

Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis

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Objective: To estimate age-specific probabilities of live birth with oocyte cryopreservation in nondonor (ND) egg cycles.

Design: Individual patient data meta-analysis.

Setting: Assisted reproduction centers.

Patient(s): Infertile patients undergoing ND mature oocyte cryopreservation.

Intervention(s): PubMed was searched for clinical studies on oocyte cryopreservation from January 1996 through July 2011. Randomized and nonrandomized studies that used ND frozen-thawed mature oocytes with pregnancy outcomes were included. Authors of eligible studies were contacted to obtain individual patient data.

Main Outcome Measure(s): Live birth probabilities based on age, cryopreservation method, and the number of oocytes thawed, injected, or embryos transferred.

Result(s): Original data from 10 studies including 2,265 cycles from 1,805 patients were obtained. Live birth success rates declined with age regardless of the freezing technique. Despite this age-induced compromise, live births continued to occur as late as ages 42 and 44 years with slowly frozen and vitrified oocytes, respectively. Estimated probabilities of live birth for vitrified oocytes were higher than those for slowly frozen.

Conclusion(s): The live birth probabilities we calculated would enable more accurate counseling and informed decisions for infertile women considering oocyte cryopreservation. Given the success probabilities, we suggest that policy makers should consider oocyte freezing as an integral part of prevention and treatment of infertility. (Fertil Steril® 2013;100:492–9. ©2013 by American Society for Reproductive Medicine.)

Key Words: Oocyte cryopreservation, slow freezing, vitrification, meta-analysis, individual patient data

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After embryo cryopreservation, oocyte cryopreservation is the second most commonly used method of fertility preservation for medical indications (1, 2). In addition, oocyte cryopreservation can be considered when there are ethical, legal, and/or religious obstacles to embryo cryopreservation (3), and more controversially, for defying reproductive aging (4, 5). The

technique can also be used to establish donor oocyte banks (6–8), as well as to minimize the risk of ovarian hyperstimulation syndrome.

More than 50% of the assisted reproductive technology clinics in the United States currently offer oocyte cryopreservation (5), and “elective use” to defer childbearing is cited as the most common indication (64%), fol-

lowed by IVF (18%) and medical reasons (18%) (5). After much debate, the American Society of Reproductive Medicine has recently removed oocyte freezing from the experimental category for patients who are unable to cryopreserve embryos and face infertility due to chemotherapy or other gonadotoxic therapies, but not for the sole purpose of circumventing reproductive aging in healthy women (9). However, oocyte cryopreservation is still considered experimental by the health insurance industry and is thus a noncovered service for women’s health (10).

One of the most critical unanswered questions about oocyte cryopreservation is the success rates among different

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age groups, especially later reproductive years. Lack of age-specific success rate information is one of the likely reasons for the overall reluctance to accept this technique as a standard treatment. Despite the fact that no study reported on age-specific success rates, the majority of the clinics consider age >38 years to be acceptable for elective oocyte cryopreservation (5). Age-specific live birth success information is essential in evidence-based medicine to be able to properly counsel women before oocyte cryopreservation so that they can weigh alternatives (such as embryo freezing) for fertility preservation and to determine the feasibility and utility of performing oocyte cryopreservation at a given age.

The main methods of oocyte cryopreservation are slow freezing (SF) and vitrification (VF), with the latter gaining more popularity in recent years. In an earlier traditional meta-analysis based on summary statistics published, we investigated the overall success of oocyte cryopreservation by SF and VF and compared it with that of IVF with fresh oocytes (11). In the present study we collected individual cycle data from 2,265 oocyte cryopreservation freeze-thaw cycles in 1,805 patients and performed a novel individual patient data (IPD) meta-analysis. Our goal was to determine the probability of live birth as a function of age, cryopreservation method (SF vs. VF), and number of oocytes thawed, injected, or embryos transferred in nondonor oocyte (NDO) cycles of infertile patients.

MATERIALS AND METHODS

This study was planned as a meta-analysis of IPD from randomized and nonrandomized studies on oocyte cryopreservation. Oocyte donors are younger and do not adequately represent the infertile population (7, 12); hence, we did not include donor oocyte cycles in the present study. We did not restrict our meta-analysis to randomized controlled trials (RCTs), because there had been only one RCT with NDO when the study was planned (13). The Institutional Review Board at New York Medical College exempted this study because deidentified existing databases were used for the purpose of the meta-analysis.

Eligibility Criteria

We requested IPD from all identified studies published in peer-reviewed journals that [1] used frozen-thawed mature oocytes without prescreening for aneuploidy, followed by intracytoplasmic sperm injection for IVF, and [2] provided pregnancy outcomes information. Case reports were not included in this analysis. We detail the inclusion and exclusion criteria in Figure 1 and summarize the key characteristics of the studies in Table 1.

Outcome Measures

The primary aim of this study was to develop three live birth probability models based on age, cryopreservation method, and [1] the number of oocytes thawed, [2] the number of oocytes injected, or [3] the number of embryos transferred, where [1–3] were separately modeled owing to high correlations.

