

# Updates on Preservation of Female Fertility in Cancer Patients: A Systematic Review and Meta-analysis

Fawaz E Edris, MD\* Iman Hamid Alenezi, MD\*\* Ahmed Baker A Alshaikh, MD, PhD\*\*\* Nada Majed AlFarrah\*\*\*\* Jinan Ali Al-Fadhel\*\*\*\* Sama Ahmed Hashim\*\*\*\* Faye Faisal Afandy\*\*\*\* Nouf Abdullrhman Alballaa\*\*\*\* Jumanah Y. Nassar\*\*\*\*

## ABSTRACT

**Objectives:** To analyze the reproductive results following two of the main techniques of fertility preservation (FP): embryo cryopreservation (Controlled ovarian stimulation, COS) and frozen-thawed embryo transfer (FTET) in female cancer patients and survivors.

**Methods:** PubMed, Web of Science, Scopus, Science Direct, and Clinical Key were systematically searched in July 2024 to comprise the relevant data. Comprehensive Meta-Analysis (Version 3.0) was the software used for data analyses.

**Results:** Our results included fifteen studies with a total of 1098 female cancer patients/ survivors who underwent FP methods. The follow-up duration ranged from 0.25 years to 23.6 years. The clinical pregnancy rate among female cancer patients/ survivors who underwent embryo cryopreservation (COS method) was (27.3%, 95% CI 0.234-0.315,  $p=0.000$ ), the live birth rate was (27.3%, 95% CI 0.234-0.315,  $p=0.000$ ), and the miscarriage rate was (23.8%, 95% CI 0.234-0.315,  $p=0.000$ ). While subjects who underwent FTET revealed a pooled prevalence of clinical pregnancy of (61.5%, 95% CI 0.234-0.315,  $p=0.049$ ) and the live birth rate was (49.3%, 95% CI 0.234-0.315,  $p=0.905$ ).

**Conclusion:** Our findings can help practitioners counsel women regarding FP approaches. A combination of diverse strategies may be the best solution, although this requires further exploration. Longitudinal studies could be the first step in improving the literature's quality, with international criteria requiring that the same factors be reported consistently.

**Keywords:** Fertility preservation; Embryo cryopreservation; Frozen-thawed embryo transfer; Pregnancy; Live birth rate; Miscarriage; Systematic review; Meta-analysis.

## INTRODUCTION

With developments in early detection and treatment, cancer patient survival rates have increased significantly over the last 20 years. As a result, almost 80% of cancer patients who are children and teenagers go on to have long lives [1, 2]. Notwithstanding, ovarian function and future fertility of cancer survivors may be jeopardized by cancer therapies such as radiation and chemotherapy. The most recent clinical practice guideline published by the American Society of Clinical Oncology (ASCO) reflects the significant increase in demand for FP among pediatric, adolescent, and young adult cancer patients [3]. According to ASCO's guidelines, healthcare practitioners ought to consider the prospect of infertility with patients handled during their prime reproductive years as part of instruction and informed authorization prior to cancer therapy. They should also be prepared to address options for preserving fertility and/or refer all potential patients to suitable reproductive professionals [4].

Because the genotoxic effects of cancer treatments reduce egg reserve and increase the chance of early menopause, infertility is a typical side effect among women receiving these treatments [5]. While the percentage of people who survive cancer is increasing overall [6], the likelihood of becoming pregnant following cancer therapy is still lower than in the general population [7]. The majority of women receiving cancer treatments emphasize early counseling on future family planning and dependable fertility-preserving medications as a top objective [8].

The provision of dependable and efficient FP treatments to young women and girls diagnosed with cancer is gaining traction globally [9], having reached a tipping point in adoption [10]. Variable reporting on the long-term reproductive and pregnancy outcomes in this group raises questions about the evidence about the long-term therapeutic effectiveness and utility of FP therapies [11].

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\* Department of Obstetrics and Gynecology, College of Medicine  
Umm AlQura University, Makkah, Saudi Arabia.

Email: faedris@uqu.edu.sa

\*\* Department of Obstetrics and Gynecology, Ministry of Health  
Arar, Kingdom of Saudi Arabia.

Email: Ihalenezi@moh.gov.sa

\*\*\* Department of Obstetrics and Gynecology, College of Medicine  
Jouf University, Sakaka, Kingdom of Saudi Arabia.

