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Effects of diabetes mellitus and cervical changes on scar healing after cesarean section

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Keywords
diabetes mellitus; niche; cesarean scar; residual myometrial thickness

Abstract

Aim: This study aimed to evaluate the effects of diabetes mellitus and cervical dilatation on cesarean section scar healing. **Material and methods:** This prospective study included pregnant women diagnosed with diabetes mellitus and healthy control pregnant women. The study group was divided into active labor and pre-active labor based on cervical dilatation, and the diabetic group was categorized into gestational diabetes and preexisting diabetes mellitus. Vaginal ultrasound was performed in the entire study group at six months postpartum, and the location of the cesarean scar was evaluated. **Results:** There were 170 participants in the study; 85 were diabetic, and the remaining 85 were healthy controls. Niche frequency in diabetes mellitus cases was not different from that in healthy controls ($p = 0.420$). The mean residual myometrial thickness, proximal residual myometrial thickness, and distal residual myometrial thickness were lower in the diabetic group ($p = 0.001$). Residual myometrial thickness and niche presence in the diabetic group with active labor was not statistically different from the diabetic group without active labor ($p > 0.05$). Additionally, residual myometrial thickness was thinner in the gestational diabetes mellitus group than in the preexisting diabetes mellitus group (3.61 ± 1.78 mm vs. 4.76 ± 2.82 mm, $p = 0.032$). **Conclusions:** There was no significant difference in niche frequency between diabetic cases and healthy controls. When comparing the gestational diabetes mellitus group and the preexisting diabetes mellitus groups, there was no difference in the presence of niches. Niche presence was more common in diet-regulated diabetic patients compared with the insulin-regulated group. Cervical dilatation at the time of cesarean section did not affect niche presence in diabetic cases.

Introduction

Cesarean section (CS) is the most frequently performed surgical procedure in the world, and its prevalence is increasing globally[1]. As there have been so many CSs in the last 20 years, there has been a growing awareness of both short-term and long-term morbidity following CSs[2]. One of these morbidities, a cesarean scar defect (niche), has been linked to several gynecological and obstetric problems. Uterine rupture and cesarean scar pregnancy are rare complications associated with niche, but their consequences can be catastrophic. The placement of the gestational sac in the niche is the precursor to the placenta accreta spectrum (PAS)[3].

A niche develops in about 60% of cases with prior CS. The rate varies depending on the methods and population[4]. An expert panel has recently defined niche as "an indentation with a minimum depth of 2 mm at an area of the CS scar."[5]. Ultrasound (USG) is utilized to diagnose a niche accurately[6]. Even though several risk factors have been suggested by retrospective and prospective studies, the exact risk of developing a niche remains unclear. The formation of a niche is significantly influenced by patient, labor, and surgical factors. Previous CS, obesity, hypertensive disorder, gestational diabetes (GDM), active labor, labor duration, short operative time, and the type of myometrial closure are known risk factors[7]. According to the International Diabetes Federation (IDF), one in six pregnancies is affected by diabetes mellitus (DM), with 13.6% of cases representing preexisting diabetes (PDM) and 86.4% representing GDM[8]. The increase in the coexistence of diabetes mellitus (DM) and CS has drawn attention to the impact of DM on wound healing. Multiple factors, such as specific metabolic deficiencies and impaired physiological reactions, inhibit wound healing.

There have been many conflicting studies on the effects of CSs performed with and without active labor on niche formation, but they have not been clarified. Feldman et al. reported that the incidence of niche is higher in planned cases than in unplanned cases, and that there is less residual myometrial thickness (RMT) in active labor cases, which may increase the risk of preterm delivery, uterine dehiscence, and uterine rupture in later pregnancy. Kamel et al. observed that cervical changes during labor did not affect the number of niches, but the niche was closer to the cervical canal in active labor[7,9,10].

Considering the potential risks associated with the presence of a uterine niche following CS, it is crucial to develop preventative strategies to decrease the risk of niche formation and avoid adverse outcomes. With this in mind, this study aimed to investigate the effects of DM and cervical dilatation, both of which are considered risk factors for niche formation, on CS scars in first-time cesarean cases.

