


Meta-analysis of the embryo freezing transfer interval

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Abstract

Background: The decision of whether frozen embryo transfer (FET) should be performed in the cycle immediately after OPU or at least one cycle later is controversial. FET could improve pregnancy rates in IVF; however, how much time is needed for the endometrium to return to optimal receptivity after ovarian stimulation is not known.

Methods: Electronic search in MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials to identify studies providing data on the influence of the interval between embryo freezing (or OPU) and FET in FET cycles published between January 1, 2007, and February 1, 2020.

Main findings: Data analyzed indicated that in the immediate FET cycles, there was a trend to an increased biochemical pregnancy rate (RR = 1.08; CI = 1.00-1.18), whereas the clinical pregnancy rate was somewhat higher, but without reaching statistical significance (RR = 1.07; CI = 0.99-1.15). The live birth rate was similar in the two groups (RR = 1.05; CI = 0.95-1.15), as was the implantation rate (RR = 0.98; CI = 0.83-1.16). Stratifying by embryo stage or FET type (freeze-all or FET after failed fresh transfer) showed no differences.

Conclusion: Systematically delaying FET does not offer benefits to IVF outcomes. In addition, immediate transfer is associated with a nonsignificant trend to better clinical pregnancy rate and it also avoids the psychological effects of prolonging the stress on prospective parents.

KEYWORDS

delayed transfer, frozen embryo transfer, immediate transfer, IVF, pregnancy rates

1 | INTRODUCTION

Since embryo freezing (EF) is performed by vitrification,¹ frozen embryo transfer (FET) is increasingly common.² Its efficacy and safety with surplus embryo are well known.² Some authors have recommended the “freeze-all” strategy for all patients,^{3,4} while others have suggested using this strategy in selected groups of patients: women with preimplantation genetic diagnosis cycles⁵; or women with high ovarian response,⁶ polycystic ovarian syndrome,^{7,8} high

progesterone levels,⁹ and conditions appearing during stimulation such as polyps,¹⁰ thin endometrium,¹¹ or hydrosalpinges.¹²

Ovarian stimulation has been associated with a number of detrimental changes in the endometrium, impairing implantation. Some of these adverse effects are related to a hyperestrogenic state,¹³ the production of reactive oxygen species,¹⁴ immunological changes in endometrial natural killer cells and cytokines,¹⁵ and advanced endometrial maturation.¹⁶ The aforementioned adverse effects are one of the main reasons for “freeze-all” programs. Nonetheless, it has not been studied

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whether these detrimental changes persist in subsequent cycles. In particular, there are no prospective randomized trials assessing the influence of EF-embryo transfer (ET) interval on pregnancy rates (PRs). In this context, the ideal interval between embryo freezing and ET has not been established. In a Web-based study, reporting data from 179 ART centers in 58 countries, the majority of responders (61%) preferred a washout period between fresh and FET cycles.¹⁷

In retrospective studies, some authors have found higher PRs when ET is performed in the immediately following menstrual cycle.¹⁸⁻²¹ On the other hand, there have also been reports of better results when ET is delayed ≥ 1 menstrual cycle²² or better clinical results in delayed FET, though the difference did not reach significance,²³ while others have reported no differences.^{9,12,24-27} Further, the differences in some of the reports that were reported in favor of immediate FET disappeared when controlling for associated variables.²⁰

The aim of our study was to perform a systematic review of the literature and meta-analysis of results found concerning the influence of EF-FET interval on IVF pregnancy outcomes.

2 | MATERIALS AND METHODS

The literature search was performed in MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials, with the following key words: "Time"+"interval"+"cycle"+"ivf" or "immediate"+"embryo"+"transfer" or "immediate"+"vs"+"delayed"+"ivf" or "optimal"+"time"+"between"+"ivf" or "delay"+"ivf"+"cycle" or "interval" + "transfer" + "IVF." The search was restricted to articles published between January 1, 2007, and February 1, 2020, written in English or Spanish. In addition, reference lists of the publications included were screened. Our search was submitted to the PROSPERO database (CRD42020204072). The meta-analysis was performed following the PRISMA methodology.²⁸

The inclusion criteria were as follows: (1) cycles of ovarian stimulation for an IVF/ICSI in which at least one embryo was cryopreserved; (2) performance of FET in a cycle other than the cycle in which oocyte pick-up (OPU) was performed; and (3) collection of data on IVF outcomes allowing comparison between at least two EF-FET interval groups. Thus, two types of patients were included: (a) patients receiving fresh ET in the OPU cycle who did not become pregnant and received FET in a subsequent cycle, and (b) patients undergoing "freeze-all" protocols.

The exclusion criteria were as follows: (1) fresh transfers in the second ET; (2) non-human studies; (3) failure to report data on PRs; and (4) lack of data to allow comparisons by EF-ET interval.

2.1 | Data extraction

The following data were extracted from every article: author, publication year, country where the study took place, number of cycles included in the study, mean age of the women, number of oocytes retrieved, IVF management, endometrial preparation and luteal

phase support, exclusion criteria, EF-FET interval(s), number of cryopreserved embryos transferred, frozen embryo outcomes (implantation rate, biochemical pregnancy, clinical pregnancy, live birth rate), and the study conclusions. In one case, the authors were contacted to obtain additional information.²⁴ The search was conducted by the same investigator (SB).

2.2 | Study quality assessment

Two reviewers (RM and IP) used the Newcastle-Ottawa Scale (NOS) for observational studies to assess the quality of the manuscripts included.²⁹ With this scale, each category is rated by awarding a maximum of one star, except "comparability by design or analysis" for which two stars may be given. A maximum of nine points is assigned indicating the least risk of bias (Table S1).

2.3 | Statistical analysis

For the statistical analysis, the following were calculated: relative risk (RR) and the corresponding 95% confidence interval (CI), and the p-value for each parameter under study. For each parameter, a "forest plot" was used to present the RR and CI for each of the studies. The threshold for statistical significance was set at $P < .05$. The heterogeneity of the results was assessed with the χ^2 and I^2 tests.

Statistical analysis was performed with Stata 15.1

3 | RESULTS

The flow of studies through the review process is shown in a PRISMA diagram²⁸ presented in Figure 1. The search strategy yielded 520 records (516 after removal of duplicates), of which 499 were excluded after reading of the title and/or abstract, indicating that they did not fulfill the selection criteria. Finally, 17 studies were screened and 12 were included in the meta-analysis. The characteristics of studies excluded³⁰⁻³⁴ are listed in Table S2. All the studies included scored well on the NOS, achieving a score of between 7 and 9 (Table S1).

3.1 | Study characteristics

3.1.1 | Origin

Our search identified 12 studies, 11 of them corresponding to full-length articles and 1 to an abstract.²¹ As we can see in Table 1, the 12 studies included a total of 18 127 FET cycles (5457 immediate and 12 570 delayed) carried out in women from centers in 6 different countries (Belgium, Spain, Australia, China, Israel, USA, and Turkey). Ten of the publications reported single-center studies,^{9,19-27} while one was based on a multisite IVF clinic¹⁸ and one¹² included two centers.