\*\*\*\* Medicine Program, Batterjee Medical College, Jeddah 21442  
Saudi Arabia.

Rather than being an optional component of the entire treatment plan, FP for cancer patients is increasingly becoming a need. Before beginning cancer therapy, patients should be referred to a reproductive clinic promptly, according to the ASCO [12]. The main objective of our study was to present a systematic review and meta-analysis of reproductive results following the two main techniques of FP: embryo cryopreservation (COS) and FTET in female cancer patients and survivors.

## METHODOLOGY

### Study design and duration

PRISMA guidelines, or Preferred Reporting Items for Systematic Reviews and Meta-Analyses, are followed in this meta-analysis [13]. We conducted this investigation in July of 2024.

### Literature search

A comprehensive and methodical search of PubMed, Web of Science, Scopus, Science Direct, and Clinical Key was performed to find relevant material. We customized our search to meet the unique needs of each database and restricted it to English. To find the pertinent research publications, the following keywords were transformed into Mesh terms in PubMed or topic terms in Scopus: "Cancer," "Tumor," "Malignancy," "Lymphoma," "Leukemia," "Hematological malignancies," "Fertility preservation," "Fertility treatments," "asthma," "Frozen-thawed embryo transfer," "Embryo cryopreservation," "Controlled ovarian stimulation," "Pregnancy rate," "Live birth rate," and "Miscarriage." Boolean operators like "OR," "AND," and "NOT," were paired with the relevant keywords.

### Study selection and Data extraction

Two verifications of the search technique's output were conducted using Rayyan (QCRI) [14]. Using inclusion/exclusion criteria, the researchers evaluated the titles and abstracts for relevancy before combining the search results. Reviewers thoroughly examined all papers meeting inclusion requirements. The authors talked about how to resolve conflicts. The approved study was uploaded using a pre-made data extraction form. Following our extensive search, the authors found plenty of similar studies that assessed the efficacy and safety of FP methods. Thus, we aimed to include the methods that were recently published to investigate the updates. We finally agreed to include embryo cryopreservation (COS) and FTET. The authors extracted data about the study titles, authors, study year, country, sample size, mean age/ range, cancer type, intervention, follow-up duration, clinical pregnancy rate, live birth rate, and miscarriage rate. A separate sheet was created for the risk of bias assessment.

### Selection criteria

The inclusion criteria are as follows: (1) retrospective cohorts, prospective cohorts, case-control studies, and observational studies that implemented embryo cryopreservation (COS) and FTET as FP methods, (2) female cancer patients, and (3) studies that reported one of the following parameters; clinical pregnancy rate, live birth rate, and miscarriage.

### Risk of bias assessment

We evaluated the quality of the included studies using the eight components of the NOS for cohort and case-control studies. The NOS scale is composed of eight components, divided into three dimensions, for a total of nine points. A study receiving a score of less than four was considered low-quality. A study was rated as high-quality if it obtained

a score of greater than 7, and as medium-quality if it received a score between 4 and 6. The higher the score, the less likely it is to be biased [15].

