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Predictive Value of MiR-192-5p for Complications after Caesarean Section with Scarred Uterus

Yang Fan,[1,*] Huiling Qin,[2,*] Lei Ma,[3] Li Bian,[3] Biao Zhao[4] and Wei Zeng[5]

[1]People's Hospital of Ningxia Hui Autonomous Region, Ningxia Medical University, Ningxia, China
[2]Department of Rehabilitation Medicine, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China
[3]Department of Obstetrics, The People's Hospital of Bozhou, Bozhou, China
[4]Department of Emergency, The People's Hospital of Bozhou, Bozhou, China
[5]Department of Obstetrics, Hubei Provincial Hospital of Traditional Chinese Medicine, Affiliated Hospital of Hubei University of Chinese Medicine, Wuhan, China

The risk of a second caesarean section with scarred uterus has attracted attention, and this study aimed to find a molecular marker to assist physicians in prenatal screening to better predict postpartum complications. Serum miR-192-5p expression was determined by qRT-PCR and 145 subjects were divided into low expression group (76) and high expression group (69) based on the miR-192-5p levels. The Receiver Operating Characteristic curve (ROC) was plotted with pelvic floor dysfunction (PFD) score, vaginal microecological environment status, and the occurrence of serious complications occurred as dependent variables. miR-192-5p expression was the test variable. Significant differences were found between the high and low MiR-192-5p expression groups in postpartum class I, class II muscle fiber strength, PFD score ($p < 0.01$), postpartum vaginal leukocyte esterase ($p < 0.001$), sialyl glycosidase ($p = 0.010$), acetylglucosaminidase ($p = 0.024$), and severe complications ($p = 0.001$). The ROC for predicting PFD showed an AUC of 0.861. The ROC for predicting vaginal microecological environment showed an AUC of 0.934. The ROC for predicting serious complications showed an AUC of 0.882. MiR-192-5p has the potential to be an adjunctive preoperative screening marker for cesarean section in patients with scarred uterus and has potential value in predicting the occurrence of complications after cesarean section, including PFD, vaginal microecological disorders, postoperative hemorrhage, abdominal incision infections, puerperal infections.

Keywords: caesarean section; complications; miR-192-5p; predictive; scarred uterus
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Introduction

With the progress of medical treatment, the number of patients choosing caesarean section has increased, leading to a higher the incidence of scarred uterus after scarred these procedures (Hoxha et al. 2017). Recently, following the implementation of the two-child policy, the rate of second pregnancy among women with a scarred uterus has risen (Sorrentino et al. 2022). At present, a scarred uterus remains a primary reason for caesarean section. However, studies have shown that scarred uterus is prone to multiple complications during caesarean section again, including pelvic floor dysfunction (PFD), vaginal microecological disturbance, postpartum haemorrhage, infection (Barbosa et al. 2013; Huser et al. 2017; Baud et al. 2020). These issues pose long-term risks for gynaecological diseases in patients, seriously jeopardized the quality of life and mental health of pregnant women, and further complicating the clinical work of obstetricians. Unfortunately, no effective and non-invasive technique has been found to predict the complications after caesarean section in women with a scarred uterus.

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*These authors contributed equally to this work.
Correspondence: Wei Zeng, Department of Obstetrics, Hubei Provincial Hospital of Traditional Chinese Medicine, Affiliated Hospital of Hubei University of Chinese Medicine, No. 856, Luoyu Road, Wuhan 430070, China.
e-mail: zengwei19870103@163.com

