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Treatment Outcomes of Blastocysts Thaw-Cycles, Comparing the Presence and Absence of a Corpus Luteum: A Systematic Review and Meta-analysis.

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Treatment Outcomes of Blastocysts Thaw-Cycles, Comparing the Presence and Absence of a Corpus Luteum: A Systematic Review and Meta-analysis.

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ABSTRACT

Objective

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.

Design

Systematic review.

Data sources

PUBMED, EMBASE, CENTRAL and CINAHL were searched for papers published between January 2017 and July 27th, 2020. Additional articles were selected from the reference list of the results and previous reviews.

Data Extraction and Synthesis

Three reviewers independently reviewed and extracted data. Any discrepancies were discussed until a consensus was reached. The meta-analysis was conducted though RevMan 5.4.1. Studies were quality assessed with the Cochrane risk of bias tool and the Newcastle Ottawa Scale.

Results

A total of nine publications were included for data-extraction and subsequent meta-analysis. Two studies were randomised control trials, and seven were cohort studies. Both study designs were included in the meta-analysis. Sub-group analysis of the different study designs was performed.

Whilst the rates of positive b-hCG results (RR 1.0, 95% CI 0.95 - 1.05) and clinical pregnancies (RR 1.06, 95% CI 0.96 -1.18) 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 - 1.22). Analysis of

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pregnancy losses demonstrated that both biochemical pregnancy (early miscarriage) (RR 0.71, 95% CI 0.62 - 0.82) and miscarriages (RR 0.72, 95% CI 0.62 - 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 a fair to moderate quality of studies and the inherent bias of retrospective cohort studies. Further, high-quality research, particularly randomised controlled trials with blastocysts embryos, is required to further explore these findings.

PROSPERO Registration Number

CRD42020209583

STRENGTHS AND LIMTATIONS

- As the use of blastocysts in thaw cycles is becoming increasingly more common, this
 review is timely and relevant
- The safety of embryo transfers without a corpus luteum is a growing area of research
- The limitations of this study include the limited number of studies in the area and lack of high quality randomised controlled trials
- Further high-quality studies are required to further explore these findings.

STUDY FUNDING/COMPETING INTEREST(S):

All authors declare no conflicts of interest. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

INTRODUCTION

 In recent years, embryo cryopreservation has become a fundamental tool in reproductive medicine. With improvements in the vitrification processes, culture mediums and desire for single embryo transfers (SETs), thaw cycles are becoming more common(1-4). The benefits of embryo verification include the need for fewer ovarian stimulation cycles, as well as an improved cumulative pregnancy(3). In Australia, the proportion of cryopreserved of cryopreserved embryo transfers increased from 47.1% in 2014 to 57.2% in 2018(2). In particular, the cryopreservation of blastocysts for frozen embryo transfer has been an increasingly adopted practice. The European IVF Monitoring Consortium reported that in 2016 more than half of frozen embryo transfers (62.2%) were performed at the blastocysts stage(5). It was also noted that pregnancy rates were higher in the frozen embryo transfers which used blastocyst (39.7%) compared to cleavage staged embryos (28.3%)(5).

Various protocols for endometrial preparation have been developed to assist with thaw-cycles transfers. One of the most widely used methods is the true natural cycle (tNC) or variations of it such as the modified natural cycle (mNC) or the mildly stimulated cycle (SC). These preparation techniques rely on the 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 normoovulatory 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 estrogen (E2) to induce endometrial proliferation and growth suppression of the dominant follicle, and the subsequent administration of progesterone (P4) to

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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 to 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(4, 6).

Previous studies have found that treatment outcomes of tNC and ACs have been comparable(7-9). Some studies, however, have noted that thaw-cycles without a CL may have experienced higher rates of early pregnancy loss. (4, 10, 11). 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(12).

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 thawcycles 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(2).

MATERIALS AND METHODS

Search Strategy

This review was registered with PROSPERO CRD42020209583. 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(7). The search strategy utilised 3 key concepts: endometrial preparation AND frozen embryos AND reproductive outcomes. The detailed search strategy can be found in supplementary 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(7, 8). No language restrictions were used in the search. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines(13).

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, 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(14).

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. Papers not written in English but had titles and abstracts available in English were assessed, however no relevant studies were identified.

Outcomes and Definitions

The primary outcome examined was live birth (LB) or ongoing pregnancy rate where LB was not available. Secondary outcomes that were analysed were rates of positive beta-human Chorionic Gonadotropin (b-hCG), clinical pregnancy, biochemical pregnancy, and miscarriage.

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Where applicable, we used the definitions agreed upon by the International Glossary on Infertility and Fertility Care, 2017(14). A LB was defined as a birth which demonstrated evidence of life after at least 22 weeks gestation(14). 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 (15), ongoing pregnancy rates were included in the analysis of live birth rates. However, we performed a sub-analysis of the studies which reported live births as their primary outcome in addition to the total LB rate which would include ongoing pregnancy rates. A positive b-hCG was defined as a b-hCG of ≥5. Where positive b-hCG was not available, it was calculated through the addition of biochemical pregnancies and clinical pregnancies. The study by Alur-Gupta et al., (2018) (16), did not report clinical pregnancy, hence it was calculated by adding the number of live births, ectopic pregnancies, stillbirths, and spontaneous abortions reported. A clinical pregnancy was defined as a positive b-hCG with evidence of at least one gestational sac on ultrasound, including ectopic pregnancies(14). Biochemical pregnancies were classified as a pregnancy which yielded a positive b-hCG result but did not reach the stage of clinical pregnancy(14). Where biochemical pregnancy was not reported, it was calculated by subtracting the reported clinical pregnancies from the number of positive b-hCG results. Where biochemical pregnancy was not reported, it was calculated by subtracting the reported clinical pregnancies from the number of positive b-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 was independently extracted by three reviewers (GR, AP, JG) for author/s, year of publication, title of the article, year of trial, study design, number cycles, demographics of

women, positive b-hCG, clinical pregnancy, biochemical pregnancy, miscarriage, live births, or ongoing births where live births were not available. The data was collated by a single reviewer (JG) and any discrepancies were discussed among three reviewers and until a consensus was reached.

Quality Assessment

Included randomised control trials were quality assessed using the Revised Cochrane Risk of Bias Tool for randomised trials (RoB 2)(17). The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses was used to assess cohort studies(18). 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.

Statistical Analysis

The meta-analysis was performed using RevMan 5.4.1 computer program, The Cochrane Collaboration, 2020(19). Meta-analyses of rates of positive b-hCG, live births, 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 X² statistic. P-values of X² that were <0.05, and I² > 50% were considered represent significant heterogeneity. Relative risk with 95% confidence intervals (CI), were 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 (Supplementary Figure 4).

As we included studies that reported ongoing pregnancy rates where LB rates were not available, we conducted a sub-group analyses which individually looked at LB rates and miscarriages from studies which reported LBs as their primary outcome. Separate analysis grouped by study design is demonstrated in Supplementary Figure 2 and 3.

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 . Fw. . cohort st. .nal meta-analys. quantitative analysis(10, 16, 20-26). Two of which were randomised controlled trials (RCTs)(22, 23) and seven were retrospective cohort studies(10, 16, 20, 21, 24-26). This process is summarized 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., 2020(10), and the smallest study included 116 cycles by Sheikhi et al., (2018)(23).

The average quality of the studies was rated with a fair to moderate risk of bias.

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Study Design Alur-Gupta et al. (2018)(16) Cohor	•	Study						2021					
Alur-Gupta et Retros	•	Study	Design			Demographics		1-05			Outcomes		
		Cycles with blastocysts (n)	Study Period	Allocation	Women (n)	Study population	Mean Age, years (SD)	BMI, kg/1122 (3	(SD)	Positive b- hCG (n)	CP (n)	LB/OP	Quality
	ort	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 = 23.9 (3 AC = 25.10(5.		With CL = 64 Without CL = 602	With CL = 55 Without CL = 523	LB	Fair
Cardenas Retros Armas et al. Cohor (2019)(24)	ort	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) AC (Oral) = 36.86 (0.19)	NC = 22,	rmal) =	With CL = 16 Without CL = 76	With CL = 13 Without CL = 60	LB	Good
Chang et al. Retros (2011)(21) Cohor	ort	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 = (2 mNC = 29.5 AC = 20.0 (2)	(3.5)	With CL = 229 Without CL = 107	With CL = 186 Without CL = 62	OP	Good
Givens (2009) Retros et al.(20) Cohor	ort	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)	from http://b NR		With CL = 369 Without CL = 141	With CL = 284 Without CL =105	LB	Fair
Greco (2016) et RCT al.(22)	(222 Cycles (with CL = 109, without CL = 113)	2015	Computer- generated randomization (non-concealed)	236	normo-ovulatory patients, PGT	mNC = 35.2 (3.6) AC + GnRHa = 35.5 (3.8)	mNC = 22.1 (AC + GnBHa (3.8)		With CL = 68 Without CL = 70	With CL = 59 Without CL = 523	LB	Some concer
Le (2017) et Retros al.(26) Cohor	ort	378 cycles (with CL 197, without CL = 181)	2006 - 2014	Clinical judgement	428 ^b	Both normo-ovulatory patients and women with ovulatory dysfunction	mNC = 34.3 (4.2) AC = 33.3 (4.8)	mNC = 25:3 (AC = 27.8 (7.		With CL= 120 Without CL = 110	With CL = 107 Without CL = 95	LB	Fair
Levi Setti et al. (2020)(25) Cohor	ort	2888 Cycles (with CL = 2304, without CL = 584) ^c	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 = 213 (3 mNC = 24.8 AC = 22.5 (3.4)	(3.0)	With CL = 1012 Without CL = 243	With CL = 930 Without CL = 217	LB	Fair
Pakes et al. Retros (2020)(10) Cohor	ort	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)	2024 by gu NR		With CL = 802 Without CL = 376	With CL = 627 Without CL = 260	LB	Fair
Sheikhi et al. RCT	(116 Cycles (with CL = 57, without CL = 59)	2015 - 2016	Computer- generated randomization (non-concealed)	123°	normo-ovulatory patients, without severe endometriosis	mNC = 29.71 (3.79) mSC = 30.31 (4.58) AC = 30.5 (5.59)		0 (3.29)	With CL = 10 Without CL = 12	With CL = 10 Without CL = 9	OP	Some concer

Positive b-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 b-hCG. In the 3491 cycles without a CL, 1737 (50%) resulted in a positive b-hCG. The individual and combined estimates for positive-hCG are shown in r μα in the final is a second secon Figure 2. The pooled estimates for positive b-hCG (RR 1.00, 95% CI 0.95 – 1.05) demonstrated no statistically significant difference in rates of positive b-hCG between cycles with and without a CL. Subgroup analysis of positive b-hCG rates by study design are shown in Supplementary

Figure 2.

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Figure 2: Meta-analysis comparing rates of positive b-hCG, clinical pregnancy and live

births in cycles with and without a corpus luteum

Rates of Positive b-hCG

	With	CL	Without CL			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Alur-Gupta 2018	64	104	602	917	7.7%	0.94 [0.80, 1.10]	
Cardenas Armas 2019	16	32	76	175	1.5%	1.15 [0.78, 1.69]	
Chang 2011	229	444	107	204	9.2%	0.98 [0.84, 1.15]	
Givens 2009	369	858	141	261	13.5%	0.80 [0.69, 0.91]	
Greco 2016	68	109	70	113	4.3%	1.01 [0.82, 1.24]	
Le 2017	120	197	110	181	7.2%	1.00 [0.85, 1.18]	
Levi Setti 2020	1012	2304	243	584	24.3%	1.06 [0.95, 1.17]	
Pakes 2020	802	2033	376	997	31.6%	1.05 [0.95, 1.15]	
Sheikhi 2018	10	57	12	59	0.7%	0.86 [0.40, 1.84]	
Total (95% CI)		6138		3491	100.0%	1.00 [0.95, 1.05]	•
Total events Heterogeneity: Chi² = 13	2690 1.86, df = 8	(P = 0.	1737 09); I² = 4	2%		8 0 2 1 <mark>2</mark>	0.5 0.7 1 1

Favours no CL Favours CL

Clinical Pregnancy Rates

	With	CL	Withou	t CL		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% C
Alur-Gupta 2018	55	104	523	917	12.9%	0.93 [0.77, 1.12]	
Cardenas Armas 2019	13	32	60	175	4.0%	1.18 [0.74, 1.89]	
Chang 2011	186	444	62	204	10.5%	1.38 [1.09, 1.74]	
Givens 2009	284	858	105	261	13.7%	0.82 [0.69, 0.98]	
Greco 2016	59	109	57	113	9.7%	1.07 [0.83, 1.38]	
Le 2017	107	197	95	181	12.9%	1.03 [0.86, 1.25]	
Levi Setti 2020	930	2304	217	584	17.6%	1.09 [0.97, 1.22]	+
Pakes 2020	627	2033	260	997	17.2%	1.18 [1.05, 1.34]	
Sheikhi 2018	10	57	9	59	1.5%	1.15 [0.50, 2.62]	
Total (95% CI)		6138		3491	100.0%	1.06 [0.96, 1.18]	•
Total events	2271		1388				
Heterogeneity: Tau ² = 0.0	01; Chi ² =	18.35,	df = 8 (P =	= 0.02);	l² = 56%		0.5 0.7 1 1.5
Test for overall effect Z =	1.15 (P=	0.25)	an 1938	11520878			0.5 0.7 1 1.5 Favours No CL Favours 1

Live Births and Ongoing Pregnancy Rates

	With	CL	Withou	t CL		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Alur-Gupta 2018	47	104	425	917	8.7%	0.98 [0.78, 1.22]	
Cardenas Armas 2019	10	32	42	175	1.3%	1.30 [0.73, 2.32]	
Chang 2011	229	444	107	204	14.8%	0.98 [0.84, 1.15]	
Givens 2009	245	858	77	261	11.9%	0.97 [0.78, 1.20]	
Greco 2016	50	109	47	113	4.6%	1.10 [0.82, 1.49]	
Le 2017	93	197	79	181	8.3%	1.08 [0.87, 1.35]	
Levi Setti 2020	722	2304	151	584	24.2%	1.21 [1.04, 1.41]	
Pakes 2020	496	2033	188	997	25.4%	1.29 [1.11, 1.50]	
Sheikhi 2018	10	57	8	59	0.8%	1.29 [0.55, 3.04]	
Total (95% CI)		6138		3491	100.0%	1.14 [1.06, 1.22]	•
Total events	1902		1124				
Heterogeneity: Chi# = 11.	23, df = 8	(P = 0.	19); I*= 2	9%		t.	2 0.5 1

Live Births Rates Only

	With		Withou	tCL		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Alur-Gupta 2018	47	104	425	917	10.3%	0.98 [0.78, 1.22]	
Cardenas Armas 2019	10	32	42	175	1.5%	1.30 [0.73, 2.32]	
Givens 2009	245	858	77	261	14.1%	0.97 [0.78, 1.20]	
Greco 2016	50	109	47	113	5.5%	1.10 [0.82, 1.49]	
Le 2017	93	197	79	181	9.8%	1.08 [0.87, 1.35]	
Levi Setti 2020	722	2304	151	584	28.7%	1.21 [1.04, 1.41]	
Pakes 2020	496	2033	188	997	30.1%	1.29 [1.11, 1.50]	
Total (95% CI)		5637		3228	100.0%	1.16 [1.07, 1.26]	•
Total events	1663		1009				· · · ·
Heterogeneity: Chi# = 8.0)7, df = 6 (P = 0.2	3); I# = 26	%		_	0.5 0.7 1 1.5



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CL, Corpus Luteum; CI, Confidence interval

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 – 1.18) demonstrated 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.*, (2009) (20) which was the only study to observe a higher clinical pregnancy rate in AC compared to NCs. The results of this are shown in Supplementary Figure 1. The sensitivity analysis showed that live birth rates were statistically higher in the cycles involving the presence of a CL (RR 1.12, 95% Cl 1.05 - 1.20).

Based on these two analyses, it can be concluded that the most likely point estimate lays somewhere between 1.06 and 1.12, favouring cycles with CL. The confidence interval of this point estimate may include 1, but there is a clear trend towards cycles with CL resulting in a higher clinical pregnancy rate. While statistical significance may not be demonstrable, this finding is likely to be clinically significant. Subgroup analysis of clinical pregnancy rates by study design is shown in Supplementary Figure 2.

Live Birth Rates

Seven studies reported LB rates as their primary outcome (one prospective randomised trial and five retrospective studies)(10, 16, 20, 22, 24-26). Two studies reported ongoing pregnancy rates as their primary outcome (one prospective randomised trial, and one cohort study)(21, 23).

Of the 6138 cycles which involved the presence of a CL, 1902 (31%) resulted in a LB or progressed to an ongoing pregnancy. In the 3491 cycles without a CL, 1124 (32%) resulted in a live birth or ongoing pregnancy. The individual and combined estimates for live births are shown

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in Figure 2. The pooled estimates for live births (RR 1.14, 95% CI 1.06 - 1.22) demonstrated a statistically significant difference in favour of cycles with a CL. This translates into a clinically significant approximate 14% increase chance of live birth 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 live birth rate remained significantly higher in the thaw-cycles with a CL (RR 1.16, 95% CI 1.07 - 1.26). Subgroup analysis of LB rates by study design is shown in Supplementary Figure 2.

Biochemical Pregnancy Rates

In the 2690 positive b-hCG results in the cycles with a CL, 416 (15%) were biochemical pregnancies that did not progress to a clinical pregnancy (i.e., ended in an early miscarriage). In the 1737 positive b-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% Cl 0.62 – 0.82) were significantly lower in the cycles with a CL. Subgroup analysis of biochemical pregnancy rates by study design is shown in Supplementary Figure 3.

Figure 3: Meta-analysis comparing biochemical pregnancy and miscarriage rates in cycles with and without a corpus luteum

Biochemical Pregnancy Rates

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Chudu on Cub and	With		Withou		Malaka	Risk Ratio	Risk Ratio
Study or Subgroup			Events			M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Alur-Gupta 2018	8	64	79	602		0.95 [0.48, 1.88]	
Cardenas Armas 2019	3	16		76	·		
Chang 2011	43 83	229 369		107			
Givens 2009 Greco 2016	9	68		70			
Le 2017	13	120		110			
Levi Setti 2020	82			243			_
Pakes 2020	175	802		376			-
Sheikhi 2018	0	10		12			· · · · · · · · · · · · · · · · · · ·
						Second Englished Strength	
Total (95% CI)		2690		1737	100.0%	0.71 [0.62, 0.82]	•
Total events	416		347				
Heterogeneity: Chi ² = 11				8%			0.1 0.2 0.5 1 2 5 10
Test for overall effect: Z =	: 4.90 (P =	0.000	01)				Favours no CL Favours CL
Miscarriage Rates							
	With C		Without	C1		Risk Ratio	Risk Ratio
Study or Subgroup					Weight I	M-H, Random, 95% Cl	
7.1.1 Miscarriage Rates						1-11, Nandolli, 554 CI	Men, Kundoni, 55/FCI
Alur-Gupta 2018	9	55	98	523	5.1%	0.87 [0.47, 1.63]	
Cardenas Armas 2019	3	13	18	60	1.8%	0.77 [0.27, 2.23]	
Givens 2009	41	284	30	105	11.6%	0.51 [0.33, 0.76]	
Greco 2016	9	59	10	57	2.9%	0.87 [0.38, 1.98]	
Le 2017	14	107	16	95	4.5%	0.78 [0.40, 1.51]	
Levi Setti 2020	217	930	70	217	39.2%	0.72 [0.58, 0.91]	-
Pakes 2020 Subtotal (95% CI)	131	627 2075	72	260 1317	32.2% 97.3%	0.75 [0.59, 0.97] 0.72 [0.62, 0.83]	T
Total events	424	2015	314	1317	51.5%	0.12 [0.02, 0.03]	•
Heterogeneity: Tau ² = 0.0		.58, df		.73); P	= 0%		
Test for overall effect: Z =	4.56 (P <	0.0000	1)				
7.4.2 Miccorrigge Dates	from Stud	line Day	oorting O	aadaa	Drognon		
7.1.2 Miscarriage Rates Chang 2011	17	186	portung O	62	2.5%		
Sheikhi 2018	0	10	1	9	0.2%	0.94 [0.39, 2.29] 0.30 [0.01, 6.62]	←
Subtotal (95% CI)	•	196		71	2.7%	0.87 [0.37, 2.03]	
Total events	17	0.000	7		Street Control of Cont		
Heterogeneity: Tau ² = 0.0		.48, df		.49); I [#] :	= 0%		
Test for overall effect: Z =			80	100			
Total (05% CI)		2271		1300	100.0%	0 72 [0 63 0 92]	•
Total (95% CI) Total events	441	22/1	321	1268	100.0%	0.72 [0.63, 0.83]	•
Heterogeneity: Tau ² = 0.0		25 df		83) 17	= 0%		
Test for overall effect: Z =			(1) (1) (2)		0.0		0.1 0.2 0.5 1 2 5 10
Test for subgroup differen				= 0.67)	l² = 0%		Favours no CL Favours CL
Corpus Luteum;		nfid	ence	inte	rval		
Corpus Luteum,	01, 00	mu	CIUC	me	i vai		
· · · · · · · ·							
Miscarriage Rate	S						
-							CL, 441 (19%) did not progress a

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 – 0.83) were statistically lower in the cycles with a CL. A subgroup analysis was conducted which only included studies which reported LB rates.

r subgroup analysis was conducted which only included studies which reported LD fates.

However, this had no material impact on the results. Subgroup analysis of miscarriage rates by

study design is shown in Supplementary Figure 3.

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DISCUSSION

This meta-analysis demonstrates that while there were no statistically significant differences in rates of positive b-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(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., (2020), which retrospectively analysed treatment outcomes after mNC and ACs with GnRHa, concluded that LBs rates and pregnancy loss rates were comparable between the two groups(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. Similarly, a study by Hill et al., (2010), demonstrated higher birth rates in the AC compared to the NC group, however, the AC group had more blastocysts transferred which would have likely biased the results to favour the AC(28). A recent Cochrane review was inconclusive regarding its ability to determine an optimal endometrial technique in terms of reproductive outcomes(7). Similar inconclusive results were also observed in other systematic reviews and meta-analyses (8, 29, 30). These studies also included data on cleavage staged embryos, which may not be generalizable to our research question.

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 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 to women with regular menstrual cycles. Women with PCOS may have an increased risk of adverse pregnancy outcomes such as early miscarriage(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(7).

Previous studies have also noted higher miscarriage rates in cycles without a CL. A large retrospective analysis by Tomás et al., (2012), demonstrated a higher miscarriage rate in the AC cycle group compared to the group receiving the NC protocol(32). Similar findings were observed in the study by Givens et al., (2009)(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., (2008), found that miscarriage rates were higher in the AC group (23.0%) compared to the NCs (11.4%, p-value < 0.0001)(33). However, the BMI of the women in the AC were statistically higher compared to the NC (25.3 ± 5.4, 22.9 \pm 3.6, p-value < 0.0001) which may have influenced the miscarriage rate. Similarly, a retrospective study by Guan et al., (2016) (34), which analysed 1482 thawed cleavage-staged embryos noted that women in the NC group experienced significantly lower rates of miscarriage (2.8%) compared to those in the women receiving the AC with GnRHa (14.0%, p-value = 0.003)(34). This may be influenced by the statistically older age of women receiving the AC with GnRHa compared to the women in the NC group. Another retrospective study involving normoovulatory women by Cerillo et al., (2017), observed statistically higher miscarriage rates in the women receiving AC (21.2%), compared to the women receiving mNC (12.9%) and the tNC

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(11.1%)(35). In a recent retrospective analysis by Liu *et al.*, (2020), 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 to the mNC arm (8.37%, p value 0.034)(36). Again, as these studies included cleavage-stage embryos their findings may not be generalizable to our research question, which involves data on blastocyst embryos. A recent large retrospective study by Pakes *et al.*, (2020) which analysed blastocyst thaw cycles, observed that the AC group experienced a higher pregnancy loss compared to the women in the NC group(10). In this study, women in the AC group were significantly younger and received a higher proportion of good quality day-5 blastocysts compared to the NC which may have biased results to favour the AC, however, the AC group still demonstrated more pregnancy losses compared to the NC group.

There may be several contributing factors influencing this observed increased rate of pregnancy loss in thaw-cycles without a CL. Firstly, we may be disregarding the physiology of the CL. In a recent study,(37) it was observed that cycles without a CL had a significantly lower level of serum progesterone on the day of embryo transfer compared to cycles involving a CL. In the AC, estrogen 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(4, 38, 39), indicating that there may be complex interaction between the CL and pregnancy support extending beyond P4 and E2 production. Secondly, 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(40-42), however, other studies suggest serum progesterone levels are not well correlated with the intra-uterine levels(43-45). This poor correlation is likely due to the first uterine pass effect(43, 45) and unpredictable levels of progesterone absorption from exogenous vaginal progesterone.

