EMBRYONICS

Embryonics personalized fertility assessment tool (Egg Freezing Calculator)

Outline

A. Introduction

The rise in late childbirth and planned oocyte cryopreservation (OC) as a risk mitigating factor

For the past few decades there has been a rise in later childbirth. In the US, the rate of first-time motherhood among women over 35 rose by 23% between 2000 and 2014(1). UK and OECD data also indicates that women defer childbearing to older ages(2–4). A study of women who went through planned OC showed that the main reason for electing fertility preservation is lack of a partner, while other studies list educational, financial, and professional reasons(5,6). Concurrently with the growth of the later childbearing trend, the performance of oocyte cryopreservation (OC) is also on the rise(4). The European Society of Human Reproduction and Embryology (ESHRE) recommended that OC will be available to women in order to allow them to potentially have genetically-related children(7). Some of the evidence published already on planned OC outcomes demonstrated the great impact age has on female fertility with significantly better measurements at younger ages of oocyte yield, oocyte survival and cumulative obstetric outcomes, suggesting patients should be counseled about planned OC earlier than age 35(7–11). Regardless of any motivation that leads to it, deferring childbearing isn't recommended due to maternal, reproductive and pregnancy complications related to age(12,13). Nonetheless, Current evidence of the safety of using frozen oocytes seemes reassuring and there is no greater risk of adverse reproductive, obstetric, perinatal or neonatal outcomes when using cryopreserved oocytes versus fresh oocytes in IVF(7,8,14,15). Moreover, longer periods of storage appear to not have a significant impact on oocyte survival rate or clinical outcomes(8,16). Planned OC was shown in previous works to be cost-effective depending if done up to turning 38, while not only reducing costs it increases the odds of live birth(17–19). However, some patients view this as health insurance and study has shown that up to 90% of women will not regret going through this process, even if it won't eventually be of use(20).

Planned OC counseling is essential for OC and IVF success

Unfortunately, not enough women are sufficiently informed on the natural age-led decline of female fertility. One study even goes on to show up to 80% of the women reported that they wished they had undergone OC earlier(5). Current guidelines address the issues of raising women's awareness of family planning and specifically to age-related fertility decline. Although planned OC is a rising measure to mitigate older

childbearing, women should be properly informed about their expected take-home baby likelihood by having their eggs frozen, including the number of oocytes and the number of cycles they would need for a reasonable chance at live birth. Moreover, women should be counseled that either using assisted reproductive technologies or going through planned OC as preventive measures can't guarantee a live birth(2,7,21,22). Predicting an individual's own success rates of planned OC, as defined as the number of oocytes retrieved needed to achieve one live birth, continues to be a challenge. Most evidence collected today is of medically indicated IVF outcomes, and there is insufficient data on the outcomes of planned OC done for age-related decline in order to counsel women on the optimal age for going through planned OC, number of oocytes needed or their expected outcomes(17,23–25).

B. Embryonics personalized fertility assessment tool

Embryonics personalized fertility assessment tool is an evidence-based educational tool intended to assist patients in fertility planning based on data-driven literature integration approach. By using several demographic and medical factors, the designed algorithm predicts the following outcomes: the likelihood of oocyte yield following controlled ovarian stimulation (COS) and the CLBR dependent on oocyte yield and patient factors. The factors included have been deemed to have a significant and calculable impact on patients' reproductive health (written in detail below). This list includes medical conditions the patient is likely to know about with the exception of AMH test results which are vital for better prediction. The number of planned OC cycles needed to achieve these estimations is also presented so patients will be fully informed and have a better understanding of the process. In addition to data from a leading fertility clinic in the United States, special attention has been paid to literature evaluating planned oocyte cryopreservation (OC) cycles (i.e., IVF-controlled ovarian stimulation cycles performed for elective, non-medical reasons). This assessment tool is an online, free access platform to allow women to educate themselves on fertility preservation prior to specialist consultation and to connect them with fertility clinics in their area. It is not meant to provide medical advice or replace the role of healthcare professionals.