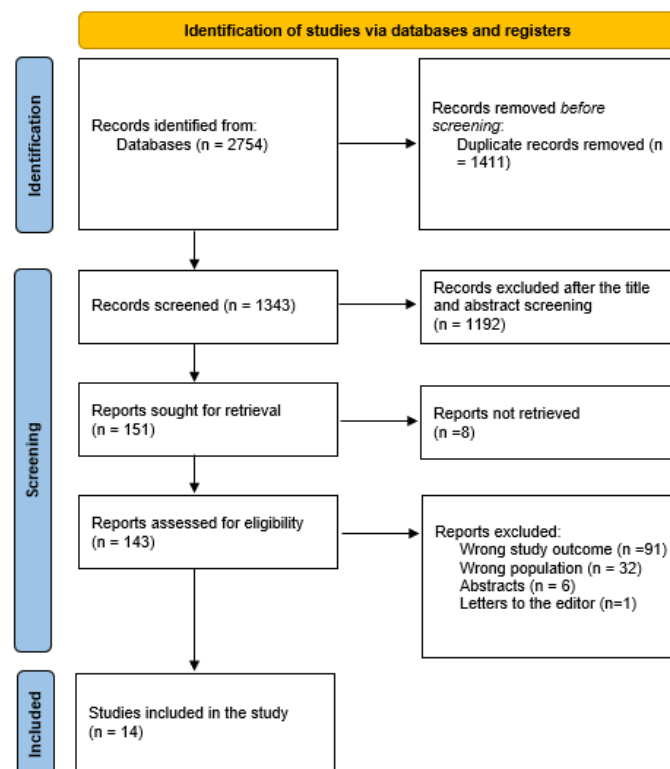
## Statistical analysis

The program used for data analysis was Comprehensive Meta-Analysis (Version 3.0) [16]. Since the random effect model allows us to account for study-to-study variance when determining study weights, we choose to employ it.  $P < 0.05$  served as the statistical significance cutoff point. Cochran's Q and  $I^2$  statistics were used to examine effect size heterogeneity. While the  $I^2$  statistics measured the percentage of variance in observed effects that reflected variance in genuine effects rather than sampling error, a statistically significant Q value ( $p < 0.05$ ) revealed heterogeneity across studies.

## RESULTS

### Search results

Following a comprehensive search, 2754 research publications were discovered; 1411 duplicates were removed. 1192 studies were excluded after the titles and abstracts of 1343 studies were examined. Out of the 151 reports that were requested, 8 were not located. Following the screening, 143 papers were selected for full-text review; 91 were discarded because the study's conclusions were erroneous, 32 because the population type was inaccurate, 6 were abstracts, and 1 article was an editor's letter. There were fourteen legitimate research articles in this analysis. An overview of the procedure used to choose studies is provided in **Figure 1**.



**Figure 1.** Study selection is summed up in a PRISMA flowchart

### Characteristics of the included studies

**Table (1)** presents the sociodemographic characteristics of the included study articles. Our results included fifteen studies with a total of 1098 female cancer patients/ survivors who underwent FP methods. Ten of the included studies were cohort retrospective studies [18, 19, 20, 23,

24, 25, 26, 27, 28, 30], three were cohort prospective studies [17, 21, 29], and one was a case-control study [22]. Five studies were conducted in the USA [21, 22, 24, 28, 30], four in the UK [17, 19, 23, 26], two in Korea [20, 25], one in France [18], one in Belgium [27], and one in Sweden [29]. The earliest study was conducted in 2010 [22] and the latest in 2023 [17, 19, 20].

**In table (2)**, the follow-up duration ranged from 0.25 years to 23.6 years [29]. Eleven studies implemented Embryo cryopreservation [17-19, 20, 23, 24, 26-30] and four studies investigated FTET [20-22, 25]. Most of the included studies [17-20, 23, 24, 26-28] did not specify a certain cancer type to investigate and four studies specifically included breast cancer patients [21, 25, 29, 30].

**Table 1.** Sociodemographic characteristics of the included participants

Study ID	Study design	Country	Participants (N)	Age range/ mean
Tsonis et al., 2023 [17]	Prospective cohort	UK	15	30.1 ± 5.3
Mayeur et al., 2021 [18]	Retrospective cohort	France	31	30–38
Duffin et al., 2023 [19]	Retrospective cohort	UK	431	17.4–27.6
Kim et al., (a) 2023 [20]	Retrospective cohort	Korea	11	19-46
Kim et al., (b) 2023 [20]	Retrospective cohort	Korea	63	19-46
Oktay et al., 2015 [21]	Prospective cohort	USA	18	41.5 ± 4.3
Grifo et al., 2010 [22]	Case-control	USA	23	21-38
Alvarez & Ramanathan, 2018 [23]	Retrospective cohort	UK	22	23-40
Robertson et al., 2011 [24]	Retrospective cohort	USA	38	34 ± 5
Lee et al., 2012 [25]	Retrospective cohort	Korea	26	36.2 ± 4.1
Barcroft et al., 2013 [26]	Retrospective cohort	UK	22	31.9±3.9
Dolmans et al., 2015 [27]	Retrospective cohort	Belgium	9	21-41
Luke et al., 2016 [28]	Retrospective cohort	USA	270	32.1 ± 5.4
Marklund et al., 2020 [29]	Prospective cohort	Sweden	99	32.1 ± 5.4
Chien et al., 2017 [30]	Retrospective cohort	USA	20	24-42

