Does maternal age affect assisted reproduction technology success rates after euploid embryo transfer? A systematic review and meta-analysis

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Importance: Maternal age-related embryo aneuploidy is considered the most significant limiting factor for a favorable outcome after assisted reproduction technology (ART) procedures. Thus, preimplantation genetic testing for aneuploidies has been proposed as a strategy to genetically evaluate embryos before transfer to the uterus. However, whether embryo ploidy justifies all the aspects of age-related fertility decline remains controversial.
Objective: To investigate the effect of different maternal ages on ART success rates after transfer of euploid embryos.
Data Sources: ScienceDirect, PubMed, Scopus, Embase, the Cochrane library, Clinicaltrials.gov, EU Clinical Trials Register, and World Health Organization International Clinical Trials Registry were searched from inception until November 2021 using combinations of relevant keywords.
Study Selection and Synthesis: Observational and randomized controlled studies were included if they investigated the impact of maternal age on ART outcomes after the transfer of euploid embryos and reported frequencies of women achieving ongoing pregnancy or live birth.
Main Outcomes: The ongoing pregnancy rate or live birth rate (OPR/LBR) after euploid embryo transfer comparing women <35 vs. women ≥35 years old was the primary outcome. Secondary outcomes included implantation rate and miscarriage rate. Subgroup and sensitivity analyses were also planned to explore the sources of inconsistency among studies. The quality of studies was assessed using a modified version of the Newcastle-Ottawa Scale, and body of evidence was evaluated using the Grading of Recommendations Assessment Development and Evaluation working group methodology.
Results: A total of 7 studies were included (n = 11,335 ART embryo transfers of euploid embryos). A higher OPR/LBR (odds ratio, 1.29; 95% confidence interval [CI], 1.07–1.54; $I^2 = 40\%$) in women aged <35 years than in women ≥35 with a risk difference equal to 0.06 (95% CI, 0.02–0.09) was found. In line, implantation rate was higher in the youngest group (odds ratio, 1.22; 95% CI, 1.12–1.32; $I^2 = 0\%$). A statistically significant higher OPR/LBR was also found comparing women aged <35 to women 35–37, 38–40, or 41–42. A gradient relationship between age and OPR/LBR could be observed in proportion meta-analysis, especially if restricted to studies with low risk of bias.
Conclusion and Relevance: Increasing maternal age is associated with a decline in ART success rates independent of embryo ploidy. This message contributes to an appropriate patient's counseling before starting preimplantation genetic testing for aneuploidies procedures.
PROSPERO Registration Number: CRD42021289760. (Fertil Steril® 2023;120:251-65. ©2023 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Maternal age, euploid blastocyst, PGT-A, embryo implantation, ongoing pregnancy, live birth

Despite improvements in assisted reproduction technology (ART) procedures, live birth rates (LBRs) remain suboptimal, especially in advanced age women. The inefficiency in ART may result from many factors, but from the 1990s, age-related embryo aneuploidy has been considered the most significant determinant of cycle outcomes (1–3). The prevalence of aneuploidy relative to the age of the female partner demonstrates the lowest risk in women from their middle to late 20s and rises steadily from age 31 through age 43. Hence, preimplantation genetic testing for aneuploidies (PGT-A) has been integrated into ART practice as a strategy to genetically evaluate embryos before transfer to

Received November 4, 2022; revised and accepted February 27, 2023; published online March 5, 2023.
A.V. has nothing to disclose. A.P. has nothing to disclose. P.V. has nothing to disclose.
Supported in part by the Italian Ministry of Health – Current Research IRCC.
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Fertility and Sterility® Vol. 120, No. 2, August 2023 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2023.02.036

the uterus. The procedure was supposed to theoretically decrease the risk of implantation failure and miscarriage while mitigating the need to perform multiple embryo transfers (4). However, because of its uncertain benefits, PGT-A remains one of the most intensely contested procedures in reproductive medicine. In a recent opinion article, the procedure was defined "a conflict capable of boiling the ocean" (5). The rapid popularity gained by PGT-A and its consequent widespread adoption without proper validation have resulted, in recent years, to a consistent body of literature focused on its limitations (6, 7). This has probably somehow diverted attention from other age-related factors potentially associated with a decline in human fertility independent of ploidy (8). Indeed, whether ploidy determination for embryo selection can mitigate all the aspects of age-related fertility drop remains uncertain (9). Notably, some studies have investigated the possible impact of growing maternal age on sustained implantation rates (IRs) of euploid embryos, with controversial results (10–12). Elucidating this issue has both clinical and scientific implications. On one hand, adding complexity to age-related fertility decline may contribute to more appropriate patient counseling regarding the possibility to conceive later in life. On the other hand, it represents an unprecedented incentive to investigate further age-related obstacles to a successful pregnancy.

A summary of the available studies investigating the possibility that factors other than embryo chromosome segregation errors may be detrimental to reproductive outcomes is utterly needed. The aim of this study was to investigate whether increasing maternal age may limit ART success independent of ploidy status. Specifically, the main objective was to evaluate whether maternal age can influence ART success rates after the transfer of euploid embryos through a systematic review and meta-analysis of published data.

MATERIALS AND METHODS

This is a systematic review and meta-analysis of published data. A protocol was prospectively registered in PROSPERO (Centre for Reviews and Dissemination, University of York, UK; http://www.crd.york.ac.uk/PROSPERO/; National Institute for Health Research, 2021) as CRD42021289760. The recommendations of the PRISMA statement for systematic reviews and meta-analyses were followed (13).

Information Sources, Search, and Eligibility Criteria

Search strategy from electronic databases and key search terms are reported in a companion file (Information sources and search strategy).

Study Selection and Data Collection Process

Inclusion was based on the following criteria: evaluation of the impact of maternal age on ART outcomes after the transfer of euploid embryos (i.e., defined as normal with PGT-A performed with comprehensive chromosomal screening technology, including real-time quantitative polymerase chain reaction, array, comparative genomic hybridization and next-generation sequencing [NGS]); and reported frequencies of women achieving ongoing pregnancy rate (OPR) or LBR. The following exclusion criteria were applied: evaluation of the effects of maternal age on the reproductive outcomes not planned a priori (i.e., not declared in the methods section); oocytes or embryo donation cycles; impossibility to isolate/extract primary outcome data; case reports; non-original or duplicated data; and articles not in English.

Two investigators (A.V., A.P.) extracted data about study features, populations (number and inclusion criteria), embryonic culture stage and technique for PGT-A, ovarian stimulation protocols, embryo transfer cycle (protocol for endometrial preparation, luteal phase support) and study outcomes. Outcome data were extracted from the text and/or tables of original studies. When not explicitly mentioned by investigators, the missing outcome data was calculated based on other outcome data available (e.g., miscarriage rate (MR) calculated as the difference between clinical and ongoing pregnancies). One investigator (P.V.) reviewed the entire data extraction process.

Assessment of the Risk of Bias

Two reviewers (A.V., A.P.) independently judged the methodological quality of studies included in the meta-analysis using a modified version of the "Newcastle-Ottawa Scale" (14). To note, because the present analysis was focused on the effects of the variable "age" and in view of the observational nature of this variable, a methodological evaluation tool for observational studies was adopted for all the studies included in this review. The quality of the studies was evaluated in 5 different domains: "sample representativeness," "sampling technique," "study aim," "quality of description of the population," and "incomplete outcome data" (Supplemental Table 1, available online). According to the total number of points assigned, each study was judged to be at low risk of bias ($\geq$3 points) or high risk of bias ($<$3 points). Any discrepancies concerning the investigators' judgments were referred to a third reviewer (P.V.) and resolved by consensus.

