ABSTRACT

Purpose This study aims to review the literature and perform a meta-analysis to determine if the presence of a corpus luteum has an impact on treatment outcomes in thaw cycles, where blastocyst embryos are transferred.

Method PubMed, EMBASE, CENTRAL and CINAHL were searched for papers published between January 2017 and 27 July 2020. Additional articles were selected from the reference list of the results and previous reviews. Three reviewers independently reviewed and extracted data. The meta-analysis was conducted through RevMan V.5.4.1. Studies were quality assessed with the Cochrane risk of bias tool and the Newcastle-Ottawa Scale.

Results Nine publications were included for data extraction and subsequent meta-analysis. Two studies were randomised controlled trials, and seven were cohort studies. Subgroup analysis of the different study designs was performed. While the rates of positive human chorionic gonadotropin results (relative risk, RR 1.06, 95% CI 0.95 to 1.18) and clinical pregnancies (RR 1.06, 95% CI 0.95 to 1.22) were comparable between the two groups, the rates of live births were higher in thaw cycles with a corpus luteum (RR 1.14, 95% CI 1.06 to 1.22). Analysis of pregnancy losses demonstrated that both biochemical pregnancy (early miscarriage) (RR 0.71, 95% CI 0.62 to 0.83) and miscarriages (RR 0.72, 95% CI 0.62 to 0.83) were increased in cycles without a corpus luteum.

Conclusion Where clinically appropriate, the use of cycle types that have a functional corpus luteum should be favoured. There were several limitations to this study, including the quality of studies and the inherent bias of retrospective cohort studies. Further, high-quality research, particularly randomised controlled trials with blastocyst embryos, is required to further explore these findings.

PROSPERO registration number CRD42020209583.
patient ovulating, either spontaneously, or with the assistance of ovulation induction agents or trigger. These protocols result in the formation of a corpus luteum (CL), which produces endogenous hormonal support for early pregnancy, with or without further luteal phase support with exogenous progesterone. These methods are typically used in normo-ovulatory women and uses no or minimal medications. However, these methods require extensive monitoring, which may be inconvenient for the patient and clinician. These cycles may also result in some degree of unpredictability in terms of embryo transfer timing, with some clinics preferring not to perform embryo transfers on certain days, such as weekends. The artificial cycle (AC) is an alternative method of endometrial preparation which relies on the administration of exogenous oestrogen (E2) to induce endometrial proliferation and growth suppression of the dominant follicle, and the subsequent administration of progesterone (P4) to induce the secretory phase of the endometrium. This protocol aims to mimic the body’s physiological process of endometrial priming and maturation. As the AC does not involve ovulation, a CL is not formed during this process and hormone supplementation is continued until placental autonomy is established at 10–12 weeks gestation. The AC is typically used in situations where a woman has ovulatory dysfunction and is unable to produce a healthy CL, or in normo-ovulatory women due to its convenience for both the patient and clinician.

Previous studies have found that treatment outcomes of tNC and ACs have been comparable. Some studies, however, have noted that thaw cycles without a CL may have experienced higher rates of early pregnancy loss. This review aimed to explore these findings further. Trials in reproductive medicine are often small and not adequately powered, hence a meta-analysis is a useful technique to observe trends that may not be obvious with smaller, individual studies.

Our objective is to compare the treatment outcomes of blastocyst embryo transfers in thaw cycles with and without a CL.

To our knowledge, this is the first review to specifically look at treatment outcomes of thaw cycles comparing the presence and absence of a CL. Similarly, to align more closely with the contemporary clinical practices, this review focuses on data from blastocysts transfers only.

**MATERIALS AND METHODS**

**PICO statement**

Population—women undergoing thaw embryo transfer cycles.

Intervention—thaw cycles which include CL formation and therefore endogenous progesterone production (natural and ovulation induction cycles).

Comparison—thaw cycles that rely solely on exogenous progesterone production (artificial thaw cycles).

Outcomes—live birth (LB), clinical pregnancy, biochemical pregnancy, pregnancy loss (miscarriage rate).

Clinical question—are clinical outcomes of thaw embryo transfer cycles differ, depending on the presence or absence of CL (endogenous progesterone production)?

**Patient and public involvement**

No patients involved.

**Search strategy**

We conducted a search on the 27 July 2020, using four databases: PubMed/MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL). The search strategies were based on an earlier Cochrane systematic review that was published in 2017. The search strategy used three key concepts: endometrial preparation AND frozen embryos AND reproductive outcomes. The detailed search strategy can be found in online supplemental file 1. Searches were limited to 2017 to July 2020 as we looked through the reference lists of studies from previously conducted systematic reviews prior to 2017 for potential additional studies. No language restrictions were used in the search. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

After the removal of 644 duplications, the search yielded 2184 studies. Four additional studies were hand selected from the references of the retrieved articles. The initial search was independently screened based on title and abstract by three reviewers (AP, GR and JG). Any discrepancies were discussed among the three reviewers and a consensus decision was reached.

