Dashti *et al.*
Middle East Fertility Society Journal (2022) 27:6
https://doi.org/10.1186/s43043-022-00097-4

Middle East Fertility Society Journal

RESEARCH Open Access

Is there any difference between the obstetric and perinatal complications of pregnancy in patients with and without repeated implantation failure in fresh and frozen-thawed embryo transfer cycles?

Saeideh Dashti[1], Maryam Mirzaei[2], Maryam Eftekhar[1] and Esmat Mangoli[3*]

Abstract

Background: Repeated implantation failure (RIF) is the main challenge in assisted reproduction; the present study aimed to compare the obstetric and perinatal outcomes between RIF and control patients who experienced a successful pregnancy after fresh embryo transfer (ET) or frozen-thawed embryo transfer (FET) cycles. Data were obtained from 1150 women experiencing embryo transfer(s), consisting of 720 fresh ET and 430 FET cycles, at the Research and Clinical Center for Infertility, Yazd, Iran. The 370 women, in total, reached chemical pregnancies and finally 321 cases in fresh ET (n=216) and FET (n=105) cycles with singleton deliveries divided into two groups of control and RIF according to the number of last implantation failures. Then, the rate of obstetric and prenatal complications was compared between two groups in fresh ET and FET cycles.

Results: The results showed a higher abortion rate in the RIF group compared to the control group in fresh and FET cycles. In the assessment of the data from the cases with singleton pregnancies in fresh and FET cycles, the results showed almost similar obstetric and perinatal complications in the patients of RIF and control groups. Although the rates of some complications like vaginal bleeding, PROM, preterm delivery, and NICU administration were higher in the RIF patients, these were not significant ($P > 0.05$).

Conclusion: There was some variation in the normal rates of obstetric and perinatal outcomes between RIF patients compared to control. But, it seems necessary to run studies on more patients to endorse this conclusion.

Keywords: Repeated implantation failure, Obstetric complication, IVF, Embryo transfer

Introduction

Assisted reproductive techniques (ART) have witnessed considerable developments particularly in terms of sufficiently selecting embryos and cryostorage. However, still, a high number of patients encounter serial in vitro fertilization (IVF) failure [1]. The conditions for repeated implantation failure (RIF) have been defined in different ways. Totally, unsuccessful implantation following over 2 transfers of high-quality embryos or placement of over 10 embryos in multiple transfers have been recommended as factors of recognizing these patients [1].

The failure of implantation can have a variety of reasons; nonetheless, the embryo, especially the effect of aneuploidy, has been primarily focused of attentions [2, 3]. Now, maternal features contributing to the implantation failure could be named autoimmune conditions,

*Correspondence: es.mangoli@gmail.com
[3] Department of Reproductive Biology, Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Full list of author information is available at the end of the article

thrombophilic gene mutations, and uterine anomalies. Unfortunately, in most cases, the real cause cannot be recognized; however, constitutive endometrial dysfunction has been introduced as a key factor leading to RIF and infertility recently [4–6]. While some conditions have been reported for RIF, such as high abnormality of sperm DNA, uterine etiologies, cytogenetic abnormalities, immunological disturbance [7, 8], disorders in hormones and metabolism [9], and/or inherited thrombophilias [5], there is a necessity to investigate its exact causes. Therefore, RIF is seemed to remain a challenge in front of IVF-embryo transfer (ET) practitioners.

Recently, a lot of activities have been made to increase the pregnancy rate, resulting in the trial of some procedures such as the endometrial scratching prior to ET, tumor necrosis factor-α (TNF-α) antagonist, high-dose progesterone support, hydroxychloroquine, granulocyte colony-stimulating factor (G-CSF), or intravenous immunoglobulin supplement [4, 6, 10–12]. Despite limited proof, the effectiveness of these efforts in boosting the rate of implantation in RIF patients has been reported, resulting in the delivery of live birth in some patients. However, the obstetric and perinatal outcomes in the RIF patients with successful pregnancies have rarely been studied. Since there is a high risk of obstetric and perinatal complications in the pregnancies made by IVF [2, 13–15], we hypothesized that the probability of the risk of obstetric and perinatal complications in RIF patients was higher than others; so, a retrospective comparative study was designed to compare the obstetric and perinatal outcomes of RIF and control patients with successful pregnancy in the fresh and frozen-thawed IVF-ET (FET) cycles.

