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Effect of intrauterine perfusion of human chorionic gonadotropin before embryo transfer after two or more implantation failures: A systematic review and meta-analysis

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ABSTRACT

Objective: To investigate whether intrauterine perfusion of hCG before embryo transfer (ET) is effective in women experienced two or more implantation failures.
Study design: Systematic review and meta-analysis. In the current meta-analysis, Pubmed, EMBASE and The Cochrane Library were searched for trials which compared the efficacy of intrauterine perfusion of hCG with no perfusion of hCG in women undergoing in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or frozen embryo transfer (FET) before ET. The primary outcomes are the clinical pregnancy rate (CPR) and live birth rate (LBR).
Results: Six trials consisted of 1432 women were eligible for quantitative analysis. CPR (including 6 trials consisted of 1432 women) and LBR (including 3 trials consisted of 870 women) were significantly improved in the hCG group compared to the control group, with a CPR of 41.8 % vs. 31.2 % (RR 1.30, 95 % CI 1.14∼1.50, $P < .001$), an LBR of 27.8 % vs. 18.0 % (RR 1.52, 95 % CI 1.18∼1.96, $P = .001$).
Conclusion: Intrauterine perfusion of hCG is effective in improving clinical pregnancy rate and live birth rate in women who experienced two or more implantation failures, which might provide a potential therapeutical intervention for recurrent implantation failure (RIF). Although promising, further evidence from multicenter, randomized controlled trials are needed to confirm the conclusion from the current meta-analysis.

Introduction

Successful embryo implantation depends on a good-quality embryo, normal-receptive endometrium, and the synchronized interaction between the embryo and the endometrium [1,2]. It is well known that the quality of the embryo is a key factor for implantation, however, the role of endometrial factors and synchronization between the embryo and the endometrium should not be underestimated. Endometrial receptivity is reported to be regulated by various factors, among them, hCG is an embryo-derived factor which takes an important role in embryo implantation. HCG mRNA is transcribed at the 8-cell stage [3,4], and it is expressed by the blastocyst before its implantation [5]. Afterward, hCG is synthesized by the syncytiotrophoblast after embryo implantation [6]. It has been shown recently that a hyperglycosylated form of hCG (hCG-H) is produced by the cytotrophoblast and acts as an autocrine factor regulating embryo implantation, trophoblast invasion, and cell growth [7]. Moreover, hCG was found to be secreted by the endometrium in the secretory phase, hCG receptors were expressed mostly in the mid-luteal phase, indicating that hCG secreted by the endometrium works as a paracrine factor and benefits endometrial pre-decidualization [8,9]. Furthermore, hCG induces endometrial decidualization, promotes endometrial synchrony, regulates endometrial receptivity and the maternal immune system [10–13]. Based on the above potential benefits within intrauterine perfusion of hCG, clinicians have performed several clinical trials to investigate whether hCG perfusion benefits the assisted reproductive technology (ART) outcomes. To our disappointment, results from previous trials are conflicting [14]. Based on the conflicting results, several meta-analyses were performed. However, the meta-analyses fail to draw

Abbreviations: HCG, human chorionic gonadotropin; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; FET, frozen embryo transfer; ET, embryo transfer; CPR, clinical pregnancy rate; LBR, live birth rate; RR, risk ratio; CI, confidence index; RIF, recurrent implantation failure; ART, assisted reproductive technology.

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a unanimous conclusion. The largest limitation of the meta-analyses is that great heterogeneity exists among the studies. The heterogeneity of the trials is deemed to derive from the differences in hCG dose and embryo stage. However, one origin of heterogeneity has seldom been underlined is the difference in population. It has been reported recently that the endometrial protein expression is not altered after intrauterine perfusion of 500 IU hCG in fertile women. However, the endometrial protein expression and related pathways are significantly changed in recurrent implantation failure (RIF) patients within intrauterine perfusion of 500 IU hCG, besides, RIF patients have a CPR of 19 % and an LBR of 14 % after intrauterine perfusion of 500 IU hCG before ET compared to their failed cycles and all live births have resulted from blastocyst transfers and infusion with 500 IU hCG. The results suggest that RIF patients differ from fertile women on gene expression and endometrial proteome expression, which indicates that different populations may respond differently to hCG perfusion. Therefore, it is a question of whether hCG perfusion should be used in all patients who underwent IVF, especially those who underwent their first IVF cycle or those who ask for IVF due to male factors. Selecting the right population suitable for intrauterine hCG perfusion is important for enhancing the efficacy of hCG perfusion and minimize possible complications. The previous trials or meta-analyses were performed on the "mixed population". So far, no meta-analysis has been performed in RIF patients or patients who experienced two or more implantation failures. Therefore, we conducted the present meta-analysis to figure out if intrauterine perfusion of exogenous hCG before ET is efficient in improving reproductive results in patients who experienced two or more implantation failures, which might provide a potential therapeutical intervention for RIF.