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Consequently, some women may not be receiving adequate luteal support, and thus an optimized 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 odds ratio 1.61, 95% CI 1.22 - 2.10), post-partum haemorrhage (adjusted odds ratio 2.87, 95% CI 2.29 - 2.60), post-term birth (adjusted odds ratio 1.59, 95% CI 1.47 – 2.68) and macrosomia (adjusted odds ratio 1.62, confidence interval 1.03-1.90)(46). 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 odds ratio 1.43, 95% confidence interval 1.14-1.8) and placenta accreta (adjusted odds ratio, 6.91; 95% CI 2.87 – 16.66) compared to cycles involving the presence of a CL(47). Similar findings have been noted in other studies(48-53). In a recent study which investigated the relation between pregnancy related hypertensive disorders and corpus luteum number, it was noted that pregnancies without a CL did not exhibit the physiologic decline in mean arterial pressure associated with pregnancy(52). 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 utilizing 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 sub-group of embryo

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transfers which is also clinically relevant, with an increasing number of blastocyst transfers observed in clinical practice.

This study has several limitations. Firstly, 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 (Supplementary figure 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 utilised worldwide, this review is timely and important. We conclude that cycles involving a CL may be superior to cycles without a CL as they may produce 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 occytes. Since the quality of studies included in the analysis is suboptimal, further high-quality research utilizing adequately powered randomised controlled trials involving blastocyst thaw-cycles is urgently required.

LIST OF ABBREVIATIONS

AC – Artificial Cycle

CI – Confidence Intervals

CL – Corpus Luteum

GnRHa - Gonadotropin-Releasing Hormone analogue

LB – Live Birth

mNC – Modified Natural Cycle

PCOS – Polycystic Ovarian Syndrome

SC – Stimulated Cycle

SET – Single Embryo Transfer

tNC - True Natural Cycle

RCT – Randomised Control Trial

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AUTHORS' CONTRIBUTIONS

G.R. and A.P. were involved in the conception and creation of the study design. G.R., A.P., and J.G. wrote the protocol. All authors were involved in the screening of articles for eligibility and data extraction. A.P. provided expertise on statistical analysis. A.P. and J.G. performed the meta-analysis. All authors have contributed significantly to, seen, and approved the final submitted version of the manuscript.

CONFLICTS OF INTEREST

All authors declare no conflicts of interests.

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DATA AVAILABILITY

All relevant data to the study is included in the article or in the supplementary materials

supplied.

REFERENCES

 Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Clinical rationale for cryopreservation of entire embryo cohorts in lieu of fresh transfer. Fertil Steril 2014;1:3-9.
 Newman JE, Repon PC, Chambers GM. Assisted reproductive technology in Australia

14 and New Zealand 2018. Available at:

https://npesu.unsw.edu.au/sites/default/files/npesu/data_collection/Assisted%20Reproductive%
 20Technology%20in%20Australia%20and%20New%20Zealand%202018.pdf. Accessed
 September 9, 2020.

Wong KM, Mastenbroek S, Repping S. Cryopreservation of human embryos and its
 contribution to in vitro fertilization success rates. Fertil Steril. 2014;1:19-26.

- Lawrenz B, Coughlan C, Melado L, Fatemi HM. The ART of frozen embryo transfer: back
 to nature! Gynecol Endocrinol 2020;6:479-83.
- Wyns C, Bergh C, Calhaz-Jorge C, De Geyter C, Kupka MS, Motrenko T, et al. ART in
 Europe, 2016: results generated from European registries by ESHRE. Hum Reprod Open
 2020;3:hoaa032.
- 6. Groenewoud ER, Cohlen BJ, Al-Oraiby A, Brinkhuis EA, Broekmans FJ, de Bruin JP, et
 al. A randomized controlled, non-inferiority trial of modified natural versus artificial cycle for
 cryo-thawed embryo transfer. Hum Reprod 2016;7:1483-92.
- ³⁰ 7. Ghobara T, Gelbaya TA, Ayeleke RO. Cycle regimens for frozen-thawed embryo
 ³¹ transfer. Cochrane Database Syst Rev 2017;7:Cd003414.
- B. Groenewoud ER, Cantineau AEP, Kollen BJ, Macklon NS, Cohlen 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, Yarali I, Bozdag G. Preparation of endometrium for
 frozen embryo replacement cycles: a systematic review and meta-analysis J Assist Reprod
 Genet 2016;10:1287-304.
- 10. Pakes C, Volovsky M, Rozen G, Agresta F, Gardner DK, Polyakov A. Comparing
 pregnancy outcomes between natural cycles and artificial cycles following frozen-thaw embryo
 transfers. Aust N Z J Obstet Gynaecol 2020;5:804-9.
- Lelaidier C, de Ziegler D, Gaetano J, Hazout A, Fernandez H, Frydman R. Controlled
 preparation of the endometrium with exogenous oestradiol and progesterone: a novel regimen
 not using a gonadotrophin-releasing hormone agonist*. Hum Reprod 1992;10:1353-6.
- Stocking K, Wilkinson J, Lensen S, Brison DR, Roberts SA, Vail A. 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;4:659-65.
- 13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic
 reviews and meta-analyses: the PRISMA statement. *Bmj* 2009;339:b2535.
- I4. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al.
 The International Glossary on Infertility and Fertility Care, 2017. Fertil Steril 2017;3:393-40.
 Michels TC, Tiu AY. Second trimester pregnancy loss. Am Fam Physician 2007;76:1341-

6.

Alur-Gupta S, Hopeman M, Berger DS, Gracia C, Barnhart KT, Coutifaris C, et al. Impact
 of method of endometrial preparation for frozen blastocyst transfer on pregnancy outcome: a
 retrospective cohort study. Fertil Steril 2018;110:680-6.

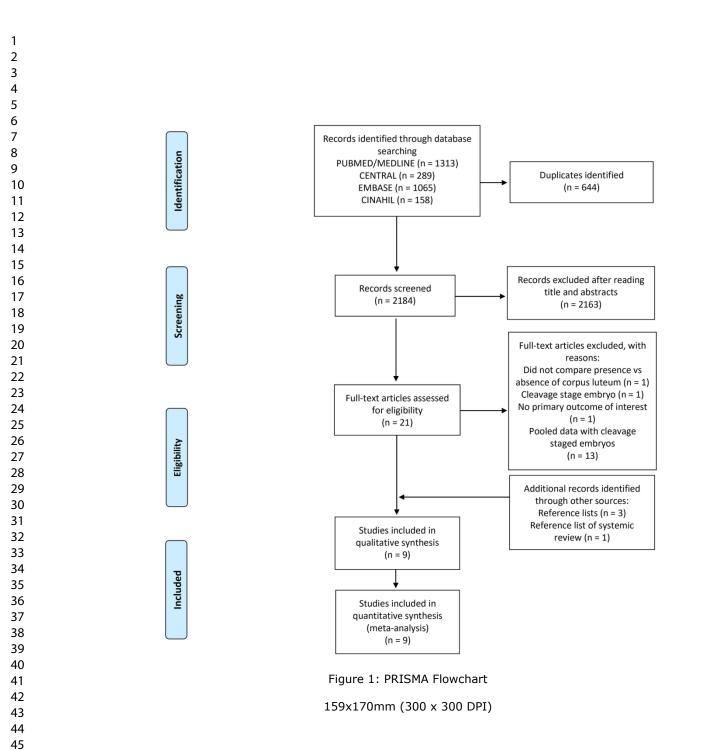
BMJ Open

17. Sterne JAC SJ, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, et al. RoB 2: a 1 2 revised tool for assessing risk of bias in randomised trials. bmj 2019;366:I4898. 3 GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-18. 4 Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 5 Ottawa Hospital Research Institute. Available from: 6 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 9, 2020. 7 19. The Cochrane Collaboration. Review Manager (RevMan). Version 5.4.1 ed2020. 8 20. Givens CR, Markun LC, Ryan IP, Chenette PE, Herbert CM, Schriock ED. Outcomes of 9 10 natural cycles versus programmed cycles for 1677 frozen-thawed embryo transfers. Reprod 11 Biomed Online 2009;19:380-4. 12 21. Chang EM, Han JE, Kim YS, Lyu SW, Lee WS, Yoon TK. Use of the natural cycle and 13 vitrification thawed blastocyst transfer results in better in-vitro fertilization outcomes : cycle 14 regimens of vitrification thawed blastocyst transfer. J Assist Reprod Genet 2011;28:369-74. 15 22. Greco E, Litwicka K, Arrivi C, Varricchio MT, Caragia A, Greco A, et al. The endometrial 16 preparation for frozen-thawed euploid blastocyst transfer: a prospective randomized trial 17 18 comparing clinical results from natural modified cycle and exogenous hormone stimulation with 19 GnRH agonist. J Assist Repro Genet 2016:33:873-84. 20 Sheikhi O, Golsorkhtabaramiri M, Esmaeilzadeh S, Mahouti T, Heidari FN. Reproductive 23. 21 outcomes of vitrified blastocyst transfer in modified natural cycle versus mild hormonally 22 stimulated and artificial protocols: A randomized control trial. JBRA Assist Reprod 2018;22:221-23 7. 24 24. Cardenas Armas DF, Peñarrubia J, Goday A, Guimerá M, Vidal E, Manau D, et al. 25 26 Frozen-thawed blastocyst transfer in natural cycle increase implantation rates compared 27 artificial cycle. Gynecol Endocrinol 2019;35:873-7. 28 Levi Setti PE, Cirillo F, De Cesare R, Morenghi E, Canevisio V, Ronchetti C, et al. Seven 25. 29 Years of Vitrified Blastocyst Transfers: Comparison of 3 Preparation Protocols at a Single ART 30 Center. Front Endocrinol (Lausanne) 2020;11:346. 31 Le QV, Abhari S, Abuzeid OM, DeAnna J, Satti MA, Abozaid T, et al. Modified natural 26. 32 33 cycle for embryo transfer using frozen-thawed blastocysts: A satisfactory option. Eur J Obstet 34 Gynecol Reprod Biol 2017;213:58-63. 35 27. Sahin G, Acet F, Calimlioglu N, Meseri R, Tavmergen Goker EN, Tavmergen E. Live birth 36 after frozen-thawed embryo transfer: which endometrial preparation protocol is better? J 37 Gynecol Obstet Hum Reprod 2020;8:101782. 38 Hill MJ, Miller KA, Frattarelli JL. A GnRH agonist and exogenous hormone stimulation 28. 39 protocol has a higher live-birth rate than a natural endogenous hormone protocol for frozen-40 41 thawed blastocyst-stage embryo transfer cycles: an analysis of 1391 cycles. Fertil Steril 42 2010:93:416-22. 43 Groenewoud ER, Cantineau AEP, Kollen BJ, Macklon NS, Cohlen BJ. What is the 29. 44 optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles? A 45 systematic review and meta-analysis. Hum Reprod Update 2017;23:255-61. 46 30. Mackens S, Santos-Ribeiro S, van de Vijver A, Racca A, Van Landuyt L, Tournaye H, et 47 al. Frozen embryo transfer: A review on the optimal endometrial preparation and timing. Hum 48 49 Reprod 2017;32:2234-42. 50 Luo L, Gu F, Jie H, Ding C, Zhao Q, Wang Q, et al. Early miscarriage rate in lean 31. 51 polycystic ovary syndrome women after euploid embryo transfer - a matched-pair study. Reprod 52 Biomed Online 2017;35:576-82. 53 Tomás C. Alsbierg B. Martikainen H. Humaidan P. Pregnancy loss after frozen-embryo 32. 54 transfer--a comparison of three protocols. Fertil Steril 2012;98:1165-9. 55 56 33. Veleva Z, Tiitinen A, Vilska S, Hydén-Granskog C, Tomás C, Martikainen H, et al. High 57 and low BMI increase the risk of miscarriage after IVF/ICSI and FET. Hum Reprod 2008;23:878-58 84. 59 60

1 2 3	34. Guan Y, Fan H, Styer AK, Xiao Z, Li Z, Zhang J, 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.
4 5	35. Cerrillo M, Herrero L, Guillén A, Mayoral M, García-Velasco JA. Impact of Endometrial Preparation Protocols for Frozen Embryo Transfer on Live Birth Rates. Rambam Maimonides
6 7	Med J 2017;8:e0020. 36. Liu X, Shi W, Shi J. Natural cycle frozen-thawed embryo transfer in young women with
8 9	regular menstrual cycles increases the live-birth rates compared with hormone replacement
10 11	treatment: a retrospective cohort study. Fertil Steril. 2020;113:811-7. 37. Olivier P, Irma Z, Marine B, Marie Laure T, Sylvie N-R, Nathalie R-M, et al. Comparison
12 13	of Serum Progesterone Levels of the Day of Frozen Embryo Transfers According to Type of Endometrial Preparation: A Monocentric, Retrospective Study. Res Sq 2021.
14 15	38. Kor NM. The effect of corpus luteum on hormonal composition of follicular fluid from
16	different sized follicles and their relationship to serum concentrations in dairy cows. Asian Pac J
17	Trop Med 2014;7 Suppl 1:S282-8.
18 19	39. Conrad KP. Emerging role of relaxin in the maternal adaptations to normal pregnancy: implications for preeclampsia. Semin Nephrol 2011;31:15-32.
20 21	40. Cedrin-Durnerin I, Isnard T, Mahdjoub S, Sonigo C, Seroka A, Comtet M, et al. Serum
22	progesterone concentration and live birth rate in frozen-thawed embryo transfers with
23	hormonally prepared endometrium. Reprod Biomed Online. 2019;38:472-80. 41. Labarta E, Mariani G, Holtmann N, Celada P, Remohí J, Bosch E. Low serum
24 25	progesterone on the day of embryo transfer is associated with a diminished ongoing pregnancy
26	rate in oocyte donation cycles after artificial endometrial preparation: a prospective study. Hum
27	Reprod 2017;32:2437-42.
28 29	42. Volovsky M, Pakes C, Rozen G, Polyakov A. Do serum progesterone levels on day of
29 30	embryo transfer influence pregnancy outcomes in artificial frozen-thaw cycles? J Assist Reprod
31	Genet 2020;37:1129-35.
32 33	43. Tavaniotou A, Smitz J, Bourgain C, Devroey P. Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. Hum Reprod
34	Update 2000;6:139-48.
35 36	44. Penzias AS, Alper MM. Luteal support with vaginal micronized progesterone gel in assisted reproduction. Reprod Biomed Online 2003;6:287-95.
37 38	45. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. Obstet Gynecol 2000;95:403-6.
39 40	46. Ginström Ernstad E, Wennerholm UB, Khatibi A, Petzold M, Bergh C. Neonatal and
41 42	maternal outcome after frozen embryo transfer: Increased risks in programmed cycles. Am J Obstet Gynecol 2019;221:126.e1e18.
43	47. Saito K, Kuwahara A, Ishikawa T, Morisaki N, Miyado M, Miyado K, et al. Endometrial
44 45	preparation methods for frozen-thawed embryo transfer are associated with altered risks of
46 47	hypertensive disorders of pregnancy, placenta accreta, and gestational diabetes mellitus. Hum Reprod 2019;34:1567-75.
47 48	48. von Versen-Hoynck F, Schaub AM, Chi YY, Chiu KH, Liu J, Lingis M, et al. Increased
49 50	Preeclampsia Risk and Reduced Aortic Compliance With In Vitro Fertilization Cycles in the Absence of a Corpus Luteum. Hypertension 2019;73:640-9.
51 52	49. Jing S, Li XF, Zhang S, Gong F, Lu G, Lin G. Increased pregnancy complications
53	following frozen-thawed embryo transfer during an artificial cycle. J Assist Reprod Genet
54 55	2019;36:925-33. 50. Saito K, Kuwahara A, Ishikawa T, Nakasuji T, Miyado M, Miyado K, et al. Pregnancy
55 56	after frozen-thawed embryo transfer during hormonal replacement cycle is associated with
57	hypertensive disorders of pregnancy and placenta accreta. Hum Reprod 2018;33 Suppl 1:i128-
58	i9.
59 60	

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Sakai Y, Ono M, lizuka T, Kagami K, Masumoto S, Nakayama M, et al. Embryo transfer 51. associated with hormone replacement therapy cycles using assisted reproductive technology increases placenta accreta spectrum. J Obstet Gynaecol Res 2019;45:2394-9. von Versen-Höynck F, Narasimhan P, Selamet Tierney ES, Martinez N, Conrad KP, 52. Baker VL, et al. Absent or Excessive Corpus Luteum Number Is Associated With Altered Maternal Vascular Health in Early Pregnancy. Hypertension 2019;73:680-90. Asserhøj LL, Spangmose AL, Aaris Henningsen A-K, Clausen TD, Ziebe S, Jensen RB, 53. 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 2021:0;https://doi.org/10.1016/j.fertnstert.2020.10.039 for peet teriew only