With the development and application of high-throughput sequencing technology, the application of microRNA (miRNA) detection for disease diagnosis and treatment has been gradually revealed. Changes in miRNA expression can help predict a patient's disease progression and create individualized treatment plans accordingly (Ning et al. 2016; Donkers et al. 2021; Liu et al. 2023). MiR-330-3p is effective in predicting the prognosis of patients with gestational diabetes mellitus, which is closely linked to the incidence of primary caesarean sections (Sebastiani et al. 2017). Detection serum miR-200a-3p levels is a good predictor of pregnancy outcomes in patients with gestational hypertension and assists doctors create personalized treatment plans (He and Ding 2022). This highlights the significant value of miRNA in predicting pregnancy outcomes and aiding in the development of pregnancy treatment protocols. Therefore, this study aims to find a miRNA that can help doctors predict the complications after caesarean section in women with scarred uterus. This would help determine more appropriate treatment plans, avoid further development of the disease, and reduce the risk of complications in pregnant women. MiR-192-5p has been found to play an important role in many human diseases. It can be used as a predictor of chemotherapy efficacy for oesophageal cancer (Furuke et al. 2023), assisting both doctors and patients in planning treatment. MiR-192-5p also has high application value in the diagnosis acute hepatitis and prediction drug therapy efficacy (Harms et al. 2020). Recent studies have shown that miR-192-5p is involved in scar formation regulation and is aberrantly expressed during pregnancy (Liang et al. 2020; Li et al. 2021). Therefore, it is speculated that miR-192-5p may have value in prediction complications after caesarean section in women with scarred uterus. In addition, Yang et al. (2023) found that abdominal scar score correlated with PFD, vaginal microecological environment, postoperative bleeding, infection and other complications. Based on this, this study speculates that miR-192-5p could predict postoperative complications such as PFD, vaginal microecology, postoperative bleeding, and infection after caesarean section with scarred uterus.

These complications seriously affect women's healthy, making it important to find an efficient and non-invasive prediction method. This would help in planning suitable delivery methods and postoperative care and rehabilitation programmed for patients. In this study, the occurrence of postoperative complications in patients with scarred uterus and the expression level of miR-192-5p in serum were collected. The predictive value of miR-192-5p for postoperative complications after caesarean section with scarred uterus was preliminarily investigated, with a view to providing a more reasonable treatment plan for patients.

Materials and Methods

Study subjects

Initially, 459 pregnant women with scarred uterus who underwent caesarean sections in Bozhou People's Hospital from 2017 to 2018 were collected for this study. Screening was performed according to the specific criteria, and 145 patients were finally identified to participate. This retrospective cohort trial aimed to collect information about the occurrence of postoperative complications after caesarean section with scarred uterus. The baseline data of the patients were obtained from medical databases, hospital computer records, and case notes including age, BMI, duration of surgery, gestational weeks, abdominal scar score, postpartum haemorrhage, puerperal infection, abdominal incision infection, pelvic floor muscle function status and laboratory indicators related to the vaginal microenvironment in the 6-8 weeks postoperative period.

Inclusion criteria: (1) Gestational age is 36-41 weeks. (2) All are second pregnancies, with the first being a caesarean section. (3) There is a two-year gap between this pregnancy and the last one. (4) Patients have complete medical records.

Exclusion criteria: (1) The woman has a history of other types of abdominal surgery. (2) Pregnant women unable to voluntarily cooperate with researchers to complete the survey. (3) The mother has serious heart, liver, kidney and other diseases. (4) The mother had chronic diseases such as bronchitis, asthma, or diabetes before pregnancy. (5) There were complications such as hematoma and poor wound healing after the first cesarean section. (6) Abnormal development of the fetus, fetal distress, macrosomia, maternal pelvic anomalies, cephalopelvic disproportion, soft birth canal abnormalities, vaginitis before delivery and other symptoms. (7) Pregnant women with contraindications to epidural anesthesia such as coagulation abnormalities, local or systemic infections, overt or covert hemorrhage, severe underlying diseases, or drug allergies. (8) Pre-pregnancy incontinence, pelvic organ prolapses, or pelvic surgery history. (9) Patients with long-term increased abdominal pressure or emergency deliver.

All the researchers included in this study signed informed consent voluntarily, and this study was conducted in compliance with the approval and supervision of the Ethics Committee of The People's Hospital of Bozhou. This study was conducted in accordance with the Declaration of Helsinki and relevant Chinese laws and regulations.

Abdominal scar score

The abdominal scar status of all pregnant women was evaluated by patient and observer scar Assessment Scale (POSAS) (Ekin et al. 2018). Blood vessel distribution, color, thickness, surface roughness, softness and surface area were scored independently and averaged by 3 physicians. Pain degree, itching degree, color, thickness, softness, and self-perception are to be filled in by the patient. Each parameter is scored from 1 to 10, with 1 representing normal and 10 representing the worst condition. The lower the score, the better the scar skin condition.