**Inclusion criteria**

To be included, studies had to contain data on blastocyst transfers which utilised thaw cycles involving the presence and absence of a CL. Cycles which involved the presence of a CL included tNC, mNC and mildly SC. Cycles without a CL included ACs with or without gonadotropin-releasing hormone analogue (GnRHa) suppression. Blastocysts were defined as day 5 or 6 embryos.

**Exclusion criteria**

Studies that included cleavage stage embryos or blastocysts data pooled with cleavage staged embryos were excluded. We also excluded data from donor eggs, or from non-primary sources such as reviews, letters, book chapters and conference abstracts.

**Outcomes and definitions**

The primary outcome examined was LB or ongoing pregnancy rate where LB was not available. Secondary outcomes that were analysed were rates of positive human chorionic gonadotropin (hCG), clinical pregnancy, biochemical pregnancy and miscarriage.

Where applicable, we used the definitions agreed on by the International Glossary on Infertility and Fertility...
Care, 2017. An LB was defined as a birth which demonstrated evidence of life after at least 22 weeks gestation. An ongoing pregnancy was defined as a viable pregnancy which reached a gestational age of at least 20 weeks. Due to the low rates of pregnancy loss after 29 weeks gestation, ongoing pregnancy rates were included in the analysis of LB rates. However, we performed a subanalysis of the studies which reported LBs as their primary outcome in addition to the total LB rate which would include ongoing pregnancy rates. A positive hCG was defined as a hCG of ≥5. Where positive hCG was not available, it was calculated through the addition of biochemical pregnancies and clinical pregnancies. The study by Alur-Gupta et al. did not report clinical pregnancy, hence it was calculated by adding the number of LBs, ectopic pregnancies, stillbirths and spontaneous abortions reported. A clinical pregnancy was defined as a positive hCG with evidence of at least one gestational sac on ultrasound, including ectopic pregnancies. Biochemical pregnancies were classified as a pregnancy which yielded a positive hCG result but did not reach the stage of clinical pregnancy.

Where biochemical pregnancy was not reported, it was calculated by subtracting the reported clinical pregnancies from the number of positive hCG results. Similarly, miscarriage referred to any pregnancy that did not progress past 20 weeks gestation. Where therapeutic abortions were reported, those cycles were removed from the analysis. Due to the nature of the studies included, we reported data per thaw cycle, as data per woman was not possible to calculate.

**Data extraction process**

The data were independently extracted by three reviewers (GR, AP and JG) for author/s, year of publication, title of the article, year of trial, study design, number cycles, demographics of women, positive hCG, clinical pregnancy, biochemical pregnancy, miscarriage, LBs, or ongoing births where LBs were not available. The data were collated by a single reviewer (JG) and any discrepancies were discussed among three reviewers and until a consensus was reached.

**Quality assessment**

Included randomised controlled trials (RCTs) were quality assessed using the Revised Cochrane Risk of Bias Tool for randomised trials (RoB 2). The Newcastle-Ottawa Scale for assessing the quality of non-randomised studies in meta-analyses was used to assess cohort studies. Both tools were used to assess bias at an individual study level. The quality assessment was used to judge the strength of evidence reported, and to guide our interpretations of the reported findings. Results of this can be found in online supplemental files 2 and 3.

**Statistical analysis**

The meta-analysis was performed using RevMan V.5.4.1 computer programme, The Cochrane Collaboration, 2020. Meta-analyses of rates of positive hCG, LBs, biochemical pregnancy and miscarriage were conducted with a fixed-effect model where there was low heterogeneity among the studies, and a random-effect model where there was a significant heterogeneity. Heterogeneity was assessed with both the I² and χ² statistic. P values of χ² that were <0.05, and I² >50% were considered representative significant heterogeneity. Relative risk with 95% CIs was used as the principal summary measure. The Mantel-Haenszel method was applied to estimate the pooled effect size. A funnel plot analysis was conducted for each meta-analysis to assess for reporting bias (online supplemental file 4).

As we included studies that reported ongoing pregnancy rates where LB rates were not available, we conducted a subgroup analysis which individually looked at LB rates and miscarriages from studies which reported LBs as their primary outcome. Separate analysis grouped by study design is shown in online supplemental files 5 and 6, respectively.

**RESULTS**

After the removal of duplicates, the search yielded 2184 articles. After screening by title and abstract, we reviewed 20 full-text and included an additional 4 articles from the reference lists of included articles and previous systematic reviews. We included nine studies in our final quantitative analysis. Two of which were RCTs, both of which studied small sample sizes. The remaining seven were retrospective cohort studies, which followed a much larger sample size. This protocol is summarised in figure 1. The final meta-analysis included a total of 6138 cycles with a CL and 3491 cycles without a CL.

A summary of the studies included in the meta-analysis can be found in table 1. The largest study included 3030 cycles by Pakes et al., and the smallest study included 116 cycles by Sheikhi et al. The average quality of the studies was rated with a fair to moderate risk of bias.