The secondary outcomes were success rates for survival, fertilization, and implantation.

Search Strategy

We used *oocyte cryopreservation*, *slow freezing*, and *vitrification* as the key words for the title and abstract search in PubMed. The search strategy is summarized as a flow chart in Figure 1. Studies were identified for the period from January 1986 (when the first pregnancy from oocyte cryopreservation was reported) until July 2011, as well as by directly contacting experts in the field. We also obtained unpublished follow-up data on pregnancy outcomes via personal communications (Drs. J. Boldt and E. Lucena).

Data collection process and time frame of the study. After identifying the studies eligible to be included, we contacted the majority of the authors by e-mail and a few others by telephone. To consider the author as nonresponsive, we made at least three additional attempts to contact the author. Thus the study ran from October 2009 until July 2011, when the last contact was made.

Data items. Data extraction sheets that included a summary of information from their studies were sent to all the authors. With this information given, the authors were asked to verify whether we had retrieved the right information from their studies and to show whether any of their study data covered a previous study (overlapping data). After obtaining and checking the raw data sent, if there was a mismatch or if there were missing or abstruse data, the author was contacted again. Any disagreement was resolved unanimously by discussion. If the author did not reply to resolve the disagreement, the data under discussion were excluded.

Statistical Analysis

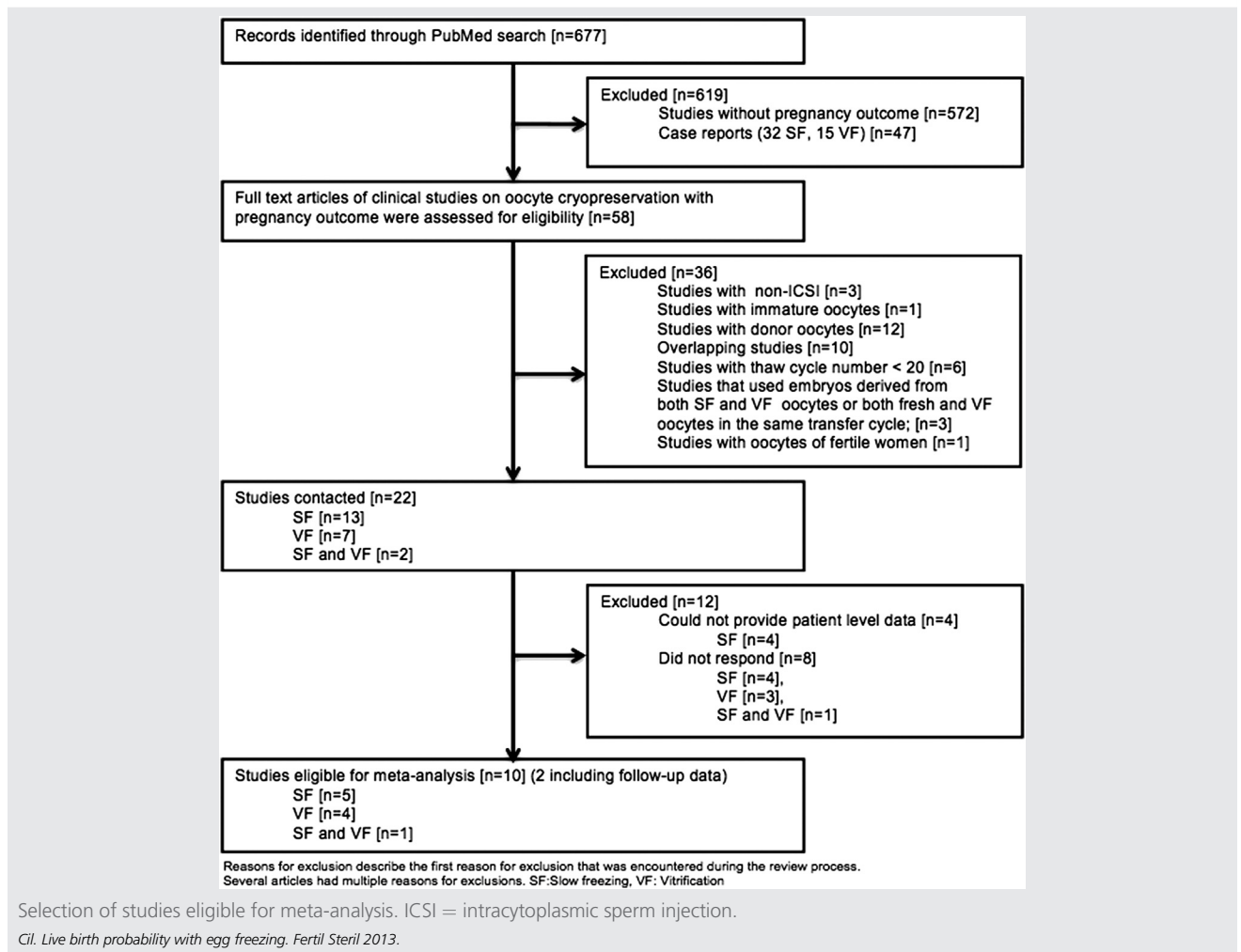
Summary statistics were used to describe individual studies and thaw cycle characteristics, such as mean, standard deviation (SD) and range for continuous variables, and percentage for categorical variables.