Pelvic floor function rehabilitation

At 6-8 weeks postpartum, the muscle fiber strength of postpartum women was quantitatively measured with PHENIX USB8 neuromuscular stimulation therapy instrument, a French innovative electronic concept company. Pelvic floor muscle class I and II muscle fibers contracted for 0-5s, which corresponded to muscle strength class 0-V in that order, and a duration of 5s was considered normal muscle strength. Pelvic floor Distress Scale (PFDI-20) was used to score pelvic floor symptom-related dysfunction in patients. The PFDI-20 score was 0-300 points and consisted of 20 items and 3 subscales. The higher the score, the more severe the symptoms of PFD. According to the PFDI-20 total score, patients were classified as having mild (PFDI-20 total score ≤ 100) or moderate and severe (PFDI score > 100) PFD (Singh et al. 2019).

Vaginal microecology

Within 6-8 weeks after delivery, vaginal secretions were collected from the upper 1/3 wall of the vagina, and vaginal microecology was detected within 30 minutes. The secretions were stained with gram, and then the potential of hydrogen (PH), catalase (H_2O_2), leukocyte esterase (LE), sialyl glycosidase (SNA), β-Glucuronidase (βGD), acetylglucosaminidase (NAG) level were detected by bd-500 vaginal microecological detector and vaginal microecological test kit (The intra-assay coefficient of variation was < 10%, and the inter-assay coefficient of variation was < 15%. As reported by the manufacturer, the assay has a sensitivity of < 1 pg/ml, is highly specific and does not cross over with other structural analogues). According to the Expert Consensus on the Clinical Application of Vaginal Microecological Evaluation (Hu et al. 2015), each indicator is divided into normal and abnormal, the normal range of vaginal pH value is 3.8-4.5; if other indicators test positive, it is considered abnormal. When any of the above indicators are abnormal, they are recorded as vaginal microecology abnormal, and none of the abnormalities is normal vaginal microecology.

Serious complication

Postpartum hemorrhage, puerperal infection and abdominal incision infection were observed and recorded. Participants were divided into two groups according to the occurrence of complications. Group yes: The occurrence of any of the above complications was classified as complications; Group no: No complications occurred.

miR-192-5 expression assay

Fasting blood samples were collected from patients 2 h before delivery, and the supernatant (serum) was obtained after centrifugation and stored at –80°C. Total RNA was isolated from preserved serum using Trizol reagent (Lianmai Biotechnology Co., Ltd., Shanghai, China), purified according to the instructions of the Ultra-Pure RNA Kit (Lianmai, Shanghai, China), reverse transcribed using the miRNA PCR kit (Takara, Biotechnology, Co., Ltd, Dalian, China), and then detected by qRT-PCR (Lianmai, Shanghai, China). Finally U6 was used as an internal reference for miR-192-5p, and the expression was calculated by using $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

Data were analyzed using SPSS 23.0 statistical software. The distribution of continuous variables were determined by the Kolmogorov-Smirnov test. At the test level of $\alpha = 0.05$, $P > 0.05$, the data were considered to follow a normal distribution. Normally distributed variables were expressed as mean ± standard deviation, and an independent samples t-test was performed. Non-normally distributed data were expressed as median (25th-75th percentiles) and Mann-Whitney U-test was utilized. Categorical variables are expressed as a percentage (%) and analyzed using chi-square test. If the chi-square test validity condition was not satisfied (theoretical number < 5), the Fisher exact test was used. For correlation analysis, Pearson correlation analysis was used for the parameters distributed with normally distribution and Spearman correlation analysis should be used for the parameters distributed with non-normally distribution. A Receiver Operating Characteristic (ROC) curve assessed the predictive usefulness of miR-192-5p in PFD, vaginal microecology, and complications following cesarean section was assessed. A difference of $p < 0.05$ was considered statistically significant.