Material and method

Study design and setting

Pregnant women diagnosed with DM and healthy control pregnant women who were followed up at the Necmettin Erbakan University Faculty of Medicine Hospital in Turkey between May 2021 and May 2023 were included in this prospective study. The study was designed to evaluate the effects of cervical changes on CS scars and niche formation in pregnant women with DM and healthy pregnant women. Ethical approval for this study was obtained from the university's ethics committee (Ethical Approval No. 2023/4375; ID: 14112). The study complied with the Helsinki Declaration, and written informed consent was obtained from all patients.

Patient selection

All pregnant participants in the study were carrying singletons. It was the first CS performed in a tertiary center, either elective or unplanned, for various reasons (cephalopelvic incompatibility, presentation anomalies, labor arrest). The control group was formed by randomly matching low-risk patients who were followed during the same period. Twin pregnancies, pregnancies in women under the age of 18 and above the age of 45, pregnancies with anomalies, history of uterine surgery, previous CS, PAS, in vitro fertilization pregnancies, smokers, those on immunosuppressive drugs, hypertensive disorders during pregnancy, postpartum infections, and chorioamnionitis cases were excluded from the study.

After performing a 75-gram oral glucose tolerance test (OGTT) according to the American Diabetes Association guidelines at 24–28 gestational weeks, when one of the fasting, 1st, or 2nd-hour blood glucose values exceeded the threshold, it was recorded as GDM (fasting 92 mg/dl, postprandial 1st hour 180 mg/dl, postprandial 2nd hour 153 mg/dl)[11]. PDM cases consisted of pregnant women who were diagnosed before pregnancy. Patients diagnosed with GDM in our clinic receive diet or insulin therapy after consultation with the endocrine department. We do not prescribe oral antidiabetic therapy to any of our pregnant PDM patients, we only follow up with insulin therapy.

A digital vaginal examination was performed to evaluate cervical dilatation before CS. The patients were divided into two groups based on their cervical dilatation during labor. Those with cervical dilation of 4 cm and above were considered in active labor, and those below were considered pre-labor. Cases with DM were divided into GDM and PDM. Then, a subgroup was formed of diet-regulated patients and insulin users. All patients were contacted by phone and scheduled for evaluation by vaginal ultrasonography six months after CS.

Surgical technique

Two surgeons (SD and KG) performed all CSs, using a Pfannenstiel incision to enter the abdomen and a lower segment Monroe Kerr incision. Scissors were used to create the bladder flap. The entire uterus was repaired primarily with continuous double-layer sutures (through the decidua) and No. 1 Vicryl sutures (Ethicon). There was no visceral and parietal peritoneal repair. Two grams of cefazolin were given 30 minutes prior to the operation. After the fetus was removed, 20 IU of oxytocin was administered intravenously.

Ultrasound examination

All examinations were performed with a 4–9 MHz transvaginal probe on a Voluson V8 Expert ultrasound machine (General Electric Medical Systems, Chicago, USA). Women underwent evaluation with an empty bladder while in the lithotomy position. The vaginal probe was gently inserted into the vagina. The examination was initiated after visualizing the internal and external os without applying pressure to the cervix. A niche can be described as an anechoic defect in the anterior wall of the lower uterine segment, connecting to the endometrial cavity (an indentation in one area of the CS scar with a minimum depth of 2 mm). After detecting a niche, RMT between the upper border of the niche and the uterine serosa was measured. The values of RMT and proximal RMT (on the fundal side closest to the end of the niche) and distal RMT (on the cervical side closest to the end of the niche) were measured in the midsagittal plane[12] (Fig. 1). In cases where no niche was observed, the CS

