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Predicting the likelihood of live birth for elective oocyte cryopreservation: a counseling tool for physicians and patients

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STUDY QUESTION: Can a counseling tool be developed for women desiring elective oocyte cryopreservation to predict the likelihood of live birth based on age and number of oocytes frozen?

SUMMARY ANSWER: Using data from ICSI cycles of a population of women with uncompromised ovarian reserve, an evidence-based counseling tool was created to guide women and their physicians regarding the number of oocytes needed to freeze for future family-building goals.

WHAT IS KNOWN ALREADY: Elective oocyte cryopreservation is increasing in popularity as more women delay family building. By undertaking elective oocyte freezing at a younger age, women hope to optimize their likelihood of successful live birth(s) using their thawed oocytes at a future date. Questions often arise in clinical practice regarding the number of cryopreserved oocytes sufficient to achieve live birth(s) and whether or not additional stimulation cycles are likely to result in a meaningful increase in the likelihood of live birth. As relatively few women who have electively cryopreserved oocytes have returned to use them, available data for counseling patients wishing to undergo fertility preservation are limited.

STUDY DESIGN, SIZE, DURATION: A model was developed to determine the proportion of mature oocytes that fertilize and then form blastocysts as a function of age, using women with presumably normal ovarian reserve based on standard testing who underwent ICSI cycles in our program from January, 2011 through March, 2015 ($n = 520$). These included couples diagnosed exclusively with male-factor and/or tubal-factor infertility, as well as cycles utilizing egg donation. Age-specific probabilities of euploidy were estimated from 14 500 PGS embryo results from an external testing laboratory. Assuming survival of thawed oocytes at 95% for women <36 y and for egg donors, and 85% for women ≥36 y, and 60% live birth rate per transferred euploid blastocyst, probabilities of having at least one, two or three live birth (s) were calculated.

PARTICIPANTS/MATERIALS, SETTING, METHOD: First fresh male-factor and/or tubal-factor only autologous ICSI cycles ($n = 466$) were analyzed using Poisson regression to calculate the probability that a mature oocyte will become a blastocyst based on age. Egg donation cycles ($n = 54$) were analyzed and incorporated into the model separately. The proportion of blastocysts expected to be euploid was determined using PGS results of embryos analyzed via array comparative genomic hybridization. A counseling tool was developed to predict the likelihood of live birth, based on individual patient age and number of mature oocytes.

MAIN RESULTS AND THE ROLE OF CHANCE: This study provides an evidence-based model to predict the probability of a woman having at least one, two or three live birth(s) based on her age at egg retrieval and the number of mature oocytes frozen. The model is derived from a surrogate population of ICSI patients with uncompromised ovarian reserve. A user-friendly counseling tool was designed using the model to help guide physicians and patients.

LIMITATIONS, REASONS FOR CAUTION: The data used to develop the prediction model are, of necessity, retrospective and not based on patients who have returned to use their cryopreserved oocytes. The assumptions used to create the model, albeit reasonable and data-driven, vary by study and will likely vary by center. Centers are therefore encouraged to consider their own blastocyst formation and thaw survival rates when counseling patients.

WIDER IMPLICATIONS OF THE FINDINGS: Our model will provide a counseling resource that may help inform women desiring elective fertility preservation regarding their likelihood of live birth(s), how many cycles to undergo, and when additional cycles would bring diminishing returns.

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Key words: elective egg freezing / oocyte cryopreservation / fertility preservation / blastocyst formation / egg thaw / blastocyst euploidy / prediction model / family building

Introduction

As more women choose to delay childbearing, elective oocyte preservation is increasing in popularity (Rudick *et al.*, 2010; Stoop *et al.*, 2011; Cil *et al.*, 2013; Mesen *et al.*, 2015). By electively freezing oocytes, women hope to optimize their likelihood of successful live birth(s) using their thawed oocytes at a future date. One question that often arises in clinical practice is: How many cryopreserved oocytes are sufficient to achieve a live birth?