C. Rationale for requested data points

A large number of factors are likely to influence various outcomes of controlled ovarian stimulation and subsequent embryo transfers. Literature is often conflicting and needs thorough and careful analysis. Embryonics personalized fertility assessment tool was developed by using factors consistently showing significant and quantifiable impact on oocyte yield and/or cumulative live birth rate in the current literature. Therefore we mainly used large cohort studies and meta-analyses that had significant results, and ideally which had been independently reproduced or validated externally. inputs with a significant impact but likelihood to be of only low relevance to the target users weren't included. Several key factors with calculable impact are unlikely to be known by the patient prior to health professional consultation and were therefore not included since it is outside the scope of the current intended use of this calculator. Included factors that affect the predicted number of oocytes retrieved following controlled ovarian stimulation and factors that affect cumulative live birth rate are presented in table 1.

	Predicted number of retrieved oocytes	Predicted CLBR
Age	V	V
BMI	-	V
Ethnicity	-	V
AMH	V	-
PCOS	V	-
Endometriosis	V	V

Table 1: *Summary of included factors as algorithm inputs and affected outcomes*

Age

fertility is highly dependent on maternal age. Age-related fertility decline begins around age 32 and rapidly declines at age 37 with a depletion of ovarian reserve and impaired oocyte quality(26). A recent review on planned OC demonstrated going through planned OC in younger ages resulted in higher oocyte yield, with fewer COS cycles and higher live birth rate(27). In oocyte donor programs there is usually an upper limit of age 35 for optimizing both ovarian response and oocyte quality(28). In addition to a decrease in the number and quality of oocytes retrieved, older women are more likely to have a lower percentage of mature (MII) oocytes(29,30). Up until the age of 35, the intrinsic fertility of a single oocyte is approximately 25%, followed by approximately 10% decrease every year(31). Molecular and cellular processes are affected by oocyte aging and may decrease the rate of fertilization and blastocyst formation and increase aneuploidy rate and pregnancy loss(8,32–34). Even though the post-thaw survival rate improved significantly in the past decade, it was found post-thaw survival is lower in women older than 35, probably affected by age-dependent oocyte competence(9,11,14). Moreover, long periods of storage appear not to have a negative effect on oocyte survival rate in healthy women younger than 35(16). When looking at both ART and naturally conceived pregnancies, unfavorable outcomes and pregnancy-related complications are rising with maternal age(12). Pregnancy-related outcomes of either fersh or frozen oocytes cycles, decreases with age including positive beta-HCG test, fetal heartbeat, ongoing pregnancy, live birth rate and good perinatal outcomes, and miscarriage rate rise with age(9,31,35–39). The number of OC cycles, the number of oocytes-to-baby and the number of thawed oocytes needed to achieve an estimated live birth rises with older age(38,40,41). autologous-IVF cycles outcomes show patients who underwent OC before turning 38 had a better chance of a child per oocyte or blastocyst(42). Other reported results, though not statistically significant, show that patients with more than 9 thawed oocytes had more than double the chances of live birth(30). Cumulative live birth rate depends on the age at OC and the number of oocytes retrieved. In planned OC cycles, there is up to 95% probability of live birth under the age of 35 with 24 vitrified oocytes and only up to 50% probability of live birth in older women(9). In the cycles using donor oocytes, the number of mature oocytes needed to live birth was comparable to the number needed under 35 age group, and cumulative live birth improved significantly with each additional oocyte up to 25 oocytes(16). Others

have demonstrated that either age under 38 at the first OC or more than 20 thawed mature oocytes had a probability of approximately 50% of live birth, while patients under age 38 who thawed more than 20 mature oocytes had a 70% live birth rate(43).

