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# Effectiveness of social egg freezing: protocol for systematic review and meta-analyses

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## ABSTRACT

**Introduction** Social egg freezing is storing egg for the purpose of preserving fertility and delayed childbearing. Currently, little is known about the utilisation and effectiveness of this approach. This review aims to determine (1) the proportion of women who used their stored eggs, and (2) the egg survival rate through vitrification, and the clinical pregnancy rate and live birth rate per 100 women partaking in the procedure, and among women who stored their eggs for medical reasons.

**Methods and analyses** This systematic review will be done according to the items listed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. PubMed, Embase, Scopus, The Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Library and Health Technology Assessment databases will be searched to identify eligible studies published since 2012. Two reviewers will independently appraise the eligibility and quality of the studies based on preset checklists and extract the data using a data extraction template. Outcomes of interest are proportion of women who used their stored eggs, egg survival rate, pregnancy rate and live birth rates. We will determine the presence heterogeneity among studies using the Cochrane's Q test. The percentage of total variation across studies, which is due to statistical heterogeneity, will be calculated using the $I^2$ statistics. Outcomes of interest will be pooled together using metaprop programme STATA V.14.

**Ethics and dissemination** For this review, ethical committee approval is not required. We will use publically available data from previously published studies. The final report of the review will be disseminated through publication on national or international journal, and it will be presented on different scientific conferences.

**PROSPERO registration number** CRD42018114254.

## Strengths and limitations of this study

- To the best knowledge of the investigators, this will be the first systematic review and meta-analyses investigating the proportion of women who had used their stored egg, the egg survival rate through vitrification among women who underwent social egg freezing and the reproductive outcomes.
- Two reviewers will independently conduct abstracts and full-text screening, data extraction and risk-of-bias assessment of the included studies.
- Social egg freezing is a recent application of assisted reproductive technology; there may be a limited number of published studies.
- Since primary studies are likely to be limited to observational studies, confidence in estimates is likely to be low.

## INTRODUCTION

In women, fertility begins to decline in their fourth decade of life.[1] Fecundity is well publicised[2]; therefore, some women delay time of childbearing in order to fulfil other personal goals such as education, employment and/or overcome financial constraint.[3 4] Relationship status has also been identified as a possible reason to preserve childbearing time.[3 5 6] With the intention to share parenthood with a future partner, and defy the natural age-related fertility decline, some women have chosen to store their eggs,[7–9] despite concerns about complications, limited success rates and costs.[7] A number of international companies such as Facebook, Google and Apple are offering female employees the chance to freeze their eggs, with the aim to give employees more freedom to pursue family planning according to their own timeline.[10 11] This is variously labelled as 'social egg freezing', or 'non-medical egg freezing' or 'elective egg freezing.[12] The chance of having the desired outcomes such as high oocyte survival and live birth rates depend on womens' age,[13] the number of retrieved mature oocytes[14] and the number of frozen eggs.[13] Previous studies' report lack agreement regarding the optimal timing of oocyte cryopreservation.[9 14 15] One study showed the live birth rate was higher among women aged ≤35 years compared the older women (>35 years).[14] Another study based on a decision analysis model verified that the probability of having live birth is the largest at the age of 37 years.[15]

Despite the high media profile in recent times,[16 17] information about the effectiveness (live birth) and utilisation of their stored egg[18] and the long-term outcomes in family formation[19] is scarce. Given the absence of systematic review and meta-analysis on the topic, this review will generate evidence on the proportions of women who used their stored eggs, egg survival rate and overall outcomes for women who store egg for fertility preservation that could help women to make informed decisions to freeze oocytes.[2 18] Few individual study results demonstrate the diverse potential reproductive outcomes of women who stored their egg for non-medical reasons. A study of 23 women who underwent fertility preservation found that two women have used their stored eggs, of whom one of gave birth.[20] In another study, of 875 women who had stored vitrified oocytes for future autologous in vitro fertilisation (IVF) treatment, 117 (13.4%) women returned to undergo IVF treatment.[21] Two studies reported that 9.3%[14] and 6%[6] of women have returned to use their stored eggs. In another study conducted in Melbourne Australia, of 91 women who stored their egg for non-medical reasons, 6 had used their stored oocytes, 3 of whom had given birth as a result. Of the three women who had not achieved a pregnancy with their stored oocytes, two had given birth after using fresh oocytes.[18]

The aim of this systematic review is to determine the proportion of women who used their stored egg (for non-medical reason) for autologous reproduction; to determine the effectiveness of social egg freezing (clinical pregnancy rate and live birth rate); and to calculate egg survival rate through vitrification among women who underwent social egg freezing.

### Research questions

1. What proportion of women who had social egg freezing used their eggs for autologous reproduction?
2. What is the egg survival rate through vitrification among women who underwent social egg freezing?
3. What is the effectiveness of social egg freezing, measured by clinical pregnancy rate and live birth rate per 100 women undergoing social egg freezing?
4. What is the effectiveness of egg freezing, measured by clinical pregnancy rate and live birth rate per 100 women who stored egg for medical reason?

