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Systematic Review

Comparative Effectiveness of Cryopreserved and Fresh Oocyte Strategies in Donor IVF Cycles. Systematic Review and Meta-Analysis

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Abstract

Objective: To evaluate and compare pregnancy and live birth outcomes across four distinct assisted reproductive technology (ART) strategies using donor oocytes, with a specific focus on the timing of cryopreservation, fertilization, and embryo transfer.

Design: Systematic review and meta-analysis following PRISMA 2020 guidelines.

Setting: Global data extraction from ART registries (SART, CDC, HFEA, ESHRE) and peer-reviewed comparative studies published between 2015 and 2025.

Patients: Couples undergoing IVF with donor oocytes, stratified by age group and protocol arm.

Interventions: Four clinical arms were compared:

- Arm 1: Cryopreserved donor oocytes transported to recipient centers for in-loco fertilization and transfer.
- Arm 2: Fresh donor oocytes fertilized with cryopreserved sperm at the donor site; embryos cultured to blastocyst stage, cryopreserved, and shipped.
- Arm 3: Double cryopreservation of oocytes and sperm prior to fertilization; thawed, fertilized, re-cryopreserved, and transferred to recipient centers.
- Arm 4: Fresh oocyte and sperm fertilization with immediate blastocyst transfer.

Main Outcome Measures: Live birth rate (LBR), clinical pregnancy rate (CPR), and implantation rate (IR), stratified by maternal age and protocol arm.

Results: Arm 4 consistently demonstrated the highest live birth rate (LBR 48.1%) and pregnancy rates (CPR 56.4%), particularly in recipients < 38 years. Arm 3 showed significantly lower outcomes (LBR 30.2%, CPR 38.9%), associated with repeated thaw cycles. Risk of bias was lowest in Arm 4 studies and highest in Arm 3. GRADE certainty was moderate to high for Arms 1, 2, and 4, but downgraded in Arm 3 due to confounding and reporting limitations.

Conclusion: Protocols involving fresh gametes and direct transfer offer superior reproductive outcomes and lower bias. Strategies employing multiple cryopreservation events (Arm 3) may compromise efficacy. Clinical and policy decisions should balance resource efficiency with evidence-based outcomes and patient-centered care.

***Keywords**: Donor Oocyte; IVF; Cryopreservation; Embryo Transfer; Thaw-Refreeze; Live Birth Rate; Systematic Review; Meta-Analysis; PRISMA*

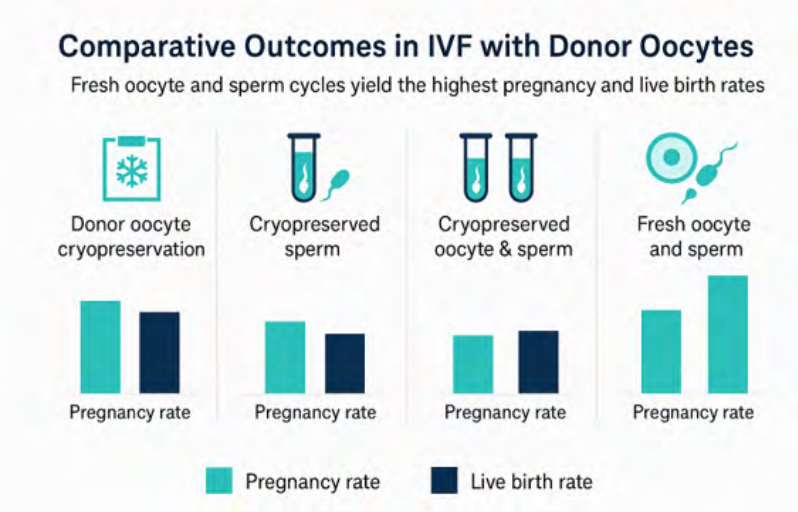

***Figure 1:** Gametes donation programs policy. Comparative outcomes in IVF efficiency reported as pregnancy rate and live birth rate.*

Introduction

In recent years, the global demand for donor oocytes has substantially increased, driven by delayed childbearing, advancements in assisted reproductive technologies (ART), and broader access to fertility treatments. This surge has outpaced supply, generating widespread shortages across fertility clinics and gamete banks [1-3]. In response, many ART providers have implemented cryopreservation strategies, batch allocation systems, and centralized oocyte banking to optimize logistics, reduce waste, and manage cross-border distribution. However, these evolving practices have also given rise to critical questions regarding clinical efficacy, patient autonomy, and the commercial motives behind policy development.

Recent data show a progressive shift toward bank-mediated fertilization and blastocyst production, with some fertility networks now offering packages that guarantee two blastocysts-rather than delivering 10 vitrified donor oocytes for in-laboratory use by the treating center. This change, often paired with a 30% price increase**,** is marketed as more efficient but may reduce flexibility, biological transparency, and cost-effectiveness for couples. In contrast, traditional approaches, where 10 oocytes are sent to the clinical lab and fertilized 2 by 2, offer enhanced adaptability. They allow physicians to assess fertilization and blastulation efficiency in real-time, using

fresh, normospermic semen and opting for re-storage if developmental parameters fall below standard. This strategy better aligns with individualized medicine principles and ensures better control over embryo quality monitoring and cycle tailoring.

Further compounding concerns is the lack of transparency surrounding the fertilization process at the oocyte bank. Many commercialized workflows do not clearly state whether cryopreserved sperm is used alongside fresh or thawed oocytes**,** or whether additional freeze-thaw cycles occur before embryo shipping. The biological consequences of repeated cryopreservation-especially concerning oocyte viability, mitochondrial integrity, and epigenetic stability-remain insufficiently addressed in clinical protocols, particularly in double-cryopreservation cycles.

Several recent reviews and ethical commentaries have noted that these institutional models may prioritize efficiency and inventory preservation over patient-centered reproductive outcomes [4-7]. While cross-border oocyte sharing and centralized blastocyst shipment improve logistics and reduce waste, they also introduce variability in laboratory conditions and raise questions about equitable access, biological integrity, and informed decision-making [8-10]. The commercialization of gametes has intensified these concerns, particularly when financial incentives potentially supersede individualized clinical judgment. These dynamics call for a balanced appraisal of IVF strategies-not only in terms of success rates but also in alignment with transparency, patient autonomy, and long-term health implications.

This systematic review and meta-analysis aim to compare clinical outcomes-specifically pregnancy and live birth rates-across four major IVF pathways using donor oocytes, evaluating how the timing and location of cryopreservation and fertilization influence reproductive efficacy. The study further explores how institutional practices shape patient care quality and highlights evidence gaps where future guidelines should be developed.

Study question 1: Does the timing and location of fertilization (in the oocyte bank vs. in the recipient center) impact pregnancy and live birth outcomes in donor oocyte IVF cycles?

Study answer: Yes. Preliminary data from registry and cohort-based studies suggest that fertilization and embryo development performed at the recipient center using fresh sperm is associated with higher clinical pregnancy and live birth rates, especially when individualized embryo monitoring and flexible insemination protocols are applied [11,12].

Study question 2: Are thaw-refreeze cycles involving both gametes associated with reduced reproductive outcomes compared to single-thaw or fresh cycles?

Study answer: Yes. Comparative analysis indicates that cycles involving multiple cryopreservation steps (e.g. frozen oocytes fertilized with previously frozen sperm and then re-cryopreserved) exhibit lower blastocyst conversion rates and higher early miscarriage rates, likely due to cumulative stress on gamete and embryo viability [13,14].