Body Mass Index (BMI)

BMI impact on reproductive and obstetric outcomes was assessed in numerous studies, however, data evaluating its effect on planned oocyte cryopreservation outcomes is lacking. Analysis of SART data demonstrated underweight (bmi<18) and obese (bmi>30) women had a statistically significantly decreased chance of clinical pregnancy and live birth(44). Similar results were shown in a recent meta-analysis of more than 600,000 IVF cycles of patients mainly from the US; obese women (BMI>30) have decreased probability of LBR compared to normal-weight women(45). Another meta-analysis found similar results for ongoing pregnancy rate(46). In a subgroup analysis, unfavorable outcomes were seen in patients with obesity diagnosed with PCOS(45,46). notably, analysis of donation and autologous cycles demonstrated oocyte origin did not modify outcomes, reinforcing BMI's independent impact on live birth(45). obesity, as compared with normal weight, was associated with a statistically significant increased miscarriage risk and cancellation rate(44,46). BMI's effect on oocyte yield, oocyte competence, embryo formation, and aneuploidy is researched in small to medium-scale studies with some negative effects observed in obese women(46–51). BMI's impact on ovarian reserve needs further evaluation, and therefore BMI isn't included as a factor affecting the number of predicted retrieved oocytes.

Ethnicity

Multivariate analysis of factors affecting the probability of pregnancy and live birth with IVF done on SART data found that compared to Caucasians, all ethnic groups were significantly less likely to achieve a clinical pregnancy and at higher risk for miscarriages(37). Other researchers also found differences in outcomes based on ethnicity on SART data with reduced odds of live birth in blacks, Hispanics and Asians(52). In a systematic review of ethnic disparity in SART-reported outcomes, all references reported a statistically significant ethnic disparity in one or more SART-reported reproductive outcomes. Compared to Caucasians, Hispanic, Asian, and Black had lower live birth rates either per cycle or per pregnancy, with blacks having the lowest LBR(53). An analysis of the UK national database also demonstrated similar findings on ethnicity's impact on fertility. After adjusting for age, cause of subfertility, and type of treatment, lower live birth rate and lower cumulative live birth rates per fresh embryo transfer cycle were demonstrated in blacks, Asians, and other ethnic minorities compared to British white women. The number of oocytes and clinical pregnancy was also lower compared to British whites, in both blacks and Asians. notably, some of the other ethnic groups or women of mixed ethnicities had similar live birth rates to those of British white women. In addition, according to HFEA reported results, above the age of 40 less significant differences between ethnicities were observed, reinforcing age's effect on fertility(54,55).

AMH

Recent systematic review has suggested that due to the high prediction power of AMH, it should be considered a covariate in prediction models(56). AMH levels gradually decline with age. A large cohort study on the US population that evaluated AMH test results from a single laboratory show a decline from 3.4 ng/mL at age 24 to approximately 0.2 ng/ml per year and after age 35 a more moderate decline of 0.1 ng/ml with increasing age is expected(57). AMH was found to be indicative of ovarian reserve and correlates with ovarian response following controlled ovarian stimulation measured as oocyte yield(58,59). Moreover, it can be of assistance in identifying potential responses to hyperstimulation, either excessive response or poor response(59–61). There is some evidence that AMH might have predictive value independent of age on cumulative live birth rates in patients with diminished ovarian reserve or with recurrent pregnancy loss(62,63). A statistically significant correlation between live birth rate and higher AMH was observed in women over 40 years of age(64). AMH was also found to correlate independently of age to euploid blastocyst rate with increased euploidy rate with increased AMH(34). However, systemic review and meta-analysis suggested it requires further research as AMH predictive accuracy of live birth is low(56). In a paper assessing ovarian reserve markers, there was no impact of low AMH indicating diminished ovarian reserve on time-to-pregnancy in natural conception(65). Other ART cycle outcomes, including implantation and clinical pregnancy, were also not correlated with AMH. However, the results of the AMH test indicative of diminished ovarian reserve can be helpful when counseling patients intended for IVF(66). According to these recent findings, there is no threshold from which patients should be withheld fertility treatments(56). Due to the controversial impact on CLBR, AMH was included in the algorithm to affect the predicted number of oocytes retrieved. In the absence of a personal AMH test result a nominal value of AMH based on the median AMH according to age is selected(57).

