#### REVIEW



# Association of embryo transfer type with infertility in endometriosis: a systematic review and meta-analysis

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# Abstract

**Purpose** The study aims to evaluate whether frozen embryo transfer can restore optimal receptivity leading to better assisted reproductive technology outcomes in women with endometriosis.

**Methods** This systematic review and meta-analysis, conducted from January 10, 2021 to July 1, 2021, searched the Cochrane Library, PubMed, Embase, Web of Science, OVID, and Clinicaltrials.gov databases from inception to January 10, 2021. The search strategy combined search terms as follows: ("endometriosis" OR "deep endometriosis" OR "endometrioma") AND ("frozen-thawed embryo transfer" OR "frozen embryo transfer" OR "freeze-all strategy") AND ("pregnancy outcome" OR "live birth rate" OR "clinical pregnancy rate" OR "miscarriage rate"). No publication time or language limits were set during the searches. In addition, references of the related articles were searched by hand. Patients were included if they had a history of endometriosis and had received fresh or frozen embryo transfer. Only the first transfer cycle was included. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to express outcomes, and data synthesis was conducted using RevMan, version 5.4 software.

**Results** A total of six studies with moderate methodologic quality were retrieved in the meta-analysis. The studies included 3010 women with endometriosis who wanted to conceive; 1777 (59.0%) had frozen embryo transfer, and 1233 (41.0%) had fresh embryo transfer. There was a significantly higher frequency of live births in the frozen embryo group than in the fresh embryo group (OR, 1.53; 95% CI, 1.13–2.08; P = .007). Despite a similar clinical pregnancy rate in the two groups (OR, 1.26; 95% CI, 0.95–1.69; P = .11), the difference in miscarriage rate was significant (OR, 0.70; 95% CI, 0.50–0.97; P = .03). Evidence quality was considered moderate.

**Conclusion** Cryopreserved embryo transfer has resulted in preferable reproduction outcomes when compared with fresh embryo transfer in patients with endometriosis, but the evidence is not yet abundant. More strictly designed research is needed to evaluate whether frozen embryo transfer leads to better reproductive outcomes in women with endometriosis compared with those receiving fresh embryo transfer.

Registration number PROSPERO CRD42021248313.

Keywords Endometriosis  $\cdot$  Fertility  $\cdot$  Fresh embryo transfer  $\cdot$  Frozen-thawed embryo transfer  $\cdot$  Meta-analysis

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# Introduction

Endometriosis is a common condition found in 10 to 15% of reproductive-age women. A hallmark of the disease is the presence of endometrial glands and stroma outside the uterus. Symptoms include ovarian mass, pelvic pain, and infertility. Studies have shown that 30 to 50% of women with infertility have endometriosis [1] and that women with endometriosis have less successful pregnancy outcomes than those who are not diagnosed with the condition [2, 3]. The negative effect of endometriosis on a woman's fertility is in part caused by distortion of pelvic

anatomy and pelvic organ adhesions found in the more advanced severe stages of the disease. However, because patients with a normal pelvis in minimal, mild, and moderate stages of endometriosis may also have adverse fertility outcomes, the pathogenesis remains unclear [4]. Recent research has suggested that infertility in endometriosis may be related to both oocyte development and embryo implantation. The endometrium must be receptive for successful embryo implantation to take place [5, 6].

Currently, more women with endometriosis are achieving pregnancy through assisted reproductive technology (ART) [7], and studies have suggested similar success rates in women with an endometriosis diagnosis compared with those with other diagnoses [8]. However, some other studies showed that compared with women with other causes of infertility (i.e., tubal factors), women with endometriosis have pregnancy rates that are almost 50% less [9]. Researchers have hypothesized that the endometriosis potentially causes some detrimental effects on reproduction [10]. In addition, despite great advancements in ART, particularly the improvement in embryo quality, implantation rate remains low [11]. Studies have shown that controlled ovarian stimulation may alter endometrial receptivity through the expansion of the implantation window and higher levels of estrogen [12, 13]. As endometriosis is an estrogen-dependent condition with dysregulated steroid hormone pathways in the eutopic endometrium [14], it is reasonable to hypothesize that a supraphysiological concentration of estrogen may alter endometrial receptivity and then contribute to a lower rate of pregnancy.

