Long term pregnancy outcomes of women with cancer following fertility preservation: A systematic review and meta-analysis

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ABSTRACT

Objective: As cancer survivorship increases, there is higher uptake of fertility preservation treatments among affected women. However, there is limited evidence on the subsequent use of preserved material and pregnancy outcomes in women who underwent fertility preservation (FP) before cancer treatments. We aimed to systematically review the long-term reproductive and pregnancy outcomes in this cohort of women.

Patients: Women who underwent any type of the following FP treatments: embryo cryopreservation (EC), oocyte cryopreservation (OC) and ovarian tissue cryopreservation (OTC)) before any planned cancer treatment.

Evidence Review: We searched electronic databases (MEDLINE, Embase, Cochrane CENTRAL, and HTA) from inception until May 2021 for all observational studies that met our inclusion criteria. We extracted data on reproductive and pregnancy outcomes in duplicate and assessed the risk of bias in included studies using the ROBINS-I tool. We pooled data using a random-effects model and reported using odds ratios (OR) with 95% confidence intervals (CI).

Main Outcome Measures: Our primary outcome was live birth rate and other important reproductive and pregnancy outcomes.

Results: Of 5405 citations, we screened 103 and included 26 observational studies (n= 7061 women). Hematologic malignancy was the commonest cause for seeking FP treatments, followed by breast and gynecology cancers. Twelve studies reported on OTC (12/26, 46%), eight included EC (8/26, 30%), and twelve reported on OC (12/26,

46%). The cumulative live birth rate following any FP treatment was 0.046 (95%CI 0.029-0.066). Only 8% of women returned to use their frozen reproductive material (558/7037, 8.0%), resulting in 210 live births in total, including assisted conceptions following EC/OC/OTC and natural conceptions following OTC. The odds for live birth was OR 0.38 (95%CI 0.29-0.48 I^2 83.7%). The odds for live birth was the highest among women who had EC (OR 0.45, 95%CI 0.14-0.76, I^2 95.1%), followed by the OTC group (OR 0.37, 95%CI 0.22-0.53, I^2 88.7%) and OC group (OR 0.31, 95%CI 0.15-0.47, I^2 78.2%).

Conclusions: Fertility preservation treatments offered good long-term reproductive outcomes for women with cancer with a high chance to achieve a live birth. Further research is needed to evaluate the long-term pregnancy and offspring outcomes in this cohort.

Keywords: Fertility preservation; embryo cryopreservation; oocyte cryopreservation; ovarian tissue cryopreservation; cancer; systematic review

Highlights:

- Only 8% of women returned to use their frozen reproductive material (558/7037, 8.0%), resulting in 210 live births in total, including assisted conceptions following EC/OC/OTC and natural conceptions following OTC.
- The cumulative live birth rate following any fertility preservation treatment was 0.046 (95%CI 0.029-0.066).
- The overall LBR was highest in women who had EC (OR 0.45, 95 %CI 0.14-0.76), followed by OTC group (OR 0.37, 95 %CI 0.22-0.53) and OC group (OR 0.31, 95 %CI 0.15-0.47).
- There was limited reporting on other important reproductive outcomes in this cohort including miscarriages, ectopic pregnancies and Caesarean sections rate.

Introduction

Infertility is a common side-effect in women undergoing cancer treatments due to the associated gonadotoxic effects, reducing egg reserve and increasing the risk of early menopause(1, 2). Whilst overall cancer survivorship is rising (3), the chance of pregnancy after cancer treatment remains lower than that in the general population (4). Early counselling on future family planning and reliable fertility preserving treatments is highlighted as a priority by most women undergoing cancer treatments (5, 6).

Providing effective and reliable fertility preservation (FP) treatments to girls and young women with cancer is becoming mainstream (7) with a rapid increase in uptake worldwide (8, 9). The 2018 American Society of Clinical Oncology (ASCO) guidelines (10) support offering embryo cryopreservation (EC) and oocyte cryopreservation (OC) as routine established treatments for female patients with cancer. The ASCO guidelines also removed the label 'experimental' when describing ovarian tissue cryopreservation (OTC) in 2019 (11) which was also supported in the new ESHRE guideline (12).

However, the evidence on the long-term clinical effectiveness and value of FP treatments remains unclear with varied reporting on the long-term reproductive and pregnancy outcomes in this cohort (13, 14). Reports from several countries indicate an overall low utility of cryopreserved gametes and embryos (15, 16), raising dilemmas on the ethical use and storage of abandoned gametes (17).

