RBMO

Approaches to frozen embryo transfer: a Canadian Fertility and Andrology Society guideline

BIOGRAPHY

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KEY MESSAGE

Elective frozen embryo transfer cycles are not superior to fresh transfers in terms of live birth rate or pregnancy loss. Moreover, neither the type of endometrial preparation (ovulatory versus artificial) nor the route of progesterone administration appears to significantly impact IVF outcomes.

ABSTRACT

This guideline provides evidence-based recommendations, drawn exclusively from recent randomized control trials, for the clinical management of frozen embryo transfers (FET). In Canada, the incidence of freeze-all cycles has increased from 24.0% to 78.4% over the last decade. While a freeze-all strategy can be a pivotal tool for preventing ovarian hyperstimulation syndrome, the available data do not support its routine use for improving live birth rates, reducing pregnancy loss or enhancing obstetric outcomes in the general IVF population. Similarly, ovulatory FET cycles do not offer advantages over artificial FET cycles for live birth or pregnancy loss, and current evidence remains conflicting for obstetric and perinatal outcomes. The route of progesterone administration in artificial FET cycles does not significantly affect live birth or pregnancy loss rates. FET approaches should be individualized based on patient characteristics and clinical context, and further research is necessary to optimize outcomes and inform best practices.

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KEY WORDS
Artificial cycle
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SUMMARY STATEMENTS AND RECOMMENDATIONS

TABLE 1A QUALITY OF EVIDENCE ASSESSMENT AND RECOMMENDATION DEVELOPMENT PERFORMED USING THE GRADING OF RECOMMENDATIONS ASSESSMENT, DEVELOPMENT AND EVALUATION (GRADE)

Recommendations	Certainty, adapted from (GRADE)	Recommendation strength
A freeze-all strategy should be used in patients at risk of OHSS	High ●●●●	A
A freeze-all strategy should not be used to improve live birth rate	Low ●●●○○	A*
A freeze-all strategy should not be used to reduce pregnancy loss	Low ●●○○	A*
A freeze-all strategy should not be used to improve obstetric outcomes	Moderate ●●●○	A
FET with routine pituitary down-regulation with GnRH agonists should not be used to increase live births	Low ●●○○	B
FET with routine pituitary down-regulation with GnRH agonists should not be used to decrease pregnancy loss	Low ●●○○	B
In adenomyosis patients there are insufficient data to recommend pituitary down-regulation (Statement)	Very low ●○○○	C
Compared with artificial FET cycles: Ovulatory FET cycles do not increase live birth rate (Statement)	Low ●●○○	B
Compared with artificial FET cycles: Ovulatory FET cycles do not decrease the risk of pregnancy loss (Statement)	Low ●●○○	B
Compared with artificial FET cycles: Ovulatory FET cycles do not decrease the risk of obstetric and perinatal complications	Moderate ●●●○	B
Route of progesterone administration does not impact live birth rate or pregnancy loss in artificial FET (Statement)	Low ●●○○	B

* Despite low certainty of evidence for live birth rate and pregnancy, the clear lack of benefit, increased risk of hypertensive disorders of pregnancy, greater resource use and delayed time to pregnancy justify a strong recommendation (Level A) against routine FET for all patients.

FET, frozen embryo transfer; GnRH, gonadotrophin-releasing hormone; OHSS, ovarian hyperstimulation syndrome.

TABLE 1B GRADING DEFINITIONS FOR STRENGTH OF EVIDENCE

Strength of evidence	Definition
Grade A	High confidence in the evidence. A larger or further study would be very unlikely to change the reported effect. Most evidence was supported by well-constructed RCT or extremely strong and consistent observational studies with generalizable results, sufficient sample sizes for the study design, adequate controls, a definitive conclusion and minimal risk of bias
Grade B	Moderate confidence in the evidence. Larger or further studies would not be likely to change the reported effect but might more precisely identify the magnitude. Most evidence comprised RCT with potential weaknesses, including small sample size or low generalizability, or moderately strong and consistent observational studies with reasonably consistent results, sufficient sample sizes for the study designs, identified appropriate controls, a fairly definitive conclusion and low risk of bias
Grade C	Low confidence in the evidence. Evidence was lacking to support the conclusion based on the reported effect. Evidence comprised observational studies with significant methodological flaws and/or inconsistent findings on the basis of poor evidence, inconsistent results, insufficient sample size for the study design, inability to draw a conclusion and/or a high risk of bias

RCT, randomized controlled trials.

INTRODUCTION

From 2013 to 2023 the incidence of freeze-all cycles in Canada increased from 24.0% to 78.4% (*Canadian Fertility and Andrology Society, 2024*), largely due to the increasing use of preimplantation genetic testing for aneuploidies, which accounts for almost 50% of the freeze-all cycles (CFAS). Prevention of the risk of ovarian hyperstimulation syndrome (OHSS) and an improvement in vitrification techniques have also contributed to the rise in freeze-all cycles (*Nagy et al., 2020*).

Despite the increase in frozen embryo transfer (FET) use worldwide, there is no consensus on its superiority over fresh embryo transfer. Moreover, uncertainty remains regarding the optimal methods for preparing the endometrium (*De Geyter et al., 2020*; *Hsueh et al., 2023*). This guideline exclusively uses randomized controlled trials (RCT) to compare FET with fresh embryo transfer, and to evaluate which endometrial preparation protocols optimize live birth rates (LBR) and obstetric outcomes (Table 10).

METHODOLOGY

An electronic database search (CENTRAL, Embase, PubMed) was conducted for relevant clinical trials comparing fresh embryo transfer with an elective freeze-all embryo strategy and subsequent FET treatment. Additionally, articles evaluating different endometrial preparations for FET were included in this review. The search was limited to articles in English from peer-reviewed journals. To reflect current assisted reproductive technology (ART) practices, the time frame for eligibility was set to studies published after 2014, when the use of vitrification became widespread in IVF practice (*Nagy et al., 2020*). Only RCT were included in the analysis for developing the recommendations in this guideline.

Assessment of quality of evidence and development of the recommendations were performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Supplementary Table 1). Risk of bias was assessed with the Cochrane Risk of Bias assessment tool (*Higgins et al., 2011*). In addition, the trustworthiness of the included trials was evaluated using the Trustworthiness in RAndomised Controlled Trials (TRACT) checklist (*Mol et al., 2023*). The complete methodology, search strategies, sensitivity analysis, trial characteristics and risk of bias assessment can be found in Appendixes 1 and 2, Supplementary Figure 1 (the PRISMA flow chart) and Supplementary Figure 2 (the risk of bias summary).

Measurement of treatment effect and data synthesis

The Mantel–Haenszel method was used to generate odds ratios (OR) with 95% confidence intervals (CI). Meta-analyses were performed using Review Manager 5 software (https://revman.chocrane.org). A random-effects model was selected for all primary and secondary outcomes (Appendix 1).

For the outcomes of OHSS, live birth and pregnancy loss, the unit of analysis was per intention-to-treat (ITT). For obstetric outcomes such as gestational diabetes, gestational hypertension, hypertensive disorders of pregnancy (HDP), preterm birth and large or small for gestational age, the unit of analysis was also ITT; however, given that these outcomes occur in ongoing pregnancies beyond the second trimester, a complementary subanalysis was performed per live birth to account for denominator variability. Given the higher cancellation rates observed in ovulatory cycles, additional complementary per-protocol analyses were also conducted.