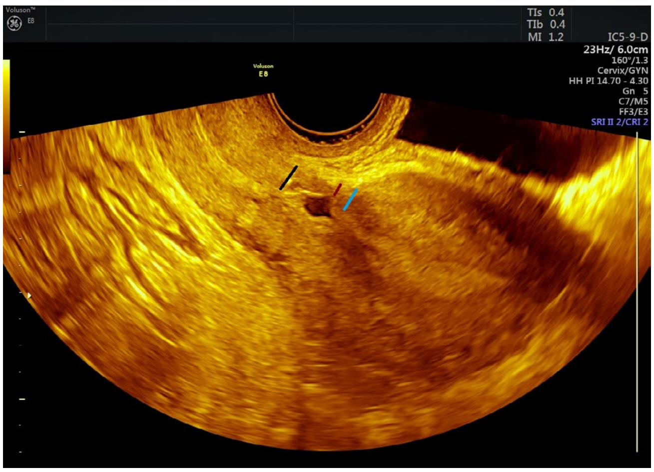

Fig. 1. *Cesarean section incision area healed with a niche. The red line indicates residual myometrial thickness (RMT), the blue line indicates proximal RMT, and the black line indicates distal RMT*

area that healed leaving a fibrotic scar (a hyperechoic area where the continuity of the uterine tissue was lost), was evaluated. RMT was measured above, proximal to, and distal to the fibrotic area (Fig. 2). All USG measurements were performed by one person (SD).

Statistical analyses

The data were analyzed using SPSS 26 (Statistical Package for Social Sciences) (IBM, Armonk, N.Y., USA). The conformity of the variables to normal distribution was analyzed using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk Test). For the comparison of groups, independent t-test was used for paired groups, one-way analysis of variance (one-way ANOVA) was applied for multiple groups, and post-hoc (Bonferroni) test was used for normally distributed continuous data. For non-normally distributed numerical data, the Mann-Whitney U test was applied for paired groups and the Kruskal-Wallis test was used in multiple groups. The Pearson chi-square test and Fisher's exact test were applied for the evaluation of categorical variables. $P < 0.05$ was accepted as statistically significant. We performed a post hoc power analysis to determine the statistical power of the study. With the significance level (α) at 0.05 and the sample size at 85 for each group, the power of the study was found to be 0.99. This means that we had a very high chance of detecting a significant difference, if one existed, between the means of the two groups.

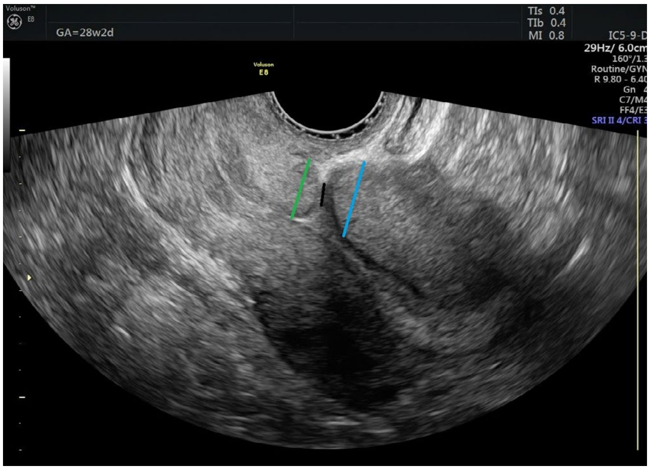

Fig. 2. *Cesarean scar incision area healed with fibrosis. The black line indicates residual myometrial thickness (RMT), the blue line indicates proximal RMT, and the green line indicates distal RMT*

Results

The study included 170 pregnant women, of whom 85 had diabetes, while the remaining 85 were healthy controls.

Evaluation of sociodemographic and cesarean scar characteristics of study groups

The mean maternal age at the time of CS was 31.15 years (standard deviation (SD) ± 4.77) in the DM group and 28.48 years (SD ± 5.76) in the control group ($p = 0.0001$). The mean body mass index (BMI) was higher in the diabetic group compared to the control group (32.5 ± 4.70 vs. 28.68 ± 4.78, $p = 0.0001$). The mean RMT, proximal RMT, and distal RMT were lower in the diabetic group ($p = 0.001$). A niche was identified in 27 (31.8%) patients in the diabetic group and 32 (37.6%) patients in the control group, but this difference was not statistically significant ($p = 0.420$). In the diabetic group, 64 (75.3%) cases were GDM and 21 (24.7%) cases were PDM. Regarding treatment, 43 (50.6%) were followed by diet, and 42 (49.4%) were followed by insulin (Tab. 1).