Material and methods

Ethics approval

The present retrospective investigation was conducted according to the analysis of data collected from January 2016 to January 2017 at the Research and Clinical Center for Infertility, Yazd, Iran, and was approved by the Ethics Committee of our institute (Code: IR.SSU.RSI.REC.1399.009).

Data collection

Data were obtained from women who had embryo transfer(s) in 1 year at the Research and Clinical Center for Infertility, Yazd, Iran. Among them, the women with the age of more than 44 years, the cases involving oocyte donation, surrogacy, twins, fertility preservation cases, pre-implantation genetic diagnosis (i.e., chromosomal or single genetic abnormality), thrombophilia positive screening, and severe male infertility were excluded. Finally, 1150 women, consisting of 720 fresh and 430 FET cycles, were included. Among the 370 cases of chemical pregnancies signified by positive βHCG test, 49 cases due to loss of obstetrical records were excluded. Finally, the obstetric and perinatal outcomes of 321 cases in fresh and FET cycles were analyzed (Fig. 1).

These patients were 216 fresh ET and 105 FET cycles. In each group, the cases were divided into control and RIF's group considering the number of prior implantation failures. The RIF group and the control group patients consisted of the patients experiencing $\geq$3 times and <3 times of prior implantation failure, respectively. Endometrial preparation in the FET cycles was done according to our routine procedure, and Estradiol Valerate 6 mg per day was started orally. When endometrial thickness reached 7.5 mm, vaginal progesterone pessaries 400 mg twice daily were added and were continued until fetal heart activity can be detected.

The clinical and laboratory properties of the patients, comprising age, anti-Mullerian hormone (AMH), number of ET, cycle day, gonadotropin dose, duration of infertility, protocols of stimulation, the IVF treatment indications (female factors, male factor, and unexplained factor), transfers at the cleavage stage, and blastocyst stage, as well as the incidences of diabetes mellitus and hypertension, were evaluated. Also, the rate of abortions, preterm birth (delivered at age <32 weeks), vaginal bleeding, fetal distress, and fetal body weight was evaluated.

Statistical analysis

Kolmogorov–Smirnov test was utilized to assess the data's normality. The chi-square, independent *t*-test, and Mann–Whitney test were hired to carry out the analysis. The results are presented as mean ± standard deviation (SD) for parametric data, median ± interquartile range for non-parametric data, and percentage for categorical variables. A *P*-value $\leq$ 0.05 was selected to show statistical significance. Finally, the Statistical Package for the Social Sciences V20 (SPSS Inc., Chicago, IL, USA) was used to carry out the statistical analysis.

Results

Data were recorded from 321 singleton chemical pregnancies (Fig. 1), among whom, the number of patients belonging to the RIF group and control groups was 74 cases and 247 cases, respectively.

In the fresh ET group (n=216), there were 191 control and 25 RIF. For this group, there were significant differences in chemical abortion (20.9% vs 28%, $P < 0.001$, respectively) and clinical abortion (6.8% vs 40%, $P < 0.001$, respectively) between the control and RIF groups. In the fresh ET group finally, 138 cases in control and 8 cases in the RIF group reached live birth and the rate