FRESH VERSUS FROZEN EMBRYO TRANSFER (FIGURE 1)

Eleven RCT, with over 8000 patients undergoing primary FET versus primary fresh transfer, compared live birth, pregnancy loss rates and OHSS risk (*Aflatoonian et al., 2018*; *Aghahosseini et al., 2017*; *Chen et al., 2016*; *Maheshwari et al., 2022*; *Santos-Ribeiro et al., 2020*; *Shi et al., 2018*; *Stormlund et al., 2020*; *Vuong et al., 2018*; *Wei et al., 2019*, *2025*; *Wong et al., 2021*) (Supplementary Table 2). Most patients were aged 34 years or less, and had varying diagnoses of infertility except for the studies by Aflatoonian and colleagues, Chen and collaborators and Santos-Ribeiro and colleagues, who included only patients with polycystic ovary syndrome (PCOS) or who were at risk of OHSS, respectively (*Aflatoonian et al., 2018*; *Chen et al., 2016*; *Santos-Ribeiro et al., 2020*), and Wei and co-workers, who assessed poor-prognosis patients (*Wei et al., 2025*).

Although some of the studies specifically targeted high responders, most of them had ovarian responses that felt in the normo-responder category (10–15 oocytes at egg retrieval; *Esteves et al., 2018*; *Polyzos and Sunkara, 2015*). Of the 11 studies, the average egg yield ranged from 6 to 19.6 in the FET group and 6 to 18.5 in the fresh transfer group. Only seven trials reported oestradiol concentrations at the trigger date; average oestradiol ranged from 2672 to 12,419 pmol/l in the FET group and 2714 to 12,341 pmol/l in the fresh embryo transfer group.

Studies included a mix of cleavage-stage and blastocyst transfers, with artificial endometrial preparation being most common. Progesterone dose and routes of administration varied (see Supplementary Table 2 for additional information).

OHSS risk varied from 0% to 5.8% in FET and from 0.4% to 8% in fresh embryo transfers. Freeze-all demonstrated a reduction if OHSS of almost 70% (OR 0.36, 95% CI 0.22–0.57; FIGURE 1a).

LBR in the included trials ranged from 6.8% to 49.3% for FET and 21.6% to 50.1% for fresh embryo transfer. There was no significant difference (OR 0.97, 95% CI 0.78–1.20; FIGURE 1b) between FET and fresh embryo transfer, nor were any differences observed when the analysis was restricted to blastocyst or cleavage-stage transfer (Supplementary Figure 3). However, the only study to date in poor-prognosis patients found a higher LBR with fresh transfer (*Wei et al., 2025*).

Pregnancy loss rates varied from 0% to 22.6% (overall rate 11.6%) in FET and from 3.8% to 21.1% (overall rate 11.97%) in fresh embryo transfer, without a significant difference between the groups (OR 1.04, 95% CI 0.82–1.32; FIGURE 1c).

Recommendations:

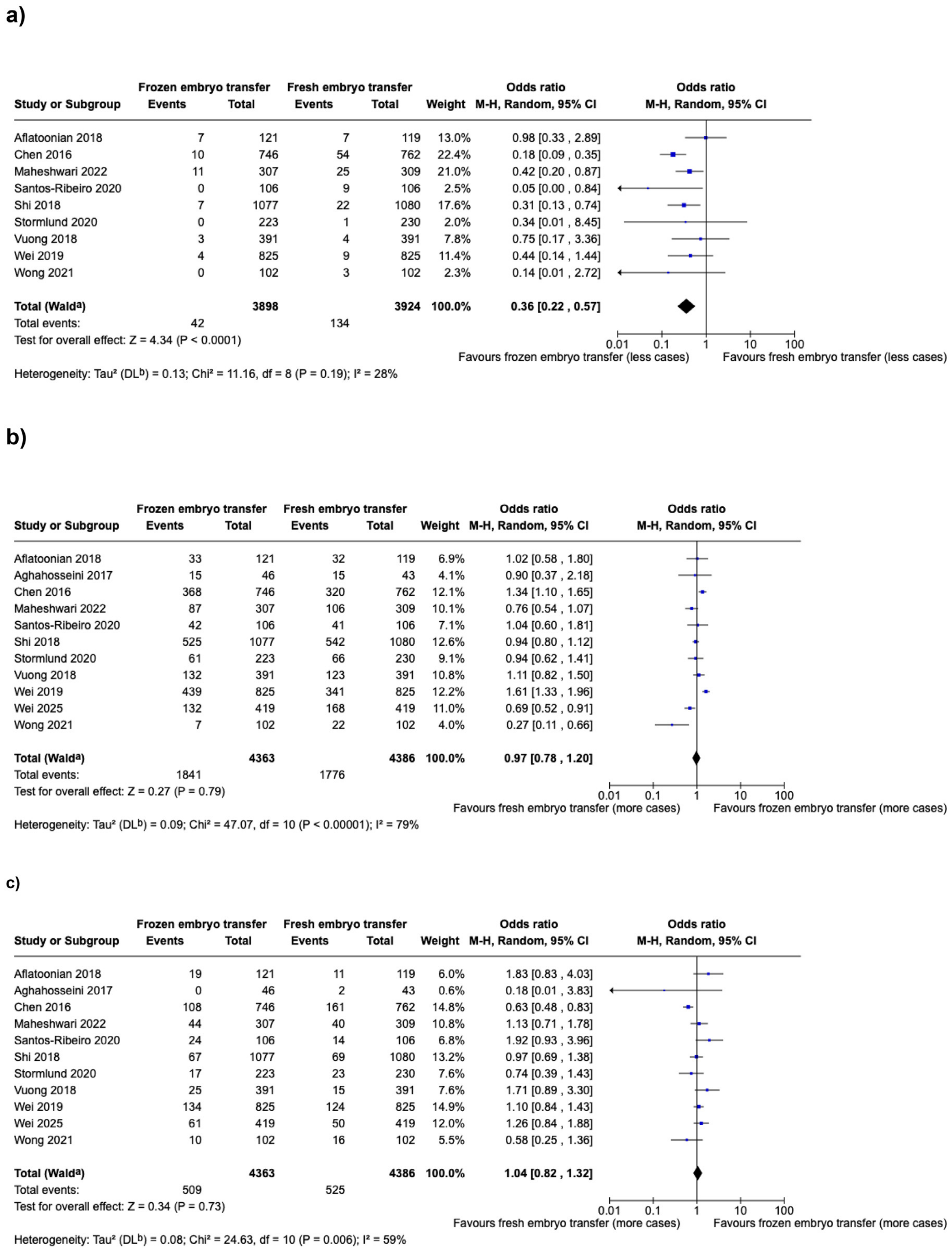
1. A freeze-all strategy should be used in patients at risk of OHSS (Grade A).
2. A freeze-all strategy should not be used to improve LBR (Grade A).
3. A freeze-all strategy should not be used to reduce pregnancy loss (Grade A).

Despite the low certainty of evidence for LBR and pregnancy loss, the clear lack of benefit, increased risk of HDP, greater resource use and delayed time to pregnancy justify a strong recommendation (Level A) against routine FET for all patients.

OBSTETRIC OUTCOMES IN FRESH EMBRYO TRANSFER VERSUS PRIMARY FET (FIGURE 2)

Eight randomized trials compared obstetric and perinatal outcomes in fresh versus frozen embryo transfer. Of these, four studies used exogeneous oestrogen and progesterone (artificial or medicated cycles) for endometrial preparation for FET (*Aflatoonian et al., 2018*; *Chen et al., 2016*; *Maheshwari et al., 2022*; *Vuong et al., 2018*) while the remaining trials used ovulatory cycles (natural or modified natural cycles) for all or most of their FET (*Shi et al., 2018* [74%]; *Stormlund et al., 2020* [99%]; *Wei et al., 2019* [64%]; *Wei et al., 2025* [59%]). Many of these patients in both groups were young (<34 years old) and had a normal body mass index (<24 kg/m^2), and around 1 in 3 had had a previous conception.