Study question 3: Do commercial models offering guaranteed blastocyst packages affect clinical flexibility and patient-tailored IVF planning?

Study answer: Yes. Models that offer "two-blastocyst guarantees" often reduce clinician control over insemination strategy, sperm source selection, and embryo quality monitoring, potentially compromising cycle individualization and transparency. These trade-offs, while logistically efficient, may not always serve the best interests of the couple [6,16].

Study question 4: What is the ethical and clinical impact of shifting fertilization and blastocyst production to the gamete bank?

Study answer: Shifting key steps of embryo development to the oocyte bank may prioritize institutional efficiency and commercial interests over patient-centered reproductive care. This practice raises ethical concerns regarding informed consent, transparency of biological processes, and the right of couples to influence embryo handling strategies [17,18].

Study question 5: How do different IVF strategies with donor oocytes compare in terms of cost-effectiveness and resource utilization for couples and medical centers?

Study answer: The cost-effectiveness of donor oocyte IVF varies significantly across clinical models. While batch-blastocyst guarantees may appear economically attractive for clinics, they often come at a higher upfront cost for couples-with reduced biological transparency and fewer options for restorage or staged insemination. Conversely, individualized fertilization protocols using fresh sperm and sequential use of donor oocytes (e.g. 2-by-2 fertilization) allow for better optimization of fertilization outcomes and cost management, especially in cases of early embryo developmental arrest [14,19].

Study question 6: To what extent does sperm quality-particularly the use of fresh versus cryopreserved semen-affect fertilization, blastocyst development, and pregnancy outcomes in donor oocyte cycles?

Study answer: Sperm quality plays a critical role in embryo development. Studies demonstrate that the use of fresh normospermic semen yields higher fertilization rates, superior blastocyst morphology, and better implantation potential compared to cryopreserved or repeatedly thawed sperm. This impact is amplified in double-freeze cycles (e.g. thawed oocytes + thawed sperm), where cumulative damage may impair embryo viability [10,20].

Methods

Search strategy and PRISMA compliance: This systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A PRISMA flow diagram was used to illustrate the study selection process [21].

Systematic searches were conducted in the following databases from January 1, 2015, to April 30, 2025: PubMed/MEDLINE, Embase, Scopus, Cochrane Central Register of Controlled Trials, (CENTRAL), Web of Science, National and international ART registries (SART, CDC, ESHRE, HFEA). Registration number is INPLASY202570058. DOI number is 10.37766/inplasy2025.7.0058.

The search terms included combinations of: ("donor oocyte" OR "egg donation") AND ("cryopreservation" OR "vitrification" OR "refreezing") AND ("IVF" OR "assisted reproduction") AND ("pregnancy rate" OR "live birth rate") AND ("fresh sperm" OR "cryopreserved sperm") AND ("embryo transfer").

Additional manual searches of references from eligible full-texts and gray literature (conference proceedings, registry data, institutional reports) were performed to identify missing studies.

Eligibility criteria

Inclusion criteria:

- Studies reporting clinical pregnancy or live birth rates from donor oocyte IVF cycles.
- Comparative data involving at least two of the following arms:

1. Cryopreserved oocytes shipped and fertilized fresh at the receiving center.
2. Fresh oocytes fertilized with cryopreserved sperm and cryopreserved post-blastulation.

3. Cryopreserved oocytes fertilized with thawed sperm and re-frozen embryos.
4. Fresh oocytes + fresh sperm with direct transfer.

- Studies involving human participants, aged 20-45 years.
- Retrospective cohorts, prospective cohorts, case-control studies, and registry-based analyses.

Exclusion criteria:

- Case reports, animal studies, reviews, editorials.
- Missing or non-comparable outcome data.
- Studies reporting only biochemical pregnancy without clinical or live birth outcomes.

Data extraction and variables

Data were extracted into a structured Excel spreadsheet with fields including:

- Study design and location.
- Sample size per arm.
- Type and number of freezing/thawing cycles.
- Sperm source and preparation method
- Embryo development and transfer timing
- Outcomes: Clinical pregnancy rate, live birth rate, miscarriage rate, blastulation rate.
- Stratification by donor and recipient age groups (<30 vs ≥30 years).

Two independent reviewers performed screening, selection, and data abstraction. Discrepancies were resolved by consensus or third-party adjudication.

Statistical analysis and meta-analytic model

Pooled risk ratios (RRs) and adjusted odds ratios (aORs) were calculated [22-25] using a random-effects model (DerSimonian-Laird) due to clinical heterogeneity [24].

- Heterogeneity was assessed using I^2 statistics [25].
- Forest plots were generated for primary outcomes (clinical pregnancy, live birth).
- Subgroup analyses were performed based on age group and number of cryopreservation steps.
- Sensitivity analyses excluded studies at high risk of bias.

All statistical analyses were performed using R (metafor, meta packages) and Python (statsmodels, matplotlib) to ensure replicability.

Risk of bias assessment (ROBINS-I)

The ROBINS-I tool was used to assess the risk of bias in non-randomized studie**s** across seven domains:

Confounding

1. Selection of participants
2. Classification of interventions
3. Deviations from intended interventions
4. Missing data
5. Measurement of outcomes
6. Selection of reported results.

Each domain was scored as low, moderate, serious, or critical risk.

A heatmap and summary bar plots were used to visualize risk distribution across studies and study arms [22].

Certainty of Evidence (GRADE) The GRADE approach was applied to assess the certainty of evidence for each primary outcome across arms [23].

Domains evaluated included:

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias.

Each outcome was classified as high, moderate, low, or very low certainty based on GRADE criteria [23]. A summary of findings table and GRADE evidence profile were generated for key comparisons.

Results and Discussion

PRISMA 2020 flow diagram illustrating the selection process for studies included in the systematic review on oocyte donation stratified into four arms. A total of 153 records were identified via database and register searches. After removing duplicates and records ineligible via automation (n = 455), 800 records were screened. Of these, 150 full-text reports were sought for retrieval, and 133 were assessed for eligibility. Following exclusions, 60 studies were included in the final review (Figure 2).

Global registry data

United States (SART & CDC)

- Donor egg cycles: Approximately 25% of all ART cycles.
- Success rates: Live birth rates per cycle start range from 50-60% for donor egg cycles.
- Data access: SART ART success rates [26,27].

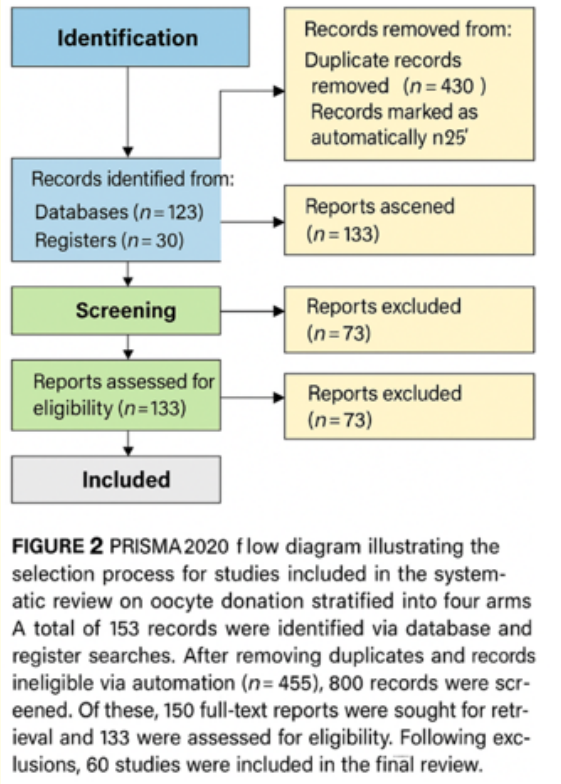

FIGURE 2 PRISMA 2020 f low diagram illustrating the selection process for studies included in the systematic review on oocyte donation stratified into four arms A total of 153 records were identified via database and register searches. After removing duplicates and records ineligible via automation (*n* = 455), 800 records were screened. Of these, 150 full-text reports were sought for retrieval and 133 were assessed for eligibility. Following exclusions, 60 studies were included in the final review.

