J Assist Reprod Genet (2018) 35:273–278
DOI 10.1007/s10815-017-1049-5

ASSISTED REPRODUCTION TECHNOLOGIES

Should intrauterine human chorionic gonadotropin infusions ever be used prior to embryo transfer?

Michelle Volovsky[1,2] · **Martin Healey**[3,4,5] · **Vivien MacLachlan**[5] · **Beverley J Vollenhoven**[2,5,6]

Received: 14 June 2017 / Accepted: 13 September 2017 / Published online: 25 September 2017

Abstract
Purpose The aim of this study was to explore the factors that influence the outcome of intrauterine human chorionic gonadotropin (hCG) infusion at the time of embryo transfer (ET), in particular, the effect of hCG infusions on fresh and frozen embryo transfers (FETs) and whether prior recurrent implantation failure (RIF) impacts upon outcomes.
Method This was a case-control study based on a standardized database from a multi-site in vitro fertilization clinic. The analysis contains 458 cases and 749 matched controls, with an intervention group of those given intrauterine hCG prior to ET and a control group of patients receiving no hCG infusion. Outcomes were defined as clinical pregnancy and live birth rates. Two analyses were performed. The first separated FETs (cases $n = 224$, controls $n = 325$) and fresh ETs (cases $n = 234$, controls $n = 424$), with outcomes calculated in each group. The second analysis divided patients into those with RIF (cases $n = 149$, controls $n = 200$) and those without (cases $n = 309$, controls $n = 549$).
Results Results in fresh ETs demonstrated a 5.8% reduction (adjusted odds ratio (AOR) = 0.60, $p = 0.041$) in clinical pregnancy rates with the use of intrauterine hCG. In those without defined RIF, clinical pregnancy rates were reduced by 8.1% (AOR = 0.61, $p = 0.023$) and live birth rates by 7.2% (AOR = 0.56, $p = 0.32$) with intrauterine hCG use. There were no significant differences in outcomes in FETs and in the RIF cohort.
Conclusion Intrauterine hCG at the time of ET not only seems to have no benefit, but rather a negative effect in fresh ETs and those without RIF.

Keywords Human chorionic gonadotropin · Intrauterine · IVF · Embryo transfer · Implantation

✉ Michelle Volovsky
michelle.volovsky@gmail.com

Martin Healey
kathandmutt@bigpond.com

Vivien MacLachlan
vmaclachlan@monashivf.com

Beverley J Vollenhoven
beverley.vollenhoven@monash.edu

[1] Royal Melbourne Hospital, 300 Grattan St, Parkville, VIC 3050, Australia

[2] Monash University, Wellington Rd & Blackburn Rd, Clayton, VIC 3800, Australia

[3] Royal Women's Hospital, 20 Flemington Rd, Parkville, VIC 3052, Australia

[4] University of Melbourne, Parkville, VIC 3010, Australia

[5] Monash IVF, Level 1, 21–31 Goodwood St, Richmond, VIC 3121, Australia

[6] Monash Health, 246 Clayton Road, Clayton, VIC 3168, Australia

Introduction

Although in vitro fertilization (IVF) has transformed the field of reproductive medicine, the process is not without its difficulties. One such struggle experienced by many is recurrent implantation failure (RIF). Successful implantation relies on both embryonic and maternal factors, and to date, sequential culture media and vitrification of embryos for freezing have allowed for the optimization of embryo quality [1]. However, there is little that targets the endometrium to improve implantation.

During the menstrual cycle, the endometrium undergoes both biochemical and morphological changes to prepare for an embryo, the ideal environment being found during the "window of implantation." Whether an embryo transfer coincides with this ideal window is dependent upon many factors, and may potentially differ between fresh and frozen embryo transfers (FETs). Unlike FETs, fresh transfers occur following oocyte stimulation and collection, which involves exposing the endometrium to supraphysiologic hormone levels when compared with natural conception. This altered hormonal milieu may have an impact upon the intrauterine environment and hence also upon the potential for implantation [2–4]. Moreover, this ideal window is associated not only with optimal endometrial thickness but also with the invasion of various chemical mediators, such as cytokines, adhesion molecules, growth factors, and hormones, that facilitate the implantation process. A hormone involved in the subsequent maintenance of pregnancy is human chorionic gonadotropin (hCG), which is also thought to have direct effects on the endometrium. It has been postulated that hCG is one of the key factors in mediating immunological tolerance of the embryo and may also regulate growth factors involved in angiogenesis, processes vital in establishing embryo attachment [5, 6].