The associations between the covariates and the outcomes are modeled and fitted via generalized estimating equations (GEE), accounting for two-level clustering (i.e., within study, and within patient within study) (14, 15). In the GEEs, compound symmetry was assumed for within-cluster correlation. For binary outcome the logit link was used, and for continuous outcome (e.g., survival rate) the normal link was used. Information criterion for GEEs, QIC, was computed as the model fit statistic (16), where a lower value indicates improved fit. To assess the ability to discriminate successes vs. failures using covariates, the area under the receiver operating characteristic curve (AUC) was computed from standard logistic regression model; AUC = 1 means perfect discrimination between events vs. nonevents, and 0.5 means noninformative, random discrimination.

Different age cutoff points were examined in terms of discriminatory ability, with subdividing of the dataset into two by each age (i.e., 25 to 42 by 1-year increment). In this task, AUCs from simple (age as the sole covariate) and multiple (further adjusting other covariates) regression were used.

As an ancillary analysis we repeated regression analyses, restricting the study sample to data from the first thaw attempt. Because we achieved results qualitatively similar to

FIGURE 1



what we obtained from the analysis based on all available data, we elected not to report the results from these ancillary analyses.

Two-sided tests were used for inference. Probability (P) values and confidence intervals were not adjusted for multiple comparisons. Analyses were performed by SAS 9.3 (SAS Institute), and graphs were made in Microsoft Excel.

Of note, our study is not an ordinary meta-analysis that aims to estimate treatment effects or associational measures, and we did not conduct sensitivity analyses and bias assessments concerning unmeasured confounders and/or unavailable data. If they had been included in our analysis the results could be potentially affected, and selection bias (e.g., publication or nonresponse bias) is not avoidable. Yet, using raw data, we could control key covariates in individual levels.

RESULTS

Study Exclusions and Inclusions

The search in PubMed yielded 677 potential records. After the exclusions shown in Figure 1, 22 reports remained (17–38). Of

those, we were able to obtain the IPD from 10 studies (17–26), 2 of which included unpublished updated data (18, 23) (Table 1). Of the 10, 4 were prospective (17, 22, 24, 26), 1 of which (26) also included the data from a randomized controlled trial on NDO cycles (27). The remaining 6 studies were retrospective (18–21, 23, 25). In one study, in which both NDO and donor oocyte cycles were reported (23), we only used data from NDO cycles. In one study in which both SF and VF cycles were reported, we could not verify SF data and hence only VF cycles were included (25).

This amounted to 2,265 thawing/warming cycles from 1,805 patients in the final dataset. All studies used surplus oocytes after IVF cycle, which were cryopreserved either because embryo freezing was legally forbidden or the patients did not wish to freeze embryos. All embryo transfers were done on day 2 or 3. Mean (\pm SD) ages of the patients at freezing were 33.8 ± 4.0 (range, 20–48) and 34.1 ± 4.7 (20–51) years for SF and VF, respectively. Of the thawing/warming cycles, 1,962 and 303 were after SF and VF. These cycles involved 11,122 SF and 1,957 VF oocytes originally retrieved and frozen between 1997 and 2009.

TABLE 1

Characteristics and success rates of the studies from which IPD were available and used for meta-analysis.

Age (y)	Country	First author/year (reference)	Study type	Method	n	No. thawed oocytes	No. thaw cycles	SR (%)	FR (%)	IR (%)	CPT/T (%)	LB/T (%)
31.7 ± 4.7	Taiwan	Chen/2005 (17)	Prospective	SF	21	159	21	76.1	66.1	10.7	33.3	33.3
31.7 ± 4.1	United States	Boldt/2006 (18)	Retrospective	SF	82	556	87	55.4	65.4	12.6	26.5	19.1
32.0 ± 3.6	United States	Boldt/2006 ^a	VF	VF	25	168	28	78.0	76.7	11.5	29.2	20.8
32.3 ± 3.6	Hungary	Konc/2008 (19)	Retrospective	SF	54	215	64	80.0	84.3	11.0	20.3	15.6
35.7 ± 5.7	Italy	Albani/2008 (20)	Retrospective	SF	949	7,584	1,280	58.1	70.2	6.9	12.8	8.4
34.1 ± 3.9	Italy	Parmegiani/2009 (21)	Retrospective	SF	424	2,608	510	70.7	82.6	8.2	16.3	8.8
34.5 ± 3.8	Korea	Yoon/2003 (22)	Prospective	VF	34	474	34	68.6	71.7	5.6	22.2	22.2
33.6 ± 4.3	Colombia	Lucena/2006 (23) ^b	Retrospective	VF	37	179	37	81.0	85.8	3.5	10.8	10.8
32.5 ± 5.8	Korea	Yoon/2007 (24)	Prospective	VF	28	364	30	83.0	77.1	14.2	43.3	36.7
35.7 ± 4.9	Italy	Fadini/2009 (25)	Retrospective	VF	46	285	59	78.9	72.8	9.3	19.2	11.5
31.9 ± 4.5	Italy	Ubaldf/2010 (26)	Prospective	VF	105	487	115	89.7	85.4	16.2	31.5	26.1
	Total				1805	13,079	2,265					

Note: For age, mean ± SD. The success rates of IPD available studies were recomputed from the data obtained. SR = survival rate; FR = fertilization rate; IR = implantation rate (sacs/embryos transferred); CPT = clinical pregnancy/transfer; LB/T = live birth/transfer.