To date, relatively few healthy women who have electively cryopreserved oocytes to delay childbearing have returned to use their oocytes (Cobo *et al.*, 2013; Garcia-Velasco *et al.*, 2013; Hodes-Wertz *et al.*, 2013; Schattman, 2015). It is therefore difficult to find an appropriate sample population from which to counsel presumably fertile women about the optimal number of oocytes to electively cryopreserve. Some practices that offer elective oocyte preservation suggest that patients freeze at least 10–20 oocytes based on age, though there is little concrete data to support recommendations on the ideal number of oocytes to store (Stoop, 2010; Doyle *et al.*, 2016). Assuming it takes an average couple 6 months to conceive (Hilgers *et al.*, 1992; Gnoth *et al.*, 2003), freezing at least six oocytes should theoretically yield a high quality embryo capable of supporting a viable pregnancy. Extrapolating this assumption further, 20 frozen oocytes should enable up to three thaw cycles of six to seven oocytes each, with each having the capability of resulting in a birth. However, even among similarly aged young women, the number and quality of oocytes obtained per cycle is heterogeneous (Munné *et al.*, 2006, 2012). Furthermore, since the increase in chromosomal abnormalities with maternal age is strongly correlated with a decrease in embryo viability (Ata *et al.*, 2012; Harton *et al.*, 2013; Franasiak *et al.*, 2014a), it is reasonable to assume that older women will require more frozen oocytes to achieve a live birth compared to younger women. It is therefore challenging to predict how many oocytes each woman should freeze to optimize her probability of a having a future live birth.

Finally, although data examining the success rates from frozen versus fresh oocyte IVF cycles have been mixed, most recent studies have concluded that outcomes are comparable, particularly with the increased use of vitrification when compared with slow-freezing techniques (Almodin *et al.*, 2010; Cobo *et al.*, 2010; Grifo and Noyes, 2010; Rienzi *et al.*, 2010; Kushnir *et al.*, 2015; Rienzi *et al.*, 2016). Interestingly, a recent retrospective analysis of Society for Assisted Reproductive Technology (SART) data challenges the notion that frozen cycles are as good as fresh, finding that among patients using donor oocytes, live birth was 19% more likely for those who used fresh as compared to frozen oocytes (Kushnir *et al.*, 2015).

The purpose of the present study was to develop a counseling tool for women who wish to undergo elective oocyte cryopreservation, which predicts the likelihood of achieving at least one, two, or three live birth(s) based on patient age and the number of mature oocytes frozen. In order to optimize accuracy of predictions for a presumed fertile woman who is electively preserving her oocytes for prevention of age-related infertility in the future, analyses were limited to couples diagnosed with only male factor and/or tubal factor (without hydosalpinx) infertility and who underwent ICSI; additional analyses were performed for cycles in which egg donation was used. Moreover, given the established age-related increased incidence of oocyte aneuploidy (Franasiak *et al.*, 2014b), expected euploid blastocyst rates by age were also incorporated into the model (Ata *et al.*, 2012 and unpublished data).

The overall goal of this study was to create a tool to guide women and their physicians regarding the estimated number of oocytes needed to freeze for their specified future family-building goals. This model could also be used to inform women whether undergoing additional oocyte cryopreservation cycles would result in a meaningful increase in their likelihood of having a live birth.

Materials and Methods

IVF cycles and laboratory protocols

We conducted a retrospective analysis of 520 first fresh autologous cycles using ICSI performed from 1/2011 to 3/2015 at the Center for Infertility and Reproductive Surgery at Brigham and Women's Hospital. Cycles were included if male-factor (n = 423) and/or tubal factor (n = 43) infertility were the only diagnoses, or if egg donation was used (n = 54). Notably, cycles were excluded if (i) patients with tubal-factor infertility had a hydrosalpinx; (ii) if diminished ovarian reserve was reported in the electronic record based on standard testing; or (iii) if PGD/PGS was used. Approval for this study was obtained from the Partners HealthCare Institutional Review Board.

All gametes and embryos were cultured at 37°C in a humidified incubator under an atmosphere of CO_2 (5–6%), O_2 (5%) and N_2 (89–90%). ICSI

was used for all cycles studied and was performed 3–5 h after oocyte retrieval, followed by a fertilization check 16–18 h later. A single step medium (25 uL microdrops; Global Total, IVFOnLine, Guelph, Ontario, Canada) was used to culture zygotes with two pronuclei. Embryos were evaluated on Day 3 between 66 and 69 h post-insemination, and then moved to a fresh drop of equilibrated Global Total medium for culture to Day 5. Blastocyst morphology was then evaluated on Day 5 between 112 and 115 h and scored according to the stage of development, and the quality of the inner cell mass and trophectoderm.

Statistical methods

The 520 first fresh ICSI cycles were used to predict the blastulation potential of each mature oocyte retrieved. Poisson regression was used to predict the proportion of mature oocytes that ultimately developed into usable blastocysts as a function of patient age using the male-factor and/or tubal-factor only cycles; egg donation cycles were considered separately. For patients who underwent embryo transfer on Day 5, this fraction was calculated as:

$$\frac{(\text{Number of blastocysts frozen} + \text{Number of blastocysts transferred})}{(\text{Number of mature oocytes})}$$

For patients who underwent embryo transfer on Day 3, since it is unknown whether transferred embryos would have blastulated in culture, the fraction was calculated as:

$$\frac{(\text{Number of blastocysts frozen})}{(\text{Number of mature oocytes} - \text{Number of embryos transferred})}$$

This model assumes 95% survival of thawed mature oocytes for patients <36 y and egg donors, and 85% survival for patients ≥36 y, based on previously published data (Practice Committees of American Society for Reproductive Medicine and Society for Assisted Reproductive Technology, 2013; Cobo *et al.*, 2016).