\*NA=Not-applicable

**Table 2.** Clinical characteristics of the included participants

Study ID	Type of cancer	Intervention	Follow-up (years)	NOS
Tsonis et al., 2023 [17]	Cervical, endometrial, and ovarian	Embryo cryopreservation	17	7
Mayeur et al., 2021 [18]	Breast cancer, HL, ALL, MALT lymphoma, idiopathic medullary hypoplasia, and ovarian borderline tumors	Embryo cryopreservation	10	7
Duffin et al., 2023 [19]	NM	Embryo cryopreservation	2.5–12.2	7
Kim et al., (a) 2023 [20]	Breast cancer, GI cancer, Hematologic cancer, Gynecologic cancer, and Others	FTET	NM	6
Kim et al., (b) 2023 [20]	Breast cancer, GI cancer, Hematologic cancer, Gynecologic cancer, and Others	Embryo cryopreservation	NM	7
Oktay et al., 2015 [21]	Breast cancer	FTET	3.4 ± 2.2	7
Grifo et al., 2010 [22]	NM	FTET	1 - 4 (months)	7
Alvarez & Ramanathan, 2018 [23]	Breast cancer, Haematological cancer, Gynaecological cancer, GI cancer, and Others	Embryo cryopreservation	0.4 – 4.5	7
Robertson et al., 2011 [24]	Breast cancer, cervical cancer, colorectal cancer, endometrial cancer, malignant brain tumor, mesenchymal chondrosarcoma, and ovarian epithelial carcinoma	Embryo cryopreservation	NM	6
Lee et al., 2012 [25]	Breast cancer	FTET	NM	7
Barcroft et al., 2013 [26]	Breast cancer, HL, NHL, cervical, ALL, sarcoma, CML, Cutaneous T cell lymphoma, and Endometrial carcinoma	Embryo cryopreservation	0.5–15.1	7
Dolmans et al., 2015 [27]	Breast cancer, ovarian cancer, rectal adenocarcinoma, and colon adenocarcinoma	Embryo cryopreservation	2	7
Luke et al., 2016 [28]	Cancer; Bone, Brain, Breast, GIT, Endocrine, Eye, Female genitalia, Leukemia, Lymphoma, Oral cavity and pharynx, Respiratory system, Skin, Soft tissue, and Urinary	Embr236yo cryopreservation	2	7
Marklund et al., 2020 [29]	Breast cancer	Embryo cryopreservation	0.25 - 23.6	7
Chien et al., 2017 [30]	Breast cancer	Embryo cryopreservation	6.2	6

\*HL=Hodgkin lymphoma, NHL=non-Hodgkin lymphoma, ALL= Acute lymphoblastic leukemia, CML= Chronic lymphoblastic leukemia, MALT= Mucosa-assisted lymphoid tissue, GI= Gastrointestinal

**Meta-analysis of primary effect size**

**Embryo cryopreservation**

A meta-analysis of 9 studies involving 730 female cancer patients/survivors who underwent embryo cryopreservation (COS method) has revealed a pooled prevalence of clinical pregnancy of (27.3%, 95% CI 0.234-0.315, p= 0.000) **Figure (2A)**, 9 studies involving 526 subjects were reported in the live birth rate (27.3%, 95% CI 0.234-0.315, p= 0.000) **Figure (2B)**, and 3 studies involving 53 subjects were reported in the miscarriage rate (23.8%, 95% CI 0.234-0.315, p= 0.000) **Figure (2C)**.

Visual inspection of the funnel plots shows the asymmetrical distribution of the included studies with significant inter-heterogeneity between studies ( $I^2=94.5%$  ( $P=0.000$ )) in **Figure (3A)**, ( $I^2=82.9%$

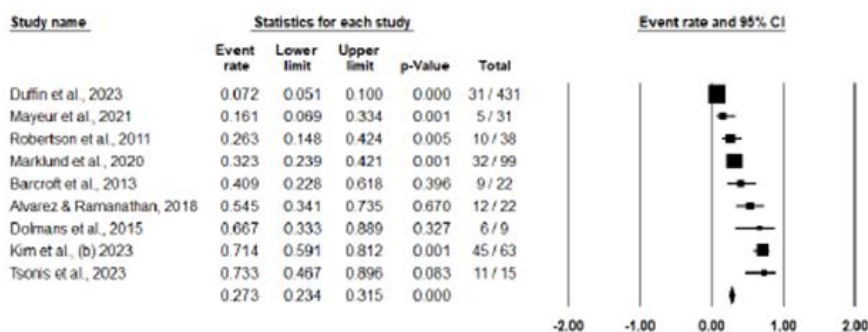
( $P=0.000$ )) in **Figure (3B)**, and insignificant heterogeneity ( $I^2=51.9%$  ( $P=0.125$ )) in **Figure (3C)**.