Data Synthesis

Ongoing pregnancy or live birth rate after euploid embryo transfer comparing women $<$35 years old vs. women $\geq$35 years old was our primary outcome. Secondary outcomes included the evaluation of IR and MR in women $<$35 years old compared with women $\geq$35 years old. Additional analyses included the paired comparison of the reproductive outcomes between different age groups (i.e., $<$35 vs. 35–37, 38–40, 41–42, $>$42 years old; $<$38 vs. $\geq$38 years old) and the calculation of pooled success rates within each age group (i.e., proportion meta-analysis for each study outcome). Measures included:

- OPR/LBR (per embryo transfer). "Ongoing pregnancy" was defined as a pregnancy beyond 12 weeks' gestation. "Live birth" was defined as the delivery of one or more living infants.

- IR was defined as the number of gestational sacs on transvaginal ultrasound divided by the number of embryos transferred.
- MR (per clinical pregnancy) was defined as fetal loss before the 20th week of gestation divided by the number of clinical pregnancies (11).

Meta-analysis of binary outcomes was performed independently by 2 investigators (A.V., A.P.) with Review Manager version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration). The random effects model (DerSimonian and Laird method) was employed. All results were compared, and differences were discussed. Study outcomes were expressed using odds ratio (OR) with 95% confidence interval (CI). Finally, the difference between the observed risks (proportions of individuals with the outcome of interest) in the 2 groups was expressed as absolute risk difference (RD) with 95% CI. *P* value less than 0.05 was considered statistically significant. Higgins I^2 was used to assess heterogeneity (defined as low when I^2 was $<3\%$, moderate if between 30% and 50%, and high if I^2 was $>50\%$). Subgroup and sensitivity analyses were also planned to explore the sources of inconsistency among studies (when at least 3 studies were included in meta-analysis) for the comparison between women <35 years old and those ≥ 35 years old. Proportion meta-analysis was completed using MedCalc 16.4.3. The proportion of patients was analyzed at 95% CI. The random effects model was applied. We followed Cochrane Handbook recommendations for the assessment of publication bias (Cochrane Handbook. 10.4.3.1 Recommendations on testing for funnel plot asymmetry).

To corroborate results from the meta-analysis, data stored in the Society for Assisted Reproductive Technology (SART) website (https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx) (15) were acquired and analyzed. Available data was filtered to include PGT-A cycles performed both at the blastocyst or cleavage stage from 2014–2020. The total number of LBRs was calculated including first and subsequent frozen embryo transfers. The cumulative LBR per embryo transfer was graphically reported according to female age including the CI according to the Wilson score interval. Cumulative LBRs were compared between groups with a chi-squared test.

Grading of Evidence

The body of evidence was assessed by 2 investigators (A.V., A.P.) using the GRADE (Grading of Recommendations Assessment Development and Evaluation working group) methodology (16). The final score was obtained by evaluating the following domains: study design, risk of bias, indirectness, inconsistency, imprecision, large effect size, plausible confounding, and publication bias. Dose response gradient was not evaluated because the intervention was dichotomous.

RESULTS

After screening the records, 31,941 titles were found, 31,188 of which were excluded after screening the titles and 737 were excluded after screening the abstracts. Sixteen full text records were assessed for eligibility. Therefore, after the evaluation of the full text, 9 studies were excluded (9, 17–24). Six studies were excluded because of the inability to retrieve data about OPR/LBR (9, 18, 20, 21, 22, 24). Two additional studies were excluded because the analysis of the effect of maternal age on the embryo transfer outcome was not planned a priori (17–19). Another study was excluded because PGT-A was performed by using fluorescence in situ hybridization (22). Finally, a total number of 7 studies were included in the present meta-analysis (10, 12, 25–28) (Fig. 1).

The studies embedded a total number of 11,335 embryo transfer cycles (Table 1). Two were multicenter randomized controlled trials (RCTs) (10,27). The other studies were retrospective, including one multicenter study (11, 12, 25–28). The studies by Whitney et al. (27) and Yan et al. (28) were designed to evaluate ART outcomes with or without PGT-A. Therefore, only patients belonging to the PGT-A group were extracted for meta-analysis. One study was available only as a meeting abstract (27).

Patients

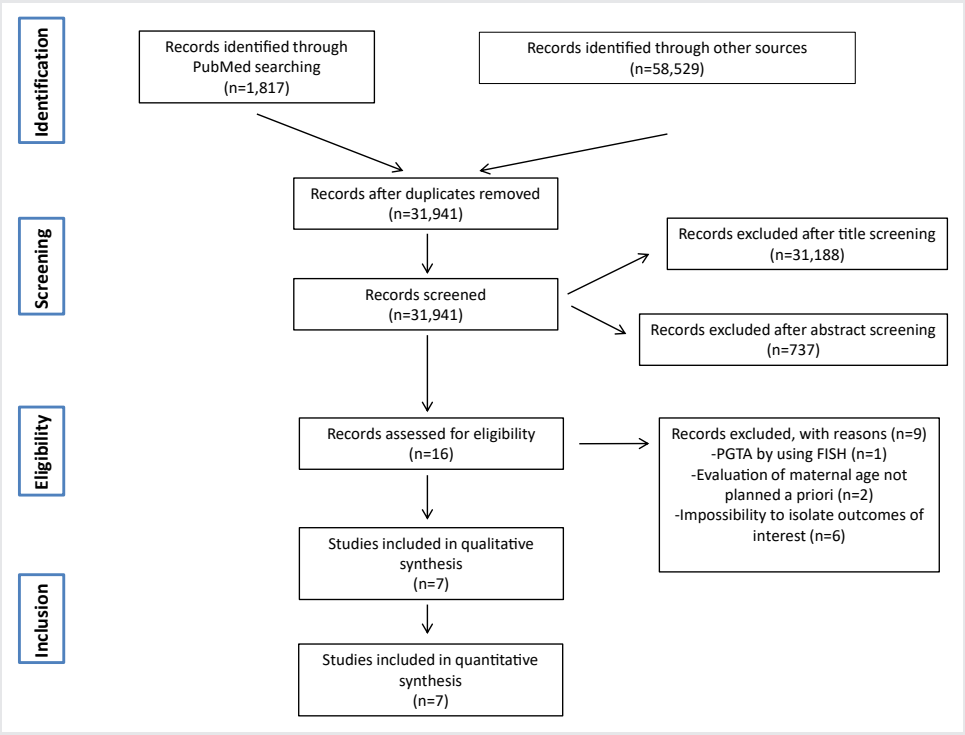
Information about patients' history of ART attempts was not available for 2 studies (25, 27). The study by Tong et al. (26) included patients with $\geq$ 2 embryo implantation failures. Yan et al. (28) included patients undergoing their first ART cycle. The other studies included populations with an unselected number of previous embryo transfers (10, 26, 28).

Regarding the causes of infertility, 4 studies did not report precise information (i.e., percentages of infertility indication of the study population not reported) (11, 12, 25, 27). Three studies included women with heterogeneous causes of infertility (i.e., male factor, tubal factor, diminished ovarian reserve) (10, 26, 28).