Improvements in cryopreservation have made feasible the deferment of frozen embryo transfer as an alternative to the transfer of fresh embryos. Cryopreservation was developed initially to prevent ovarian hyperstimulation syndrome; however, its use has evolved to include the improvement of endometrial implantation. One study [15] found that frozen embryo transfer improved infertility outcomes in women with endometriosis. Endometriosis causes fluctuations in serum progesterone and estradiol levels, which result in asynchrony between the endometrium and embryo; use of frozen-thawed embryo transfer may alter this asynchrony [16]. Administration of both progesterone and estradiol creates a natural endometrial environment for the embryo. The use of frozen embryo transfer is currently considered controversial by many scholars and as such, is not accepted as an alternative procedure to fresh embryo transfer in infertile women with endometriosis [17].

Therefore, this study was conducted with the goal of assessing the relationship between frozen embryo transfer and fertility in women with endometriosis.

#### **Materials and methods**

This study was a systematic review and meta-analysis; it was conducted from January 10, 2021. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (PROSPERO: CRD42021248313).

#### Search strategy

A literature search was conducted by two authors (Y.C., M.S.) using OVID, the Cochrane Library, Web of Science, PubMed, Embase, and Clinicaltrials.gov databases from inception to January 10, 2021. Search terms were combined as follows: ("endometriosis" OR "deep endometriosis" OR "endometrioma") AND ("frozen-thawed embryo transfer" OR "frozen embryo transfer" OR "freeze-all strategy") AND ("pregnancy outcome" OR "live birth rate" OR "clinical pregnancy rate" OR "miscarriage rate"). The related articles were searched by hand. During the searches, no limits were set for publication time or language.

#### Study selection

Studies were included in this meta-analysis if they (1) enrolled patients with endometriosis; (2) were randomized clinical trials, case-control studies, or cohort trials; (3) included patients who received transfer of frozen or fresh embryos (and this was their first transfer cycle during the time period); and (4) their outcomes included rates of miscarriage, live births, or clinical pregnancy. Studies were excluded if they (1) were case reports; (2) did not include the first transfer cycle; or (3) included animal subjects.

Studies were independently selected by two authors (Y.C., S.W.). From the searches, first the abstracts and titles were scanned; next, the full text of the chosen articles was analyzed. In any disagreements arose, they were resolved via discussion or consensus with a third author (H.D.).

#### **Risk of bias**

The risk of bias was independently assessed by two authors (S.W., M.S.) using the Newcastle–Ottawa Scale (http://www.ohri.ca/programs/clinical\_epidemiology/ oxford.asp). Three items in the Newcastle–Ottawa Scale totaled 9 points: case and control selection, case and control comparability, and exposure ascertainment.

Sensitivity analysis was conducted for the primary outcome (live birth rate) to test the stability of the metaanalysis result. In a table of findings summary, the evidence quality was shown using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria (GRADEpro GDT software [McMaster University, Hamilton, Ontario, Canada]). Two review authors (S.W., M.S.) independently performed the evaluation. A resolution was found for any disagreements through discussion or evaluation by a third author (H.D.).

# Data extraction and synthesis

Data were independently extracted by two authors (Y.C., M.S.) using a data extraction form containing patient characteristics and outcome data. Patients were included in the frozen embryo group if they received transfer of frozen embryos, and patients were included in the control group if they received transfer of fresh embryos. Reproductive outcomes (i.e., rates for miscarriage, live births, and clinical pregnancy) were compared between the groups. Data synthesis was performed using RevMan software, version 5.4 (The Cochrane Collaboration). Data were synthesized and analyzed from March 10, 2021 to May 1, 2021, using Rev-Man software, version 5.4 (The Cochrane Collaboration).

For dichotomous data, the  $I^2$  statistic was used to examine odds ratio (OR) heterogeneity;  $I^2$  statistic analysis (where an  $I^2$  value < 50% suggested no substantial heterogeneity) was conducted using random-effect or fixed-effect models. Significance level for all two-sided P values was set at less than 0.05.

### Result

#### Study selection

Using standard searching techniques, a total of 919 studies were found. The selection procedure is illustrated in the flow diagram (Fig. 1). Of the 919 studies, 316 were duplicates, 294 were excluded after review of the abstract and title, and 304 were excluded because their control groups included patients who did not have endometriosis. In addition, one article [15] was included from a manual search of the references.