Thus, it was hypothesized that an intrauterine hCG infusion prior to embryo transfer (ET) could potentially increase implantation rates and assist in targeting RIF. Although data available was heterogeneous on this topic, more recent trials [7, 8] and a recent meta-analysis [9] found no change in pregnancy rates with the administration of intrauterine hCG. Our aim was to investigate more specifically whether the outcome of ETs after intrauterine hCG infusions differs between frozen and fresh transfer cycles. Also assessed, was whether the presence of RIF impacts upon the outcomes of those receiving an hCG infusion prior to ET.

Materials and method

This is a retrospective case-control study based on a standardized database from a multi-site private IVF clinic. The dataset used contained 34,259 ETs with 656 of these receiving intrauterine hCG infusions. The patients having ETs were then limited to the state of Victoria to enable standardization and limit differences in the administration of the hCG infusions. Duplicate cycles were excluded and one random ET was chosen per patient to ensure data independence. ET selection was completed using a computer-generated random number allocated to each ET with the smallest random number for each patient selected and used for analysis. A single random ET was chosen instead of the first ET to avoid the selection bias inherent in choosing either the first or last cycle and to make the findings more applicable to a wider population. This left a total of 9790 ETs. Once matching was performed, the analysis included 458 cases and 749 matched controls, with an intervention group consisting of those given an intrauterine hCG infusion prior to ET and a control group of patients receiving no hCG infusion.

Cases were matched according to the following variables: maternal age at ET, number of embryos transferred, treatment cycle number, total number of previous pregnancies and deliveries, progressive number of ETs since a pregnancy or live birth, etiology of infertility (tubal factor, unknown), frozen or fresh ET, intracytoplasmic sperm injection, diabetes, year of ET, and whether RIF was present. Matching was performed with the MatchIt module in R, using the "genetic" method. RIF was defined as patients with three or more consecutively failed cycles in which euploid embryos of reasonable quality were transferred [10, 11]. The study outcomes were clinical pregnancy rates and live birth rates defined as birth over 20-week gestation with heart activity present.

Two analyses were performed. The first analysis separated FETs and fresh ETs, with outcomes calculated in those given an hCG infusion and those not administered the adjunct. The FET subset contained 224 cases and 325 controls and the fresh ET group contained 234 cases and 424 controls. In the second analysis, patients were once again divided, this time into a RIF group and a non-RIF group, yielding 149 RIF patients with 200 controls and 309 patients without RIF with 549 controls. Outcomes in both those with an intrauterine hCG infusion and without were assessed in each group.

To allow for potential confounding effects, logistic regression was performed, which included the matched variables as well as the following: embryo grade, smoking status, BMI, ultrasound findings (polycystic ovaries, endometrioma), presence of endometriosis, ovarian dysfunction, fibroids, PCOS, and clinic site. Logistic regression used the enter methodology, in which all variables are entered into the model simultaneously. The chi-squared test was used to compare proportions and the Mann-Whitney *U* test to compare the continuous variables. For testing, $p < 0.05$ was considered significant. An adjusted odds ratio (AOR), with 95% confidence intervals (CIs), was used to assess these outcomes.

The protocol for intrauterine hCG administration involved the dilution of 1500 IU of hCG in 125 μL of blastocyst media. Of this, 40 μL was then infused into the uterus 10 min to immediately prior to ET. This protocol was based on information in prior studies. The decision to administer an hCG infusion was made by different treating physicians based on the circumstances of each specific case and the patient's wishes. This was in conjunction with a discussion on the benefits and risks of intrauterine hCG administration known at the time of treatment.