To determine the probability that any one blastocyst would be euploid, aggregate data by individual year of age from Reprogenetics was utilized, which included 14 500 PGS results obtained using array CGH (Ata *et al.*, 2012 and unpublished data). In order to reflect the presumably fertile population of women desiring elective oocyte freezing, these PGS cycles from Reprogenetics were restricted to those in which patients had only male-factor infertility, or if cycles were run 'by request', which excludes patients with reported female infertility. According to their data, the percentage of euploid blastocysts was associated with female partner's age, and was, importantly, independent of embryo cohort size.

The projected fraction of euploid blastocysts, patient age and the number of mature oocytes retrieved were used to predict the probability of having at least one, two or three live birth(s). Our model assumed that the outcome from each future embryo transfer was a statistically independent event, and that approximately 60% of transferred euploid blastocysts would ultimately result in a live birth (Forman *et al.*, 2013, 2014; Schoolcraft and Katz-Jaffe, 2013; Scott *et al.*, 2013; Fiorentino *et al.*, 2014). All statistical analyses were performed using Matlab (version R2015a, MathWorks, Natick MA). Demographic data are presented as mean ± standard deviation.

Results

Patient demographic and cycle information are shown in Table I. The diagnosis in the majority of cycles was male-factor only infertility (81.3%; $n = 423$). A smaller proportion of cycles were performed for tubal-factor infertility (8.3%; $n = 43$). There were 54 egg donation cycles, and the average donor age was 28.5 y. On average, women <38 y of age were more likely to have a day five embryo transfer than older women; women ≥43 y exclusively underwent Day 3 ET. The total number of mature oocytes retrieved from the 520 cycles used in this analysis was 6415. As expected, the number of oocytes retrieved, number of mature oocytes, and number of embryos obtained decreased with increasing age. The average fertilization rate (No. 2PN embryos/No. mature oocytes) for the population was 73%.

The first equation was developed using individual patient-level data from male-factor and/or tubal-factor only cycles using Poisson regression. This equation (Equation 1 below) calculated the probability that one mature oocyte will become a blastocyst [*p(blast)*] for any given patient age (years, y). The 0.95 in the equation represents the assumed 95% survival of thawed mature oocytes for patients <36 y, and is replaced by 0.85 for patients ≥36 y, representing 85% survival. As the age-dependent decrease in live birth begins appreciably after the age of 35 y in our patient population (data not shown), all patients ≤35.0 y were categorized together into one group.

$$p(blast) = 0.95 * \exp(2.8043 - 0.1112 \times \text{Age}) \quad (1)$$

Table I Population demographics. Unless stated otherwise values are mean ± SD.

	Age									
Variable	**Egg Donor**	**≤35 y**	**36 y**	**37 y**	**38 y**	**39 y**	**40 y**	**41 y**	**42 y**	**≥43 y**
N	54	266	42	38	30	24	19	15	14	18
Age (y)	28.5 ± 4.2	32.1 ± 2.7	36.5 ± 0.3	37.5 ± 0.3	38.5 ± 0.3	39.4 ± 0.3	40.4 ± 0.3	41.4 ± 0.3	42.3 ± 0.3	43.6 ± 0.4
BMI (kg/m^2)	23.2 ± 3.2	25.4 ± 6.0	26.7 ± 6.2	24.9 ± 5.2	27.8 ± 8.3	26.3 ± 5.7	25.1 ± 4.8	27.7 ± 6.9	29.0 ± 8.8	25.9 ± 4.7
Day 3 FSH (mIU/ml)	–	7.0 ± 1.7	7.0 ± 1.7	7.4 ± 2.1	8.9 ± 6.4	8.9 ± 5.2	8.8 ± 2.9	8.5 ± 2.3	7.4 ± 1.4	8.6 ± 1.7
Day 3 ET (%)	48.1	68.0	61.9	73.7	86.7	91.7	94.7	93.3	92.9	100
Day 5 ET (%)	51.9	32.0	38.1	26.3	13.3	8.3	5.3	6.7	7.1	0
Number of oocytes retrieved	16.9 ± 9.1	17.0 ± 8.3	17.2 ± 8.4	14.7 ± 8.0	10.5 ± 7.0	11.0 ± 6.4	11.3 ± 7.0	12.6 ± 5.1	11.4 ± 6.8	9.1 ± 5.6
Number of mature oocytes retrieved	12.5 ± 6.7	13.7 ± 7.5	14.6 ± 7.4	11.8 ± 6.9	8.5 ± 5.7	8.5 ± 4.9	8.3 ± 5.6	9.7 ± 4.2	10.3 ± 6.9	6.9 ± 5.6
Number of 2PN embryos	10.5 ± 5.9	9.8 ± 5.9	10.5 ± 6.6	8.4 ± 5.9	6.3 ± 4.3	5.9 ± 4.9	5.6 ± 4.5	6.7 ± 3.4	7.1 ± 4.5	5.3 ± 4.4