Results

Correlation between miR-192-5p and pregnancy scar in pregnant women

The flowchart of this study is shown in Fig. 1. The abdominal scar score of patients undergoing cesarean section was found to be negatively correlated with the prenatal serum miR-192-5p expression ($r = –0.8254$, $p < 0.0001$, Supplementary Fig. S1), indicating that the more severe the scarring, the lower the expression of miR-192-5p. Patients were divided into high and low expression groups based on the mean value of miR-192-5p expression in their prenatal serum, as shown in Table 1, and there was no significant differences in age, BMI, Gestational weeks or Operation time between the two groups ($p > 0.05$).

Predictive value of miR-192-5p on pelvic floor muscle function

It was found that women in the low-miR-192-5p and high-miR-192-5p groups were significantly different in terms of postpartum class I and class II muscle fiber strength and PFD score ($p < 0.0001$, Table 1). In addition, miR-192-5p expression level in serum of patients with moderate and severe impairment was significantly down-regulated (Fig. 2A). Using PFD as the dependent variable and miR-192-5p expression as the test variable, a ROC curve was constructed, and the AUC was found to be 0.861, the specificity was 81.3%, and the sensitivity was 82.7%

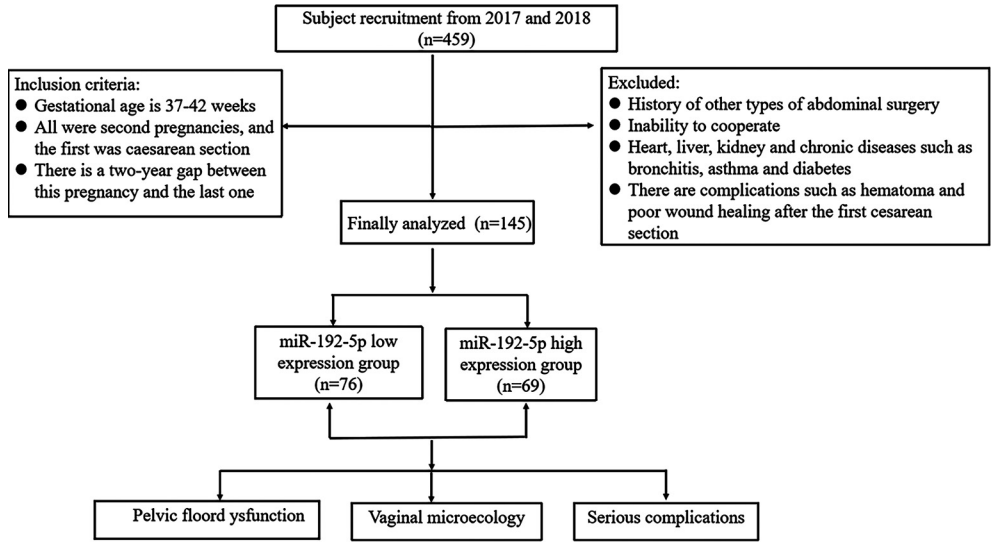

Fig. 1. Flowchart of miR-192-5p Expression Analysis for Predicting Post-Caesarean Complications in Scarred Uterus Patients.

Table 1. Basic information statistics of subjects.

Items	MiR-192-5p		F/χ2/Z	*P* value
	Low expression (n=76)	High expression (n=69)		
Age (years) median (25th-75th percentiles)	28 (26, 29)	28 (26, 30)	–0.663	0.507
BMI (kg/m^2) (Mean+SD)	25.26 ± 2.52	24.67 ± 2.66	0.019	0.164
Gestationl weeks median (25th-75th percentiles)	38 (38, 40)	38 (37, 39)	–1.203	0.229
Operation time (min) (Mean+SD)	84.43 ± 29.96	82.02 ± 27.00	2.245	0.613
Class I muscle fiber strength grade (n/%)			12.185	< 0.001
0 Level	4 (5.26)	18 (26.09)		
I Grade	8 (10.53)	16 (23.19)		
II Grade	10 (13.16)	12 (17.39)		
III Grade	12 (15.79)	9 (13.05)		
IV Grade	18 (23.68)	7 (10.14)		
V Grade	24 (31.58)	7 (10.14)		
Class II muscle fiber strength grade (n/%)			14.038	< 0.001
0 Level	1 (1.32)	14 (20.29)		
I Grade	6 (7.89)	15 (21.74)		
II Grade	7 (9.21)	10 (14.49)		
III Grade	16 (21.05)	11 (15.95)		
IV Grade	20 (26.32)	8 (11.59)		
V Grade	26 (34.21)	11 (15.94)		
Pelvic floor dysfunction score	128.5 (106,153.75)	63.0 (38.5, 75.0)	–10.381	< 0.001

BMI, body mass index.