There was no difference in gestational diabetes (OR 1.08, 95% CI 0.83–1.41; FIGURE 2a), gestational hypertension (OR 1.03, 95% CI 0.63–1.68; FIGURE 2b), preterm birth (OR 1.03, 95% CI 0.83–1.29; FIGURE 2e), pre-eclampsia (overall rate 1.87% versus 1.11%; OR 1.66, 95% CI 0.87–3.19; FIGURE 2d) or large for gestational age (OR



a)

Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Aflatoonian 2018	7	121	7	119	13.0%	0.98 [0.33 , 2.89]
Chen 2016	10	746	54	762	22.4%	0.18 [0.09 , 0.35]
Maheshwari 2022	11	307	25	309	21.0%	0.42 [0.20 , 0.87]
Santos-Ribeiro 2020	0	106	9	106	2.5%	0.05 [0.00 , 0.84]
Shi 2018	7	1077	22	1080	17.6%	0.31 [0.13 , 0.74]
Stormlund 2020	0	223	1	230	2.0%	0.34 [0.01 , 8.45]
Vuong 2018	3	391	4	391	7.8%	0.75 [0.17 , 3.36]
Wei 2019	4	825	9	825	11.4%	0.44 [0.14 , 1.44]
Wong 2021	0	102	3	102	2.3%	0.14 [0.01 , 2.72]
Total (Wald[a])		**3898**		**3924**	**100.0%**	**0.36 [0.22 , 0.57]**
Total events:	42		134			

Test for overall effect: Z = 4.34 (P < 0.0001)

Heterogeneity: Tau² (DL[b]) = 0.13; Chi² = 11.16, df = 8 (P = 0.19); I² = 28%

b)

Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Aflatoonian 2018	33	121	32	119	6.9%	1.02 [0.58 , 1.80]
Aghahosseini 2017	15	46	15	43	4.1%	0.90 [0.37 , 2.18]
Chen 2016	368	746	320	762	12.1%	1.34 [1.10 , 1.65]
Maheshwari 2022	87	307	106	309	10.1%	0.76 [0.54 , 1.07]
Santos-Ribeiro 2020	42	106	41	106	7.1%	1.04 [0.60 , 1.81]
Shi 2018	525	1077	542	1080	12.6%	0.94 [0.80 , 1.12]
Stormlund 2020	61	223	66	230	9.1%	0.94 [0.62 , 1.41]
Vuong 2018	132	391	123	391	10.8%	1.11 [0.82 , 1.50]
Wei 2019	439	825	341	825	12.2%	1.61 [1.33 , 1.96]
Wei 2025	132	419	168	419	11.0%	0.69 [0.52 , 0.91]
Wong 2021	7	102	22	102	4.0%	0.27 [0.11 , 0.66]
Total (Wald[a])		**4363**		**4386**	**100.0%**	**0.97 [0.78 , 1.20]**
Total events:	1841		1776			

Test for overall effect: Z = 0.27 (P = 0.79)

Heterogeneity: Tau² (DL[b]) = 0.09; Chi² = 47.07, df = 10 (P < 0.00001); I² = 79%

c)

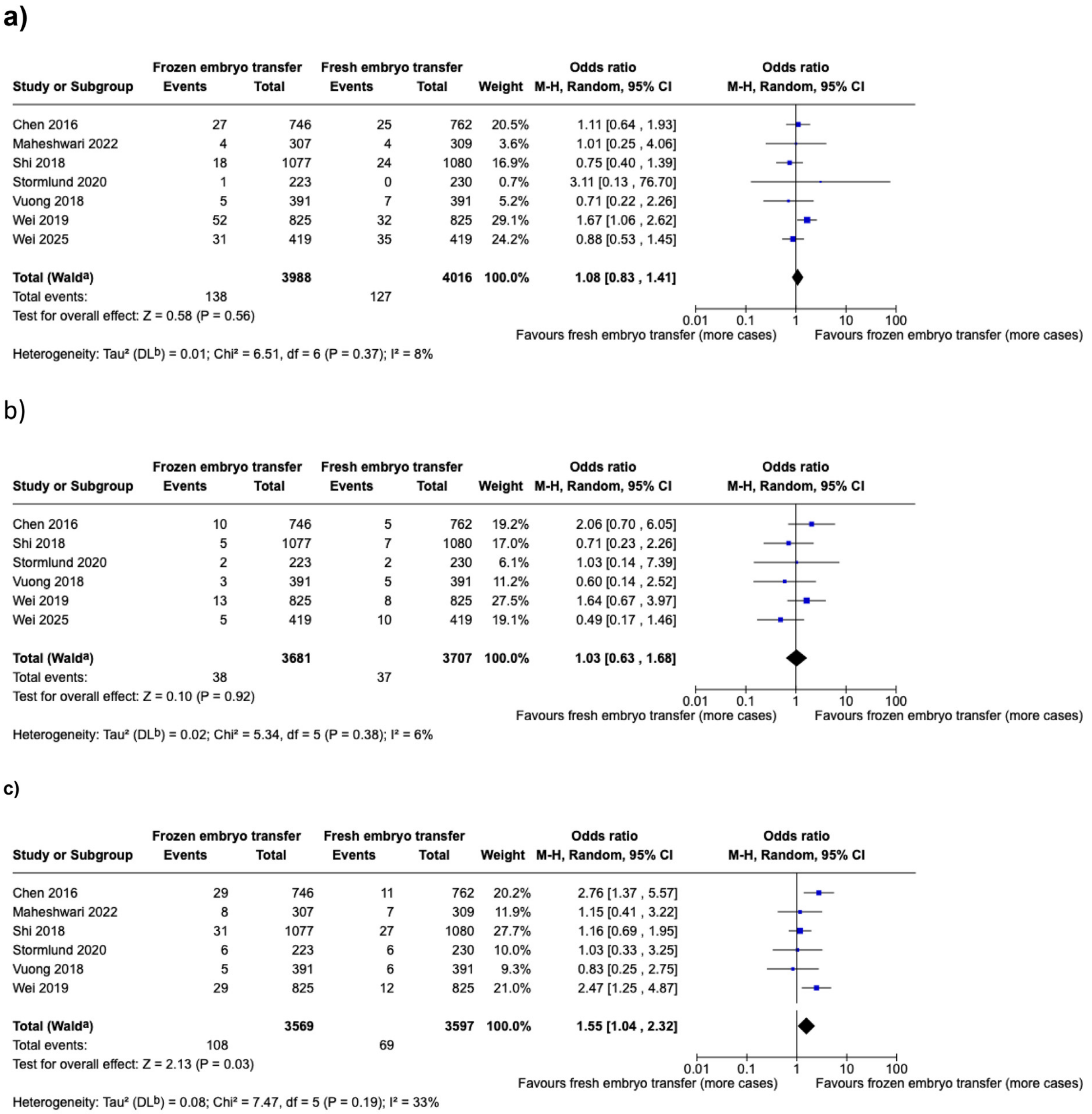
Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Aflatoonian 2018	19	121	11	119	6.0%	1.83 [0.83 , 4.03]
Aghahosseini 2017	0	46	2	43	0.6%	0.18 [0.01 , 3.83]
Chen 2016	108	746	161	762	14.8%	0.63 [0.48 , 0.83]
Maheshwari 2022	44	307	40	309	10.8%	1.13 [0.71 , 1.78]
Santos-Ribeiro 2020	24	106	14	106	6.8%	1.92 [0.93 , 3.96]
Shi 2018	67	1077	69	1080	13.2%	0.97 [0.69 , 1.38]
Stormlund 2020	17	223	23	230	7.6%	0.74 [0.39 , 1.43]
Vuong 2018	25	391	15	391	7.6%	1.71 [0.89 , 3.30]
Wei 2019	134	825	124	825	14.9%	1.10 [0.84 , 1.43]
Wei 2025	61	419	50	419	12.0%	1.26 [0.84 , 1.88]
Wong 2021	10	102	16	102	5.5%	0.58 [0.25 , 1.36]
Total (Wald[a])		**4363**		**4386**	**100.0%**	**1.04 [0.82 , 1.32]**
Total events:	509		525			

Test for overall effect: Z = 0.34 (P = 0.73)

Heterogeneity: Tau² (DL[b]) = 0.08; Chi² = 24.63, df = 10 (P = 0.006); I² = 59%

FIGURE 1 Does a freeze-all strategy improve assisted reproductive technology outcomes? Forest plots comparing fresh embryo transfer versus frozen embryo transfer assessing (a) rates of ovarian hyperstimulation syndrome, (b) live birth rate for the primary transfer, and (c) risk of pregnancy loss in the primary transfer. Odds ratios with 95% CI were calculated using the Mantel–Haenszel (M-H) method under a random-effects model. [a] Confidence intervals (CI) calculated by a Wald-type method. [b] Tau^2 calculated by the DerSimonian and Laird method.