^a Follow-up data of reference 18, written in a different row because different cryopreservation method is used.

^b Includes follow-up data.

^c Includes RCT data from a previous study by the same group (27).

Cil. Live birth probability with egg freezing. Fertil Steril 2013.

Overall Number of Pregnancies Resulting from SF and VF Oocytes

In the final dataset there were 328 clinical pregnancies resulting in 281 singletons, 43 twins, and 4 triplets or higher-order pregnancies. Of the 328 clinical pregnancies, 253 were from SF and 75 from VF. Of SF and VF cycles, 14.2% and 14.7% of the clinical pregnancies were multiple pregnancies, respectively. These pregnancies resulted in a total of 224 live births: 163 after SF and 61 after VF. Included in the live births were few ongoing pregnancies (four SF and one VF).

Description of Studies for Which IPD Were Unavailable

Overall we were able to retrieve 40% and 55.5% of SF and VF cycles from NDO studies published, respectively. The 12 studies for which we were not able to obtain IPD included 8 retrospective SF studies (28–35), 3 prospective VF studies (36–38), and 1 RCT comparing SF vs. VF (39). The one RCT included 30 thawing and 48 warming cycles. The mean age range among these studies was 32.3–35.5 years.

The reported success rates of the studies from which IPD were available vs. unavailable are given in Supplemental Figure 1 (available online).

Thaw Cycle Characteristics

In 13.5%, 21.1%, 19.2%, 19.4%, and 18% of the cycles, three, four, five, six, and more than six oocytes were thawed, respectively. There were no cycles with single-oocyte thaw and only 17 cycles (0.8%) with two-oocyte thaw. In 5.5%, 14.2%, 64.3%, 4.6%, 3.0%, 2.0%, and 3.2% of the cycles, one, two, three, four, five, six, and more than six oocytes were injected, respectively. In a majority of the cycles, either two (33.3%) or three embryos (32.6%) were transferred. Single (17.8%) and supernumerary embryo (4.2%) transfers were less common.

Mean numbers of thawed, survived, injected, fertilized oocytes, and embryos transferred were significantly different between the SF and VF cycles (Supplemental Table 1). In none of the studies were embryos generated from thawed oocytes frozen for future use.

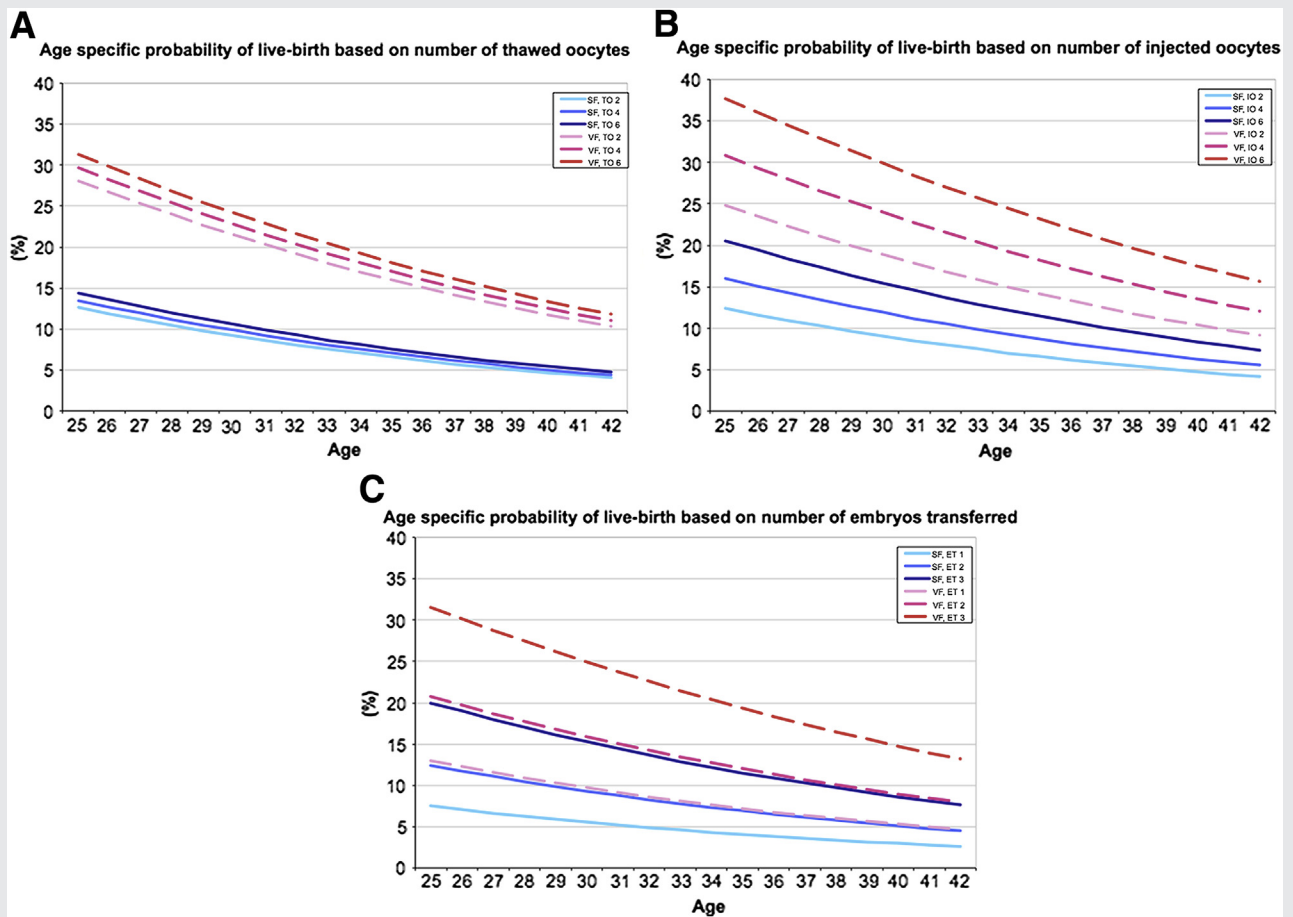
After adjusting for age and method, a higher percentage of cycles were cancelled with SF, compared with VF (12.9% vs. 7.3%; $P=.006$). Thaw cycle cancellation rates increased with age for both SF and VF ($P=.009$), indicating age-induced decline in oocyte reserve and quality.