**Positive hCG rates**

From the eight studies, a total of 6138 cycles involving a CL were assessed. Of these, 2690 cycles (44%) resulted in a positive hCG. In the 3491 cycles without a CL, 1737 (50%) resulted in a positive hCG. The individual and combined estimates for positive-hCG are shown in figure 2. The pooled estimates for positive hCG (relative risk, RR 1.00, 95% CI 0.95 to 1.05) showed no statistically significant difference in rates of positive hCG between cycles with and without a CL. Subgroup analysis of positive hCG rates by study design are shown in online supplemental file 5.

**Clinical pregnancy rates**

Out of the 6138 cycles which involved the presence of a CL, 2271 (37%) progressed to a clinical pregnancy. In the 3491 cycles without a CL, 1388 (40%) progressed to a clinical pregnancy. The individual and combined estimates
for clinical pregnancy are shown in figure 2. The pooled estimates for clinical pregnancy rates (RR 1.06, 95% CI 0.96 to 1.18) showed no statistical difference between the two groups.

Due to the heterogeneity of the studies a random effect model was used. To overcome the statistical heterogeneity of the studies we performed a sensitivity analysis after removing the study by Givens et al which was the only study to observe a higher clinical pregnancy rate in AC compared with NCs. The results of this are shown in online supplemental file 7. The sensitivity analysis showed that LB rates were statistically higher in the cycles involving the presence of a CL (RR 1.12, 95% CI 1.05 to 1.20).

Based on these two analyses, it can be inferred that the likely point estimate lays somewhere between 1.06 and 1.12, favouring cycles with CL. The CI of this point estimate may include 1, but there is a trend towards cycles with CL resulting in a higher clinical pregnancy rate. While statistical significance may not be demonstrable, this finding may be clinically significant. Subgroup analysis of clinical pregnancy rates by study design is shown in online supplemental file 5.

**LB rates**

Seven studies reported LB rates as their primary outcome (one prospective randomised trial and five retrospective studies). Two studies reported ongoing
| Study | Design | Cycles with blastocysts (n) | Study Period | Allocation | Women (n) | Study population | Mean age, years (SD) | BMI, kg/m² (SD) | Positive hCG (n) | CP (n) | LB/OP | Quality* |
|-------|--------|----------------------------|--------------|------------|-----------|-----------------|---------------------|------------------|----------------|--------|-------|----------|
| Alur-Gupta (2018)16 | Retrospective Cohort | 1021 Cycles (with CL=104, without CL=917) | 2013–2017 | Clinical judgement | NR | Both normo-ovulatory patients and women with ovulatory dysfunction | NC=35.6 (3) | AC=35.4 (4) | NC=23.2 (3.7) | AC=25.1 (5.3) | Wt CL=64, With CL=55 | With CL=602, Without CL=523 | LB | Fair |
| Cardenas Armas (2019)14 | Retrospective Cohort | 207 Cycles (with CL=32; without CL=175) | 2014–2017 | Preference, cycle characteristics | 860 | normo-ovulatory patients, no PGT | NC=36.15 (0.29) | AC (Transdermal)=35.71 (0.17) | NC=22.6 (2.1) | AC (Transdermal)=21.6 (2.2) | Wt CL=16, With CL=76 | With CL=186, Without CL=60 | LB | Good |
| Chang (2011)11 | Retrospective Cohort | 648 Cycles (with CL=444, without CL=204) | 2007–2009 | Convenience, Cost | 611 | normo-ovulatory patients with regular menstruation | NC=34.2 (3.7) | mNC=33.7 (3.3) | AC=33.7 (3.7) | NC=20.7 (2.8) | mNC=20.5 (3.5) | AC=20.7 (2.4) | With CL=229, Without CL=107 | OP | Good |
| Givens (2009)10 | Retrospective Cohort | 1119 Cycles (with CL=858, without CL=261) | 2000–2006 | Clinical judgement | 807 | Both normo-ovulatory patients and women with ovulatory dysfunction | mNC=35.1 (4.1) | AC=34.8 (5.0) | NR | With CL=369, Without CL=141 | With CL=284, Without CL=105 | LB | Fair |
| Greco (2016)12 | RCT | 222 Cycles (with CL=109, without CL=113) | 2015 | Computer-generated randomisation (non-concealed) | 236 | normo-ovulatory patients, PGT | mNC=35.2 (3.6) | AC + GnRHa = 35.5 (3.8) | mNC=22.1 (8.1) | AC + GnRHa = 22.1 (3.8) | With CL=68, Without CL=70 | With CL=59, Without CL=523 | LB | Some concerns |
| Le (2017)13 | Retrospective Cohort | 378 cycles (with CL 197, without CL=181) | 2006–2014 | Clinical judgement | 428† | Both normo-ovulatory patients and women with ovulatory dysfunction | mNC=34.3 (4.2) | AC=33.3 (4.8) | mNC=25.3 (5.5) | AC=27.7 (7.0) | With CL=120, Without CL=110 | With CL=107, Without CL=95 | LB | Fair |
| Levi Setti (2020)15 | Retrospective Cohort | 2888 Cycles (with CL=2304, without CL=584)‡ | 2011–2017 | Clinical judgement | NR | Both normo-ovulatory patients and women with ovulatory dysfunction; no PGT | NC=35.4 (4.3) | mNC=35.3 (4.0) | AC=34.4 (4.2) | NC=21.8 (3.0) | mNC=21.8 (8.0) | AC=22.5 (3.3) | With CL=1012, Without CL=243 | LB | Fair |