Ovarian Stimulation and Embryo Transfer

All patients underwent homologous ART cycles (Table 1). Four studies reported data about the ovarian stimulation protocols (11, 12, 26, 28), and they are described in Table 1. A single blastocyst was transferred in all studies with the exception of the studies by Irani et al. (11) and Whitney et al. (27) (i.e. up to 2 blastocysts transferred). All the transferred embryos were frozen-thawed, except in the study by Harton et al. (25) (i.e. some blastocysts were fresh-transferred after day 3 biopsy). The technique for embryo freezing was vitrification in all studies, with the exception of the study by Harton et al. (25) (vitrification or slow cooling). Protocols for endometrial preparation and luteal phase support were not described in the majority of studies. In the study by Irani et al. (11), natural cycles or artificial cycles (including escalating doses of estradiol via transdermal patches followed by intramuscular progesterone) were applied. Two studies reported the use of double embryo transfers: in particular, 46/171 (27%) and 85/785 (11%) of patients received a double embryo transfer in the studies by Whitney et al. (27) and Irani et al. (11), respectively, accounting for ~1% of the total number of included embryo transfer procedures.

FIGURE 1



PRISMA flow diagram of article screening for the review.

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PGT-A

Preimplantation genetic testing for aneuploidy was generally performed at the blastocyst stage on day 5 or 6 of embryo development; Harton et al. (25) also included day 3 embryos (biopsy at cleavage stage with fresh embryo transfer on day 5). Genetic testing was performed through comparative genomic hybridization arrays or NGS-based assays; Reig et al. (12) used 24 chromosome real-time polymerase chain reaction and NGS.

Aneuploidy rate in biopsied blastocysts was reported in 4 studies and ranged between 28.9% and 54.2% (10, 25, 26, 28). Aneuploidy rate was reported according to female age <35 or ≥ 35 years, being 31.7% and 51.9% in the study by Harton et al. (25) and 49.3% and 61.9% in the study by Munné et al. (10), respectively. Similarly, Tong et al. (26) reported that the blastocyst aneuploidy rate was higher in women aged ≥ 38 years (74.1%) compared with women <38 years (49.2%).

Embryos eligible for transfer were those classified as euploid after comprehensive chromosome screening. Tong et al. (26) classified embryos with aneuploid percentage under 20% as euploid; in the study by Yan et al. (28), 6 of 606 couples received mosaic embryos. In the remaining studies, mosaic blastocysts were not considered for embryo transfer.

Assessment of Study Quality and Risk of Bias of Included Studies

Sample representativeness: All studies had adequate sample representativeness based on our criteria. Therefore, no study was judged at high risk of bias.

Sampling technique: Five studies had adequate sampling strategy (10–12, 26, 28). The other studies did not provide data (25, 27).

Study aim: Three studies were judged at high risk of bias as their primary outcome did not comply with the aim of our review (10, 26, 28). The other studies were at low risk of bias (11, 12, 25, 27).

Quality of description of the population: A single study was considered at low risk of bias (28). The other studies failed to provide adequate information about ovarian stimulation, endometrial preparation strategy, luteal phase support and/or baseline characteristics of the study population (10–12, 25–27).

Incomplete outcome data: Three studies provided incomplete outcome data (outcome data not explicitly mentioned by the investigators in the articles) (26–28).

According to the total number of points assigned, 5 studies were judged at low risk of bias (≥ 3 points), whereas 2 studies were at high risk of bias (<3 points) (Supplemental Table 2) (10–12, 25–28). Assessment of

TABLE 1

General characteristics of the studies included

Investigator and year	Study design; country	Participants and main inclusion criteria (number)	Ovarian stimulation (drugs)	Embryo transfer cycle	Age class Confounders adjusted	Outcomes
Harton et al. 2013 (25)	Multicenter retrospective study; United States	913 cycles of patients undergoing PGT-A - PGT-A was made on culture day 3 (single blastomere tested) or day 5-6 tested with microarray-CGH	ICSI or c-IVF - Data about ovarian stimulation and luteal phase support not described	- Fresh embryo transfer for embryos tested on day 3 - Frozen-thawed embryo transfer for embryos tested on day 5-6 (protocol not reported) (single embryo transfer) Endometrial preparation and luteal phase support not described	<35 y 35–37 y 38–40 y 41–42 y >42 y Data split based on the day of biopsy (day 3; day 5–6) No adjustment for confounders	- Implantation rate - Miscarriage rate - Ongoing pregnancy rate
Whitney et al. 2014[a] (27)	Retrospective study; United States	195 patients undergoing PGT-A - PGT-A was made on day 5-6 tested with microarray-CGH	No data available	- Frozen-thawed embryo transfer for embryos tested on day 3 or 5–6 (protocol not reported) Endometrial preparation and luteal phase support not described	<35 y 35–37 y 38–40 y 41–42 y >42 y No adjustment for confounders	- Implantation rate - Miscarriage rate - Live birth rate
Irani et al. 2019 (11)	Retrospective study; United States	870 embryos screened with PGT-A (785 cycles) - PGT-A was made on culture day 5-6 tested with microarray-CGH	- rFSH or hMG with dose based on ovarian reserve - long agonist or short antagonist cycles - U-hCG (10,000 IU) or GnRH agonist (0.4 mg) at follicle size 17 mm (≥2). - Oocyte pick up 35–37 h later - ICSI	- Frozen-thawed embryo transfer for embryos tested on day 5-6 Luteal phase support with vaginal progesterone (400 mg/d in natural cycle) or intramuscular progesterone (artificial cycle)	<35 y 35–37 y 38–40 y 41–42 y >42 y Data split based on the day of biopsy (day 5–6) and blastocyst quality Adjusted for blastocyst quality and day of biopsy	- Implantation rate - Miscarriage rate - Live birth rate
Munnè et al. 2019[b] (10)	Multicenter RCT [NCT02268786]; United States, Canada, United Kingdom, Australia	2,178 embryos screened with PGT-A (330 patients) - Patients 25–40 y of age with at least 2 blastocysts - PGT-A was performed by day 6 of development with NGS-based assay	Each clinic followed their own standard of care (no specific data available)	- Frozen-thawed embryo transfer (single embryo transfer) Endometrial preparation and luteal phase support based on each center practice	25–34 y 35–40 y Data split based on blastocyst quality and participating centers	-Implantation rate -Miscarriage rate -Ongoing pregnancy rate
Reig et al. 2020 (12)	Retrospective study; United States	8,175 embryos screened with PGT-A - PGT-A was made on culture day 5 tested with microarray-CGH	- Gonadotropin dose based on ovarian reserve - Short antagonist, short flare up of long agonist cycles - U-hCG (10,000 IU) or GnRH agonist (0.4 mg) at follicle size 17–18 mm (≥2). - Oocyte pick up 34–36 h later - ICSI	- Frozen-thawed embryo transfer (single embryo transfer) Endometrial preparation and luteal phase support not described	<35 y 35–37 y 38–40 y 41–42 y >42 y Adjusted for AMH, blastocyst quality and day of biopsy	- Implantation rate - Live birth rate - Miscarriage rate

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TABLE 1

Continued.