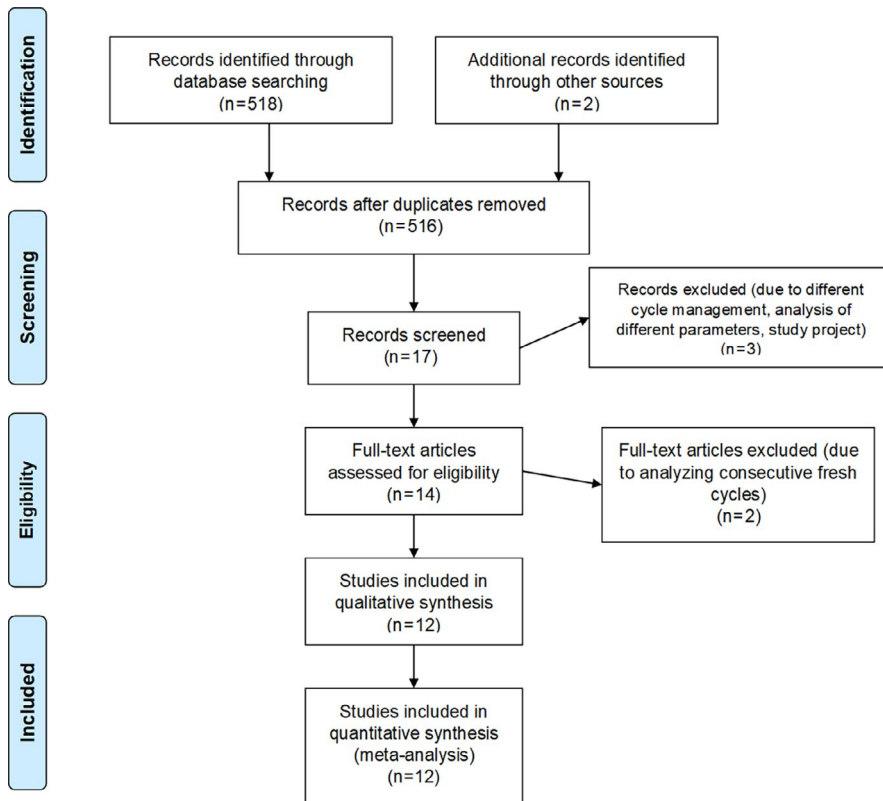


FIGURE 1 PRISMA flowchart [Colour figure can be viewed at wileyonlinelibrary.com]

Two studies were performed by the same group, in different populations.^{12,26} Regarding the size of the populations included, in two studies, >4000 cases were analyzed,^{18,24} and in five, <500.^{9,12,21-23} In one study, the interval comparison was made considering two different populations separately, with data provided for: women receiving GnRH agonists and those receiving GnRH antagonists.²⁴ Since no combined data were given, for the purpose of the meta-analysis, this research was considered as two different studies: He et al, GnRH agonist protocol; and He et al, GnRH antagonist protocol. Most studies had data collection periods of 3-5 years, and all can be considered relatively recent (having been published between 2016 and 2020), except that of Maas et al.²¹

3.1.2 | Inclusion and exclusion criteria

There were six studies including only freeze-all patients,^{19,20,24-27} four including only patients with FET after failure of a previous fresh ET^{9,12,21,22} and two including both freeze-all and previously failed fresh transfers^{18,23} (Table S3).

Six studies reported an upper limit of age in the inclusion criteria: >38 years,²² >40 years,^{23,24} >42 years,²⁵ and >45 years.^{9,27} Four reported a lower limit: <18 years^{9,23} and <20 years.^{22,24}

Eight studies excluded preimplantation genetic diagnosis/preimplantation genetic screening cycles,^{9,12,19,22,24-27} and five excluded donor oocyte cycles.^{9,12,19,24,26} The other inclusion/exclusion criteria are listed in Table 1.

3.1.3 | Intervals considered

In six studies, FET was considered immediate when performed within the first menstrual cycle after OPU, and delayed when performed after at least 2 menses.^{12,19,20,22,23,27} Another author applied the same criteria but with the limit that in delayed ET, the transferred embryos were cryopreserved for less than 6 months²⁴ (Table S3).

Other authors established a cutoff of days for immediate and delayed transfer: start of the FET cycle of ≤ 22 or >22 days after OPU,^{9,26} fresh ET-FET interval of ≤ 50 and >50 days,²¹ and EF-FET interval of 25-35 days (1 cycle) or 50-70 days (2 cycles).¹⁸ In another study, the patients were grouped by time interval between OPU and FET [32-46, 47-61, 62-76, 77-91, and ≥ 92 days].²⁵

3.1.4 | OPU cycle management

For the study published as an abstract, no data at all were provided concerning cycle management (Table 1).²¹ In other cases, regarding the management of the OPU cycle, for downregulation, one study used GnRH agonists in a long protocol,²² three studies used daily GnRH antagonists,^{12,25,26} one study used either GnRH agonists in a short protocol or priming with progestins,¹⁹ four studies used either GnRH agonists in a long protocol or daily GnRH antagonists,^{9,20,23,24} and one study GnRH agonists or antagonists, reporting the data separately for these two groups.²⁴ Further, in one study, three different

protocols were used: boost GnRH agonists, GnRH agonists in a long protocol, or GnRH antagonists,¹⁸ while in another, six different protocols were used: ultra-short, short, long, and modified ultra-long GnRH agonist protocols, a GnRH antagonist protocol, or a mini-stimulation protocol.²⁷

Ovarian stimulation was performed with recombinant FSH and HMG in six studies.^{9,12,22,23,25-27} In two studies, moreover long-acting FSH was also employed.^{12,26} One study only reported the use of “exogenous gonadotropins”,²⁰ while only recombinant FSH was used in two studies^{18,24} and only HMG was employed in another.¹⁹

Triggering was performed with recombinant hCG in three studies,^{9,22,26} with either recombinant hCG or urinary hCG in two,^{18,24} with GnRH antagonist in one,¹² and with hCG and/or GnRH antagonist in five.^{19,20,23,25,27}

3.1.5 | FET cycle management

For the study published as an abstract, no data were given at all concerning the FET cycle management (Table 1).²¹ Concerning the FET cycle preparation, GnRH agonist or contraceptive pill pretreatment was used in one study²⁵ and GnRH agonist downregulation was given to some women in another.²³ In the other publications, no mention was made of GnRH agonists or contraceptive pills for FET cycle preparation.

In four studies, some women underwent FET in a natural cycle^{18,23,24,27} or in a modified natural cycle,¹⁹ whereas in one study, all underwent transfer in a modified natural cycle.⁹

In five studies, some patients received exogenous estrogens. The dose used was specified in three studies employing oral estradiol, 2 mg/d,²⁷ 6 mg/d,¹⁸ or 8 mg/d,¹⁹ but not reported in two: one employing oral estradiol²⁴ and the other oral and/or transdermal estradiol.²³ In four other studies, all the women received exogenous estrogens. The doses used were as follows: 2 mg/d,^{12,26} 4-6 mg,²² 6 mg/d, or 150 mg/d transdermal estradiol hemihydrate.²⁰

In another, all women received oral estradiol in a step-up protocol (dose of 2-4-8 mg).²⁵ Lastly, in one report, a small proportion of patients underwent FET in a stimulated cycle.