(Fig. 2B). It indicated that miR-192-5p had a good predictive value for pelvic muscle floor function.

Prediction value of miR-192-5p in vaginal microecology in two groups of patients

Comparison of vaginal microecology between women in two groups with high or low expression of miR-192-5p revealed significant differences in the rates of abnormalities in LE ($p < 0.001$), SNA ($p = 0.010$), and NAG ($p = 0.024$) (Table 2). MiR-192-5p expression in the serum of patients in the abnormal group was significantly down-regulated (Fig. 2C). Using whether the vaginal microecology was normal or not as the dependent variable, miR-192-5p expression as the test variable, a ROC curve demonstrated the predictive value of miR-192-5p in abnormal vaginal microecology with the AUC of 0.934, the specificity of 94.5%, and the sensitivity of 84.4% (Fig. 2D).

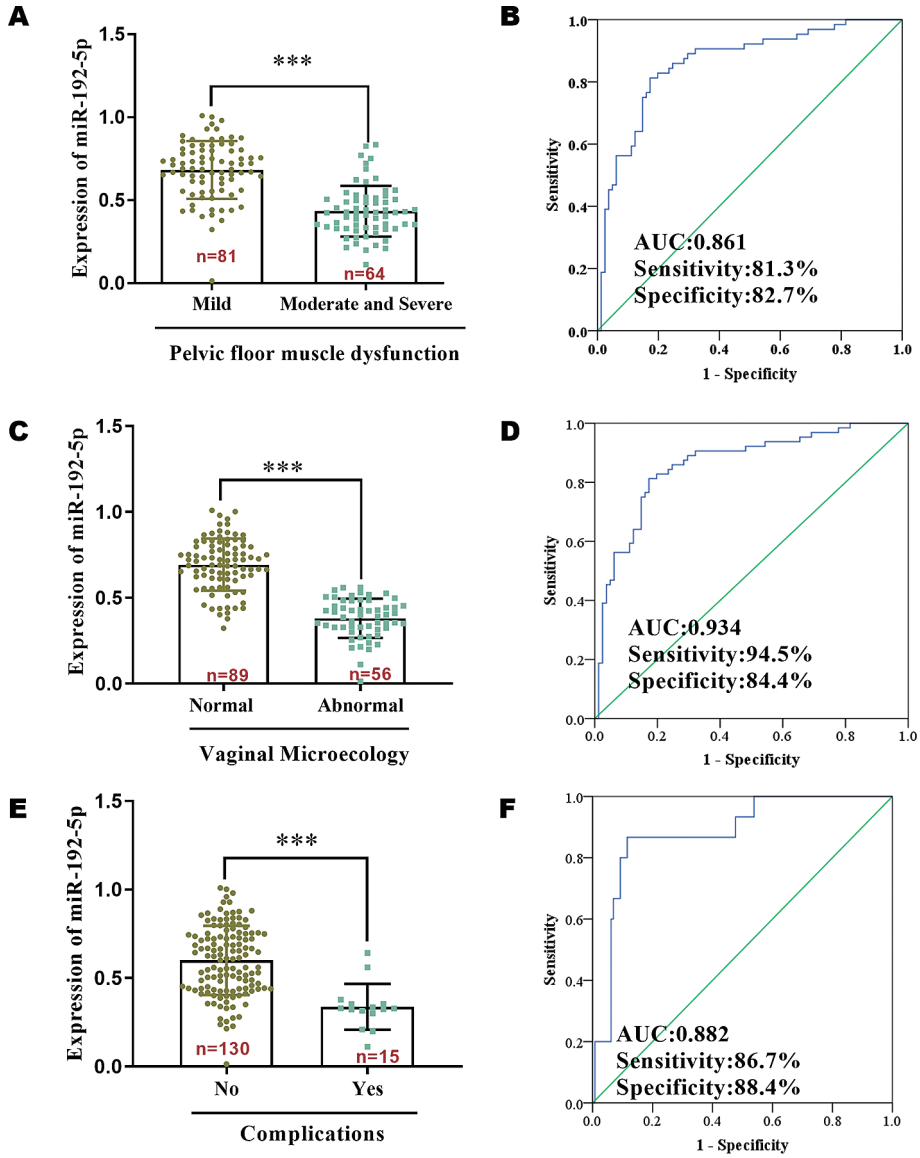

Fig. 2. Predictive value of miR-192-5p expression.
A, miR-192-5p expression was down-regulated in the moderately severe pelvic floor dysfunction group. B, miR-192-5p can better predict postpartum pelvic floor dysfunction. C, miR-192-5p expression was down-regulated in the group with abnormal vaginal microecology. D, miR-192-5p can better predict vaginal microecology in postnatal patients. E, miR-192-5p expression was downregulated in the uncomplicated group. F, miR-192-5p can better predict postpartum postnatal complications.

Predictive value of miR-192-5p in two groups of maternal complications

Postpartum hemorrhage, puerperal infection, and abdominal incision infection are relatively serious complications with a relatively low incidence. Therefore, the three complications were combined into a whole for comprehensive analysis when analyzing the data. The analysis found that there was a notable disparity in overall incidence of such serious complications between the miR-192-5p high and low expression groups ($p < 0.001$, Table 2). MiR-192-5p expression in patients with complications was significantly down-regulated (Fig. 2E). Based on the occurrence of complications, the ROC curve revealed the miR-192-5p could diagnose complications and the AUC was 0.882 with the specificity and the sensitivity of 86.7% and 88.4%, respectively (Fig. 2F).