#### Study characteristics

All six articles retrieved from the search were retrospective cohort studies. There were no available randomized clinical trials on this topic. A total of six studies with moderate methodologic quality were retrieved in the meta-analysis. The studies included 3010 women with endometriosis who wanted to conceive; 1777 (59.0%) had frozen embryo transfer, and 1233 (41.0%) had fresh embryo transfer. Five studies [15, 18–21] reported live birth rate and miscarriage,

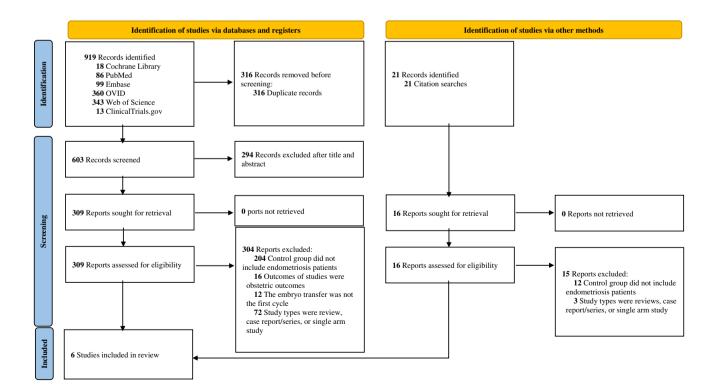


Fig. 1 Flow diagram

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and all six studies [15, 18–22] reported clinical pregnancy rate. Two studies [19, 21] clarified the endometriosis phenotypes, and three [15, 18, 20] clarified stages. Five studies [18–22] described the stimulation protocol and the frozen embryo transfer protocol. Three studies [19, 21, 22] clarified prior endometriosis surgery. Four studies [15, 18, 19, 21] described concomitant infertility factors. Only one study [18] used a subgroup analysis according to the age of the participants; another study [15] performed a subgroup analysis by the number of oocytes retrieved, and one study [18] performed a subgroup analysis by preimplantation genetic testing (PGT-A). Characteristics of the retrieved articles are displayed in Table 1.

#### **Meta-analysis**

A random-effect model revealed an  $I^2$  statistic of 55% for live birth rate and 68% for clinical pregnancy rate, which was interpreted as obvious heterogeneity. A fixed-effect model revealed no significant heterogeneity for miscarriage rate ( $I^2 = 22\%$ ). Analysis of ORs was conducted via the Mantel–Haenszel technique. The frozen embryo transfer group had better reproductive outcomes in patients with endometriosis than in the control group (OR, 1.53; 95% CI, 1.13–2.08; P = 0.007) (Fig. 2a). The two groups had a similar clinical pregnancy rate (OR, 1.26; 95% CI, 0.95–1.69; P = 0.11) (Fig. 3), but the difference in the rate of miscarriage between the two groups was significant (OR, 0.70; 95% CI, 0.50–0.97; P = 0.03) (Fig. 4).

We did not test for funnel plot asymmetry because of the possibility of achieving a false-positive result (<10 included studies according to *Cochrane Handbook for Systematic Reviews of Interventions*) (https://training.cochrane.org/handbook). Because there were only six studies included in this analysis, we chose not to assess for publication bias. Quality assessment scores were in the range of 8 to 9 scores (Table 2).

Using the GRADE approach, evidence quality was classified as moderate (Table 3). There were not enough data to conduct a subgroup analysis according to endometriosis phenotypes, stages, age of participants, stimulation protocol, or frozen embryo transfer protocol.

# Sensitivity analysis

### Discussion

# **Main finding**

This study aimed to evaluate the relationship between the transfer of frozen embryos and fertility in patients with endometriosis.

Results suggest that the transfer of frozen embryos was associated with improved rates of live birth and fertility among women with endometriosis, whereas the rate of clinical pregnancy between both groups was similar. Further, there was a significantly lower rate of miscarriage in the group with frozen embryo transfer. However, results of a sensitivity analysis suggested that our results were unstable. This may have been the result of the small number of retrieved studies. All of these studies were retrospective cohort trials, and their allocation was not entirely random. Whether the study participants received frozen or fresh embryo transfer was based on discussion rather than randomization.