Concerning luteal phase support, in three studies in which natural cycles were used, no mention was made of progesterone supplementation,^{18,24,27} whereas in one study, vaginal progesterone was used (progesterone gel or micronized progesterone).²³ Regarding the two series of women undergoing modified natural cycle IVF, in one, ovulation was triggered with hCG and the luteal phase supported by micronized vaginal progesterone (200-400 mg/24 h) or a single daily application of progesterone gel, and in the other, ovulation was triggered with 5000 IU of urinary hCG and the luteal phase supported by 40 mg/d of dydrogesterone.¹⁹ In studies in which exogenous estrogens were used, progesterone supplementation was only given vaginally in five cases: with

600 mg/d of micronized vaginal progesterone in one case,²⁰ with vaginal micronized progesterone without stating the dose in two cases,^{12,26} with vaginal progesterone gel in one case,²⁵ and with vaginal progesterone pessaries 400-800 mg/d or 8% progesterone gel in one case.¹⁸ In three cases, progesterone was administered intramuscularly: at the dose of 40 mg/d in one study²⁴ and 20 mg/d in another,²⁷ while the dose was not reported in the third.²³ In one case, either vaginal micronized progesterone (200-300 mg/d) or intramuscular progesterone was used,²² and in another, the oral and vaginal routes were combined, women receiving both 40 mg/d of oral dydrogesterone and 400 mg/d of micronized vaginal progesterone.¹⁹ Regarding the few cases of FET in stimulated cycles, no specific mention was made to luteal phase support.²⁷

In the study published as an abstract, no mention was made of progesterone supplementation.²¹

3.1.6 | Embryo characteristics

FET involved only cleavage stage embryos in two studies,^{20,27} only blastocysts in four,^{9,21,23,25} and both cleavage stage embryos and blastocysts in five.^{12,19,22,24,26} In one study, embryo development stage was not reported¹⁸ (Table S3).

3.2 | Homogeneity of study groups

3.2.1 | Age

In one study, the age was significantly higher in the immediate transfer group,¹⁸ while in another, the age was significantly higher in the delayed transfer group.²⁴ The resulting mean age was very similar in both groups (Figure 2A).

3.2.2 | Oocytes retrieved in the OPU cycle

The mean number of oocytes retrieved ranged from nearly 11^{19,26} to nearly 22.¹² In all the studies, the mean number of oocytes retrieved was similar in the immediate and delayed transfer groups. The meta-analysis showed no statistical differences (Figure 2B).

3.2.3 | Transferred embryos

In three studies, the number of embryos transferred in the FET cycle was significantly higher in delayed transfers,^{9,12,18} whereas in eight, there were no significant differences.^{19-24,26,27} In one study, the mean number of embryos transferred was not reported, although it was stated that the frequency of single blastocyst transfer was similar in both groups.²⁵ The meta-analysis showed no statistical differences (Figure 2C).

TABLE 1 Characteristics of the studies included

Author	Year, country (region)	Study	Number of cycles (immediate + delayed transfers)	Age (y)	OPU cycle management
He et al	2020 (2014-2017), China (Guangzhou)	RC	3110 GnRH agonist protocol (1585 + 1525)	IT: 31.74 ± 4.33 DT: 31.98 ± 4.23	Long GnRH agonist protocol (triptorelin [Diphereline]) Recombinant FSH (Gonal-F or Puregon) Urinary HCG (uHCG) or recombinant HCG (Ovitrelle)
			1294 GnRH antagonist protocol (778 + 516)	IT: 31.37 ± 4.03 DT: 31.53 ± 4.23	GnRH antagonist protocol (cetrotirelix [Cetrotide]) Recombinant FSH (Gonal-F or Puregon) Urinary HCG (uHCG) or recombinant HCG (Ovitrelle)
Higgins et al	2018 (2000-2014), Australia (Victoria)	RC	4994 (635 + 4359)	IT: 36.0 (26.5-45.9) DT: 35.5 (26.2-43.9) (P = .001)	Three GnRH analog protocols were used: (a) Short GnRH agonist (Synarel) protocol (b) GnRH agonist starting in the midluteal phase of the previous cycle (c) GnRH antagonist (Cetrotide, Orgalutran) on day 5 or when the leading follicle was ≥ 14 mm In all cases, ovarian stimulation was performed with rec FSH (400-600 UI/d) (Gonal, Puregon). In all cases, the beginning of the cycle could be spontaneous or after the intake of contraceptive pills (30 µg ethinyl estradiol and 150 µg levonorgestrel) Triggering with HCG (Ovidrel or Pregnyl)
Horowitz et al	2019 (January 2009-December 2016), Israel (Tel Aviv)	RC	198 (118 + 80)	IT: 32.8 ± 5.0 DT: 34.1 ± 5.6	GnRH antagonist or agonist protocols. Triggering with rec HCG
Huang et al	2019 (01/2013-12/2016), China (Shanghai)	RC	2998 (280 + 2718)	IT: 30.6 ± 4.3 DT: 30.9 ± 4.2	(a) GnRH agonist short protocol: 0.1 triptorelin (Decapeptyl; Ferring) Ovarian stimulation with 150-225 hMG (hMG; Anhui Fengyuan) Triggering with 5000-10 000 IU of urinary hCG (hCG; Lizhu Pharmaceutical Trading) (b) Progestin-primed ovarian stimulation (10 mg medroxyprogesterone acetate (Shanghai Xinyi Pharmaceutical)) Ovarian stimulation with hMG (150-225 hMG . Triggering with (a) single use of 5000-1000 IU of urinary hCG, (b) single dose of triptorelin (0.1-0.2 mg) or (c) dual trigger with 1,000 IU of urinary hCG and 0.1 mg of triptorelin.
Kaye et al	2018 (2013-2016), USA	RC	344 (80 + 264)	IT: 33.6 ± 3.8 DT: 33.52 ± 3.7	GnRH antagonist or agonist (leuprolide) + rFSH and/or, hMG (Gonal-F, Follistim, Menopur) + hCG (Pregnyl or Novarel) or GnRH agonist or both

Endometrial preparation/ luteal phase support	Day of embryo development	Inclusion criteria	Exclusion criteria
(a) Natural cycle (b) Daily oral estradiol valerate tablets and 40 mg/d of intramuscular progesterone	D3 or D5	Age: 20-40 y Normal menstrual cycle. Basal FSH < 12 mIU/mL First FET cycle after whole embryo freezing using vitrification method Analog protocol with GnRh agonists or antagonists	Donated oocytes PGD cycles Polycystic ovarian syndrome or ovulatory disorders Uterine anomalies Hydrosalpinx Uncontrolled endocrine or immune disorders or other systemic diseases
(a) Natural cycle (b) Estradiol valerate 6 mg/ day and vaginal progesterone pessaries (400-800 mg/d) or 8% progesterone gel	NR	FET cycles with a prior fresh cycle ("fresh cycle- FET" interval = 25-35 d or 50-70 d)	Cases from before 2000 or after 2014 FET preceded by another FET Cycles with other gaps
Modified natural cycle Ovulation triggering with hCG Vaginal progesterone: 400 mg Utrogestan/24 h or 200 mg Endometrin (Ferring) or a single daily application of Crinone (Merck)	Embryos/ blastocysts	Age: 18-45 y Regular ovulatory cycles First FET cycles after failed fresh embryo transfer	Cycles involving donors PGD cycles Freeze-all protocols.
(a) Modified natural cycles were recommended (in case of regular menstrual cycles) Ovulation was triggered with 5,000 IU of urinary hCG. Luteal phase was supplemented with 40 mg/d of dydrogesterone (Duphaston; Abbott) (b) In irregular cycles 8 mg/d of oral micronized estradiol (Fematon, Abbott) Luteal phase was supplemented with 40 mg/d of oral dydrogesterone and 400 mg/d of vaginal progesterone (Utrogestan)	Day 3-4 cleavage stage embryos or day 5-6 blastocysts	Infertile women who underwent their first FET after the first IVF/ICSI cycle using the freeze-all policy Day 3 or day 5 transfer	Abnormal parental karyotyping Unilateral oophorectomy Recurrent miscarriage Uterine anomalies (congenital or acquired) Donor sperm or testicular/epididymal sperm. Moderate or severe ovarian OHSS during ovarian stimulation cycle Embryo cryopreservation > 120 d Core information missing in medical records Donated oocytes In vitro maturation oocytes PGD
Natural cycle and vaginal progesterone (Crinone; Merck; or Endometrin; Ferring) or GnRH agonist downregulation + oral and/or transdermal estradiol + intramuscular progesterone	Blastocyst	Age: 18-40 y (a) FET after a previous ovarian stimulation cycle with one failed fresh ET (b) Freeze-all protocol (PGD, ovarian hyperresponse/ OHSS risk, progesterone rise, planned surgery, pregnancy contraindication, lack of suitable D5 with blastocyst cryopreservation on day 6, patient preference)	Patients without a stimulation cycle before FET (donated oocytes). Patients in whom embryo freezing was performed 120 or more days before the FET Endometrial biopsy or endometrial scratching in the cycle prior to ET