Tab. 1. Evaluation of sociodemographic and cesarean scar characteristics of study groups

		Diabetes group (*n* = 85)	Control group (*n* = 85)	*p*
Maternal age (year)		31.15 ± 4.77	28.48 ± 5.76	**0.0001¥**
Gestational age (week)		37.40 ± 1.94	37.72 ± 2.21	0.315Φ
BMI (kg/m²)		32.5 ± 4.70	28.68 ± 4.78	**0.0001Φ**
Fetal weight (gram)		3307.69 ± 671.17	2905.24 ± 704.20	**0.001¥**
RMT		3,90 ± 2,12	6,73 ± 4,00	**0.0001Φ**
Proximal RMT		7,09 ± 2,36	11,12 ± 4,14	**0.0001Φ**
Distal RMT		6,95 ± 2,00	9,25 ± 3,55	**0.0001¥**
Niche positivity		27(31.8%)	32 (37.6%)	0.420ψ
Weight gain (kg)		14.6 ± 8.4		
Diabetic status	**GDM**	64 (75.3%)		
	PDM	21 (24.7%)		
Treatment method	**Diet**	43 (50.6%)		
	Insulin	42 (49.4%)		

Values are given as mean + SD and n (%).
ΦIndependent t-test; ¥Mann-Whitney U test; ψChi-square test
GDM – gestational diabetes mellitus; PDM – preexisting diabetes mellitus; RMT – residual myometrial thickness

Evaluation of the CS area in the study group based on cervical changes

Based on the changes in the cervix, there were 29 (34.12%) CSs in active labor and 56 (65.88%) pre-labor CSs in the DM group. In the control group, there were 35 (41.18%) pregnant women with CS in active labor and 50 (58.82%) pregnant women with pre-labor CS. However, RMT after active labor or pre-labor CS was not statistically different in the DM group (4.35 ± 2.40 mm vs. 3.66 ± 1.95 mm, p >0.05). RMT after active labor or pre-labor CS in the control group was statistically different (5.13 ± 2.57 mm vs. 7.85 ± 4.45 mm, p = 0.0001) (Fig. 3). Niche presence was not statistically different according to cervical changes in either group (Tab. 2). RMTs of the niche positive and niche negative groups in the diabetic group were not different (3.69 ± 2.10 mm vs. 3.99 ± 2.14 mm, p = 0.550) (Tab. 3).

Evaluation of CS area depending on diabetes type and treatment

According to DM types, RMT was thinner in the GDM group than the PDM group (3.61 ± 1.78 mm vs. 4.76 ± 2.82 mm, p = 0.032). All patients with PDM used insulin. The presence of niche did not differ between the GDM and PDM groups. When the presence of niche in the DM group was evaluated, it was found to be higher in the diet-regulated group than in the insulin-treated group (p = 0.043) (Tab. 4). The presence of diabetes had a significant negative impact on RMT. This effect is −2.704 beta coefficient, −0.388 standardized beta coefficient, and p = 0.001. In contrast, other factors such as age, body mass index (BMI), and fetal weight did not show a statistically significant association with RMT (p = 0.693, p = 0.997, and p = 0.222, respectively) (Tab. 5).