Rates of Positive b-hCG

Live Birth Rates Num-Gupta 2018 With CL Risk Ratio Risk Ratio Study or Subgroup With CL Risk Ratio Risk Ratio Study or Subgroup With CL Risk Ratio Risk Ratio Study or Subgroup With CL Risk Ratio Mike Ratio Alur-Gupta 2018 47 104 425 917 8.7% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 425 1010 100 72, 2.32] Gree 2016 50 1019 7 261 1.10 [0.72, 1.20] Cardenas Armas 2019 7 261 1.10 [0.87, 1.35] Levi Setti 2020 722 2304 151 68 Total (95% CI) 106 56 Total events 10 67 <th></th> <th>With</th> <th></th> <th>Withou</th> <th></th> <th></th> <th>Risk Ratio</th> <th>Risk Ratio</th>		With		Withou			Risk Ratio	Risk Ratio
Cardenias Armas 2019 16 22 76 175 15% 115 [D_{15}^{2} 1.16 [D_{15}^{2} 1.69] Chang 2011 229 444 107 224 92% 0.98 (0.84.115 Givens 2009 369 656 141 221 13.5% 0.80 [0.68,0.61] Greco 2016 66 109 70 113 43% 1.01 [0.85,1.12] Lev Setti 2020 802 2033 376 997 31.6% 0.95 [0.61,0.61,0.61] Total (95% C1) 6138 3491 100.0% 1.00 [0.95, 1.05] Total events 28 2600 1737 Heterogenetic, Chi = 13.86, df = 8 (P = 0.03), P = 42% Test for overall effect Z = 0.16 (P = 0.87) Clinical Pregnancy Rates Study or Subgroup Without CL Without CL Risk Ratio MH, Random, 95% CI Aut-Outpla 2018 55 104 523 917 12 29% 109 (0.78, 1.38] Great 2018 103 230 2304 217 544 17.8% 109 (0.95, 1.05] Cardensa Armas 2019 13 22 60 175 444 107 204 11.38 (0.98,0.68] Great 2017 107 197 197 113 1.37% 0.429 (0.88,0.68] Great 2016 559 (10) 67 113 9.7% 1.107 (0.83,0.68] Great 2016 559 (10) 67 113 9.7% 1.107 (0.83,0.68] Great 2016 559 (10) 67 113 9.7% 1.109 (0.95, 1.02] Total events 2020 303 2304 217 544 17.8% 1.198 (0.96,0.68] Great 2016 559 (10) 67 113 9.7% 1.107 (0.83,0.68,0.28] Total (95% C1) 6138 3491 100.0% 1.16 [0.96,1.18] Total events 2019 10 57 9 59 11.5% 1.15 (0.50,2.62] Total (95% C1) 6138 3491 100.0% 1.16 [0.96,1.18] Total events 2017 107 197 7 197 118 1.15 (0.50,2.62] Total (95% C1) 6138 3491 100.0% 1.16 [0.96,1.18] Total events 2017 103 197 79 181 1.15 (0.50,2.62] Total (95% C1) 6138 3491 100.0% 1.16 [0.96,1.18] Cardensa Armas 2019 10 32 42 175 1.3% 0.98 [0.78,1.22] Cardensa Armas 2019 10 32 42 175 1.3% 0.98 [0.78,1.22] Cardensa Armas 2019 10 32 42 175 1.3% 0.98 [0.78,1.22] Cardensa Armas 2019 10 32 42 175 1.3% 0.98 [0.78,1.23] Greco 2016 50 109 47 113 4.68 1.10 [0.25,1.47] Pakes 2020 722 2304 151 584 72.8% 1.15 [0.50,2.52] Total events 163 1009 Heterogenetic, Chi = 2.37, (P = 0.02), (P = 29%) Test for overall effect Z = 0.01 (P = 0.99) Total (95% C1) 6138 3491 100.0% 1.14 [1.06,1.22] Total events 163 1009 Heterogenetic, Chi = 2.37, (P = 0.005) Total (95% C1) 6138 3491 100.0% 1.14 [1.06,1.22] Tot	Study or Subgroup	Events	Total	Events	Tota	Weight	t M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chang 2011 229 444 107 204 92% 0.98 [0.84, 115] Givens 2009 396 95% 141 221 135% 0.88 [0.66, 0.91] Greco 2016 68 109 70 113 43% 1.01 [0.82, 1.24] Lev Setti 2020 1012 2304 243 584 24.3% 1.05 [0.95, 115] Pakes 2020 802 2033 376 997 31.6% 1.05 [0.95, 115] Total (95% CI) 6138 3491 100.0% 1.00 [0.95, 1.05] Total versts 2690 1737 Heterogenetic, Ch ² = 13.86, df = 8 (P = 0.92), P = 42% Test for overall effect Z = 0.16 (P = 0.92) Clinical Pregnancy Rates Clinical Pregnancy Rates	Alur-Gupta 2018	64	104	602	917	7.7%	0.94 [0.80, 1.10]	
Opens 2009 369 858 141 221 135% 0.80 0.60 0.60 0.11 Le 2017 120 197 110 181 7.2% 1.00 10.55 1.01 10.55 1.01 10.55 1.01 10.55 1.05 10.55 1.05 10.51 1.01 10.57 12 59 0.7% 0.86 10.61 0.55 1.05 10.55 1.05 10.57 1.00 10.57 1.00 10.57 1.00 10.57 1.00 1.00 1.05 1.00 </td <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>								
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		229	444	107	204	9.2%	0.98 [0.84, 1.15]	
Lev Sett 2200 Lev Sett 2200 1012 2304 243 584 243 243 164 243 584 243 584 243 581 248 243 581 244 585 581 244 581 581 244 581 581 244 581 581 244 581 581 244 581 581 244 581 241 241 144 583 581 244 581 241 241 144 583 581 244 581 241 241 144 583 581 244 581 241 241 144 583 581 244 581 241 241 144 583 581 244 581 241 241 144 584 581 244 581 241 241 144 584 581 244 581 241 241 144 584 581 244 581 241 241 144 584 581 244 241 241 241 241 241 241 241 241 24		369						
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		68	109	70	113	4.3%	1.01 [0.82, 1.24]	
Pakes 2020 802 2033 376 997 31.6% 1.05 [0.95, 1.16] Sheikh 2018 10 57 12 59 0.7% 0.86 [0.40, 1.84] Total (95% CI) 6138 3491 100.0% 1.00 [0.95, 1.05] 0.05 [0.7, 1.16] Total events 2600 1727 Heterogeneity Chr = 1.36, df = 6 (P = 0.09); P = 42% Fearours no CL. Favours no CL. Favours no CL. Clinical Pregnancy Rates With CL With Ot A Mith Without CL. Risk Ratio Aur Gupta 2019 55 104 52 2017 12 2% 0.9107, 112 Chardensa Armas 2019 55 104 52 2017 12 9% 0.9107, 112 Chardensa Armas 2019 108 444 50 57 13 10, 100, 107, 112 14 100, 108, 123 Chardensa Armas 2019 108 148 107, 107, 107 107, 112 13 100, 108, 123 Chardensa Armas 2019 103 220, 17, 128 100, 109, 17, 123 100, 109, 17, 123 Lew Staft 2020 2030 2030 204, 17, 584 100, 109, 17, 123 100, 109, 17, 123 Lew Staft 2020 103 2017 103 10	Le 2017	120	197	110	181	7.2%	1.00 [0.85, 1.18]	
Sheikhi 2018 10 57 12 59 0.7% 0.86 (p. 40, 1.84) Total (95% CI) 6138 3491 100.0% 1.00 (p.95, 1.05) Total (95% CI) 6138 3491 100.0% 1.00 (p.95, 1.05) Test for overall effect Z = 0.16 (P = 0.07) Events Total Weight MH, Random, 95% CI MH, Random, 95% CI Alur-Gupta 2018 Study or Subgroup With CL Without CL Risk Ratio Risk Ratio Chardenas Armas 2019 13 32 60 175 4.0% 1.18 (p.07, 1.12) Chardenas Armas 2019 13 32 60 175 4.0% 0.03 (p.07, 1.12) Chardenas Armas 2019 13 32 60 175 4.0% 0.03 (p.08) 7.11 Oreno 2016 59 109 57 113 10.6 (p.09, 7.1.2) MH, Random, 95% CI Levi Setti 2020 930 2304 217 5% 1.03 (p.08, 1.28) 1.03 (p.08, 1.28) Levi Setti 2020 9203 2217 1.38 3491 100.0% 1.06 (p.0.96, 1.18) 0.5 0.5 0.7 1.5 Favours N	Levi Setti 2020	1012	2304	243	584	24.3%	1.06 [0.95, 1.17]	
Total (95% CI) 6138 3491 100.0% 1.00 [0.95, 1.05] Total events 2600 1727 Heterogeneity Ch ² = 13.86, df = 8 (P = 0.09); P = 42% Test for overall effect Z = 0.16 (P = 0.87) Clinical Pregnancy Rates Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Aun-Oupta 2018 55 104 523 917 12.9% Chang 2011 186 444 62 204 10.5% 1.38 [10.91, 74] Overs 2008 2048 658 105 261 13.7% 0.82 (D68, 0.98) Greco 2016 59 109 57 113 9.7% 1.07 (D83, 1.38) Le 2017 107 197 95 181 12.9% 1.03 (D86, 1.28) Pakes 2020 390 2304 217 564 17.8% 1.98 (D86, 1.88) Total (95% CI) 6138 3491 100.0% 1.06 [0.96, 1.18] Total (95% CI) 6138 3491 100.0% 1.06 [0.96, 1.12] Cardenas Armas 2019 10 32 42 175 1.3% 0.98 [0.78, 1.20] Cardenas Armas 2019 10 32 42 175 0.1% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 0.1% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 0.1% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 0.1% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 0.4% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 0.4% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 0.4% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 0.72 2.2304 151 544 2.42% 1.21 [1.04, 1.14] Pakes 2020 722 2304 151 544 2.42% 1.21 [1.04, 1.14] Pakes 2020 722 2304 151 544 2.42% 1.21 [0.04, 1.14] Total events 1683 1009 Heterogeneity: Ch ² = 0.030; P= 0.30; P= 26% Test for overall effect Z = 0.07 (P = 0.0002) 3.12 Oroging Pregnancy Rates Chang 2011 229 444 107 204 14.8% 0.98 [0.84, 1.15] Subtotal (95% CI) 501 229 444 107 204 14.8% 0.98 [0.84, 1.15] Subtotal (95% CI) 501 229 4124 Heterogeneity: Ch ² = 0.99; 115 Total events 1902 1124 Heterogeneity: Ch ² = 0.99; 115 To	Pakes 2020	802	2033	376	997	31.6%	1.05 [0.95, 1.15]	
Total events 2690 1727 Heterogeneily: ChP = 13.86, df = 6 (P = 0.09); P = 42% Test for overall effect Z = 0.16 (P = 0.07); P = 42% Test for overall effect Z = 0.16 (P = 0.07); P = 42% Clinical Pregnancy Rates With CL Without CL Risk Ratio Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CL Aur-Oupta 2018 55 104 522 917 12.9% Chang 2011 186 444 62 204 10.5% 1.38 [10.91, 7.4] Overa 2008 224 858 105 261 13.7% 0.82 (D.69, 0.98) Greeo 2016 59 109 57 113 9.7% 1.07 [0.88, 1.38] Le 2017 107 197 95 181 12.9% 1.03 (D.88, 1.28] Pakes 2020 930 2304 217 564 17.8% 1.09 [0.97, 1.22] Pakes 2020 930 2304 217 564 17.8% 1.09 [0.95, 1.12] Total (95% CL) 6138 3491 100.0% 1.06 [0.96, 1.18] Total (95% CL) 6138 3491 100.0% 1.06 [0.96, 1.12] Cardenas Armas 2019 10 32 42 175 1.3% 0.98 [0.78, 1.22] Total (95% CL) 6138 3491 100.0% 1.106 [0.95, 1.12] Cardenas Armas 2019 10 32 42 175 1.3% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 0.1% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 1.09 [0.87, 1.32] Givens 2020 722 2304 151 584 24.2% 1.10 [0.82, 1.49] Le 2017 93 197 79 181 8.3% 1.08 [0.87, 1.35] Lev Birth Rates Aur-Oupta 2018 47 104 425 917 8.7% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 1.00 [0.85, 1.18] Total events 1683 1009 Heterogeneily: ChP = 0.72, df = 6 (P = 0.23); F = 26% Test for overall effect Z = 3.70 (P = 0.0002) 3.12 Onging Pregnancy Rates Chang 2011 228 444 107 204 14.8% 0.98 [0.84, 1.15] Subtotal (95% CL) 501 239 115 Total events 1902 1124 Heterogeneily: ChP = 0.39, df = (P = 0.59); F = 30% Test for overall effect Z = 0.01 (P = 0.0002) 3.12 Onging Pregnancy Rates Chang 2011 228 444 107 204 14.8% 0.98 [0.84, 1.15] Subtotal (95% CL) 613 3491 100.0% 1.14 [1.06, 1.22] Total events 1902 1124 Heterogeneily: ChP = 0.39, df = (P = 0.59); F = 30% Test for overall eff	Sheikhi 2018	10	57	12	59	0.7%	0.86 [0.40, 1.84]	
Heterogeneity: Chi ^m = 13.86, df = 6 (P = 0.09); P = 42% Test for overall effect Z = 0.16 (P = 0.87) Clinical Pregnancy Rates Study or Subgroup With CL Risk Ratio Study or Subgroup With CL Risk Ratio Risk Ratio Aur-Outpla 2018 Other and 2018 NH CL Risk Ratio Cardenas Armas 2019 13 32 60 NT Aur-Outpla 2018 NH CL Risk Ratio Risk Ratio Cardenas Armas 2019 322 Risk Ratio Risk Ratio Cardenas Armas 2019 Study or Subgroup Cervice Total Vent 10 Study or Subgroup Cervice Total Study or Subgroup Events Total (95% CI) Galden Strates Total (95% CI) Galden Strates Study or Subgroup Events Total Weight ML, Fixed, 95% CI Fis Ratio </td <td>Total (95% CI)</td> <td></td> <td>6138</td> <td></td> <td>3491</td> <td>100.0%</td> <td>1.00 [0.95, 1.05]</td> <td>•</td>	Total (95% CI)		6138		3491	100.0%	1.00 [0.95, 1.05]	•
Test for overall effect Z = 0.16 (P = 0.87) Diffect Z = 0.16 (P = 0.87) Clinical Pregnancy Rates Mith CL With CL Risk Ratio Mith CL With CL Risk Ratio Aur-Gupta 2018 Study or Subgroup Events Total Weight M-H, Random, 95% CL Aur-Gupta 2018 Study or Subgroup Risk Ratio Aur-Gupta 2018 Study or Subgroup Risk Ratio Clinical Pregnancy Rates Condensa Armas 2019 Study or Subgroup Risk Ratio Clinical Pregnancy Rates Condensa Armas 2010 Study or Subgroup Risk Ratio Mith CL With CL Risk Ratio Mith CL With CL Risk Ratio Total (95% CL) 6138 3491 100.0% 1.06 (0.96, 1.18) Total (95% CL) 6138 3491 Risk Ratio <td>Total events</td> <td>2690</td> <td></td> <td>1737</td> <td></td> <td></td> <td></td> <td></td>	Total events	2690		1737				
$\begin{aligned} \begin{array}{c} \text{Study or Subgroup} & \underbrace{\text{With CL}}_{\text{Vents Total}} & \underbrace{\text{Without CL}}_{\text{Vents Total}} & \underbrace{\text{Risk Ratio}}_{\text{Vents Total}} & \underbrace{\text{Risk Ratio}}_{\text{Risk Ratio}} & \underbrace{\text{Risk Ratio}}_{\text{Risk Ratio} & \underbrace{\text{Risk Ratio}}_{\text{Risk Ratio}} & \underbrace{\text{Risk Ratio}}_{\text{Risk Ratio} & \underbrace{\text{Risk Ratio}}_{\text{Risk Ratio}} & \underbrace{\text{Risk Ratio}}_{\text{Risk Ratio} & \text{Risk Rati$				09); I ^z = 4	12%			
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Alur-Gupta 2018 65 104 623 917 12.9% 0.93 [0.77, 1.12] Cardenas Armas 2019 13 32 60 175 4.0% 1.18 [0.74, 1.89] Chang 2011 186 444 62 204 10.5% 1.38 [1.09, 1.74] Ghens 2009 284 688 105 261 13.7% 0.82 [0.69, 0.98] Greec 2016 59 109 57 113 0.7% 1.07 [0.83, 1.38] Lev 3017 107 197 95 181 12.9% 1.0910.86, 1.28] Pakes 2020 627 2033 260 997 17.2% 1.18 [1.05, 1.34] Sheikhi 2018 10 57 9 59 1.5% 1.15 [0.50, 2.62] Total (95% Cl) 6138 3491 100.0% 1.06 [0.96, 1.18] 1.06 [0.96, 1.18] Total (95% Cl) 6138 3491 100.0% 1.06 [0.96, 1.22] Favours Wot Live Birth Rates Alur-Gupta 2018 47 104 425 917 8.7% 0.98 [0.78, 1.22] Cardrenas Armas 2019 10 2.4<		With (L	Without	CL		Risk Ratio	Risk Ratio
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$\begin{array}{c} \mbox{Cardenias} Armas 2019 & 13 & 32 & 60 & 175 & 4.0\% & 1.18 [0.74, 1.89] \\ \mbox{Chang} 2011 & 186 & 444 & 62 & 204 & 10.5\% & 1.38 [1.08, 1.74] \\ \mbox{Olvens} 2009 & 244 & 858 & 105 & 201 & 13.7\% & 0.82 [0.88, 0.98] \\ \mbox{Orecc} 2016 & 59 & 109 & 57 & 113 & 9.7\% & 1.07 [0.83, 1.38] \\ \mbox{Le 2017} & 107 & 197 & 95 & 118 & 12.9\% & 1.03 [0.86, 1.25] \\ \mbox{Levi Setti} 2020 & 9.30 & 2304 & 217 & 584 & 17.6\% & 1.09 [0.97, 1.23] \\ \mbox{Packed} 2020 & 627 & 2033 & 260 & 997 & 17.2\% & 1.18 [1.06, 1.34] \\ \mbox{Sheikhi} 2018 & 10 & 57 & 9 & 59 & 1.5\% & 1.15 [0.50, 2.62] \\ \mbox{Total events} & 2271 & 1388 \\ \mbox{Heterogeneity}. Tau*= 0.01; Ch^{\mu}= 18.35, dr=8 (P=0.02); P=56\% & \\ \mbox{Test for overall effect} Z=1.15 (P=0.25) \\ \mbox{Live Birth Rates} & \\ \mbox{Aur-Gupta} 2018 & 47 & 104 & 425 & 917 & 8.7\% & 0.98 [0.78, 1.22] & \\ \mbox{Overs 2009} & 245 & 858 & 77 & 261 & 11.9\% & 0.97 [0.78, 1.20] & \\ \mbox{Overs 2016} & 50 & 109 & 47 & 113 & 4.5\% & 1.09 [0.82, 1.49] & \\ \mbox{Lev Girth Rates} & \\ \mbox{Aur-Gupta} 2018 & 47 & 104 & 425 & 917 & 8.7\% & 0.98 [0.78, 1.22] & \\ \mbox{Overs 2016} & 50 & 109 & 47 & 113 & 4.5\% & 1.09 [0.78, 1.20] & \\ \mbox{Overs 2016} & 50 & 109 & 47 & 113 & 4.5\% & 1.09 [0.78, 1.20] & \\ \mbox{Overs 2016} & 50 & 109 & 47 & 113 & 4.5\% & 1.09 [0.78, 1.20] & \\ \mbox{Overs 2016} & 50 & 109 & 47 & 113 & 4.5\% & 1.09 [0.78, 1.20] & \\ \mbox{Overs 2016} & 50 & 109 & 47 & 113 & 4.5\% & 1.09 [0.78, 1.20] & \\ \mbox{Overs 2016} & 50 & 109 & 47 & 113 & 4.5\% & 1.09 [0.78, 1.20] & \\ \mbox{Overs 2016} & 50 & 109 & 47 & 113 & 4.5\% & 1.00 [0.85, 1.17] & \\ \mbox{Deta GeV} 7 & 6138 & 3491 & 100.0\% & 1.14 [1.06, 1.22] & \\ \mbox{Total events} & 1663 & 1009 & \\ \mbox{Heterogeneity}; \mbox{Ch} = 8.07, dr=6 (P=0.03); P=20\% & \\ \mbox{Test for overall effect} Z=3.50 (P=0.0005) & \\ \mbox{Total events} & 239 & 115 & \\ \mbox{Heterogeneity}; \mbox{Ch} = 11.23, dr=6 (P=0.0005) & \\ \mbox{Total events} & 1002 & 1124 & \\ \mbox{Heterogeneity}; \mbox{Ch} = 1.23, 0.07 = 0.0005) & \\ \mbox$								-+-
Chang 2011 186 444 62 204 10.5% 1.38 $100.1, 74$ Ohvens 2009 284 858 105 261 13.7% 0.82 $100.69, 0.89$ Oraco 2016 59 109 57 113 0.7% 1.07 $10.83, 1.38$ Le 2017 107 197 95 181 12.9% 1.03 $10.86, 1.22$ Pakes 2020 627 2033 260 997 17.2% 1.18 $10.05, 1.34$ Sheikhi 2018 10 57 9 59 15% 1.5% 1.06 $[0.96, 1.18]$ Total (95% CI) 6138 3491 100.0% 1.06 $[0.96, 1.18]$ Total (95% CI) 6138 3491 100.0% 1.06 $[0.96, 1.18]$ Total events 2271 1388 Heterogeneily, Tau ² = 0.01, Ch ² = 18.35, df = 8 (P = 0.02), P = 56% Test for overall effect Z = 1.15 (P = 0.25) Live Birth Rates Alur-Gupta 2018 47 104 425 917 8.7% 0.98 $[0.76, 1.22]$ Cardenas Armas 2019 10 32 42 175 1.3% 1.30 $[10.37, 1.32]$ Givens 2009 245 858 77 261 11.9% 0.97 $[0.78, 1.20]$ Givens 2009 245 858 77 261 11.9% 0.97 $[0.78, 1.22]$ Cardenas Armas 2019 10 32 44 2175 1.3% 1.30 $[0.37, 1.32]$ Levi Setti 2020 722 2304 151 584 24.2% 1.29 $[1.11, 1.50]$ Subtotal (95% CI) 5637 32228 84.5% 1.16 $[1.07, 1.28]$ Total events 1663 1009 Heterogeneity, ChP = 0.39, df = 6 (P = 0.23), P = 26% Test for overall effect Z = 3.07 (P = 0.0005) Total (95% CI) 6138 3491 100.0% 1.14 $[1.06, 1.22]$ Total events 1663 1009 Heterogeneity, ChP = 0.39, df = 1 (P = 0.53), IP = 0% Test for overall effect Z = 3.07 (P = 0.009) Total (95% CI) 6138 3491 100.0% 1.14 $[1.06, 1.22]$ Total events 1602 1124 Heterogeneity, ChP = 0.39, df = 1 (P = 0.53), IP = 0% Test for overall effect Z = 3.07 (P = 0.009) Total (95% CI) 6138 3491 100.0% 1.14 $[1.06, 1.22]$ Total events 1902 1124 Heterogeneity, ChP = 1.123, df = 8 (P = 0.19), IP = 29% Test for overall effect Z = 3.07 (P = 0.0005)								
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$ \begin{array}{c} \mbox{Greco} 2016 & 59 & 109 & 57 & 113 & 9.7\% & 1.07 (0.83, 1.28) \\ \mbox{Le} 2017 & 107 & 197 & 95 & 181 & 12.9\% & 1.03 (0.86, 1.26) \\ \mbox{Levi Setti} 2020 & 930 & 2304 & 217 & 584 & 17.6\% & 1.09 (0.97, 1.22) \\ \mbox{Pakes} 2020 & 627 & 2033 & 260 & 997 & 17.2\% & 1.18 (1.05, 1.24) \\ \mbox{Sheikhi} 2018 & 10 & 57 & 9 & 59 & 1.5\% & 1.15 (1.05, 0.2.62) \\ \mbox{Total events} & 2.271 & 1388 \\ \mbox{Heterogeneiky} Tau*e .0.1; ChI*= 18.35, df= 8 (P=0.02); P= 56\% \\ \mbox{Testfro overall effect} Z= 1.15 (P=0.25) \\ \mbox{Live Birth Rates} \\ \mbox{Alur-Cupta} 2018 & 47 & 104 & 425 & 917 & 8.7\% & 0.98 [0.78, 1.22] \\ \mbox{Grees} 2009 & 245 & 858 & 77 & 261 & 11.9\% & 0.97 (0.78, 1.22) \\ \mbox{Grees} 2019 & 10 & 32 & 42 & 175 & 1.3\% & 1.30 (0.73, 2.32) \\ \mbox{Grees} 2019 & 245 & 858 & 77 & 261 & 11.9\% & 0.97 (0.78, 1.20) \\ \mbox{Grees} 2019 & 245 & 858 & 77 & 261 & 11.9\% & 0.97 (0.78, 1.20) \\ \mbox{Grees} 2019 & 245 & 858 & 77 & 261 & 11.9\% & 0.97 (0.78, 1.20) \\ \mbox{Grees} 2019 & 245 & 858 & 77 & 261 & 11.9\% & 0.97 (0.78, 1.20) \\ \mbox{Grees} 2019 & 245 & 858 & 77 & 261 & 11.9\% & 0.97 (0.78, 1.20) \\ \mbox{Grees} 2019 & 245 & 858 & 77 & 261 & 11.9\% & 0.97 (0.78, 1.20) \\ \mbox{Grees} 2019 & 245 & 858 & 77 & 263 & 11.08 (0.87, 1.35) \\ \mbox{Levis Bit 2020 } 722 & 2034 & 151 & 584 & 242 & 271 & 71 & 113 & 4.6\% & 1.10 (0.21, 1.49) \\ \mbox{Levis Bit 2020 } 722 & 2034 & 151 & 584 & 242 & 271 & 71 & 113 & 4.5\% & 1.10 (0.08, 1.14] \\ \mbox{Grees} 2020 & 496 & 2033 & 188 & 997 & 2.6.4\% & 1.29 (1.11, 1.50) \\ \mbox{Subtoal} (95\% CI) & 501 & 229 & 444 & 107 & 204 & 14.9\% & 0.98 [0.84, 1.15] \\ \mbox{Sheikh} 2018 & 10 & 57 & 8 & 69 & 0.3\% & 1.29 [0.55, 3.04] \\ \mbox{Subtoal} (95\% CI) & 501 & 229 & 414 & 107 & 204 & 14.9\% & 0.98 [0.84, 1.15] \\ \mbox{Sheikh} 2018 & 10 & 57 & 8 & 69 & 0.3\% & 1.29 [0.55, 3.04] \\ \mbox{Subtoal} (95\% CI) & 6138 & 3491 & 100.0\% & 1.14 [1.06, 1.22] \\ \mbox{Total events} & 1902 & 1124 \\ \mbox{Heterogeneiky} ChI*= 1.23, df= 8 (P=0.19), F= 29\% \\ \mbox{Testfro overail effect} Z= 3.50, (P=0.0005) \\ \mbox$		284	858	105	261	13.7%		
Le 2017 107 197 95 181 12.9% 1.03 [0.86, 1.20] Levi Setti 2020 930 2304 217 584 17.6% 1.09 [0.97, 1.22] Pakes 2020 627 203 260 997 17.2% 1.18 [1.05, 1.34] Sheikhi 2018 10 57 9 59 1.5% 1.15 [0.50, 2.62] Total (95% CI) 6138 3491 100.0% 1.06 [0.96, 1.18] Total events 2271 1388 Heterogeneity: Tau ² = 0.01; Ch ² = 1.8.5, df = 8 (P = 0.02); P = 56% Test for overall effect Z = 1.15 (P = 0.25) Live Birth Rates Alur-Gupta 2018 47 104 425 917 8.7% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 1.30 [0.73, 2.32] Givens 2009 245 658 77 261 11.9% 0.97 [0.78, 1.20] Givens 2009 245 658 77 72 61 11.9% 0.97 [0.78, 1.20] Givens 2009 245 658 77 72 61 11.9% 0.97 [0.78, 1.20] Givens 2009 496 2033 188 997 25.4% 1.29 [1.01, 1.41] Pakes 2020 496 2033 188 997 25.4% 1.29 [1.01, 1.41] Pakes 2020 496 2033 188 997 25.4% 1.29 [1.01, 1.41] Pakes 2020 496 2033 188 997 25.4% 1.29 [1.01, 1.41] Pakes 2020 496 2033 188 997 25.4% 1.29 [1.01, 1.41] Pakes 2020 496 2033 188 997 25.4% 1.29 [0.53, 3.04] Subtotal (95% CI) 501 263 15.5% 1.00 [0.85, 1.17] Total events 1663 1009 Heterogeneity: Ch ² = 0.79 (P = 0.00); P = 0% Test for overall effect Z = 3.70 (P = 0.00); P = 0% Test for overall effect Z = 3.50 (P = 0.19); P = 0% Test for overall effect Z = 3.50 (P = 0.19); P = 2% Total (95% CI) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 1902 1124 Heterogeneity: Ch ² = 1.123, df = 8 (P = 0.19); P = 2% Total (95% CI) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 1902 1124 Heterogeneity: Ch ² = 1.123, df = 8 (P = 0.19); P = 2% Total (95% CI) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 1902 1124 Heterogeneity: Ch ² = 1.5, df = 8 (P = 0.19); P = 2% Total (95% CI) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 1902 1124 Heterogeneity: Ch ² = 1.50 (P = 0.19); P = 2% Total events 1902 1124 Heterogeneity: Ch ² = 1.50 (P = 0.005)		59	109	57	113	9.7%		
Levi Setti 2020 930 2304 217 584 17.6% 1.09 (9.97, 1.22) Pakes 2020 627 2033 260 997 17.2% 1.18 (1.05, 1.34) Sheikhi 2018 10 67 9 59 1.5% 1.15 (0.50, 2.62) Total (95% CI) 6138 3491 100.0% 1.06 [0.96, 1.18] Total events 2271 1388 Heterogeneily, Tau* = 0.01; Chi*= 18.35, df = 8 (P = 0.02); P = 56% Test for overall effect: Z = 1.15 (P = 0.25) Live Birth Rates Alur-Gupta 2018 47 104 425 917 8.7% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 442 175 1.3% 1.30 [0.78, 1.22] Givens 2009 245 858 77 261 11.9% 0.97 [0.78, 1.20] Greco 2016 50 109 47 113 4.6% 1.10 [0.82, 1.49] Levi Setti 2020 722 2304 151 584 24.2% 1.21 [1.04, 1.41] Pakes 2020 496 2033 188 997 25.4% 1.29 [1.11, 1.50] Subtotal (95% CI) 5637 3228 84.5% 1.16 [1.07, 1.26] Total events 1663 1009 Heterogeneity, Chi* = 0.39, df = 1 (P = 0.59); P = 26% Test for overall effect: Z = 3.70 (P = 0.0002) 3.1.2 Ongoing Pregnancy Rates Chang 2011 229 444 107 204 14.8% 0.98 [0.84, 1.15] Sheikhi 2018 10 57 8 69 0.8% 1.29 [0.55, 3.04] Subtotal (95% CI) 551 1263 15.5% 1.00 [0.85, 1.17] Total events 239 115 Heterogeneity, Chi* = 0.39, df = 1 (P = 0.59); P = 0% Test for overall effect: Z = 3.70 (P = 0.0002) 3.1.2 Ongoing Pregnancy Rates Chang 2011 229 414 107 204 14.8% 0.98 [0.84, 1.15] Sheikhi 2018 10 57 8 69 0.8% 1.29 [0.55, 3.04] Subtotal (95% CI) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 239 115 Heterogeneity, Chi* = 0.39, df = 1 (P = 0.59); P = 0.6% Test for overall effect: Z = 3.07 (P = 0.0002) Total (95% CI) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 11002 1124 Heterogeneity, Chi* = 0.39, df = 1 (P = 0.59); P = 0.6% Test for overall effect: Z = 3.50 (P = 0.0005)		107	197	95	181	12.9%		
Pakes 2020 627 2033 260 997 17.2% 1.18 [1.05, 1.24] Sheikhi 2018 10 67 9 59 1.5% 1.15 [0.50, 2.62] Total (95% CI) 6138 3491 100.0% 1.06 [0.96, 1.18] Total events 2271 1388 Heterogeneity: Tau" = 0.01; Chi" = 18.35, df = 8 (P = 0.02); P = 56% Testfor overall effect Z = 1.15 (P = 0.25) Live Birth Rates With CL Without CL Risk Ratio Study or Subgroup Events Total Events 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 0.98 [0.78, 1.22] Givens 2009 245 568 77 1.11 (1.9%, 0.97 [0.78, 1.20] M.H, Fixed, 95% CI M.H, Fixed, 95% CI Givens 2009 245 568 77 1.13 (0.73, 2.32] Image: Cardenas Armas 2019 10 32 42 175 1.3% (0.80, 71.35] Image: Cardenas Armas 2019 10 32 42 175 1.28 (1.04, 1.41] Image: Cardenas Armas 2019 <	Levi Setti 2020	930	2304	217	584	17.6%		+
Sheikhi 2018 10 57 9 59 1.5% 1.15 [0.50, 2.62] Total (95% Cl) 6138 3491 100.0% 1.06 [0.96, 1.18] Total events 2271 1388 Heterogeneily, Tau" = 0.01; Ch" = 18.35, df = 8 (P = 0.02); P = 56% Test for overall effect Z = 1.15 (P = 0.25) Live Birth Rates With CL Without CL Risk Ratio 3.1.1 Live Birth Rates With CL Risk Ratio Risk Ratio Alur-Gupta 2018 47 104 425 917 8.7% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 1.30 [0.73, 2.32] Oreco 2016 50 109 47 113 4.6% 1.08 [0.87, 1.32] Cardenas Armas 2019 07 22 304 15 1.32 (0.27, 22 304 1.11 [0.4, 1.41] Pakes 2020 462 2033 188 997 2.64% 1.29 [1.11, 1.50] Subtotal (95% Cl) 5637 3228 8.4.5% 1.16 [1.07, 1.26] 4.107 Total events 10.63 10.09 1.29 [0.55, 3.04] 1.04 [0.56, 1.7] <t< td=""><td></td><td></td><td></td><td></td><td>997</td><td></td><td></td><td></td></t<>					997			
Total events 2271 1388 Heterogeneity: Tau" = 0.01; Ch" = 18.35, df = 8 (P = 0.02); P = 56% Testfor overall effect Z = 1.15 (P = 0.25) Discrete Study or Subgroup With CL Risk Ratio Study or Subgroup With CL Without CL Risk Ratio Risk Ratio Alur-Oupta 2018 47 104 425 917 8.7% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 17 13 4.6% 1.10 [0.82, 1.49] Lev Setti 2020 722 2304 15 584 1.28 1.08 [0.87, 1.25] Givens 2009 245 658 77 261 11.9% 0.97 [0.78, 1.20] Orec 2016 50 109 47 113 4.6% 1.10 [0.82, 1.49] Lev Setti 2020 722 2304 15 584 24.2% 1.21 [1.04, 1.14] Pakes 2020 496 0.33 108 0.98 [0.84, 1.15] 0.98 [0.84, 1.15] Subtotal (95% CI) 501 239 15.5% 1.00 [0.85, 1.17] 0.16 [0.53, 1.17] Total events 1057 239 <t< td=""><td></td><td></td><td>57</td><td></td><td></td><td>1.5%</td><td></td><td></td></t<>			57			1.5%		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Total (95% CI)		6138		3491	100.0%	1.06 [0.96, 1.18]	•
Heterogeneity: Tau ² = 0.01; Chi ² = 18.35, df = 8 (P = 0.02); P = 56% Test for overall effect Z = 1.15 (P = 0.25) Live Birth Rates $\frac{\text{With CL}}{3.11 \text{ Live Birth Rates}}$ $\frac{\text{With CL}}{3.11 \text{ Live Birth Rates}}$ Aur-Gupta 2018 47 104 425 917 8.7% 0.98 [0.78, 1.22] Cardenas Armas 2019 10 32 42 175 1.3% 1.30 [0.73, 2.32] Givens 2009 245 858 77 261 11.9% 0.97 [0.78, 1.20] Greco 2016 50 109 47 113 4.6% 1.10 [0.87, 1.36] Levi Setti 2020 722 2304 151 564 24.2% 1.21 [1.04, 1.41] Pakes 2020 446 2033 188 997 25.4% 1.28 [1.14, 1.60] Subtotal (95% Ch) 5637 3228 84.5% 1.16 [1.07, 1.26] Total events 1663 1009 Heterogeneity: Chi ² = 8.07, df = 6 (P = 0.23); P = 26% Test for overall effect Z = 3.70 (P = 0.0002) 3.1.2 Ongoing Pregnancy Rates Chang 2011 229 444 107 204 14.8% 0.98 [0.84, 1.15] Sheikhi 2018 10 57 8 59 0.8% 1.29 [0.55, 3.04] Subtotal (95% Ch) 501 263 15.5% 1.00 [0.85, 1.17] Total events 239 115 Heterogeneity: Chi ² = 0.39; df = 1 (P = 0.53); P = 0% Test for overall effect Z = 0.10 (P = 0.99) Total events 1902 1124 Heterogeneity: Chi ² = 11.23, df = 8 (P = 0.19); P = 29% Total events 1902 1124 Heterogeneity: Chi ² = 11.23, df = 8 (P = 0.09); P = 29% Total events 1902 1124 Heterogeneity: Chi ² = 11.23, df = 8 (P = 0.09); P = 29%		2271		1388				-
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Test for overall effect Z = Live Birth Rates <u>Study or Subgroup</u> 3.1.1 Live Birth Rates Alur-Gupta 2018	1.15 (P = With Events 47	0.25) CL Total 104	Withou Events 425	t CL Total 917	Weight 8.7%	M-H, Fixed, 95% CI 0.98 [0.78, 1.22]	Favours No CL Favours With (Risk Ratio
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Pakes 2020 496 2033 188 997 25.4% 1.29 [1.1] 1.50] Subtotal (95% CI) 5637 3228 84.5% 1.16 [1.07, 1.26] Total events 1663 1009 Heterogeneity. Chi ^P = 8.07, df = 6 (P = 0.23); P = 26% Test for overall effect Z = 3.70 (P = 0.0002) 3.1.2 Ongoing Pregnancy Rates Chang 2011 229 444 107 204 14.8% 0.98 [0.84, 1.15] Sheikhi 2018 10 57 8 59 0.8% 1.29 [0.55, 3.04] Subtotal (95% CI) 501 263 15.5% 1.00 [0.85, 1.17] Total events 239 115 Heterogeneity. Chi ^P = 0.39, df = 1 (P = 0.53); P = 0% Test for overall effect Z = 0.01 (P = 0.99) Total (95% CI) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 1902 1124 Heterogeneity. Chi ^P = 11.23, df = 8 (P = 0.19); P = 29% Test for overall effect Z = 3.50 (P = 0.0005) Feature State 2 = 3.50 (P = 0.005)	Test for overall effect Z = Live Birth Rates Study or Subgroup 3.1.1 Live Birth Rates Alur-Gupta 2018 Cardenas Armas 2019 Gireco 2016	1.15 (P = With Events 47 10 245 50	0.25) CL Total 104 32 858 109	Withou Events 425 42 77 47	t CL Total 917 175 261 113	Weight 8.7% 1.3% 11.9% 4.6%	M-H, Fixed, 95% Cl 0.98 [0.78, 1.22] 1.30 [0.73, 2.32] 0.97 [0.78, 1.20] 1.10 [0.82, 1.49]	Favours No CL Favours With (Risk Ratio
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Heterogeneity: $Ch^{P} = 8.07$, $df = 6$ ($P = 0.23$); $P = 26\%$ Test for overall effect $Z = 3.70$ ($P = 0.0002$) 3.1.2 Ongoing Pregnancy Rates Chang 2011 229 444 107 204 14.8% 0.98 [0.84, 1.15] Sheikhi 2018 10 57 8 59 0.8% 1.29 [0.55, 3.04] Subtotal (95% Cl) 501 263 15.5% 1.00 [0.85, 1.17] Total events 239 115 Heterogeneity: $Ch^{P} = 0.39$, $df = 1$ ($P = 0.53$); $P = 0\%$ Test for overall effect $Z = 0.01$ ($P = 0.99$) Total (95% Cl) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 1902 1124 Heterogeneity: $Ch^{P} = 11.23$, $df = 8$ ($P = 0.19$); $P = 29\%$ Test for overall effect $Z = 3.50$ ($P = 0.005$)	Test for overall effect Z = Live Birth Rates <u>Study or Subgroup</u> 3.1.1 Live Birth Rates Alur-Gupta 2018 Cardenas Armas 2019 Givens 2009 Greco 2016 Le 2017 Lew Getti 2020 Pakes 2020	1.15 (P = With Events 47 10 245 50 93 722	0.25) CL Total 104 32 858 109 197 2304 2033	Withou Events 425 42 77 47 79 151	t CL Total 917 175 261 113 181 584 997	Weight 8.7% 1.3% 1.9% 4.6% 8.3% 24.2% 25.4%	M-H, Fixed, 95% CI 0.98 [0.78, 1.22] 1.30 [0.73, 2.32] 0.97 [0.78, 1.20] 1.10 [0.82, 1.49] 1.08 [0.87, 1.35] 1.21 [1.04, 1.41] 1.28 [1.11, 1.50]	Favours No CL Favours With Risk Ratio
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Test for overall effect Z = 0.01 (P = 0.99) Total (95% Cl) 6138 3491 10.0% 1.14 [1.06, 1.22] Total (95% Cl) 6138 3491 10.0% 1.14 [1.06, 1.22] Total events 102 1124 Heterogeneity. Ch ² = 1.123, df = 8 (P = 0.19); P = 29% 0.5 0.7 1.5 2 Test for overall effect Z = 3.50 (P = 0.0005) Examples Model	Test for overall effect Z = Live Birth Rates Study or Subgroup 3.1.1 Live Birth Rates Alur-Gupta 2018 Cardenas Armas 2019 Givens 2009 Greco 2016 Le 2017 Levi Setti 2020 Pakes 2020 Subtotal (95% CI) Total events Heterogeneity: Ch ² = 8.0 Test for overall effect: Z = 3.1.2 Ongoing Pregnand Chang 2011 Shelkhi 2018 Subtotal (95% CI)	1.15 (P = With Events 47 10 245 37 225 496 1663 7, df = 6 (3.70 (P = 229 10	0.25) CL Total 104 32 858 109 197 2304 2033 5637 P = 0.23 0.0002 444 57	Withou <u>Events</u> 425 42 77 47 79 151 188 1009 3); ₱ = 26) 107 8	t CL 917 175 261 113 181 584 997 3228 %	Weight 8.7% 1.3% 11.9% 4.6% 8.3% 24.2% 25.4% 84.5%	M-H, Fixed, 95% Cl 0.98 [0.78, 1.22] 1.30 [0.73, 2.32] 0.97 [0.78, 1.20] 1.10 [0.82, 1.49] 1.08 [0.87, 1.35] 1.21 [1.04, 1.41] 1.29 [1.11, 1.50] 1.16 [1.07, 1.26] 0.98 [0.84, 1.15] 1.29 [0.55, 3.04]	Favours No CL Favours With (Risk Ratio
Total (95% Cl) 6138 3491 100.0% 1.14 [1.06, 1.22] Total events 1902 1124 Heterogeneity. Chi ^a = 11.23, df = 8 (P = 0.19); P = 29% 0.5 0.7 1.5 2 Test for overall effect. Z = 3.50 (P = 0.0005) Eavours With Eavours With Eavours With Eavours With	Test for overall effect Z = Live Birth Rates Study or Subgroup 3.1.1 Live Birth Rates Alur-Gupta 2018 Cardenas Armas 2019 Gireco 2016 Lev Setti 2020 Pakes 2020 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 8.0 Test for overall effect Z = 3.1.2 Ongoing Pregnanc Chang 2011 Sheikhi 2018 Subtotal (95% CI) Total events	1.15 (P = With Events 47 10 245 50 93 7,22 496 1663 7, df = 6(3.70 (P = y Rates 229 10 239	0.25) CL Total 104 32 858 109 197 2304 2033 5637 P = 0.23 0.0002 444 57 501	Withou Events 425 42 77 47 79 151 188 1009 3); I [≠] = 26) 107 8 115	t CL Total 917 175 261 113 181 584 997 3228 %	Weight 8.7% 1.3% 11.9% 4.6% 8.3% 24.2% 25.4% 84.5%	M-H, Fixed, 95% Cl 0.98 [0.78, 1.22] 1.30 [0.73, 2.32] 0.97 [0.78, 1.20] 1.10 [0.82, 1.49] 1.08 [0.87, 1.35] 1.21 [1.04, 1.41] 1.29 [1.11, 1.50] 1.16 [1.07, 1.26] 0.98 [0.84, 1.15] 1.29 [0.55, 3.04]	Favours No CL Favours With (Risk Ratio
Total events 1902 1124 Heterogeneity. Chi# = 11.23, df = 8 (P = 0.19); P = 29% 0.5 0.7 1.5 2 Test for overall effect. Z = 3.50 (P = 0.0005) Eavours With Eavours With Eavours With	Test for overall effect Z = Live Birth Rates <u>Study or Subgroup</u> 3.1.1 Live Birth Rates Alur-Gupta 2018 Cardenas Armas 2019 Givens 2009 Greco 2016 Le 2017 Levi Setti 2020 Pakes 2020 Subtotal (95% CI) Total events Heterogeneity. ChIP = 8.0 Test for overall effect. Z = 3.1.2 Ongoing Pregnanc Chang 2011 Sheikhi 2018 Subtotal (95% CI) Total events Heterogeneity. ChIP = 0.3	1.15 (P = With Events 47 100 245 50 93 7,22 496 1663 7, df = 6 (3.70 (P = 9) Rates 229 100 239 9, df = 1 (0.25) CL Total 104 32 858 109 197 2304 2033 5637 P=0.23 0.0002 444 57 501 P=0.53	Withou Events 425 42 77 47 79 151 188 1009 3); I [≠] = 26) 107 8 115	t CL Total 917 175 261 113 181 584 997 3228 %	Weight 8.7% 1.3% 11.9% 4.6% 8.3% 24.2% 25.4% 84.5%	M-H, Fixed, 95% Cl 0.98 [0.78, 1.22] 1.30 [0.73, 2.32] 0.97 [0.78, 1.20] 1.10 [0.82, 1.49] 1.08 [0.87, 1.35] 1.21 [1.04, 1.41] 1.29 [1.11, 1.50] 1.16 [1.07, 1.26] 0.98 [0.84, 1.15] 1.29 [0.55, 3.04]	Favours No CL Favours With (Risk Ratio
Heterogeneity. Chi ^a = 11.23, df = 8 (P = 0.19); I ^a = 29% Test for overall effect: Z = 3.50 (P = 0.0005) Eavours With Eavours With	Test for overall effect Z = Live Birth Rates Study or Subgroup 3.1.1 Live Birth Rates Alur-Gupta 2018 Cardenas Armas 2019 Givens 2009 Givens 2008 Le 2017 Levi Setti 2020 Pakes 2020 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 8.0 Test for overall effect Z = 3.1.2 Ongoing Pregnanc Chang 2011 Sheikhi 2018 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0.3 Test for overall effect Z = 5.1.2 Ongoing Pregnanc Chang 2011 Sheikhi 2018 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0.3 Test for overall effect Z =	1.15 (P = With Events 47 100 245 50 93 7,22 496 1663 7, df = 6 (3.70 (P = 9) Rates 229 100 239 9, df = 1 (0.25) CL Total 104 32 858 109 197 2304 2033 5637 P = 0.23 0.0002 444 57 501 P = 0.53 0.99)	Withou Events 425 42 77 47 79 151 188 1009 3); I [≠] = 26) 107 8 115	t CL <u>Total</u> 917 175 261 113 181 997 3228 % 204 49 263 5	Weight 8.7% 1.3% 11.9% 8.3% 24.2% 84.5% 84.5%	M-H, Fixed, 95% Cl 0.98 [0.78, 1.22] 1.30 [0.73, 2.32] 0.97 [0.78, 1.20] 1.10 [0.82, 1.49] 1.08 [0.87, 1.35] 1.21 [10.41, 4.11] 1.29 [1.11, 1.50] 1.16 [1.07, 1.26] 0.98 [0.84, 1.15] 1.29 [0.55, 3.04] 1.00 [0.85, 1.17]	Favours No CL Favours With
Test for overall effect: Z = 3.50 (P = 0.0005) U.5 U.7 1 1.5 2 Eavours No CI Eavours N	Test for overall effect Z = Live Birth Rates <u>Study or Subgroup</u> 3.1.1 Live Birth Rates Alur-Gupta 2018 Cardenas Armas 2019 Greco 2016 Le 2017 Lev Getti 2020 Pakes 2020 Subtotal (95% CI) Total events Heterogeneity. Chi ⁹ = 8.0 Test for overall effect Z = 3.1.2 Ongoing Pregnanc Chang 2011 Sheikhi 2018 Subtotal (95% CI) Total events Heterogeneity. Chi ⁹ = 0.3 Test for overall effect Z = Total (95% CI)	1.15 (P = With Events 47 10 245 57 496 1663 7, df = 6 (3.70 (P = 9) Rates 229 10 239 9, df = 1 (0.01 (P =	0.25) CL Total 104 32 858 109 197 2304 2033 5637 P = 0.23 0.0002 444 57 501 P = 0.53 0.99)	Withou Events 425 42 77 47 79 151 188 1009 9); P=26 9) 107 8 115 107 8 115 107 8	t CL <u>Total</u> 917 175 261 113 181 997 3228 % 204 49 263 5	Weight 8.7% 1.3% 11.9% 8.3% 24.2% 84.5% 84.5%	M-H, Fixed, 95% Cl 0.98 [0.78, 1.22] 1.30 [0.73, 2.32] 0.97 [0.78, 1.20] 1.10 [0.82, 1.49] 1.08 [0.87, 1.35] 1.21 [10.41, 4.11] 1.29 [1.11, 1.50] 1.16 [1.07, 1.26] 0.98 [0.84, 1.15] 1.29 [0.55, 3.04] 1.00 [0.85, 1.17]	Favours No CL Favours With (Risk Ratio
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Test for subgroup differences: Chi ² = 2.78, df = 1 (P = 0.10), i ² = 64.0%	Test for overall effect Z = Live Birth Rates Study or Subgroup 3.1.1 Live Birth Rates Alur-Gupta 2018 Cardenas Armas 2019 Greco 2016 Le 2017 Levi Setti 2020 Pakes 2020 Subtoal (95% CI) Total events Heterogeneity. Ch ^a = 8.0 Test for overall effect Z = 3.1.2 Ongoing Pregnanc Chang 2011 Sheikhi 2018 Subtoal (95% CI) Total events Heterogeneity. Ch ^a = 0.3 Test for overall effect Z = Total (95% CI) Total events Heterogeneity. Ch ^a = 1.3 Test for overall effect Z = Total (95% CI) Total events Heterogeneity. Ch ^a = 1.1 Test for overall effect Z = Total (95% CI)	1.15 (P = With h <u>Events</u> 47 10 245 50 93 372 496 1663 3.70 (P = 10 239 9, of = 1 (0 239 9, of = 1 (0 0.01 (P = 1902 23, of = 8 1002 23, of = 8 1002 10	0.25) Total 104 32 2304 109 197 2304 2033 5637 P=0.23 0.0002 444 57 501 P=0.53 0.99) 6138 (P=0.1 0.0055	Withou Events 425 42 77 79 151 188 1009)); IP = 26)) 107 8 115 115 115 119 9); IP = 09	t CL Total 917 175 261 113 181 584 997 3228 % 204 59 263 5 3491 9%	Weight 8.7% 11.3% 8.3% 25.4% 84.5% 14.8% 0.8% 15.5%	M-H, Fixed, 95% Cl 0.98 [0.78, 1.22] 1.30 [0.73, 2.32] 0.97 [0.76, 1.20] 1.00 [0.82, 1.49] 1.08 [0.87, 1.35] 1.21 [1.04, 1.41] 1.29 [1.11, 1.50] 1.16 [1.07, 1.26] 0.98 [0.84, 1.15] 1.29 [0.55, 3.04] 1.00 [0.85, 1.17] 1.14 [1.06, 1.22]	Favours No CL Favours With 0 Risk Ratio M-H, Fixed, 95% Cl