Continued
| Study       | Design            | Cycles with blastocysts (n) | Study Period | Allocation           | Women (n) | Study population                                           | Mean age, years (SD) BMI, kg/m² (SD) | Outcomes | Positive hCG (n) | CP (n) | LB/OP | Quality* |
|-------------|-------------------|-----------------------------|--------------|-----------------------|-----------|----------------------------------------------------------|-------------------------------------|-----------|----------------|--------|-------|----------|
| Pakes (2020) | Retrospective Cohort | 3030 Cycles (with CL=2033, without CL=997) | 2015–2018 | Clinical judgement   | NR        | Both normo-ovulatory patients and women with ovulatory dysfunction; no PGT | NC=35.56 (0.89) AC=33.79 (0.14)     | NR        | With CL=802 | With CL=627 | LB     | Fair     |
| Sheikhi (2018) | RCT               | 116 Cycles (with CL=57, without CL=59) | 2015–2016 | Computer-generated randomisation (non-concealed) | 123‡       | Normo-ovulatory patients, without severe endometriosis | mNC=29.71 (3.79) mSC=30.31 (4.58) AC=30.5 (5.59) | mNC=26.19 (3.24) mSC=25.80 (3.29) AC=25.36 (5.27) | With CL=10 | With CL=10 | Without CL=12 | Without CL=9 | OP | Some concerns |

First author stated only.
*Quality assessed with Cochrane Risk of Bias tool 2 or Newcastle-Ottawa Scale.
†66 women excluded due to various reasons.
‡Therapeutic abortion cycles excluded.
§Demographic data extracted from table 1 of study (conflicted data reported in written results section).
¶7 women lost to follow-up.
AC, artificial cycle; CL, corpus luteum; GnRHa, gonadotropin-releasing hormone analogue; LB, live birth; mNC, modified natural cycle; mSC, mildly stimulated cycle; NR, not reported; PGT, preimplantation genetic testing; RCT, randomised controlled trial.
Figure 2  Meta-analysis comparing rates of positive hCG, clinical pregnancy, and live births in cycles with and without a CL. CL, Corpus Luteum; hCG, human chorionic gonadotropin; M-H, Mantel-Haenszel.
pregnancy rates as their primary outcome (one prospective randomised trial and one cohort study).\textsuperscript{21,23}

Of the 6138 cycles which involved the presence of a CL, 1902 (31\%) resulted in an LB or progressed to an ongoing pregnancy. In the 3491 cycles without a CL, 1124 (32\%) resulted in an LB or ongoing pregnancy. The individual and combined estimates for LBs are shown in figure 2. The pooled estimates for LBs (RR 1.14, 95\% CI 1.06 to 1.22) showed a statistically significant difference in favour of cycles with a CL. This translates into a clinically significant approximate 14\% increase chance of LB from cycles with a CL.

A subgroup analysis was conducted which looked at studies that only reported LB as their outcome. The results of this can be found in figure 2. When including only the studies which included LB rates, the estimated LB rate remained significantly higher in the thaw cycles with a CL (RR 1.16, 95\% CI 1.07 to 1.26). Subgroup analysis of LB rates by study design is shown in online supplemental file 5.

**Biochemical pregnancy rates**

In the 2690 positive hCG results in the cycles with a CL, 416 (15\%) were biochemical pregnancies that did not progress to a clinical pregnancy (ie, ended in an early miscarriage). In the 1737 positive hCG results in the cycles without a CL, 347 (20\%) of these resulted in biochemical pregnancies, which likewise did not progress to a clinical pregnancy. The individual and combined estimates for biochemical pregnancies are shown in figure 3. The estimated biochemical pregnancy rates (RR 0.71, 95\% CI 0.62 to 0.82) were significantly lower in the cycles with a CL. Subgroup analysis of biochemical pregnancy rates by study design is shown in online supplemental file 6.

**Miscarriage rates**

Of the 2271 clinical pregnancies in the cycles with a CL, 441 (19\%) did not progress and resulted in a miscarriage. Of the 1388 clinical pregnancies which resulted from cycles without a CL, 321 clinical pregnancies (23\%) did not progress. The individual and combined estimates for biochemical pregnancies are shown in figure 3. The estimated miscarriage rates (RR 0.72, 95\% CI 0.63 to 0.83) were statistically lower in the cycles with a CL.

A subgroup analysis was conducted which only included studies which reported LB rates. However, this had no material impact on the results. Subgroup analysis of miscarriage rates by study design is shown in online supplemental file 6.

**DISCUSSION**

This meta-analysis demonstrates that while there were no statistically significant differences in rates of positive hCG and clinical pregnancies between thaw cycles with and without a CL, there were statistically higher rates of LBs and lower rates of both early and late pregnancy losses in thaw cycles in the presence of a CL. This suggests that a CL may not influence initial implantation but may play a significant role in sustaining a pregnancy once an embryo has implanted.