**Frozen-thawed embryo transfer (FTET)**

A meta-analysis of 4 studies involving 78 female cancer patients/survivors who underwent FTET has revealed a pooled prevalence of clinical pregnancy of (61.5%, 95% CI 0.234-0.315, p= 0.049) **Figure (4A)**, and 3 studies involving 67 subjects were reported in the live birth rate (49.3%, 95% CI 0.234-0.315, p= 0.905) **Figure (4B)**.

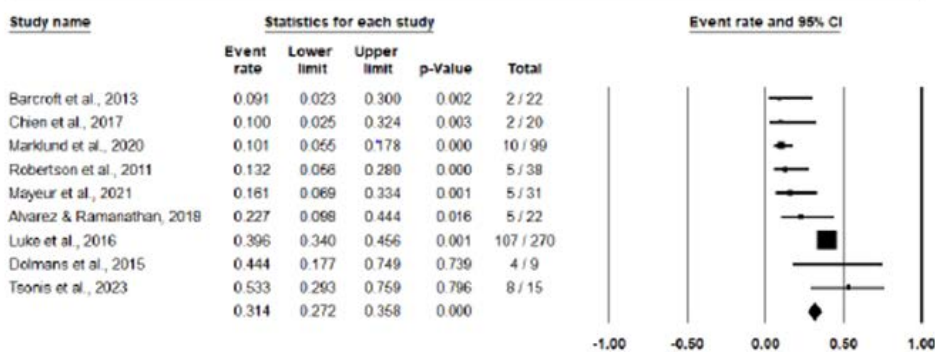
Visual inspection of the funnel plots shows the symmetrical distribution of the included studies with no inter-heterogeneity between studies ( $I^2=15.3%$  ( $P=0.315$ )) in **Figure (5A)**, and insignificant heterogeneity ( $I^2=0%$  ( $P=0.611$ )) in **Figure (5B)**.

**Clinical pregnancy rate in patients underwent embryo cryopreservation**



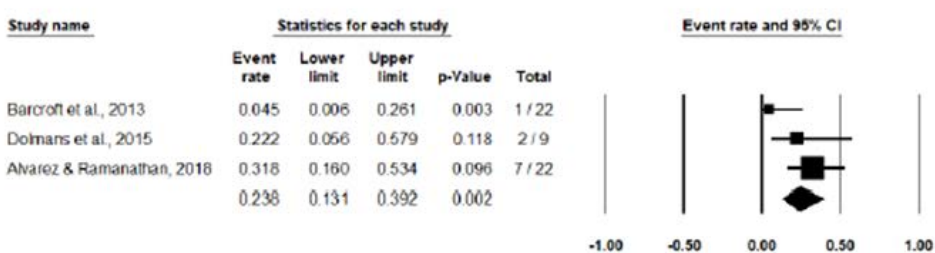
(A)

**Live birth rate in patients underwent Embryo cryopreservation**



(B)

**Miscarriage rate in patients underwent Embryo cryopreservation**



(C)

**Figure 2.** Forest plot of FP outcomes: (A) clinical pregnancy rate, (B) live birth rate, and (C) miscarriage rate in embryo cryopreservation group