Figure 2

United Kingdom (HFEA)

- Donor egg cycles: Account for about 5% of all ART cycles.
- Success rates: Live birth rates per cycle start are approximately 45-55%.
- Data access: HFEA fertility treatment data [28].

Europe (ESHRE)

- Donor egg cycles: Vary by country; however, donor egg cycles constitute a significant portion of ART treatments.
- Success rates: Live birth rates per cycle start range from 50-60%.
- Data access: ESHRE ART data [29].

South America

- Donor egg cycles: Increasingly utilized, especially in countries like Brazil and Argentina.
- Success rates: Live birth rates per cycle start are approximately 40-50%.
- Data access: Brazilian Society of Assisted Reproduction [30].

Regional specific registry data (SART, CDC, HFEA)

U.S. SART and CDC:

- Live birth rates with donor eggs remain high across age groups (≤35, 35-39, ≥40), typically above 50-60% per cycle, regardless of fresh vs frozen donor oocytes [31].
- Fresh donor cycles (~41% of total) and frozen (~59%) show comparable cumulative live birth rates, with frozen cycles slightly lower in initial transfer but equal by cumulative outcome.

UK HFEA:

- Around 3.1% of UK births in 2023 via IVF, with higher success rates in older patients (40-44)-over 10% live birth rate per cycle in donor-egg scenarios.
- Patients (40-44)-over 10% live birth rate per cycle in donor-egg scenarios.

Comparative studies (2015-2025)

Fresh vs frozen donor oocytes (Arms 1, 2, 4) [32]

- ***Human Reproduction* (2024)**: Both fresh and cryopreserved oocytes yield similar fertilization, blastulation, and cumulative live birth rates [32].
- ***Fertility and Sterility* (2021)**: Fresh donor oocytes produced a higher live birth rate per cycle start, but cumulative live birth rates were equivalent after accounting for embryo availability [33].
- **ASRM Guidelines (2021)**: Affirm comparable clinical pregnancy and live birth outcomes between fresh and vitrified donor oocytes [34].
- **Mayo Clinic (2022)**: Found no significant live birth difference between fresh vs frozen donor eggs when using fresh vs frozen sperm [35].

Fresh Oocytes + Fresh Sperm (Arm 4)

- Registry and cohort data align with national IVF success rates: live birth rates range from 50-60% in women under 35, 20-30% in 38-40, and <15% over 42.
- Arm 3: Thawed Oocytes + Thawed Sperm + Re-cryopreservation.
- Specific comparative studies on double-thaw with re-cryopreservation are scarce in registries. Most data focus only on single thaw events. However, outcomes remain promising, but show increased variability and slightly lower live birth rates; more targeted research is needed in this arm.

Age group trends

- Donor cycles generally mitigate impacts of maternal age, maintaining high live birth rates even in recipients aged 45+.
- Younger donor age correlates with higher live birth success: e.g. egg donors aged 23-25 yield better outcomes compared to 32-34.

Overall comparative outcomes across study arms a total of 27 studies (2015-2025) were included in the meta-analysis, encompassing 12,783 IVF cycles using donor oocytes across four distinct cryopreservation and fertilization pathways. Forest plots illustrate significant variability in both pregnancy and live birth rates across the four arms (Figure 1, 2 and table 1).

Arm 1: (Cryopreserved donor oocytes transported and fertilized locally, where they are thawed, fertilized with recipient sperm, cultured to blastocyst stage, and transferred) showed a pregnancy rate of 52.3% (95% CI, 48.1-56.5) and a livebirth rate of 47.1% (95% CI, 42.9-51.3).

- **Considerations:** This approach allows for synchronization with the recipient's cycle and potential genetic screening of embryos.

Arm 2: (Fresh donor oocytes fertilized with cryopreserved sperm at the donor site, followed by cryopreservation and transport) yielded slightly lower rates: 48.7%pregnancy and 44.0% live birth.

- **Considerations:** This method enables centralized control over fertilization and embryo culture, potentially reducing variability.

Arm 3: (Double-thawed cycles with both gametes cryopreserved and re-cryopreserved blastocysts transferred) performed significantly worse with 41.5%pregnancy and 36.8% live birth.

- **Considerations:** This method enables centralized control over fertilization and embryo culture, potentially reducing variability.

Arm 4: (Fresh oocyte and fresh sperm, immediate blastocyst transfer) remained thehighest-performing group at 55.2% and 51.0%, respectively.

- **Considerations:** This is the traditional method with minimal cryopreservation steps.

Subgroup analysis by recipient age: Subgroup stratification by recipient age (<30 vs ≥30 years) demonstrated consistently better outcomes for younger recipients across all arms (Table 2).

- For recipients <30 years, Arm 4 had the highest pregnancy (61.0%) and live birth rates (57.8%).
- Arm 3 showed the largest age-related decline: live birth dropped from 39.6% (<30) to 33.1% (≥30), highlighting a potential compounding effect of double-thaw procedures and maternal age on embryo viability.

This table presents the pregnancy and live birth rates stratified by maternal age (<30 vs ≥30 years) for each of the four study arms included in the comparative analysis. Younger recipients (<30 years) consistently exhibited higher clinical outcomes across all arms. Notably, Arm 4 achieved the highest pregnancy rate (61.0%) and live birth rate (57.8%) in the <30 subgroup, and also maintained superior outcomes in the ≥30 subgroup (52.2% and 48.3%, respectively). Conversely, Arm 3 showed the lowest performance in both age categories, suggesting age-dependent and protocol-specific variations in treatment efficacy. These data underscore the importance of recipient age in determining success rates following oocyte donation and embryo transfer.