Age-Specific Success Rates after SF and VF

Survival and fertilization rates. Overall survival and fertilization rates were lower after SF (65% and 74%) compared with VF (85% and 79%) ($P<.001$). However, age was not significantly associated with oocyte survival ($P=.24$) and fertilization success rates ($P=.56$) for both SF and VF.

Implantation rates. Implantation rates were higher after VF ($P=.002$) and showed a decline with age for both SF and VF ($P<.0001$). For women aged <30 years, the likelihood of an embryo deriving from SF oocytes to implant was >8.9%. This probability declined to 4.3% after age 40 years, but live

FIGURE 2



Age-specific probabilities of live birth based on oocyte cryopreservation method and the number of oocytes thawed (A), number of oocytes injected (B), or number of embryos transferred (C). TO = thawed oocytes; IO = injected oocytes; ET = embryos transferred.

Cil. Live birth probability with egg freezing. *Fertil Steril* 2013.

births—despite lower frequencies—continued to occur with SF until 42 years of age. Success of implantation also declined from 13.2% for age 30 years to 8.6% for age 40 years with VF, but live births continued to occur until age 44 years.

Miscarriage rates. Miscarriage rates were higher after SF ($P=.005$) and showed slight age-related trends, 36%–41% and 19%–22%, between ages 30 and 40 years for SF and VF, respectively.

Age-specific probabilities of live birth based on number of thawed, injected oocytes or embryos transferred. From models fitted by GEEs (Supplemental Table 2), the probability of live birth (y axis) as a function of age (x axis) was derived with the method and the number of oocytes fixed at some values. Specifically, we presented plots to give probabilities of live birth for two, four, or six thawed and two, four, or six injected oocytes, and one, two, or three embryos transferred (Fig. 2A–C). Of note, there were no cycles with single-oocyte thaw and only 17 cycles (0.8%) with two-oocyte thaw. We limited age at freezing up to 42 years in the plots because the reliability of predictions could be limited, given that there were only 29 cycles from patients who were older than 42 years when their oocytes were frozen (of those, two were 48 and one

was 51 years old). Median (interquartile range) of the number of thawed, injected oocytes and embryos transferred was 5 (4–7), 3 (3–3), and 2 (1–3), respectively. For example, the probability of live birth for a 30-year-old woman who has two to six oocytes to thaw is 9.1%–10.5% and 21.4%–24.1% after SF and VF, respectively. If the same individual has two to six oocytes to be injected and one to three embryos to be transferred, her chances of having a live birth would likely be 9.1%–15.4% and 18.9%–29.9% for injected oocytes and 5.5%–15.3% and 9.7%–24.9% for embryos transferred after SF and VF, respectively.

In addition, selected probabilities of live births (e.g., for ages 25–42 years based on two to six oocytes thawed and injected, one to three embryos transferred) are tabulated in Table 2, which may be used for patient counseling or self-assessment (a livebirth probability estimator can be found online at www.i-fertility.net or www.fertilitypreservation.org).