Previous publications have demonstrated conflicting results regarding efficacy of thaw cycles with and without a CL. The ‘ANTARCTICA’ trial which compared treatment outcomes of mNC to AC protocols did not find any statistical difference in reproductive outcomes among the two groups.\textsuperscript{6} However, this study did not achieve adequate statistical power to examine the outcomes in question. Furthermore, a large proportion of cleavage stage embryos were included in their data, and data on blastocysts transfers was not clearly separated or analysed. Similarly, a study by Sahin et al, which retrospectively analysed treatment outcomes after mNC and ACs with GnRHa, concluded that LB rates and pregnancy loss rates were comparable between the two groups.\textsuperscript{27} However, a statistically greater number of thawed embryos and percentage of blastocysts were transferred in the AC group which may have biased the results to improve the outcomes of the AC.\textsuperscript{28} A recent Cochrane review was inconclusive regarding its ability to determine an optimal endometrial technique in terms of reproductive outcomes.\textsuperscript{7} Similar inconclusive results were also observed in other systematic reviews and meta-analyses.\textsuperscript{8,29,30} These studies also included data on cleavage staged embryos, which may not be generalisable to our research question.

Most of the studies included in our analysis were of fair to moderate quality. This is largely due to the possibility of non-comparable groups of women undertaking thaw cycles involving the presence or absence of a CL. Women with oligo or amenorrhea due to medical conditions like polycystic ovarian syndrome (PCOS), are more likely to undergo the AC for embryo transfer, compared with women with regular menstrual cycles. Women with PCOS may have an increased risk of adverse pregnancy outcomes such as early miscarriage,\textsuperscript{31} which may be contributing to the observed results. Regarding the RCTs assessed, their quality was affected by the nature of the intervention that makes concealment and blinding challenging to implement. However, as mentioned by a previous Cochrane review, the non-blinding may not affect the measurement of outcomes, which are measured objectively.\textsuperscript{7}

Previous studies have also noted higher miscarriage rates in cycles without a CL. A large retrospective analysis by Tomás et al, demonstrated a higher miscarriage rate in the AC cycle group compared with the group receiving the NC protocol.\textsuperscript{32} Similar findings were observed in the study by Givens et al.\textsuperscript{20} In both these studies, there were a significantly higher proportion of women with PCOS in the AC group, which may have contributed to this result. An older study by Veleva et al found that miscarriage rates were higher in the AC group (23.0\%) compared with the NCs (11.4\%, p<0.0001).\textsuperscript{33} However,
the BMI of the women in the AC were statistically higher compared with the NC (25.3±5.4, 22.9±3.6, p<0.0001) which may have influenced the miscarriage rate. Similarly, a retrospective study by Guan et al., which analysed 1482 thawed cleavage-staged embryos noted that women in the NC group experienced significantly lower rates of miscarriage (2.8%) compared with those in the women receiving the AC with GnRHa (14.0%, p=0.003). This may be influenced by the statistically older age of women receiving the AC with GnRHa compared with the women in the NC group. Another retrospective study involving normo-ovulatory women by Cerillo et al., observed statistically higher miscarriage rates in the women receiving AC (21.2%), compared with the women receiving mNC (12.9%) and the tNC (11.1%). In a recent retrospective analysis by Liu et al., which compared mNC and AC protocols in young women with regular menses, it was noted that the women in the AC group exhibited a higher miscarriage rate (13.69%) compared with the mNC arm (8.37%, p=0.034). Again, as these studies included cleavage-stage embryos their findings may not be generalisable to our research question, which involves data on blastocyst embryos. A recent large retrospective study by Pakes et al. which analysed blastocyst thaw cycles, observed that the AC group experienced a higher pregnancy loss compared with the women in the NC group.
In this study, women in the AC group were significantly younger and received a higher proportion of good quality day-5 blastocysts compared with the NC which may have biased results to favour the AC; however, the AC group still demonstrated more pregnancy losses compared with the NC group.

There may be several contributing factors influencing this observed increased rate of pregnancy loss in thaw cycles without a CL. First, we may be disregarding the physiology of the CL. In a recent study, it was observed that cycles without a CL had a significantly lower level of serum progesterone on the day of embryo transfer compared with cycles involving a CL. In the AC, oestrogen and P4 only are administered exogenously to provide early pregnancy support. However, it is known that the presence of a CL may alter the concentrations of other hormones in the body such as relaxin, indicating that there may be complex interaction between the CL and pregnancy support extending beyond P4 and E2 production. Second, as the dosage of P4 is typically a standard dose, with different routes of administration in AC, the amount delivered may be inadequate for optimal luteal support at an individual level. Some studies suggest that serum P4 level may be helpful in guiding the level of supplementation; however, other studies suggest serum progesterone levels are not well correlated with the intrauterine levels. This poor correlation is likely due to the first uterine pass effect and unpredictable levels of progesterone absorption from exogenous vaginal progesterone. Consequently, some women may not be receiving adequate luteal support, and thus an optimised uterine environment for early pregnancy development may not be achieved.