(Continues)

TABLE 1 (Continued)

Author	Year, country (region)	Study	Number of cycles (immediate + delayed transfers)	Age (y)	OPU cycle management
Lattes et al	2017 (1/2012-12/2014), Spain (Barcelona)	RC	512 (263 + 249)	IT: 34.7 ± 4.13 DT: 35.3 ± 3.98 (P = .067)	GnRH antagonist or GnR agonist protocol, exogenous gonadotropins and GnRH agonist (triptorelin) or rhCG (Ovitrelle)
Mass et al	2008 (2003-2007), USA (San Francisco)	RC	271 (105 + 166)	IT: 36.3 ± 5.5 DT: 36.6 ± 5.6	NR
Ozgun et al	2017 (February 2015-January 2016), Turkey (Antalya)	RC	1121 (756 + 365)	IT:31.5 DT: 31.6	GnRH Antagonist (Cetrotide) + rFSH (Gonal-F) + hMG (Menopur) + hCG/GnRH agonist (Gonapeptyl) or both
Santos -Ribeiro et al (1)	2016 (January 2010-November 2014), Belgium (Brussels)	RC	1183 (197 + 986)	IT: 32.4 ± 4.4 DT: 32.5 ± 4.3 (P = .69)	GnRH antagonist (Cetrotide or Ganirelix) + rFSH (Gonal-F, Puregon, Elonva) + HMG (Menopur) + HCG
Santos -Ribeiro et al (2)	2016 (October 2010-October 2015), Belgium (Brussels), Vietnam (Ho Chi Minh)	RC	333 (208 + 125)	IT: 30.9 ± 4.1 DT: 31.8 ± 4.2 (P = .045, OR 0.97)	GnRH Antagonist (Cetrorelix o Ganirelix). rFSH (Gonal-F, Puregon, Elonva) + HMG (Menopur) + GnRH agonist (Triptorelin)
Song et al	2019 (January 2016-September 2018), China (Jinan)	RC	1540 (385 + 1155)	IT: 31.38 ± 5.19 DT: 30.99 ± 4.45 (P = .19)	Ultra-short, short, long and modified ultra-long GnRH agonist protocol, GnRH antagonist protocol, mini-stimulation protocol Recombinant FSH (Gonal, Merck or Puregon; MSD (150-450 IU/d) and urinary hMG (hMG, Livzon) Triggering with GnRH agonist (0.2 mg triptorelin; Decapeptyl) or 250 µg rhCG (Ovitrelle; Merck)
Volodarsky-Perel et al	2017 (1/2010-6/2015), Israel (Jerusalem)	RC	129 (67 + 62)	IT : 29.9 ± 4.4 DT: 29.6 ± 4.2	GnRH Agonist (triptorelin: 3.75mg im or 0.1 mg/d sc) + rFSH (Gonal-F) and HMG (Menogon) and hCG

Abbreviations: D3, day 3 cleavage embryo; D5, day 5 blastocysts, DT, delayed transfer; ET, embryo transfer; IT, immediate transfer; FET, frozen embryo transfer, FISH, fluorescence in situ hybridization; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; OHSS, ovarian hyperstimulation syndrome; OPU, oocyte pick-up; PGD, preimplantation genetic diagnosis; RC, retrospective cohort; rFSH, recombinant follicle stimulating hormone.

Endometrial preparation/ luteal phase support	Day of embryo development	Inclusion criteria	Exclusion criteria
Estradiol valerate (6 mg) or transdermal estradiol hemihydrate (150 mg/d) Vaginal micronized progesterone (600 mg/d)	Day 3/4 embryos	Freeze-all cycles	BMI > 30 kg/m ² Endocrine pathologies Uterine abnormalities Chronic, autoimmune, or metabolic diseases Testicular sperm extraction Meiotic chromosomal abnormalities in testicular biopsy or altered sperm FISH Participation within the previous 6 mo, in a clinical trial with medication
NR	Day 5-6 blastocysts	First FET cycles after unsuccessful fresh ET	
GnRH agonist (Lucrin Depot) or Contraceptive pill (Ginera) + oral estradiol in step-up regime (2-4-8 mg) + vaginal progesterone gel (Crinone)	Blastocysts	"Freeze-all" program	>42 y Hysteroscopy between follicular aspiration and FET PGD
Estradiol valerate (2 mg) Vaginal micronized progesterone	Day 4 embryos and day 5/6 blastocysts	GnRH antagonist for downregulation hCG alone for triggering At least one FET after a previous ovarian stimulation cycle with 1 failed fresh ET	Donated oocytes In vitro maturation PGD Triggering with GnRh agonists (alone or in combination with hCG) hCG administration for reasons other than ovulation triggering FET cycles performed with downregulation with GnRH agonist or with exogenous concomitant ovarian stimulation
Estradiol valerate (2 mg) Vaginal micronized progesterone	D3 and day 5/6 blastocysts	First FET after a freeze-all protocol.	Donated oocytes In vitro maturation Blastocyst biopsy for preimplantation genetic diagnosis Previous cycle with fresh ET canceled due to thin endometrium
(a) Artificial cycle (61.7%) Estradiol valerate (2 mg/ twice daily for at least 14-16 d, adjusting the dose afterward) Injectable progesterone (20 mg/d) (b) Natural cycle (29.5%) (c) Stimulation cycle (8.8%)	D3	Age < 45 y Stimulation cycle completed with a freeze-all protocol. D3 cleavage stage embryo transferred	Patients not undergoing a stimulation cycle prior to FET Donated oocytes Embryos derived from vitrified oocytes Preceding cycles with missing data
Estradiol valerate (4-6mg/d) Vaginal micronized progesterone (200-300 mg/d) or intramuscular progesterone	D 3 and D5	First FET cycles after fresh ET with negative β -hCG Age 20-38 y FET of 1-2 vitrified embryos \leq 3 previous ET Artificial cycle for FET	Severe OHSS PGD