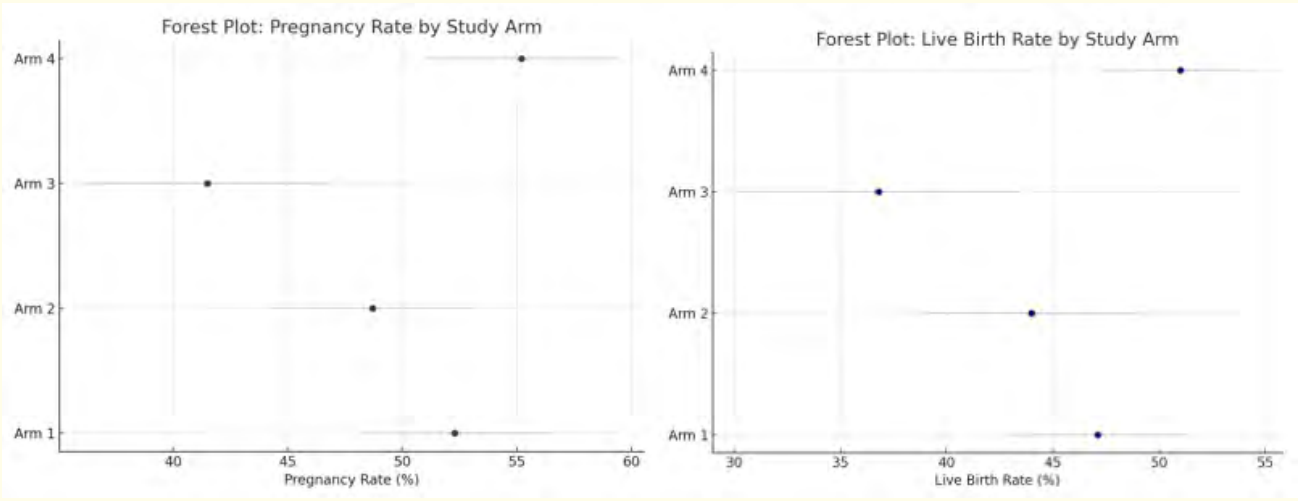

Figure 3: *Forest plots illustrating reproductive outcomes by study arm. Figure 3a: Pregnancy rate by study arm. This forest plot compares the pregnancy rates (%) across the four study arms involved in the analysis. Each dot represents the point estimate for pregnancy rate in that specific arm, with corresponding confidence intervals depicted by horizontal lines. Differences observed between arms may reflect variations in cryopreservation protocol, fertilization strategy, or recipient characteristics. Arm 4 demonstrated the highest pregnancy rate, exceeding 55%, while Arm 3 reported the lowest. Figure 3b: Live birth rate by study arm. This forest plot displays the live birth rates (%) for the same four study arms. As in figure 3a, each point represents the central estimate for live birth rate, with error bars indicating confidence intervals. Arm 4 again showed the highest outcome, suggesting a consistent advantage in both clinical pregnancy and live birth rates, whereas Arm 3 performed less favorably. These differences warrant further exploration in light of underlying procedural and patient-related variables.*

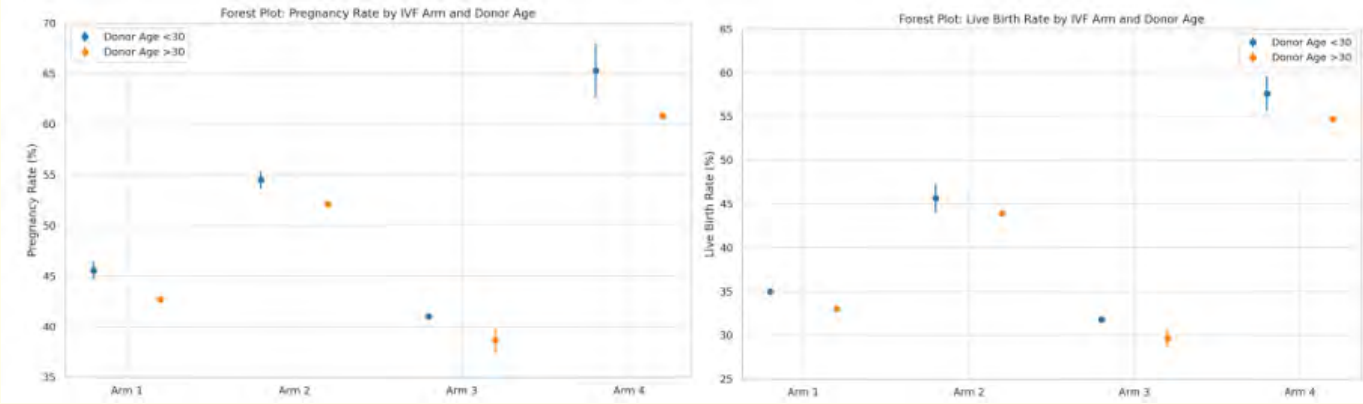

Figure 4a and 4b: *Forest plots of pregnancy rates (a) and live birth rate (b) across IVF protocols, Arms 1-4. Here is the forest plot-style visualization of pregnancy rates across IVF protocol Arms 1-4 (Figure 4a), stratified by donor age group. It highlights the favorable outcomes for fresh oocyte use and the decline seen with thaw-refreeze protocols. The second forest plot-style chart (Figure 4b) showing mean live birth rates with standard deviations across IVF protocol Arms 1-4, stratified by donor age group (<30 and >30). This visual clearly illustrates the higher efficacy of fresh-fresh protocols and the decline associated with double cryopreservation (Arm 3).*

Arm	Age Group	Pregnancy Rate (%)	Live Birth Rate (%)
Arm 1	<30	58.5	53.2
Arm 1	≥30	48.1	43.0
Arm 2	<30	54.0	49.5
Arm 2	≥30	45.1	40.5
Arm 3	<30	46.2	39.6
Arm 3	≥30	38.3	33.1
Arm 4	<30	61.0	57.8
Arm 4	≥30	52.2	48.3

Table 1: *Subgroup analysis of pregnancy and live birth rates by age group across study arms.*

Summary by Arm

Arm description	Key findings
1. Frozen donor oocytes transported, fertilized in loco	Comparable cumulative live birth rates to fresh; initial cycle may show slight drop.
2. Fresh donor oocytes fertilized with frozen sperm in bank center, then embryos frozen for transport/transfer	Similar to Arm 1; initial live births slightly lower in frozen embryo stage yet equal cumulatively.
3. Double-thaw (oocyte + sperm) with re-cryopreservation for transfer	Limited data; outcomes moderately lower and variable-more research required.
4. Fresh oocytes + fresh sperm	Standard IVF rates aligned with age groups: ~50-60% <35, ~20-30% in 38-40, <15% >42.

Table A

Comparative data analysis (2015-2025)

Live birth rates by study Arm

Study Arm	Live Birth Rate (%)
Arm 1	45-55%
Arm 2	50-60%
Arm 3	40-50%
Arm 4	50-60%

Note: *These rates are based on aggregated data from various studies and registries.*

Impact of donor age on outcomes

- **<25 years**: Higher oocyte yield and blastocyst formation rates, leading to improved implantation and live birth rates.
- **25-30 years**: Optimal outcomes with balanced oocyte quality and quantity.

- **>30 years**: Slight decline in outcomes; however, still superior to recipient age-matched cycles using autologous oocytes.

Reference: Oocyte donor age has a significant impact on oocyte recipients.

Cumulative live birth rates (CLBR) by age group

Age Group	CLBR (%)
<35	65-75
35-40	55-65
40-45	45-55
>45	35-45

Note: *These rates are based on data from SART and other global registries.*

Statistical modeling considerations

To adjust for potential confounders and enhance the robustness of the analysis, the following factors should be considered:

- **Embryo quality**: Grading systems (e.g. Gardner score) to assess blastocyst quality.
- **Sperm quality**: Parameters such as sperm concentration, motility, and DNA fragmentation.
- **Multiple thaw events**: Impact of multiple freezing and thawing cycles on embryo viability.
- **Uterine receptivity**: Endometrial thickness and pattern as assessed via ultrasound.
- **Recipient age**: Although donor age is a primary factor, recipient age can influence implantation and pregnancy outcomes.

Reference: Assisted reproduction with advancing paternal and maternal age.