Determining the Potential Age Threshold for Live-Birth Outcome

We found that age 36 (≥ 36 vs. <36) years showed the highest discrimination capability for success vs. failure (AUC 0.72) after adjusting for the method and number of embryos

TABLE 2

Representative probabilities (%) of live birth for ages 25–42 years, according to number of oocytes thawed, injected, or embryos transferred.

Age (y)	SF									VF								
	Oocytes thawed			Oocytes injected			Embryos transferred			Oocytes thawed			Oocytes injected			Embryos transferred		
	2	4	6	2	4	6	1	2	3	2	4	6	2	4	6	1	2	3
25	12.6	13.5	14.4	12.4	16.0	20.5	7.5	12.4	20.0	28.1	29.7	31.3	24.8	30.9	37.7	13.0	20.7	31.5
26	11.8	12.7	13.5	11.6	15.1	19.4	7.0	11.8	19.0	26.7	28.2	29.8	23.5	29.4	36.0	12.2	19.7	30.1
27	11.1	11.9	12.7	10.9	14.3	18.4	6.6	11.1	18.0	25.3	26.8	28.3	22.3	28.0	34.5	11.6	18.7	28.8
28	10.4	11.2	11.9	10.3	13.4	17.3	6.2	10.5	17.1	24.0	25.4	26.8	21.1	26.6	32.9	10.9	17.7	27.4
29	9.8	10.5	11.2	9.6	12.6	16.4	5.9	9.9	16.2	22.7	24.0	25.4	20.0	25.2	31.4	10.3	16.8	26.2
30	9.1	9.8	10.5	9.1	11.9	15.4	5.5	9.3	15.3	21.4	22.7	24.1	18.9	24.0	29.9	9.7	15.9	24.9
31	8.6	9.2	9.8	8.5	11.2	14.6	5.2	8.8	14.5	20.2	21.5	22.8	17.8	22.7	28.5	9.2	15.0	23.7
32	8.0	8.6	9.2	8.0	10.5	13.7	4.9	8.3	13.7	19.1	20.3	21.6	16.8	21.5	27.1	8.6	14.2	22.6
33	7.5	8.1	8.6	7.5	9.9	12.9	4.6	7.8	12.9	18.0	19.2	20.4	15.9	20.4	25.7	8.1	13.5	21.5
34	7.0	7.5	8.1	7.0	9.3	12.1	4.3	7.3	12.2	17.0	18.1	19.2	15.0	19.3	24.4	7.7	12.7	20.4
35	6.6	7.0	7.6	6.6	8.7	11.4	4.0	6.9	11.5	16.0	17.0	18.1	14.1	18.2	23.1	7.2	12.0	19.3
36	6.1	6.6	7.1	6.2	8.2	10.7	3.8	6.5	10.9	15.0	16.0	17.1	13.3	17.2	21.9	6.8	11.3	18.3
37	5.7	6.2	6.6	5.8	7.7	10.1	3.6	6.1	10.3	14.1	15.1	16.1	12.5	16.2	20.8	6.4	10.7	17.4
38	5.4	5.8	6.2	5.4	7.2	9.5	3.4	5.7	9.7	13.3	14.2	15.1	11.8	15.3	19.6	6.0	10.1	16.5
39	5.0	5.4	5.8	5.1	6.7	8.9	3.1	5.4	9.1	12.5	13.3	14.2	11.1	14.4	18.6	5.6	9.5	15.6
40	4.7	5.0	5.4	4.7	6.3	8.3	3.0	5.1	8.6	11.7	12.5	13.4	10.4	13.6	17.5	5.3	9.0	14.8
41	4.4	4.7	5.0	4.4	5.9	7.8	2.8	4.8	8.1	11.0	11.8	12.6	9.8	12.8	16.6	5.0	8.5	14.0
42	4.1	4.4	4.7	4.1	5.5	7.3	2.6	4.5	7.6	10.3	11.0	11.8	9.2	12.0	15.6	4.7	8.0	13.2

Cil. Live birth probability with egg freezing. *Fertil Steril* 2013.

transferred, whereas age 35 years showed the highest AUC without adjustment.

DISCUSSION

This unique IPD meta-analysis is the first to report age-specific probabilities of live birth for oocyte cryopreservation after SF and VF. In this study all measurements of successful outcome declined with patient age, regardless of the freezing method used, which is highly expected. When the number of thawed, injected oocytes and embryos transferred were controlled, probability of live birth after VF was higher than for SF across all age groups.

Meta-analyses based on IPD are still scarce in medicine, though they are likely to replace conventional meta-analysis whenever feasible in the near future (40). Individual patient data meta-analysis offers numerous advantages over conventional meta-analysis (15) or modeling based on hypothetical data or simulation. Most importantly, access to IPD enabled us to account for patient characteristics. There are also a few disadvantages of IPD meta-analysis. The newest data may not be included because obtaining, processing, and analyzing raw data takes time; for example, our study included studies until 2010. Additionally, some authors may not share their raw data. Yet our meta-analysis and models can be naturally updated as more raw data are available.