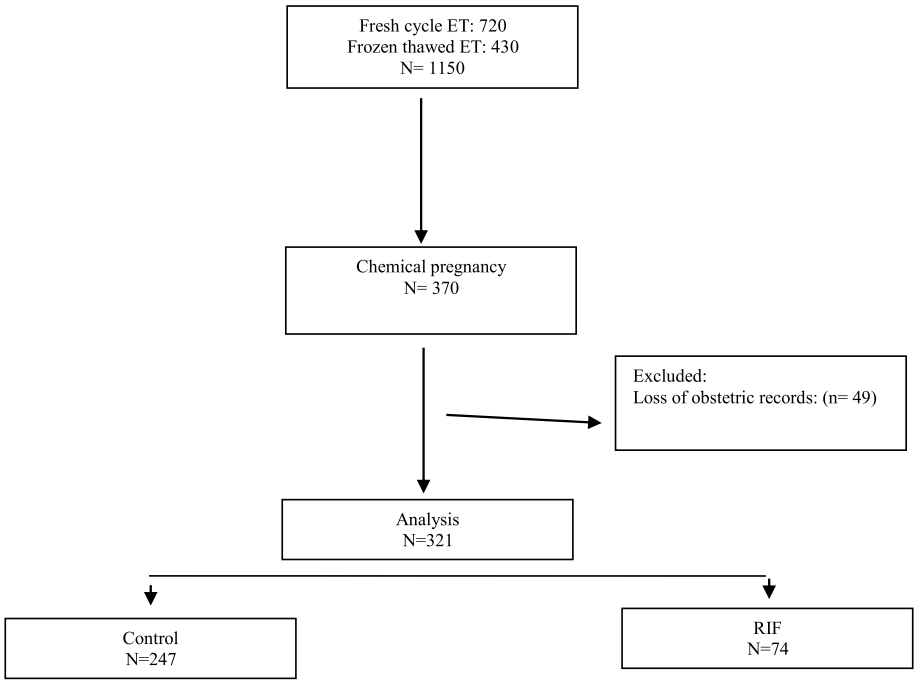

Fig. 1 Flow chart of clinical data collection

of obstetric and perinatal complications of them were analyzed.

In the FET group (n=105), there were 49 control and 56 RIF cases. In this group, there were higher chemical and clinical abortions between the control and RIF groups (14.3% vs 25% and 8.2% vs 14.3%, $P = 0.17$, respectively) but, statistically, it was insignificant. In this group finally, 38 cases in control and 34 cases in the RIF group reached live birth and the rate of obstetric and perinatal complications of them was analyzed.

Table 1 presents the maternal characteristics of the patients in the control and RIF groups of the fresh ET cycles according to which no significant differences were noticed between groups (Table 1).

Table 2 shows the laboratory characteristics of the patients in the control and RIF groups of the fresh ET cycles. There were no significant differences between them in the two groups ($P > 0.05$) (Table 2).

As well as in the fresh ET cycles according to Table 3, there was a significantly higher abortion rate in the RIF group compared to the control. According to obstetric and perinatal complications, there were insignificant differences between the control and RIF groups ($P > 0.05$), although there were higher rates of NICU administration, PROM, preterm delivery, and vaginal bleeding in the RIF group compared to control (Table 3).

Table 4 presents the maternal characteristics of the patients in the control and RIF groups of the FET cycles according to which no significant differences were noticed between groups (Table 4).

Table 5 shows the laboratory characteristics of the patients in the control and RIF groups of the FET cycles. There were no significant differences between them in the two groups ($P > 0.05$) (Table 5).

According to Table 6, there were no differences in obstetric and perinatal complications between the control and RIF groups of the FET cycles (Table 6). However, the data showed the rate of abortion, hypertension, vaginal bleeding, and preterm delivery was higher in RIF patients compared to control ($P > 0.05$).

Discussion

In this study, we saw a higher abortion rate in the RIF group compared to the control in fresh and frozen-thawed ET cycles. In the assessment of the data from the cases with singleton pregnancies in fresh and frozen-thawed IVF-ET cycles, the results showed almost similar obstetric and perinatal complications in the patients of RIF and control groups. Although the rates of some complications like vaginal bleeding, PROM, preterm delivery, and NICU administration were higher in the RIF patients, these were not significant ($P > 0.05$). Therefore, considering the relatively small sample size in the current study, it is necessary to conduct studies with a large cohort of RIF patients in the

Table 1 Maternal characteristic of the patients in the control and RIF groups of the fresh ET cycles (*n*=216)