Materials and methods

This meta-analysis was reported under the guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [15].

Search strategies

We searched Pubmed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) from their inception to January 2019. The references of included studies were also searched. The searching syntax included the following Medical Subject Headings (Mesh) and text words which are varied individually according to different databases: human chorionic gonadotropin, intrauterine, embryo transfer, IVF, ICSI. The searching strategy in the Pubmed is listed as the following: (intrauterine [Title/Abstract] OR uterine cavity [Title/Abstract]) AND (IVF [Title/Abstract] OR ICSI [Title/Abstract] OR embryo transfer [Title/Abstract]) AND (hCG [Title/Abstract] OR human chorionic gonadotrophin [Title/Abstract]).

Inclusion criteria

Studies that compared the efficacy of intrauterine perfusion of hCG with no perfusion of hCG in patients experienced two or more implantation failures. Studies published in abstract form were also included if the extraction of data was possible. All studies, including randomized controlled trials, cohort studies, conference abstracts, were included in the systematic review.

Exclusion criteria

Patients undergoing their first IVF/ICSI/FET cycle, patients experienced <2 implantation failures, no relevant exposure or outcome.

Primary outcomes

Clinical pregnancy rate (CPR), live birth rate (LBR). CRP is defined as a viable pregnancy evaluated by sonography per ET cycle. LBR is defined as the delivery of a live foetus after 24 weeks of gestational age per ET cycle.

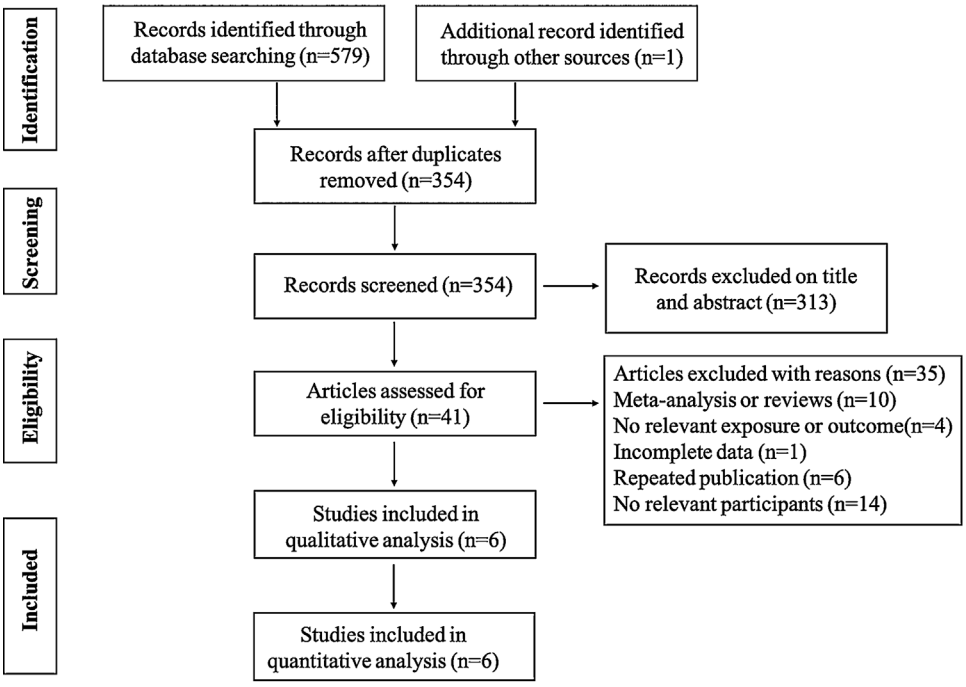

Fig. 1. Flow chart of the study selection process.