Discussion

The risk of caesarean section with a scarred uterus has received much attention due to the many complications that can seriously harm the physical and mental health of mothers (Zheng et al. 2019). To better predict the occurrence of complications after caesarean section with scarred uterus and help doctors and patients develop more effective personalized treatment and rehabilitation programs, a non-invasive, rapid, and convenient diagnostic index is urgently needed. With the gradual deepening of miRNA research and continuous exploration of their roles, it has been found

Table 2. Association of vaginal microecology and complications with miR-192-5p expression.

Index	MiR-192-5p		χ^2	*P* value
	Low expression (n=76)	High expression (n=69)		
PH (n/%)			0.038	0.845
Normal	22 (28.95)	21 (30.43)		
Abnomal	54 (71.05)	48 (69.57)		
H2O2 (n/%)			1.053	0.305
Normal	20 (26.32)	14 (20.29)		
Abnomal	56 (73.68)	55 (79.71)		
LE (n/%)			15.590	<0.001
Normal	32 (42.11)	54 (78.26)		
Abnomal	44 (57.89)	15 (21.74)		
SNA (n/%)			6.688	0.010
Normal	51 (67.11)	59 (85.51)		
Abnomal	25 (32.89)	10 (14.49)		
B-GD (n/%)			0.119	0.730
Normal	73 (96.05)	67 (97.10)		
Abnomal	3 (3.95)	2 (2.90)		
NAG (n/%)			5.114	0.024
Normal	45 (59.21)	53 (76.91)		
Abnomal	31 (40.79)	16 (23.19)		
Postpartum hemorrhage (n/%)	4 (5.26)	1 (1.45)		
Puerperal infection (n/%)	2 (2.63)	0		
Abdominal incision infection (n/%)	8 (10.53)	0		
Total incidence (%)	14 (18.42)	1 (1.45)	11.232	0.001

PH, potential of hydrogen; H_2O_2, catalase; LE, leukocyte esterase; SNA, sialyl glycosidase; β-GD, β-Glucuronidase; NAG, acetylglucosaminidase.

that miRNA shows good application prospects in predicting postpartum complications (Pfeiffer et al. 2020; Ali et al. 2021). For example, it has been reported that the upregulation of miR-100-5p and miR-125b-5p in the postpartum serum may predict the occurrence of postpartum complications (Hromadnikova et al. 2019). MiR-27b-3p can be used as a predictor of preeclampsia severity (Yang et al. 2022). The aim of this study was to identify a potential miRNA as a predictive marker for complications after caesarean section with a scarred uterus.