#### Strengths and limitations

This was the first systematic review and meta-analysis, to our knowledge, of frozen embryo transfer in women with endometriosis. We screened the references manually and performed a systematic search of the literature. The inclusion and exclusion criteria were strict, and the methodology was rigorous. Live birth rate, the ideal outcome variable, was the primary outcome for this study. In addition, all the included participants underwent their first transfer cycle.

This study had several limitations. First, this analysis lacked the inclusion of randomized clinical trials, as there were none available on this subject. Moreover, there were some factors contributing to the heterogeneity of the metaanalysis, including maternal age, phenotype, and stage of endometriosis, and concomitant infertility factors including adenomyosis, prior endometriosis surgery, stimulation protocol, number of retrieved oocytes, frozen embryo transfer protocol, and number of embryo transfers, which were inconsistent across the included studies. Meanwhile, there were not enough data to conduct a subgroup analysis according to these factors.

#### Implications for clinical practice

Endometriosis is the etiology of infertility in millions of women worldwide. Assisted reproductive technology has allowed for the improved management of endometriosisrelated infertility. After controlled ovarian stimulation, the transfer of fresh embryos is typically performed; this process

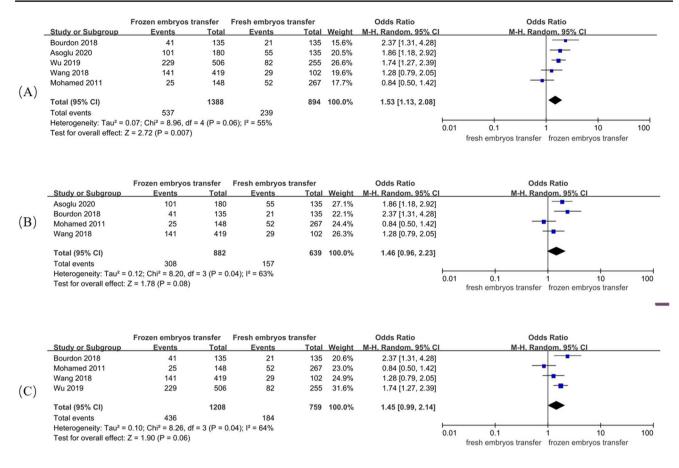
Miscar- riage	15 (OG) 12 (CG)	11 (OG) 16 (CG)	2 (OG) 2 (CG)
Clinical preg- nancy	1113 (OG) 65 (CG)	58 (OG) 40(CG)	27 (OG) 54 (CG)
Live birth	101 (OG) (CG)	41 (0G) (CG)	25 (OG) 52 (CG)
No. of transfers (mean±SD)	1.4±0.5 (OG) 1.3±0.5 (CG)	1.7±0.9 (0G) (CG) (CG)	SON
High- quality embryo rate (trans- ferred)	(0G) 82 (CG)	SON	NOS
FET protocol	cycle	cycle	Down-reg- ulated hormo- nally con- trolled cycle
No. of retrieved oocytes	8.5±3.5 (OG) 8.5±3.2 (CG)	9.9±7.0 (OG) 7.4±4.3 (CG)	SON
Stimula- tion protocol	GnRH- antag- onist pro- tocol, long agonist proto- col col	Long GnRH- agonist pro- tocol, antago- nist pro- tocol, short agonist proto- col	Long GnRH- agonist proto- col
Embryo transfer option	Based on a joint decision by the patient and doc- tor, but strongly recom- mend FET in those with pre- mature proges- terone eleva- tion ovarian hyper- stimula- tion strone recom-	Based on a joint decision by the patient and doc- tor	SON
Prior endo- metrio- sis surgery	(00) 0 (CC) 0	43 (OG) (CG) (CG)	148 (OG) 267 (CG)
No. of previous attempts	0.8±1.2 (0G) 0.9±1.5 (CG)	(CG) (CG) (CG) (CG)	SON
Concomi- tant infertil- ity factors	Tubal fac- tor, male factor (severe male factor or ovulatory dysfunc- tion was excluded)	Male infertil- ity, tubal factor, adeno- myosis	SON
Diagnos- tic testing	Ultra- sonog- raphy	Imaging criteria using TVUS, MRI, or tran- srectal ultra- sonog- raphy or sur- gery and histo- logic proof	Laparos- copy
Duration of infer- tility	32±2 (0G) 2.9±2 (CG)	4.7±2.7 (0G) 4.4±2.3 (CG)	SON
Phenotype and stage	Endome- trioma	SUP, OMA, 4.7 ± 2.7 DIE (OG) 4.4 ± 2.3 (CG)	SON
Patient age, mean ± SD, years	315 ± 180 33.1 ± 4.2 GG (OG) 55 (CG) 33.3 ± 3.4 (CG) (CG)	270±13534.3±4.1 0G) (OG) 55 (CG) 34.3±3.9 (CG) (CG)	415±148 34 (OG) 0G) 34 (CG) 37 (CG)
No. of patients	315±180 33.1±4.2 (OG) (OG) 135 (CG) 33.3±3.4 (CG) (CG) (CG)	270±135343±4.1 (OG) (OG) 34.3±3.9 135 (CG) 34.3±3.9 (CG) (CG)	415±148 (OG) 267 (CG)
Design	Retro- spec- tive cohort	Retro- spec- tive cohort	Retro- spec- tive cohort
Study	Asoglu (2020)	Bourdon (2018)	Mohamed (2011)