Data extraction, risk of bias (quality) assessment, and statistical analysis

Two authors (X.HB. and H.DM.) independently selected the studies that fulfilled the inclusion criteria, with disagreements solved through discussion with a third reviewer (Z.H.). The data extraction was performed by two investigators (X.HB. and Z.H.) independently, and the data extraction was done using a standardized extraction form. Randomized controlled trials were assessed for risk of bias using the Cochrane risk assessment tool [16]. The evaluations were categorized as 'low risk', 'unclear risk' or 'high risk' of bias. Quality of the nonrandomized studies were assessed using the Newcastle-Ottawa Scale method. The scores of the Newcastle-Ottawa scale range from 0 to 9. Scores ≥ 7 indicating high quality and all other scores indicating low quality. All Statistical analyses were conducted using the Stata software (version 14, StataCorp, USA). We performed an intention-to-treat (ITT) analysis if it is possible. All the data were dichotomous, therefore, we analyzed the data using the Mantel-Haenszel method with the fixed-effect model if there was no obvious heterogeneity ($P_{\text{heterogeneity}}>.1$), or else DerSimonian and Laird method was used with the random-effect model if the heterogeneity was significant ($P_{\text{heterogeneity}}<.1$). The risk ratio (RR) and 95 % confidence interval were reported. Homogeneity of data from the included trials was analyzed using the Q test, it was considered heterogeneous if $P_{\text{heterogeneity}}<.1$. Moreover, heterogeneity was quantified using the I^2 test. The interpretation of I^2 was guided by the Cochrane Handbook for Systematic Reviews of interventions (Version 5.2.0, updated June 2017). I^2 range from 0 % to 40 % indicates that the heterogeneity might not be important; I^2 range from 30 % to 60 % may represent moderate heterogeneity; I^2 range from 50 % to 90 % may represent substantial heterogeneity; I^2 range from 75 % to 100 % indicates considerable heterogeneity. Publication bias was not assessed since there were less than 10 studies in this meta-analysis.

Results

580 records were identified through an initial search, 160 records from PubMed, 365 records from EMBASE, 54 records from CENTRAL, one additional record was found through reference searching. There were 354 records left after 226 duplicates were removed, 313 records were excluded through browsing title or abstract. There were 41 articles assessed for eligibility, 35 articles were excluded with reasons, finally, six trials (3 randomized trials and 3 non-randomized trials) were included in quantitative synthesis with a total of 1432 participants (692 participants received hCG, 740 participants didn't receive hCG) [17–22]. The flow chart of selecting studies was shown in Fig. 1. The basic characteristics of each trial were listed in Table 1. Overall, the trials were conducted in Brazil, India, China, and Australia from 2006 to 2017. Three trials enrolled RIF patients, the other three trials enrolled patients experienced at least two implantation failures. The hCG dose ranged from 480IU to 1000IU. Both cleavage embryos and blastocysts were transferred in fresh or frozen cycles. The scales of included studies using the Newcastle-Ottawa quality assessment method were presented in Table 2. The three cohort studies are assessed high-quality. The risk of bias of included RCTs was presented in Table 3. Most items of the three RCTs are assessed unclear risk of bias.

Table 1
Basic characteristics of the included studies.

Study	Country	Period	Design	Patients (n)	Age (y) Mean ± SD	Type of patients	HCG dose (IU)	Perfusion volume (μl)	HCG timing	ET cycle	Embryo stage at transfer	Outcomes
Leao [18] 2013	Brazil	January to December 2012	RCT	HCG: 18	Not mentioned	Patients with 2 IFs	500	Not mentioned	6 hours before ET	Not mentioned	Not mentioned	CPR
				No hCG: 18								
Singh [19] 2014	India	2006-2013	RCT	HCG: 108	35	RIF	500	40	5 minutes before ET	Not mentioned	Cleavage	CPR
				No hCG: 108	34.5							LBR
												Miscarriage
Huang [20] 2017	China	January to December 2015	RCT	HCG: 65	33.95 ± 4.14	Patients with 2 or more IFs	1000	1000	3 days before ET	Frozen	Cleavage	CPR
				No hCG: 100	33.08 ± 4.38							Miscarriage
Huang [21] 2018	China	May 2015 to July 2017	Retrospective cohort	HCG: 199	≤ 38	Patients with 2 or more IFs	1000	1000	3 days before ET	Frozen	Cleavage	CPR
				No hCG: 212								Miscarriage
Volovsky [22] 2018	Australia	2011-2015	Retrospective cohort	HCG: 149	38.5	RIF	480	40	10 minutes before ET	Fresh and frozen	Cleavage and blastocyst	CPR
				No hCG: 200	38.3							LBR
Liu [23] 2019	China	January to December 2016	Prospective cohort	HCG: 153	34.83 ± 4.31	RIF	500	50	3 days before ET	Frozen	Cleavage and blastocyst	CPR
				No hCG: 152	35.25 ± 4.94							LBR
												Miscarriage

Note: HCG = Human Chorionic Gonadotrophin; RCT = Randomized Controlled Trial; Ifs = Implantation Failures; RIF = Recurrent Implantation Failure; ET = Embryo Transfer; CPR = Clinical Pregnancy Rate; LBR = Live Birth Rate; FET = Frozen-thawed Embryo Transfer.