Although the most popular applications of oocyte freezing are for cancer patients or for patients undergoing oocyte cryopreservation electively, the majority of available data in the literature reflecting clinical success is from infertile patients. Hence, our results may not be generalizable to excluded populations (e.g., cancer patients) or to patients pursuing elective oocyte freezing. New studies and models are warranted for these populations in the future.

Because of the small number of RCTs available, the comparison of SF vs. VF may be biased, and our analysis should be understood as “as observed” rather than “intent to treat.” Because our primary goal is to estimate the probability of live birth as a function of patient age rather than treatment assigned, age-based probability derived from predominantly observational studies can be still valuable. We hope to update our models when a sufficient number of RCTs are available or a good combination of RCTs and observational studies can be assembled.

An important question for current and future patients and clinicians is: What is the upper age limit to offer oocyte cryopreservation? First, if one considers the possibility of live birth, this age seems to be 42 years for SF and 44 years for VF, according to the data presented here. However, if one considers a “reasonable” chance of conception, such a cutoff is less clear. Our analysis revealed age 36 years as the cut point to provide the best discrimination between successes vs. failures, hence optimal results may be expected in patients who are younger than this age threshold. Nevertheless, because one cannot place an absolute value on childbearing, the upper age limit for considering oocyte cryopreservation may vary according to individual preferences, values, and available resources.

Although we found that oocyte cryopreservation was performed in women aged 20–51 years in clinics across the world, we limited the probability plots for the age range 25–42 years because there were few cycles outside this range (1.3% of all cycles above or below the range). Although it is unlikely that the live birth probabilities would be higher for those younger than 25 years, our data do not clarify the efficiency of oocyte cryopreservation after age 42 years. Further studies are needed to understand the feasibility of offering oocyte freezing to women aged >42 years.

Of note, the raw data used in our analysis are from infertile patients. It is probable that the success rates are more favorable with fertile individuals undergoing elective cryopreservation before cancer treatments or elective reasons. Furthermore, even though we showed that VF results in significantly higher success rates compared with SF, the latter protocol is still undergoing evolution, and its efficiency may catch up with VF. Recently, Bianchi et al. (41) reported higher success rates using a modified SF protocol, showing that future studies are likely to have enhanced success with SF. This feature will be accounted for in newer or updated models as more data become available. Nevertheless, the pregnancy rates presented in our IPD meta-analysis may be sufficiently high for policy makers to argue for the acceptance of oocyte cryopreservation into the routine practice of infertility treatment and fertility preservation.

In conclusion, this IPD meta-analysis shows that VF success rates are superior to SF (on the basis of mostly observational evidence) and that the success rates with either technique may begin to decline meaningfully after the age of 36 years. Age-induced decline of live birth probability after oocyte cryopreservation is highly anticipated but has not been estimated empirically using raw data to date. Although an upper age limit could not be specified with the available data, it may be safe to say that we would cautiously approach egg freezing in the age range of 42 to 45 years. Although it is generally preferred that each center generates its own model with important predictors, most clinics currently do not have the critical mass to provide that information to their patients. For the majority of centers in the United States and around the world and infertile patients who consider or choose oocyte freezing, age-based success rates estimated using the best available empirical data and statistical modeling would provide an important tool for informed decision making and counseling that is currently unavailable (an online oocyte cryopreservation success rate estimator, based on the data from this IPD-meta-analysis, is available at www.i-fertility.net or www.fertilitypreservation.org). A future direction would be for more specific or individualized models to be developed for specific populations, such as for cancer patients or women pursuing oocyte cryopreservation electively. Finally, we surmise that it is time for managed care companies to consider oocyte cryopreservation as an integral part of the treatment and prevention of infertility.