Figure 2: Meta-analysis comparing rates of positive b-hCG, clinical pregnancy, and live births in cycles with and without a corpus luteum

232x326mm (96 x 96 DPI)

Biochemical Pregnancy Rates With CL Without CL **Risk Ratio Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI Alur-Gupta 2018 8 64 79 602 4.2% 0.95 [0.48, 1.88] Cardenas Armas 2019 3 16 16 76 1.5% 0.89 [0.29, 2.70] Chang 2011 43 229 45 107 16.9% 0.45 [0.31, 0.63] Givens 2009 83 369 34 141 13.6% 0.93 [0.66, 1.32] Greco 2016 9 68 13 70 3.5% 0.71 [0.33, 1.56] Le 2017 13 120 15 110 4.3% 0.79 [0.40, 1.59] Levi Setti 2020 82 1012 26 243 11.6% 0.76 [0.50, 1.15] Pakes 2020 175 802 116 376 43.5% 0.71 [0.58, 0.86] Sheikhi 2018 0 10 12 0.9% 0.17 [0.01, 2.93] 3 0.71 [0.62, 0.82] Total (95% CI) 2690 1737 100.0% Total events 416 347 Heterogeneity: Chi2 = 11.18, df = 8 (P = 0.19); I2 = 28% 0.1 0.2 0.5 2 10 Test for overall effect Z = 4.90 (P < 0.00001) Favours no CL Favours CL Miscarriage Rates With CL Without CL **Risk Ratio Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% CI 7.1.1 Miscarriage Rates from Studies Reporting Live Births Alur-Gupta 2018 9 55 98 523 5.1% 0.87 [0.47, 1.63] 0.77 [0.27, 2.23] Cardenas Armas 2019 13 18 60 1.8% 3 Givens 2009 30 0.51 [0.33, 0.76] 41 284 105 11.6% Greco 2016 9 59 10 57 2.9% 0.87 [0.38, 1.98] 107 Le 2017 14 16 95 4.5% 0.78 [0.40, 1.51] Levi Setti 2020 70 217 39.2% 0.72 [0.58, 0.91] 217 930 Pakes 2020 627 72 0.75 [0.59, 0.97] 131 260 32.2% Subtotal (95% CI) 2075 1317 97.3% 0.72 [0.62, 0.83] 424 314 Total events Heterogeneity: Tau² = 0.00; Chi² = 3.58, df = 6 (P = 0.73); l² = 0% Test for overall effect: Z = 4.56 (P < 0.00001) 7.1.2 Miscarriage Rates from Studies Reporting Ongoing Pregnancy Chang 2011 17 186 6 62 2.5% 0.94 [0.39, 2.29] Sheikhi 2018 Subtotal (95% CI) 0.2% 0 10 1 9 0.30 [0.01, 6.62] 71 0.87 [0.37, 2.03] 196 Total events 17 Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0% Test for overall effect: Z = 0.33 (P = 0.74)

Figure 3: Meta-analysis comparing biochemical pregnancy and miscarriage rates in cycles with and without a corpus luteum

0.72 [0.63, 0.83]

0.1 0.2 0.5

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Favours no CL Favours CL

241x238mm (96 x 96 DPI)

Supplementary Files for "Treatment Outcomes of Blastocysts Thaw-Cycles, Comparing the Presence and Absence of a Corpus Luteum: A Systematic Review and Meta-analysis.