There have been growing concerns regarding the safety of cycles without a CL. A large retrospective study conducted in Sweden from 2005 to 2015, observed that cycles without a CL were more likely to develop pregnancy-related hypertensive disorders (adjusted OR 1.61, 95% CI 1.22 to 2.10), postpartum haemorrhage (adjusted OR 2.87, 95% CI 2.29 to 2.60), post-term birth (adjusted OR 1.59, 95% CI 1.47 to 2.68) and macrosomia (adjusted OR 1.62, CI 1.03 to 1.90). Furthermore, a retrospective study conducted in Japan which compared obstetric outcomes of NC and AC embryo transfers found that cycles without a CL exhibited higher rates of pregnancy related hypertensive disorders (adjusted OR 1.43, 95% CI 1.14 to 1.8) and placenta accreta (adjusted OR, 6.91; 95% CI 2.87 to 16.66) compared with cycles involving the presence of a CL. Similar findings have been noted in other studies. In a recent study which investigated the relation between pregnancy related hypertensive disorders and CL number, it was noted that pregnancies without a CL did not exhibit the physiological decline in mean arterial pressure associated with pregnancy. This may imply that the presence of a CL may play a vital role in the priming phase of the uterine environment and maternal vasculature for early pregnancy support.

However, in certain circumstances, the use of cycles without a CL may be necessary. Women who are unable to ovulate and hence unable to produce a CL, do not have the option of using the NC or ovulatory induction agents to prime their endometrium. Hence, ACs are still a very import method in frozen embryo transfers.

Strengths of this study included its meta-analysis which has been able to increase the power of individual studies to observe differences that may not have been evident on their own. In addition to this, we limited papers to those that contained data which analysed blastocyst-staged embryos. This narrowed our research question to a particular subgroup of embryo transfers which is also clinically relevant, with an increasing number of blastocyst transfers observed in clinical practice.

This study has several limitations. First, as most of these studies were of fair to moderate risk of bias due to the nature of the study designs implemented, there is a potential for confounders and selection bias to influence the results. However, most studies had accounted for this by using a multivariate logistic regression to control for confounders. In this study, the Mantel-Haenszel method was used to account for this. Furthermore, as there were less than 10 studies included in the meta-analysis, funnel plots constructed (online supplemental file 4) had a limited utility in assessing publication bias. The aforementioned heterogeneity of the patient populations studied may also play a factor, with four of the studies only including normo-ovulatory patients, while the other four included women with ovulatory dysfunction in the cycles without a CL. Lastly, due to the ways that the included studies were reported, it was not able to calculate data per woman, which may have been another avenue for bias.

CONCLUSION

As blastocyst thaw cycles are increasingly being used worldwide, this review is timely and important. We conclude that cycles involving a CL may be slightly superior to cycles without a CL as they may produce marginally better reproductive outcomes. Furthermore, due to the higher rates of pregnancy loss and potential obstetric complications of AC, CL cycles should be the treatment of choice where clinically appropriate. However, cycles without a CL are still important as they may be necessary for women with irregular or absent periods and for cycles involving donor oocytes. As a result of this and the retrospective study design of many of the included studies, it should be noted that the population in whom artificial thaw cycles are performed may have an inherently different, possibly higher risks of pregnancy losses. However, the AC approach is routinely used in many centres and therefore would not be subject to this bias. Since the quality of studies included in the analysis is suboptimal, further high-quality research using adequately powered RCTs involving blastocyst thaw cycles is urgently required.
Acknowledgements We thank Professor Kate Stern and Ms Frances Agresta for their assistance in facilitating this project.

Contributors GR and AP were involved in the conception and creation of the study design, GR, AP and JG wrote the protocol. All authors were involved in the screening of articles for eligibility and data extraction, AP provided expertise on statistical analysis. AP and JG performed the meta-analysis. All authors have contributed significantly to, seen and approved the final submitted version of the manuscript. JG is the guarantor of this study, under the direct supervision of AP and GR.

Funding The authors received funding from Melbourne NF to assist with publication costs. No specific grant was received for initiating or conducting the research.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants but an Ethics Committee(s) or Institutional Board(s) exempted this study. This is a systematic review, hence review by an ethics committee is not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Joselyn Gan http://orcid.org/0000-0002-9471-2724