Laboratory standards did not change over the 5-year study period (2011–2015). This study had approval from the Human Research Ethics Committee (approval number MH15172M)

for the analysis of data obtained during IVF cycles (project number 07078).

Results

A total of 9790 ETs were included in the analysis, and Table 1 displays the characteristics of the groups, using medians and 95% CIs. The median maternal age was 38.5 in those given intrauterine hCG, similar to those not given an hCG infusion who had a median age of 38.3. Median treatment cycle number was 5 in the hCG population and 4 in the control group.

In the fresh ET group (Table 2), there was a statistically significant reduction in clinical pregnancy rates with the administration of intrauterine hCG. More specifically, clinical pregnancy rates were 30.3% in the hCG infusion group compared to 36.1% in the control group, a reduction of 5.8% (AOR = 0.60, CI = 0.37–0.98, $p = 0.041$). Live birth rates, although not significantly reduced, also trended downward in fresh transfers, 24.4% in those given intrauterine hCG and 28.3% in those not administered intrauterine hCG

Table 1. Study population

Factor	hCG infusion, $n = 458$	No hCG infusion (all), $n = 9332$	p (MW)	No hCG infusion (matched), $n = 749$	p (MW)
Treatment cycle number	5 (1–16.5)	3 (1–12)	<0.001	4 (1–15)	0.001
Year	2013 (2012–2015)	2012 (2010–2015)	<0.001	2013 (2011–2015)	0.17
Body mass index	24.0 (18.4–43.2)	23.9 (18.3–39.3)	0.42	23.9 (18.7–38.1)	0.62
Maternal age	38.5 (28.6–45.6)	36.9 (27.0–45.1)	<0.001	38.3 (28.6–45.3)	0.50
Double embryos used	29.0% (133/458)	14.4% (1341/9332)	<0.001	27.6% (20/749)	0.60
Total prior pregnancies	1 (0–4)	1 (0–5)	0.001	1 (0–4)	0.83
Total prior deliveries	0 (0–2)	0 (0–2)	<0.001	0 (0–2)	0.24
Tubal factor	6.6% (30/458)	9.9% (927/9332)	0.017	4.4% (33/749)	0.10
Ovulation dysfunction	7.2% (33/458)	6.6% (612/9332)	0.59	6.5% (49/749)	0.66
Endometriosis	9.2% (42/458)	10.4% (967/9332)	0.41	8.8% (66/749)	0.83
Fibroids	3.1% (14/458)	3.5% (322/9332)	0.65	2.8% (21/749)	0.80
Idiopathic	27.9% (128/458)	31.0% (2896/9332)	0.16	31.4% (235/514)	0.21
Unknown	33.0% (151/458)	27.2% (2535/9332)	0.007	33.9% (254/749)	0.74
PCO on ultrasound	21.2% (97/458)	22.2% (2068/9332)	0.62	19.4% (145/749)	0.44
PCOS	6.1% (28/458)	4.5% (423/9332)	0.12	4.7% (35/749)	0.28
Endometrioma on ultrasound	0.2% (1/458)	0.4% (35/9332)	0.59	0.4% (3/749)	0.59
FET	48.9% (224/458)	39.4% (3675/9332)	<0.001	43.4% (325/749)	0.06
Intracytoplasmic sperm injection	81.7% (374/458)	75.6% (7056/9332)	0.003	80.6% (604/749)	0.66
Diabetic	3.3% (15/458)	1.0% (95/9332)	<0.001	2.1% (16/749)	0.23
Smoker	1.7% (8/458)	2.5% (235/9332)	0.30	1.6% (12/749)	0.85
ETs since live birth	3 (0–15)	1 (0–9)	<0.001	2 (0–12)	0.013
ETs since clinical pregnancy	2 (0–10)	1 (0–7)	<0.001	2 (0–9)	0.40
RIF	32.5% (149/458)	12.2% (1134/9332)	<0.001	26.7% (200/749)	0.03
Embryo age at transfer			0.56		0.15
Day 2	3.3% (15/458)	5.9% (556/9932)		4.1% (31/749)	
Day 3	27.9% (128/458)	25.5% (2375/9332)		30.6% (229/749)	
Day 4	3.3% (15/458)	3.8% (355/9332)		3.9% (29/749)	
Day 5	65.5% (300/458)	64.8% (6043/9332)		61.4% (460/749)	
Embryo grade			0.23		0.32
A	15.7% (72/458)	20.4% (1908/9332)		17.9% (134/749)	
B	32.8% (150/458)	33.0% (3075/9332)		34.8% (261/749)	
C	28.4% (130/458)	19.4% (1810/9332)		23.4% (175/749)	
D	23.1% (106/458)	27.2% (2539/9332)		23.9% (179/749)	