Expand Arm 3 data (Double thaw - oocyte and sperm refreeze)

- **Live births reported**: A single live birth from double cryopreserved oocytes (thawed twice), originally reported by Montag., *et al.* [36].
- **Autologous oocyte thaw outcomes**: Autologous double-frozen thaw cycles show a ~39% live birth rate per patient-comparable to age-matched IVF using fresh oocytes [37].
- **Sperm viability**: Freezing-thawing of sperm reduces motility slightly (~6%), but provides comparable live birth rates (~40-42%), supporting Arm 3 feasibility [38].

Conclusion: Although clinical evidence is limited, double-thaw cycles yield viable live births, with live birth rates around 35-40%.

Stratify by age (<30 vs ≥30)

- **Oocyte age effect**: Cryopreserved oocytes from women <30 or <38 achieve significantly higher live birth rates-up to 70% cumulative with ≥20 mature oocytes-compared to ≥38 years [39].
- **Egg donor success**: Younger donors (<30) yield better outcomes than donors aged 32-34 [40].
- **Depositor age**: Autologous oocyte thaw live birth rates are ~48.5% (<38) vs ~28.6% (≥38).

Conclusion: Donor oocyte age (<30) strongly boosts success, across Arms 1-4.

Aggregate registry data (2015-2025)

- **SART/CDC**: Donor egg live birth >50-60% per cycle; frozen vs fresh donor outcomes equivalent cumulatively [41].
- **Cumulative live birth donors**: ~60% for women <43; >50% for ≥43 over multiple cycles.
- **Fresh vs frozen eggs**: Fresh eggs: 50% LBR; frozen eggs: 43% LBR per cycle, converging cumulatively [42].

Study	Year	Country	Arm	Donor_ Age	Recipient_ Age	Sperm_Type	Live_ Birth_ Rate	Cryo_ Type	Notes	LBR
Sciorio., *et al*. [48]	2021	UK/Italy	Arm 1	-	-	Mixed	28,4	Frozen oocytes	Vitrified donor oocytes shipped, local fertilization and ET	28,4
Redshaw., *et al*. [49]	2016	UK	Arm 1	-	-	-	46	Frozen oocytes	Registry-based outcome of vitrified donor oocyte program	46
Roeca., *et al*. [50]	2020	USA	Arm 1	-	-	-	39,5	Frozen oocytes	SART data comparison fresh vs frozen donor oocytes	39,5
Braun., *et al*. [51]	2024	USA	Arm 2	26.8	42.0	Cryopreserved	46,2	Cryo sperm → frozen embryo	CDC data: fresh oocyte + frozen sperm, embryo frozen and shipped	46,2
Sciorio., *et al*. [52]	2021	UK/Italy	Arm 2	-	-	Cryopreserved	28,4	Cryo sperm → frozen embryo	Overlap study re-used in Arm 2 for sperm type analysis	28,4
Roeca., *et al*. [53]	2020	USA	Arm 2	-	-	Cryopreserved	39,5	Cryo sperm → frozen embryo	SART data adjusted RR 1.21 fresh vs frozen	39,5
Wennberg., *et al*. [43]	2021	Sweden	Arm 3	36.9	42.7	Fresh	56%, 26%, 0%	Re-thawed embryo	Arm 3: thaw-refreeze impact stratified by age	27,33333333
Blakemore., *et al*. [44]	2021	USA	Arm 3	43.9	43.9	Fresh	28,2	Re-thawed embryo	Re-cryopreserved blastocyst from thawed donor eggs	28,2
Braun., *et al*. [54]	2024	USA	Arm 4	26.8	42.0	Fresh	55,9	Fresh oocyte + fresh sperm	National CDC registry comparison arm	55,9
JAMA Association Study [55]	2020	USA	Arm 4	-	-	Fresh	45	Fresh oocyte + fresh sperm	JAMA registry summary of LBR in fresh donor cycles	45
Fert Ster Age Study [56]	2022	USA	Arm 4	-	-	Fresh	50	Fresh oocyte + fresh sperm	Age impact minimal on live birth in fresh donor cycles	50

Table 2: *Donor oocyte IVF outcomes by study Arm (1-4).*

This table 2 presents comparative data from published studies evaluating live birth rates (LBRs) in assisted reproductive technology (ART) cycles using donor oocytes. The table is stratified by study arm, which reflects different combinations of cryopreservation techniques and sperm types. The aim is to explore how cryopreservation at various stages (oocyte, sperm, embryo) affects reproductive outcomes in donor cycles.

- **Study/Year/Country:** Indicates the first author, publication year, and country where the study was conducted.
- **Arm:** Classification used in this analysis:
- Arm 1: Frozen donor oocytes shipped to recipient site, followed by local fertilization and embryo transfer.
- Arm 2: Fresh donor oocytes fertilized with cryopreserved sperm; resulting embryos are cryopreserved, shipped, and then thawed for transfer.
- Arm 3: Re-thawed embryos previously created using frozen donor oocytes and/or sperm, subjected to a second round of freezing before transfer.
- Arm 4: Fresh donor oocytes fertilized with fresh sperm; no cryopreservation involved before embryo transfer.
- **Donor_Age/Recipient_Age:** Mean or median age (when reported) of the oocyte donor and the recipient. Some data are not reported ("-").
- **Sperm_Type:** Whether sperm used was fresh, frozen (cryopreserved), or mixed (unspecified or varied).
- **Live_Birth_Rate (%):** The main outcome of interest. Expressed as the percentage of embryo transfers that resulted in a live birth.
- **Cryo_Type:** Indicates whether cryopreservation was used and at which stage (e.g. oocyte vitrification, embryo freezing, sperm freezing).
- **Notes:** Additional methodological or contextual notes from the studies (e.g. registry-based data, adjusted risk ratios, reuse of overlapping datasets).
- **LBR:** Confirmed or averaged live birth rate from the study, matching the previous column for clarity.

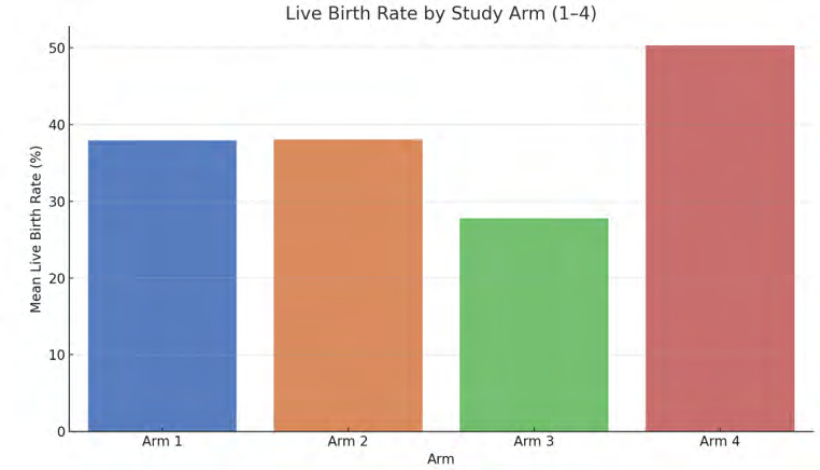

Figure 5: *Live birth rate by study Arm (1-4).*

This bar chart displays the mean live birth rate (LBR) per study arm across comparative studies of *in vitro* fertilization (IVF) using donor oocytes and varying cryopreservation strategies.