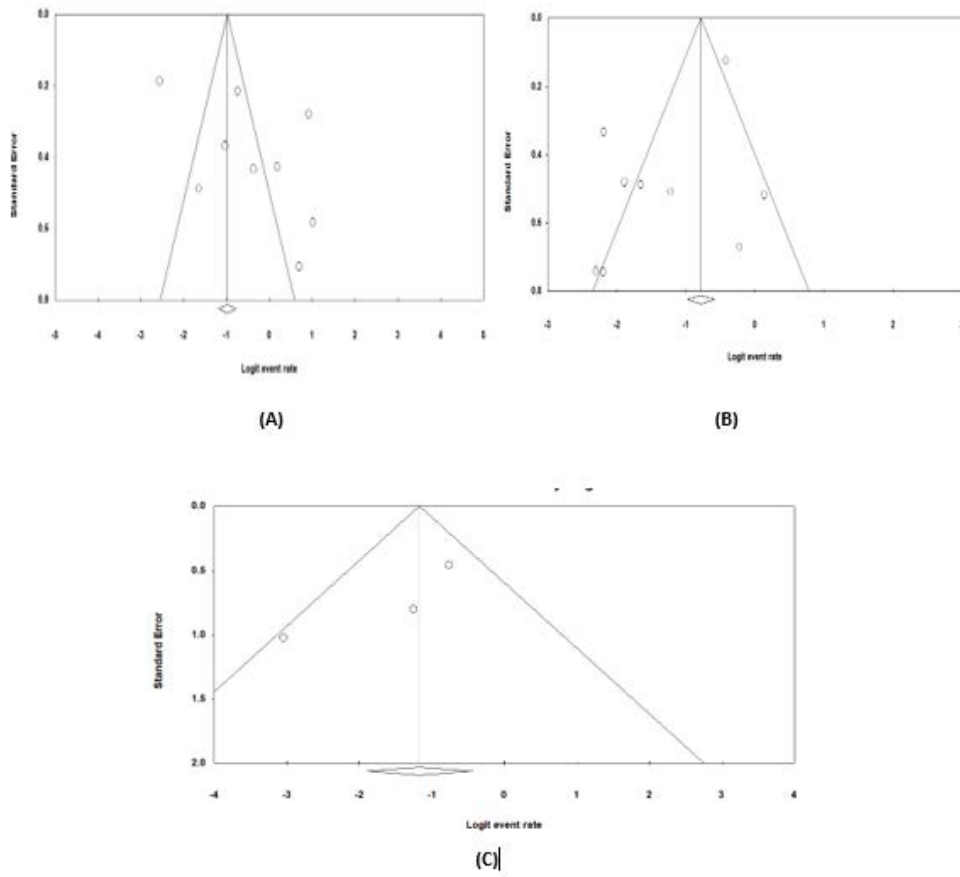


Figure 3. Funnel plot of publication bias detection

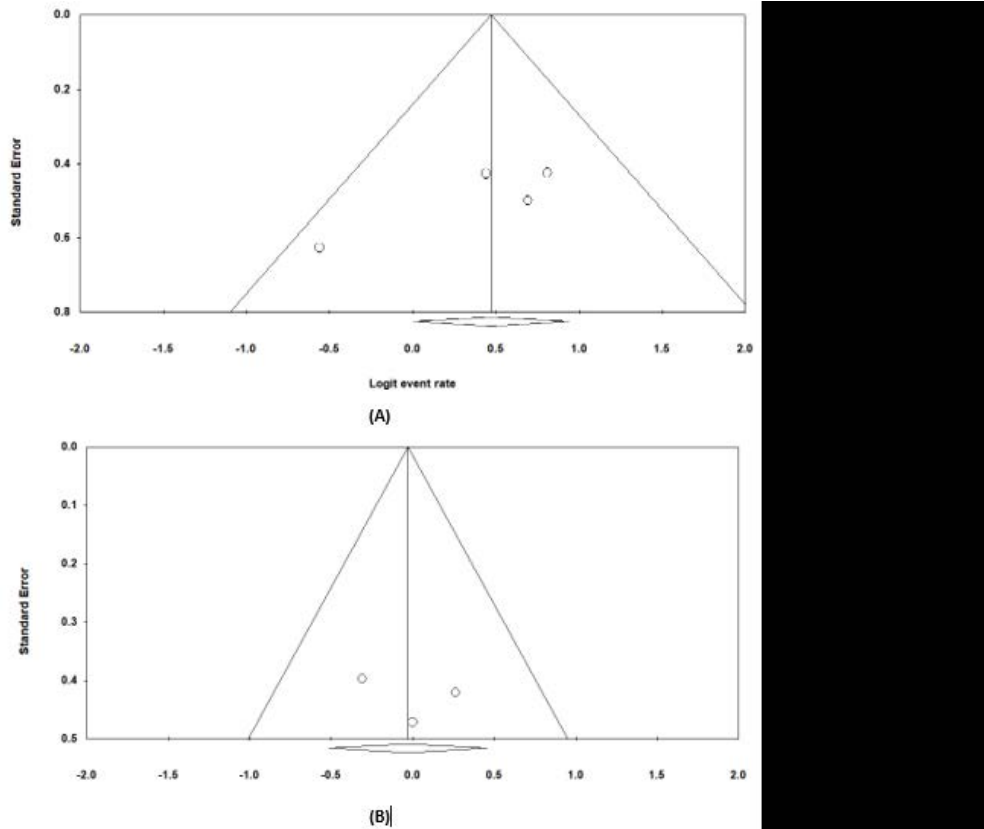


Figure 4. Forest plot of FP outcomes: (A) clinical pregnancy rate, and (B) live birth rate in FTET group