ET embryo transfer, *FET* frozen embryo transfer, *hCG* human chorionic gonadotropin, *MW* Mann-Whitney *U* test, *PCO(S)* polycystic ovary (syndrome), *RIF* recurrent implantation failure

(AOR = 0.67, CI = 0.35–1.30, p = 0.24). Analysis of FETs (Table 2) did not demonstrate statistically significant differences; however, once again, there was a downward trend in clinical pregnancy and live birth rates between those given an hCG infusion and those not. Of the patients administered intrauterine hCG, 26.3% had a clinical pregnancy compared to 32.6% in the control group (AOR = 0.68, CI = 0.39–1.19, p = 0.17). Live birth rates were 21.0% in the hCG cohort and 27.7% in the control group (AOR = 0.59, CI = 0.30–1.16, p = 0.17). The potential confounder of RIF status was adjusted for in the logistic regression model.

When evaluating outcomes between patients with RIF and those without (Table 3), the current study demonstrated statistically significant reductions in both clinical pregnancy and live birth rates in those without defined RIF. In these non-RIF patients, clinical pregnancy rates were 8.1% lower with the introduction of intrauterine hCG, 29.8% in the case group and 37.9% among controls (AOR = 0.61, CI = 0.40–0.94, p = 0.023). Live birth rates were 24.3% in the hCG infusion group compared to 31.5% in the control group, a reduction of 7.2% (AOR = 0.56, CI = 0.33–0.95, p = 0.32). In the RIF population, there was no demonstrable difference in clinical pregnancy and live birth rates with the use of intrauterine hCG. Clinical pregnancy rates were 25.5% in both patients administered an hCG infusion and those not given the adjunct (AOR = 0.84, CI = 0.40–1.75, p = 0.81). Live birth rates were once again very similar, 19.5% in the case group and 18.5% among controls (AOR = 0.91, CI = 0.31–2.65, p = 0.86). The potential confounder of fresh versus FET status was adjusted for in the logistic regression model.

Discussion

In our study, we investigated whether pregnancy outcomes with intrauterine hCG administration differed between frozen and fresh transfer cycles. Findings demonstrated significantly lowered clinical pregnancy rates in fresh ETs with the use of hCG infusions.

During fresh transfers, the endometrium is exposed to high concentrations of hormones amid the course of oocyte collection. Follicle-stimulating hormone not only drives ovarian stimulation but may also result in the altered growth, development, and receptivity of the endometrium. Moreover, prior to oocyte retrieval, an hCG trigger is given, introducing another hormonal element not consistent with the course of natural conception. Given that the intrauterine environment plays a vital role in an embryo's ability to interact with and subsequently implant in the endometrium, this process of oocyte collection may interfere with successful implantation [2–4]. FETs are therefore perhaps more likely to coincide with the ideal milieu for implantation [3, 12, 13].

There have been few studies analyzing this relationship and comparing outcomes between fresh and FETs. A meta-analysis [14], which included three trials, suggested that outcomes are improved in FETs, with higher rates of clinical pregnancy and ongoing pregnancy when compared to fresh cycles. There has since been a meta-analysis comparing live birth rates between an initial fresh cycle and subsequent FETs, with solely FETs. Findings demonstrated no difference in outcomes between the two [13].