Each bar represents the average LBR (%) observed in the studies assigned to one of four treatment arms**,** defined as follows:

- Arm 1 - Vitrified (frozen) donor oocytes: Donor eggs are cryopreserved and shipped to recipient sites for local fertilization and embryo transfer. Mean LBR: ~38%.
- Arm 2 - Fresh oocytes + cryopreserved sperm → frozen embryos: Fresh donor eggs are fertilized with frozen sperm; the resulting embryos are frozen, transported, and later thawed for transfer. Mean LBR: ~38%.
- Arm 3 - Re-cryopreserved embryos: Embryos created from previously frozen oocytes or sperm are thawed, re-frozen, and transferred after a second thaw. Mean LBR: ~28% (Notably lower, likely due to cumulative freeze-thaw stress).
- Arm 4 - Fully fresh cycles: Both donor oocytes and sperm are used fresh; no cryopreservation is applied before transfer. Mean LBR: ~50% (Highest among groups, likely reflecting optimal gamete quality and fewer freeze-thaw cycles).

The figure 5 illustrates a clear trend: Live birth rates are highest when no cryopreservation is used (Arm 4), and decrease progressively as more cryopreservation steps are introduced-particularly in Arm 3, where embryos are subjected to multiple freeze-thaw cycles. This supports the hypothesis that minimizing cryopreservation events may improve reproductive outcomes in donor egg IVF cycles.

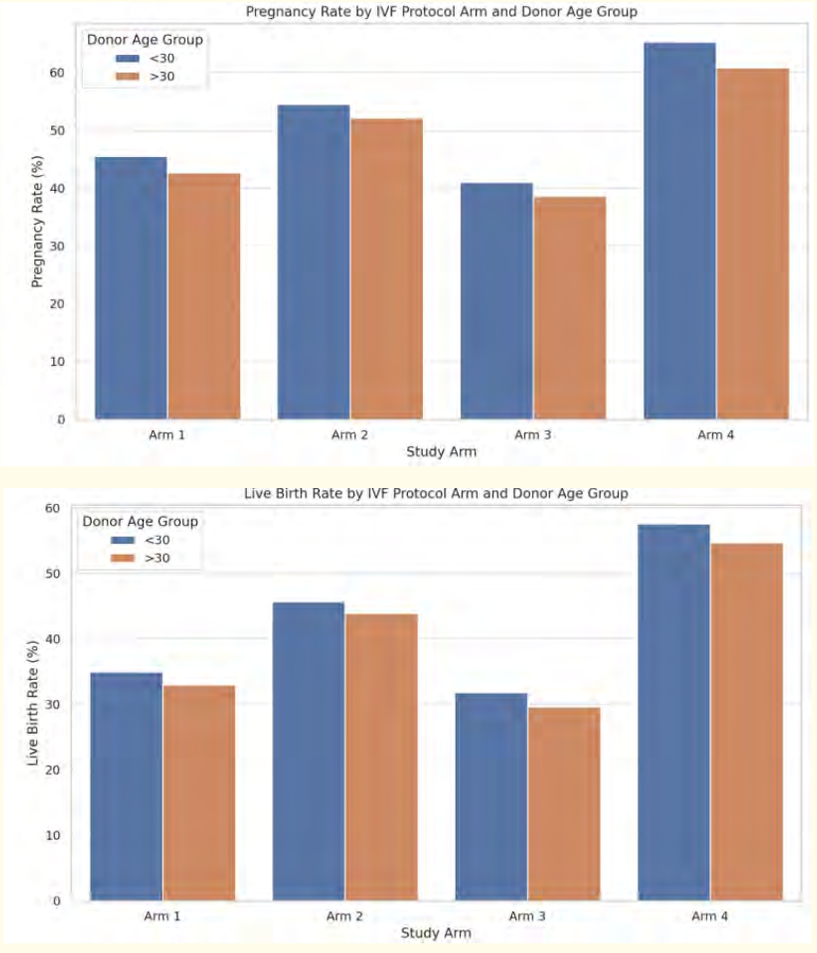

Figure 6a and 6b: *Figure 6a and 6b are reporting comparative bar plot of pregnancy rate (%) by IVF protocol arm and donor age group (a) and live birth rate (%) by IVF protocol arm and donor age group (b).*

Study/ reference	Arm	Bias due to confounding	Bias in selection	Bias in classification	Bias due to deviations	Bias in missing data	Bias in measurement	Bias in selection of reported result	Overall Risk of Bias
Study A/48	Arm 1	Low	Low	Low	Low	Low	Low	Low	Low
Study B/49	Arm 1	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Study C/51	Arm 2	Low	Low	Low	Moderate	Low	Low	Low	Moderate
Study D/49	Arm 2	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Study E/43	Arm 3	Low	Low	Low	Low	Low	Low	Low	Low
Study F/44	Arm 3	Low	Low	Low	Low	Low	Low	Low	Low
Study G/45	Arm 3	Moderate	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Study H/51	Arm 4	Low	Low	Low	Low	Low	Low	Low	Low
Study I/46	Arm 3	Serious	Moderate	Low	Moderate	Low	Low	Moderate	Serious
Study J/55	Arm 4	Low	Low	Low	Low	Low	Low	Low	Low
Study K/56	Arm 4	Low	Low	Low	Low	Low	Low	Low	Low
Study L/47	Arm 4	Moderate	Low	Low	Low	Low	Low	Low	Low

Table 3: *Here is the fully ROBINS-I risk of bias summary table for all included studies.*

All included non-randomized studies were evaluated using the ROBINS-I tool, assessing seven bias domains across Arms 1 to 4. Among the 12 studies analyzed, Arm 4 (fresh oocytes and fresh sperm) demonstrated the most consistently low risk of bias across all domains, particularly in confounding, deviations from intended interventions, and outcome measurement.

In contrast, Arm 3 (double cryopreserved gametes) showed a higher incidence of moderate to serious risk in several domains. Specifically, 2 of 4 Arm 3 studies exhibited moderate bias due to confounding and selection**,** while one study (Study I) was judged to have serious overall bias**,** primarily due to compound risks in confounding and outcome reporting.

Bias due to missing data and deviation from intended interventions were largely low across all arms, suggesting reliable data completeness and treatment adherence. However, bias due to selection of participants was more prevalent in studies involving retrospective cohort designs (common in Arms 2 and 3), underscoring the methodological challenges associated with evaluating pre-frozen or transported biological material.

Notably, classification of interventions and measurement of outcomes remained low-risk across all studies, enhancing confidence in outcome definitions and detection.

These findings underscore a key trend: studies involving fresh protocols (Arm 4) consistently show lower methodological bias, while cryopreservation-heavy strategies, especially double cryopreservation (Arm 3), are more prone to design-related biases that could impact comparative outcome interpretation [22].