Variables	Control (*n*=191)	RIF (*n*=25)	*P*-value
Age (yr.)[a]	31.00 (7.00)	34.50 (2.50)	0.09
AMH (ng/ml)[a]	2.97 (2.93)	3.95 (4.00)	0.93
Cycle day[a]	15.00 (3.00)	14.00 (4.50)	0.61
Gonadotropin dose (IU)[a]	1725.00 (1068.75)	1875.00 (712.50)	0.92
Duration of infertility (yr.)[a]	6.00 (6.00)	7.50 (6.50)	0.27
Protocols			
Agonist	30 (15.7)	3 (12)	0.57
Antagonist	117 (61.3)	18 (72)	
Micro dose	44 (23)	4 (16)	
Trigger			
HCG	138 (72.3)	15 (60)	0.42
Agonist	24 (12.6)	5 (20)	
Double	29 (15.2)	5 (20)	
Number of ET			
1	22 (11.5)	5 (20)	0.23
2	145 (75.9)	15 (60)	
3	24 (12.6)	5 (20)	
Indications for IVF treatment			
Male factor	87 (45.5)	8 (32)	0.33
Female factor	46 (24.1)	6 (24)	
Unexplained factor	5 (2.6)	2 (8)	
Male and female factors	53 (27.7)	9 (36)	
Type of infertility			0.54
Primary	161 (84.3)	23 (92)	
Secondary	30 (15.7)	2 (8)	

[a] Non-parametric data were presented with median (interquartile range). The numerical data were presented with frequency (percent). $P < 0.05$ was considered as significant. *AMH* anti-Mullerian hormone, *ET* embryo transfer

Table 2 Laboratory characteristic of the patients in the control and RIF groups of the fresh ET cycles (*n*=216)

Variables	Control (*n*=191)	RIF (*n*=25)	*P*-value
COC[a]	7.00 (4.00)	7.50 (5.50)	0.48
MII oocytes[a]	6.00 (4.00)	7.50 (5.50)	0.40
2PN[a]	4.00 (3.00)	5.50 (5.00)	0.57
ART technique			
ICSI	142 (74.3)	19 (76)	0.96
IVF	39 (20.4)	5 (20)	
IVF and ICSI	10 (5.2)	1 (4)	
Type of embryo			
Cleavage stage	188 (98.4)	23 (92)	0.10
Blastocyst stage	0 (0)	0 (0)	
Compaction stage	3 (1.6)	2 (8)	
Embryo grade			
A	52 (27.2)	9 (36)	0.65
B	114 (59.7)	13 (52)	
C	25 (13.1)	3 (12)	

[a] Non-parametric data were presented with median (interquartile range). The numerical data were presented with frequency (percent). $P < 0.05$ was considered as significant. *COC* cumulus oophorous complex, *MII* metaphase 2 oocyte, *PN* pronucleus, *ICSI* intracytoplasmic sperm injection, *IVF* in vitro fertilization

Table 3 Rates of obstetric and perinatal complications in control and RIF patients of the fresh ET cycles (*n*=216)

Complications	Control (*n*=191)	RIF (*n*=25)	*P*-value
Chemical abortion	40 (20.9)	7 (28)	0.00*
Clinical abortion	13 (6.8)	10 (40)	
Live birth	138 (72.3)	8 (32)	
Hypertension	10/138 (7.2)	0/8 (0)	1.00
Diabetes mellitus	16/138 (11.6)	1/8 (12.5)	1.00
Preterm	17/138 (12.3)	3/8 (37.5)	0.07
Vaginal bleeding	54/138 (39.1)	4/8 (50)	0.71
PROM	5/138 (3.6)	1/8 (12.5)	0.29
NICU admission	14/138 (10.1)	2/8 (25)	0.21
Anomaly	6/138 (4.3)	1/8 (12.5)	0.33
Birth weight (g)	3042.53 ± 549.67	3008.12 ± 881.41	0.86

The data were presented with mean ± SD and frequency/*n* (percent). *$P < 0.05$ was considered as significant. *PROM* premature rupture of the membrane

future to endorse this conclusion. Therefore, we cannot say exactly patients in the RIF group do not encounter obvious adverse outcomes.