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Revised Cochrane Risk-of-Bias tool 2
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Supplementary File 5 - Supplementary Table 4: Excluded Studies
Supplementary File 6 - Supplementary Figure 1: Meta-analysis comparing clinical pregnancy rates in cycles with and without a corpus luteum – sensitivity analysis
Supplementary File 7 - Supplementary Figure 2: Meta-analysis comparing rates of positive b-hCG, clinical pregnancy and live births in cycles with and without a corpus luteum – separated by study design
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Supplementary File 9 - Supplementary Figure 4: Funnel Plot Analyses

Supplementary File 1 – Search Strategy

PUBMED/MEDLINE

Set	Search	Results
1	Cryopreservation[All Fields]	47,444
2	frozen embryo transfer[All Fields]	3,740
3	Frozen embryo*[All Fields]	8,561
4	frozen-thawed cycle[All Fields]	1,209
5	frozen-thawed embryo transfer[All Fields]	1,457
6	frozen thawed embryos[All Fields]	3,703
7	"FET"[All Fields]	3,577
8	cryopreserved embryos[All Fields]	9,714
9	Cryopreserved-thawed embryos[All Fields]	131
10	vitrification[All Fields]	4,568
11	Vitrified[All Fields]	3,077
12	"vitrified-warmed embryos"[All Fields]	440
13	"frozen-thawed"[All Fields]	5,134
14	embryo vitrification[All Fields]	2,144
	blastocyst transfer[All Fields]	28,636
15		
	((((((((((((cryopreservation) OR (frozen embryo transfer)) OR	81,001
	(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	
	embryo transfer)) OR (frozen thawed embryos)) OR (FET)) OR	
	(cryopreserved embryos)) OR (cryopreserved-thawed embryos))	
	OR (vitrification)) OR (vitrified)) OR (vitrified-warmed embryos)) OR	
	(frozen-thawed)) OR (embryo vitrification)) OR (blastocyst	
16	transfer)[All Fields]	
17	endometrial preparation[All Fields]	2,129
	natural cycle[All Fields]	56,766
18	4	
19	ovulation induction[All Fields]	16,378
20	modified natural cycle[All Fields]	2,401
21	hormone therapy[All Fields]	659,266
	Estrogen OR oestrogen OR oestrogens OR estrogens OR	286,275
22	oestradiol[All Fields]	
23	progesterone[All Fields]	119,710
24	stimulated cycle[All Fields]	63,307
25	stimulation of endometrium embryo transfer[All Fields]	426
26	artificial cycle	13,886
	(((((((endometrial preparation) OR (natural cycle)) OR (ovulation	1,012,876
	induction)) OR (modified natural cycle)) OR (hormone therapy)) OR	
	(Estrogen or oestrogen or oestrogens or estrogens or estradiol))	
	OR (progesterone)) OR (stimulated cycle)) OR (stimulation of	
27	endometrium embryo transfer)) OR (artificial cycle)[All Fields]	
	((((((((endometrial preparation) OR (natural cycle)) OR (ovulation	11,974
	induction)) OR (modified natural cycle)) OR (hormone therapy)) OR	
	(Estrogen or oestrogen or oestrogens or estrogens or estradiol))	
	OR (progesterone)) OR (stimulated cycle)) OR (stimulation of	
	endometrium embryo transfer)) OR (artificial cycle)) AND	
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	987,880
	32,374
	47,358
	8,897
clinical pregnancy[All Fields]	190,084
chemical pregnancy[All Fields]	45,767
(((((pregnancy) OR (live birth*)) OR (miscarriage)) OR (ongoing	1,001,238
pregnancy)) OR (clinical pregnancy)) OR (chemical pregnancy) [All	
Fields]	
((((((((endometrial preparation) OR (natural cycle)) OR (ovulation	7,913
induction)) OR (modified natural cycle)) OR (hormone therapy)) OR	
(Estrogen or oestrogen or oestrogens or estrogens or estradiol))	
OR (progesterone)) OR (stimulated cycle)) OR (stimulation of	
endometrium embryo transfer)) OR (artificial cycle)) AND	
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(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	
embryo transfer)) OR (frozen thawed embryos)) OR (FET)) OR	
(cryopreserved embryos)) OR (cryopreserved-thawed embryos))	
OR (vitrification)) OR (vitrified)) OR (vitrified-warmed embryos)) OR	
(frozen-thawed)) OR (embryo vitrification)) OR (blastocyst	
<pre>transfer))) AND ((((((pregnancy) OR (live birth*)) OR (miscarriage))</pre>	
OR (ongoing pregnancy)) OR (clinical pregnancy)) OR (chemical	
pregnancy)) [All Fields]	
animal[All Fields]	6,843,446
((((((((endometrial preparation) OR (natural cycle)) OR	6,386
(ovulation induction)) OR (modified natural cycle)) OR (hormone	
therapy)) OR (Estrogen or oestrogen or oestrogens or estrogens or	
estradiol)) OR (progesterone)) OR (stimulated cycle)) OR	
(stimulation of endometrium embryo transfer)) OR (artificial cycle))	
AND (((((((((((((((((((())	
(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	
embryo transfer)) OR (frozen thawed embryos)) OR (FET)) OR	
(cryopreserved embryos)) OR (cryopreserved-thawed embryos))	
OR (vitrification)) OR (vitrified)) OR (vitrified-warmed embryos)) OR	
(frozen-thawed)) OR (embryo vitrification)) OR (blastocyst	
transfer))) AND ((((((pregnancy) OR (live birth*)) OR (miscarriage))	
OR (ongoing pregnancy)) OR (clinical pregnancy)) OR (chemical	
pregnancy))) NOT (animal) [All Fields]	
(((((((((endometrial preparation) OR (natural cycle)) OR	6,375
(ovulation induction)) OR (modified natural cycle)) OR (hormone	
therapy)) OR (Estrogen or oestrogen or oestrogens or estrogens or	
therapy)) OR (Estrogen or oestrogen or oestrogens or estrogens or	
therapy)) OR (Estrogen or oestrogen or oestrogens or estrogens or estradiol)) OR (progesterone)) OR (stimulated cycle)) OR	
	(((((pregnancy) OR (live birth*)) OR (miscarriage)) OR (ongoing pregnancy)) OR (clinical pregnancy)) OR (chemical pregnancy) [All Fields] ((((((((((((((((((((((((((((((((((((

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	(cryopreserved embryos)) OR (cryopreserved-thawed embryos))))	
	OR (vitrified-warmed embryos)) OR (frozen-thawed)) OR (embryo	
	vitrification)) OR (blastocyst transfer))) AND ((((((pregnancy) OR	
	(live birth*)) OR (miscarriage)) OR (ongoing pregnancy)) OR (clinical	
	pregnancy)) OR (chemical pregnancy))) NOT (animal) [All Fields]	
	((((((((endometrial preparation) OR (natural cycle)) OR	1,089
	(ovulation induction)) OR (modified natural cycle)) OR (hormone	
	therapy)) OR (Estrogen or oestrogen or oestrogens or estrogens or	
	estradiol)) OR (progesterone)) OR (stimulated cycle)) OR	
	(stimulation of endometrium embryo transfer)) OR (artificial cycle))	
	AND (((((((((((((cryopreservation) OR (frozen embryo transfer)) OR	
	(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	
	embryo transfer)) OR (frozen thawed embryos)) OR (FET)) OR	
	(cryopreserved embryos)) OR (cryopreserved-thawed embryos))	
	OR (vitrification)) OR (vitrified)) OR (vitrified-warmed embryos)) OR	
	(frozen-thawed)) OR (embryo vitrification)) OR (blastocyst	
	transfer))) AND ((((((pregnancy) OR (live birth*)) OR (miscarriage))	
	OR (ongoing pregnancy)) OR (clinical pregnancy)) OR (chemical	
	pregnancy))) NOT (animal) [All Fields] -	
40	from 2017 - 2020	
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JAJL		

EMBASE

Set	Search	Results
1	cryopreservation.mp. or cryopreservation/	45195
2	(Cryopreserv\$ adj7 embryo\$).tw.	5646
3	(Cryopreserv\$ adj7 blastocyst\$).tw.	1080
4	freezing/ or vitrification/	43414
5	(vitrifi\$ adj5 embryo\$).tw.	2410
6	(vitrifi\$ adj5 blastocyst\$).tw.	1803
7	(frozen adj5 embryo\$).tw.	5929
8	(freez\$ adj5 embryo\$).tw.	2056
9	(freez\$ adj5 blastocyst\$).tw.	367
10	(frozen adj5 blastocyst\$).tw.	1032
11	FET.tw.	4837
12	freeze thawing/ or freezing/	45930
13	vitrification/	5997
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	95117
15	exp ovulation induction/	16413
16	((ovar\$ adj5 stimula\$) or (ovulat\$ adj5 induc\$)).tw.	26000
17	(endometri\$ adj2 prepar\$).tw.	1032
18	hormon\$ regimen\$.tw.	373
19	Clomiphene.tw. or Clomiphene/	11562
20	clomid.tw.	1284
21	(Tamoxifen or Letrozole).tw.	37754
22	aromatase inhibitor\$.tw.	11798
23	exp human menopausal gonadotropin/	10498
24	(Menotropin\$ or menopausal gonadotrop\$ or HMG).tw.	20554
25	exp follitropin/	64748

27 gonadorelin/ 38181 28 Gonadotropin Releasing Hormone\$.tw. 16215 29 Gonadotrophin Releasing Hormone\$.tw. 3366 30 GnRH\$.tw. 29904 31 exp estrogen/ 300360 32 (?estrogen\$ or ?estradiol).tw. 240982 33 exp progesterone/ 104475 34 exp Progesterone/ or progesterone.tw. 145928 35 (natural\$ adj2 cycle\$).tw. 633 37 (cycle\$ adj2 regimen\$).tw. 633 37 (cycle\$ adj2 regimen\$).tw. 486 39 human menopausal.tw. 2684 40 spontaneous oulation.tw. 615 41 (HCG adj3 trigger\$).tw. 1039 42 (stimulat\$ adj3 cycle\$).tw. 5831 43 exogenous steroid\$.tw. 708 44 exogenous steroid\$.tw. 708 45 (hormone adj2 therap\$)tw. 41571 46 (endometri\$ adj2 stimulat\$).tw. 835 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	26	(Follicle Stimulating Hormone or FSH or rFSH or rhFSH).tw.	57786
28 Gonadotrophin Releasing Hormone\$.tw. 16215 29 Gonadotrophin Releasing Hormone\$.tw. 3366 30 GnRH\$.tw. 29904 31 exp estrogen/ 300360 32 (?estrogen\$ or ?estradiol).tw. 240982 33 exp progesterone/ 104475 34 exp progesterone/ or progesterone.tw. 145928 35 (natural\$ adj2 cycle\$).tw. 633 37 (cycle\$ adj2 regimen\$).tw. 670 38 pituitary suppression.tw. 486 39 human menopausal.tw. 2684 40 spontaneous ovulation.tw. 615 41 (HCG adj3 trigger\$).tw. 1039 42 (stimulat\$ adj2 cycle\$).tw. 5831 43 exogenous steroid\$.tw. 708 44 exogenous steroid\$.tw. 708 45 (hormone adj2 therap\$).tw. 835 45 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 7970 46 14 and 47 7970			
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66prospective study/617823	64		1215
	65	placebo\$.tw.	315943
	66	prospective study/	617823
b/ retrospective study/ 946322	67	retrospective study/	946322
68 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 3142742	68		3142742
or 61 or 62 or 63 or 64 or 65 or 66 or 67		or 61 or 62 or 63 or 64 or 65 or 66 or 67	5172/92
69 case study/ 80054	69	case study/	80054
70case report.tw.444799		•	
71abstract report/ or letter/1155908			
72 69 or 70 or 71 1669914	72	69 or 70 or 71	1669914

73	68 not 72	3064021
74	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)	7230873
75	73 not 74	2969724
76	48 and 75	2373
77	76 – limited 2017 to 2020	1065

Cochrane Register of Controlled Trials (CENTRAL)

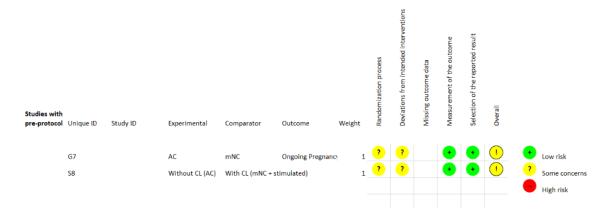
Set	Search	Results
1	((Endometrial Preparation OR Cycle OR Natural Cycle OR Artificial	289
	Cycle OR Modified Natural Cycle OR Stimulated Cycle) AND	
	(Pregnancy OR Pregnancy Outcomes OR Clinical Pregnancy OR Live	
	Birth)) – Limited to 2017-2020	

CINAHL

Set	Search	Results
1	MM Cryopreservation+	1,545
2	TX Cryopreserv* N7 embryo*	792
3	TX Cryopreserv* N7 blastocyst*	80
4	MM Freezing	229
5	TX vitrification N7 embryo*	124
6	TX vitrification N7 blastocyst*	58
7	TX frozen N5 embryo*	1,186
8	TX freez* N5 embryo*	360
9	TX freez* N5 blastocyst*	22
10	TX frozen N5 blastocyst*	128
11	TX FET	1,353
12	(TX FET) AND (S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11)	1,353
13	MM ovulation induction	973
14	TX (ovar* N5 stimula*) or (ovulat* N5 induct*)	3,738
15	TX (endometri* N2prepar*)	181
16	MM Clomiphene	250
17	TX Clomiphene or TX clomid	1,128
18	TX Menotropin* or menopausal gonadotrop* or HMG)	3,785
19	MM Follicle-Stimulating Hormone	602
20	TX Follicle Stimulating Hormone or FSH	6,532
21	MM Gonadorelin	989
22	MM Pituitary Hormone Release Inhibiting Hormones	3
23	TX Gonadotrop?in-Releasing Hormone*	344
24	TX GnRH*	2,961
25	MM Estrogens	3,969
26	TX oestrogen or estrogen	46,066
27	MM Progesterone	1,914
28	TX Progesterone	17,782
29	TX natural* N2 cycle*	1,104
30	TX (artificial* N2 cycle*)	137

31	TX (cycle* N2 regimen*)	626
32	TX pituitary suppression	472
33	TX spontaneous* ovulat*	145
34	TX stimulat* N3 cycle	1,335
35	((TX stimulat* N3 cycle OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34)) AND (S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34)	65,832
	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7OR S8 OR S9	4,623
36	OR S10 OR S11	
37	(35 AND 36)	2,453
38	MH Clinical Trials+	303,701
39	PT Clinical trial	107,329
40	TX clinic* n1 trial*	393,652
41	TX(singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl*n1 mask*))	1,177,377
42	TX randomi* control *trial*	298,795
43	MH "Random Assignment"	63,059
44	TX random* allocat*	22,292
45	TX placebo*	125,194
46	MH Placebos	12,837
47	MH Quantitative Studies	27,500
48	TX allocat* random*	22,292
49	S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48	1,648,483
50	S37 AND S49	817
51	S37 AND S49	225
52	51 – Limited 2017-2020	158

Supplementary File 2 - Supplementary Table 1: Quality of Randomised Controlled Trials using the Revised Cochrane Risk-of-Bias tool 2



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Domain	Signalling question	Response	Comments
	1.1 Was the allocation sequence random?	Y	Two hundred thirty-six patients were included in the study and randomized in two groups according to computer- generated, not cancelled, simple randomization list with
Bias arising from the randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Ν	allocation assignment. Both the patient and the clinicians were informed of the assigned treatment. Difficult to conceal due to the nature the intervention.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	Baseline characteristics of the patients were not significantly different.
	Risk of bias judgement	Some concerns	
	2.1 Were participants aware of their assigned intervention during the trial?	Y	Both pateints and clinicians were aware of the assigned intervention. However, due to the nature of the intervention
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	it would have been difficult to conceal.
Bias due to deviations	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
from intended interventions	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		
interventions	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NA	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Missing data was accounted for e.g. premature LH surg inadequate endometrial thickness
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement		
	4.1 Was the method of measuring the outcome inappropriate?	Ν	Live birth rates is an appropriate outcome measuremen
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Ν	Definitions used for the measurement of outcomes was same in both groups
Bias in measurement of the outcome	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	Probably not, as the outcomes are objective rather than subjective
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
	5.1 were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
Bias in selection of the reported result	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	
		Q	32

Sheikhi 2018:

Domain	Signalling question	Response	Comments
	1.1 Was the allocation sequence random?	Y	The randomization was done at the start of the cycle sequential numbering based on a computer-generate that had been prepared at the Statistics Center of the
Diag aniain n faons tha	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	N	University of Medical Science and sent to them. Both participants and clinicians were aware of the treatment allocation.
Bias arising from the randomization process	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics were fairly similar across be treatment groups.
	Risk of bias judgement	Some concerns	Difficult to implement blinding and concealment due nature of the intervention.
	2.1 Were participants aware of their assigned intervention during the trial?	Y	Yes, as it is difficult to blind participants and clinician
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	to the nature of the intervention
Discussion de la ciciliana	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
Bias due to deviations from intended	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PY	Seven women were lost to follow-up (with explaination
interventions	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NA	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
outcome data	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true	NA	-
	value? Risk of bias judgement		
	4.1 Was the method of measuring the outcome inappropriate?	PN	Live births would have been a better measure of out however as pregnancy loss after 20 weeks is very ra still an appropriate outcome.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Outcome measurements are objective rather than subjective due to the nature of the study.
Bias in measurement of	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by	NA	Outcome measurements are objective rather than subjective due to the nature of the study.
	knowledge of intervention received? Risk of bias judgement	Low	
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
Bias in selection of the	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
reported result	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

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Supplementary File 3 - Supplementary Table 2: Quality of Observational Studies using the Newcastle-Ottawa Scale

Authors		Alur-Gupta et al, 2018	Cardenas Armas et al, 2019	Chang et al, 2011	Givens et al, 2009	Le et al, 2017	Levi Setti et al, 2020	Pakes et al, 2020
	Item							
Α	Selection							
	Exposed cohort is truly representative of the average	-	-	•	-	•	•	e
	Selection of the non-exposed cohort from the same community	•	-	•	•	•	•	
	Exposure ascertained by a secure record or interview	•	+	+	+	•	•	•
	Demonstration of outcome of interest was not present at the start of the study	+	•	•	•	•	•	•
В	Comparability*							
	Study controls for additional variables	•	•	•	•	÷	•	
С	Outcome							
	Follow-up was adequate for outcome to occur	•	+	-	•	•	•	•
	Complete follow-up of all subjects was accounted for	•	•	•	+	•	•	
	Subjects lost to follow up were unlikely to introduce bias	+	•	•	•	•	•	•
	Score (_/9)	6	7	7	5	6	6	6
	Conversion to AHRQ Standards	fair	good	good	fair	fair	fair	fa

AHRQ, Agency for Healthcare Research and Quality

*Comparability may have up to a maximum of 2 points

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Supplementary File 4 - Supplementary Table 3: PRISMA Checklists

Section/topic	#	Checklist item	Reported on page #
TITLE		A pri	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; similations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION		from	
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits us d, such that it could be repeated.	Supplementar material 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
		þyright.	

	BMJ Open <u>3</u> .	
12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
13	State the principal summary measures (e.g., risk ratio, difference in means).	10
14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	10
15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supplementa material 9
16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10, 13
•		
17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, page 26
19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1 & supplementa files
20	For all outcomes considered (benefits or harms), present, for each study: (a) simple sugmary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plog	Refer to figures II & III
21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15
22	Present results of any assessment of risk of bias across studies (see Item 15).	12, table I & supplementa files
23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, metaੱregression [see Item 16]). ਸੂ	12, supplementa files
24	Summarize the main findings including the strength of evidence for each main outcome consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
	13 14 15 16 17 18 19 20 21 22 23	 12 Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. 13 State the principal summary measures (e.g., risk ratio, difference in means). 14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., P) for each meta-analysis. 15 Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., pablication bias, selective reporting within studies). 16 Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. 17 Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. 18 For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. 19 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). 20 For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest ptot. 21 Present results of each meta-analysis done, including confidence intervals and measures of consistency. 22 Present results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-fore sterier, if and analyses, if done (e.g., sensitivity or subgroup analyses, meta-fore regression [see Item 16]). 23 Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-fore regression [see Item 16]). 24 Summarize the main findings including the strength of evidence for each main outcome.

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Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e_{23}^{\rightarrow} , incomplete retrieval of identified research, reporting bias).	16-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-20
FUNDING		0 7 2	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply obdata); role of funders for the systematic review.	22
		022. Downloaded from http://tmiopen.bmj.com/ on April 23. 2024 by guest. Protected by copyright	13

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 Supplementary File 5 - Supplementary Table 4: Excluded Studies
 Supplementary Table IV: Excluded studies in a systematic review and meta-analysis of treatment outcomes of blastocysts the w-cycles, comparing the presence and advances of a server laterer

 absence of a corpus luteum

Year of PublicationReason for exclusional cycle in frozen-Thawed embryo transfer: A randomized prospective2018Data contains both cleavage and blastocyst stage embryosaration Protocols for Frozen Embryo Transfer on Live Birth Rates.2017Data contains both cleavage and blastocyst stage embryosal cycle in frozen-thawed embryo transfer: A randomized prospective2018Data contains both cleavage and blastocyst stage embryosal cycle in frozen-thawed embryo transfer: A randomized prospective2018Data contains both cleavage and blastocyst stage embryosal cycle in frozen-thawed embryo transfer: A randomized prospective2018Data contains both cleavage and blastocyst stage embryosm-inferiority trial of modified natural versus artificial cycle for cryo- ne replacement therapy cycle in frozen-thawed embryo transfer2018Data contains both cleavage and blastocyst stage embryosmain for contrains both cleavage and blastocyst stage embryosData contains both cleavage and blastocyst stage embryosmain for contains both cleavage and blastocyst stage embryosData contains both cleavage and blastocyst stage embryosmain for contrains for more agonist2018Data contains both cleavage and blastocyst stage embryosrations and transfer red embryo types on pregnancy outcome from real contains both cleavage and blastocyst stage embryosData contains both cleavage and blastocyst stage embryostendometrial preparation methods in frozen cleavage-stage embryosData contains both cleavage and blastocyst stage embryostendometrial preparation methods in frozen cleavage-stage embryosData contains
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ionorial preparation by terosole versus normone replacement cycle. A n Data contains four cleavage and
ed embryo transfer: which endometrial preparation protocol is better? 2019 blasto 2020 2020 2020 2020

Supplementary File 6 - Supplementary Figure 1: Meta-analysis comparing clinical pregnancy rates in cycles with and without a corpus luteum – sensitivity analysis

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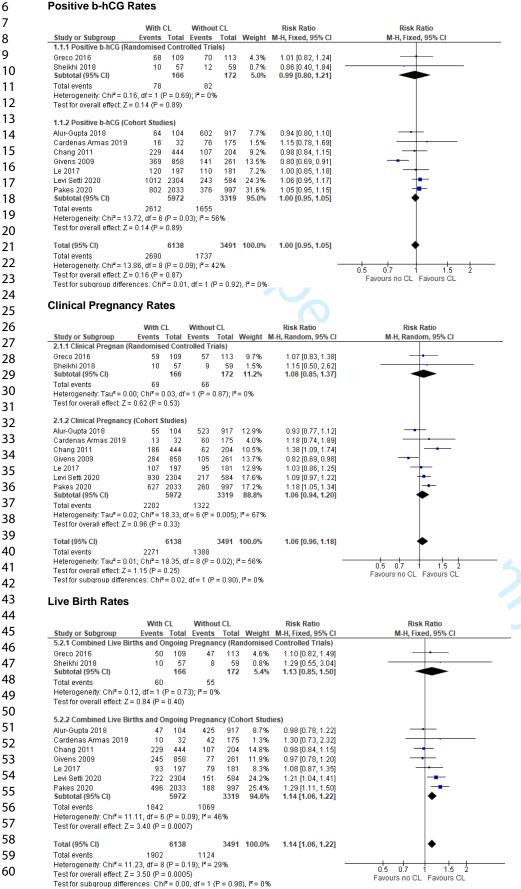
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6 7		With CL	Without CL		Risk Ratio	Risk Ratio
	Study or Subgroup			al Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
8	Alur-Gupta 2018	55 10				
9 10	Cardenas Armas 2019 Chang 2011	13 3 186 44		75 1.7%)4 7.9%		
10	Greco 2016	59 10	9 57 11			
11	Le 2017	107 19				-+ <u>-</u>
12	Levi Setti 2020 Pakes 2020	930 230 627 203		34 32.4% 37 32.6%		† -
13	Sheikhi 2018	10 5		57 32.6% 59 0.8%		
14						
15	Total (95% CI) Total events	528 1987	0 323 1283	30 100.0%	1.12 [1.05, 1.20]	
16	Heterogeneity: Chi ² = 8.7					0.5 0.7 1 1.5 2
17	Test for overall effect: Z =					0.5 0.7 1 1.5 2 Favours No CL Favours With CL
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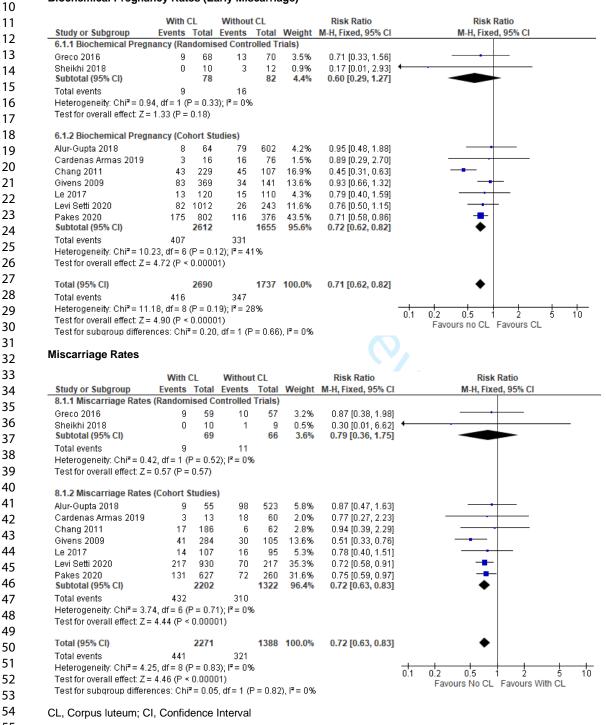
Supplementary File 7 - Supplementary Figure 2: Meta-analysis comparing rates of positive b-hCG, clinical pregnancy and live births in cycles with and without a corpus luteum – separated by study design

Positive b-hCG Rates

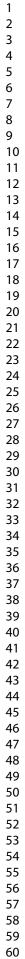


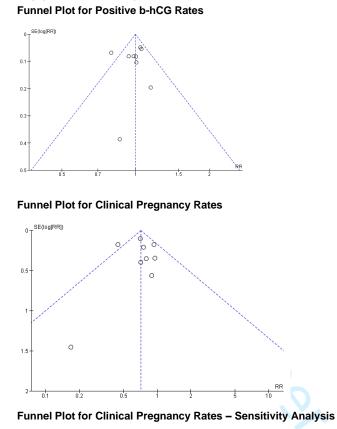
Supplementary File 8 - Supplementary Figure 3: Meta-analysis comparing rates of pregnancy losses in cycles with and without a corpus luteum – separated by study design

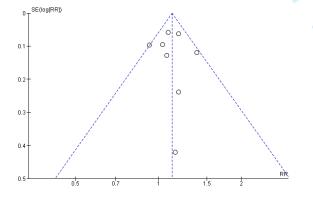
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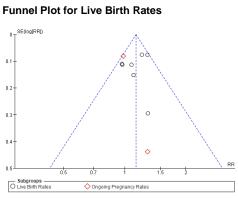


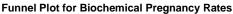
Supplementary File 9 - Supplementary Figure 4: Funnel Plot Analyses

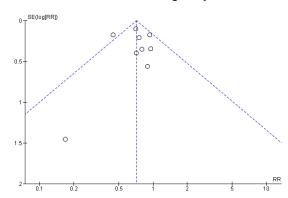




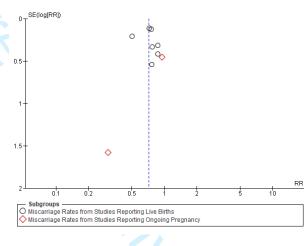












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4 5 Section/topic	#	Checklist item 15	Reported on page #
7 TITLE		9	
⁸ 9 Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
		nii 20	
12 Structured summary 13	2	Provide a structured summary including, as applicable: background; objectives; data sources study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-5
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16 17 Rationale	3	Describe the rationale for the review in the context of what is already known.	7-8
18 Objectives 19	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
20 METHODS			
22 Protocol and registration 23	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and of available, provide registration information including registration number.	9
24 25 26	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9-10
27 Information sources28	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
²⁹ Search 30	8	Present full electronic search strategy for at least one database, including any limits used, sught that it could be repeated.	Supplementary materials
32 Study selection 33	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
34 35 Data collection process 36	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	11
37 Data items 38	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and and simplifications made.	10-11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data somethies is.	11
42 Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11-12
43 44 Synthesis of results 45	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (erg, er, fer, each metaranalysis, pen.bmj.com/site/about/guidelines.xhtml	11-12
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5 6 Section/topic	#	Checklist item	Reported on page #
 8 Risk of bias across studies 9 	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publicaon bias, selective reporting within studies).	11
10 Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12
13 RESULTS			
14 Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
17 Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table I (separate file to manuscript)
 19 Risk of bias within studies 20 21 22 23 	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table I & supplementary files (separate file to manuscript
24 Results of individual studies25	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Refer to figures II & III
²⁶ ₂₇ Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-17
 28 Risk of bias across studies 29 30 31 	22	Present results of any assessment of risk of bias across studies (see Item 15).	11, table I & supplementary files
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36 DISCUSSION		ָּרָּ דַרַ יַרַ	
37 Summary of evidence 38 39	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
40 Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
42 Conclusions 43	26	Provide a general interpretation of the results in the context of other evidence, and implication for future research.	22
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Treatment Outcomes of Blastocysts Thaw-Cycles, Comparing the Presence and Absence of a Corpus Luteum: A Systematic Review and Meta-analysis.