Table 2
Newcastle-Ottawa quality assessment scale of the included studies.

Study	Design	Case-cohort representative	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome negative at start	Comparability by design	Comparability by analysis	Outcome assessment	Duration of follow-up	Adequacy of follow up	Score	Quality
Huang [21] 2018	Retrospective cohort	*	*	*	*	–	*	*	*	*	8	High
Volovsky [22] 2018	Retrospective cohort	*	*	*	*	–	*	*	*	*	8	High
Liu [23] 2019	Prospective cohort	*	*	*	*	*	*	*	*	*	9	High

Table 3
Risk of bias using the Cochrane risk assessment tool for included randomized controlled trials.

Study	Random sequence generation	Blinding	Allocation concealment	Incomplete outcome data	Selective outcome reporting	Other bias	Summary assessment
Leao [18] 2013	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Singh [19] 2014	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk
Huang [20] 2017	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk

Clinical pregnancy rate

Six trials reported the clinical pregnancy rate. A total of 1432 participants were included in the six trials. The result showed that CPR was significantly improved in the hCG group compared to the control group, with a value of 41.8 % vs. 31.2 % (RR 1.30, 95 % CI 1.14∼1.50, $P < .001$) (Fig. 2). A subgroup analysis based on study design (RCT or cohort study) was performed, the data showed that the study design makes no difference to the result (see supplementary materials, supplementary Fig. 1).

Live birth rate

Three trials reported the live birth rate. A total of 870 participants were included in the three trials. The data showed that LBR was significantly improved in the hCG group compared to the control group, with a value of 27.8 % vs. 18.0 % (RR 1.52, 95 % CI 1.18∼1.96, $P = .001$) (Fig. 3).

Discussion

The result of the current meta-analysis indicates that patients experienced two or more implantation failures benefit from the intrauterine perfusion of hCG before ET. Patients experienced two or more implantation failures are diagnosed with RIF or potential RIF patients, the conclusion from our meta-analysis is promising as it suggests a potential therapeutical intervention for RIF.

Molecular properties of hCG involved in interactions between the maternal and fetal interface have been studied intensively. HCG plays a broad role in trophoblast differentiation [23], extravillous cytotrophoblast (EVT) cell proliferation, EVT invasion [24], endometrial decidualization and vascularization [25]. A study using the intrauterine microdialysis system has found that intrauterine perfusion of exogenous hCG decreases insulin-like growth factor binding protein-1 (IGFBP-1) and macrophage-colony stimulating factor (M-CSF), but increases leukemia inhibitory factor (LIF), vascular endothelial growth factor (VEGF), and matrix metalloproteinase-9 (MMP-9) [26]. Moreover, hCG protects the decidualized endometrial stromal cells (ESC) from apoptosis induced by oxidative stress [27]. Furthermore, hCG regulates the immune system. It is reported that regulatory T cells (Treg) are attracted by hCG-producing trophoblasts [28], hCG is also involved in inducing Treg differentiation [29], inhibiting T lymphocyte [30], regulating macrophage migration and uterine natural killer (uNK) cell proliferation [29]. Taken together, the above studies support

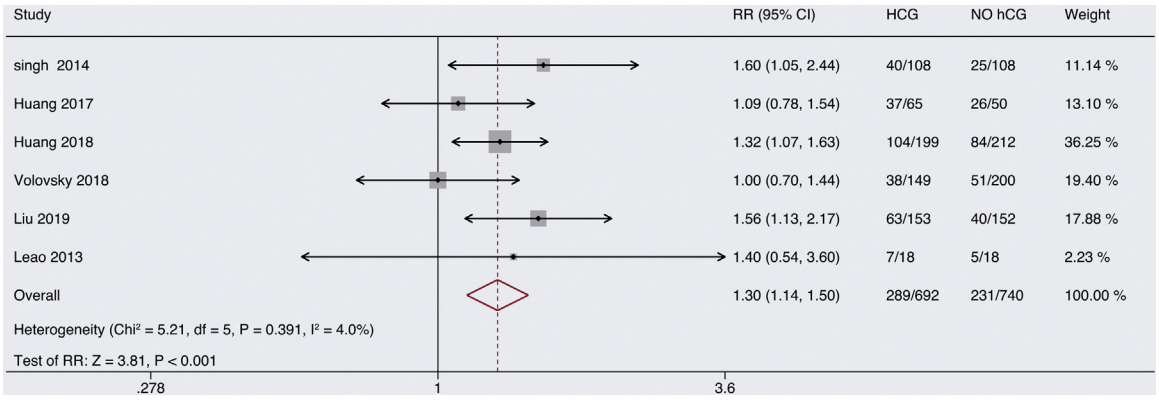

Fig. 2. Clinical pregnancy rate of the patients with intrauterine perfusion of hCG compared to those without hCG after two or more implantation failures. Note: RR = Risk Ratio.