Investigator and year	Study design; country	Participants and main inclusion criteria (number)	Ovarian stimulation (drugs)	Embryo transfer cycle	Age class Confounders adjusted	Outcomes
Tong et al. 2021 (26)	Retrospective study; People's Republic of China	265 couples screened with PGT-A (346 cycles)- patients with ≥ 2 recurrent implantation failures	- Gonadotropin dose and type of protocol based on ovarian reserve - U-hCG (10000 IU) for ovulation induction - ICSI	- Frozen-thawed embryo transfer (single embryo transfer) Endometrial preparation and luteal phase support not described	<38 y ≥38 y Data split based on blastocyst quality No adjustment for confounders	- Implantation rate - Ongoing pregnancy rate - Miscarriage rate
Yan et al. 2021[b] (28)	Multicenter RCT [NCT03118141]; People's Republic of China	1,809 blastocysts screened with PGT-A (606 couples)- good-prognosis patients aged 20–37 y with 3 or more good-quality blastocysts	- GnRH agonist (long or short protocol) or GnRH antagonist + gonadotropin - hCG, GnRH agonist, or both for final oocyte maturation. - Oocyte pick up 34–36 h later - ICSI	- Frozen-thawed embryo transfer (single embryo transfer) for embryos tested on day 5 Endometrial preparation and luteal phase support based on each center practice	≤30 y >30, ≤35 y >35 y No adjustment for confounders	- Live birth rate

AMH = antimüllerian hormone; CGH = comparative genomic hybridization; c-IVF = conventional in vitro fertilization; GnRH = gonadotropin releasing hormone; hMG = human menopausal gonadotropin: ICSI = intracytoplasmic sperm injection; IU = international unit; NGS = next-generation sequencing; PGT-A = preimplantation genetic testing for aneuploidies; RCT = randomized controlled trial; rFSH = recombinant FSH; r-hCG = recombinant human chorionic gonadotropin; U-hCG = Urinary Human chorionic gonadotropin.

[a] Abstract.

[b] Registered Trials: identification code in brackets [].

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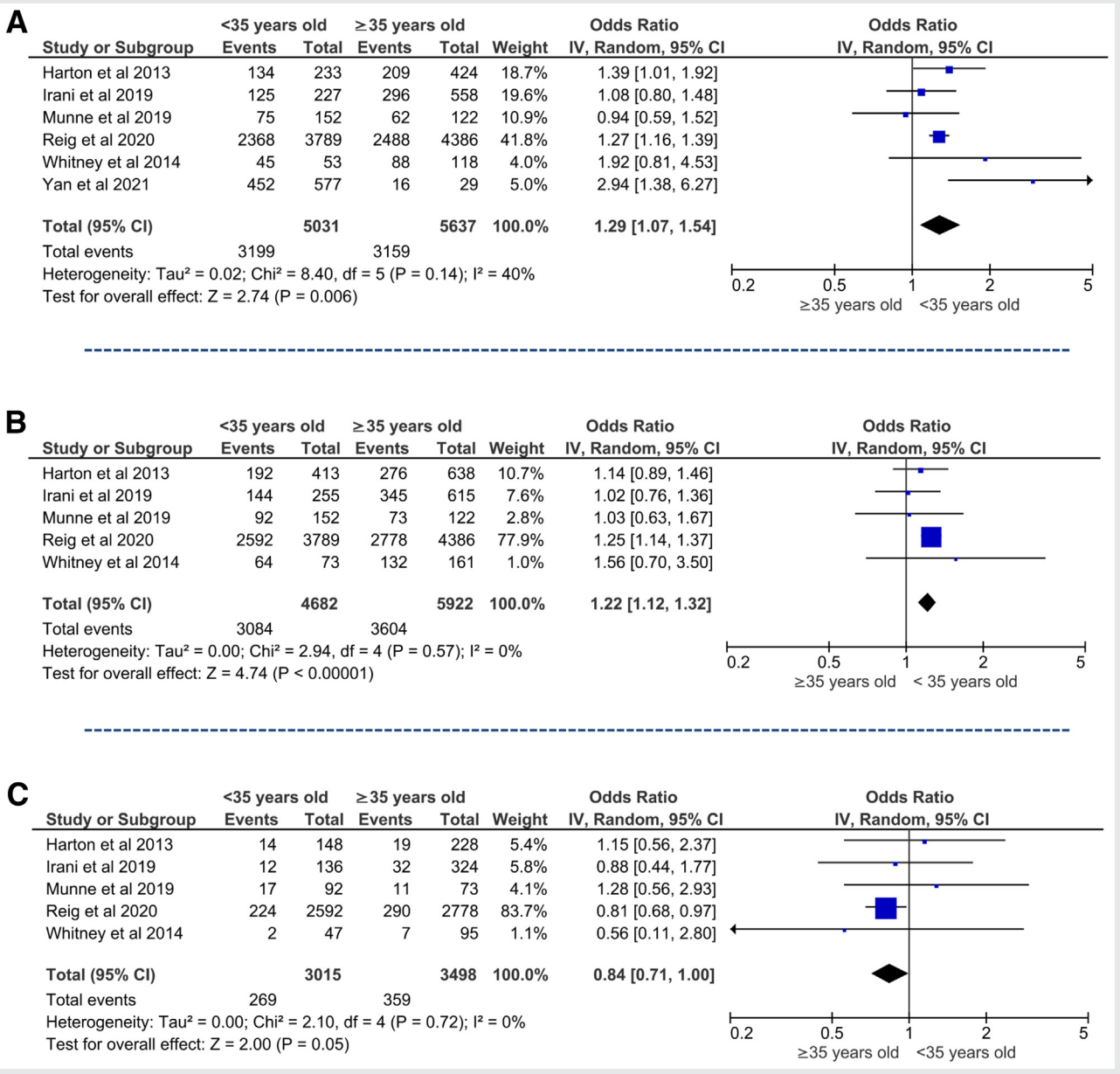
publication bias was not possible because an insufficient number of studies (less than 10) was included in pooled analysis for the primary outcome.

Meta-Analysis

Analysis of outcomes in women aged < 35 years vs. women aged ≥35 years. Analysis of data from 6 studies showed significantly higher OPR/LBR (OR, 1.29; 95% CI, 1.07–1.54; I^2 = 40%, P=.006; RD, 0.06; 95% CI, 0.02–0.09) in women aged <35 years compared with women ≥35 years (Fig. 2A) (10–12, 25, 27, 28). IR was significantly higher in the youngest group (OR, 1.22; 95% CI, 1.12–1.32; I^2 = 0%, P<.00001; RD, 0.04; 95% CI, 0.02–0.06; Fig. 2B), with a trend toward a lower MR (OR, 0.84, 95% CI, 0.71–1.00, I^2 = 0%, P=.05; RD, -0.02; 95% CI, -0.03 to 0.00; Fig. 2C).

Sensitivity analysis. A sensitivity analysis was conducted by serially excluding specific data (i.e., day 3 PGT-A) and/or study subgroups (studies at high risk of bias, with a double embryo transfer) from pooled analysis.

FIGURE 2



(A) Forest plots for ongoing pregnancy/live birth rate. **(B)** Implantation rate. **(C)** Miscarriage rate. Euploid embryo transfer in <35 years old women versus ≥35 years old women meta-analysis.

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Exclusion of studies with high risk of bias. The sensitivity analysis based on study quality (i.e., by excluding studies at high risk of bias from pooled analysis) did not provide statistical changes to OPR/LBR (OR, 1.27; 95% CI, 1.05–1.53; I^2 = 47%; *P*=.01; RD, 0.06; 95% CI, 0.02–0.10), IR (OR, 1.21; 95% CI; 1.12–1.32; I^2 = 0%; *P*<.00001; RD, 0.04; 95% CI, 0.02–0.06) and MR (OR, 0.85; 95% CI, 0.72–1.00; I^2 = 0%; *P*=.05; RD, -0.01; 95% CI, -0.03 to 0.00) (27).

Exclusion of data with day 3 PGT-A. The exclusion of data referred to embryos analyzed by PGT-A in day 3 from meta-analysis did not change the results in terms of OPR/LBR, but reduced statistical heterogeneity (OR, 1.28; 95% CI, 1.13–1.45; I^2=14%; *P*<.0001; RD, 0.06; 95% CI, 0.04–0.08) (25). IR was almost unmodified (OR, 1.22; 95% CI, 1.12–1.33; I^2 = 0%; *P*<.00001; RD, 0.04; 95% CI, 0.02–0.06; data not shown). Different from the primary analysis, the MR was significantly higher in women aged ≥35 years (OR, 0.83; 95% CI, 0.70–0.98; I^2 = 0%; *P*=.03; RD, -0.02; 95% CI, -0.03 to 0.00).