1.41, 95% CI 0.68–2.91; FIGURE 2f). However, FET was associated with increased rates of HDP (overall rate 3.03% versus 1.92%; OR 1.55, 95% CI 1.04–2.32; FIGURE 2c), while fresh embryo transfer was associated with increased rates of small-for-gestational age newborns (overall rate 2.26% versus 3.86%; OR 0.51, 95% CI 0.30–0.88; FIGURE 2g).



a)

Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Chen 2016	27	746	25	762	20.5%	1.11 [0.64 , 1.93]
Maheshwari 2022	4	307	4	309	3.6%	1.01 [0.25 , 4.06]
Shi 2018	18	1077	24	1080	16.9%	0.75 [0.40 , 1.39]
Stormlund 2020	1	223	0	230	0.7%	3.11 [0.13 , 76.70]
Vuong 2018	5	391	7	391	5.2%	0.71 [0.22 , 2.26]
Wei 2019	52	825	32	825	29.1%	1.67 [1.06 , 2.62]
Wei 2025	31	419	35	419	24.2%	0.88 [0.53 , 1.45]
Total (Wald[a])		**3988**		**4016**	**100.0%**	**1.08 [0.83 , 1.41]**
Total events:	138		127			

Test for overall effect: Z = 0.58 (P = 0.56)

Heterogeneity: Tau^2 (DL[b]) = 0.01; Chi^2 = 6.51, df = 6 (P = 0.37); I^2 = 8%

b)

Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Chen 2016	10	746	5	762	19.2%	2.06 [0.70 , 6.05]
Shi 2018	5	1077	7	1080	17.0%	0.71 [0.23 , 2.26]
Stormlund 2020	2	223	2	230	6.1%	1.03 [0.14 , 7.39]
Vuong 2018	3	391	5	391	11.2%	0.60 [0.14 , 2.52]
Wei 2019	13	825	8	825	27.5%	1.64 [0.67 , 3.97]
Wei 2025	5	419	10	419	19.1%	0.49 [0.17 , 1.46]
Total (Wald[a])		**3681**		**3707**	**100.0%**	**1.03 [0.63 , 1.68]**
Total events:	38		37			

Test for overall effect: Z = 0.10 (P = 0.92)

Heterogeneity: Tau^2 (DL[b]) = 0.02; Chi^2 = 5.34, df = 5 (P = 0.38); I^2 = 6%

c)

Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Chen 2016	29	746	11	762	20.2%	2.76 [1.37 , 5.57]
Maheshwari 2022	8	307	7	309	11.9%	1.15 [0.41 , 3.22]
Shi 2018	31	1077	27	1080	27.7%	1.16 [0.69 , 1.95]
Stormlund 2020	6	223	6	230	10.0%	1.03 [0.33 , 3.25]
Vuong 2018	5	391	6	391	9.3%	0.83 [0.25 , 2.75]
Wei 2019	29	825	12	825	21.0%	2.47 [1.25 , 4.87]
Total (Wald[a])		**3569**		**3597**	**100.0%**	**1.55 [1.04 , 2.32]**
Total events:	108		69			

Test for overall effect: Z = 2.13 (P = 0.03)

Heterogeneity: Tau^2 (DL[b]) = 0.08; Chi^2 = 7.47, df = 5 (P = 0.19); I^2 = 33%

FIGURE 2 Obstetric outcomes in fresh embryo transfer versus primary frozen embryo transfer (FET). Forest plots comparing fresh embryo transfer versus FET assessing (a) gestational diabetes mellitus, (b) gestational hypertension, (c) hypertensive disorders of pregnancy, (d) pre-eclampsia, (e) preterm birth, (f) large for gestational age, and (g) small for gestational age. Odds ratios with 95%CI were calculated using the Mantel–Haenszel (M-H) method under a random-effects model. [a] Confidence intervals (CI) were calculated by a Wald-type method. [b] Tau^2 was calculated by the DerSimonian and Laird method.

Given that absolute differences are small and that outcomes are not consistently better with fresh compared with frozen embryo transfer (HDP risk difference [RD] +1.11%, 95% CI +0.39% to +1.83%; small for gestational age (RD) −1.6%, 95% CI −2.62% to −0.58%), it is not possible to recommend a freeze-all strategy to improve obstetric and perinatal outcomes.

A duplicate supplementary analysis for obstetric outcomes using per live birth was also carried out, showing similar results as per the ITT analysis (Supplementary Figure 4).

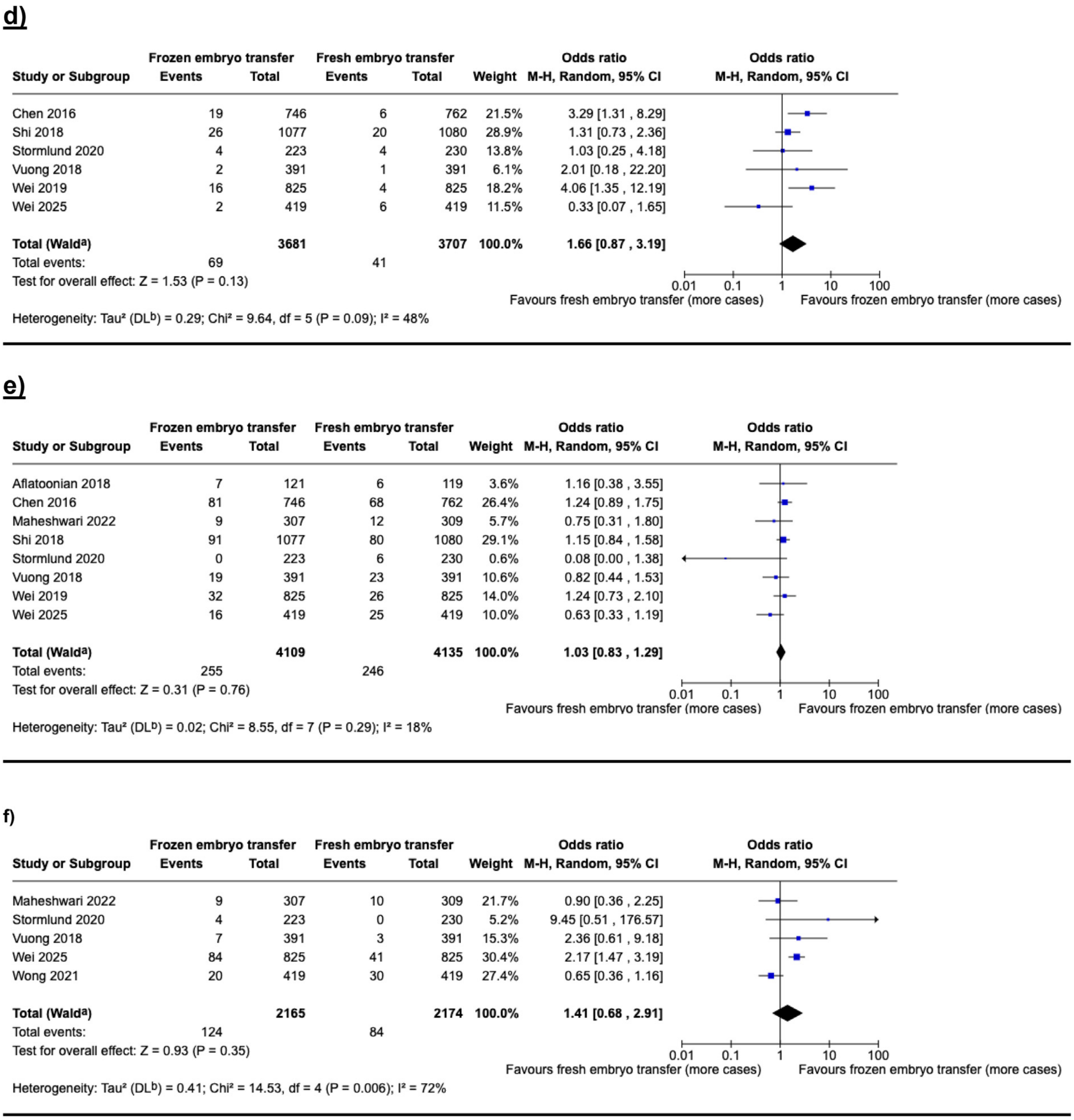
Recommendation:

4. A freeze-all strategy should not be used to improve obstetric outcomes (Grade A).

HOW CAN WE OPTIMIZE FET OUTCOMES?

Pituitary down-regulation before FET (FIGURE 3)

Pituitary down-regulation generally involves the administration of gonadotrophin-releasing hormone (GnRH) agonists prior to starting oestrogen, in order to suppress spontaneous ovarian activity including ovulation.



d)

Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Chen 2016	19	746	6	762	21.5%	3.29 [1.31 , 8.29]
Shi 2018	26	1077	20	1080	28.9%	1.31 [0.73 , 2.36]
Stormlund 2020	4	223	4	230	13.8%	1.03 [0.25 , 4.18]
Vuong 2018	2	391	1	391	6.1%	2.01 [0.18 , 22.20]
Wei 2019	16	825	4	825	18.2%	4.06 [1.35 , 12.19]
Wei 2025	2	419	6	419	11.5%	0.33 [0.07 , 1.65]
Total (Wald^a)		**3681**		**3707**	**100.0%**	**1.66 [0.87 , 3.19]**
Total events:	69		41			

Test for overall effect: Z = 1.53 (P = 0.13)

Heterogeneity: Tau^2 (DL^b) = 0.29; Chi^2 = 9.64, df = 5 (P = 0.09); I^2 = 48%

e)

Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Aflatoonian 2018	7	121	6	119	3.6%	1.16 [0.38 , 3.55]
Chen 2016	81	746	68	762	26.4%	1.24 [0.89 , 1.75]
Maheshwari 2022	9	307	12	309	5.7%	0.75 [0.31 , 1.80]
Shi 2018	91	1077	80	1080	29.1%	1.15 [0.84 , 1.58]
Stormlund 2020	0	223	6	230	0.6%	0.08 [0.00 , 1.38]
Vuong 2018	19	391	23	391	10.6%	0.82 [0.44 , 1.53]
Wei 2019	32	825	26	825	14.0%	1.24 [0.73 , 2.10]
Wei 2025	16	419	25	419	10.0%	0.63 [0.33 , 1.19]
Total (Wald^a)		**4109**		**4135**	**100.0%**	**1.03 [0.83 , 1.29]**
Total events:	255		246			

Test for overall effect: Z = 0.31 (P = 0.76)

Heterogeneity: Tau^2 (DL^b) = 0.02; Chi^2 = 8.55, df = 7 (P = 0.29); I^2 = 18%

f)

Study or Subgroup	Frozen embryo transfer Events	Frozen embryo transfer Total	Fresh embryo transfer Events	Fresh embryo transfer Total	Weight	Odds ratio M-H, Random, 95% CI
Maheshwari 2022	9	307	10	309	21.7%	0.90 [0.36 , 2.25]
Stormlund 2020	4	223	0	230	5.2%	9.45 [0.51 , 176.57]
Vuong 2018	7	391	3	391	15.3%	2.36 [0.61 , 9.18]
Wei 2025	84	825	41	825	30.4%	2.17 [1.47 , 3.19]
Wong 2021	20	419	30	419	27.4%	0.65 [0.36 , 1.16]
Total (Wald^a)		**2165**		**2174**	**100.0%**	**1.41 [0.68 , 2.91]**
Total events:	124		84			

Test for overall effect: Z = 0.93 (P = 0.35)

Heterogeneity: Tau^2 (DL^b) = 0.41; Chi^2 = 14.53, df = 4 (P = 0.006); I^2 = 72%

FIGURE 2 Continued.

Eleven recent RCT have evaluated pituitary agonist down-regulation for FET (Supplementary Table 3). Most of these included patients with different infertility diagnoses (Chao et al., 2022; Davar et al., 2020; Ebrahimi et al., 2023; Greco et al., 2016; Li et al., 2021; Madani et al., 2019; Movahedi et al., 2018; Xu et al., 2021), while the remaining trials assessed only individuals with PCOS (Aghahoseini et al., 2020; Luo et al., 2021; Salemi et al., 2021). LBR did not differ significantly with GnRH agonist down-regulation (overall rate 37.9%, study range 18.9–49.4%) or without it (39.2%, study range 19.8–53.8%) (OR 0.95, 95% CI 0.74–1.21; FIGURE 3a). The rate of pregnancy loss was also not influenced by down-regulation (overall rate 10.3%, study range 2.9–19.5% versus overall rate 11.3%, study range 3–17.8%) (OR 0.92, 95% CI 0.70–1.21; FIGURE 3b). Similarly, no difference was found in LBR or pregnancy loss when the analysis was restricted to trials examining only PCOS patients (Supplementary Figure 5). Similar findings were reported in a recent meta-analysis by Li and colleagues (Li et al., 2023, 2024).

In patients with adenomyosis, GnRH agonist pretreatment has been shown to reduce tissue inflammation and angiogenesis, thereby creating a more favourable endometrial environment for embryo implantation (Khan et al., 2010). In this population, only one RCT has evaluated the benefit of down-regulated versus non-down-regulated FET, without evidence of an improvement in LBR (21.5% versus 20.1%, *P* = 0.89) or pregnancy loss (10.8% versus 10.8%) (Eslami Moayed et al., 2023); these findings are similar to those of the meta-analyses by Galati and collaborators and

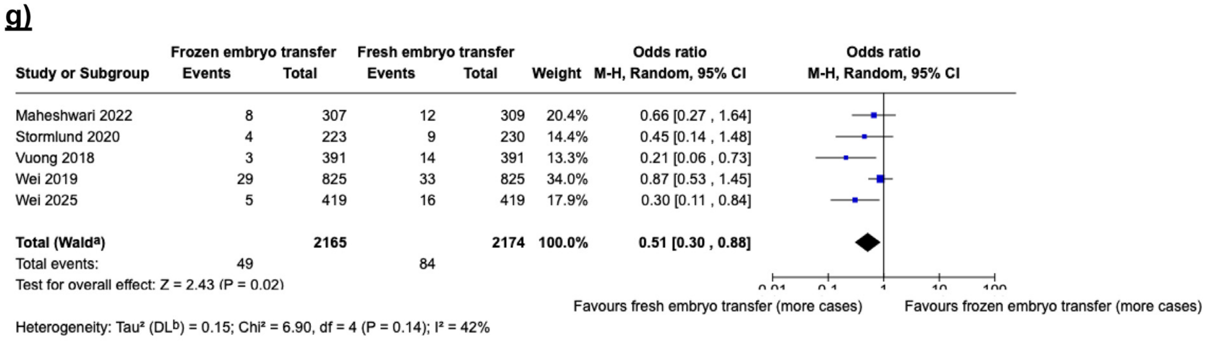


FIGURE 2 Continued.