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Secondary Subject Heading:	Reproductive medicine
Keywords:	Reproductive medicine < GYNAECOLOGY, REPRODUCTIVE MEDICINE, Subfertility < GYNAECOLOGY

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ABSTRACT

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 July 27th, 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 though RevMan 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 control trials, and seven were cohort studies. Sub-group analysis of the different study designs was performed.

Whilst the rates of positive hCG results (RR 1.0, 95% CI 0.95 - 1.05) and clinical pregnancies (RR 1.06, 95% CI 0.96 -1.18) 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 - 1.22). Analysis of pregnancy losses demonstrated that both biochemical pregnancy (early miscarriage) (RR 0.71, 95% CI 0.62 - 0.82) and miscarriages (RR 0.72, 95% CI 0.62 - 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 blastocysts embryos, is required to further explore these findings.

PROSPERO Registration Number: CRD42020209583

STRENGTHS AND LIMITATIONS

- As the use of blastocysts in thaw cycles is becoming increasingly more common, this review is timely and relevant
- The safety of embryo transfers without a corpus luteum is a growing area of research
- The limitations of this study include the limited number of studies in the area and lack of high quality randomised controlled trials
- Further high-quality studies are required to further explore these findings.

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.

STUDY FUNDING/COMPETING INTEREST(S):

All authors declare no conflicts of interest. This research received no specific grant from any funding agency in the public,

commercial or not-for-profit sectors.

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INTRODUCTION

In vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatments conventionally include a fresh embryo transfer, sometimes followed by one or more cryopreserved embryo transfers in subsequent cycles. Alternatively, all suitable embryos are cryopreserved and transferred in subsequent cycles. In recent years, embryo cryopreservation has become a fundamental tool in reproductive medicine. With improvements in the vitrification processes, culture mediums and desire for single embryo transfers (SETs), thaw cycles are becoming more common(1-4). The benefits of embryo verification include the need for fewer ovarian stimulation cycles, as well as an improved cumulative pregnancy(3). In Australia, the proportion of cryopreserved embryo transfers increased from 47.1% in 2014 to 57.2% in 2018(2). In particular, the cryopreservation of blastocysts for frozen embryo transfer has been an increasingly adopted practice. The European IVF Monitoring Consortium reported that in 2016 more than half of frozen embryo transfers (62.2%) were performed at the blastocysts stage(5). It was also noted that pregnancy rates were higher in the frozen embryo transfers which used blastocyst (39.7%) compared to cleavage staged embryos (28.3%)(5).

Various protocols for endometrial preparation have been developed to assist with thaw-cycles transfers. One of the most widely used methods is the true natural cycle (tNC) or variations of it such as the modified natural cycle (mNC) or the mildly stimulated cycle (SC). These preparation techniques rely on the 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 estrogen (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 to 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(4, 6). Previous studies have found that treatment outcomes of tNC and ACs have been comparable(7-9). Some studies, however, have noted that thaw-cycles without a CL may have experienced higher rates of early pregnancy loss. (4, 10, 11). 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(12).

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(2).

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, 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 patient involved.

Search Strategy

This review was registered with PROSPERO CRD42020209583. 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(7). The search strategy utilised 3 key concepts: endometrial preparation AND frozen embryos AND reproductive outcomes. The detailed search strategy can be found in supplementary 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(7, 8). No language restrictions were used in the search. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines(13).

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, 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

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included ACs with or without gonadotropin-releasing hormone analogue (GnRHa) suppression. Blastocysts were defined as day 5 or 6 embryos(14).

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 live birth (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 upon by the International Glossary on Infertility and Fertility Care, 2017(14). A LB was defined as a birth which demonstrated evidence of life after at least 22 weeks gestation(14). 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 (15), ongoing pregnancy rates were included in the analysis of live birth rates. However, we performed a sub-analysis of the studies which reported live births 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 \geq 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.*,(2018) (16), did not report clinical pregnancy, hence it was calculated by adding the number of live births, 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(14). Biochemical pregnancy(14). Where biochemical pregnancy was not reported, it was calculated by subtracting the reported clinical pregnancy(14). 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 was independently extracted by three reviewers (GR, AP, 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, live births, or ongoing births where live births were not available. The data was collated by a single reviewer (JG) and any discrepancies were discussed among three reviewers and until a consensus was reached.

Quality Assessment

Included randomised control trials were quality assessed using the Revised Cochrane Risk of Bias Tool for randomised trials (RoB 2)(17). The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses was used to assess cohort studies(18). 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 Supplementary File 2 and 3.

Statistical Analysis

The meta-analysis was performed using RevMan 5.4.1 computer program, The Cochrane Collaboration, 2020(19). Metaanalyses of rates of positive hCG, live births, 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 X² statistic. P-values of X² that were <0.05, and I² > 50% were considered represent significant heterogeneity. Relative risk with 95% confidence intervals (CI), were 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 (Supplementary File 4).

As we included studies that reported ongoing pregnancy rates where LB rates were not available, we conducted a sub-group analyses 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 Supplementary File 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(10, 16, 20-26). Two of which were randomised controlled trials (RCTs)(22, 23) both of which studied small sample sizes. The remaining seven were retrospective cohort studies(10, 16, 20, 21, 24-26) which followed a much larger sample size. This process is summarized in Figure 1. The final meta-analysis included a total of 6138 cycles with a CL and 3491 cycles without a CL.

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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., 2020(10), and the smallest study included 116 cycles by Sheikhi et al., (2018)(23).

The average quality of the studies was rated with a fair to moderate risk of bias.

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Table 1: Overview of studies included in a meta-analysis comparing reproductive outcomes in blastocyst	ප s transfers using thaw-cycles

	Study Design					Demographic	S	2021-05	Outcomes			
Study	Design	Cycles with blastocysts (n)	Study Period	Allocation	Women (n)	Study population	Mean Age, years (SD)	BMI, kgim2 (SD)	Positive - hCG (n)	CP (n)	LB/OP	Quality
Alur-Gupta et al. (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 = 2 (3.7) AC = 2 (3.7) AC = 2 (3.7) BC = 2 (3.7)	With CL = 64 Without CL = 602	With CL = 55 Without CL = 523	LB	Fair
Cardenas Armas et al. (2019)(24)	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) AC (Oral) = 36.86 (0.19)	NC = 2 (2.1) $AC(Traisdermal) = 21.6 (2.2)$ $AC(Ora) = 23.3$ (1.7)	With CL = 16 Without CL = 76	With $CL =$ 13 Without CL = 60	LB	Good
Chang et al. (2011)(21)	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)	$NC = 2 \overline{\textcircled{e}7}^{7} (2.8)$ mNC = 2 0.5 (3.5) AC = 2 \overline{\textcircled{e}7}^{7} (2.4)	With CL = 229 Without CL = 107	With CL = 186 Without CL = 62	OP	Good
Givens (2009) et al.(20)	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 ^{mj} open.bmj.	With CL = 369 Without CL = 141	With CL = 284 Without CL =105	LB	Fair
Greco (2016) et al.(22)	RCT	222 Cycles (with CL = 109, without CL = 113)	2015	Computer- generated randomization (non-concealed)	236	normo-ovulatory patients, PGT	mNC = 35.2 (3.6) AC + GnRHa = 35.5 (3.8)	mNC = 2.1 (3.1) AC + GaRHa = 22.1 (3.8)	With CL = 68 Without CL = 70	With CL = 59 Without CL = 523	LB	Some concern
Le (2017) et al.(26)	Retrospective Cohort	378 cycles (with CL 197, without CL = 181)		Clinical judgement	428 ^b	Both normo-ovulatory patients and women with ovulatory dysfunction	mNC = 34.3 (4.2) AC = 33.3 (4.8)	mNC = 25.3 (5.5) $AC = 2787 (7.0)$	With CL= 120 Without CL = 110	With CL = 107 Without CL = 95	LB	Fair
Levi Setti et al. (2020)(25)	Retrospective Cohort	2888 Cycles (with CL = 2304, without CL = 584) ^c	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)	$NC = 2 \frac{2}{8} 8 (3.0)$ mNC = $\frac{2}{21.8} (3.0)$ AC = $2\frac{2}{50} (3.3)$	With $CL =$ 1012 Without CL = 243	With CL = 930 Without CL = 217	LB	Fair
Pakes et al. (2020)(10)	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 copyright.	With $CL =$ 802 Without CL = 376	With $CL =$ 627 Without CL = 260	LB	Fair

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1 2 3 4	Sheikhi et al. (2018)(23) ^d	RCT	116 Cycles (with CL = 57, without CL = 59)	2015 - 2016	Computer- generated randomization (non-concealed)	123e	normo-ovulatory patients, without severe endometriosis	mNC = 29.71 (3.79) mSC = 30.31 (4.58) AC = 30.5 (5.59)	mSC = 2	5 6.19 (3.24) 5.80 (3.29) 5.36 (5.27)	With CL = 10 Without CL = 12	With CL = 10 Without CL = 9	OP	Some concerns
5 6 7 8 9 10 11 12 13 14 15 16 17 18 20 21 22 23 24 25 26 27 28 9 30 31 32 33 4 35 36 37 38	gonadotropin	-releasing ho ded due to va	rmana analagua: D(T nro imr	Instation constin to	ting: MI	atural cycle; mNC, modifie R, not reported. ^a quality as nographic data extracted from the second seco	ed natural cycle; A	C, artificia ane Risk (y (conflict)	d cycle; mS) or Nowcoot	le-Ottawa So	cale. ^b 6	6
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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 (RR 1.00, 95% CI 0.95 - 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 Supplementary File 5.

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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 - 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.*, (2009) (20) which was the only study to observe a higher clinical pregnancy rate in AC compared to NCs. The results of this are shown in Supplementary File 7. The sensitivity analysis showed that live birth rates were statistically higher in the cycles involving the presence of a CL (RR 1.12, 95% CI 1.05 - 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 confidence interval 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 Supplementary File 5.

Live Birth Rates

Seven studies reported LB rates as their primary outcome (one prospective randomised trial and five retrospective studies)(10, 16, 20, 22, 24-26). Two studies reported ongoing pregnancy rates as their primary outcome (one prospective randomised trial, and one cohort study)(21, 23).

Of the 6138 cycles which involved the presence of a CL, 1902 (31%) resulted in a LB or progressed to an ongoing pregnancy. In the 3491 cycles without a CL, 1124 (32%) resulted in a live birth or ongoing pregnancy. The individual and combined estimates for live births are shown in Figure 2. The pooled estimates for live births (RR 1.14, 95% CI 1.06 - 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 live birth 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 live birth rate remained significantly higher in the thaw-cycles with a CL (RR 1.16, 95% CI 1.07 - 1.26). Subgroup analysis of LB rates by study design is shown in Supplementary 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 (i.e., 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 - 0.82) were significantly lower in the cycles with a CL. Subgroup analysis of biochemical pregnancy rates by study design is shown in Supplementary 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 - 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 Supplementary 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(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.*, (2020), which retrospectively analysed treatment outcomes after mNC and ACs with GnRHa, concluded that LBs rates and pregnancy loss rates were comparable between the two groups(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. Similarly, a study by Hill *et al.*, (2010), demonstrated higher birth rates in the AC compared to the NC group, however, the AC group had more blastocysts transferred which would have likely biased the results to favour the AC(28). A recent Cochrane review was inconclusive regarding its ability to determine an optimal endometrial technique in terms of reproductive outcomes(7). Similar inconclusive results were also observed in other systematic reviews and meta-analyses (8, 29, 30). These studies also included data on cleavage stage dembryos, which may not be generalizable 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 noncomparable groups of women undertaking thaw-cycles involving the presence or absence of a CL. Women with oligo or

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amenorrhea due to medical conditions like polycystic ovarian syndrome (PCOS), are more likely to undergo the AC for
embryo transfer, compared to women with regular menstrual cycles. Women with PCOS may have an increased risk of adverse
pregnancy outcomes such as early miscarriage(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(7).

Previous studies have also noted higher miscarriage rates in cycles without a CL. A large retrospective analysis by Tomás et al., (2012), demonstrated a higher miscarriage rate in the AC cycle group compared to the group receiving the NC protocol(32). Similar findings were observed in the study by Givens et al., (2009)(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., (2008), found that miscarriage rates were higher in the AC group (23.0%) compared to the NCs (11.4%, p-value < 0.0001)(33). However, the BMI of the women in the AC were statistically higher compared to the NC (25.3 ± 5.4, 22.9 ± 3.6 , p-value < 0.0001) which may have influenced the miscarriage rate. Similarly, a retrospective study by Guan *et al.*, (2016) (34), which analysed 1482 thawed cleavage-staged embryos noted that women in the NC group experienced significantly lower rates of miscarriage (2.8%) compared to those in the women receiving the AC with GnRHa (14.0%, p-value = 0.003)(34). This may be influenced by the statistically older age of women receiving the AC with GnRHa compared to the women in the NC group. Another retrospective study involving normo-ovulatory women by Cerillo et al., (2017), observed statistically higher miscarriage rates in the women receiving AC (21.2%), compared to the women receiving mNC (12.9%) and the tNC (11.1%)(35). In a recent retrospective analysis by Liu et al., (2020), 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 to the mNC arm (8.37%, p value 0.034)(36). Again, as these studies included cleavage-stage embryos their findings may not be generalizable to our research question, which involves data on blastocyst embryos. A recent large retrospective study by Pakes et al., (2020) which analysed blastocyst thaw cycles, observed that the AC group experienced a higher pregnancy loss compared to the women in the NC group(10). In this study, women in the AC group were significantly younger and received a higher proportion of good quality day-5 blastocysts compared to the NC which may have biased results to favour the AC, however, the AC group still demonstrated more pregnancy losses compared to the NC group.

There may be several contributing factors influencing this observed increased rate of pregnancy loss in thaw-cycles without a CL. Firstly, we may be disregarding the physiology of the CL. In a recent study,(37) it was observed that cycles without a CL had a significantly lower level of serum progesterone on the day of embryo transfer compared to cycles involving a CL. In the AC, estrogen 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(4, 38, 39), indicating that there

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may be complex interaction between the CL and pregnancy support extending beyond P4 and E2 production. Secondly, 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(40-42), however, other studies suggest serum progesterone levels are not well correlated with the intra-uterine levels(43-45). This poor correlation is likely due to the first uterine pass effect(43, 45) and unpredictable levels of progesterone absorption from exogenous vaginal progesterone. Consequently, some women may not be receiving adequate luteal support, and thus an optimized 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 odds ratio 1.61, 95% CI 1.22 - 2.10), post-partum haemorrhage (adjusted odds ratio 2.87, 95% CI 2.29 - 2.60), post-term birth (adjusted odds ratio 1.59, 95% CI 1.47 – 2.68) and macrosomia (adjusted odds ratio 1.62, confidence interval 1.03-1.90)(46). 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 odds ratio 1.43, 95% confidence interval 1.14-1.8) and placenta accreta (adjusted odds ratio, 6.91; 95% CI 2.87 – 16.66) compared to cycles involving the presence of a CL(47). Similar findings have been noted in other studies(48-53). In a recent study which investigated the relation between pregnancy related hypertensive disorders and corpus luteum number, it was noted that pregnancies without a CL did not exhibit the physiologic decline in mean arterial pressure associated with pregnancy(52). 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 utilizing 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 sub-group of embryo transfers which is also clinically relevant, with an increasing number of blastocyst transfers observed in clinical practice.

This study has several limitations. Firstly, 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 (Supplementary File 4) had a limited utility in assessing publication bias. The aforementioned

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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 utilised 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 utilizing adequately powered randomised controlled trials involving blastocyst thaw-cycles is urgently required.

LIST OF ABBREVIATIONS

AC – Artificial Cycle

- CI Confidence Intervals
- CL Corpus Luteum
- GnRHa Gonadotropin-Releasing Hormone analogue
- ICSI intracytoplasmic sperm injection
- IVF In vitro fertilisation
- LB Live Birth
- mNC Modified Natural Cycle
- PCOS Polycystic Ovarian Syndrome
- SC Stimulated Cycle

SET – Single Embryo Transfer

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29 30 31 RCT – Randomised Control Trial

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AUTHORS' CONTRIBUTIONS

G.R. and A.P. were involved in the conception and creation of the study design. G.R., A.P., and J.G. wrote the protocol. All

authors were involved in the screening of articles for eligibility and data extraction. A.P. provided expertise on statistical

analysis. A.P. and J.G. performed the meta-analysis. All authors have contributed significantly to, seen, and approved the final

submitted version of the manuscript.

CONFLICTS OF INTEREST

All authors declare no conflicts of interests.

DATA AVAILABILITY

All relevant data to the study is included in the article or in the supplementary materials supplied.

REFERENCES

- 32 Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Clinical rationale for cryopreservation of entire 1. 33 embryo cohorts in lieu of fresh transfer. Fertil Steril 2014;1:3-9. 34 Newman JE, Repon PC, Chambers GM. Assisted reproductive technology in Australia and New Zealand 2018. 2. 35 Available at: 36 https://npesu.unsw.edu.au/sites/default/files/npesu/data_collection/Assisted%20Reproductive%20Technology%20in%20Austr 37 alia%20and%20New%20Zealand%202018.pdf. Accessed September 9, 2020. 38 Wong KM, Mastenbroek S, Repping S. Cryopreservation of human embryos and its contribution to in vitro 3. 39 fertilization success rates. Fertil Steril. 2014;1:19-26. Lawrenz B, Coughlan C, Melado L, Fatemi HM. The ART of frozen embryo transfer: back to nature! Gynecol 40 4. Endocrinol 2020:6:479-83. 41 Wyns C, Bergh C, Calhaz-Jorge C, De Geyter C, Kupka MS, Motrenko T, et al. ART in Europe, 2016: results 42 5. generated from European registries by ESHRE. Hum Reprod Open 2020;3:hoaa032. 43 Groenewoud ER, Cohlen BJ, Al-Oraiby A, Brinkhuis EA, Broekmans FJ, de Bruin JP, et al. A randomized controlled, 6. 44 non-inferiority trial of modified natural versus artificial cycle for cryo-thawed embryo transfer. Hum Reprod 2016;7:1483-92. 45 Ghobara T, Gelbaya TA, Ayeleke RO. Cycle regimens for frozen-thawed embryo transfer. Cochrane Database Syst 7. 46 Rev 2017;7:Cd003414. 47 Groenewoud ER, Cantineau AEP, Kollen BJ, Macklon NS, Cohlen BJ. What is the optimal means of preparing the 8. 48 endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis. Hum Reprod Update 49 2017;2:255-61. 50 Yarali H, Polat M, Mumusoglu S, Yarali I, Bozdag G. Preparation of endometrium for frozen embryo replacement 9. 51 cycles: a systematic review and meta-analysis J Assist Reprod Genet 2016;10:1287-304. 52 Pakes C, Volovsky M, Rozen G, Agresta F, Gardner DK, Polyakov A. Comparing pregnancy outcomes between 10. 53 natural cycles and artificial cycles following frozen-thaw embryo transfers. Aust N Z J Obstet Gynaecol 2020;5:804-9. 54 11. Lelaidier C, de Ziegler D, Gaetano J, Hazout A, Fernandez H, Frydman R. Controlled preparation of the endometrium 55 with exogenous oestradiol and progesterone: a novel regimen not using a gonadotrophin-releasing hormone agonist*. Hum 56 Reprod 1992;10:1353-6. 57 12. Stocking K, Wilkinson J, Lensen S, Brison DR, Roberts SA, Vail A. Are interventions in reproductive medicine 58 assessed for plausible and clinically relevant effects? A systematic review of power and precision in trials and meta-analyses. 59 Hum Reprod 2019;4:659-65. 60 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the 13
 - PRISMA statement. *Bmj* 2009;339:b2535.

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1	14. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on
2	Infertility and Fertility Care, 2017. Fertil Steril 2017;3:393-40.
3	 Michels TC, Tiu AY. Second trimester pregnancy loss. Am Fam Physician 2007;76:1341-6. Alur-Gupta S, Hopeman M, Berger DS, Gracia C, Barnhart KT, Coutifaris C, et al. Impact of method of endometrial
4	preparation for frozen blastocyst transfer on pregnancy outcome: a retrospective cohort study. Fertil Steril 2018;110:680-6.
5	17. Sterne JAC SJ, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, et al. RoB 2: a revised tool for assessing risk
6	of bias in randomised trials. bmj 2019;366:14898.
7	18. GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for
8	assessing the quality of nonrandomised studies in meta-analyses Ottawa Hospital Research Institute. Available from:
9	http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 9, 2020.
10	19. The Cochrane Collaboration. Review Manager (RevMan). Version 5.4.1 ed2020.
11 12	20. Givens CR, Markun LC, Ryan IP, Chenette PE, Herbert CM, Schriock ED. Outcomes of natural cycles versus
12	programmed cycles for 1677 frozen-thawed embryo transfers. Reprod Biomed Online 2009;19:380-4.
14	21. Chang EM, Han JE, Kim YS, Lyu SW, Lee WS, Yoon TK. Use of the natural cycle and vitrification thawed
15	blastocyst transfer results in better in-vitro fertilization outcomes : cycle regimens of vitrification thawed blastocyst transfer. J Assist Reprod Genet 2011;28:369-74.
16	22. Greco E, Litwicka K, Arrivi C, Varricchio MT, Caragia A, Greco A, et al. The endometrial preparation for frozen-
17	thawed euploid blastocyst transfer: a prospective randomized trial comparing clinical results from natural modified cycle and
18	exogenous hormone stimulation with GnRH agonist. J Assist Repro Genet 2016;33:873-84.
19	23. Sheikhi O, Golsorkhtabaramiri M, Esmaeilzadeh S, Mahouti T, Heidari FN. Reproductive outcomes of vitrified
20	blastocyst transfer in modified natural cycle versus mild hormonally stimulated and artificial protocols: A randomized control
21	trial. JBRA Assist Reprod 2018;22:221-7.
22	24. Cardenas Armas DF, Peñarrubia J, Goday A, Guimerá M, Vidal E, Manau D, et al. Frozen-thawed blastocyst transfer
23	in natural cycle increase implantation rates compared artificial cycle. Gynecol Endocrinol 2019;35:873-7.
24	25. Levi Setti PE, Cirillo F, De Cesare R, Morenghi E, Canevisio V, Ronchetti C, et al. Seven Years of Vitrified
25	Blastocyst Transfers: Comparison of 3 Preparation Protocols at a Single ART Center. Front Endocrinol (Lausanne)
26	 2020;11:346. 26. Le QV, Abhari S, Abuzeid OM, DeAnna J, Satti MA, Abozaid T, et al. Modified natural cycle for embryo transfer
27	using frozen-thawed blastocysts: A satisfactory option. Eur J Obstet Gynecol Reprod Biol 2017;213:58-63.
28	27. Sahin G, Acet F, Calimlioglu N, Meseri R, Tavmergen Goker EN, Tavmergen E. Live birth after frozen-thawed
29	embryo transfer: which endometrial preparation protocol is better? J Gynecol Obstet Hum Reprod 2020;8:101782.
30	28. Hill MJ, Miller KA, Frattarelli JL. A GnRH agonist and exogenous hormone stimulation protocol has a higher live-
31	birth rate than a natural endogenous hormone protocol for frozen-thawed blastocyst-stage embryo transfer cycles: an analysis
32 33	of 1391 cycles. Fertil Steril 2010;93:416-22.coww
33 34	29. Groenewoud ER, Cantineau AEP, Kollen BJ, Macklon NS, Cohlen BJ. What is the optimal means of preparing the
35	endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis. Hum Reprod Update
36	2017;23:255-61.
37	30. Mackens S, Santos-Ribeiro S, van de Vijver A, Racca A, Van Landuyt L, Tournaye H, et al. Frozen embryo transfer: A review on the optimal endometrial preparation and timing. Hum Reprod 2017;32:2234-42.
38	31. Luo L, Gu F, Jie H, Ding C, Zhao Q, Wang Q, et al. Early miscarriage rate in lean polycystic ovary syndrome women
39	after euploid embryo transfer - a matched-pair study. Reprod Biomed Online 2017;35:576-82.
40	32. Tomás C, Alsbjerg B, Martikainen H, Humaidan P. Pregnancy loss after frozen-embryo transfera comparison of
41	three protocols. Fertil Steril 2012;98:1165-9.
42	33. Veleva Z, Tiitinen A, Vilska S, Hydén-Granskog C, Tomás C, Martikainen H, et al. High and low BMI increase the
43	risk of miscarriage after IVF/ICSI and FET. Hum Reprod 2008;23:878-84.
44	34. Guan Y, Fan H, Styer AK, Xiao Z, Li Z, Zhang J, et al. A modified natural cycle results in higher live birth rate in
45	vitrified-thawed embryo transfer for women with regular menstruation. Syst Biol Reprod Med 2016;62:335-42.
46	35. Cerrillo M, Herrero L, Guillén A, Mayoral M, García-Velasco JA. Impact of Endometrial Preparation Protocols for
47	 Frozen Embryo Transfer on Live Birth Rates. Rambam Maimonides Med J 2017;8:e0020. Liu X, Shi W, Shi J. Natural cycle frozen-thawed embryo transfer in young women with regular menstrual cycles
48	increases the live-birth rates compared with hormone replacement treatment: a retrospective cohort study. Fertil Steril.
49	2020;113:811-7.
50	37. Olivier P, Irma Z, Marine B, Marie Laure T, Sylvie N-R, Nathalie R-M, et al. Comparison of Serum Progesterone
51 52	Levels of the Day of Frozen Embryo Transfers According to Type of Endometrial Preparation: A Monocentric, Retrospective
52 53	Study. Res Sq 2021.
53 54	38. Kor NM. The effect of corpus luteum on hormonal composition of follicular fluid from different sized follicles and
55	their relationship to serum concentrations in dairy cows. Asian Pac J Trop Med 2014;7 Suppl 1:S282-8.
56	39. Conrad KP. Emerging role of relaxin in the maternal adaptations to normal pregnancy: implications for preeclampsia.
57	 Semin Nephrol 2011;31:15-32. 40. Cedrin-Durnerin I, Isnard T, Mahdjoub S, Sonigo C, Seroka A, Comtet M, et al. Serum progesterone concentration
58	40. Cedrin-Durnerin I, Isnard T, Mahdjoub S, Sonigo C, Seroka A, Comtet M, et al. Serum progesterone concentration and live birth rate in frozen-thawed embryo transfers with hormonally prepared endometrium. Reprod Biomed Online.
59	2019;38:472-80.
60	2012,50.172.00.