Exclusion of studies with double embryo transfers. The results were substantially unchanged for OPR/LBR when excluding 131 cycles with double embryo transfer from 2 studies (11, 27) thus including only vitrified-warmed single euploid blastocyst transfers (OR, 1.33; 95% CI, 1.04–1.70; I^2 = 23%; *P*=.02; RD, 0.07; 95% CI, 0.01–0.12). Similar findings were observed in terms of IR (OR, 1.23, 95% CI, 1.13–1.34; I^2 = 0%; *P*<.00001; RD, 0.04; 95% CI, 0.03–0.06; data not shown) and MR (OR, 0.84; 95% CI, 0.71–1.00; I^2 =0%; *P*=.06; RD, -0.02; 95% CI, -0.03 to 0.00; data not shown).

Exclusion of studies with high risk of bias, double embryo transfers, and data on day 3 PGT-A. When evaluating only studies with fair quality on patients undergoing a single euploid embryo transfer after PGT-A at blastocyst stage, OPR/LBR still favored women <35 years old, with low inconsistency (OR, 1.31; 95% CI, 1.12–1.53; I^2 = 23%; *P*=.0009; RD, 0.06; 95% CI, 0.04–0.08). The results were unchanged after excluding data on cumulative LBR after 3 embryo transfers (OR, 1.26; 95% CI, 1.09–1.47; I^2 = 15%; *P*=.002; RD, 0.06; 95% CI, 0.02–0.09) (28). Additionally, women <35 years old had higher IR (OR, 1.24; 95% CI, 1.13–1.35; I^2 = 0%; *P*<.00001; RD, 0.04; 95% CI, 0.02–0.06; data not shown) and lower MR (OR, 0.83; 95% CI, 0.70–0.99; I^2 = 0%; *P*=.04; RD, -0.02; 95% CI, -0.03 to 0.00; data not shown) compared with women ≥35 years old.

Analysis of outcomes in women <35 years old vs. women 35–37 years old. Analysis of 6,922 embryo transfer cycles from 4 studies showed significantly higher OPR/LBR (OR, 1.19; 95% CI, 1.08–1.32; I^2 = 0%; *P*=.0005; RD, 0.04; 95% CI, 0.02–0.07) in women aged <35 years compared with women aged 35–37 years (Supplemental Fig. 1A, available online) (11, 12, 25, 27). Similarly, IR was significantly higher in the youngest group (OR, 1.13; 95% CI, 1.02–1.25; I^2 = 0%; *P*=.02; RD, 0.03; 95% CI, 0.01–0.06; data not shown), with no significant difference in terms of MR (OR, 0.82; 95% CI, 0.67–1.00; I^2 = 0%; *P*=.06; RD, -0.02; 95% CI, -0.03 to 0.00; data not shown). An additional analysis including adjusted data from those studies in which confounders adjustment was reported is shown in Supplemental Fig. 2A.

Analysis of outcomes in women <35 years old vs. women 38–40 years old. Analysis of 6,331 embryo transfer cycles from 4 studies showed significantly higher OPR/LBR (OR, 1.29; 95% CI, 1.16–1.44; I^2 = 0%; *P*<.00001; RD, 0.06; 95% CI, 0.04–0.09) in women aged <35 years than in women aged 38–40 years (Supplemental Fig. 1B) (11, 12, 25, 27). Similarly, IR was significantly higher in the youngest group (OR, 1.22; 95% CI, 1.04–1.44; I^2 = 24%, *P*=.02; RD, 0.04; 95% CI, 0.02-0.06; data not shown), with no significant difference in terms of MR (OR, 0.81; 95% CI, 0.65–1.02; I^2 = 0%, *P*=.07; RD, -0.02; 95% CI, -0.04 to 0.00; data not shown). An additional analysis including adjusted data from those studies in which confounders adjustment was reported is shown in Supplemental Fig. 2B.

Analysis of outcomes in women <35 years old vs. women 41–42 years old. Analysis of 4,816 embryo transfer cycles from 4 studies showed significantly higher OPR/LBR in women aged <35 years than in women 41–42 years old (OR, 1.46; 95% CI, 1.21–1.76; I^2 = 0%; *P*<.0001; RD, 0.09; 95% CI, 0.04–0.14) (Supplemental Fig. 1C) (11, 12, 25, 27). Additionally, IR was significantly higher in women <35 years old (OR, 1.42; 95% CI, 1.02–1.98; I^2 = 54%; *P*=.04; RD, 0.07; 95% CI, 0.01–0.13; data not shown), with no significant difference in terms of MR (OR, 0.86; 95% CI, 0.55–1.34; I^2 = 0%; *P*=.51; RD, 0.01; 95% CI, -0.04 to 0.07; data not shown). An additional analysis including adjusted data from those studies in which confounders adjustment was reported is shown in Supplemental Fig. 2C.

Analysis of outcomes in women <35 years old vs. women >42 years old. The analysis included 4,625 embryo transfer cycles from 4 studies. The size of the younger group (<35 years) was 13.32-fold greater than the older group (>42 years) (n = 4,302 and n = 323 embryo transfers, respectively). No significant differences were found between groups in terms of OPR/LBR (OR, 1.56; 95% CI, 0.80–3.06; I^2 = 70%, *P*=.20; RD, 0.09; 95% CI, -0.08 to 0.25; Supplemental Fig. 1D), IR (OR, 1.31; 95% CI, 0.66–2.61; I^2 = 73%; *P*=.45; RD, 0.04; 95% CI, -0.11 to 0.19; data not shown) and MR (OR, 0.88; 95% CI, 0.52–1.51; I^2 = 0%, *P*=.64; RD, -0.00; 95% CI -0.05 to 0.04, data not shown). An additional analysis including adjusted data from those studies in which confounders adjustment was reported is shown in Supplemental Fig. 2D.

Analysis of outcomes in women <38 years old vs. women ≥38 years old. Analysis of 9,913 embryo transfer cycles showed significantly higher OPR/LBR (OR, 1.23, 95% CI, 1.05–1.43, I^2 = 28%, *P*=.01; RD, 0.04; 95% CI, 0.01–0.09) in women aged <38 years than in women aged ≥38 years (Supplemental Fig. 1E), with a trend toward a higher IR (OR, 1.27; 95% CI, 1.00–1.62; I^2 = 68%; *P*=.05; RD, 0.05; 95% CI, 0.00–0.09; data not shown). No between-group difference was found in terms of MR (OR, 0.94; 95% CI, 0.70–1.25; I^2 = 15%; *P*=0.67; RD, 0.01; 95% CI, -0.03 to 0.04; data not shown). Data was derived from 5 studies (11, 12, 25–27).