To address this knowledge gap, we aimed to evaluate long-term reproductive and pregnancy outcomes following FP treatments by systematically reviewing of the literature on women who underwent FP treatments.

Materials and methods

Study Design

We conducted a systematic review and meta-analysis using a registered protocol (PROSPERO CRD42021269016) and reported its findings following established guidelines (18).

Literature search

We searched electronic databases (MEDLINE, Embase, Cochrane CENTRAL, and HTA) from inception until May 2021 using set keywords and subject Mesh headings (**Supplementary Table 1)**. We included all observational studies that reported on the reproductive and pregnancy outcome of women with cancer who underwent any type of FP treatment. We excluded studies reporting on mixed patient population (e.g. male infertility) and those reporting on fundamental or animal research. We also excluded studies evaluating novel FP tools or systems, case reports, review articles, conference abstracts with insufficient information, letters, editorials, and those not published in English. Studies that evaluated non-cryopreservation FP treatment (e.g. ovarian transposition, conservative gynecologic surgery, and ovarian suppression) were excluded. Before data synthesis, the eligibility of data was checked manually in case of overlapping and duplication by comparing FP centres, the duration of the cohort, and the first/corresponding authors of every study.

Risk of bias assessment

Two independent reviewers (Z.X., S.I.) assessed the quality of included studies using the ROBINS-I tool, with disagreement solved by consensus within the whole team. In short, seven domains were evaluated, including confounding, selection, classification, deviation from intended intervention, missing data, measurement, and reporting of the outcomes (19). Each domain was classified as low, moderate, serious or critical risk of bias according to the answers towards preset signaling questions, and then combined to get the overall risk of bias.

The quality of evidence of the included studies was then evaluated according to the

GRADE principles for primary outcomes, including the risk of bias, inconsistency, indirectness, imprecision, publication bias and other considerations (20).

Data extraction and synthesis

Data were extracted by two reviewers independently (Z.X., S.I.), using pretested screening and data collection forms. The details of included studies, the outcome parameters and related details of interventions were captured precisely, including study basic information, patient information (age, cancer type, patients' childbearing intent or pregnancy attempts), intervention and reproductive outcomes.

The primary outcome was the chance of live birth, defined as the ratio of live birth (from FP treatments only) to the number of patients involved. We also reported the proportion of women who returned to use their frozen gametes, embryos and ovarian tissues, and the risk of adverse pregnancy outcomes, including miscarriage, ectopic pregnancy, stillbirth, neonatal death, Caesarean section and maternal death.

Statistical analysis

We reported on dichotomous outcome using odd ratio (OR) with 95% confidence intervals (CI). We conducted Meta-analyses using the *metan* package in STATA 16.0 (STATA Corp., College Station, TX, USA) and applied a random-effects model to pool data for each outcome across included studies (21). Freeman-Tukey Double Arcsine Transformation was used for the proportion that was close to the margins in data transformation (22). Heterogeneity was assessed using I^2 statistic with I^2 of 25, 50, and 75% representing low, medium, or large heterogeneity (Cochran's Q test) (23). For significant (I^2>50%) heterogeneity, sensitivity analysis was performed after exclusion of studies, and the random-effects model was used to combine study results in this condition. Publication bias was assessed using a funnel plot (24) and Egger's regression test (25).

Results

Study characteristics

Our electronic search identified 5405 citations. After removing duplicates (n=1436) and after screening titles and abstracts, we retrieved 97 studies for full assessment against our inclusion criteria (**Figure 1**). Of 56 eligible studies, 30 studies were excluded because of no data available (n=11, 19.6%) and potential overlapping data (n=19, 33.9%) (See details in **Supplementary Table 2**). Finally, 26 studies in total, reporting on 7061 women, met our inclusion criteria: 16 were retrospective cohort studies, seven were surveys of retrospective cohorts or FP centres, and three were prospective or ongoing cohort studies **(Table 1).** The median sample size was 122.5 [6, 1608]. The majority of studies (n=17) were from European countries, six were from the United States, and the other three from Brazil, Canada and Japan.

Patient characteristics

Hematologic malignancy (69.2%, 18/26) was the commonest cause to seek FP treatments followed by breast (65.4%, 17/26) and gynecology cancers (46.2%, 12/26).