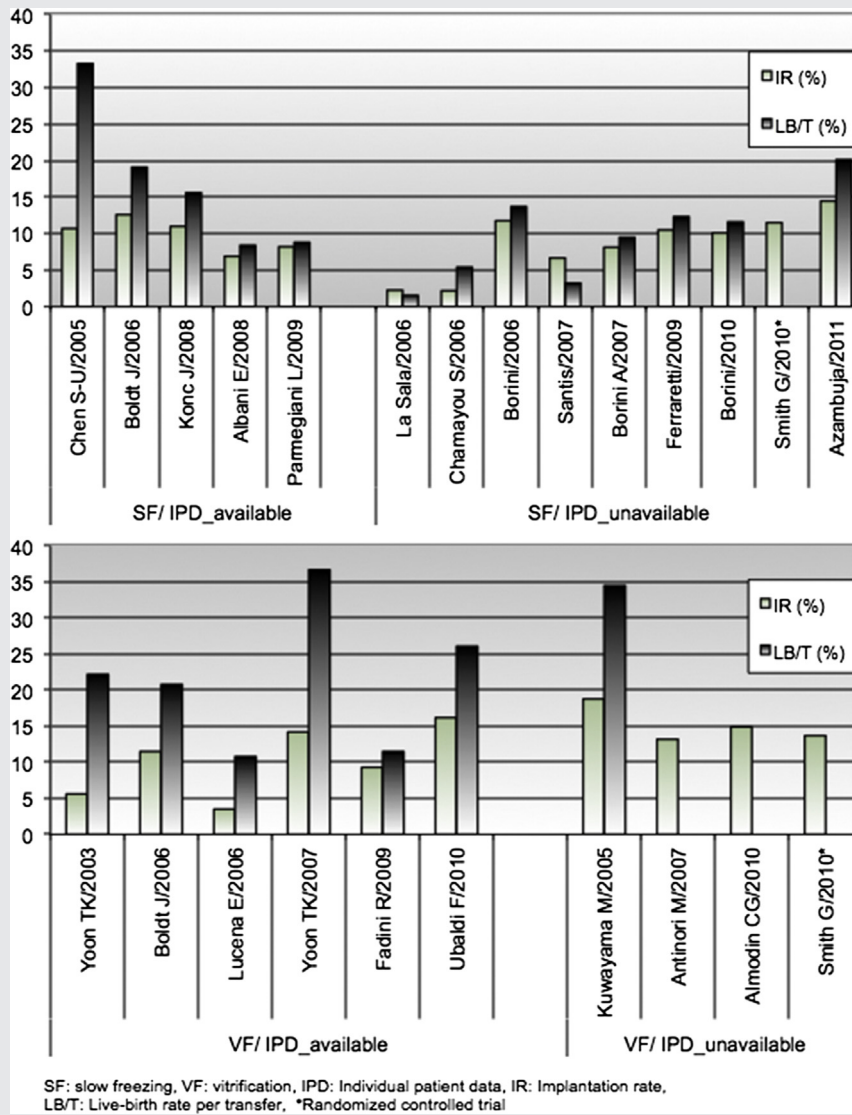
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SUPPLEMENTAL FIGURE 1



Clustered column charts of implantation and live-birth rates per transfer from studies in which IPD was available vs. unavailable.
Cil. Live birth probability with egg freezing. Fertil Steril 2013.

SUPPLEMENTAL TABLE 1

Comparison of thaw cycle characteristics between SF and VF.

Characteristic	SF (n = 1,962)	VF (n = 303)	P value
Age (y)			.53
Mean ± SD	33.8 ± 4.0	34.1 ± 4.7	
Range	20–48	20–51	
Thawed oocytes			.003
Mean ± SD	5.7 ± 2.3	6.5 ± 4.5	
Range	2–18	2–32	
Survived			<.001
Mean ± SD	3.6 ± 1.6	5.2 ± 3.4	
Range	1–14	1–23	
Injected			<.001
Mean ± SD	3.0 ± 1.1	4.0 ± 2.3	
Range	1–11	1–18	
Fertilized			<.001
Mean ± SD	2.3 ± 1.0	3.2 ± 1.9	
Range	1–9	1–14	
Embryos transferred			<.001
Mean ± SD	2.2 ± 0.8	2.8 ± 1.3	
Range	1–6	1–8	
Cancellation rate (%)	12.9	7.3	.006

Note: Sample sizes are reduced for some rows owing to missing data. For some patients, multiple observations were included. Cancelled cycles were not included in calculations. P values are computed from GEE accounting for two-level clustering (i.e., within study and within patient).

Cil. Live birth probability with egg freezing. *Fertil Steril* 2013.

SUPPLEMENTAL TABLE 2

Regression models for the outcome of live birth.

Predictors	Log (OR)	OR	95% CI	P value	AUC/QIC
Basic model					0.645/1,413.5
Age at freezing	-0.076	0.93	0.90-0.96	< .0001	
Method (SF vs. VF)	-1.04	0.35	0.25-0.49	< .0001	
Constant	1.18				
Model based on no. of thawed oocytes					0.651/1,412.4
Age at freezing	-0.072	0.93	0.90-0.96	< .0001	
Method (SF vs. VF)	-0.996	0.37	0.26-0.52	< .0001	
No. of thawed oocytes	0.038	1.04	1.0-1.08	.07	
Constant	0.785				
Model based on no. of injected oocytes					0.664/1,410.6
Age at freezing	-0.070	0.93	0.90-0.96	< .0001	
Method (SF vs. VF)	-0.848	0.43	0.30-0.61	< .0001	
No. of injected oocytes	0.152	1.16	1.08-1.26	.0001	
Constant	0.327				
Model based on no. of embryos transferred					0.726/1,339.4
Age at freezing	-0.065	0.94	0.91-0.97	.0001	
Method (SF vs. VF)	-0.610	0.54	0.37-0.79	.0013	
No. of embryos transferred	0.564	1.76	1.54-2.01	< .0001	
Constant	-0.84				

Note: GEE was used to account for two-level clustering (i.e., within study and within patient). Log (OR) and OR is per 1 unit increase in predictor (say, 1 year for age). AUC was computed from standard logistic regression model ignoring clusters. QIC is the model fit statistic for GEE. Lower value indicates better model fit. CI = confidence interval; OR = odds ratio.

Cil. Live birth probability with egg freezing. *Fertil Steril* 2013.