## METHODS

### Protocol and registration

This protocol for systematic review is registered by the International Prospective Register of Systematic Reviews https://www.crd.york.ac.uk/prospero/searchadvanced.php.[22] This protocol was written according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Components of the protocol were evaluated and addressed following items in the PRISMA-P checklist[23] (online supplementary file 1). We will include a proposed flow diagram that shows the search process (figure 1).

### Search strategy

The primary literature search will be carried out from different databases. We will include studies from both English-language and non-English language articles published since 2012 when the American Society for Reproductive Medicine (ASRM) declared that egg freezing no longer be considered as experimental.[24] We will use a freely available web-based Babelfish and Bing translators to translate the non-English language articles into English. We will employ Medical Subject Headings (MeSH) terms, Emtree, CINAHL headings and combined keywords to identify studies in the databases. We will use PubMed, Embase, Scopus, CINAHL, Health Technology Assessment, the Cochrane Library Databases, Translating Research into Practice, ProQuest Dissertations and Theses, and Conference Proceedings Citation Index-Science to identify the relevant literatures for the review. The second author (FAK) will conduct all literature search, article retrieval and contact research authors for additional information if the paper is a conference preceding or in case of missing data. The search terms will emerge from the following keywords (social egg freezing, elective egg freezing, fertility preservation, delaying childbearing, non-medical egg freezing, oocyte freezing, oocyte cryopreservation, egg cryopreservation, oocyte survival, live birth) (online supplementary file 2). We will customise the search strategy for each database search. The review will be commenced on 1 May 2017 and completed on 31 July 2019.

### Eligibility criteria

The studies will be selected based on the criteria outlined next.

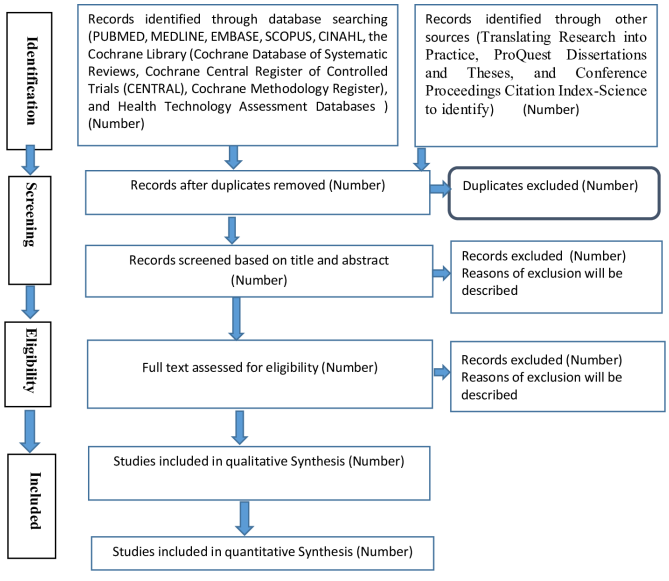


**Figure 1** Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram for article selection and screening.

### Study design

All observational studies (including prospective and retrospective cohort studies, case-control studies and cross-sectional studies) will be included.

### Population

The study will include women who underwent social egg freezing. To be included, the literature should examine the proportion of women who had social egg freezing and used their eggs, egg survival rate through the freezing/thawing process and/or live birth rate among women who underwent social egg freezing. A literature that examined egg survival rate, clinical pregnancy rate and live birth rate among women who stored egg for medical reasons will also be included into the review.

### Intervention and comparisons

There is no intervention group. We will compare clinical pregnancy rate and live birth rate among women of different age groups.

### Outcomes

The primary outcomes of interest are proportion of women who used their stored egg, egg survival rate, pregnancy rate and live birth rate among women who underwent social egg freezing. Secondary outcomes are egg survival rate, pregnancy rate and live birth rate among women who stored their egg for medical reason.

### Exposures of interest

Age of the women at oocyte retrieval and vitrification is the main exposure for live birth rate. In addition, the total number of oocyte harvested, the number of oocytes thawed and survived, the number of oocytes fertilised, the number of embryos obtained and transferred, and the number of surplus embryos for cryopreservation are also exposure of interests.

## Patient and public involvement

Patients were not involved in the development of this study protocol. This study will use publically available data without patient's identification.