RIF's patients experience a twenty-fold lower rate of implantation, compared to non-RIF patients [1]. In order to decrease the pregnancy complications in patients with RIF, in the last two decades, a vast array of surgical and pharmacological techniques such as transcutaneous electrical acupoint stimulation (TEAS) [16], hysteroscopic injury [17], and the use of immunomodulatory drugs (e.g., IVIG and glucocorticoids) [18, 19], intrauterine instillation of G-CSF [20], and administration of autologous peripheral blood mononuclear cells or platelet-rich plasma [21], as well as the use of endometrial receptivity array for predicting the optimal implantation window [22], have been applied. In confirmation of our study, there was a pilot study on RIF patients (2015) that showed RIF and non-RIF patients share similar obstetric complications [23].

Notwithstanding contradictory reports, ART pregnancies are generally subjected to increased risk of many obstetric outcomes, consisting of placenta previa, PROM, hypertensive disorders, preterm delivery, small for gestational age, GDM, placental abruption, and antepartum hemorrhage [2, 14, 15, 24]. Besides, as a consequence of increased previously failed IVF treatment cycle in the

Table 4 Maternal characteristics of the patients in the control and RIF groups of the frozen-thawed ET cycles (*n*=105)

Variables	Control (*n*=49)	RIF (*n*=56)	*P*-value
Age (yr.)	28.67 ± 4.02	30.01 ± 4.14	0.09
AMH (ng/ml)[a]	6.70 (5.59)	3.1 (2.53)	0.06
Cycle day[a]	17.00 (1.00)	18.00 (2.00)	0.44
Gonadotropin dose (IU)[a]	1500.00 (825.00)	1350.00 (768.75)	0.95
Duration of infertility (yr.)	8.04 ± 4.03	9.01 ± 4.27	0.23
Protocols			
Agonist	5 (10.2)	9 (16.1)	0.67
Antagonist	40 (81.6)	43 (76.8)	
Micro dose	4 (8.2)	4 (7.1)	
Trigger			
HCG	24 (49)	32 (57.1)	0.69
Agonist	15 (30.6)	15 (26.8)	
Double	10 (20.4)	9 (16.1)	
Number of ET			
1	3 (6.1)	10 (17.9)	0.18
2	35 (71.4)	36 (64.3)	
3	11 (22.4)	10 (17.9)	
Indications for IVF treatment			
Male factor	19 (38.8)	24 (42.9)	0.81
Female factor	18 (36.7)	16 (28.6)	
Unexplained factor	3 (6.1)	5 (8.9)	
Male and female factors	9 (18.4)	11 (19.6)	
Type of infertility			
Primary	42 (85.7)	51 (91.1)	0.54
Secondary	7 (14.3)	5 (8.9)	

The parametric data were presented with mean ± SD. [a]Non-parametric data were presented with median (interquartile range). The numerical data were presented with frequency (percent). $P < 0.05$ was considered as significant. *AMH* anti-Mullerian hormone, *ET* embryo transfer

Table 5 Laboratory characteristic of the patients in the control and RIF groups of the frozen-thawed ET cycles (*n*=105)

Variables	Control (*n*=49)	RIF (*n*=56)	*P*-value
COC	9.12 ± 2.21	9.14 ± 2.17	0.96
MII oocytes	7.75 ± 2.01	7.82 ± 2.18	0.87
2PN	6.06 ± 1.86	6.10 ± 2.17	0.90
ART technique			
ICSI	31 (63.3)	39 (69.6)	0.12
IVF	15 (30.6)	9 (16.1)	
IVF and ICSI	3 (6.1)	8 (14.3)	
Type of embryo			
Cleavage stage	43 (87.8)	43 (76.8)	0.28
Blastocyst stage	5 (10.2)	9 (16.1)	
Compaction stage	1 (2)	4 (7.1)	
Embryo grade			
A	15 (30.6)	15 (26.8)	0.88
B	31 (63.3)	38 (67.9)	
C	3 (6.1)	3 (5.4)	

The data were presented with mean ± SD and frequency (percent). $P < 0.05$ was considered as significant. *COC* cumulus oophorous complex, *MII* metaphase 2 oocyte, *PN* pronucleus, *ICSI* intracytoplasmic sperm injection, *IVF* in vitro fertilization