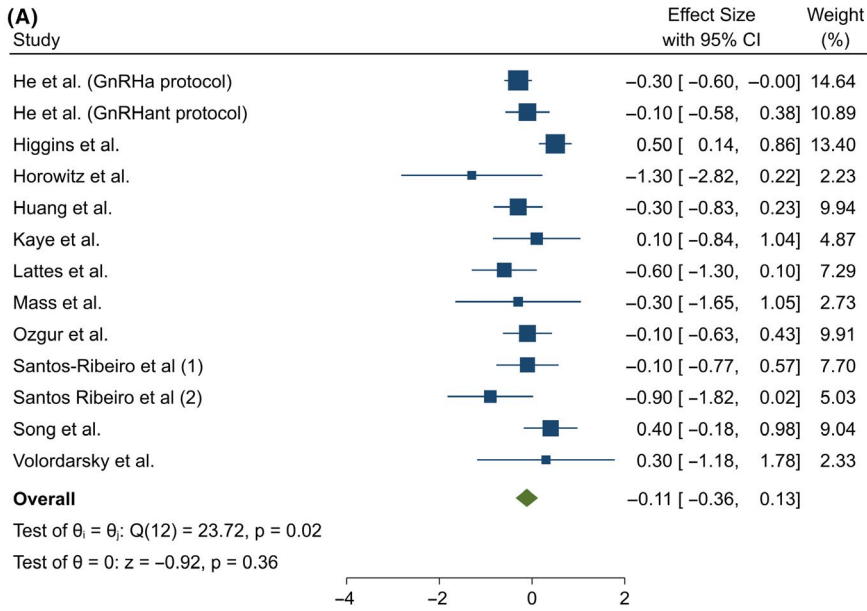
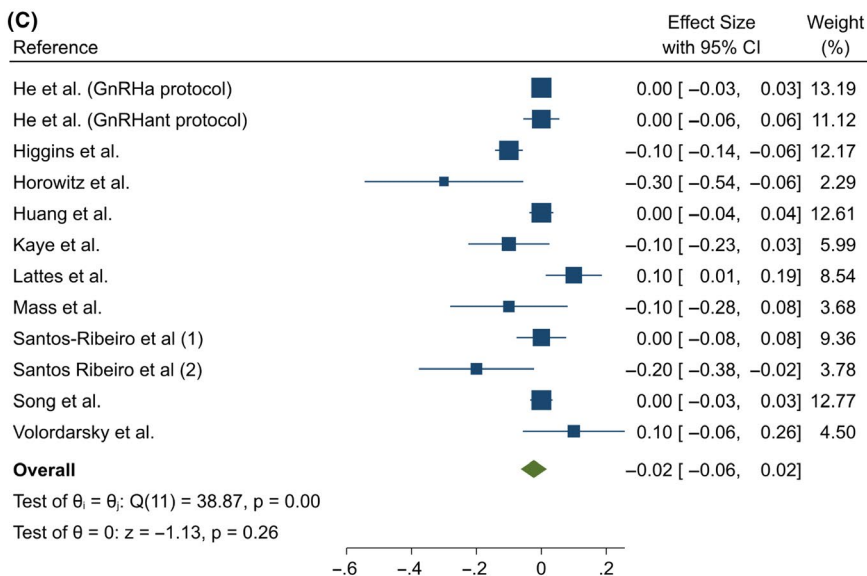
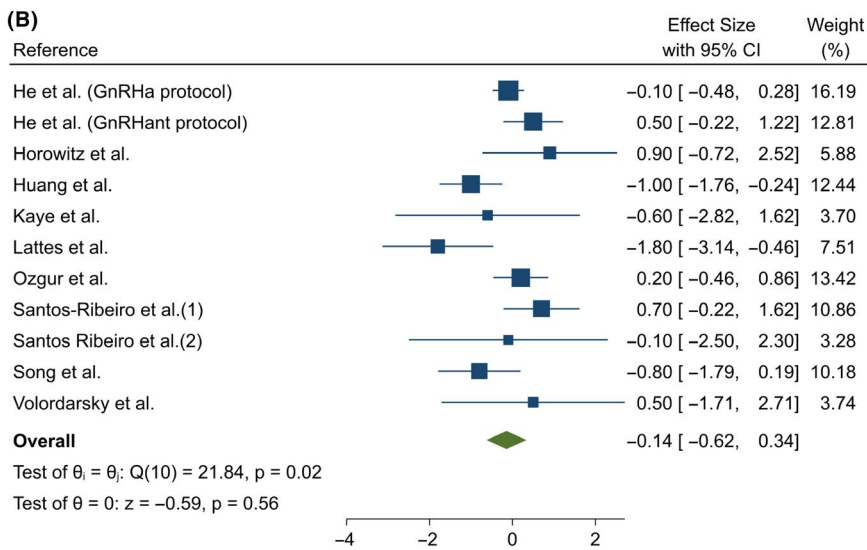


FIGURE 2 Comparison of (A) maternal age, (B) oocytes retrieved, and (C) embryos transferred in the immediate and delayed FET. No significant differences were observed. REML, restricted maximum likelihood [Colour figure can be viewed at wileyonlinelibrary.com]



Random-effects REML model

3.3 | IVF outcomes

3.3.1 | Implantation rate (IR)

The IR was reported in five of the studies,^{19,20,22-24} one of them²⁴ being the study that reported results in two populations separately: GnRH agonist and GnRH antagonist groups. In one case, the authors²⁴ were contacted to correct an inaccuracy in the data (Figure 3A).

The IR was defined differently in three studies as follows: the number of gestational sacs visualized on transvaginal ultrasound divided by the number of embryos transferred,¹⁹ the percentage of gestational sacs per total number of embryos transferred,²² or

the number of embryos transferred that develop to the stage of ultrasound documented gestational sac, divided by the number of transferred embryos, calculated for each woman.²⁰ In the other two studies, IR was not defined^{23,24}

In one study, the IR was significantly higher in the immediate group,¹⁹ and in another, it was significantly higher in the delayed group.²² There was statistically significant heterogeneity between the studies included (Cochran's $q = 22.94$, $P < .001$), $I^2 = 90.7\%$. Notably, the study by Volordarsky-Perel et al reported results quite divergent from those of the others. The meta-analysis obtained a similar RR in the immediate and delayed groups (RR = 0.98 [0.83-1.16], $P = .826$).