## Study selection

The identified studies will be uploaded to Covidence[25] and duplicates will be removed. Two review authors (AW and FAK) will screen the abstract, and review full text papers independently based on information contained in titles and abstracts as per the inclusion criteria. We will obtain the full texts of all titles and abstracts that meet the inclusion criteria during the screening. Any discrepancy between the two reviewers will be resolved through discussion. In the case of further disagreement, the fourth author (ZL) will arbitrate for the final decision. Studies that are not eligible will be excluded and the reasons for the exclusion will be described. A study will be excluded if it fulfils any of the following criteria: citations without abstracts; systematic reviews and meta-analysis; anonymous reports; duplicate studies. In addition, a study that does not report the number of women who used their stored egg and the outcome of the pregnancy (in terms of live birth) will be excluded. We will provide a supplementary file for reference list of all excluded studies indicating the reason(s) for exclusion.

## Data management

First, an initial set of studies will be identified by using the search terms and applying filters. We will use Covidence to store all references selected for the review and all discarded references. We also use excel spreadsheet to manage the data. All information sources in the search such as databases with dates of coverage, contact with authors to acquire additional data and last date of literature search along with the full search strategy will be carefully recorded and reported.

## Risk of bias in included studies

We will use the Newcastle-Ottawa Scale (NOS)[26] to assess the methodological quality of a study and to determine the extent to which a study has excluded or minimised the possibility of bias in its design, conduct and analysis. Attention will be given to clear description the objective of the study, identification of the study subjects and precise reports of exposure and outcomes of interest, as well as sources of bias or confounding.

## Data extraction process

For the data extraction, a structured data extraction form will be constructed. An Excel (Microsoft Corp, Redmond, WA) spreadsheet will be used for the data abstraction. Two reviewers (AW and FAK) will independently extract the data using a data extraction template. The template will include authors' name, year of publication, the country where the study was undertaken, study design, sample size, the total number of oocyte harvested, the number of oocytes thawed and survived, the number of fertilised oocytes, the number of embryos obtained and transferred, and the number of surplus embryos for cryopreservation. In addition, the proportion of women who had social egg freezing and used their eggs, number of clinical pregnancies and live birth among women who undergoing social egg freezing and who stored their egg for medical reason will be abstracted. Any discrepancy during data abstraction will be resolved by discussion.

## Data synthesis and statistical analysis

### Metabiases

The presence of small-study effects will be checked by using Doi plot and LFK index[27] using MetaXL V.5.3,[28] which is an add-on for Microsoft Excel. We will implement influence analyses to check the effect of each study on combined effect size (ie, each study will be deleted from the model once in order to examine the effects of each study on the overall results for each outcome). We will report the influence analyses result with a summary table.

### Confidence in the cumulative evidence

The Grading of Recommendations Assessment, Development and Evaluation[29] tool will be used to evaluate the quality of evidence for all outcomes. We will evaluate the quality of evidence for the outcomes through the domains of risk of bias, indirectness, inconsistency, imprecision and small-study effects. The evaluation result will be presented in a summary table using four grades of certainty ratings: high, moderate, low and very low quality.

### Calculation of effect sizes

A summary table will be prepared to describe the study characteristics of the included articles. Proportions of women who stored their egg for non-medical reason and used it, egg survival rate, pregnancy rate and live birth rate will be pooled together using metaprop programme[30] STATA (V.14, StataCorp, 2015). To calculate clinical pregnancy rate and live birth rate, women who got pregnant and with live birth will be used as a nominators; women who underwent social egg freezing and who underwent egg freezing for medical reason will be used as denominators. Mean age at the time of freezing oocytes, and at a time of fertilisation, and mean number oocyte stored will be computed. We will determine the presence heterogeneity among studies using Cochrane's Q test. We will calculate the percentage of total variation across studies, which is attributed to heterogeneity, using the $I^2$ statistics ((Q–df)/Q where Q is Cochran's heterogeneity statistic) (small, $I^2$ <25%; moderate, 25%–49%; large, 50%–74%; very large >75%).[31]

The selection of the effect model (fixed-effect or random-effect model) will be based on the $I^2$ statistics value (if the $I^2$ <50%, the fixed-effect model will be used; if the $I^2$ ≥50%, random-effect model will be used). Forest plots will be drawn to visualise effect size (proportions with 95% CI). For clinical pregnancy rate and live birth rate, subgroup analysis will also be conducted based on age of the women at oocyte verification, and at fertilisation (≤35 years and >35 years), and the average numbers oocyte stored. Where the studies are not suitable for quantitative analyses, we will present the data using narrative synthesis.

## Amendments to protocol

Not amended to date. If the protocol is amended, we will carefully report the change and a rationale for the change.

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**Contributors** AW conceived the study, participated in designing and drafting the protocol. FAK designed and drafted the protocol. IK, ZL, ES and CMF critically revised the design of the protocol. All authors read this manuscript and finally approved for submission.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study is systematic review and meta-analyses does not need ethical approval; we will use publically available data from previously published articles. The results of the review will be prepared for publication according to the PRISMA-P checklist. The final report of the review will be presented and submitted to the funding organisation (the University of Technology Sydney). It will also be disseminated through publication on national or international journal and presented on scientific conferences.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information.



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