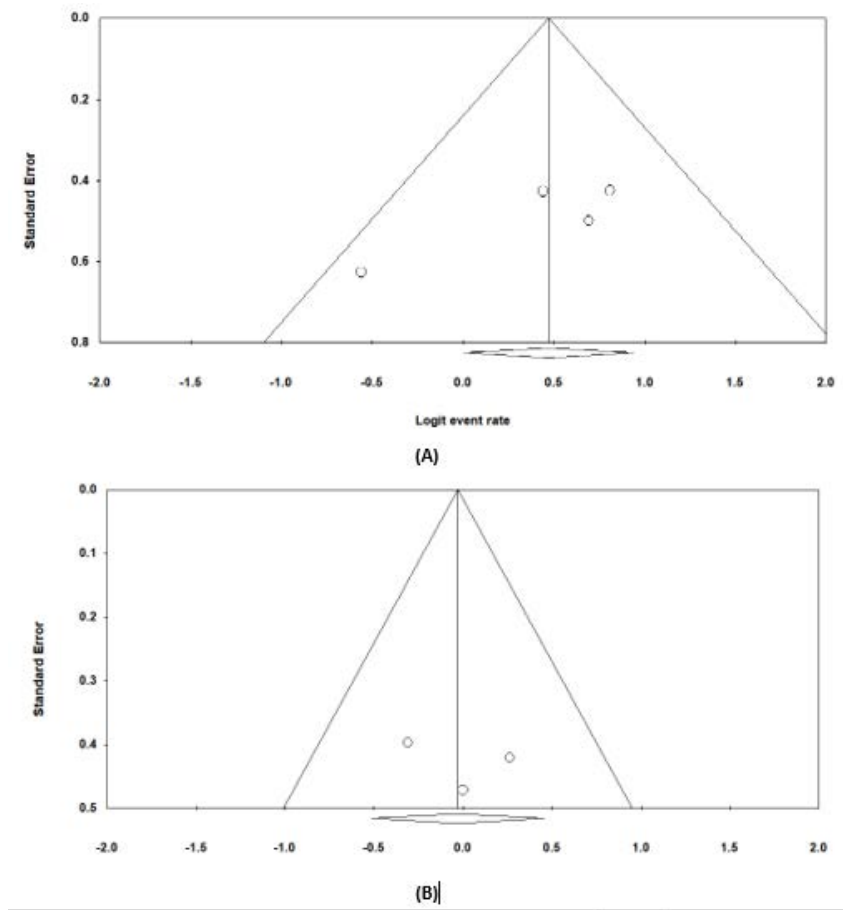


Figure 5. Funnel plot of publication bias detection

## DISCUSSION

Reproductive preservation services are regrettably not often provided or even brought up with the patient before beginning cancer treatment. Research indicates that one important survival concern is infertility. Compared to patients who did not receive information about their sexual and reproductive health, those who did showed reduced psychological discomfort. These young men and women experience less reproductive regret when they make informed decisions [31]. This present meta-analysis found that the reproductive outcomes of cancer patients and survivors with the assessment of FP methods are variable. To ensure clarity, we discuss the available evidence separately for the two listed FP methodologies by the reproductive parameters.

### Embryo cryopreservation

The most recent ESHRE recommendations, which were released in 2020, only recognized oocyte and embryo cryopreservation as proven methods for frozen plasma transfer following adolescence [32]. We recorded that the pooled prevalence of clinical pregnancy was 27.3% in female cancer patients/ survivors who underwent embryo cryopreservation (COS method). This was slightly lower than **Rienzi et al.** who reported that embryo cryopreservation is a well-established procedure in the ART field for infertile patients, with a pregnancy rate of 30-35% per cryopreserved embryo, according to 2015 statistics from the Japan Society of Obstetrics and Gynaecology [33].