Table 6 Rates of obstetric and perinatal complications in control and RIF patients of the frozen-thawed ET cycles (*n*=105)

Complications	Control (*n*=49)	RIF (*n*=56)	*P*-value
Chemical abortion	7 (14.3)	14 (25)	0.17
Clinical abortion	4 (8.2)	8 (14.3)	
Live birth	38 (77.6)	34 (60.7)	
Hypertension	3/38 (7.9)	6/34 (17.6)	0.29
Diabetes mellitus	7/38 (18.4)	4/34 (11.8)	0.52
Preterm	6/38 (15.8)	7/34 (20.6)	0.76
Vaginal bleeding	14/38 (36.8)	20/34 (58.8)	0.09
PROM	3/38 (7.9)	3/34 (8.8)	1.00
NICU admission	5/38 (13.2)	3/34 (8.8)	0.71
Anomaly	2/38 (5.3)	2/34 (5.9)	1.00
Birth weight (g)	3041.71 ± 667.32	3078.82 ± 473.97	0.78

The data were presented with mean ± SD and frequency/*n* (percent). *$P < 0.05$ was considered as significant. *PROM* premature rupture of the membrane

aged women, their IVF-ET is associated with a lower live-birth rate and higher risk of placenta previa [25]. As multiple births made by IVF-ET are subjected to increased obstetric complications such as preterm delivery, perinatal mortality, GDM, and first-trimester bleeding and since the maternal age is considered as a risk factor for placenta previa, high cesarean section rate, small for gestational age, placental abruption, and preterm birth [9, 13, 14, 25], in this study, we only analyzed the patients with singleton pregnancy and adjusted the samples.

We compared obstetric complications in the RIF patients of fresh and frozen-thawed IVF-ET cycles and observed there was no significant difference between them but the rate of abortion was significantly higher in RIF patients of the fresh group. Our results contradicted the results of Jine et al. (2019) that declared the obstetric and neonatal complications were higher in frozen-thawed ET cycles [3]. This contradicts may be due to the low sample size of our frozen-thawed ET patients, evaluation of just singleton pregnancy in our study, and also included patients with different etiologies in their study.

Chin and coworkers (2019) evaluated the obstetric and perinatal outcomes of the two groups and showed similar obstetric and perinatal outcomes except for placental abruption rate in the RIF group (4.35%) was significantly higher, compared to the that of controls (0.50%) [26]. In our study, because of the lack of accurate data about the labor and placental information of patients, we did not analyze this complicate, and this

is one of our limitations. We suggest more studies with a sufficient sample size and exact follow-up.

There is a theory that RIF patients in ART treatment may have anomalies in the immune system that lead to implantation failure, and need immunosuppressive treatment. In this regard, Nakagawa and coworkers declared treatment with tacrolimus in RIF and RPL cases may be safe in the ART cycle and during pregnancy, but a large-scale study is needed to confirm the safety of such treatments [27].

Conclusion

There was some variation in the normal rates of obstetric and perinatal outcomes between RIF patients compared to control. But, it seems necessary to run studies on more patients to endorse this conclusion.

Acknowledgements
Not applicable

Authors' contributions
SD: conception, design, acquisition of data and literatures, drafting the article, and final approval. ME: conception, design, acquisition of data and literatures, analysis and interpretation of data, and final approval. MM: conception, design, acquisition of data and literatures, drafting the article, and final approval. EM: acquisition of data and literatures, analysis and interpretation of data, drafting the article, English and scientific revising the manuscript, and final approval.

Funding
Not applicable

Availability of data and materials
The data that support the findings of this study are available from the corresponding author.

Declarations

Ethics approval and consent to participate
The present retrospective investigation was conducted according to the analysis of data collected from January 2016 to January 2017 at the Research and Clinical Center for Infertility, Yazd, Iran, and was approved by the Ethics Committee of our institute (Code: IR.SSU.RSI.REC.1399.009).