For subanalysis by embryo development stage (cleavage embryos; blastocysts; cleavage embryo or blastocysts), there was only

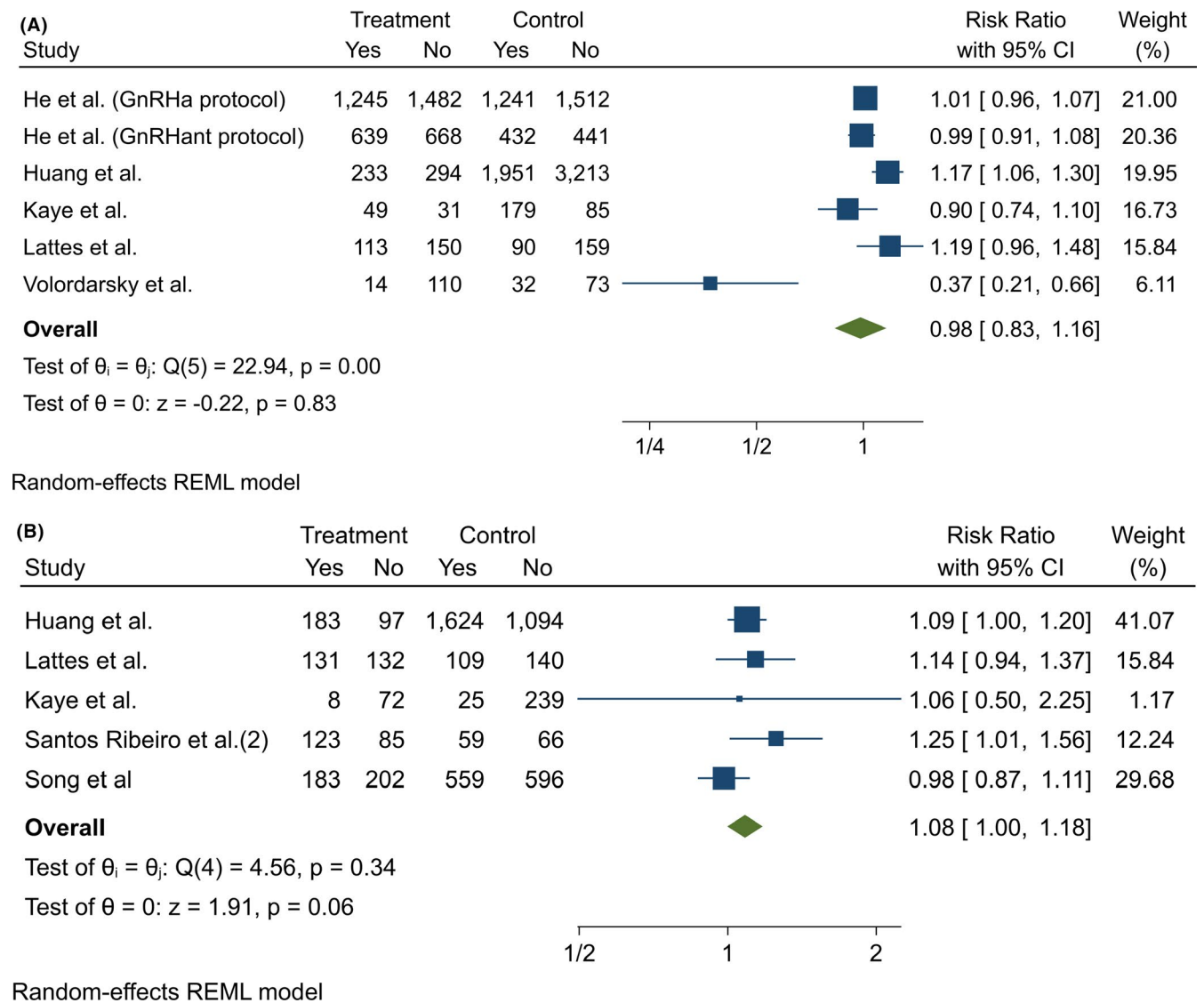


FIGURE 3 (A) Meta-analysis of studies reporting implantation rates by FET interval. Meta-analysis of the data from 6 included series (5 publications) that reported implantation rate as an outcome showed that there were no significant differences between immediate and delayed FETs. (B) Meta-analysis of studies reporting biochemical pregnancy rates by FET interval. Meta-analysis of the data from 5 publications that reported biochemical pregnancy rate as an outcome showed a RR of 1.08 (CI 1.00-1.18) in favor of immediate FET. REML, restricted maximum likelihood [Colour figure can be viewed at wileyonlinelibrary.com]

more than one publication for the subgroup of studies including both cleavage embryos and blastocysts. In this meta-analysis, no differences reached statistical significance (Figure S1).

Similarly, for subanalysis by FET indication (freeze-all, FET after failed fresh transfer, both), there was only more than one publication in the case of freeze-all cycles. Again, no differences reached significance (Figure S2).

3.3.2 | Biochemical pregnancy rate

Of the 12 studies analyzed, 5 provided data on biochemical PR^{12,19,20,23,27} (Figure 3B). In one study, biochemical pregnancy was defined as a serum β -hCG level ≥ 5 IU/L at 14 days after FET,¹⁹ while in the others, no definition was given.^{20,23,26,27}

In four studies, a somewhat higher biochemical PR was observed in the immediate group,^{12,19,20,23} although the difference was only statistically significant in one.¹² On the other hand, the biochemical PR was somewhat higher in the delayed group in one study.²⁷

There was no significant heterogeneity in the data analyzed (Cochran's $q = 4.56$, $P = .336$), $I^2 = 24.5\%$. The meta-analysis showed a trend to higher biochemical PRs in the immediate group. The RR was 1.08 (CI = 1.00-1.18), $P = .056$.

For subanalysis by embryo development stage, there were two studies concerning cleavage embryos and two concerning studies including both cleavage embryos and blastocysts. No significant differences were detected (Figure S3).

For subanalysis by FET indication, there was only more than one publication concerning freeze-all cycles. This meta-analysis showed no significant differences (Figure S4).

3.3.3 | Clinical pregnancy rate

In 11 studies, data were provided on clinical PR, and one of them was the study in which data were presented separately for GnRH agonist and antagonist groups.²⁴ Thus, 12 populations were considered (Figure 4A).

The definition of clinical pregnancy differed between the studies. Some authors defined it as the presence of gestational sac on ultrasound at 6-8 weeks²⁴ or at 7 weeks of gestation^{12,18,26} or as at least one gestational sac visualized within the uterus on transvaginal ultrasound at 8 weeks of gestation.²³ Similarly, in one other study, clinical pregnancy was defined as at least one gestational sac with or without fetal heart activity at 7 weeks of gestation.¹⁹ On the other hand, other authors defined clinical pregnancy as an intrauterine gestational sac with embryonic cardiac activity at 7 weeks²⁰ or as an intrauterine gestational sac with fetal heart activity on ultrasound without specifying the gestational age.^{9,22} Finally, in two reports, no definition was given^{21,27}

In three studies, significantly higher clinical PRs were reported in the immediate group^{18,19,21} whereas in one, that of Volordasky-Perel

et al, a higher clinical PR was reported in the delayed group. In the other eight series, no significant differences were observed.

From a statistical point of view, there was very significant heterogeneity (Cochran's $q = 34.97$, $P < .001$), $I^2 = 68.03\%$. Again, the aforementioned study,²² although small in sample size, obtained results apparently inconsistent with the other studies.

The meta-analysis showed a trend to somewhat higher clinical PRs in the immediate group, but without statistical significance. The RR was 1.07 (CI = 0.99-1.15), $P = .098$.

In the subanalysis by embryo development stage (cleavage embryos; blastocysts; cleavage embryo or blastocysts), the meta-analysis obtained similar RRs in the immediate and delayed FETs in all three categories considered, none of the differences reaching significance (Figure S5).

When subanalysis was performed by FET indication (freeze-all, FET after failed fresh transfer, both), the meta-analysis showed no significant differences between immediate and delayed rates in the freeze-all or FET-after-failed-fresh-transfer subgroups (Figure S6). Further, as only one study considered both freeze all and FET after failed fresh transfer, no meta-analysis could be performed.