Proportion Meta-Analysis

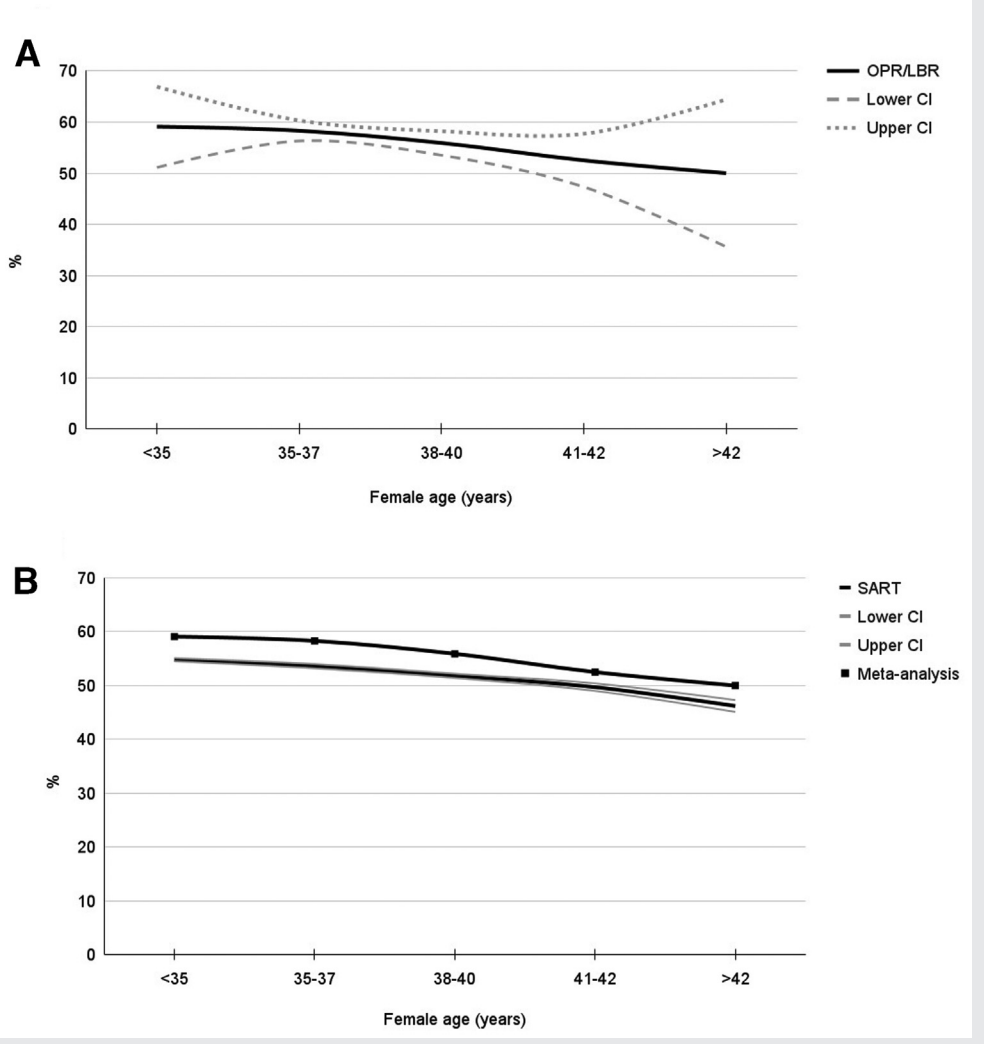
Women <35 years old: A total number of 5,098 embryo transfer cycles from 6 studies was analyzed (10–12, 25, 27, 28). Pooled OPR/LBR was 64.54% (95% CI, 55.77%–72.85%; I^2 = 94.95%). When the analysis was restricted to studies with low risk of bias and single blastocyst transfer after day 5–6 PGT-A, the pooled OPR/LBR out of 4,073 patients was 59.14% (95% CI, 51.14%–66.89%; I^2 = 81.25%) (10, 12, 25).

Women ≥35 years old: A total number of 5,637 patients from 6 studies was analyzed. Pooled OPR/LBR was 56.13% (95% CI, 50.92%–61.26%; I^2 = 83.29%) (10–12, 25, 27, 28). When the analysis was restricted to studies with low risk of bias and single blastocyst transfer after day 5–6 PGT-A, the pooled OPR/LBR out of 4,719 patients was 55.82% (95% CI, 53.21%–58.42%; I^2 = 17.82%) (10, 12, 25).

Women 35–37 years old: A total number of 2,620 patients from 4 studies was analyzed. Pooled OPR/LBR was 57.16% (95% CI, 52.02%–62.23%; I^2 = 60.84%) (11, 12, 25, 27). When the analysis was restricted to studies with low risk of bias and single blastocyst transfer after day 5–6 PGT-A, the pooled OPR/LBR out of 2,278 patients was 58.33% (95% CI, 56.30%–60.35%; I^2 = 0%) (12, 25).

Women 38–40 years old: A total number of 2,029 patients from 4 studies was analyzed. Pooled OPR/LBR was 57.35% (95% CI, 50.56%–64.00%; I^2 = 75.67%) (11, 12, 25, 27). When the analysis was restricted to studies with low risk of

FIGURE 3



Ongoing pregnancy/live birth rate (OPR/LBR) after euploid embryo transfer according to female age. **(A)** Results from the proportion meta-analysis restricted to studies with low risk of bias and single blastocyst transfer after day 5-6 PGT-A. **(B)** SART cumulative birth rate for first and additional frozen embryo transfer after PGT 2014-2020 (*black line with square markers* with upper and lower limits of the 95% CI in *gray*) compared with results from the present meta-analysis (*solid black line*). Linear interpolation was used to center the outcome rates on each integer of age; upper and lower limits of the 95% CI in *gray*. CI = confidence interval. SART = Society for Assisted Reproductive Technology.

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TABLE 2

Evidence profile: comparison of women < 35 years old vs. women ≥35 years old undergoing euploid embryo transfer.

Summary of findings:

Patient or population: Women undergoing euploid embryo transfer
Setting: not applicable
Comparators: < 35 y versus ≥35 y

	Anticipated absolute effects[a] (95% CI)					
Outcomes	**Risk if ≥35 y**	**Risk if < 35 y**	**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Ongoing pregnancy/live birth rate	560 per 1,000	622 per 1,000 (577 to 663)	OR 1.29 (1.07 to 1.54)	10.668 (6 studies)	⨁⨁⨁◯ MODERATE [b,c,d]	–
Implantation rate	624 per 1,000	675 per 1,000 (656 to 693)	OR 1.25 (1.15 to 1.36)	10.062 (5 studies)	⨁⨁⨁⨁ HIGH [b,d]	–
Miscarriage rate	103 per 1,000	88 per 1,000 (75 to 103)	OR 0.84 (0.71 to 1.00)	6.513 (5 studies)	⨁⨁◯◯ LOW [b,d,e]	–

Note: GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

CI = confidence interval; OR = odds ratio.

[a] **The risk in < 35 years old group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of age **< 35 years** (and its 95% CI).

[b] **Study design**. Quality of evidence downgraded by one level: data from both randomized controlled trials and observational studies

[c] **Inconsistency**. Quality of evidence downgraded by one level: moderate statistical heterogeneity (Higgings I^2 between 30 and 50%)

[d] **Strength of association**. Quality of evidence upgraded by one level: the effect size was consistent and unmodified after sensitivity analysis

[e] **Imprecision**. Quality of evidence downgraded by 2 levels: 95% CI around the pooled estimate of effect includes no effect; low number of events (n=255 in women <35 years old; n=320 in women ≥35 years old)

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bias and single blastocyst transfer after day 5–6 PGT-A, the pooled OPR/LBR out of 1,708 patients was 55.85% (95% CI, 53.49%–58.19%; $I^2 = 0\%$) (12, 25).

Women 41–42 years old: A total number of 514 patients from 4 studies was analyzed. Pooled OPR/LBR was 52.64% (95% CI, 45.67%–59.56%; $I^2 = 46.20\%$) (11, 12, 25, 27). When the analysis was restricted to studies with low risk of bias and single blastocyst transfer after day 5–6 PGT-A, the pooled OPR/LBR out of 352 patients was 52.54% (95% CI, 47.34%–57.72%; $I^2 = 0\%$) (12, 25).