For example, patients aged 34, 37 and 42 y, each having eight mature oocytes, would be predicted to have, on average, 3, 2, and one blastocysts, respectively. The blastulation rate for egg donation cycles was calculated separately. An egg donor who produced eight mature oocytes would be expected to have three blastocysts.

A second model was developed to determine the probability that any single blastocyst would be euploid [*p(euploid)*] using age-specific Reprogenetics data (Ata *et al.*, 2012 and unpublished data). The percentage of euploid blastocysts ranged from 57.4% for a woman ≤35 y to 12.7% for a 44-year-old (Supplementary Table SI). As an example, in a 37-year-old patient, the probability that a blastocyst is euploid is 0.486. In other words, 48.6% of her blastocysts are expected to be euploid, independent of her total number of blastocysts. The percentage of euploid blastocysts decreased linearly with patient age from 35 to 44 y ($P < 0.01$, test of linear trend).

The probability of having a live birth with a given number of mature oocytes can be approximated using Equation 2 below, which combines the regression from Equation 1 [*p(blast)*] with the *p(euploid)* Reprogenetics data, and assumes that, on average, a transferred euploid blastocyst will result in a live birth 60% of the time (Forman *et al.*, 2013, 2014). The predictions from Equation 2 assume that the probabilities of each mature oocyte resulting in a live birth are statistically independent.

$$p(\text{livebirth}) = 1 - [1 - 0.6p(\text{euploid}) \times p(\text{blast})]^{\text{Number of mature oocytes}} \quad (2)$$

Using the above equation, the probability of having at least one live birth as a function of the number of mature oocytes is shown in Figure 1 and Supplementary Table SII, stratified by year above age 35. The probability of having at least two or three live births is shown in Supplemental Tables SIII and SIV, respectively.

According to this final model, we find, for example, that women age 34, 37 or 42 y, each with 20 mature oocytes frozen, would be expected to have a 90, 75 and 37% likelihood of having at least one live birth, respectively. Correspondingly, women age 34, 37 or 42y would have to freeze 10, 20 and 61 oocytes, respectively, to have a 75% likelihood of having at least one live birth. A patient similar to an egg donor (average age 28.5 y in our population) would be expected to have a 94% likelihood of having a live birth with 20 mature oocytes frozen. Women age 34, 37 or 42 y, each with 20 mature oocytes frozen, would be expected to have a 66, 39 and 7% likelihood of having at least two live births, and a 38, 15 and 1% likelihood of having at least three live births, respectively.

Discussion

As the number of women who elect to cryopreserve their oocytes increases, so does the demand for counseling tools that can adequately predict their probabilities of having a live birth. Frequently, patients will ask about the 'ideal' number of oocytes to store for future use. This is, of course, challenging to determine as it depends on a number of factors, including maternal and paternal health, the goals of

