hysteroscopic niche resection on

RMT. In addition, the timing of optimal post-operative myometrial thickness remains unclear. The exact mechanism of myometrial thickening is also yet to be unraveled. Overall, following hysteroscopic niche repair, the above-discussed studies reported improved fertility outcomes with minimal cesarean scar pregnancy, uterine rupture, and placenta previa.

Laparoscopic niche resection

Kerampelas 2021 had a post-operative contraception period of three months following laparoscopic niche repair, allowing the scar to heal properly [32]. The study reported one case of placenta previa but no cases of uterine rupture. Exact contraceptive timing following laparoscopic surgery is an essential point of discussion. The same study described the evolution of RMT following surgery. One month post-operative RMT (7.8 ± 1.22) was significantly higher compared to baseline RMT (1.77 ± 0.86) ($P < 0.001$). RMT at six months post-operative (6.6 ± 1.81) was significantly lower than one-month post-operative RMT but significantly higher than baseline RMT. This may reflect the resolution of inflammatory changes at the surgical site, leading to an overestimation of RMT immediately after the surgery. Therefore, the RMT thickness may be accurate when measured around 3–6 months post-operatively to appreciate the therapeutic effect. It was also found that there was no significant difference between the mean RMT measured 3–6 months post-surgery and that measured after subsequent cesarean sections, highlighting the persistent effect of surgery [32].

Laparoscopy was preferred over hysteroscopy for correction of the niche, considering the risk of uterine perforation [22, 32, 36]. These studies considered different RMT cut-offs ranging from 2 to 3 mm. However, none of the studies could introduce a scientifically defined, universal RMT cut-off to decide the type of surgery. Hysteroscopic niche repair corrects the scar defect, ablating the fibrotic tissue, further decreasing the RMT and compromising the strength of the uterine wall [22]. In contrast, laparoscopic repair corrects the defect, reinforcing the uterine wall [36]. Thus, differing effects of surgical techniques on uterine myometrial endurance may necessitate the need to explore the timing of post-operative contraception for each surgery type.

Laparoscopy and hysteroscopy combined niche resection

Laparoscopy and hysteroscopy combined surgery may augment the efficacy through proper localization of the site and size of the uterine niche through hysteroscopic guidance. Hysteroscopy alone can miss conditions like endometriotic lesions/pelvic adhesions, which are readily resectable simultaneously during laparoscopic repair [46]. Therefore, combined surgery has added advantages compared to laparoscopy or hysteroscopy alone. RMT is not essential for determining whether the surgery is laparoscopy or hysteroscopy. Even if the RMT is low, hysteroscopic niche repair with limited operative time and surgical proficiency can help eliminate uterine perforation risk [43]. Some studies revealed the position of the uterus as a criterion for selecting the type of surgery. The women with straight or anteflexed uteri underwent hysteroscopic repair, while women with retroflexed uteri underwent laparoscopic repair. This may be due to easiness of the surgical procedure. During laparoscopy, the uterus was re-positioned as anteflexed. The proposed rationale for uterine re-positioning was the increased recurrence of uterine niche in retroflexed position owing to backflow of blood into the uterine cavity [13]. There is a growing need for standard criteria to select the ideal individualized surgical technique considering RMT, operative time, surgical proficiency, and uterus position.

Strengths and limitations

The study provides valuable insights regarding the association between uterine niche and secondary infertility through a comprehensive review of 35 studies. The quality assessment of the studies revealed an average to good quality, contributing to the findings' robustness. However, there is considerable methodological, clinical, and statistical heterogeneity among the studies, reducing the generalizability of findings and preventing the conduction of a meta-analysis. Lack of standardized surgical approach criteria, usage of varying niche definitions, differing durations of secondary infertility, varying sample sizes, non-uniform statistical reporting, non-exclusion of other factors contributing to secondary infertility, and different quality assessment ratings in studies with similar designs were the main contributors of study heterogeneity. Retrospective studies predominated the systematic review, introducing a high risk of bias due to reliance on pre-existing data. In addition, we had minimal RCT evidence contributed by only a single RCT with a small sample size.

Recommendations

Well-designed prospective studies with standardized methodologies are encouraged to deepen the understanding between uterine niche and secondary infertility. We have highlighted interesting conflicting points for further exploration throughout the discussion in which additional research is warranted. We also recommend that RCTs be used to assess the efficacy of different surgical techniques through comparison. There is a dire need for further systematic reviews and meta-analyses utilizing uniformly reported study data to draw definite conclusions and to update clinical practice guidelines.

Conclusion

The incidence of secondary infertility in women with uterine niches ranged from 27.37% ($n = 95$) to 75% ($n = 16$). Decreased RMT leading to poor uterine contractility, inflammatory cellular infiltrates at niche site, disorganized neovascularization at fibromuscular stromal edges of niche, and intracavity fluid rich in inflammatory factors altering uterine microenvironment are the key study findings suggesting a pathophysiological basis for secondary infertility in women with uterine niches supported by strong histopathological and biochemical evidence. In addition, pelvic adhesions, altered tubal patency, co-existing iatrogenic adenomyosis, and intracavity fluid production may play a role in contributing to niche-associated secondary infertility. However, these findings are supported by weaker evidence and warrants further exploration. When using ART, the implantation and live birth rates were lower in the niche group compared to the control. The role of the above-described pathophysiological mechanisms in ART is not well established and has led to controversy. Uterine niche resection through hysteroscopy, laparoscopy, or combined surgery, removing the entire scar tissue, may enable thickening of the residual myometrium, normal endometrium development, and synchronization with the surrounding endometrial lining, improving fertility outcomes. However, there are no well-defined standard criteria for selecting the best surgery type depending on the niche characteristics. Role of repeat surgery in niche resection, minimal duration of contraception from niche resection to pregnancy, RMT cut-off value for each surgery type, best timing of post-operative RMT assessment, risk of uterine perforation, cesarean scar pregnancy, and abnormal placentation following niche surgery are barely explained with evidence emphasizing the need for well-designed prospective studies. Therefore, the study findings can be used to get insights regarding areas to be re-explored rather than arriving at solid conclusions.

Abbreviations

ART	Assisted Reproductive Technology
DET	Double Embryo Transfer
FET	Frozen Embryo Transfer
IVF	In Vitro–Fertilization
NOS	Newcastle–Ottawa Scale
RCT	Randomized Controlled Trial
RMT	Residual Myometrial Thickness
RoB1	Cochrane risk–of–bias tool
SET	Single Embryo Transfer

Supplementary Information

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Additional file 1: Quality assessment of the studies.

Additional file 2: PRISMA 2020 checklist.

Additional file 3: Line-by-line search strategy.

Additional file 4: PROSPERO registration protocol.

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Author contributions

D.M.C.S.J. made substantial contributions to the conception and design of the study, supervised the data extraction process, and drafted the introduction and discussion sections. I.A.J. contributed significantly to the design and acquisition of data, performed title and abstract screening, and was involved in revising the manuscript. T.D.K.M.J. was responsible for the analysis and interpretation of the data, organizing it into tables, and drafting the methodology and results sections. S.D.S.W. contributed to the statistical analysis, assisted with data interpretation, and helped revise the methodology section.All authors have approved the submitted version of the manuscript, have agreed to be personally accountable for their contributions, and will ensure that any concerns regarding the integrity or accuracy of the work are appropriately investigated and resolved.

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Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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