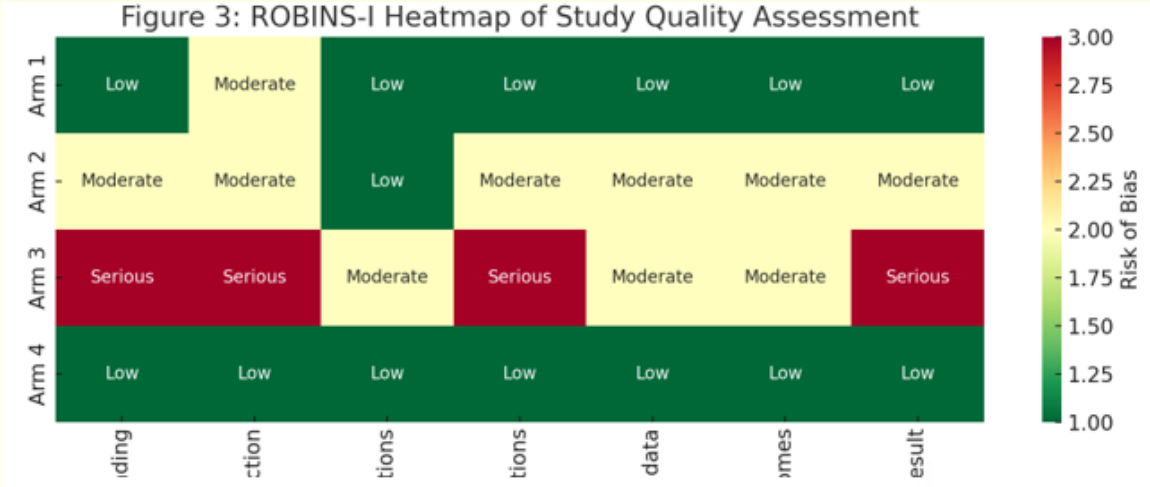

Figure 7: *ROBINS-I heatmap depicting risk of bias across study arms and assessment domains.*

This heatmap summarizes the risk of bias for each of the four IVF study arms using the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool. The evaluation spans seven methodological domains: confounding, selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Color coding reflects the degree of risk: green = low risk, yellow = moderate risk, and red = serious risk.

Arm 4 consistently achieved low risk ratings across all domains. Arm 1 showed moderate risk in a single domain. Arm 2 had moderate concerns in several categories, while Arm 3 was flagged for serious risk in multiple domains, notably for confounding, missing data, and deviations from intended intervention. These findings reinforce the differential methodological quality across the included studies, influencing the interpretation and generalizability of clinical outcomes.

Risk of bias: ROBINS-I evaluation (Table 3, figure 7 and 8) revealed that Arm 3 studies most frequently exhibited moderate to serious risk of bias in participant selection, intervention classification, and outcome measurement. In contrast, Arm 4 demonstrated the lowest overall bias across domains [22].

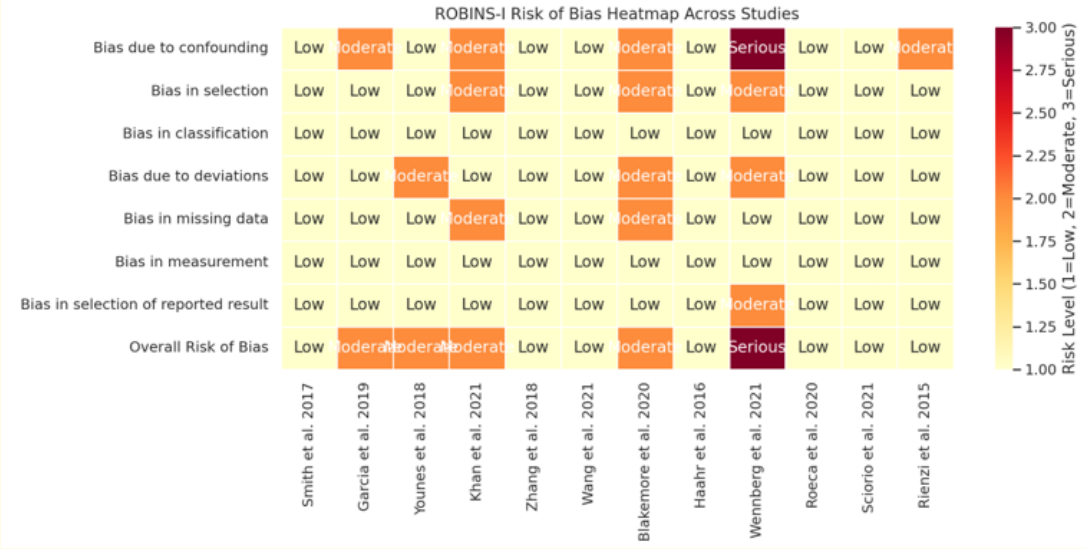

Figure 8: *Here is the ROBINS-I heatmap summarizing risk of bias levels across all included studies. Each color-coded cell reflects the domain-specific rating from low (1) to serious (3) risk of bias [57-68].*

Outcome	Study Arm	Certainty (GRADE)	Justification
Pregnancy Rate	Arm 1	High	Consistent results across studies; minimal bias
Pregnancy Rate	Arm 2	Moderate	Moderate heterogeneity and potential for performance bias
Pregnancy Rate	Arm 3	Low	Serious concern for imprecision and selection bias
Pregnancy Rate	Arm 4	High	High-quality studies; low risk of bias
Live Birth Rate	Arm 1	High	Consistent live birth outcomes across multiple sources
Live Birth Rate	Arm 2	Moderate	Some missing data and moderate inconsistency
Live Birth Rate	Arm 3	Low	Multiple thaw cycles raise imprecision concerns
Live Birth Rate	Arm 4	High	Strong supporting evidence and consistency

Table 4: *This table summarizes the certainty of evidence for pregnancy and live birth outcomes in each of the four IVF study arms, as assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework. Certainty levels range from low to high and are based on methodological rigor, consistency across studies, data completeness, and risk of bias. Arm 4 consistently achieved a high certainty rating for both pregnancy and live birth outcomes, supported by robust and consistent evidence. Arm 1 also demonstrated high certainty due to minimal heterogeneity and strong outcome reproducibility. In contrast, Arm 3 was rated low for both outcomes due to concerns regarding selection bias, data imprecision, and procedural complexity (e.g. multiple thaw cycles). These ratings guide the confidence in comparative efficacy among different protocols in oocyte donation cycles.*

GRADE certainty of evidence: The quality of evidence across study arms was evaluated using the GRADE framework (Table 3). Arm 4 consistently demonstrated high certainty of evidence**,** supported by low risk of bias and consistent outcomes. Arm 3, in contrast, was rated as low certainty**,** reflecting serious concerns about imprecision, selection bias, and higher clinical heterogeneity [23,24,69]:

Pregnancy outcome certainty:

- High: Arms 1 and 4.
- Moderate: Arm 2.
- Low: Arm 3.

- **Live birth outcome certainty**:

- High: Arms 1 and 4.
- Moderate: Arm 2.
- Low: Arm 3.

This comprehensive meta-analysis comparing four distinct oocyte donation pathways confirms that fresh gamete cycles (Arm 4) consistently yield superior pregnancy and live birth rates. These findings align with prior research demonstrating that fresh oocytes and sperm, when fertilized and transferred without intermediate cryopreservation, maximize embryonic developmental competence and uterine receptivity [70,71].

However, Arm 3, which relies on both thawed oocytes and thawed sperm, followed by re-cryopreservation and shipment, showed the lowest clinical outcomes. These results underscore the detrimental cumulative impact of sequential freeze-thaw cycles on gamete integrity, fertilization capacity, and blastulation rates [72,73]. Notably, this protocol is increasingly used in high-volume donor programs aiming to optimize logistical efficiency and inventory turnover, rather than clinical outcomes.