Women >42 years old: A total number of 323 patients from 4 studies was analyzed (11, 12, 25, 27). Pooled OPR/LBR was 51.08% (95% CI, 33.51%–68.52%; $I^2 = 80.44\%$). When the analysis was restricted to studies with low risk of bias and single blastocyst transfer after day 5–6 PGT-A, the pooled OPR/LBR out of 301 patients was 49.98% (95% CI, 35.62%–64.35%; $I^2 = 69.09\%$). The overall graphical representation of this analysis is presented in Figure 3A.

Overall Quality of Evidence

For all the outcomes (OPR/LBR, IR, MR), the evidence quality was initially downgraded by one level (-1) because most of the studies were not RCTs (11, 12, 25–27). Subsequently, the evidence for specific outcomes was downgraded because of moderate inconsistency (OPR/LBR) or very serious imprecision (MR). For those outcomes in which the effect size was robust and consistent after the sensitivity analysis (OPR/LBR, IR), the quality of evidence was upgraded by one level (+1).

Finally, the quality of evidence was rated as moderate for OPR/LBR, high for IR, low for MR (Table 2).

Comparison with Data Retrieved in the SART Database

As shown in Figure 3B, the cumulative LBR per embryo transfer in PGT-A cycles recorded in the SART database showed a progressive and statistically significant decrease across female age ranges. In particular, it was found to be 54.8% (95% CI, 54.5%–55.1%), 53.6% (95% CI, 53.2%–54.0%), 51.8 (95% CI, 51.4%–52.2%), 49.7 (95% CI, 49.0%–50.4%), and 46.2% (95% CI, 45.1%–47.3%) in women aged <35 years, 35–37, 38–40, 41–42 and >42 years, respectively ($P<.0001$ for each comparison).

DISCUSSION

Based on the results presented herein, the increase of maternal age is associated with lower OPR/LBR even after the transfer of euploid blastocysts. Specifically, the OPR/LBR after PGT-A was significantly higher in women <35 years old than in those ≥35 years old. In a sensitivity analysis restricted to studies without high risk of bias, in which PGT-A was performed on day 5 of embryo development and without double embryo transfers, the association between age and OPR/LBR was seen to persist. A gradient relationship between age and OPR/LBR could be observed in the proportion meta-analysis especially if restricted to studies with low risk of bias. The OPR/LBR rate was the highest in women <35 years old and the lowest in women >42 years old. A significantly higher OPR/LBR after PGT-A was also observed in women <38 years old than in those ≥38 years old.

Results for IR mirrored those for OPR/LBR showing that IR after PGT-A was higher in women <35 years old than in older women in all the other age categories considered. The only exception was represented by the group of women >42 years old for whom no difference in terms of OPR/LBR and IR compared with women <35 years was found. In this case, a type II error is likely due to the large disproportion of samples between groups (i.e., ratio between groups of 13.32).

Along this line, a borderline significance toward a higher MR increasing maternal age independently from embryo ploidy was observed. The sensitivity analysis with the exclusion of studies with high risk of bias, double embryo transfers and data on day 3 PGT-A supported the statistical association between maternal age ≥35 years and increased MR after transfer of a euploid embryo. It is worth mentioning that the inclusion of embryos biopsied on day 3 in younger patients may have diluted the effect of age on MR; in fact, it is likely that the decision to biopsy cleavage stage embryos is linked to a lower prognosis of the couple independent of female age or embryo ploidy, implying a higher chance of negative outcomes than those biopsied at the blastocyst stage.

Nevertheless, the evidence quality for the outcome MR was low because of the severe imprecision, limiting our confidence in the effect estimate. In particular, we need to underline that MR was considerably low in both groups (i.e., 8.8% vs. 10.3% in women <35 and in those ≥35 years old, respectively), and the absolute number of events in each group was insufficient to draw firm conclusions (n = 255 and n = 320).

Comparison with other studies

This is the first comprehensive meta-analysis aimed to determine if increasing maternal age is associated with a decline in success rates after ART procedures independent of aneuploidy. Notably, to confirm our results, we have acquired and analyzed data stored in the SART website regarding PGT-A cycles performed between 2014 and 2020 (15), highlighting that the slope of the curve in relation to age substantially overlapped with that deriving from our proportion meta-analysis.

Interpretation

Results can be explained by the presence of factors other than chromosome segregation errors in determining age-related reproductive potential. Three main hypotheses can be proposed. First, a pivotal role of endometrial aging may be claimed. Recent findings suggest that age significantly affects endometrial gene expression and that major changes in endometrial function occur after 35 years of age (29). Using a genome-wide functional non-targeted approach, changes in molecular processes affected by age have been observed in the endometrium, including reduced epithelial cell proliferation owing to cell cycle arrest and upregulation of ciliary processes. Confirmation of this possibility is derived from some clinical evidence. In a study aimed to assess the reproductive

and neonatal outcomes of donor oocyte cycles in which embryos were transferred to gestational carriers compared with intended parent recipients, decreased pregnancy rates and poorer neonatal outcomes were observed in the group of the intended parent recipients (30). This would suggest that a history of infertility adversely affects the uterine microenvironment, independent of the oocyte. Notably, increasing age of the intended parent was associated with lower rates of LBR, with a sharp decline after age 45. Similarly, data from the SART registry on 40,485 oocyte donation cycles in 2016–2018 showed a progressive decline in LBR from recipient age <30 years to >49 years (i.e., from 56.1% to 46.4% in LBR) (31).

According to the second hypothesis, embryonic factors other than aneuploidy could influence the competence of euploid embryos in an age-dependent manner. Changes in embryo gene expression, metabolism, and epigenetic health may concur in explaining the adverse fate of some euploid embryos. For instance, advanced paternal age (which is often associated with advanced maternal age) is thought to contribute to alterations in early embryonic growth via non-genetic mechanisms. Aging-induced hypomethylation at specific binding sites in the sperm genome can be a key molecular feature modulating embryo and offspring developmental programs (32, 33).

The third hypothesis is based on the possibility that some uterine pathologies, apparently not clinically relevant, may interfere with embryo implantation. It is well known that the incidence of fibroids increases with age and the common perception for adenomyosis is that it affects older reproductive-age women (34, 35). Adenomyosis and uterine fibroids, by modifying the vascular architecture, impairing the normal contractility, and changing the production of angiogenic factors, might alter local and distant endometrial milieu and consequently endometrial function (36). We cannot exclude that other less known factors may concur to our findings.

Although the quality of evidence was high for IR and moderate for OPR/LBR, it was low for the MR outcome. The sensitivity analysis showed statistically significant results in relation to an increased MR in women ≥35 years old after PGT-A with single blastocyst transfer based on studies with low risk of bias. In this case, in addition to the above mentioned explanations for the herein reported findings, other factors could be considered. With the increasing maternal age, there is an increased risk of a history of uterine surgery (especially cesarean sections and myomectomies) and glucose metabolism disorders. Both factors have been strongly associated with increased risk of spontaneous miscarriage in a recent large, prospective register-based study (37). Moreover, an increased risk of miscarriage is observed in thyroid autoantibody-positive patients. The exact pathophysiological mechanism remains controversial, but it is known that euthyroid women with positive thyroid autoantibodies are older than euthyroid women with negative autoantibodies (38).