The median participant age at baseline was within 18-35 age range in 22 studies, over 35 (35.8 ± 4.1) in one study (26), and below 18 (14.8 ± 2.3) in another (27). The median follow-up time was 9 [5, 18] years (19 studies) with three studies not reporting the exact follow-up year (26, 28, 29) and the rest did not specify exact time (27, 30-32).

As for FP treatments, OTC was reported in twelve studies (12/26, 46%), eight reported on EC (8/26, 30%), and twelve reported on OC (12/26, 46%). Majority of included studies offered one type of FP treatment (18/26, 69%), five studies offered two options of either EC or OC (5/26, 19%), and the other three offered EC, OC and

OTC (3/26, 11.5%). In general, FP centres tended to offer OTC to patients of a younger age, and EC or OC to adult patients. Specifically, one study focused on prepubertal and adolescent girls only offered OTC (27). Among 11 studies including patients with median age below 30, 72.2% (8/11) OTC was offered, and 36.4% (4/11) offered EC/OC. In the remaining 13 studies including patients with median age over 30, 92.3% (12/13) offered EC/OC, and 30.8% (4/13) offered OTC.

Reproductive and pregnancy outcomes

We pooled data from 25 studies that reported the number of women who returned to use their frozen gametes/embryos or auto-transplantation of frozen ovarian tissue. The pooled LBR was OR 0.046 (95 %CI 0.029-0.066, I^2 89.0%) across all women who had any FP treatment before cancer treatments (**Figure 2**).

In total, only 8% of these women returned to use their frozen reproductive material (558/7037, 8.0%), resulting in 210 live births in total, including assisted conceptions following EC/OC/OTC and natural conceptions following OTC. The odds for live birth among this group of women was OR 0.38 (95 %CI 0.29-0.48 I^2 83.7%) (**Figure 3**).

The odds for live birth was the highest among women who had EC (OR 0.45, 95 %CI 0.14-0.76, I^2 95.1%), followed by the OTC group (OR 0.37, 95 %CI 0.22-0.53, I^2 88.7%) and OC group (OR 0.31, 95 %CI 0.15-0.47, I^2 78.2%) (**Figure 4**). Notably, of 114 live births reported in the OTC subgroup, 67% (76/114) came from natural conception after OTC patients had their ovarian tissues transplanted, and 33% (38/114) were achieved by assisted reproductive technology.

About a half of all included studies (14/26, 54%) reported on other important pregnancy outcomes. These included a total of 49 miscarriages in 14/14 studies, three biochemical pregnancies in 3/14 studies (29, 33, 34), one ectopic pregnancy (32) and one surgical termination for fetal anomalies (35). There were 14 ongoing pregnancies (0.3%, 14/4700) in 7/14 studies. In live births, six Caesarean sections (33.3%, 6/18) (34-36) and two cases of pre-eclampsia (28.6%, 2/7) (35) were

reported.

We conducted sensitivity analyses including to explore the effect of studies with a small sample size and those with potentially high risk of bias on the overall LBR (**Supplementary Figure 3**), however our findings did not suggest a significant impact of these factors on the pooled effect estimate. We also explored the risk of publication bias using a funnel plot which suggest some outliers evidence by a significant p value on Egger's test ($p<0.05$) (**Supplementary Figure 4**.)

Risk of bias assessment

More than half of the included studies (15/26, 57%) were assessed to have a low risk of bias, with the remaining studies (11/26, 43%) showing a moderate risk of bias **(Supplementary Table 5)**. 11 studies were assessed as being at moderate risk of bias because of potential confounding in study design. Other pre-intervention and at-intervention bias in neither selection of participants into study nor classification of interventions was found in all 26 studies. In post-intervention domains, two studies were assessed as being at moderate risk of bias in selection of the reported result: one study due to missing data, and another one study due to outcomes measurement respectively.

Using the GRADE approach, we considered the quality of synthesized evidence across included studies to be 'Very low' evidence quality due to high study inconsistency and heterogeneity (**Supplementary Table 6**).

Discussion

Our findings suggest an overall good live birth rate among women who preserved their reproductive material before cancer treatment demonstrating the good long-term value of FP treatments in this context. While the overall reported number of women returning to use their frozen material was relatively low at 8%, the success rate was very reassuring among all used FP treatment options compared to rates reported in older studies (13, 37).