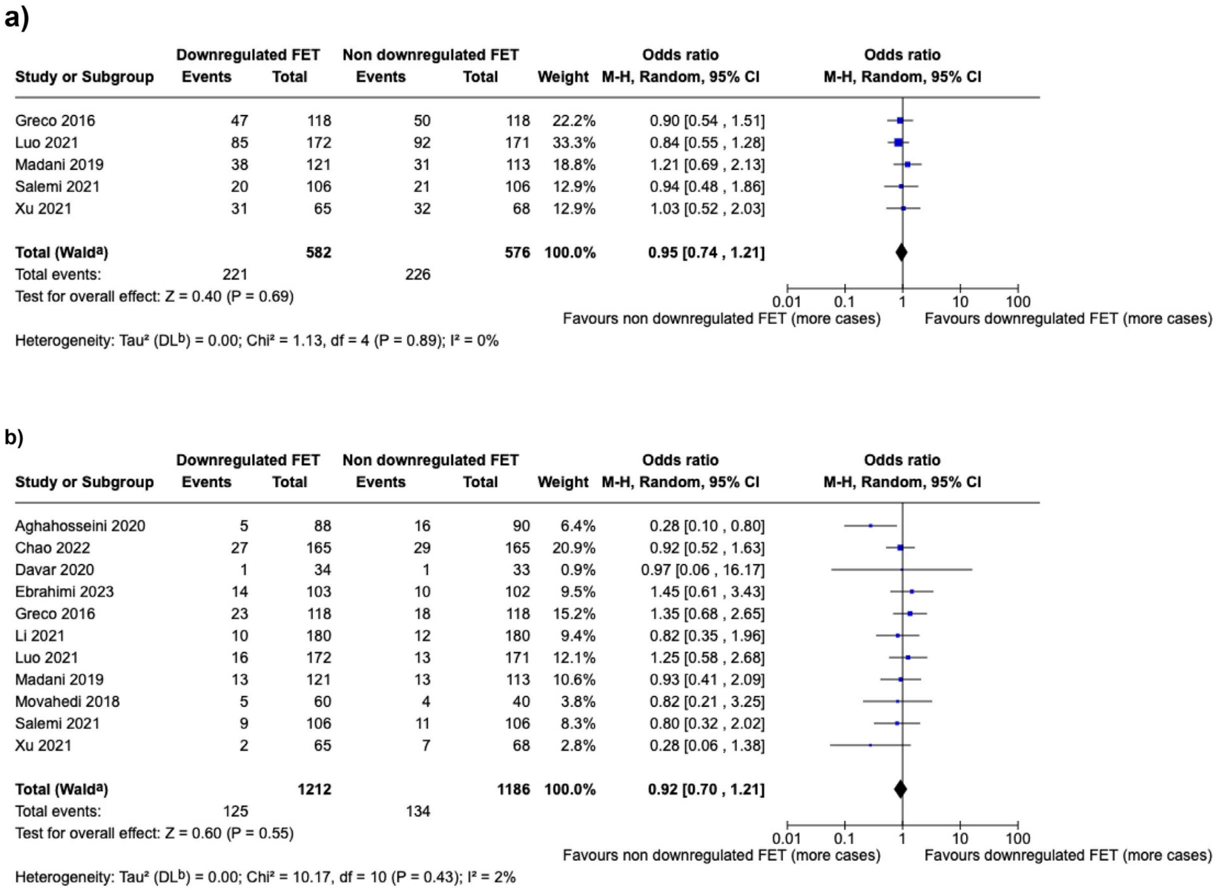


FIGURE 3 Pituitary down-regulation before frozen embryo transfer (FET). Forest plots comparing FET cycles with or without pituitary down-regulation assessing (a) live birth rate, and (b) risk of pregnancy loss. Odds ratios with 95% CI were calculated using the Mantel–Haenszel (M-H) method under a random-effects model. ^{a} Confidence intervals (CI) calculated by a Wald-type method. ^{b} Tau^2 was calculated by the DerSimonian and Laird method.

Li and colleagues (*Galati et al., 2025*; *Li et al., 2023*).

Currently, there are insufficient data supporting any particular endometrial preparation protocol for FET in adenomyosis. Management should therefore be individualized and tailored to patients' preferences and medical/obstetric history. Results from ongoing RCT (NCT03946722, NCT04356664, NCT03421639, NCT06239376) will clarify if any specific medical approach might potentially improve reproductive outcomes in these pathologies.

Recommendations:

5. FET with routine pituitary down-regulation with GnRH agonists should not be used to increase live births (Grade B).
6. FET with routine pituitary down-regulation with GnRH agonists should

not be used to decrease pregnancy loss (Grade B).

Summary statement:

1. In adenomyosis patients there are insufficient data to recommend pituitary down-regulation (Grade C).

Are ovulatory FET cycles better than artificial FET cycles (FIGURE 4)?

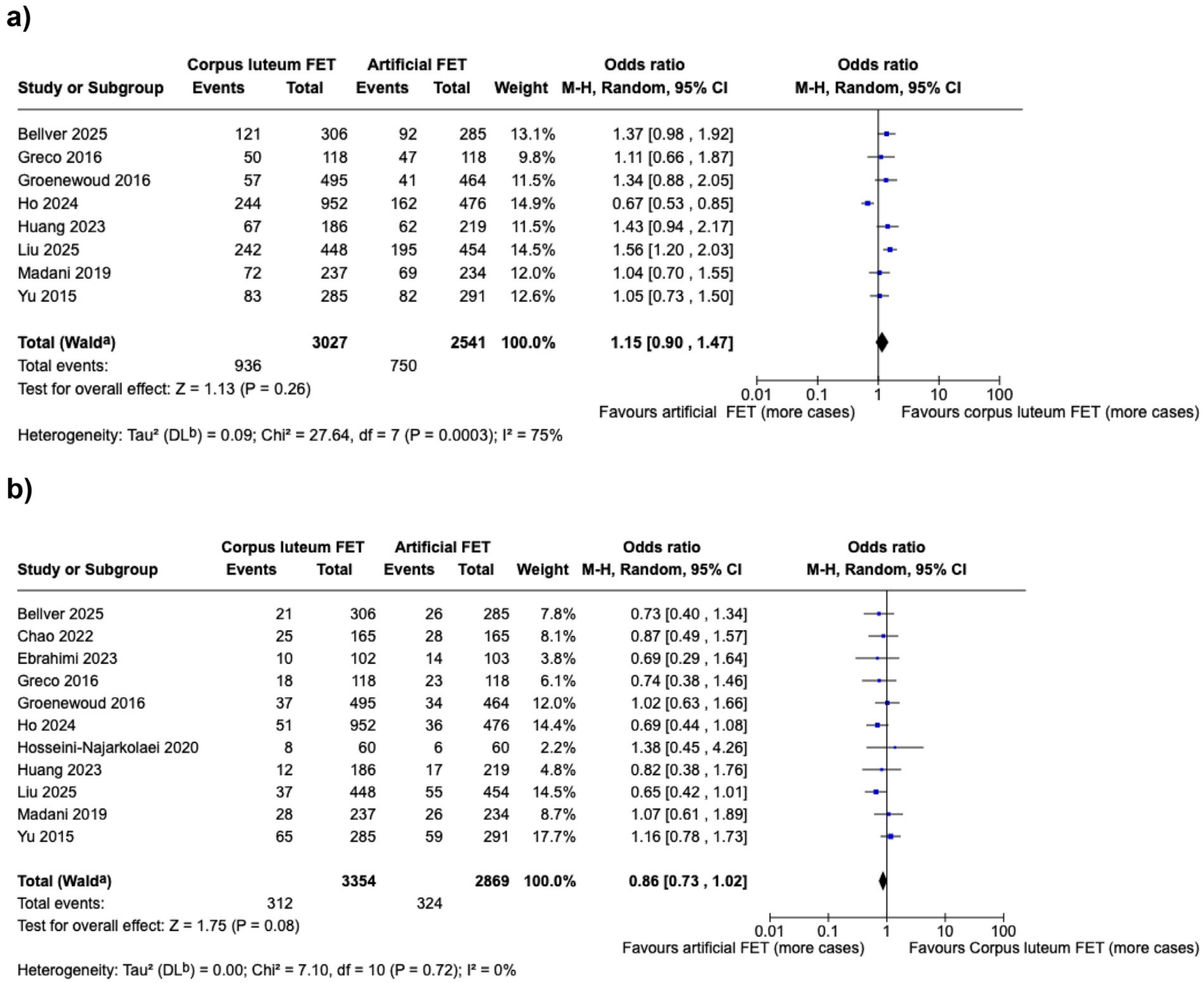
The corpus luteum is a transitory endocrine organ that plays a crucial role in implantation, early pregnancy maintenance and maternal vascular adaptation. Its absence or dysregulation has been linked with adverse obstetric outcomes (*Pereira et al., 2021*; *von Versen-Höynck et al., 2019*).