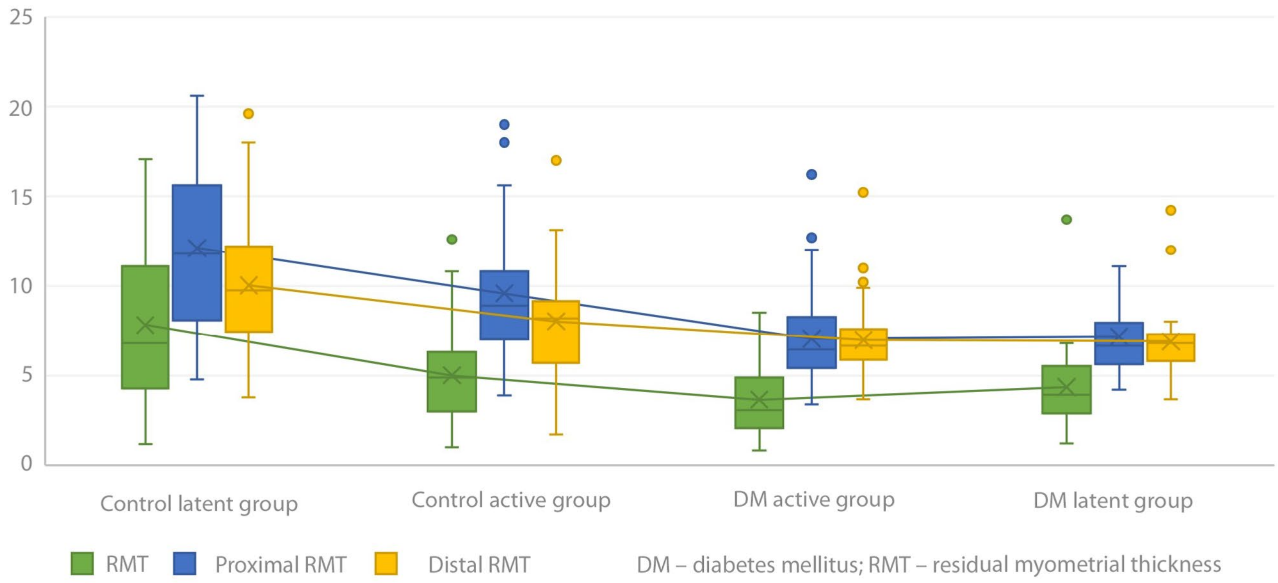

Fig. 3. *Residual myometrial thickness (RMT), proximal RMT, and distal RMT values of the entire study group based on cervical changes*

Tab. 2. Evaluation of cesarean section area in the study group according to cervical changes

Parameters		DM active labor (n = 29)	DM latent labor (n = 56)	Control active labor (n = 35)	Control latent labor (n = 50)	p
Age		30.03 ± 4.80	31.73 ± 4.70	27.94 ± 5.02	28.86 ± 6.25	**0.005***
Gestational week		37.47 ± 2.45	37.36 ± 1.65	38.27 ± 2.46	37.33 ± 1.95	0.150*
Fetal weight		3350.41 ±739.97	3285.57 ±638.56	2835.57 ±763.50	2954.20 ± 663.08	**0.002***
BMI		31.78 ± 2.41	32.94 ± 5.51	29.32 ± 5.10	28.24 ± 4.54	**0.0001***
Fetal position	**Vertex**	29 (100%)	54 (96.4%)	28 (80.0%)	43 (86.0%)	**0.011ᵠ**
	Breech	0 (0%)[a]	2 (3.6%)[a]	7 (20.0%)[b]	7 (14.0%)[a]	
Niche positivity		9 (31.0%)	18 (32.1%)	15 (42.9%)	17 (34.0%)	0.712ᵠ
RMT		4.35 ± 2.40	3.66 ± 1.95	5.13 ± 2.57	7.85 ± 4.45	**0.0001***
Proximal RMT		7.17 ± 2.43	7.05 ± 2.34	9.65 ± 3.44	12.16 ± 4.31	**0.0001***
Distal RMT		6.90 ± 2.00	6.98 ± 2.02	8.09 ± 3.04	10.06 ± 3.69	**0.0001***

Values are given as mean+SD and n (%).
* One-way ANOVA (post-hoc Bonferroni test); ᵠ Chi-square test
If the superscript letters are the same (a-a), there is no statistical difference; if they are different, (a–b) there is a statistical difference between them.
DM – diabetes mellitus; GDM – gestational diabetes mellitus; RMT – residual myometrial thickness

Tab. 3. Distribution of myometrial thicknesses according to niche presence

	DM group (*n* = 85)		*p*	Control group (*n* = 85)		*p*
	Niche(+) (*n* = 27)	Niche(−) (*n* = 58)		Niche(+) (*n* = 32)	Niche(−) (*n* = 53)	
RMT	3.69 ± 2.10	3.99 ± 2.14	0.550$^{\phi}$	5.39 ± 3.74	7.53 ± 3.96	**0.016$^{\phi}$**
Proximal RMT	7.37 ± 2.77	6.95 ± 2.15	0.447$^{¥}$	10.73 ± 3.43	11.36 ± 4.53	0.474$^{\phi}$
Distal RMT	7.23 ± 2.24	6.82 ± 1.88	0.381$^{¥}$	8.77 ± 2.09	9.53 ± 4.19	0.265$^{¥}$