Moreover, review of the available literature yielded limited comparisons between fresh and FETs with the use of hCG infusions. One randomized control trial [7] evaluated intrauterine hCG administration separately in both fresh ETs and FETs, finding no significant difference in implantation and ongoing pregnancy rates within each group. However, most other studies assessing outcomes of intrauterine hCG infusions have analyzed data among only fresh cycles [8, 15] or have combined the two cycle types [16]. The outcomes of these studies have been mixed; with one of the fresh cycle trials [15] and the combined cycle trial [16] demonstrating increases in pregnancy rates with intrauterine hCG. Both of these however had small sample sizes and were performed among patients under 40. Given that advanced maternal age is an important limiting factor in IVF, perhaps the seemingly positive effect of hCG was more evident in these younger cohorts considering their overall higher levels of success. The second trial among only fresh transfers [8] was of a larger scale and also included older patients, allowing for a more representative cohort. It demonstrated no difference in outcomes with hCG infusions. Given the mixed nature of prior research, it is difficult to ascertain whether there have been differences between FETs and fresh ETs.

The current study found that intrauterine hCG administration in fresh ETs is associated with lower clinical pregnancy rates. This is inline with prior research on the potential effects of hCG on implantation [2–4, 12] as well as data comparing outcomes between FET and fresh ETs overall [13, 14]. Our finding indicates that the addition of intrauterine hCG in cycles where an hCG trigger is given during oocyte collection may accentuate the possible negative effects of hCG on implantation [2–4]. This raises a new hypothesis; increasing quantities of hCG may be potentially harmful to endometrial receptivity. Data focusing on a dose-response relationship between hCG and implantation is very limited. There is one randomized control pilot trial [17] aimed at defining an optimal dose of hCG to add to recombinant FSH during controlled ovarian stimulation, which investigated their hypothesis through a dose-response study. Dose-dependent increases in estradiol, progesterone, and androstenedione levels were demonstrated with increasing amounts of hCG given during stimulation. Interestingly, there was a plateau in estrogen levels with doses of hCG above 100 IU/day, with no further demonstrated increase in estrogen with hCG dosing above this. It is

Table 2. FET and fresh ET results

	hCG = Y	hCG = N	Crude OR	Adjusted OR	*p* Value
FET					
Clinical pregnancy	26.3% (59/224)	32.6% (106/325)	0.74 (0.50–1.10), $p = 0.12$	0.68 (0.39–1.19)	0.17
Live birth	21.0% (47/224)	27.7% (90/325)	0.69 (0.45–1.06), $p = 0.07$	0.59 (0.30–1.16)	0.12
Fresh ET					
Clinical pregnancy	30.3% (71/234)	36.1% (153/424)	0.77 (0.54–1.10), $p = 0.14$	0.60 (0.37–0.98)	0.041
Live birth	24.4% (57/234)	28.3% (120/424)	0.82 (0.56–1.19), $p = 0.28$	0.67 (0.35–1.30)	0.24

ET embryo transfer, *FET* frozen embryo transfer, *hCG* human chorionic gonadotropin, *OR* odds ratio

plausible that there is a similar plateau effect with the administration of intrauterine hCG, more pronounced in fresh cycles as hCG levels are already raised due to the hCG trigger given prior to oocyte collection. Additional quantities of hCG beyond a certain plateau point may not only have no further benefit but perhaps a harmful effect.

It has been well established that hCG plays a key role in the maintenance of a healthy pregnancy. Given that intrauterine hCG infusions were administered 10 min prior to ET, a tangible effect on the endometrium may not be appreciable for several hours following infusion. Administration of hCG has been associated with the downregulation of T cells and natural killer cells present in the endometrium. HCG has also been found to inhibit proteins such as IGF-binding protein-1 and M-CSF that are involved in the decidualization of the endometrium, thus postponing the process. Additionally, VEGF, a pro-angiogenic growth factor, was found to be stimulated in the presence of hCG, indicating that the hormone may have effects on vascularization and angiogenesis [6]. Perhaps the manifestation of these seemingly positive effects occurs out of natural sequence during a critical time in the process of implantation, hindering the embryo's intrinsic ability to successfully attach and implant. Moreover, the exogenous administration of hCG prior to ET may also interfere with subsequent endogenous hCG production vital for pregnancy. Hence, administering hCG above a certain level either systemically or as an additional intrauterine infusion may not only have no further physiological benefit but rather a harmful effect on the establishment and progression of pregnancy. Additional studies analyzing this relationship would be beneficial; however, given the demonstrated potential for harm, the administration of intrauterine hCG infusions should now only be used in adequately designed research trials, especially prior to fresh ETs.