For the purpose of this guideline, FET cycles with the presence of a corpus luteum (natural, modified natural cycles, or stimulated cycles with oral or injected medications, with or without luteal progesterone supplementation) will be called ovulatory FET cycles. In contrast artificial cycles utilize oestrogen and progesterone for both endometrial preparation and luteal support, and exclude the presence of a corpus luteum (*Mumusoglu et al., 2021*).

There are 11 RCT totalling over 4000 cases that compare ovulatory and artificial cycles (Supplementary Table 3). Nine trials focused on a population with mixed causes of infertility (*Bellver et al., 2025*; *Chao et al., 2022*; *Ebrahimi et al., 2023*; *Greco et al., 2016*; *Groenewoud et al., 2016*; *Ho et al., 2024*; *Huang et al., 2023*; *Liu et al., 2025*; *Madani et al., 2019*) while two evaluated only individuals with PCOS (*Hosseini-Najarkolaei et al., 2020*; *Yu et al., 2015*).

Most trials included a very young population (≤30 years old on average) with the exception of those by the groups of Bellver, Greco Groenewoud and Ho, where the mean ages were 38, 35, 33 and 33 years, respectively (*Bellver et al., 2025*; *Greco et al., 2016*; *Groenewoud et al., 2016*; *Ho et al., 2024*).

Cancellation rates for ovulatory cycles ranged from 0% to 23% (overall rate 14.8%) versus 0–26% (overall rate 8.5%) for artificial cycles (RD +6.2%, 95% CI +4.6% to +7.8%), with precocious ovulation accounting for 1.5% of cancellations in both the ovulatory and artificial cycles. Both protocols resulted in a comparable overall LBR: 30.9% and 29.5% in ovulatory and artificial cycles, respectively (OR 1.15, 95% CI 0.90–1.47; FIGURE 4a). Pregnancy loss rates were also similar in both groups: 9.3% versus



a)

Study or Subgroup	Corpus luteum FET Events	Corpus luteum FET Total	Artificial FET Events	Artificial FET Total	Weight	Odds ratio M-H, Random, 95% CI
Bellver 2025	121	306	92	285	13.1%	1.37 [0.98 , 1.92]
Greco 2016	50	118	47	118	9.8%	1.11 [0.66 , 1.87]
Groenewoud 2016	57	495	41	464	11.5%	1.34 [0.88 , 2.05]
Ho 2024	244	952	162	476	14.9%	0.67 [0.53 , 0.85]
Huang 2023	67	186	62	219	11.5%	1.43 [0.94 , 2.17]
Liu 2025	242	448	195	454	14.5%	1.56 [1.20 , 2.03]
Madani 2019	72	237	69	234	12.0%	1.04 [0.70 , 1.55]
Yu 2015	83	285	82	291	12.6%	1.05 [0.73 , 1.50]
Total (Wald^a)		**3027**		**2541**	**100.0%**	**1.15 [0.90 , 1.47]**
Total events:	936		750			

Test for overall effect: Z = 1.13 (P = 0.26)

Heterogeneity: Tau² (DL^b) = 0.09; Chi² = 27.64, df = 7 (P = 0.0003); I² = 75%

b)

Study or Subgroup	Corpus luteum FET Events	Corpus luteum FET Total	Artificial FET Events	Artificial FET Total	Weight	Odds ratio M-H, Random, 95% CI
Bellver 2025	21	306	26	285	7.8%	0.73 [0.40 , 1.34]
Chao 2022	25	165	28	165	8.1%	0.87 [0.49 , 1.57]
Ebrahimi 2023	10	102	14	103	3.8%	0.69 [0.29 , 1.64]
Greco 2016	18	118	23	118	6.1%	0.74 [0.38 , 1.46]
Groenewoud 2016	37	495	34	464	12.0%	1.02 [0.63 , 1.66]
Ho 2024	51	952	36	476	14.4%	0.69 [0.44 , 1.08]
Hosseini-Najarkolaei 2020	8	60	6	60	2.2%	1.38 [0.45 , 4.26]
Huang 2023	12	186	17	219	4.8%	0.82 [0.38 , 1.76]
Liu 2025	37	448	55	454	14.5%	0.65 [0.42 , 1.01]
Madani 2019	28	237	26	234	8.7%	1.07 [0.61 , 1.89]
Yu 2015	65	285	59	291	17.7%	1.16 [0.78 , 1.73]
Total (Wald^a)		**3354**		**2869**	**100.0%**	**0.86 [0.73 , 1.02]**
Total events:	312		324			

Test for overall effect: Z = 1.75 (P = 0.08)

Heterogeneity: Tau² (DL^b) = 0.00; Chi² = 7.10, df = 10 (P = 0.72); I² = 0%

FIGURE 4 Are ovulatory frozen embryo transfer (FET) cycles better than artificial FET cycles? Forest plots comparing ovulatory (corpus luteum) FET versus artificial FET assessing (a) live birth rate, and (b) risk of pregnancy loss. Odds ratios with 95% CI were calculated using the Mantel–Haenszel (M-H) method under a random-effects model. ^{a} Confidence intervals (CI) were calculated by a Wald-type method. ^{b} Tau^2 was calculated by DerSimonian and Laird method.

11.3% (OR 0.86, 95% CI 0.73–1.02; FIGURE 4b).

A supplementary per-protocol analysis was also carried out for the LBR and pregnancy loss outcomes, with similar results (Supplementary Figure 6).

Summary statements:

Compared with artificial FET cycles:
2. Ovulatory FET cycles do not increase live birth (Grade B).
3. Ovulatory FET cycles do not decrease the risk of pregnancy loss (Grade B).

Are obstetric outcomes better in ovulatory versus artificial FET?

A recent systematic review that included 30 observational and retrospective studies (ovulatory FET *n* = 56,445 versus artificial FET *n* = 57,231) suggested that ovulatory cycles have improved obstetric outcomes (*Zaat et al., 2023*). However, this review did not include any randomized trials and thus may reflect bias in which patients were offered ovulatory versus artificial cycles.