A thorough knowledge on the influence of maternal age on sustained implantation of euploid embryos may have several important implications from a scientific angle. The clarification of age impact on embryo implantation independent of ploidy may represent an unprecedented incentive to investigate additional embryonic defects (i.e., unrelated to oocyte meiotic or post-zygotic mitotic errors) as well as uterine factors. Overall, there are hints to potentiate various lines of research. One option would be to compare the outcomes of single blastocyst transfers in oocyte donation cycles vs. PGT-A autologous cycles considering the age classes herein evaluated. If differences in success rates among groups will be stable with the age increase, the recipient status should be the main object of investigation. Conversely, if any gap in favor of oocyte donation cycles widens with age, future studies should also focus on non-genetic aspects of gametogenesis and early embryo development.

Strengths and limitations

Strengths of this study include the large sample size and the application of age subgroup analyses to show possible gradients in OPR/LBR determined by age increase. To overcome the existing limitations of the present available data, we also conducted a sensitivity analysis to validate the results of the main analysis. The analysis of included studies did not reveal important heterogeneity, and the quality of evidence was rated as moderate for OPR/LBR, high for IR, and low for MR.

Adjustments for relevant confounders were not possible in our main analysis owing to a lack of individual patient data, but the sensitivity analysis confirmed that the OPR/LBR after the transfer of euploid embryos was significantly higher in women aged <35 years than in those ≥35 years. We cannot, however, exclude the presence of residual confounders. In particular, we were not able to control for blastocyst morphology and pace of embryo development (11). Indeed, the idea of a critical role of morphological grading in the fate of euploid blastocysts is a matter of debate. Capalbo et al. (39) reported that top-quality and lower-quality euploid blastocysts have similar pregnancy outcomes. Irani et al. (11) have shown that poor morphologic grading of euploid blastocyst conveys a statistically significantly higher spontaneous abortion rate. However, the investigators failed to demonstrate that this morphology-related risk was age dependent (11). Even if our findings do not allow us to draw inferences on the chances of sustained implantation of euploid blastocysts based on their quality and pace, this limitation is unlikely to affect the reliability of our effect estimates. Notably, our analyses imply an underlying distribution of embryonic characteristics (quality and pace) which is proper to each age class and could not be influenced by data pooling.

Most of the data was generated from observational studies with differences in terms of study populations, ovarian stimulation protocols, and number and morphologic assessment of embryos transferred. Nevertheless, because we were evaluating the impact of a demographic, independent variable (age) on euploid embryo transfer outcome, both data extracted from RCTs and non-RCTs were equally suitable for our purpose. Finally, although assessment of publication bias was not possible owing to the small number of studies included, we need to highlight that only a single study (i.e., the one with the largest sample size) concluded in favor of

an age-related decline of the implantation potential of euploid blastocysts (12). In this context, it may be deduced that the majority of data presented herein refer to this latter study (12). Importantly, however, the statistical model chosen (random effect model) for our meta-analysis is influenced to a minimum extent by the sample size of each study. In contrast, the random effect model is based on the inverse-variance approach, making an adjustment to the study weights according to the extent of heterogeneity among the varying intervention effects.

CONCLUSIONS

Although aneuploidy is the most significant determinant of ART cycle outcomes, an age-related decline in success rates occurs after the transfer of euploid embryos. Notably, we have demonstrated this finding not only for the age limit commonly used for good-prognosis patients (35 years) but also for older women (38 years) (10). The message provided by this analysis is likely to be critical for the impact of PGT-A in ART practice.

The impact of maternal age even when transferring an euploid embryo cannot be ignored, representing a substantial contribution to appropriate patient counseling before starting PGT-A procedures. Although the magnitude of association might be considered modest according to the recognized criteria for causation, for pregnancy success in particular, the implications may be very relevant (40). At the age limit of 35 years old, the strength of the effect is higher than that reported for the employment of ultrasound guidance versus clinical touch at embryo transfer on clinical pregnancy rates and for the impact of a low oxygen embryo culture on LBR/OPR (41, 42).

Preimplantation genetic testing at the blastocyst stage will probably continue despite its possible negative implications (3). The main reasons are the lower rates of multiple gestations and the selection of embryos in presence of specific indications. However, there is a chance to reassess the conditions for its proposal to patients. Hence, a personalized approach in decision making on the opportunity to proceed with PGT based on individual pre-existing risk may be suggested.

Acknowledgments: The authors thank the Society of Assisted Reproductive Technology for storing the data from which Figure 3 was created.

Data availability: The data underlying this article are available in the article and in its online supplementary material.

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¿Afecta la edad materna a las tasas de éxito en las técnicas de reproducción asistida luego de la transferencia de un embrión euploide? Una revisión sistemática y metaanálisis

Importancia: La aneuploidía embrionaria relacionada a la edad materna es considerada el factor limitante más significativo para un resultado favorable luego de los procedimientos de técnicas de reproducción asistida (ART). Por lo tanto, el test genético preimplantacional para aneuploidías ha sido propuesto como una estrategia para evaluar genéticamente embriones antes de transferirlos al útero. Sin embargo, si la ploidía embrionaria justifica todos los aspectos de la disminución de la fertilidad asociada a la edad sigue siendo controvertido.

Objetivo: Investigar el efecto de diferentes edades maternas en las tasas de éxito de ART luego de la transferencia de embriones euploides.

Fuentes de datos: ScienceDirect, PubMed, Scopus, Embase, la biblioteca Cochrane, Clinicaltrials.gov, Registro de Ensayos Clínicos EU, y Registro Internacional de Ensayos Clínicos de la Organización Mundial de la Salud fueron buscados desde el inicio hasta noviembre de 2021 usando combinaciones de palabras claves.

Selección y síntesis de estudios: Estudios controlados aleatorizados y observacionales fueron incluidos si investigaban el impacto de la edad materna en los resultados de ART luego de la transferencia de embriones euploides e informaban frecuencia de mujeres logrando embarazo en curso o nacido vivo.

Resultados principales: La tasa de gestación evolutiva o la tasa de recién nacido vivo (OPR/LBR) luego de la transferencia de embrión euploide comparando mujeres <35 vs. mujeres ≥ 35 años fue el resultado principal. Resultados secundarios incluyeron tasa de implantación y tasa de aborto. Análisis por subgrupos y de sensibilidad fueron también planificados para explorar las fuentes de inconsistencias entre los estudios. La calidad de los estudios fue evaluada utilizando una versión modificada de la escala de Newcastle-Ottawa, y el cuerpo de evidencia fue evaluado utilizando la metodología de grupo de trabajo de Clasificación de Recomendaciones de Valoración de Desarrollo y Evaluación.

Resultados: Un total de 7 estudios fueron incluidos ($n = 11{,}335$ transferencias embrionarias de ART de embriones euploides). Se halló una mayor OPR/LBR (odds ratio, 1.29; intervalo de confianza de 95% [CI], 1.07 – 1.54; $I^2 = 40\%$) en mujeres <35 años que en mujeres ≥ 35 con una diferencia de riesgo igual a 0.006 (CI 95%, 0.002-0.009). La tasa de implantación fue mayor en el grupo más joven (odds ratio, 1.22; CI 95% 1.12-1.31; $I^2 = 0\%$). Una mayor OPR/LBR estadísticamente significativa fue también hallada comparando mujeres $<$ 35 con mujeres 35-37, 38-40, o 41-42. Una relación de gradiente entre edad y OPR/LBR puede ser observada en meta-análisis de proporción, especialmente si se restringe a estudios con bajo riesgo de sesgo.

Conclusión y relevancia: El incremento de la edad materna está asociado con una disminución en las tasas de éxito de ART independientemente de la ploidía embrionaria. Este mensaje contribuye a una apropiada consejería al paciente antes de empezar procedimientos de test genéticos preimplantacionales para aneuplidías.