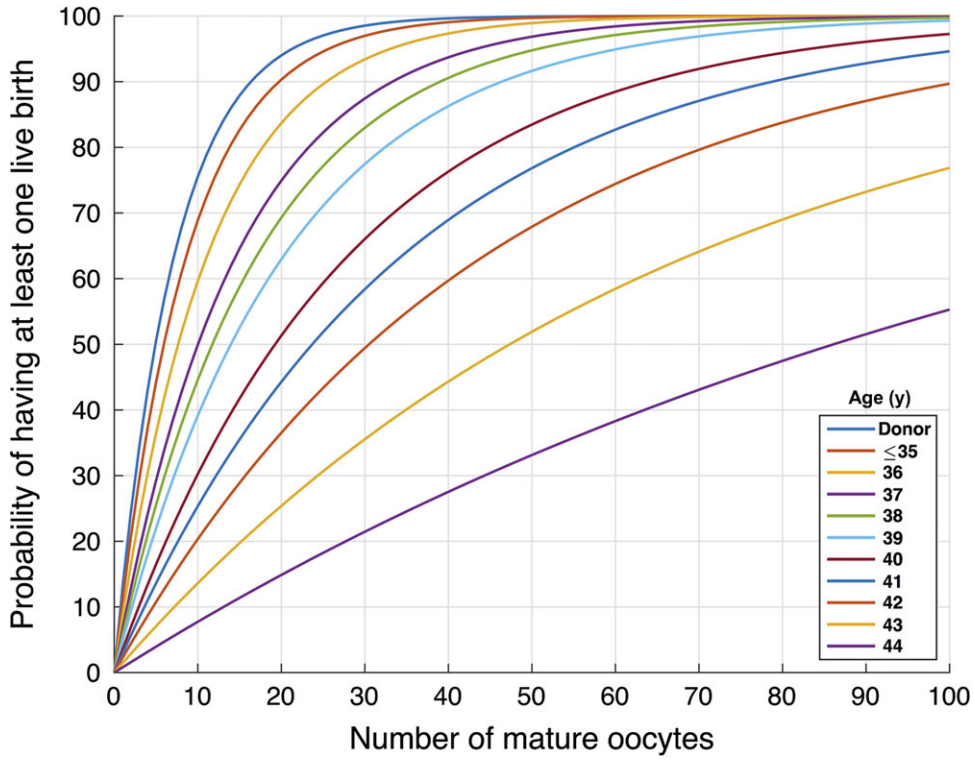

Figure 1 Live birth predictions by age and number of mature oocytes retrieved. Each curve shows the percent likelihood that a patient of a given age will have at least one live birth according to Equation 2, based on the number of mature oocytes retrieved and frozen.

the individual patient, and because no number of frozen oocytes can guarantee a live birth. While some patients may feel comfortable having a 50% likelihood of live birth in the future from their frozen eggs, others may not wish to proceed with oocyte cryopreservation unless that probability is much greater; alternatively, they may wish to undertake additional oocyte cryopreservation attempts to improve that probability. Moreover, some women may hope to have multiple children from their frozen eggs in the future.

This study provides a model to predict a patient's probability of having at least one, two, or three live birth(s) based on her age and the number of mature oocytes retrieved. Although our use of fresh male-factor and/or tubal-factor only ICSI cycles does not provide a perfect representation of women electing to undergo oocyte fertility preservation, such cycles can serve as surrogates for presumably fertile women of comparable age considering elective oocyte cryopreservation. With current technologies, women who elect to cryopreserve their oocytes will have to use ICSI after a future egg thaw. Egg donors, who are typically young, fertile and have good ovarian reserve, can also serve as a proxy population and were incorporated into this model. PGS data for prediction of euploidy was additionally restricted to cycles without a diagnosis of female infertility.

Several models have been proposed to predict the likelihood of live birth for women desiring elective egg freezing. A model by Doyle *et al.* (2016) used outcomes from both fresh and frozen IVF cycles to estimate the oocyte-to-child efficiency for each retrieved oocyte after stratification by age group. In that study, women 30–34 y with 10 frozen mature oocytes were predicted to have approximately a 60% likelihood of having at least one live birth. In contrast, in our study, women in this age range were predicted to have a 69% likelihood of live birth. As another example, Doyle *et al.* found that 35 and 38 year olds with 20 frozen oocytes would have live birth rates of 80 and 60%, respectively, whereas our model predicts rates of 90 and 69%. While our estimates are comparable to those of Doyle *et al.*, the differences may be driven by our finer categorization of women's ages by yearly increments rather than into age groups. Furthermore, Doyle *et al.* did not account for euploidy status in their study.

Cobo *et al.* (2016) retrospectively reviewed outcomes of 137 women who returned to use vitrified oocytes that were either cryopreserved electively due to age or for a non-cancer medical condition, including infertility diagnoses such as endometriosis or low ovarian reserve. In that study, Kaplan–Meier curves were created to estimate the live birth rate per oocyte used for women ≤35 and ≥36 y; the authors found that women ≤35 y who used 10 mature oocytes had a 60.5% likelihood of live birth, while women ≥36 y who used the same number of oocytes had a 29.7% likelihood of live birth.

Differences in methodology make direct comparisons between our study and previous studies challenging. Our study incorporates the probability of euploidy into the prediction, which is distinct from these prior studies. Furthermore, these previous analyses were not confined to otherwise fertile patients, and thus they could be underestimating the predicted probabilities of live birth. Moreover, both studies provided predictions by age stratifications rather than by individual age, and thus may have over- or under-estimated the likelihood of live birth given the sensitive relationship between age and fertility.