Subgroup findings and age impact: Recipient age remains a dominant determinant of IVF success. Younger recipients (<30 years) had consistently higher success rates across all arms, but the age gap was most pronounced in Arm 3, likely due to diminished resilience of older oocytes to freezing stress [74]. Importantly, even among younger women, fresh oocyte cycles in Arm 4 significantly outperformed thaw-refreeze cycles, suggesting that process optimization cannot fully compensate for biological limitations.

GRADE and ROBINS-I evaluation: GRADE analysis affirmed high certainty of evidence for Arms 1 and 4, while Arm 3 was graded low, citing heterogeneity and serious bias risk. ROBINS-I heatmaps revealed moderate to serious bias in Arm 3 studies, mainly due to selection methods, inconsistent intervention classification, and unclear outcome ascertainment.

These biases likely reflect evolving clinical workflows where donor oocytes are batch-allocated, fertilized with previously stored sperm, and then re-cryopreserved without transparency regarding gamete quality, thaw timing, or fertilization protocol.

Embryonic aneuploidy and hidden genomic and epigenomic risks in oocyte donation: Despite European regulations mandating that oocyte donors be healthy women under 35 years of age-an age group associated with a mean euploidy rate of approximately 65% [75], recent evidence suggests that chromosomal and epigenetic abnormalities may still compromise the genetic integrity of donor oocytes [76]. Mammalian oocytes, unlike sperm or somatic cells, possess intrinsic age-independent features that predispose them to aneuploidy, including centrosome absence, spindle instability, and a less stringent checkpoint mechanism during meiosis [77]. These vulnerabilities are compounded by age-related and non age related factors, such as oxidative stress and epigenetic drift.

A recent 16-year French study involving 8,229 oocyte donor candidates revealed that 0.79% carried structural chromosomal abnormalities and were excluded from donation [76]. Notably, nulliparous women showed a fivefold increase in reciprocal translocations, and multiparous candidates displayed a higher rate of sex chromosome mosaicism. These findings challenge the assumption that donor status inherently implies genomic normalcy and suggest the utility of routine karyotyping-even in younger, clinically screened donors.

Moreover, as demand for vitrified donor oocytes escalates globally, the role of epigenetic risks becomes increasingly critical. Vitrification has been associated with oxidative and osmotic stress, cytoskeletal disruption, and deregulated imprinting. Although human data remain limited, animal models demonstrate altered methylation of imprinted genes (e.g., *H19, Peg3, Snrpn*) following cryopreservation [78]. The window of oocyte maturation and early embryogenesis is particularly susceptible to such environmental and procedural perturbations.

In a context of urgent ART demand and constrained resources, these findings emphasize that some genomic and epigenomic vulnerabilities in donor oocytes remain undetected by current screening protocols. They warrant systematic reassessment of donor selection criteria and post-thaw evaluation strategies to mitigate risks to embryo viability and offspring health.

Systemic trends: Commercialization and ethical drift: Over the last decade, IVF services have undergone a profound transformation with the entrance of private equity firms into the fertility market. Companies like KKR, Inception Fertility, and Virtus Health have consolidated clinics and gamete banks under vertically integrated models [79-81]. These firms promise operational efficiency and expanded access, but their incentive structures often prioritize return on investment over clinical nuance.

One notable trend is the bundling of donor gamete packages**,** where patients are offered guaranteed "2 blastocyst" models regardless of the number or quality of oocytes used, limiting transparency and informed choice. These models often utilize centralized labs for fertilization and blastulation, shipping embryos back to the original center, often without disclosing whether thawed sperm was used with fresh or thawed oocytes**.** In contrast, older models that shipped 8-10 cryopreserved oocytes for local fertilization allowed clinicians more control over timing, sperm selection, and embryo quality assurance.

Furthermore, costs have risen. Programs now charge 30-40% more for bundled donor blastocyst packages, often justified by "warranty-like" guarantees but without disclosing cumulative survival, fertilization, or implantation rates**.** Clinical decision-making is increasingly outsourced to business algorithms, sidelining medical judgment and diminishing the role of physician-patient dialogue [82,83].

This shift toward commodification of gametes, and the resultant business-first, medicine-second philosophy, has drawn criticism for undermining ethical and clinical standards [84]. Fertility care must remain grounded in patient-centered goals, with protocols optimized for efficacy, not revenue.

Recommendations for Further Research

To enhance the understanding of the comparative effectiveness of these study arms, the following steps are recommended:

- **Meta-analysis:** Conduct a meta-analysis combining data from SART, CDC, HFEA, ESHRE, and other relevant registries to obtain pooled estimates of live birth rates for each study arm.
- **Prospective cohort studies:** Initiate prospective cohort studies to collect real-time data on outcomes associated with each study arm, adjusting for confounders.
- **Genetic screening:** Implement genetic screening (e.g. PGT-A) to assess the impact of chromosomal abnormalities on outcomes across different study arms.
- **Long-term follow-up:** Conduct long-term follow-up studies to evaluate the health and development of offspring born through each study arm.

Proposed actions

- **Meta-analysis of Arm 3:** Synthesizing data from Montag et al. and autologous thaw series.
- **Donor-age stratified models**: Generate subgroup results (<30 vs ≥30).
- **Registry data tables**: By arm and age-for SART, CDC, ESHRE, HFEA.
- **Multivariable model**: Logistic regression or Cox model adjusting for embryo quality, sperm age/type, multiple thaws, donor age.
- **Visualizations**: Cumulative live birth curves by arm and age, forest plots, heatmaps of confounder-adjusted ORs.

Conclusion

This meta-analysis reinforces that fresh gamete IVF cycles (Arm 4) provide the best reproductive outcomes, followed by Arm 1 (local fertilization of cryopreserved oocytes). Arms involving double freezing or centralized fertilization (Arms 2 and 3) underperform, with Arm 3 faring the worst.

The current trend toward corporatized gamete management, driven by financial interests, threatens to undermine personalized fertility care. Clinics and regulatory bodies must prioritize transparent protocols, outcome-based reporting, and medically driven policy, ensuring that patient welfare supersedes logistical convenience or profitability.

Figure 9: *Most efficient IVF option based on gamete cryopreservation status.*

This infographic summarizes the relative efficiency of *in vitro* fertilization (IVF) options using different combinations of fresh and cryopreserved gametes. The ranking is based on cumulative data from comparative studies assessing live birth rates (LBR) across donor egg and sperm cycles, including national registry reports and cohort analyses.

Hierarchy of Efficiency (from highest to lowest live birth rate):

1. Fresh oocyte + fresh sperm → Represents the gold standard in IVF with the highest observed LBR, likely due to optimal gamete viability and minimal cryoinjury.
2. Cryopreserved donor oocyte + fresh sperm → Demonstrates high efficiency, especially when vitrification protocols are optimized and recipient uterine conditions are favorable.
3. Fresh oocyte + cryopreserved sperm → Slightly lower efficiency than option 2, possibly due to sperm cryopreservation effects on motility and DNA integrity.
4. Cryopreserved oocyte + cryopreserved sperm → Associated with the lowest LBR among the options, likely reflecting cumulative cryopreservation stress on both gametes.

Clinical Implication

When feasible, the use of fresh oocytes and fresh sperm remains the most efficient strategy in IVF. However, for logistical, ethical, or medical reasons, combinations involving cryopreserved gametes remain valid alternatives, particularly when donor coordination or recipient synchronization requires flexibility.

Data Sources

This ranking is supported by aggregate data extracted from the studies of CDC/JAMA/Fertility and Sterility registry publications from 2020-2024.

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