Polycystic ovarian syndrome (PCOS)

PCOS is a highly prevalent endocrine and reproductive disorder, affecting between 5% to 20% of women of reproductive age (depending on the criteria used for diagnosis). Several phenotypes were identified, with some having ovulation dysfunction and variable severity of subfertility(67). There is no evidence of planned oocyte cryopreservation in patients with PCOS for fertility preservation and all the data drives from IVF cycles, which are recommended only as third-line treatment(68).In large cohort studies, it was demonstrated that PCOS patients undergoing IVF have higher oocyte yield at retrieval between 20% to 40% compared to age-matched non-PCOS IVF patients(69,70). Analysis done on the SART data cycle found that though increased oocyte count, above the age of 40 no higher pregnancy outcomes were found compared to IVF patients due to tubal factors(70). A recent retrospective analysis of PCOS patients under the age of 40 found increased oocyte yield impacts cumulative live birth only up to 15 oocytes retrieved(71). mixed results were reported for different reproductive and pregnancy-related outcomes of PCOS patients following IVF(72,73). among reported results, miscarriage rates and pregnancy-related complications were repeatedly higher in PCOS patients compared with non-PCOS patients that had undergone IVF, and live birth rate was negatively affected by the high BMI of PCOS patients(73–78). Evidence suggests pregnancy loss is not due to a higher risk of aneuploidy in high responders as PCOS patients(79–81). A recent review demonstrated that endometrial dysfunction in PCOS patients can predispose miscarriages and pregnancy complications(82). PCOS patients are also at higher risk of OHSS and are subject to higher cancellation rates(73,77). GnRH agonists as oocyte maturation triggers or using IVM and limiting ovarian stimulation, are both safe options to reduce the risk of OHSS with similar outcomes to IVF(68,83).

Endometriosis

Endometriosis is a widely common pathology, affecting one in ten women. It was included in the algorithm because of its high incidence as well its potential effect on ovarian resrve, oocyte quality, maturation rate, fertilization rate, implantation rate and other obstetric outcomes and complications(84). Up to 50% of women are treated for infertility due to endometriosis. In comparison to women with unexplained infertility their probability of having a baby is lower by 24% and they have fewer oocytes retrieved and lower blastocyst formation rate and implantation rate(85). Recent studies have confirmed the usefulness of planned OC for patients with endometriosis. Oocyte yield and clinical outcomes were better in patients younger than 35 who have not gone through endometrioma removal surgery. When comparing the young age group to age matched control group, the oocyte survival rate, implantation rate, pregnancy rate, and CLBR were lower in women diagnosed with endometriosis(86). Similar to previous findings of planned OC outcomes, CLBR rises with the number of oocytes and favorable outcomes are observed in patients younger than 35 years of age. The number needed to freeze was comparable between endometriosis and other planned OC patients(87). Notably, the endometriosis stage didn't have an effect on OC outcomes; number of oocytes retrieved, embryo quality and clinical outcomes were similar in advanced stages of endometriosis(86,87).

D. Performance

Age

Age effect on the number of retrieved oocytes was calculated by analyzing 924 IVF cycles from 2020-2022 of 599 patients in a leading fertility clinic in the US, including both IVF due to infertility and planned OC cycles. We used newly collected data to best reflect current common practice and standard of care for controlled ovarian stimulation. The data presented in figure 1 was fitted as a sigmoid to the median number of retrieved oocytes per age. We chose sigmoid to account for the possibility of a non-linear drop in ovarian response with age.
Using all the age-related effects on reproductive and obstetric outcomes in the published literature presented above, a model for the attrition rate was developed to predict the probability of a single retrieved oocyte resulting in a live birth. The integration of contradictory data from the various publications was done in a way that minimizes the difference between our model and the published numbers. Wherever the agreement among publications was too low, we have assigned more weight to publications with more patients and better methodology (as defined in Cochrane's GRADE manual). Some discrepancies were explainable by population, procedural and definition differences and were statistically corrected to be compared on equal grounds with the other existing literature. CLBR was defined as the probability of 1 live birth from 1 retrieval cycle, and is predicted based on the patient's age and expected number of oocytes retrieved.

BMI

The effect of BMI on CLBR was calculated by fitting a polynomial to data from SART in accordance with peer-reviewed publications presented above. As shown in figure 2, extremities of BMI are decreasing CLBR by up to 30%.