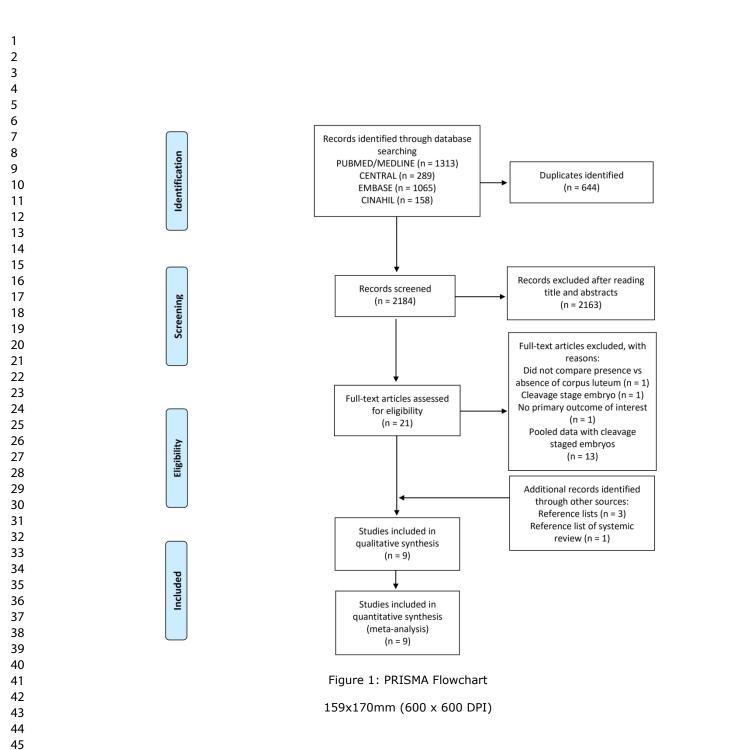
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- 41. Labarta E, Mariani G, Holtmann N, Celada P, Remohí J, Bosch E. Low serum progesterone on the day of embryo 1 transfer is associated with a diminished ongoing pregnancy rate in oocyte donation cycles after artificial endometrial 2 preparation: a prospective study. Hum Reprod 2017;32:2437-42. 3 Volovsky M, Pakes C, Rozen G, Polyakov A. Do serum progesterone levels on day of embryo transfer influence 42. 4 pregnancy outcomes in artificial frozen-thaw cycles? J Assist Reprod Genet 2020;37:1129-35. 5 Tavaniotou A, Smitz J, Bourgain C, Devroey P. Comparison between different routes of progesterone administration 43. 6 as luteal phase support in infertility treatments. Hum Reprod Update 2000;6:139-48. 7 Penzias AS, Alper MM. Luteal support with vaginal micronized progesterone gel in assisted reproduction. Reprod 44. 8 Biomed Online 2003:6:287-95. 9 Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from 45. 10 vagina to uterus. Obstet Gynecol 2000;95:403-6. 11 Ginström Ernstad E, Wennerholm UB, Khatibi A, Petzold M, Bergh C. Neonatal and maternal outcome after frozen 46. 12 embryo transfer: Increased risks in programmed cycles. Am J Obstet Gynecol 2019;221:126.e1-.e18. 13 Saito K, Kuwahara A, Ishikawa T, Morisaki N, Miyado M, Miyado K, et al. Endometrial preparation methods for 47. 14 frozen-thawed embryo transfer are associated with altered risks of hypertensive disorders of pregnancy, placenta accreta, and 15 gestational diabetes mellitus. Hum Reprod 2019;34:1567-75. 16 von Versen-Hoynck F, Schaub AM, Chi YY, Chiu KH, Liu J, Lingis M, et al. Increased Preeclampsia Risk and 48. 17 Reduced Aortic Compliance With In Vitro Fertilization Cycles in the Absence of a Corpus Luteum. Hypertension 18 2019;73:640-9. 19 49. Jing S, Li XF, Zhang S, Gong F, Lu G, Lin G. Increased pregnancy complications following frozen-thawed embryo transfer during an artificial cycle. J Assist Reprod Genet 2019;36:925-33. 20 Saito K, Kuwahara A, Ishikawa T, Nakasuji T, Miyado M, Miyado K, et al. Pregnancy after frozen-thawed embryo 50. 21 transfer during hormonal replacement cycle is associated with hypertensive disorders of pregnancy and placenta accreta. Hum 22 Reprod 2018;33 Suppl 1:i128-i9. 23 Sakai Y, Ono M, Iizuka T, Kagami K, Masumoto S, Nakayama M, et al. Embryo transfer associated with hormone 51. 24 replacement therapy cycles using assisted reproductive technology increases placenta accreta spectrum. J Obstet Gynaecol Res 25 2019:45:2394-9. 26 von Versen-Höynck F, Narasimhan P, Selamet Tiernev ES, Martinez N, Conrad KP, Baker VL, et al. Absent or 52. 27 Excessive Corpus Luteum Number Is Associated With Altered Maternal Vascular Health in Early Pregnancy. Hypertension 28 2019:73:680-90. 53. Asserhøj LL, Spangmose AL, Aaris Henningsen A-K, Clausen TD, Ziebe S, Jensen RB, 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 2021:0;https://doi.org/10.1016/j.fertnstert.2020.10.039 32 34
 - FIGURE CAPTIONS

Figure 1: PRISMA Flowchart

Figure 2: Meta-analysis comparing rates of positive hCG, clinical pregnancy, and live births in cycles with and without a corpus luteum

Figure 3: Meta-analysis comparing biochemical pregnancy and miscarriage rates in cycles with and without a corpus luteum



2 With CL Without CL **Risk Ratio Risk Ratio** 3 M-H, Fixed, 95% CI Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI 4 Alur-Gupta 2018 64 104 602 917 7.7% 0.94 [0.80, 1.10] 5 Cardenas Armas 2019 16 32 76 175 1.5% 1.15 [0.78, 1.69] 6 Chang 2011 229 444 107 204 9.2% 0.98 [0.84, 1.15] 0.80 [0.69, 0.91] Givens 2009 858 13.5% 7 369 141 261 Greco 2016 70 4.3% 1.01 [0.82, 1.24] 68 109 113 8 120 Le 2017 197 110 181 7.2% 1.00 [0.85, 1.18] 9 Levi Setti 2020 1012 2304 243 584 24.3% 1.06 [0.95, 1.17] 10 Pakes 2020 802 2033 376 997 31.6% 1.05 [0.95, 1.15] 11 Sheikhi 2018 0.7% 0.86 [0.40, 1.84] 10 57 12 59 12 Total (95% CI) 6138 3491 100.0% 1.00 [0.95, 1.05] 13 Total events 2690 1737 14 Heterogeneity: Chi² = 13.86, df = 8 (P = 0.09); l² = 42% 0.7 0.5 1.5 2 15 Test for overall effect: Z = 0.16 (P = 0.87) Favours no CL Favours CL 16 **Clinical Pregnancy Rates** 17 18 With CL Without CL **Risk Ratio Risk Ratio** 19 Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Alur-Gupta 2018 55 104 523 917 12.9% 0.93 [0.77, 1.12] 20 Cardenas Armas 2019 13 32 60 175 4.0% 1.18 [0.74, 1.89] 21 Chang 2011 186 444 62 204 10.5% 1.38 [1.09, 1.74] 22 Givens 2009 284 858 105 261 13.7% 0.82 [0.69, 0.98] 23 Greco 2016 59 109 57 113 9.7% 1.07 [0.83, 1.38] Le 2017 107 197 95 181 12.9% 1.03 [0.86, 1.25] 24 Levi Setti 2020 930 2304 217 584 17.6% 1.09 [0.97, 1.22] 25 Pakes 2020 627 2033 260 997 17.2% 1.18 [1.05, 1.34] 26 Sheikhi 2018 10 57 9 59 1.5% 1.15 [0.50, 2.62] 27 Total (95% CI) 6138 3491 100.0% 1.06 [0.96, 1.18] 28 **Total events** 2271 1388 29 Heterogeneity: Tau² = 0.01; Chi² = 18.35, df = 8 (P = 0.02); I² = 56% 30 0.5 0.7 1.5 2 Test for overall effect: Z = 1.15 (P = 0.25) Favours no CL Favours CL 31 32 Live Births and Ongoing Pregnancy Rates 33 With CL Without CL **Risk Ratio Risk Ratio** 34 Study or Subgroup **Events Total Events Total Weight** M-H, Fixed, 95% CI M-H, Fixed, 95% CI Alur-Gupta 2018 917 8.7% 0.98 [0.78, 1.22] 35 47 104 425 Cardenas Armas 2019 10 32 42 175 1.3% 1.30 [0.73, 2.32] 36 Chang 2011 229 444 107 204 14.8% 0.98 [0.84, 1.15] 37 Givens 2009 245 858 261 11.9% 77 0.97 [0.78, 1.20] 38 Greco 2016 50 4.6% 109 47 113 1.10 [0.82, 1.49] 39 Le 2017 93 197 79 181 8.3% 1.08 [0.87, 1.35] 40 Levi Setti 2020 722 2304 24.2% 151 584 1.21 [1.04, 1.41] Pakes 2020 496 2033 188 997 25.4% 1.29 [1.11, 1.50] 41 Sheikhi 2018 0.8% 10 57 8 59 1.29 [0.55, 3.04] 42 43 Total (95% CI) 3491 6138 100.0% 1.14 [1.06, 1.22] 44 Total events 1902 1124 45 Heterogeneity: Chi² = 11.23, df = 8 (P = 0.19); l² = 29% **0.2** 0.5 ż 46 Test for overall effect: Z = 3.50 (P = 0.0005) Favours No CL Favours With CL 47 Live Births Rates Only 48 4

		With O	CL	Withou	t CL		Risk Ratio	Risk Ratio
5	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
A	Alur-Gupta 2018	47	104	425	917	10.3%	0.98 [0.78, 1.22]	-+-
C	Cardenas Armas 2019	10	32	42	175	1.5%	1.30 [0.73, 2.32]	
C	Givens 2009	245	858	77	261	14.1%	0.97 [0.78, 1.20]	
C	Greco 2016	50	109	47	113	5.5%	1.10 [0.82, 1.49]	
L	_e 2017	93	197	79	181	9.8%	1.08 [0.87, 1.35]	
L	_evi Setti 2020	722	2304	151	584	28.7%	1.21 [1.04, 1.41]	
F	Pakes 2020	496	2033	188	997	30.1%	1.29 [1.11, 1.50]	
1	Fotal (95% CI)		5637		3228	100.0%	1.16 [1.07, 1.26]	♦
T	Total events	1663		1009				
H	Heterogeneity: Chi ² = 8.0	7, df = 6 (P = 0.2	3); I ² = 26	6%			0.5 0.7 1 1.5 2
Г	Test for overall effect: Z =	3.70 (P :	= 0.000	2)				Favours No CL Favours With

CL, Corpus Luteum; CI, Confidence interval

1

Rates of Positive hCG

Biochemical	Pregnancy	Rates
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	With		Withou			Risk Ratio	Risk Ratio
Study or Subgroup					Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Alur-Gupta 2018	8	64	79	602		0.95 [0.48, 1.88]	
Cardenas Armas 2019	3	16	16	76		0.89 [0.29, 2.70]	_
Chang 2011	43	229	45	107		0.45 [0.31, 0.63]	
Givens 2009	83	369	34	141	13.6%	0.93 [0.66, 1.32]	
Greco 2016	9	68	13	70	3.5%	0.71 [0.33, 1.56]	
Le 2017	13	120	15	110	4.3%	0.79 [0.40, 1.59]	
Levi Setti 2020	82	1012	26	243	11.6%	0.76 [0.50, 1.15]	
Pakes 2020	175	802	116	376	43.5%	0.71 [0.58, 0.86]	
Sheikhi 2018	0	10	3	12	0.9%	0.17 [0.01, 2.93]	←
Total (95% CI)		2690		1737	100.0%	0.71 [0.62, 0.82]	•
Total events	416		347				
Heterogeneity: Chi ² = 11		(P = 0)		28%			
Test for overall effect: Z		·					0.1 0.2 0.5 1 2 Favours no CL Favours C
Miscarriage Rates	With C		Without	CI		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Woight	M-H, Random, 95% Cl	
7.1.1 Miscarriage Rates						wi-n, Kanuoni, 55 /6 Ci	Mi-n, Kandolii, 95 /8 Cl
•			•				
Alur-Gupta 2018	9	55	98	523	5.1%	0.87 [0.47, 1.63]	
Cardenas Armas 2019	3	13	18	60	1.8%	0.77 [0.27, 2.23]	
Givens 2009	41	284	30	105	11.6%	0.51 [0.33, 0.76]	
Greco 2016	9	59	10	57	2.9%	0.87 [0.38, 1.98]	
Le 2017	14	107	16	95	4.5%	0.78 [0.40, 1.51]	
Levi Setti 2020	217	930	70	217	39.2%	0.72 [0.58, 0.91]	
Pakes 2020 Subtotal (95% CI)	131	627 2075	72	260 1317	32.2% 97.3%	0.75 [0.59, 0.97] 0.72 [0.62, 0.83]	•
Total events	424		314				
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =		· · ·).73); l²	= 0%		
7.1.2 Miscarriage Rates	from Stud	ies Rep	oorting O	ngoing	Pregnand	y	
Chang 2011	17	186	6	62	2.5%	0.94 [0.39, 2.29]	
Sheikhi 2018	0	10	1	9	0.2%	0.30 [0.01, 6.62]	<
Subtotal (95% CI)	-	196	-	71	2.7%	0.87 [0.37, 2.03]	
Total events	17		7				_
Heterogeneity: $Tau^2 = 0.0$).48. df).49): l²	= 0%		
Test for overall effect: Z =			. (.	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			
Total (95% CI)		2271		1388	100.0%	0.72 [0.63, 0.83]	•
Total events	441		321				
Heterogeneity: $Tau^2 = 0.0$.25. df).83): l²	= 0%		
				,,			0.1 0.2 0.5 1 2 5
Test for overall effect: Z =	4.55 (P <	0.0000	1)				Favours no CL Favours C

CL, Corpus Luteum; CI, Confidence interval

Supplementary Files for "Treatment Outcomes of Blastocysts Thaw-Cycles, Comparing the Presence and Absence of a Corpus Luteum: A Systematic Review and Meta-analysis.

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Supplementary File 1 – Supplementary Table 1: Search Strategy PUBMED/MEDLINE

Set	Search	Results
1	Cryopreservation[All Fields]	47,444
2	frozen embryo transfer[All Fields]	3,740
3	Frozen embryo*[All Fields]	8,561
4	frozen-thawed cycle[All Fields]	1,209
5	frozen-thawed embryo transfer[All Fields]	1,457
6	frozen thawed embryos[All Fields]	3,703
7	"FET"[All Fields]	3,577
8	cryopreserved embryos[All Fields]	9,714
9	Cryopreserved-thawed embryos[All Fields]	131
10	vitrification[All Fields]	4,568
11	Vitrified[All Fields]	3,077
12	"vitrified-warmed embryos"[All Fields]	440
13	"frozen-thawed"[All Fields]	5,134
14	embryo vitrification[All Fields]	2,144
14	blastocyst transfer[All Fields]	28,636
15		28,030
15	(((((((((((((((((((()))	81,001
	(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	01,001
	embryo transfer)) OR (frozen thawed embryos)) OR (FET)) OR	
	(cryopreserved embryos)) OR (cryopreserved-thawed embryos))	
	OR (vitrification)) OR (vitrified)) OR (vitrified-warmed embryos)) OR	
10	(frozen-thawed)) OR (embryo vitrification)) OR (blastocyst	
16	transfer)[All Fields]	2 1 2 0
17	endometrial preparation[All Fields]	2,129
10	natural cycle[All Fields]	56,766
18 19	ovulation induction[All Fields]	16,378
20		-
	modified natural cycle[All Fields]	2,401
21	hormone therapy[All Fields]	659,266
22	Estrogen OR oestrogen OR oestrogens OR estrogens OR oestradiol[All Fields]	286,275
23	progesterone[All Fields]	119,710
24	stimulated cycle[All Fields]	63,307
25	stimulation of endometrium embryo transfer[All Fields]	426
26	artificial cycle	13,886
	((((((((endometrial preparation) OR (natural cycle)) OR (ovulation	1,012,876
	induction)) OR (modified natural cycle)) OR (hormone therapy)) OR	
	(Estrogen or oestrogen or oestrogens or estrogens or estradiol))	
	OR (progesterone)) OR (stimulated cycle)) OR (stimulation of	
27	endometrium embryo transfer)) OR (artificial cycle)[All Fields]	
	(((((((((endometrial preparation) OR (artificial cycle)) OR (ovulation	11,974
		±±,9/+
	induction)) OR (modified natural cycle)) OR (hormone therapy)) OR	
	(Estrogen or oestrogen or oestrogens or estrogens or estradiol))	
	OR (progesterone)) OR (stimulated cycle)) OR (stimulation of	
	endometrium embryo transfer)) OR (artificial cycle)) AND	
28	(((((((((((((((()))))))))))) (((())))) ((()))) ((()))) ((()))) ((()))) ((())) ((()))) ((())) ((()))) ((()))) ((())) ((()))) ((()))) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((()))) ((())) ((())) ((()))) ((())) ((())) ((()))) ((())) ((())) ((()))) ((())) ((())) ((())) ((())) ((()))) ((())) ((())) ((())) ((()))) ((())) ((())) ((()))) ((()))	

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	(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	
	embryo transfer)) OR (frozen thawed embryos)) OR (FET)) OR	
	(cryopreserved embryos)) OR (cryopreserved-thawed embryos))	
	OR (vitrification)) OR (vitrified)) OR (vitrified-warmed embryos)) OR	
	(frozen-thawed)) OR (embryo vitrification)) OR (blastocyst	
20	transfer))[All Fields]	007.000
29	Pregnancy[All Fields]	987,880
30	live birth*[All Fields]	32,374
31	miscarriage[All Fields]	47,358
32	ongoing pregnancy[All Fields]	8,897
33	clinical pregnancy[All Fields]	190,084
34	chemical pregnancy[All Fields]	45,767
	(((((pregnancy) OR (live birth*)) OR (miscarriage)) OR (ongoing	1,001,238
35	pregnancy)) OR (clinical pregnancy)) OR (chemical pregnancy) [All Fields]	
	((((((((endometrial preparation) OR (natural cycle)) OR (ovulation	7,913
	induction)) OR (modified natural cycle)) OR (hormone therapy)) OR	
	(Estrogen or oestrogen or oestrogens or estrogens or estradiol))	
	OR (progesterone)) OR (stimulated cycle)) OR (stimulation of	
	endometrium embryo transfer)) OR (artificial cycle)) AND	
	<pre>((((((((((((((((((((((((((())))))))))</pre>	
	(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	
	embryo transfer)) OR (frozen thawed embryos)) OR (FET)) OR	
	(cryopreserved embryos)) OR (cryopreserved-thawed embryos))	
	OR (vitrification)) OR (vitrified)) OR (vitrified-warmed embryos)) OR	
	(frozen-thawed)) OR (embryo vitrification)) OR (blastocyst	
	transfer))) AND ((((((pregnancy) OR (live birth*)) OR (miscarriage))	
	OR (ongoing pregnancy)) OR (clinical pregnancy)) OR (chemical	
36	pregnancy)) [All Fields]	
37	animal[All Fields]	6,843,446
	((((((((endometrial preparation) OR (natural cycle)) OR	6,386
	(ovulation induction)) OR (modified natural cycle)) OR (hormone	
	therapy)) OR (Estrogen or oestrogen or oestrogens or estrogens or	
	estradiol)) OR (progesterone)) OR (stimulated cycle)) OR	
	(stimulation of endometrium embryo transfer)) OR (artificial cycle))	
	AND (((((((((((((((((((((((()) Cryopreservation) OR (frozen embryo transfer)) OR	
	(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	
	embryo transfer)) OR (frozen thawed embryos)) OR (FET)) OR	
	(cryopreserved embryos)) OR (cryopreserved-thawed embryos)) OR (vitrification)) OR (vitrified)) OR (vitrified-warmed embryos)) OR	
	(frozen-thawed)) OR (embryo vitrification)) OR (blastocyst	
	transfer))) AND ((((((pregnancy) OR (live birth*)) OR (miscarriage))	
	OR (ongoing pregnancy)) OR (clinical pregnancy)) OR (chemical	
48	pregnancy)) NOT (animal) [All Fields]	
	((((((((((((((((((((((((((((((((((((((6,375
	(ovulation induction)) OR (modified natural cycle)) OR (hormone	0,070
	therapy)) OR (Estrogen or oestrogen or oestrogens or estrogens or	
	estradiol)) OR (progesterone)) OR (stimulated cycle)) OR	
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39	(frozen embryo*)) OR (frozen-thawed cycle)) OR (frozen-thawed	

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-	 y)) OR (Estrogen or oestrogen or oestrogens or estrogens or ol)) OR (progesterone)) OR (stimulated cycle)) OR
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EMBASE

Set	Search	Results
1	cryopreservation.mp. or cryopreservation/	45195
2	(Cryopreserv\$ adj7 embryo\$).tw.	5646
3	(Cryopreserv\$ adj7 blastocyst\$).tw.	1080
4	freezing/ or vitrification/	43414
5	(vitrifi\$ adj5 embryo\$).tw.	2410
6	(vitrifi\$ adj5 blastocyst\$).tw.	1803
7	(frozen adj5 embryo\$).tw.	5929
8	(freez\$ adj5 embryo\$).tw.	2056
9	(freez\$ adj5 blastocyst\$).tw.	367
10	(frozen adj5 blastocyst\$).tw.	1032
11	FET.tw.	4837
12	freeze thawing/ or freezing/	45930
13	vitrification/	5997
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	95117
15	exp ovulation induction/	16413
16	((ovar\$ adj5 stimula\$) or (ovulat\$ adj5 induc\$)).tw.	26000
17	(endometri\$ adj2 prepar\$).tw.	1032
18	hormon\$ regimen\$.tw.	373
19	Clomiphene.tw. or Clomiphene/	11562
20	clomid.tw.	1284
21	(Tamoxifen or Letrozole).tw.	37754
22	aromatase inhibitor\$.tw.	11798
23	exp human menopausal gonadotropin/	10498
24	(Menotropin\$ or menopausal gonadotrop\$ or HMG).tw.	20554
25	exp follitropin/	64748