This study found that the more severe the abdominal scar of pregnant women, the lower the expression of miR-192-5p in serum, showing a significant relationship between the two. A study has shown that up-regulation of miR-192-5p can inhibit autophagy and fibrosis of urethral scar fibroblasts (Zhou et al. 2021). This suggests that miR-192-5p is closely associated with the formation of scarring in cesarean delivery. Combined with the past study that patients with scarred uterus are more likely to have postpartum complications than those with non-scarred uterus (You et al. 2018; Zheng et al. 2019), it is speculated that miR-192-5p, which is closely related to scarred uterus, may also be related to the occurrence of complications after cesarean section again.

The damage of pelvic floor structure, function and muscle strength after cesarean section were more serious, especially in patients with scarred uterus who undergo cesarean section again (Feng et al. 2020). Women with a history of cesarean sections during their second pregnancy had a considerably higher rate of pelvic floor muscle stretching, according to the study (Legendre et al. 2013; Luo et al. 2017). In this study, miR-192-5p expression in patients was somewhat correlated with postpartum class I and II muscle fiber strength levels and PFD of patients. Further studies showed that miR-192-5p was not only down-regulated in patients with moderate and severe PFD, but the ROC curves also indicated that miR-192-5p had a good predictive value for patients with postpartum PFD. A study pointed out that miR-222 plays an important regulatory role in pelvic organ prolapse (Zhang et al. 2024). Therefore, it is speculated that miR-192-5p has certain reference value in the treatment and diagnosis of PFD.

Abdominal scar score has been reported to indicate local vaginal infection (Yang et al. 2023). Studies have shown that poor postpartum scar healing or infection may affect the vaginal microecological environment (Koh et al. 2018). A study pointed out that miR-18a expression was downregulated in the group with abnormal vaginal microecology (Zhang et al. 2021). In the study, miR-192-5p expression was down-regulated in women with

abnormal vaginal microecology, which has good predictive value for the maternal vaginal microecological environment. During pregnancy in a scarred uterus, the embryo tends to implant in the scarred area and is prone to complications such as post-partum hemorrhage and abdominal infections. This significantly increases the risk of caesarean section and poses a serious threat to the safety of the mother and child (Vercelli et al. 2015; Zhang et al. 2023). To investigate the role of abnormal miR-192-5p expression in serious complications after caesarean section with scarred uterus, including postpartum hemorrhage, postpartum infection, and abdominal incision infection, it was found that the lower the expression of miR-192-5p, the higher the probability of postpartum complications.

This study preliminarily investigated the potential value of miR-192-5p in predicting complications after caesarean section with scarred uterus. However, with the small sample included, the predictive value of miR-192-5p for postpartum haemorrhage, puerperal infections, and abdominal incision infections has not been systematically assessed. In addition, postpartum complications are diverse and complex, and it is unclear whether miR-192-5p is associated with other complications such as postpartum anaemia, hyperthyroidism, mastitis, and depression. Subsequent studies will include a larger and more varied patient population to explore the clinical role and mechanism of miR-192-5p in depth, providing sufficient experimental support for its clinical application.

In conclusion, the study showed that miR-192-5p has the potential to be a predictive tool for caesarean section complications in patients with scarred uterus, including PFD, vaginal microecological disorders, and serious complications like postoperative haemorrhage, abdominal incision infection and puerperal infection. The scientific validity and feasibility of this study will be further verified in the future, with the aim of achieving a preliminary prediction of the likelihood of complications in patients with scarred uterus based on the miR-192-5p level in prenatal serum testing, which will help doctors and patients to formulate a more rational approach to delivery and rehabilitation care.

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Files

Please find supplementary file(s);
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