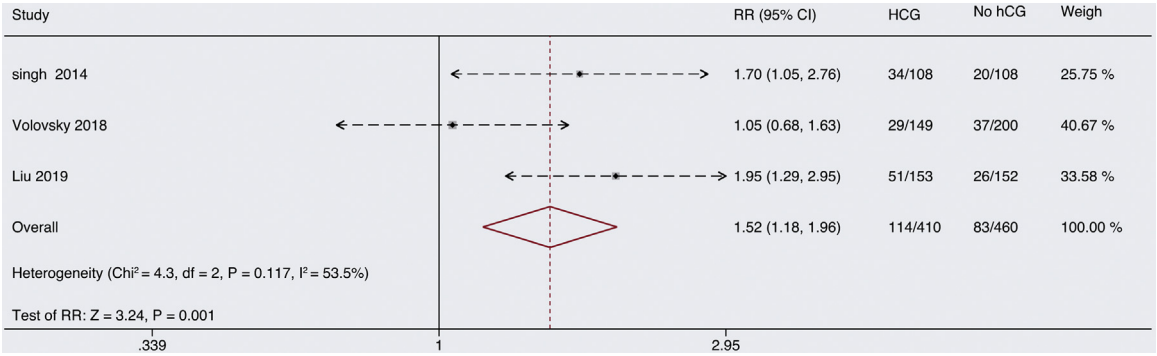

Fig. 3. Live birth rate of the patients with intrauterine perfusion of hCG compared to those without hCG after two or more implantation failures. Note: RR = Risk Ratio.

that hCG is important for trophoblast differentiation, EVT invasion, endometrial receptivity, and maternal-fetal immune tolerance.

Since 2011, several trials have been reported on the issue of whether intrauterine perfusion of hCG benefits assisted reproductive technology (ART) outcomes, however, the results from those studies are conflicting. A recent Cochrane meta-analysis suggests a minimum of 500 IU hCG before cleavage stage embryos based on subgroup analysis [31]. However, the results from the meta-analysis should be critically considered due to the small number of studies included in subgroups. It's a limitation that difference in population has seldom been considered as a source of heterogeneity in previous studies. It has been newly reported that the endometrial protein expression is not altered after intrauterine perfusion of 500 IU hCG in fertile women. However, the endometrial protein expression and related pathways are significantly changed in RIF patients within intrauterine perfusion of hCG, besides, RIF patients have a CPR of 19 % and an LBR of 14 % after intrauterine perfusion of 500 IU hCG before ET compared to their failed cycles and all live births have resulted from blastocyst transfers and infusion with 500 IU hCG [32]. The results suggest that RIF patients differ from fertile women on gene expression and endometrial proteome expression, which indicates that different populations may respond differently to hCG perfusion. Therefore, selecting the right population suitable for intrauterine hCG perfusion is important for enhancing the efficacy of hCG perfusion and minimize possible complications. The previous trials or meta-analyses were performed within the "mixed population", however, we perform the current meta-analysis in patients who experienced two or more implantation failures. It is promising that our meta-analysis showed that hCG perfusion before ET increased CPR and LBR in patients who experienced two or more implantation failures.

A limitation should be underlined is that we are not able to perform subgroup analysis based on patients' age, and age is universally acknowledged as the key factor that affects IVF outcomes. But the result of the meta-analysis should not be significantly affected since age was not significantly different between the hCG group and the control group in the trials included. Besides, except for the differences in hCG dose and embryo stage, other potential origins of heterogeneity should also be paid attention to, including the differences in hCG timing, volume of a perfusion fluid, transfer cycle (fresh or frozen). Moreover, the included RCT studies were at unclear risk, which affects the evidence grade of the meta-analysis. Another problem should be emphasized is that, though hCG exerts a beneficial effect on the endometrium as a priming molecule, however, the hCG crosstalk between the embryo and the decidua seems to need continuous hCG, thus, multi-dose of hCG, instead of single-dose of hCG may be needed in the future.

Conclusion

Intrauterine perfusion of hCG is effective in improving clinical pregnancy rate and live birth rate in women experienced two or more implantation failures, which might provide a potential therapeutical intervention for recurrent implantation failure (RIF). Although promising, further evidence from multicenter, randomized controlled trials are needed to confirm the conclusion from the current meta-analysis.

Declaration of Competing Interest

We declare we have no conflict of interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.10.039.

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