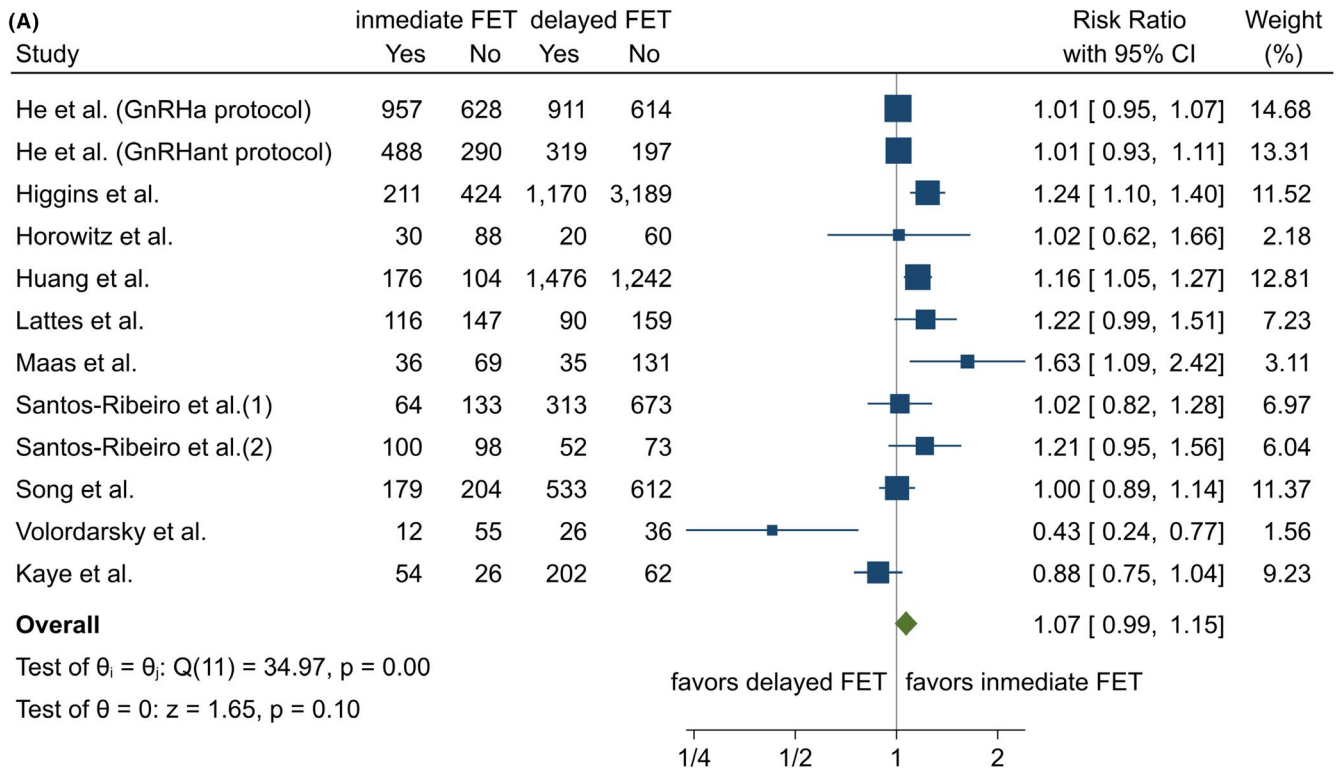
3.3.4 | Live birth rate

The live birth rate was reported in 10 studies, one of them presenting the data for GnRH agonist and antagonist groups separately (Figure 4B).²⁴ As for the other variables of interest, definitions of live birth varied between the studies. It was defined as the birth of a live infant at >20 weeks of gestation in one study,¹⁸ at ≥ 20 weeks of gestation in two,^{25,27} and at >24 weeks in two.^{9,22} In contrast, in one other study, it was defined as the delivery of a viable infant at ≥ 24 weeks.¹⁹ Other authors also set the cutoff at 24 weeks, but additionally considered unknown outcomes (patients lost to follow-up) as negative.²⁶ Further, in one study, live birth was defined as the delivery of any viable neonate ≥ 28 weeks, and twins delivered by one mother were counted as one live birth,²⁴ while in another, live birth rate was established as the number of live birth deliveries per FET.²⁰ Finally, live birth rate was not defined in two series.^{21,23}

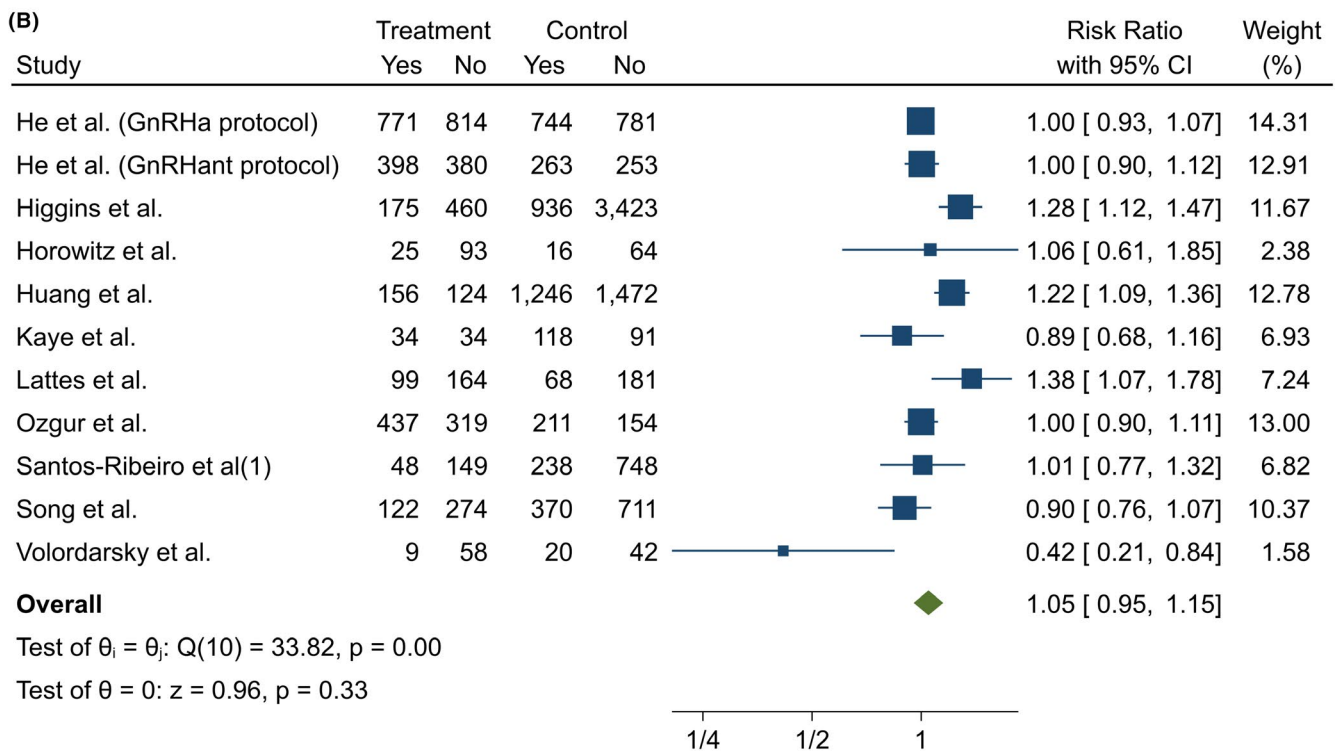
There were no statistically significant differences in the live birth rate between the immediate and delayed groups. The RR was 1.05 (CI = 0.95-1.15), $P = .335$. There was statistically significant heterogeneity (Cochran's $q = 33.8$, $P < .001$), $I^2 = 72.6\%$.