Values are given as mean + SD and n (%).
$^{\phi}$Independent t-test; $^{¥}$Mann-Whitney U test
RMT – residual myometrial thickness; DM – diabetes mellitus

Tab. 4. Evaluation of cesarean scar area according to diabetes type and treatment

	PDM (*n* = 21)	GDM (*n* = 64)	*p*
RMT	4.76 ± 2.82	3.61 ± 1.78	**0.032$^{\phi}$**
Proximal RMT	7.96 ± 3.09	6.80 ± 2.02	0.118$^{¥}$
Distal RMT	7.85 ± 2.68	6.66 ± 1.64	**0.017$^{\phi}$**
Niche positivity	5 (23.8%)	22 (34.4%)	0.367$^{\psi}$
	Diet therapy group (*n* = 43)	**Insulin therapy group (*n* = 42)**	***p***
RMT	3.47 ± 1.50	4.33 ± 2.55	0.198$^{¥}$
Proximal RMT	6.72 ± 1.71	7.45 ± 2.85	0.370$^{¥}$
Distal RMT	6.82 ± 1.62	7.08 ± 2.33	0.930$^{¥}$
Niche positivity	18 (41.9%)	9 (21.4%)	**0.043$^{\psi}$**

Values are given as mean + SD and n (%).
$^{\phi}$Independent t-test; $^{¥}$Mann-Whitney U test; $^{\psi}$Chi-square test
PDM – preexisting diabetes mellitus; GDM – gestational diabetes mellitus; RMT – residual myometrial thickness

Tab. 5. Multivariate linear regression analysis of the effects of demographic and clinical characteristics on RMT

	Beta	SE	β	95 % CI	*p*-value
Age	0.019	0.049	0.030	−0.077 – 0.116	0.693
BMI	0.001	0.054	0.001	−0.107 – 0.107	0.997
Fetal weight	0.001	0.001	−0.091	−0.001 – 0.001	0.222
Presence of diabetes	−2.704	0.557	−0.388	−3.803 – −1.604	**0.001**

RTT – residual myometrial thickness; BMI – body mass index

Discussion

In this study, although the presence of niche did not differ in CS deliveries with a history of DM compared to healthy controls, RMT, as well as proximal and distal RMTs, were lower in the diabetic group. RMT was lower in the GDM group, and niche presence was higher in cases with a history of diet-regulated diabetes. This study also showed that cervical dilatation did not affect RMT or the presence of niche in the group with a history of diabetes.

The increasing number of CSs in the world is associated with an increase in placenta previa, CSP, PAS, and uterine rupture rates in subsequent pregnancies. Changes in uterine anatomy following CS seem to be responsible for complications in subsequent pregnancies[13]. Therefore, it is essential to evaluate the anatomical healing in the surgical area after CS. In the study by Naimi et al., it was found that 5.5% of women did not show myometrial defects after CS, while 94.5% experienced a loss of myometrial tissue in the scar area, with the mean RMT of 55.5%. In the same study, 11% of cases healed with fibrosis, 45% with niches, and the remaining cases demonstrated an association between niche presence and scarring. Niche represents an interruption and disruption of the endometrial layer, while fibrosis represents an interruption of the serosal tissue. The presence of a niche increases the tendency to develop PAS in the next pregnancy, while fibrotic interruption in the serosa causes a decrease in the protective support of the serosa for the uterine myometrium, which becomes thinner under increased pressure as gestational weeks advance[14].