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Ż	No of	Datiant age	Dhenotyne	Duration	Diamos-	Concomi-	No of	Drior	Embruo	Stimula_	No of	БЕТ	Hich.	No. of	T ive	Clinical	Miccar-
patients			and stage			tant infertil- ity factors	previous attempts	endo- metrio- sis surgery	transfer option	tion protocol	retrieved oocytes	protocol	rugu- quality embryo rate (trans- ferred)	transfers (mean ± SD)	birth		riage
728 (OG) 339 (C	728 ± 389 : (OG) 339 (CG) :	728 ± 389 35.9 ± 0.3 (G) (OG) 99 (CG) 35.5 ± 0.2 (CG) (CG)	Stage I-IV (rASRM)	$\begin{array}{c} 2.9\pm0.3\\ (OG)\\ 2.8\pm0.3\\ (CG)\end{array}$	Surgery and his- tologic proof	Male factor (severe male factor, adeno- myosis, or tubal factor was excluded)	SON	SON	Based on a joint decision by the patient and doc- tor	GnRH- antag- onist proto- col	8.2±0.8 (0G) 7.4±4.3 (CG)	Artificial cycle	SON	SON	NOS	159 (OG) (CG)	34 (OG) 29 (CG)
521; 102 (C 102 (C	(CG)	521±419 30.4±3.9 (OG) (OG) 102 (CG) 31.2±3.8 (CG) (CG)	(rASRM) (rASRM)	4.0±2.2 (OG) 4.1±3.0 (CG)	Laparos- copy	SON	SON	SON	FET was con- ducted with hose with other uterine factors (such as endo- metrial polyps, submu- cosal fibroids), prema- gesterone eleva- tion, or ovarian hyper- stimula- tion	Ulltra- long pro- tocol, modi- fied ultra- long procol, proto- col	15.1±8.9 (OG) (CG) (CG)	Down-reg- ulated hormo- nally con- cycle cycle	(OG) 69.8% (CG)	SON	141 (0G) (CG)	180 (OG) 48 (CG)	7 (CG)

Table 1	Table 1 (continued)	(l																
Study	Design	No. of patients	Patient age, mean±SD, years	Phenotype and stage	Duration of infer- tility	Diagnos- tic testing	Concomi- tant infertil- ity factors	No. of previous attempts	Prior endo- metrio- sis surgery	Embryo transfer option	Stimula- tion protocol	No. of retrieved oocytes	FET protocol	High- quality embryo rate (trans- ferred)	No. of transfers (mean ± SD)	Live birth	Clinical preg- nancy	Miscar- riage
Wu (2019)	Retro- spec- trive cohort	315±18 (OG) 135 (CG)	315±180 33.1±4.2 (OG) (OG) 135 (CG) 33.3±3.4 (CG) (CG)	Stage III-IV 3.2±2 (rASRM) (OG) 2.9±2 (CO)		Laparos- copy	Tubal fac- tor, male factor	NOS	NON	Based on a joint decision by the patient and doc- tor, but strongly recom- tor, but strongly recom- mend FET in thore with pre- mature proges- terone eleva- tion or hyper- syndrome syndrome	SON	8.5±3.5 (OG) 8.5±3.2 (CG)	NON	Nos	2 (OG) 2 (CG)	101 (0G) (CG)	65 (CG)	15 (OG) 12 (CG)