AMH

The effect of AMH was calculated by fitting a Göempertz sigmoidal function according to findings in current literature. In figure 3 it is shown that measured AMH (between 0.5-5 ng/ml) divided by normal AMH, gives a factor to multiply the expected number of retrieved oocytes; the factor given is between 0.5 to 1.3. Normal AMH to age is defined as median AMH to age based on findings of a large cohort study of AMH test results of US patients from a single laboratory(57). In figure 4 it is shown the effect of AMH on the number of predicted retrieved oocytes to age and median AMH to age.

Ethnicity, PCOS, Endometriosis

Each parameter gives a factor to multiply the predicted CLBR, predicted number of retrieved oocytes, or both. Based on our literature review and national registries, ethnicity can decrease cumulative live birth by up to 20%. When multiple ethnicities apply to an individual their average effect is calculated. PCOS diagnosis increases the number of predicted retrieved oocytes by 20% while endometriosis diagnosis decreases the expected number by 10%. Endometriosis also impacts CLBR and decreases the calculated number by 20%.

Outcomes parameters

We point to the reader that there are three parameters to calculate to predict the success rate of an IVF cycle for a patient. The LBR (live birth rate per retrieved oocyte), number of retrieved oocytes, and CLBR (the cumulative live birth over the full retrieval cycle). Indeed, the number of degrees of freedom is only two – as they are related by the following relationship:

$$CLBR = (1 - (1 - LBR))^{OOCYTES}$$
$$LBR = (1 - (1 - CLBR))^{1/OOCYTES}$$
$$OOCYTES = \frac{log(1 - CLBR)}{log(1 - LBR)}$$

So when one calculates two of these, the other resolves uniquely. The existing literature is mostly focused on the two ends of the spectrum: the number of retrieved oocytes & CLBR (according to patient parameters). Data on LBR, which reflects consecutive attrition in each step between an oocyte and a live baby, is less available in encompassing studies that include enough factors and demographic groups and as such was used to resolve contradicting literature for CLBR and the number of retrieved oocytes. We note that the three equations above assume statistical independence of oocyte competence between oocytes, and we leave the needed correction for future work.

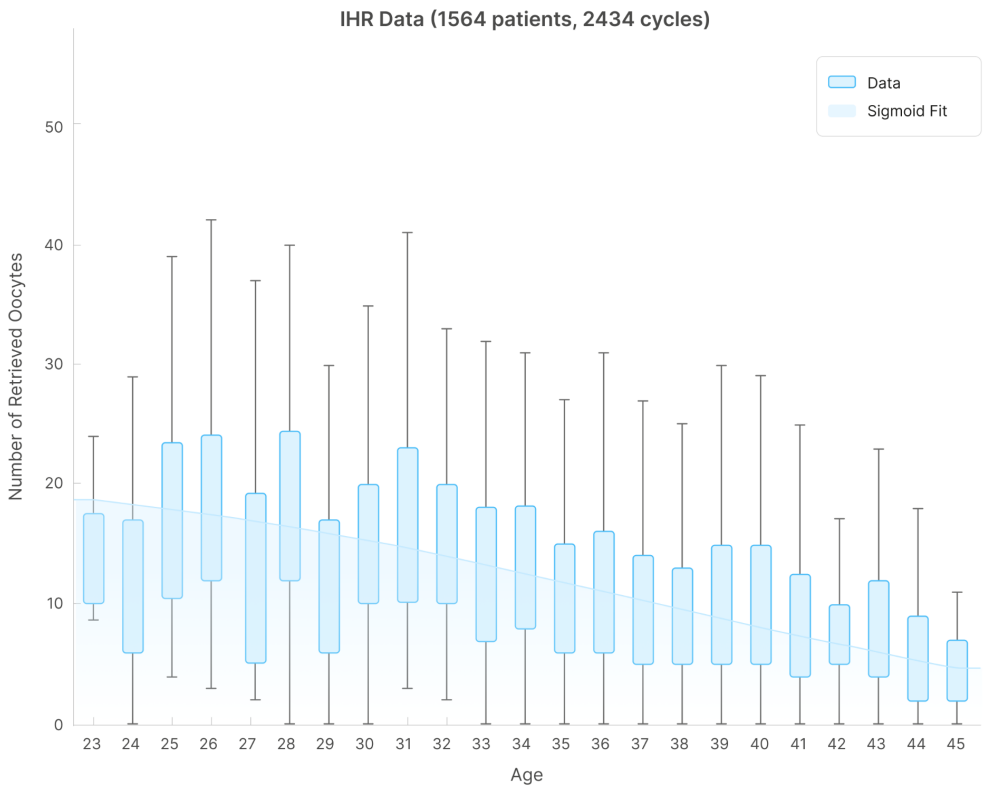

Figure 1: Impact of age on the number of retrieved oocytes from US clinic data of 924 patients.