An indirect indicator of uterine scar healing is RMT, which is also used to predict unfavorable obstetrical outcomes, particularly uterine rupture associated with the uterine scar[15]. There are conflicting reports regarding the relationship between RMT, CS scar healing, and labor onset. Some studies indicate that cesarean delivery has a negative effect on scar healing during advanced labor[16,17], while others show a positive correlation between RMT and the degree of cervical dilatation before CS[18]. In some studies, no difference was observed in RMT between planned and unplanned cesarean sections; however, they found that the scar was closer to the uterine cavity in elective CSs[19]. In this study RMT was shorter in the diabetes group compared to the control group, but in both GDM and PDM cases, RMT was unaffected by cervical dilatation. RMT was also reduced in cases of active labor in the control group. When a CS incision is made in the lower uterine segment, the incision line occurs in the myometrium, which is thin and poorly vascularized. The placenta could develop in this delicate and avascular area during the early stages of a subsequent pregnancy[20]. A significant risk factor for the formation of large niches has been identified as having lower uterine incisions[21]. Upper uterine incisions are sufficiently vascularized, thick, free of fibrous tissue, and free of infection. This could minimize the likelihood of abnormal placentation in subsequent pregnancies[22].

Numerous factors influence the healing of RMT and CS scars, including obesity, infection, smoking, DM and previous CS counts, labor phase, and surgical suturing techniques. Uterine vascular problems can impair wound healing[23]. Since studies were conducted in a study group with all of these factors, information on the effects of a single factor in isolation is limited. In previous studies, obesity and diabetes were not identified as risk factors for niche formation[18,24]. Budny-Wińska *et al*. evaluated the impact of pregnancy-related medical conditions on uterine niche development. They found no association between GDM and the prevalence and parameters of niches[25]. In the study by Antila et al., the effects of many parameters on niche formation were evaluated. It was reported that the presence of GDM increased the formation of niches, but it was not associated with PDM niche formation[26]. In the same study, it was found that cervical dilatation did not affect niche formation.

The finding that the presence of DM did not affect niche formation compared to normal healthy controls in our study suggests that factors not excluded in other studies act as cofactors in niche development. In both control and diabetic pregnancies, cervical dilatation did not affect niche formation. In the diabetic group, RMT decreased regardless of cervical dilatation. In our study, the presence of diabetes alone was associated with a decrease in RMT after adjusting for age and BMI. The niche numbers were not different when the GDM and PDM groups were compared; however, RMT was lower in the GDM group. While all PDM cases were treated with insulin, a greater proportion of GDM cases had their blood sugar regulated by diet, and niches were more prevalent in this group. This led us to consider that dietary regulation may complicate blood glucose monitoring and lead to impaired healing of CS scars. Alterations in carbohydrate, fat, and protein metabolism induced by the absence or deficiency of insulin, reduced circulation as a result of osmotic diuresis, low pH, high lactate concentration, low fibroblasts, and free radicals inhibit wound healing by interfering with collagen formation[27]. Patients diagnosed with GDM and PDM underwent scar evaluation at six months postpartum. We think that not only sugar regulation during pregnancy but also postpartum blood sugar monitoring and lifestyle choices significantly affect scar healing. Despite consensus among multiple professional societies regarding the usefulness and recommendation of postnatal glucose screening in those diagnosed with GDM during pregnancy, low patient compliance persists. Reasons for this include patient fears, provider misunderstandings, and confusion regarding guideline changes[28]. In addition, women who had previously undergone diet-controlled GDM were found to have a threefold increased risk of developing metabolic syndrome compared to age-matched controls in a Danish study[29]. All these factors underscore the need for prospective studies with more participants to determine niche frequency and low RMT in patients with GDM.

The limitations of our study include the small sample size, the lack of comparison with different suture techniques used in the uterus, the failure to evaluate the duration of active labor, and the fact that blood glucose and HbA_{1c} values during pregnancy were not included in the study.

Conclusion

Niche frequency in diabetic cases was not different from that in healthy controls. Low RMT was observed in GDM cases, and an increased niche risk was observed in diet-regulated cases. Cervical dilatation at the time of cesarean section did not affect niche presence in diabetic cases. The shorter RMT in diabetic cases compared to controls should raise awareness among care providers regarding the location of pregnancy in subsequent pregnancies. There is a lack of evidence regarding future obstetric outcomes in these patients.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: SD. Writing of manuscript: SD. Analysis and interpretation of data: HE, FA. Collection, recording and/or compilation of data: HE, FA, FKY, ECA. Critical review of manuscript: SD, KG.

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