REFERENCES

1. Shapiro BS, Daneshmand ST, Garner FC, et al. Clinical rationale for cryopreservation of embryo transfer cycles in lieu of fresh transfer. Fertil Steril 2014;102:3–9.
2. Newman JE, Repon PC, Chambers GM. Assisted reproductive technology in Australia and New Zealand. 2018. Available: https://npsu.unsw.edu.au/sites/default/files/npsu/data_collection/Assisted%20Reproductive%20Technology%20in%20Australia%20and%20New%20Zealand%202018.pdf [Accessed 9 Sep 2020].
3. Wong KM, Mastenbroek S, Repping S. Cryopreservation of human embryos and its contribution to in vitro fertilization success rates. Fertil Steril 2014;102:19–26.
4. Lawrenz B, Coughlan C, Melado L, et al. The ART of frozen embryo transfer: back to nature? Gynecol Endocrinol 2020;36:479–83.
5. European IVF-monitoring Consortium (EIM@) for the European Society of Human Reproduction and Embryology (ESHRE), Wynn C, Bergh C, et al. ART in Europe, 2016: results generated from European registries by ESHRE. Hum Reprod Open 2020;2020;hoaa032.
6. Groenewoud ER, Cohen BJ, Al-Oraiby A, et al. A randomized controlled, non-inferiority trial of modified natural versus artificial cycle for cryo-thawed embryo transfer. Hum Reprod 2016;31:1483–92.
7. Ghobara T, Gelbaya TA, Ayeleke RO. Cycle regimens for frozen-thawed embryo transfer. Cochrane Database Syst Rev 2017;7:CDO00414.
8. Groenewoud ER, Cantineau AEP, Kollen BJ. What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis. Hum Reprod Update 2017;2:255–61.
9. Yarali H, Polat M, Mumusoglu S, et al. Preparation of endometrium for frozen embryo replacement cycles: a systematic review and meta-analysis. J Assist Reprod Genet 2016;33:1287–304.
10. Pakes C, Volovksy M, Rozen G, et al. Comparing pregnancy outcomes between natural cycles and artificial cycles following frozen-thaw embryo transfers. Aust NZ J Obstet Gynaecol 2020;60:804–9.
11. Lelaidier C, de Ziegler D, Gaetano J, et al. Controlled preparation of the endometrium with exogenous oestradiol and progesterone: a novel regimen not using a gonadotrophin-releasing hormone agonist*. Hum Reprod 1992;7:1353–6.
12. Stocking K, Wilkinson J, Lensen S, et al. Are interventions in reproductive medicine assessed for plausible and clinically relevant effects? A systematic review of power and precision in trials and meta-analyses. Hum Reprod 2019;34:659–65.
13. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
14. Zegers-Hochschild F, Adamson GD, Dyer S. The International glossary on infertility and fertility care. Fertil Steril 2017;3:393–40.
15. Michels TC, Tiu AY. Second trimester pregnancy loss. Am Fam Physician 2007;76:1341–6.
16. Alur-Gupta S, Hopeman M, Berger DS, et al. Impact of method of endometrial preparation for frozen blastocyst transfer on pregnancy outcome: a retrospective cohort study. Fertil Steril 2018;110:680–8.
17. Sterne JAC, Savovic J, Page MJ, et al. Rob 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:k4898.
18. Wells BS, O’Connell JP. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute, Available: http://www.sohr.ca/programs/critical_epidemiology/oxford.asp [Accessed 9 Sep 2020].
19. The Cochrane Collaboration. Review manager (RevMan). Version 5.4.1 ed 2020.
20. Givens CR, Markun LC, Ryan IP, et al. Outcomes of natural cycles versus programmed cycles for 1677 frozen-thawed embryo transfers. Reprod Biomed Online 2009;19:380–4.
21. Chang EM, Han JE, Kim YS, et al. Use of the natural cycle and vitrification thawed blastocyst transfer results in better in-vitro fertilization outcomes: cycle regimens of vitrification thawed blastocyst transfer. J Assist Reprod Genet 2011;28:369–74.
22. Greco E, Litwicka K, Arrié C, et al. The endometrial preparation for frozen-thawed euploid blastocyst transfer: a prospective randomized trial comparing clinical results from natural modified cycle and exogenous hormone stimulation with GnRH agonist. J Assist Reprod Genet 2016;33:873–84.
23. Sheikhii O, Golsorkhtabarim K, Esmailizadeh S, et al. Reproductive outcomes of vitrified blastocyst transfer in modified natural cycle versus mild hormonally stimulated and artificial protocols: a randomized control trial. JEBRA Assist Reprod 2018;22:221–7.
24. Cardenas Armas DF, Peñarrubia J, Goday A, et al. Frozen-thawed blastocyst transfer in natural cycle increase implantation rates compared artificial cycle. Gynecol Endocrinol 2019;35:873–7.
25. Levi Setti PE, Cirillo F, De Cesare R, et al. Seven years of vitrified blastocyst transfers: comparison of 3 preparation protocols at a single art center. Front Endocrinol 2020;11:346.
26. Le QV, Abhari S, Abezuide OM, et al. Modified natural cycle for embryo transfer using frozen-thawed blastocysts: a satisfactory option. Eur J Obstet Gynecol Reprod Biol 2017;213:58–63.
27. Sahin G, Acet F, Calimoğlu N, et al. Live birth after frozen-thawed embryo transfer: which endometrial preparation protocol is better? J Gynecol Obstet Hum Reprod 2020;49:101782.
28. Hill MJ, Miller KA, Frattarelli JL. A GnRH agonist and exogenous hormone stimulation protocol has a higher live-birth rate than a natural endogenous hormone protocol for frozen-thawed blastocyst-stage embryo transfer cycles: an analysis of 1391 cycles. Fertil Steril 2010;93:416–22.
29. Groenewoud ER, Cantineau AEP, Kollen BJ, et al. What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis. Hum Reprod Update 2017;23:255–61.
30. Mackens S, Santos-Ribeiro S, van de Vijver A, et al. Frozen embryo transfer: a review on the optimal endometrial preparation and timing. Hum Reprod 2017;32:2342–82.
31. Liu L, Gu F, Jie H, et al. Early miscarriage rate in lean polycystic ovary syndrome women after euploid embryo transfer - a matched-pair study. Reprod Biomed Online 2017;35:576–82.
32 Tomás C, Alsbiège B, Martikainen H, et al. Pregnancy loss after frozen-embryo transfer-a comparison of three protocols. Fertil Steril 2012;98:1165–9.