ASRM American Society of Reproductive Medicine, CG control group, DIE deeply infiltrating endometriosis, FET frozen embryo transfer, MRI magnetic resonance imaging, NOS not otherwise specified, OG observation group, OMA ovarian endometriona, SUP superficial peritoneal endometriosis, TVUS transvaginal ultrasonography



#### Fig. 2 Forest plot of live birth rate

	Frozen embryos t	ransfer	Fresh embryos ti	ansfer		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Asoglu 2020	113	180	65	135	15.6%	1.82 [1.15, 2.86]	
Bourdon 2018	58	135	40	135	14.4%	1.79 [1.08, 2.96]	
Mohamed 2011	27	148	54	267	14.1%	0.88 [0.53, 1.47]	
Tan 2021	159	389	139	339	20.0%	0.99 [0.74, 1.34]	
Wang 2018	180	419	48	102	16.1%	0.85 [0.55, 1.31]	
Wu 2019	262	506	99	255	19.8%	1.69 [1.25, 2.30]	
Total (95% CI)		1777		1233	100.0%	1.26 [0.95, 1.69]	•
Total events	799		445				
Heterogeneity: Tau <sup>2</sup> :	= 0.09; Chi <sup>2</sup> = 15.46,	df = 5 (P =	0.009); I <sup>2</sup> = 68%			t,	
Test for overall effect	Z = 1.59 (P = 0.11)					l	0.1 0.2 0.5 1 2 5 10 fresh embryos transfer frozen embryos transfer

#### Fig. 3 Forest plot of clinical pregnancy rate

	Frozen embryos t	ransfer	Fresh embryos t	transfer		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	CI M-H, Fixed, 95% CI
Asoglu 2020	15	113	12	65	15.8%	0.68 [0.29, 1.55]	5]
Bourdon 2018	11	58	16	40	18.4%	0.35 [0.14, 0.87]	7]
Tan 2021	34	159	29	139	29.1%	1.03 [0.59, 1.80]	oj — —
Wang 2018	12	180	7	48	12.3%	0.42 [0.16, 1.13]	3]
Wu 2019	32	262	16	99	24.4%	0.72 [0.38, 1.38]	8]
Total (95% CI)		772		391	100.0%	0.70 [0.50, 0.97]	7]
Total events	104		80				
Heterogeneity: Chi <sup>2</sup> =	= 5.11, df = 4 (P = 0.2	8); I <sup>2</sup> = 22 <sup>4</sup>	%				
Test for overall effect	Z = 2.14 (P = 0.03)	100					0.1 0.2 0.5 1 2 5 1 Frozen embryos transfer Fresh embryos transfer

#### Fig. 4 Forest plot of miscarriage rate

Table 2	Study quality
assessm	ent

Authors	Year	Selec	ction			comparability	outco	ome asse	essment	Score
		1	2	3	4	5	6	7	8	
Asoglu	2020	☆	☆	☆	☆	**	☆	☆	☆	9
Bourdon	2018	☆	☆	☆	☆	☆	☆	☆	☆	8
Mohamed	2011	☆	☆	☆	☆	☆	☆	☆	☆	8
Tan	2021	☆	☆	☆	☆	**	☆	☆	☆	9
Wang	2018	☆	☆	☆	☆	☆	☆	☆	☆	8
Wu	2019	☆	☆	☆	☆	☆	☆	☆	☆	8

# **Table 3**Summary of findings(GRADE)

#### Summary of findings:

#### Frozen embryo transfer compared to fresh embryo transfer for endometriosis

Patient or population: endometriosis

Setting: no setting

Intervention: Frozen embryo transfer

Comparison: Fresh embryo transfer

	Anticipated ab			Nº of	Certainty of the	
Outcomes	Risk with Fresh embryo transfer	Risk with Frozen embryo transfer	Relative effect (95% CI)	participants (studies)	evidence (GRADE)	Comments
live birth rate	266 per 1,000	<b>296 per</b> <b>1,000</b> (248 to 348)	<b>OR 1.16</b> (0.91 to 1.47)	1446 (3 observational studies)	⊕⊕⊕⊖ MODERATE	
Clinical pregnancy rate	351 per 1,000	<b>373 per</b> <b>1,000</b> (333 to 415)	<b>OR 1.10</b> (0.92 to 1.31)	2174 (4 observational studies)	⊕⊕⊕⊖ MODERATE	
Miscarriage rate	166 per 1,000	<b>198 per</b> <b>1,000</b> (117 to 311)	<b>OR 1.24</b> (0.67 to 2.27)	838 (4 observational studies)	⊕⊕⊕⊖ MODERATE	