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Obstetrics and Gynecology, Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. [2]Department of Obstetrics and Gynecology, Jiroft University of Medical Sciences, Jiroft, Kerman, Iran. [3]Department of Reproductive Biology, Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Received: 4 December 2021 Accepted: 2 March 2022
Published online: 11 March 2022

References

1. Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T et al (2014) Recurrent implantation failure: definition and management. Reprod Biomed Online. 28(1):14–38 PubMed PMID: 24269084
2. Jackson RA, Gibson KA, Wu YW, Croughan MS (2004) Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol. 103(3):551–563 PubMed PMID: 14990421
3. Jing S, Li XF, Zhang S, Gong F, Lu G, Lin G (2019) Increased pregnancy complications following frozen-thawed embryo transfer during an artificial cycle. J Assist Reprod Genet 36(5):925–933 PubMed PMID: 30924053. PMCID: PMC6541721. Epub 2019/03/30. eng
4. Arefi S, Fazeli E, Esfahani M, Borhani N, Yamini N, Hosseini A et al (2018) Granulocyte-colony stimulating factor may improve pregnancy outcome in patients with history of unexplained recurrent implantation failure: an RCT. Int J Reprod Biomed (Yazd) 16(5):299–304 PubMed PMID: 30027145. PMCID: PMC6046207
5. Bellver J, Soares SR, Alvarez C, Munoz E, Ramirez A, Rubio C et al (2008) The role of thrombophilia and thyroid autoimmunity in unexplained infertility, implantation failure and recurrent spontaneous abortion. Hum Reprod. 23(2):278–284 PubMed PMID: 18070829
6. Dieamant F, Vagnini LD, Petersen CG, Mauri AL, Renzi A, Petersen B et al (2019) New therapeutic protocol for improvement of endometrial receptivity (PRIMER) for patients with recurrent implantation failure (RIF) - a pilot study. JBRA Assist Reprod 23(3):250–254 PubMed PMID: 31091064. PMCID: PMC6724389
7. Liang PY, Diao LH, Huang CY, Lian RC, Chen X, Li GG et al (2015) The pro-inflammatory and anti-inflammatory cytokine profile in peripheral blood of women with recurrent implantation failure. Reprod Biomed Online. 31(6):823–826 PubMed PMID: 26371706
8. Talebi AR, Fesahat F, Mangoli E, Ghasemzadeh J, Nayeri M, Sadeghian-Nodoshan F (2016) Relationship between sperm protamine deficiency and apoptosis in couples with unexplained repeated spontaneous abortions. Int J Reprod BioMed 14(3):199
9. RoyChoudhury S, Singh A, Gupta NJ, Srivastava S, Joshi MV, Chakravarty B et al (2016) Repeated implantation failure versus repeated implantation success: discrimination at a metabolomic level. Hum Reprod. 31(6):1265–1274 PubMed PMID: 27060172
10. Chou PY, Wu MH, Pan HA, Hung KH, Chang FM (2011) Use of an oxytocin antagonist in in vitro fertilization-embryo transfer for women with repeated implantation failure: a retrospective study. Taiwan J Obstet Gynecol. 50(2):136–140 PubMed PMID: 21791296
11. Eapen A, Joing M, Kwon P, Tong J, Maneta E, De Santo C et al (2019) Recombinant human granulocyte- colony stimulating factor in women with unexplained recurrent pregnancy losses: a randomized clinical trial. Hum Reprod 34(3):424–432 PubMed PMID: 30776296. PMCID: PMC6389865
12. Saccone G, Schoen C, Franasiak JM, Scott RT Jr, Berghella V (2017) Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials. Fertil Steril. 107(2):430–8 e3 PubMed PMID: 27887710
13. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A (2012) Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. Hum Reprod Update. 18(5):485–503 PubMed PMID: 22611174
14. Qin J, Liu X, Sheng X, Wang H, Gao S (2016) Assisted reproductive technology and the risk of pregnancy-related complications and adverse pregnancy outcomes in singleton pregnancies: a meta-analysis of cohort studies. Fertil Steril. 105(1):73–85 e1-6. PubMed PMID: 26453266
15. Kamath MS, Kirubakaran R, Mascarenhas M, Sunkara SK (2018) Perinatal outcomes after stimulated versus natural cycle IVF: a systematic review and meta-analysis. Reprod Biomed Online. 36(1):94–101 PubMed PMID: 29111312
16. Hsu YC, Liang IT, Huang SY, Wang HS, Soong YK, Chang CL (2017) Transcutaneous electrical acupoint stimulation (TEAS) treatment improves pregnancy rate and implantation rate in patients with implantation failure. Taiwan J Obstet Gynecol. 56(5):672–676 PubMed PMID: 29037556
17. Huang SY, Wang CJ, Soong YK, Wang HS, Wang ML, Lin CY et al (2011) Site-specific endometrial injury improves implantation and pregnancy in patients with repeated implantation failures. Reprod Biol Endocrinol 9:140 PubMed PMID: 22014336. PMCID: PMC3210086
18. Robertson SA, Jin M, Yu D, Moldenhauer LM, Davies MJ, Hull ML et al (2016) Corticosteroid therapy in assisted reproduction - immune suppression is a faulty premise. Hum Reprod. 31(10):2164–2173 PubMed PMID: 27591233