33 Velez Z, Tilitten A, Vilksa S, et al. High and low BMI increase the risk of miscarriage after IVF/ICSI and FET. Hum Reprod 2008;23:878–84.

34 Guan Y, Fan H, Styer AK, et al. A modified natural cycle results in higher live birth rate in vitrified-thawed embryo transfer for women with regular menstruation. Syst Biol Reprod Med 2016;62:335–42.

35 Cerrillo M, Herrero L, Guillén A, et al. Impact of endometrial preparation protocols for frozen embryo transfer on live birth rates. Rambam Maimonides Med J 2017;8:e0020.

36 Liu X, Shi W, Shi J. Natural cycle frozen-thawed embryo transfer in young women with regular menstrual cycles increases the live-birth rates compared with hormone replacement treatment: a retrospective cohort study. Fertil Steril 2020;113:811–7.

37 Olivier P, Irma Z, Marine B. Comparison of serum progesterone levels of the day of frozen embryo transfers according to type of endometrial preparation: a monocentric, retrospective study. Res Sq 2021.

38 Kor NM. The effect of corpus luteum on hormonal composition of follicular fluid from different sized follicles and their relationship to serum concentrations in dairy cows. Asian Pac J Trop Med 2014;7S1:S282–8.

39 Conrad KP. Emerging role of relaxin in the maternal adaptations to normal pregnancy: implications for preeclampsia. Semin Nephrol 2011;31:15–32.

40 Céd忍-Durnerin I, Isnard T, Mahdjoub S, et al. Serum progesterone concentration and live birth rate in frozen-thawed embryo transfers with hormonally prepared endometrium. Reprod Biomed Online 2019;38:472–80.

41 Labarta E, Mariani G, Holtmann N, et al. Low serum progesterone on the day of embryo transfer is associated with a diminished ongoing pregnancy rate in oocyte donation cycles after artificial endometrial preparation: a prospective study. Hum Reprod 2017;32:2437–42.

42 Volovsky M, Pakes C, Rozen G, et al. Do serum progesterone levels on day of embryo transfer influence pregnancy outcomes in artificial frozen-thaw cycles? J Assist Reprod Genet 2020;37:1129–35.

43 Tavaniotou A, Smitz J, Bourgain C, et al. Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. Hum Reprod Update 2000;6:139–48.

44 Penzias AS, Alper MM. Luteal support with vaginal micronized progesterone gel in assisted reproduction. Reprod Biomed Online 2003;6:287–95.

45 Cicinelli E, de Ziegler D, Bulletti C, et al. Direct transport of progesterone from vagina to uterus. Obstet Gynecol 2000;95:403–6.

46 Giström Ernstad E, Wennerholm U-B, Khatibi A, et al. Neonatal and maternal outcome after frozen embryo transfer: increased risks in programmed cycles. Am J Obstet Gynecol 2019;221:e1–e18.

47 Saito K, Kuwahara A, Ishikawa T, et al. Endometrial preparation methods for frozen-thawed embryo transfer are associated with altered risks of hypertensive disorders of pregnancy, placenta accreta, and gestational diabetes mellitus. Hum Reprod 2019;34:1567–75.

48 von Versen-Höynck F, Schaub AM, Chi Y-Y, et al. Increased preeclampsia risk and reduced aortic compliance with in vitro fertilization cycles in the absence of a corpus luteum. Hypertension 2019;73:540–9.

49 Jing S, Li XF, Zhang S, et al. Increased pregnancy complications following frozen-thawed embryo transfer during an artificial cycle. J Assist Reprod Genet 2019;36:925–33.

50 Saito K, Kuwahara A, Ishikawa T. Pregnancy after frozen-thawed embryo transfer during hormonal replacement cycle is associated with hypertensive disorders of pregnancy and placenta accreta. Hum Reprod 2018;33:1128–9.

51 Sakai Y, Ono M, Izuka T, et al. Embryo transfer associated with hormone replacement therapy cycles using assisted reproductive technology increases placenta accreta spectrum. J Obstet Gynaecol Res 2019;45:2394–9.

52 von Versen-Höynck F, Narasimhan P, Selamet Tierney ES, et al. Absent or excessive corpus luteum number is associated with altered maternal vascular health in early pregnancy. Hypertension 2019;73:680–90.

53 Asserhøj LL, Spangmose AL, Aaris Henningsen A-K, et al. Adverse obstetric and perinatal outcomes in 1,136 singleton pregnancies conceived after programmed frozen embryo transfer (FET) compared with natural cycle FET. Fertil Steril 2021;115:947–56.