Our results found that the live birth rate was 27.3% which was higher than **Fraisom et al.** (19%) [34]. We also reported a miscarriage rate of 23.8% which was slightly higher than **Fraisom et al.** (22%) who included cryopreserved embryos in female cancer survivors [34] and

much higher than the miscarriage rate in the general population (5%) [35]. There is no explanation for this rate of miscarriages. Since the frozen embryo transfer procedure has never been documented, we were unaware of the current notion of progesterone level monitoring during the transfer [36].

The procedure of cryopreservation of embryos has several limitations. (1) COS can cause therapy for cancer to be delayed by about two weeks starting on the second day of the period. (2) Estradiol-sensitive cancers may be adversely affected by high amounts of estradiol during stimulation. (3) Requirement for donor or partner sperm inhibits future reproductive liberty and raises stress levels. (4) The ethical, legal, and religious ramifications of disposing of embryos in the event that a patient passes away before using them or that a couple separates. (5) Ineffective for patients who are not yet in puberty [37].

### Frozen-thawed embryo transfer (FTET)

Our analysis showed that the clinical pregnancy rate and live birth rate in female cancer patients/ survivors who underwent FTET were 61.5% and 49.3%, respectively. These rates were higher than the rates obtained with embryo cryopreservation which may be due to the fact that there are few studies recruited in the FTET group with smaller sample size. **Fraisom et al.** reported a slightly lower live birth rate (41%) after FTET [34].

### Clinical implications and future directions

The strategy that provides the highest likelihood of live birth is still up for debate because there isn't enough data on the long-term effects of free pregnancy. The three approaches cannot be compared, and because

of the disparate approaches and results-reporting styles used in the literature, it is still challenging to understand. Furthermore, the kind of FP used may be influenced by the age and clinical status of the women at the time of diagnosis, which will unavoidably alter the LBR and the age of return. As a result, when presenting our findings to women, it's critical to take into account both the estimated proportion and the confidence interval. In this sector, providing realistic and appropriate counseling is still a struggle.

Patients with cancer frequently experience increased worry, low self-esteem, and poor quality of life. This psychological pressure frequently impacts their capacity to explore and actively pursue available treatment choices, particularly those aimed at preserving future fertility. With so many FP treatment options now, it is critical to inform cancer patients about the possible future utility and safety of each option. This is also important when considering additional supplementary treatments not mentioned in our analysis, such as GnRH analogs and ovarian transposition [38].

Given the wide range of therapies and patient characteristics described in our review, we highlight the importance of taking an integrated approach to care for these women in order to maximize benefits and reduce the risk of immediate adverse effects in this cohort, as suggested by recent evidence-based guidelines [32].

### Strengths

There are many reviews and pooled analyses that discuss the reproductive outcomes of FP according to the techniques, cancer type, and timing of the procedure. The reviewers in this analysis focused on analyzing the methods that hold new and recent clinical evidence. The risk of including the same population twice was carefully assessed, and sensitivity analyses were carried out if needed. Even though the three procedures cannot be compared, the study gives specific information regarding live birth ratios that clinicians can use to counsel women. Another strength is the application of precise methodology, such as the Prisma standards and the Cochrane manual. The Newcastle-Ottawa Quality Assessment Scale was used to evaluate the included studies' quality, and several had a minimal risk of bias.

### Limitations

The quality of our meta-analysis is determined by the quality of the included research. Only observational and cohort research were accessible, and randomized controlled trials could not be undertaken in this field. The majority of our included studies had a modest number of participants. Live birth rates were most likely underestimated, particularly among women monitored following embryo cryopreservation, for whom spontaneous pregnancies have not been recorded. Following up on these cohorts should be the primary focus in the future. A further piece of information that is absent is an assessment of the efficacy of IVF methods, as well as data on the number of cycles needed to achieve pregnancy.

### Conclusion

**Our findings can help practitioners counsel women regarding FP approaches. A combination of diverse strategies may be the best solution, although this requires further exploration. This meta-analysis emphasizes the importance of a multinational register with long-term cohort follow-up. Longitudinal studies could be the first step in improving the literature's quality, with international criteria requiring that the same factors be reported consistently.**

**Authorship Contribution:** All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

**Potential Conflict of Interest:** None

**Competing Interest:** None

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