Our prediction analyses relied on several important assumptions. First, we assumed that the probability of a mature oocyte fertilizing and blastulating in a frozen–thawed cycle approximates the fertilization and blastulation rate of a fresh oocyte. This assumption is based on the fact that IVF outcomes using vitrified oocytes are comparable to outcomes using fresh oocytes (Cobo *et al.*, 2010; Rienzi *et al.*, 2010; Doyle *et al.*, 2016; Rienzi *et al.*, 2016). Though well supported in the literature, a recent JAMA article has suggested that live birth rates following frozen–thawed donor oocyte cycles may be 19% lower than with fresh donor oocytes (Kushnir *et al.*, 2015). However, that study has limitations, as it is based on aggregated data and the findings may have been biased due to the lower number of oocytes available in the frozen–thaw versus fresh oocyte group. Indeed, if use of frozen oocytes truly produced inferior results, our live birth predictions may be falsely elevated. If we were to apply the more conservative estimate of a 19% lower live birth rate to our model, a 35-year-old woman with 20 mature oocytes retrieved would have a live birth rate of only 73%, not 90% as our original model suggests.

Second, we assumed that, on average, 60% of euploid blastocysts would ultimately result in a live birth based on published data, and that this figure is independent of age (Harton *et al.*, 2013); however, this rate varies widely among IVF clinics and in the literature (Forman *et al.*, 2013, 2014; Schoolcraft and Katz-Jaffe, 2013; Scott *et al.*, 2013; Fiorentino *et al.*, 2014). If a woman were to be treated at a clinic with lower success, this model would overestimate her probability of live birth. Finally, our model assumes a 95% survival of thawed mature oocytes for women <36 y and 85% for women ≥36 y, values that also vary by study and by center, and that clearly impact ultimate outcomes (Cobo *et al.*, 2008; Rienzi *et al.*, 2010; Practice Committees of American Society for Reproductive Medicine and Society for Assisted Reproductive Technology, 2013; Cobo *et al.*, 2016). While we found these assumptions appropriate for our clinical population, individual IVF clinics may need to modify our model based on their own thaw survival and live birth rates, thereby allowing for more clinic-specific patient counseling.

Our counseling tool can be used in several ways. First, it can be used during initial fertility preservation consults to help provide reasonable expectations regarding the number of mature cryopreserved oocytes potentially needed for future use, based on the patient's desired probability of having at least one, two, or three live birth(s). While our derived coefficients in Equation 1 are specific to our center, similar Poisson regressions could be performed using patient data at other institutions to derive their own blastulation rates. Second, the prediction chart generated from our analysis (Figure 1) may help patients visualize a reality in oocyte cryopreservation: no matter how many oocytes are frozen, the likelihood of live birth is not guaranteed and will never reach 100%. Third, it may help patients decide how many cycles to undergo, recognizing that there is a point beyond which undergoing additional cycles would likely bring diminishing returns.

Of note, this tool is designed to help predict live birth rates for healthy women desiring elective oocyte cryopreservation. Importantly, this model may overestimate the live birth rate for women undergoing non-elective oocyte cryopreservation for medical reasons that might compromise ovarian function, including malignancy.

There are several limitations to this study. Our model is based on a retrospective chart review of couples using ICSI to treat male-factor and/or tubal-factor only infertility, or cycles for which egg donation was used, at a single institution in an insurance-mandated state. It is possible that our model has underestimated the probability of live birth for patients wishing to electively cryopreserve oocytes given that ICSI for male-factor infertility may have a detrimental effect on

blastocyst formation (Miller and Smith, 2001), and a future partner or sperm donor may not have infertility. Furthermore, although we excluded tubal-factor patients with a hydrosalpinx, it is possible that these patients had inflammatory processes that could negatively impact oocyte quality, leading to an underestimation of live birth predictions.

The sample size in older age groups (i.e. women over 38 y) is relatively small, partly because we only included patients with normal ovarian reserve, which is less likely to be found among older patients. We excluded embryos transferred on Day 3 from the potential number of blastocysts, as it is unknown whether these embryos would have blastulated in culture. This ultimately makes the model slightly more conservative (i.e. lowers the predicted likelihood of live birth). As the older patient population was more likely to have had a day three transfer, this elimination would affect their predictions more than those of younger patients. Our model may therefore have reduced accuracy for older populations. Furthermore, in practice, most IVF centers typically thaw not just one, but a group of oocytes in preparation for an embryo transfer. If multiple thawed oocytes fertilize and then develop into blastocysts, supernumerary blastocysts might then be frozen, leading to the opportunity for multiple freeze/thaw cycles on oocytes or embryos. Such practice might negatively impact live birth outcomes, which, in turn, might lead our models to overestimate success. This possibility should be discussed when counseling patients. As we gain more experience with thawing embryos arising from thawed oocytes, oocyte thaw strategies may need further refinement to minimize the need for re-thaw. Finally, our assumed post-thaw oocyte survival rates (95% for women <36 y and 85% for women ≤36 y) may be higher than those observed in other programs, and so may lead to higher predicted live birth rates. With a less optimistic survival rate, one would expect a lower predicted live birth rate.