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the

relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

#### **GRADE Working Group grades of evidence**

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

generates high levels of estrogen. Because endometriosis is considered to be an estrogen-dependent disease, the high levels of estrogen generated from fresh embryo transfer are speculated to interfere with endometrial receptivity. This results in fewer occurrences of pregnancy. Several studies have shown that ovarian stimulation can cause a decrease in endometrial and subendometrial blood flow and can induce histopathological changes in the endometrium [23–25]. In addition, researchers have found that during fresh embryo transfer cycles, the gene transcription involved in endometrial receptivity is disrupted [26–29]. Deferred frozenthawed embryo transfer permits the embryo transfer to be carried out in a subsequent, separate cycle, which results in several potential advantages compared with fresh embryo transfer. These advantages include (1) the restoration of synchrony between endometrium and embryo and (2) the ability to reset the natural physiologic milieu of the uterus for optimal implantation. Several studies have shown a higher rate of live births and pregnancy with the use of frozen embryo transfer [15, 30]. The main question was whether frozen embryo transfer could restore optimal receptivity and improve fertility in women with endometriosis, which would lead to an increased frequency of pregnancy.

Because of the dysfunction of eutopic endometrium of endometriosis, including progesterone-resistance and decidualization defects, endometrial receptivity is thought to be the key factor in a successful pregnancy [10]. Meanwhile, numerous biomarkers have been proposed to identify the optimal endometrial receptivity [31, 32]. However, the known evidence of endometrial receptivity defects in endometriosis was based on the physiologic mechanism; none of the markers were used in clinical practice because of poor pregnancy prediction accuracy. Studies should focus on the improvement of in vitro fertilization, including the protocols of stimulation and transfer, timing of transplantation, and fertilization mode.

Our study results suggest that the transfer of cryopreserved embryos was associated with better reproduction outcomes than the transfer of fresh embryos in patients with endometriosis. However, evidence for this is not yet abundant. In addition, a cryopreservation strategy may result in the following disadvantages: increased time to pregnancy, unnecessary interventions, increased patient expense, and high concentrations of cryoprotectants, which may be toxic to embryos. Therefore, proceeding with frozen embryo transfer as a routine management strategy for endometriosis should be done cautiously. Individualized treatment of patients is necessary owing to the high level of heterogeneity with endometriosis. It should note that cryopreserved embryo transfers have been shown to provide better outcomes than fresh embryo transfers in a general population of ovulatory women [33]. Thus, the advantages of cryopreservation strategies may not be limited to endometriosis.

#### Implications for further research

All of the study objectives were not addressed owing to the limited evidence retrieved from the six retrospective cohort trials. In particular, we were unable to perform subgroup analysis based on concomitant infertility factors, prior endometriosis surgery, stimulation protocol, number of retrieved oocytes, transfer of frozen embryo protocol, and embryo transfer number. In the future, more research in the form of randomized clinical trials should be performed to establish the efficacy of frozen embryo transfer in the reproduction prognosis of endometriosis.

# Conclusions

The results suggest that the transfer of frozen embryos may improve the rate of live births and decrease the rate of miscarriages in patients with endometriosis. However, the benefit of frozen embryo transfer in the improvement of fertility outcomes remains uncertain. Evidence quality was considered moderate. More strictly designed research is needed to evaluate whether frozen embryo transfer leads to better outcomes in women with endometriosis compared with fresh embryo transfer using assisted reproductive technology. Using frozen embryo transfer as a routine management strategy for endometriosis should be performed cautiously.

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Author contribution H.D.: conception and design, data collection, analytic strategy, manuscript revision, and final article approval. Y.C.: conception and design, search and collection of data, analysis and synthesis, writing, and final article approval. M.S.: search and collection of data, analysis, manuscript revision, and final article approval. S.W.: collection of data, manuscript revision, and final article approval. X.L.: conception and design, manuscript revision, and final approval.

#### Declarations

Competing interests The authors declare no competing interests.

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