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26	(Follicle Stimulating Hormone or FSH or rFSH or rhFSH).tw.	57786
27	gonadorelin/	38181
28	Gonadotropin Releasing Hormone\$.tw.	16215
29	Gonadotrophin Releasing Hormone\$.tw.	3366
30	GnRH\$.tw.	29904
31	exp estrogen/	300360
32	(?estrogen\$ or ?estradiol).tw.	240982
33	exp progesterone/	104475
34	exp Progesterone/ or progesterone.tw.	145928
35	(natural\$ adj2 cycle\$).tw.	3444
36	(artificial\$ adj2 cycle\$).tw.	633
37		670
	(cycle\$ adj2 regimen\$).tw.	
38	pituitary suppression.tw.	486
39	human menopausal.tw.	2684
40	spontaneous ovulation.tw.	615
41	(HCG adj3 trigger\$).tw.	1039
42	(stimulat\$ adj3 cycle\$).tw.	5831
43	exogenous steroid\$.tw.	708
44	exogenous steroid\$.tw.	708
45	(hormone adj2 therap\$).tw.	41571
46	(endometri\$ adj2 stimulat\$).tw.	835
	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	
47	or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or	605551
	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46	
48	14 and 47	7970
49	Clinical Trial/	999716
50	Randomized Controlled Trial/	615254
51	exp randomization/	87897
52	Single Blind Procedure/	39662
53	Double Blind Procedure/	177011
54	Crossover Procedure/	64180
55	Placebo/	363424
56	Randomi?ed controlled trial\$.tw.	233156
57	Rct.tw.	37946
58	random allocation.tw.	2120
59	randomly allocated.tw.	35898
60	allocated randomly.tw.	2597
61	(allocated adj2 random).tw.	981
62	Single blind\$.tw.	25372
63	Double blind\$.tw.	216438
64	((treble or triple) adj blind\$).tw.	1215
65	placebo\$.tw.	315943
66	prospective study/	617823
67	retrospective study/	946322
69	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	2142742
68	or 61 or 62 or 63 or 64 or 65 or 66 or 67	3142742
69	case study/	80054
		444700
70	case report.tw.	444799
	case report.tw. abstract report/ or letter/	1155908

73	68 not 72	3064021
74	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)	7230873
75	73 not 74	2969724
76	48 and 75	2373
77	76 – limited 2017 to 2020	1065

Cochrane Register of Controlled Trials (CENTRAL)

Set	Search	Results
1	((Endometrial Preparation OR Cycle OR Natural Cycle OR Artificial	289
	Cycle OR Modified Natural Cycle OR Stimulated Cycle) AND	
	(Pregnancy OR Pregnancy Outcomes OR Clinical Pregnancy OR Live	
	Birth)) – Limited to 2017-2020	

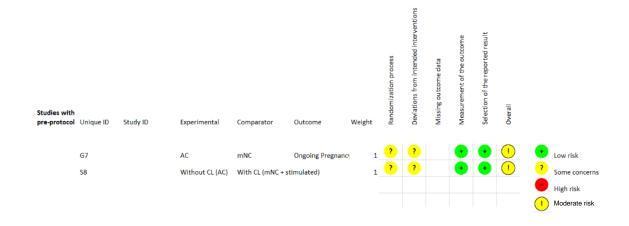
CINAHL

Set	Search	Results
1	MM Cryopreservation+	1,545
2	TX Cryopreserv* N7 embryo*	792
3	TX Cryopreserv* N7 blastocyst*	80
4	MM Freezing	229
5	TX vitrification N7 embryo*	124
6	TX vitrification N7 blastocyst*	58
7	TX frozen N5 embryo*	1,186
8	TX freez* N5 embryo*	360
9	TX freez* N5 blastocyst*	22
10	TX frozen N5 blastocyst*	128
11	TX FET	1,353
12	(TX FET) AND (S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11)	1,353
13	MM ovulation induction	973
14	TX (ovar* N5 stimula*) or (ovulat* N5 induct*)	3,738
15	TX (endometri* N2prepar*)	181
16	MM Clomiphene	250
17	TX Clomiphene or TX clomid	1,128
18	TX Menotropin* or menopausal gonadotrop* or HMG)	3,785
19	MM Follicle-Stimulating Hormone	602
20	TX Follicle Stimulating Hormone or FSH	6,532
21	MM Gonadorelin	989
22	MM Pituitary Hormone Release Inhibiting Hormones	3
23	TX Gonadotrop?in-Releasing Hormone*	344
24	TX GnRH*	2,961
25	MM Estrogens	3,969
26	TX oestrogen or estrogen	46,066
27	MM Progesterone	1,914
28	TX Progesterone	17,782
29	TX natural* N2 cycle*	1,104
30	TX (artificial* N2 cycle*)	137

31	TX (cycle* N2 regimen*)	626
32	TX pituitary suppression	472
33	TX spontaneous* ovulat*	145
34	TX stimulat* N3 cycle	1,335
35	((TX stimulat* N3 cycle OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34)) AND (S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34)	65,832
	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7OR S8 OR S9	4,623
36	OR S10 OR S11	,
37	(35 AND 36)	2,453
38	MH Clinical Trials+	303,701
39	PT Clinical trial	107,329
40	TX clinic* n1 trial*	393,652
41	TX(singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl*n1 mask*))	1,177,377
42	TX randomi* control *trial*	298,795
43	MH "Random Assignment"	63,059
44	TX random* allocat*	22,292
45	TX placebo*	125,194
46	MH Placebos	12,837
47	MH Quantitative Studies	27,500
48	TX allocat* random*	22,292
49	S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48	1,648,483
50	S37 AND S49	817
51	S37 AND S49	225
52	51 – Limited 2017-2020	158

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Supplementary File 2 - Supplementary Table 2: Quality of Randomised Controlled Trials using the Revised Cochrane Risk-of-Bias tool 2



Greco 2016:

Domain	Signalling question	Response	Comments
	1.1 Was the allocation sequence random?	Y	Two hundred thirty-six patients were included in the study and randomized in two groups according to computer- generated, not cancelled, simple randomization list with allocation assignment.
Bias arising from the randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Ν	Both the patient and the clinicians were informed of the assigned treatment. Difficult to conceal due to the nature of the intervention.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Ν	Baseline characteristics of the patients were not significantly different.
	Risk of bias judgement	Some concerns	
	2.1 Were participants aware of their assigned intervention during the trial?	Y	Both pateints and clinicians were aware of the assigned intervention. However, due to the nature of the intervention
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	it would have been difficult to conceal.
Bias due to deviations	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
from intended interventions	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		
Interventions	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	NA	
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	Missing data was accounted for e.g. premature LH surge, inadequate endometrial thickness
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
Bias due to missing outcome data	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement		
	4.1 Was the method of measuring the outcome inappropriate?	Ν	Live birth rates is an appropriate outcome measurement
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Ν	Definitions used for the measurement of outcomes was th same in both groups
Bias in measurement of	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	Probably not, as the outcomes are objective rather than subjective
the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
	5.1 were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
Bias in selection of the	5.2 multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
reported result	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

Sheikhi 2018:

Domain	Signalling question	Response	Comments
	1.1 Was the allocation sequence random?	Y	The randomization was done at the start of the cycle sequential numbering based on a computer-generat
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	N	that had been prepared at the Statistics Center of th University of Medical Science and sent to them.
Bias arising from the randomization process	1.3 Did baseline differences between intervention groups suggest a problem with the	N	Both participants and clinicians were aware of the treatment allocation. Baseline characteristics were fairly similar across b
	randomization process? Risk of bias judgement	Some concerns	treatment groups. Difficult to implement blinding and concealment due nature of the intervention.
	2.1 Were participants aware of their assigned intervention during the trial?	Y	
	2.2 Were carers and people delivering the interventions aware of participants' assigned	Y	Yes, as it is difficult to blind participants and clinician to the nature of the intervention
	intervention during the trial? 2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NA	
Bias due to deviations from intended	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	PY	Seven women were lost to follow-up (with explaination
interventions	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that	NA	
	could have affected participants' outcomes? 2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		
	Risk of bias judgement	Some concerns	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome	NA	
Bias due to missing	data? 3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
outcome data	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true	NA	-
	^{value?} Risk of bias judgement		
	4.1 Was the method of measuring the outcome inappropriate?	PN	Live births would have been a better measure of out however as pregnancy loss after 20 weeks is very ra still an appropriate outcome.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Outcome measurements are objective rather than subjective due to the nature of the study.
Bias in measurement of	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	
the outcome	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	Outcome measurements are objective rather than subjective due to the nature of the study.
	Risk of bias judgement	Low	
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	
Bias in selection of the	multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN	
reported result	5.3 multiple eligible analyses of the data?	PN	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

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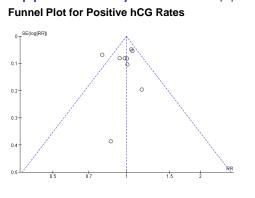
Supplementary File 3 - Supplementary Table 3: Quality of Observational Studies using the Newcastle-Ottawa Scale

Authors		Alur-Gupta et al, 2018	Cardenas Armas et al, 2019	Chang et al, 2011	Givens et al, 2009	Le et al, 2017	Levi Setti et al, 2020	Pakes et al, 2020
	Item							
Α	Selection							
	Exposed cohort is truly representative of the average	-	-	•	-	•	•	
	Selection of the non-exposed cohort from the same community	•	-	•	•	•	•	C
	Exposure ascertained by a secure record or interview	•	•	•	+	•	•	•
	Demonstration of outcome of interest was not present at the start of the study	•	+	•	+	•	•	•
В	Comparability*							
	Study controls for additional variables	+	+	•	•	÷	•	•
С	Outcome							
	Follow-up was adequate for outcome to occur	•	•	-	+	•	•	•
	Complete follow-up of all subjects was accounted for	+	+	•	+	•	•	9
	Subjects lost to follow up were unlikely to introduce bias	÷	•	•	+	•	•	•
	Score (_/9)	6	7	7	5	6	6	6
	Conversion to AHRQ Standards	fair	good	good	fair	fair	fair	fa

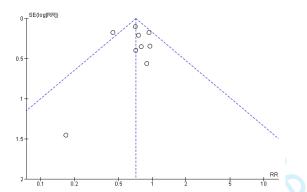
AHRQ, Agency for Healthcare Research and Quality

*Comparability may have up to a maximum of 2 points

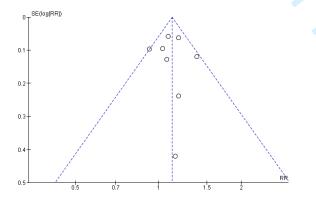
Supplementary File 4 - Supplementary Figure 1: Funnel Plot Analyses Funnel Plot for Positive hCG Rates Funnel Plot for Live Birth Rates

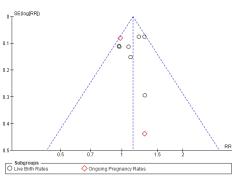


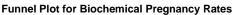
Funnel Plot for Clinical Pregnancy Rates

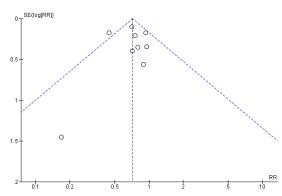


Funnel Plot for Clinical Pregnancy Rates – Sensitivity Analysis

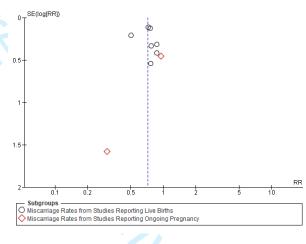












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7 of 42	BMJ Open
of positive hCG, clinical pregnancy	tary Figure 2: Meta-analysis comparing rates and live births in cycles with and without a
corpus luteum – separated by stud	y design
Positive hCG Rates	
With CL Without CL Risk Ratio Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl 1.1.1 Positive b-hCG (Randomised Controlled Trials) Greco 2016 68 109 70 113 4.3% 1.01 [0.82, 1.24] Sheikhi 2018 10 57 12 59 0.7% 0.86 [0.40, 1.84]	Risk Ratio
$\begin{array}{llllllllllllllllllllllllllllllllllll$	
Total (95% CI) 6138 3491 100.0% 1.00 [0.95, 1.05] Total events 2690 1737 Heterogeneity: Chiř = 13.86, dř = 8 (P = 0.09); P = 42%	5 0.7 1 1.5 2 Favours no CL Favours CL

Clinical Pregnancy Rates

Clinical Pregna	ancy Rat	es				
	With CL	Withou	it CL		Risk Ratio	Risk Ratio
Study or Subgroup				Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.1.1 Clinical Pregnan (
Greco 2016	59 1		113		1.07 [0.83, 1.38]	
Sheikhi 2018		57 9	59		1.15 [0.50, 2.62]	
Subtotal (95% CI)		56	172	11.2%	1.08 [0.85, 1.37]	
Total events Heterogeneity: Tau ² = 0.	69 00: 058-0.00	66	0.07\-1	z _ 00/		
Test for overall effect: Z =			0.07), 1	-= 0.%		
reation overall ellect. 2 -	- 0.02 (1 - 0.3	"				
2.1.2 Clinical Pregnancy	y (Cohort Stud	ies)				
Alur-Gupta 2018	55 1	04 523	917	12.9%	0.93 [0.77, 1.12]	
Cardenas Armas 2019		32 60	175		1.18 [0.74, 1.89]	+•
Chang 2011	186 4	44 62	204	10.5%	1.38 [1.09, 1.74]	
Givens 2009	284 8	58 105	261	13.7%	0.82 [0.69, 0.98]	
Le 2017	107 1		181		1.03 [0.86, 1.25]	_ + _
Levi Setti 2020	930 23		584		1.09 [0.97, 1.22]	+
Pakes 2020	627 20		997		1.18 [1.05, 1.34]	
Subtotal (95% CI)	59		3319	88.8%	1.06 [0.94, 1.20]	•
Total events	2202	1322				
Heterogeneity: Tau ² = 0.			= 0.005);)	
Test for overall effect: Z =	= 0.96 (P = 0.3	3)				
Total (95% CI)	61	38	3491	100.0%	1.06 [0.96, 1.18]	•
Total events	2271	1388	- 101			T
Heterogeneity: Tau ² = 0.			= 0.02)	I ² = 56%	-	
Test for overall effect: Z =			,			0.5 0.7 1 1.5 2 Favours no CL Favours CL
Test for subgroup differe			P = 0.9	0), I² = 0%		Favours no CE Favours CE
ive Birth Rate	2					
	Mariak CI	14.54			Dial: Datia	Dials Datia
Study of Subaroup	With Cl		iout CL		Risk Ratio	Risk Ratio
Study or Subgroup 5.2.1 Combined Live B					ht M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Greco 2016 Sheiliki 2010	50 10			13 4.6 59 0.8		
Sheikhi 2018 Subtotal (95% CI)	10	57 166			3% 1.29 [0.55, 3.04] 4% 1.13 [0.85, 1.50]	
Total events	60		55	12 0.4	+// 1.15 [0.05, 1.50]	
Heterogeneity: Chi ² = 0						
Test for overall effect: Z			0.70			
rescior overall effect. Z	. – 0.84 (۳ = 0	40)				
5.2.2 Combined Live B	irths and One	oina Prear	ancy (Cohort St	tudies)	
Alur-Gupta 2018	47			17 8.7		
Alui-Gupta 2016	47	104 42	20 8	0.7	->0 0.50 [0.70, 1.22]	

0.98 [0.78, 1.22] 47 104 425 917 8.7% Cardenas Armas 2019 Chang 2011 10 229 32 444 175 204 1.3% 14.8% 1.30 [0.73, 2.32] 0.98 [0.84, 1.15] 42 107 Givens 2009 245 858 77 261 11.9% 0.97 [0.78, 1.20] 93 197 722 2304 79 181 8.3% 1.08 [0.87, 1.35] 1.21 [1.04, 1.41] Levi Setti 2020 151 584 Pakes 2020 Subtotal (95% CI) 2033 5972 25.4% 94.6% 1.29 [1.11, 1.50] 1.14 [1.06, 1.22] 496 188 997 3319 1842 1069 Total events Heterogeneity: Chi² = 11.11, df = 6 (P = 0.09); l² = 46% Test for overall effect: Z = 3.40 (P = 0.0007)

55 Total (95% CI) 6138 3491 100.0% 1.14 [1.06, 1.22] 1902 1124 Total events 56 Heterogeneity: Chi² = 11.23, df = 8 (P = 0.19); l² = 29% Test for overall effect: Z = 3.50 (P = 0.0005) 57 Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%

58 CL, Corpus luteum; CI, Confidence Interval

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Le 2017

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Supplementary File 6 - Supplementary Figure 3: Meta-analysis comparing rates of pregnancy losses in cycles with and without a corpus luteum – separated by study design

Biochemical Pregnancy Rates (Early Miscarriage)

Diochemical Fregua	ncy Nat	63 (L		scarrie	age)		
	With (Withou			Risk Ratio	Risk Ratio
Study or Subgroup						M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
6.1.1 Biochemical Preg							
Greco 2016	9	68	13	70	3.5%	0.71 [0.33, 1.56]	
Sheikhi 2018	0	10	3	12	0.9%	0.17 [0.01, 2.93]	
Subtotal (95% CI)		78		82	4.4%	0.60 [0.29, 1.27]	
Total events	9		16				
Heterogeneity: Chi ² = 0.9 Test for overall effect: Z =			3), I= 0%	5			
6.1.2 Biochemical Preg	nancy (Co	hort St	udies)				
Alur-Gupta 2018	8	64	79	602	4.2%	0.95 [0.48, 1.88]	
Cardenas Armas 2019	3	16	16	76	1.5%	0.89 [0.29, 2.70]	
Chang 2011	43	229	45	107	16.9%	0.45 [0.31, 0.63]	_ _
Givens 2009	83	369	34	141	13.6%	0.93 [0.66, 1.32]	_ _
Le 2017	13	120	15	110	4.3%	0.79 [0.40, 1.59]	
Levi Setti 2020	82	1012	26	243	11.6%	0.76 [0.50, 1.15]	-++
Pakes 2020	175	802	116	376	43.5%	0.71 [0.58, 0.86]	
Subtotal (95% CI)		2612		1655	95.6%	0.72 [0.62, 0.82]	•
Total events	407		331				
Heterogeneity: Chi ² = 10				1%			
Test for overall effect: Z =	: 4.72 (P ≺	0.0000	01)				
Total (95% CI)		2690		4737	100.0%	0.71 [0.62, 0.82]	
Total events	416	2090	347	1/3/	100.0%	0.71 [0.02, 0.02]	\bullet
Heterogeneity: Chi ² = 11		/D = 0 ·		004			
Test for overall effect: Z =				0 70			0.1 0.2 0.5 1 2 5 1
Test for subgroup differe				P = 0.66) F= 0%		Favours no CL Favours CL
Correction caparoup amore		. 0.20	, ar = 1 (r	- 0.00	7.1 - 0.0		
Miscarriage Rates							
	With	CL	Withou	It CL		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
8.1.1 Miscarriage Rates	(Random	ised C	ontrolled	Trials)			
Greco 2016	9	59	10	57	3.2%	0.87 [0.38, 1.98]	· · · · · · · · · · · · · · · · · · ·
Sheikhi 2018	0	10	1	9	0.5%		
Subtotal (95% CI)		69		66	3.6%	0.79 [0.36, 1.75]	
Total events	9		11				
Heterogeneity: Chi ² = 0.4			2); I ² = 09	6			
Test for overall effect: Z =	= 0.57 (P =	0.57)					
8.1.2 Miscarriage Rates	(Cohort S	Studies	;)				
Alur-Gunta 2018		55		523	5.8%	0.87 (0.47, 1.63)	·

	With Cl	L	Without	t CL		Risk Ratio		Risk Ratio	
Study or Subgroup	Events 1	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl	
8.1.1 Miscarriage Rates	(Randomis	ed Co	ntrolled	Trials)					
Greco 2016	9	59	10	57	3.2%	0.87 [0.38, 1.98]			
Sheikhi 2018	0	10	1	9	0.5%	0.30 [0.01, 6.62]	•		
Subtotal (95% CI)		69		66	3.6%	0.79 [0.36, 1.75]			
Total events	9		11						
Heterogeneity: Chi ² = 0.4); I² = 0%	•					
Test for overall effect: Z =	0.57 (P = 0	.57)							
8.1.2 Miscarriage Rates	(Cohort St	(aoihu							
Alur-Gupta 2018	9	55	98	523	5.8%	0.87 [0.47, 1.63]			
Cardenas Armas 2019	3	13	18	60	2.0%	0.77 [0.27, 2.23]			
Chang 2011	17	186	.0	62	2.8%	0.94 [0.39, 2.29]			
Givens 2009	41	284	30	105	13.6%	0.51 [0.33, 0.76]		_ _	
Le 2017	14	107	16	95	5.3%	0.78 [0.40, 1.51]			
Levi Setti 2020	217	930	70	217	35.3%	0.72 [0.58, 0.91]			
Pakes 2020	131	627	72	260	31.6%	0.75 [0.59, 0.97]			
Subtotal (95% CI)	2	2202		1322	96.4%	0.72 [0.63, 0.83]		◆	
Total events	432		310						
Heterogeneity: Chi ² = 3.7				•					
Test for overall effect: Z =	4.44 (P < 0	1.00001	1)						
Total (95% CI)	2	2271		1388	100.0%	0.72 [0.63, 0.83]		•	
Total events	441		321						
Heterogeneity: Chi ² = 4.2	5, df = 8 (P	= 0.83)); I ² = 0%	,			0.1	0.2 0.5 1 2 5	10
Test for overall effect: Z =	4.46 (P < 0	.00002	1)				0.1	Favours No CL Favours With CL	10
Test for subgroup differe	nces: Chi ² =	= 0.05,	df = 1 (F	= 0.82), I ^z = 0%				

CL, Corpus luteum; CI, Confidence Interval

Supplementary File 7 - Supplementary Figure 4: Meta-analysis comparing clinical pregnancy rates in cycles with and without a corpus luteum – sensitivity analysis

6		With CL	Without CL		Risk Ratio	Risk Ratio
7	Study or Subgroup	Events Tota		Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
8	Alur-Gupta 2018	55 10	4 523 917	10.0%	0.93 [0.77, 1.12]	
9	Cardenas Armas 2019 Obergr 2014	13 3			1.18 [0.74, 1.89]	
10	Chang 2011 Greco 2016	186 44 59 10			1.38 [1.09, 1.74] 1.07 [0.83, 1.38]	
11	Le 2017	107 19			1.03 [0.86, 1.25]	_ _
12	Levi Setti 2020	930 230	4 217 584	32.4%	1.09 [0.97, 1.22]	
	Pakes 2020	627 203			1.18 [1.05, 1.34]	
13	Sheikhi 2018	10 5	7 9 59	0.8%	1.15 [0.50, 2.62]	
14	Total (95% CI)	528	3230	100.0%	1.12 [1.05, 1.20]	◆
15	Total events	1987	1283			
16	Heterogeneity: Chi ² = 8.7					0.5 0.7 1 1.5 2
17	Test for overall effect: Z =		-			Favours No CL Favours With CL
18						
19	CL, Corpus Luteum; CI,	Confidence i	nterval			
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PRISMA Checklists

PRISMA Checklists	5	BMJ Open	6/bmjopen-2021-051489 on 26 Ap	
Section/topic	#	Checklist item	nil 2022.	Reported on page #
TITLE			Dow	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	hloaded	Page 2 (line 22-24)
ABSTRACT			fror	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; eligibility criteria, participants, and interventions; study appraisal and synthesis i limitations; conclusions and implications of key findings; systematic review register the second structure of the second structu	ethods; results;	Page 5 (line 1 to 60) to page 6 line 1 to 5)
INTRODUCTION			ope	
Rationale	3	Describe the rationale for the review in the context of what is already known.	h.bmj.com	Page 7 (line 2 to 60) to page 8 (line 1 to 7)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participation interventions, comparisons, outcomes, and study design (PICOS).	igicipants, ≩	Page 8 (line 12 to 23)
METHODS			rii 23	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web a available, provide registration information including registration number.	address), and, if	Page 8 (line 27)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report chara considered, language, publication status) used as criteria for eligibility, giving ra	To ale	Page 8 (line 12 to 38; line 52 to 58) to Page 9 (line 2 to 5)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contato identify additional studies) in the search and date last searched.	אל with study authors איז with study authors איז איז איז איז איז איז איז איז איז איז	Page 8 (line 25 to 36)
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		BMJ Open 50 PP-2021	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementa file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 8 (line 44 to 58) to page 9 (line 3 to 5)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independer by, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10 (line 52 to 50)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 9 (line 13 to 50)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10 (line 1 to 11; line 2 to 33)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 10 (line 22 to 25)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done including measures of consistency (e.g., I ²) for each meta-analysis.	Page 10 (line 14 to 26)
		3	-
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 10 (line 3 to 10; line 2 to 25) Supplementa y file 8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 9 (line 26 to 30; pag 10 line 33)
RESULTS		g ue	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 10 (line 37 to 47) Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., stud size, PICOS, follow-up period) and provide the citations.	Table 1 (pag 12) Page 22 (line

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		051489 or	22 to 60) to Page 23 (line 1 to 17)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level a왌essment (see item 12).	Table 1 (page 12);Supplementa y file 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Refer to Figures 2 & 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	 Page 14 (line 2 to 10) Page 15 (line 1 60) Page 16 (line 1 to 60) Page 17 (line 1 to 60) Page 18 (line 1 to 7)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 10 (line 3 to 10; line 2 to 25) Supplementa y file 8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 16 (line 12 to 18; line 26; line 48 to 52) Supplementa y file 5
DISCUSSION		rote	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main officome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 18 (line 12 to 18

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		BMJ Open BMJ Open Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g.,	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 18 46 to 60) Page 20 39 to 54)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for	Page 21 3 to 18)
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 6 (I to 5)
		funders for the systematic review.	