This low utilization rate could be linked to several factors. The overall follow-up period in included studies was relatively too short, ranging from 5-18 years, considering that many women recovering from cancer would usually delay childbearing for few years after treatment completion. A recent population-based analysis using national databases in Scotland showed the time to last pregnancy was longer after cancer, e.g., 10.7 ± 6.4 years in the overall group and 6.2 ± 2.8 years in women with breast cancer, and the longest time to last pregnancy was 17.1 ± 7.7 years in women with leukaemia (38).

Many of those women would retain their natural fertility post cancer treatment and therefore, continue to have spontaneous conception. These were not captured by our review which may have increased the denominator for the estimated live birth rate.

We were unable to synthesise high quality evidence on other important reproductive outcome as planned in our protocol, however, the reported incidence of these events is overall within the normal population range.

Strengths and limitations

The strengths of our review stem mainly from its prospective design, systematic and comprehensive literature search, and the use of quality evidence synthesis methodology.

Still, our findings were limited by several factors. First, we were unable to perform a meaningful synthesis on important pregnancy outcomes due to limited reporting across included studies. Similarly, we detected a relatively high level of heterogeneity across included studies with varied population characteristics which limited the certainty in our synthesized effect estimate.

As we included observational studies with a relatively wide time range, we were unable to adjust for the potential for performance bias specifically as experience with FP treatments changed significantly overtime across centers and operators. Other potential effect modifiers should also be explored in future analysis (e.g. participant age, disease severity, co-morbidities etc..) which can be only explored using individual patient data meta-analyses.

Implications for clinical practice

Our results support the need to offer FP treatments to women with cancer to help them better plan and control their future fertility. This is particularly relevant given the gradual improvement in the cryopreservation technology that is enabling more reliable storage, thawing and use of reproductive material. EC has been utilised in IVF over 30 years and has led to hundreds of thousands of births (39). Similarly, the use of OC is well established and recommended as a standard method for FP (40) with similar pregnancy outcomes compared to using fresh oocytes (37).

While our results are supportive of the overall clinical value of OTC as an FP treatment options, there is still need to optimize the clinical experience across FP centers to facilitate its routine use. Specifically, there is a need to establish standardized patient pathways to select the patient who may best benefit from OTC over other options. For example, OTC is not recommended for patients with hematologic malignancy (41), because there is a risk of re-introducing the residual neoplastic cells, despite of evidence showing even the cancer recurrence was not directly caused by OTC (42). Some argued for the use of OTC combined with oocyte harvest and in vitro maturation with some reported success (43), however, more

research is needed to clarify the safe use of this treatment option

Considering the wide variation in treatment options and patient characteristics captured in our review, we emphasize the importance of adopting a multidisciplinary approach to caring for these women to maximize benefits and reduce the risk of immediate adverse outcomes in this cohort as recommended in recent evidence based guidelines (44).

Future research need

Giving the limitation of outcome reporting captured in our review, we emphasize the importance of establishing large, standardized national registries to prospectively capture the outcomes of patient using FP treatments. Women with ART pregnancies have a higher risk of adverse perinatal outcomes in general (45). Considering the increased health risk among cancer survivors, prospective registries are need to evaluate the perinatal risk in women returning to use their frozen reproductive material and inform optimal antenatal and intrapartum care provision to reduce the risk of health complications in this cohort. As such, there is an apparent need to establish an evidence-based treatment pathway to enable accurate risk prediction and patient selection to the most suitable FP treatment taking into account disease severity, prognosis, and each patient co-morbidity.

Standardizing outcome reporting is particularly needed to enable better evidence synthesis (46) and establishing a FP core outcome set could help to address this research need. As none of the included studies involvement lay consumers in their design, conduct and reporting, there is a need for active engagement of patients and their families to help inform the future health and research need in this domain (47).

Finally, better quality qualitative research is needed to explore patient treatment wishes and satisfaction with FP treatments on the long-term. Such research is specifically needed to identify potential barriers to the uptake of FP, return to use

frozen reproductive material, and optimal counselling on the use of FP treatments (48).

Conclusion

Fertility preservation treatments offered good long-term reproductive outcomes for women with cancer with a high chance to achieve a live birth. Further research is needed to evaluate the long-term pregnancy and offspring outcomes in this cohort.

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Data Availability: Some or all datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Contribution to authorship: ZX, SI, and BHA conducted the data extraction, primary analysis, data illustration and drafted the 1st manuscript. BHA conceived the idea and finalised the protocol. SB, LR supervised the project conducted and provided critical input to the final manuscript. MCD supervised the study conduct, analysis and edited the final manuscript.

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