While we attempted to use reasonable, conservative, evidence-based predictions for oocyte survival and live birth per transferred euploid blastocyst, it is also possible that these values are too optimistic and if so, our model would overestimate the likelihood of live birth. Clearly, the best outcome data to develop a predictive model would be obtained from women who have undergone oocyte cryopreservation with vitrification and then returned to use their oocytes. However, at the present time, there is a paucity of such validation data available.

Concluding remarks

This live birth predictive model was designed using a population of patients with presumably normal ovarian reserve to serve as a guide for women considering elective oocyte cryopreservation. As this study is based on retrospective data, our model should be validated in the future with a prospective study of women who have electively cryopreserved and then returned to use oocytes for family-building. Such validation would be valuable in light of the costs involved not only in the oocyte cryopreservation process, but also in the annual storage of frozen oocytes. However, until such prospective data is available, we expect our tool to provide a valuable resource for physicians and patients.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

R.G., J.F., C.R. and L.F. formulated the study questions and directed their implementation. S.M. and L.R. contributed to the study design. R.G. performed statistical analysis. L.F. advised on statistical analysis. S.M. and L.R. provided critical data. R.G., C.R., J.F. and L.F. drafted the article. All authors were involved in revising the article and have approved this final version.

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Conflicts of interest

C.R. has received compensation as an IVF program consultant and as a lecturer at Ferring, Inc., receives editorial royalties from Springer and University of Cambridge, UK, and is an ASRM board member for which she does not receive compensation. S.M. and L.R. report being employed at Reprogenetics. R.G., L.F. and J.F. report no conflicts of interest.

References

Almodin CG, Minguetti-Camara VC, Paixao CL, Pereira PC. Embryo development and gestation using fresh and vitrified oocytes. *Hum Reprod* 2010;**25**:1192–1198.

Ata B, Kaplan B, Danzer H, Glassner M, Opsahl M, Tan SL, Munné S. Array CGH analysis shows that aneuploidy is not related to the number of embryos generated. *Reprod Biomed Online* 2012;**24**:614–620.

Cil AP, Bang H, Oktay K. Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. *Fertil Steril* 2013;**100**:492–499.e3.

Cobo A, García-Velasco JA, Coello A, Domingo J, Pellicer A, Remohí J. Oocyte vitrification as an efficient option for elective fertility preservation. *Fertil Steril* 2016;**105**:755–764.e8.

Cobo A, Garcia-Velasco JA, Domingo J, Remohí J, Pellicer A. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? *Fertil Steril* 2013;**99**:1485–1495.

Cobo A, Kuwayama M, Pérez S, Ruiz A, Pellicer A, Remohí J. Comparison of concomitant outcome achieved with fresh and cryopreserved donor oocytes vitrified by the Cryotop method. *Fertil Steril* 2008;**89**:1657–1664.

Cobo A, Meseguer M, Remohí J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. *Hum Reprod* 2010;**25**:2239–2246.

Doyle JO, Richter KS, Lim J, Stillman RJ, Graham JR, Tucker MJ. Successful elective and medically indicated oocyte vitrification and warming for autologous in vitro fertilization, with predicted birth probabilities for fertility preservation according to number of cryopreserved oocytes and age at retrieval. *Fertil Steril* 2016;**105**:459–466.e2.

Fiorentino F, Bono S, Biricik A, Nuccitelli A, Cotroneo E, Cottone G, Kokocinski F, Michel C-E, Minasi MG, Greco E. Application of next-generation sequencing technology for comprehensive aneuploidy screening of blastocysts in clinical preimplantation genetic screening cycles. *Hum Reprod* 2014;**29**:2802–2813.

Forman EJ, Hong KH, Ferry KM, Tao X, Taylor D, Levy B, Treff NR, Scott RT. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. *Fertil Steril* 2013;**100**:100–107.e1.

Forman EJ, Hong KH, Franasiak JM, Scott RT. Obstetrical and neonatal outcomes from the BEST Trial: single embryo transfer with aneuploidy

screening improves outcomes after in vitro fertilization without compromising delivery rates. *Am J Obstet Gynecol* 2014;**210**:157.e1–e6.

Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, Scott RT. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. *Fertil Steril* 2014a; **101**:656–663.e1.

Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, Scott RT. Aneuploidy across individual chromosomes at the embryonic level in trophectoderm biopsies: changes with patient age and chromosome structure. *J Assist Reprod Genet* 2014b;**31**:1501–1509.

Garcia-Velasco JA, Domingo J, Cobo A, Martínez M, Carmona L, Pellicer A. Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications. *Fertil Steril* 2013;**99**:1994–1999.

Gnoth C, Godehardt D, Godehardt E, Frank-Herrmann P, Freundl G. Time to pregnancy: results of the German prospective study and impact on the management of infertility. *Hum Reprod* 2003;**18**:1959–1966.

Grifo JA, Noyes N. Delivery rate using cryopreserved oocytes is comparable to conventional in vitro fertilization using fresh oocytes: potential fertility preservation for female cancer patients. *Fertil Steril* 2010;**93**:391–396.

Harton GL, Munné S, Surrey M, Grifo J, Kaplan B, McCulloh DH, Griffin DK, Wells D. Diminished effect of maternal age on implantation after preimplantation genetic diagnosis with array comparative genomic hybridization. *Fertil Steril* 2013;**100**:1695–1703.

Hilgers TW, Daly KD, Prebil AM, Hilgers SK. Cumulative pregnancy rates in patients with apparently normal fertility and fertility-focused intercourse. *J Reprod Med* 1992;**37**:864–866.

Hodes-Wertz B, Druckenmiller S, Smith M, Noyes N. What do reproductive-age women who undergo oocyte cryopreservation think about the process as a means to preserve fertility? *Fertil Steril* 2013;**100**:1343–1349.

Kushnir VA, Barad DH, Albertini DF, Darmon SK, Gleicher N. Outcomes of fresh and cryopreserved oocyte donation. *J Am Med Assoc* 2015;**314**:623–624.

Mesen TB, Mersereau JE, Kane JB, Steiner AZ. Optimal timing for elective egg freezing. *Fertil Steril* 2015;**103**:1551–1556.e1–e4.

Miller JE, Smith TT. The effect of intracytoplasmic sperm injection and semen parameters on blastocyst development in vitro. *Hum Reprod* 2001;**16**:918–924.

Munné S, Ary J, Zouves C, Escudero T, Barnes F, Cinioglu C, Ary B, Cohen J. Wide range of chromosome abnormalities in the embryos of young egg donors. *Reprod Biomed Online* 2006;**12**:340–346.

Munné S, Held KR, Magli CM, Ata B, Wells D, Fragouli E, Baukloh V, Fischer R. Gianaroli L. intra-age, intercenter, and intercycle differences in chromosome abnormalities in oocytes. *Fertil Steril* 2012;**97**:935–942.

Practice Committees of American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. *Fertil Steril* 2013;**99**:37–43.

Rienzi L, Romano S, Albricci L, Maggiulli R, Capalbo A, Baroni E, Colamaria S, Sapienza F, Ubaldi F. Embryo development of fresh "versus" vitrified metaphase II oocytes after ICSI: a prospective randomized sibling-oocyte study. *Hum Reprod* 2010;**25**:66–73.

Rienzi L, Gracia C, Maggiulli R, LaBarbere AR, Kaser DJ, Ubaldi FM, Vanderpoel S, Racowsky C. Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. *Hum Reprod Update* 2016; Epub ahead of print. DOI: 10.1093/humupd/dmw038.

Rudick B, Opper N, Paulson R, Bendikson K, Chung K. The status of oocyte cryopreservation in the United States. *Fertil Steril* 2010;**94**:2642–2646.

Schattman GL. Clinical practice. Cryopreservation of oocytes. *N Engl J Med* 2015;**373**:1755–1760.

Schoolcraft WB, Katz-Jaffe MG. Comprehensive chromosome screening of trophectoderm with vitrification facilitates elective single-embryo transfer for infertile women with advanced maternal age. *Fertil Steril* 2013; **100**:615–619.

Scott RT, Upham KM, Forman EJ, Hong KH, Scott KL, Taylor D, Tao X, Treff NR. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. *Fertil Steril* 2013;**100**:697–703.

Stoop D, Nekkebroeck J, Devroey P. A survey on the intentions and attitudes towards oocyte cryopreservation for non-medical reasons among women of reproductive age. *Hum Reprod* 2011;**26**: 655–661.

Stoop D. Social oocyte freezing. *Facts Views Vis Obgyn* 2010;**2**:31–34.