19. Nyborg KM, Kolte AM, Larsen EC, Christiansen OB (2014) Immunomodulatory treatment with intravenous immunoglobulin and prednisone in patients with recurrent miscarriage and implantation failure after in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril. 102(6):1650–5 e1 PubMed PMID: 25256927
20. Zeyneloglu HB, Tohma YA, Onalan G, Moran U (2020) Granulocyte colony-stimulating factor for intracytoplasmic sperm injection patients with repeated implantation failure: which route is best?dagger. J Obstet Gynaecol. 40(4):526–530 PubMed PMID: 31496328
21. Nazari L, Salehpour S, Hoseini S, Zadehmodarres S, Ajori L (2016) Effects of autologous platelet-rich plasma on implantation and pregnancy in repeated implantation failure: a pilot study. Int J Reprod Biomed (Yazd) 14(10):625–628 PubMed PMID: 27921085. PMCID: PMC5124324
22. Sebastian-Leon P, Garrido N, Remohi J, Pellicer A, Diaz-Gimeno P (2018) Asynchronous and pathological windows of implantation: two causes of recurrent implantation failure. Hum Reprod. 33(4):626–635 PubMed PMID: 29452422
23. Tada Y, Kitaya K, Amano N, Kobatake M, Hayashi T, Taguchi S et al (2015) A pilot survey on obstetric complications in pregnant women with a history of repeated embryo implantation failure and those undergoing single local endometrial injury. Clin Exp Obstet Gynecol. 42(2):176–178 PubMed PMID: 26054113
24. Toshimitsu M, Nagamatsu T, Nagasaka T, Iwasawa-Kawai Y, Komatsu A, Yamashita T et al (2014) Increased risk of pregnancy-induced hypertension and operative delivery after conception induced by in vitro fertilization/intracytoplasmic sperm injection in women aged 40 years and older. Fertil Steril. 102(4):1065–70 e1 PubMed PMID: 25123639
25. Sazonova A, Kallen K, Thurin-Kjellberg A, Wennerholm UB, Bergh C (2011) Factors affecting obstetric outcome of singletons born after IVF. Hum Reprod. 26(10):2878–2886 PubMed PMID: 21771774
26. Chin TH, Hsu YC, Soong YK, Lee CL, Wang HS, Huang HY et al (2019) Obstetric and perinatal outcomes of pregnancy in patients with repeated implantation failure. Taiwan J Obstet Gynecol. 58(4):487–491 PubMed PMID: 31307738
27. Nakagawa K, Kwak-Kim J, Hisano M, Kasahara Y, Kuroda K, Sugiyama R et al (2019) Obstetric and perinatal outcome of the women with repeated implantation failures or recurrent pregnancy losses who received pre- and post-conception tacrolimus treatment. Am J Reprod Immunol. 82(2):e13142 PubMed PMID: 31081959. Epub 2019/05/14. eng

Publisher's Note