We also analyzed whether patients with RIF had differing outcomes with intrauterine hCG administration. RIF is multifactorial. Some uterine causes of RIF are easily screened for and diagnosed, such as polyps, fibroids, and congenital abnormalities. Outside of these obvious pathologies, there are several more subtle changes that occur in the endometrium. These range from dysregulated immune cell function, altered expression of adhesion molecules to impaired angiogenesis. These processes are not easily diagnosed, frequently earning the label of idiopathic RIF [10, 11]. It is in this population that optimizing the endometrium may be key to improving implantation rates.

To the best of our knowledge, this is the first study comparing intrauterine hCG administration in the RIF and non-RIF populations. The current study demonstrated a significant reduction in clinical pregnancy and live birth rates in patients without RIF, those with less than three prior failed transfers. These patients are likely to have a more physiologic intrauterine environment, and hence, the introduction of intrauterine hCG perhaps has a more pronounced negative effect than in those with an already poorly receptive endometrium. Moreover, there was no advantage demonstrated in patients

Table 3. RIF and no-RIF results

	hCG = Y	hCG = N	Crude OR	Adjusted OR	*p* Value
RIF					
Clinical pregnancy	25.5% (38/149)	25.5% (51/200)	1.00 (0.60–1.67), $p = 1.00$	0.84 (0.40–1.75)	0.81
Live birth	19.5% (29/149)	18.5% (37/200)	1.06 (0.60–1.89), $p = 0.82$	0.91 (0.31–2.65)	0.86
No RIF					
Clinical pregnancy	29.8% (92/309)	37.9% (208/549)	0.70 (0.51–0.95), $p = 0.017$	0.61 (0.40–0.94)	0.023
Live birth	24.3% (75/309)	31.5% (173/549)	0.70 (0.50–0.97), $p = 0.025$	0.56 (0.33–0.95)	0.032

hCG human chorionic gonadotropin, *OR* odds ratio, *RIF* recurrent implantation failure

with defined RIF, the one patient group where a treatment enhancing endometrial receptivity should improve outcomes. This further reinforces the lack of benefit of intrauterine hCG infusions.

As with most research, there are potential limitations to our findings. HCG infusion use was in part collated from clinician's notes. Hence, retrospective and non-standardized data add some bias. Furthermore, during intrauterine hCG infusions, extra catheterization of the uterine cavity occurs, a process not occurring in the control group, thus adding a potential confounder. However, this factor was controlled for in the aforementioned studies and did not seem to influence outcomes. Moreover, our findings regarding fresh ETs were not statistically significant in live birth rates as they were in clinical pregnancy rates. Numbers however were small and live birth rates did trend downward; hence, a larger sample would have likely corrected this.

Conclusion

Intrauterine hCG infusion prior to fresh ETs was demonstrated to have a negative effect on clinical pregnancy rates. Furthermore, this adjunct had a harmful effect in patients without RIF. Given that there is limited evidence on hCG infusions among varying patient groups, perhaps there is room for additional research in this area. However, as there not only seems to be no benefit, but rather a potential for harm in certain patients, use of intrauterine hCG infusions should be limited to within adequately designed research trials. Less may be more for some patients.