In the subanalysis by embryo development stage (cleavage embryos; blastocysts; cleavage embryo or blastocysts), the meta-analysis obtained similar RRs in the immediate and delayed FETs in all three categories considered, none of the differences reaching significance (Figure S7).

When the subanalysis was performed by FET indication (freeze-all, FET after failed fresh transfer, both), the RR of the live birth rate in the immediate vs delayed FETs did not differ between the subgroups (Figure S8).



Random-effects REML model



Random-effects REML model

FIGURE 4 (A) Meta-analysis of studies reporting clinical pregnancy rates by FET interval. Meta-analysis of the data from 11 series (10 publications) that reported clinical pregnancy rate as an outcome showed that the clinical pregnancy rate was significantly increased in the immediate FET. (B) Meta-analysis of studies reporting live birth rates by FET interval. Meta-analysis of the data from 11 series (10 publications) that reported live birth rate as an outcome showed that there were no significant differences between immediate and delayed FETs. REML, restricted maximum likelihood [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

Embryo freezing/thawing is a widely performed technique, either in selected patients such as those with hyperstimulation risk,³⁵ endometrial problems,¹⁰ or elevated progesterone levels,³ patients undergoing preimplantation genetic diagnosis cycles,^{20,36,37} or in all patients as proposed by a number of authors.³⁸⁻⁴⁰

One of the arguments in favor of frozen embryo cycles is that the endometrium would be more favorable to implantation,⁴¹⁻⁴⁵ since it has not been under the influence of high estrogen levels, especially in hyper-responders.^{20,45} Most of the differences in outcomes between fresh ET and FET seem to be due to the effect of ovarian stimulation on endometrial receptivity and embryo-endometrium synchrony.⁴⁶ Nonetheless, it is unknown how much time is required for the expression of endometrial genes and the immunological environment to return to their prestimulation functionality.²⁰ On the other hand, excessively postponing ET could increase the stress and the anxiety that usually accompany IVF.⁴⁷⁻⁴⁹ Moreover, although only to a small extent, postponing ET contributes to increase the time to pregnancy, a parameter that is increasingly receiving attention as an important marker of the quality of IVF.^{50,51}

There are a number of recommendations regarding the management of cycles with frozen/thawed embryos, regarding endometrial preparation, progesterone supplementation, cycle monitoring, and implantation window assessment.⁵²⁻⁵⁶ Nonetheless, there is no agreement concerning the usefulness of delaying ET.

In our search, from the 520 publications initially retrieved, we found 12 fulfilling the inclusion criteria, these including a total of 17 948 FETs (5443 immediate and 12 505 delayed). Among them, there was a remarkable methodological heterogeneity: Six included only freeze-all patients,^{19,20,24-27} four only patients with FET after failure of a previous fresh ET,^{9,12,21,22} and two both freeze-all and previously failed fresh transfers.^{18,23}

It should be highlighted that we did not find any prospective randomized trials or prospective trials. Regarding their quality as assessed by the Newcastle-Ottawa Scale, eight studies obtained the maximum score -9 and four scored -7. All of them were retrospective, and all of them were single-center studies, except one that included two centers.¹² On the other hand, there were marked differences in cycle management, both in the OPU cycle and in the cryotransfer cycle. In cryotransfer cycles, the most commonly used treatment was estradiol valerianate and micronized progesterone, although the doses used varied. FET was considered immediate when performed during the first menstrual cycle following the cycle in which OPU or EF had been performed. On the other hand, transfer was considered delayed when the ET was performed during the second menstrual cycle after OPU/EF or later.

In seven of the studies reviewed, no differences were reported in any of the IFV outcome parameters.^{9,12,23-27} At least one IVF outcome parameter was better in the delayed transfer group in just one

study,²² while at least one such parameter was better in the immediate transfer group in four studies.¹⁸⁻²¹ In one of these four, however, the differences disappeared in multivariate analysis,²⁰ and in another, no multivariate analysis was performed.²¹

Since the studies reviewed were not randomized, we performed a separate analysis of three of the most important prognostic factors in IVF, namely maternal age,^{57,58} the number of oocytes retrieved,⁵⁹ and the number of embryos transferred.^{60,61} All of them were very similar in the immediate and delayed transfer groups, and hence, these were ruled out as confounding factors.

Five studies reported the IR. Better results were obtained in immediate FET in one study¹⁹ and in delayed FET in another,²² while no differences were seen in the other three.^{20,23,24} The meta-analysis showed similar IRs in the immediate and delayed FET groups (RR = 0.98; CI = 0.83-1.16).

Concerning biochemical PR, data were given also in five reports.^{12,19,20,23,27} The meta-analysis revealed that there was a trend to higher biochemical PRs in the immediate group. The RR was 1.08 (CI = 1.00-1.18).

Regarding clinical PR, data were provided on 12 series from 10 publications.^{9,12,18-24,26,27} Two studies found significantly higher clinical PRs in the immediate group,^{19,21} whereas one observed a higher clinical PR in the delayed group.²² In the other eight series, no significant differences were observed. Our meta-analysis revealed that in the immediate FET the clinical pregnancy rate was somewhat higher, with the lower CI close to the unit (RR = 1.07; CI = 0.99-1.15).

Concerning live birth rate, the gold standard outcome parameter, data were provided in 11 series from 10 publications.^{9,18-20,22-27} In three series, the live birth rate was significantly higher in immediate FET,¹⁸⁻²⁰ and in one, it was significantly higher in delayed FET.²² Our meta-analysis reported similar live birth rates in the immediate and delayed FET groups. The RR was 1.05 (CI = 0.95-1.15).

In brief, none of the IVF outcome parameters studied was better in delayed FET than in immediate FET. On the contrary, clinical PR and biochemical PR were somewhat higher in the immediate FET, but p values were not significant ($P = .098$). Therefore, our analysis fails to confirm the theoretical beneficial effects (more receptive endometrium, resting ovaries) of waiting \geq one cycle. Indeed, it could be speculated that there could be a rebound effect similar to that described in the ovary^{62,63} or with the growth of myomas after stopping medical GnRH analog treatment.⁶⁴

When we performed meta-analyses concerning embryo development stage and FET indication (freeze-all, FET after failed fresh transfer, or both), results were similar in immediate and delayed FETs.

From our study, it is clear that systematically delaying FET does not offer benefits. First at all, immediate transfer is associated with a nonsignificant trend to better clinical PR. Moreover, it also avoids the psychological effects of prolonging the stress on prospective parents and, in any case, avoids delaying either the pregnancy or a new attempt if the current attempt has not been successful. Finally, it should be noted that the studies included have limitations, particularly due to their retrospective and non-randomized nature.

DISCLOSURES

Conflict of interest: Roberto Matorras, José Ignacio Pijoan, Irantzu Perez-Ruiz, Lucía Lainz, Iker Malaina, and Sonia Borjaba declare that they have no conflict of interest. **Human/animal rights:** This article does not contain any studies with human and animal subjects performed by the any of the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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