More recently, four RCT (*Bellver et al., 2025*; *Ho et al., 2024*; *Huang et al., 2023*; *Liu et al., 2025*) that compared ovulatory (*n* = 1586) versus artificial (*n* = 1149) FET did not individually corroborate any of the obstetric findings in the systemic review. Furthermore, the pooled data of these studies did not demonstrate any difference in the incidence of gestational diabetes, HDP, pre-eclampsia, preterm birth and small- or large-for-gestational-age neonates (Supplementary Figure 7).

Summary statement:

Compared with artificial FET cycles:
4. Ovulatory FET cycles do not decrease the risk of obstetric and perinatal complications (Grade B).

What luteal support produces better outcomes in artificial FET (LBR and pregnancy loss) (FIGURE 5)?

Exogenous progesterone can be administered via four routes: oral, vaginal, subcutaneous or intramuscular. Neither oral (dydrogesterone) nor subcutaneous progesterone is available in Canada.

Six controlled trials assessed various routes of luteal phase supplementation on FET (*Devine et al., 2021*; *Macedo et al., 2022*; *Ozer et al., 2021*; *Pabuccu et al., 2022*; *Wang et al., 2015*; *Zarei et al., 2017*) (Supplementary Table 3). Three compared intramuscular versus vaginal progesterone for luteal support in artificial FET and showed no difference in LBR (OR 0.78, 95% CI 0.41–1.48; FIGURE 5a) (*Devine et al., 2021*; *Pabuccu et al., 2022*; *Wang et al., 2015*).

One of these trials (*Pabuccu et al., 2022*) evaluated the impact of oral progesterone (dydrogesterone) versus vaginal or

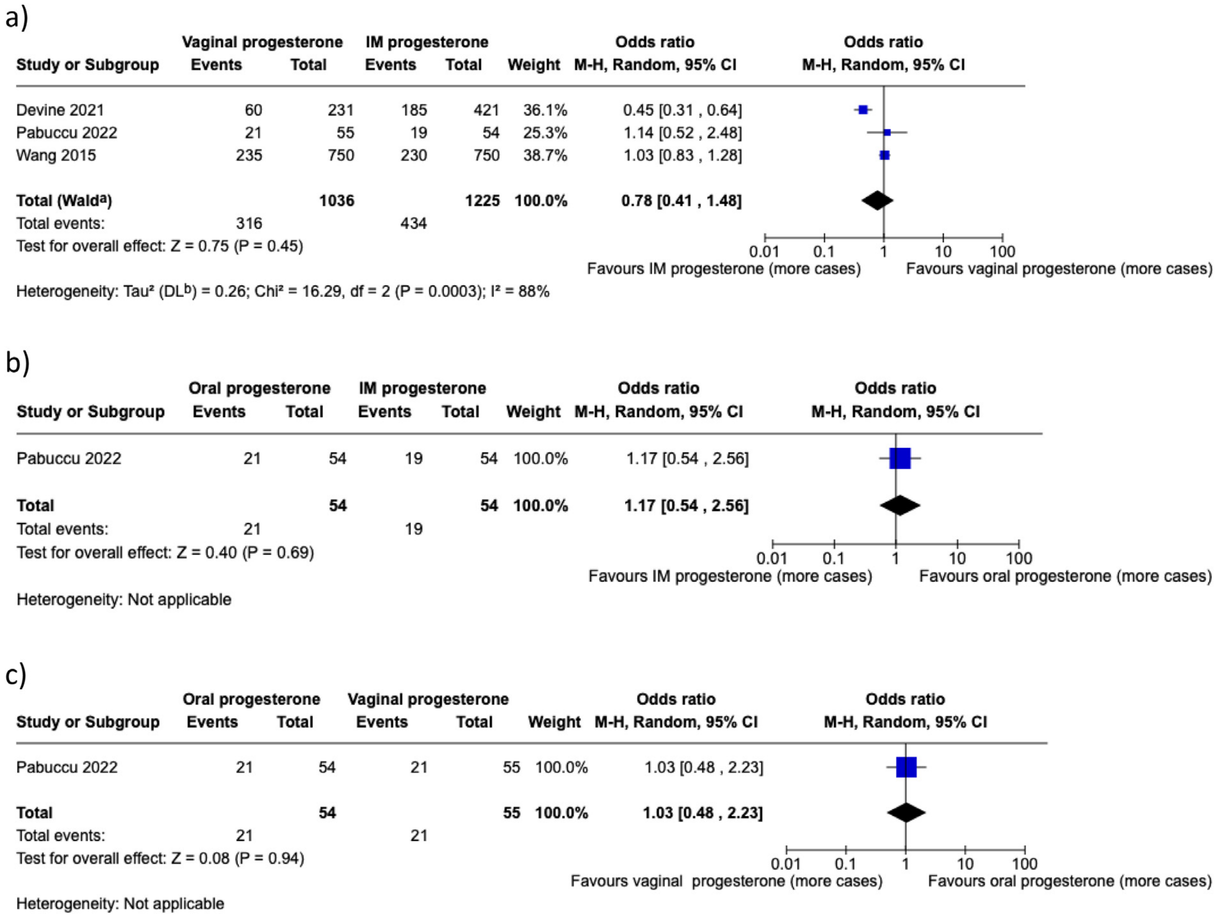


FIGURE 5 What luteal support produces better live birth outcomes in artificial frozen embryo transfer (FET)? Forest plots assessing live birth rate comparing (a) intramuscular (IM) progesterone versus vaginal progesterone, (b) intramuscular progesterone versus oral progesterone, and (c) oral progesterone versus vaginal progesterone. Odds ratios with 95% CI were calculated using the Mantel–Haenszel (M-H) method under a random-effects model. [a] Confidence intervals (CI) were calculated by a Wald-type method. [b] Tau^2 was calculated by DerSimonian and Laird method.

intramuscular progesterone on LBR after FET. No improvement was reported with the oral versus intramuscular (OR 1.17, 95% CI 0.54–2.56; FIGURE 5.b) or vaginal (OR 1.03, 95% CI 0.48–2.23; FIGURE 5c) route.

Pregnancy loss did not differ by route of progesterone administration; intramuscular versus vaginal (OR 1.10, 95% CI 0.79–1.54), oral versus intramuscular (OR 1.56, 95% CI 0.42–5.88) or oral versus vaginal (OR 0.99, 95% CI 0.51–1.93) (Supplementary Figure 8).

Currently, there is insufficient evidence to recommend one route of progesterone administration over another.

The progesterone preparations and doses used are described in Supplementary Table 3.

Summary statement:

5. Route of progesterone administration does not impact live birth or pregnancy loss in artificial FET (Grade B).

The robustness of these findings was supported by funnel plots and a leave-one-out sensitivity analysis (Appendix 2). Detailed justification for the certainty grading of all Summary Statements and Recommendations is provided in Supplementary Table 1.

CONCLUSION

This guideline provides evidence-based recommendations for the clinical management of FET, based on the available RCT published since 2014. While the freeze-all strategy is a very important tool for preventing OHSS, the available data do not support its routine use for improving embryo transfers, reducing pregnancy loss or enhancing obstetric outcomes in the general IVF population.

Ovulatory FET cycles do not offer advantages over artificial FET cycles in terms of live birth or pregnancy loss, and current evidence remains conflicting regarding obstetric and perinatal outcomes. Furthermore, progesterone administration routes in artificial FET cycles do not significantly affect live birth or pregnancy loss rates. The decision between fresh and frozen embryo transfer, as well as the choice of endometrial preparation protocols for FET, should be individualized based on the patient's clinical presentation, safety considerations, protocol tolerability and success rates associated with institutional practices.

DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

During the preparation of this work the authors used ChatGPT-4 and Copilot in order to improve readability. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2025.105373.

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