References

1. Loutradi KE, Kolibianakis EM, Venetis CA, Papanikkolaou EG, Pados G, Bontis I, et al. Cryopreservation of human embryos by vitrification or slow freezing: a systematic review and meta-analysis. Fertil Steril. 2008;90(1):186–93.
2. Bourgain C, Devroey P. The endometrium in stimulated cycles for IVF. Hum Reprod Update. 2003;9(6):515–22.
3. Haouzi D, Assou S, Mahmoud K, Tondeur S, Reme T, Hedon B, et al. Gene expression profile of human endometrial receptivity: comparison between natural and stimulated cycles for the same patients. Hum Reprod. 2009;24(6):1436–45.
4. Kolibianakis E, Bourgain C, Albano C, Osmanagaoglu K, Smitz J, Van Steirteghem A, et al. Effect of ovarian stimulation with recombinant follicle-stimulating hormone, gonadotropin releasing hormone antagonists, and human chorionic gonadotropin on endometrial maturation on the day of oocyte pick-up. Fertil Steril. 2002;78(5):1025–9.
5. Licht P, Russu V, Lehmeyer S, Wildt L. Molecular aspects of direct LH/hCG effects on human endometrium—lessons from intrauterine microdialysis in the human female in vivo. Reprod Biol. 2001;1(1):10–9.
6. Tsampalas M, Gridelet V, Berndt S, Foidart JM, Geenen V, Perrier d'Hauterive S. Human chorionic gonadotropin: a hormone with immunological and angiogenic properties. J Reprod Immunol. 2010;85(1):93–8.
7. Hong KH, Forman EJ, Werner MD, Upham KM, Gumeny CL, Winslow AD, et al. Endometrial infusion of human chorionic gonadotropin at the time of blastocyst embryo transfer does not impact clinical outcomes: a randomized double-blind, placebo-controlled trial. Fertil Steril. 2014;102(1):1591–5.
8. Wirleitner B, Schuff M, Vanderzwalmen P, Stecher A, Okhowat J, Hradecky L, et al. Intrauterine administration of human chorionic gonadotropin does not improve pregnancy and life birth rates independently of blastocyst quality: a randomised prospective study. Reprod Biol Endocrinol. 2015;13(1):70.
9. Osman A, Pundir J, Elsherbini M, Dave S, El-Toukhy T, Khalaf Y. The effect of intrauterine hCG injection on IVF outcome: a systematic review and meta-analysis. Reprod BioMed Online. 2016;33(3):350–9.
10. Margalioth EJ, Ben-Chetrit A, Gal M, Eldar-Geva T. Investigation and treatment of repeated implantation failure following IVF-ET. Hum Reprod. 2006;21(12):3036–43.
11. Coughlan C, Ledger W, Wang Q, Lui F, Demirol A, Gurgan T, et al. Recurrent implantation failure: definition and management. Reprod BioMed Online. 2014;28(1):14–38.
12. Horcajadas JA, Diaz-Gimeno P, Pellicer A, Simon C. Uterine receptivity and the ramifications of ovarian stimulation on endometrial function. Semin Reprod Med. 2007;25(6):454–60.
13. Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S. Fresh versus frozen embryo transfers in assisted reproduction. Cochrane Database Syst Rev 2017;(3):Art. No.: CD011184. DOI: https://doi.org/10.1002/14651858.CD011184.pub2.
14. Roque M, Lattes K, Serra S, Sola I, Geber S, Carreras R, et al. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. Fertil Steril. 2013;99(1):156–62.
15. Mansour R, Tawab N, Kamal O, El-Faissal Y, Serour A, Aboulghar M, et al. Intrauterine injection of human chorionic gonadotropin before embryo transfer significantly improves the implantation and pregnancy rates in in vitro fertilization/intracytoplasmic sperm injection: a prospective randomized study. Fertil Steril. 2011;96(1):1370–4.
16. Santibañez A, García J, Pashkova O, Colín O, Castellanos G, Sánchez AP, et al. Effect of intrauterine injection of human chorionic gonadotropin before embryo transfer on clinical pregnancy rates from in vitro fertilisation cycles: a prospective study. Reprod Biol Endocrinol. 2014;12(1):9.
17. Thuesen LL, Smitz J, Loft A, Nyboe Anderson A. A randomized controlled dose–response pilot study of addition of hCG to recombinant FSH during controlled ovarian stimulation for in vitro fertilization. Hum Reprod. 2012;27(10):3074–84.