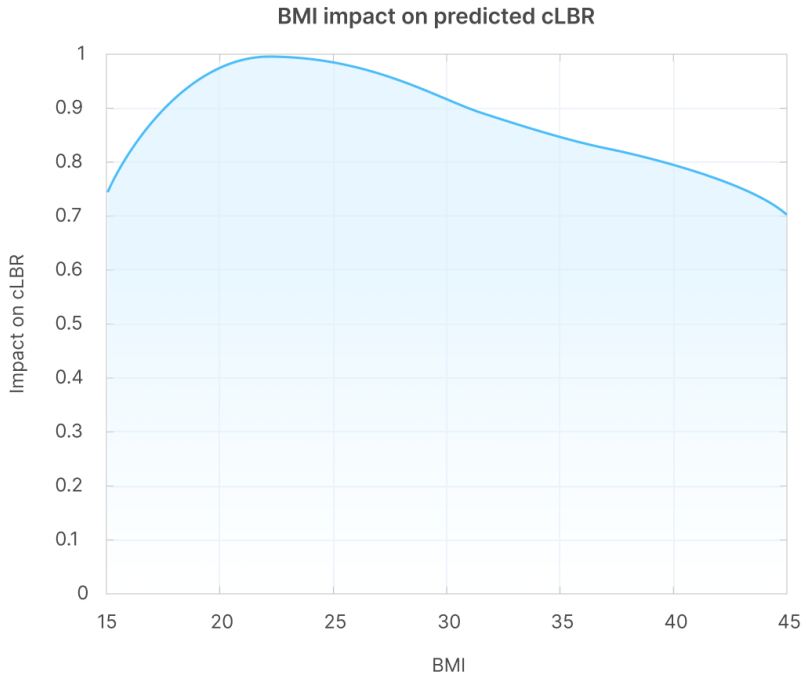

Figure 2: Impact of BMI on CLBR.

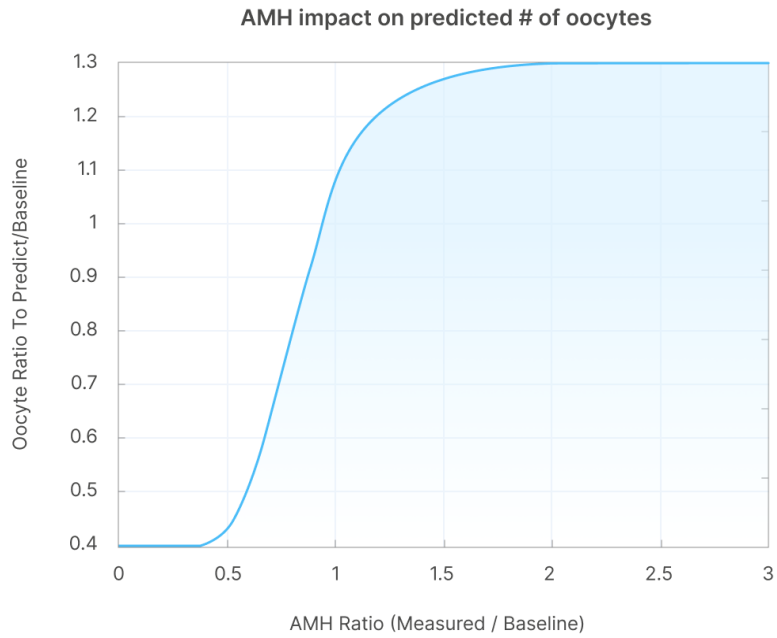

Figure 3: Impact of AMH on predicted number of retrieved oocytes.

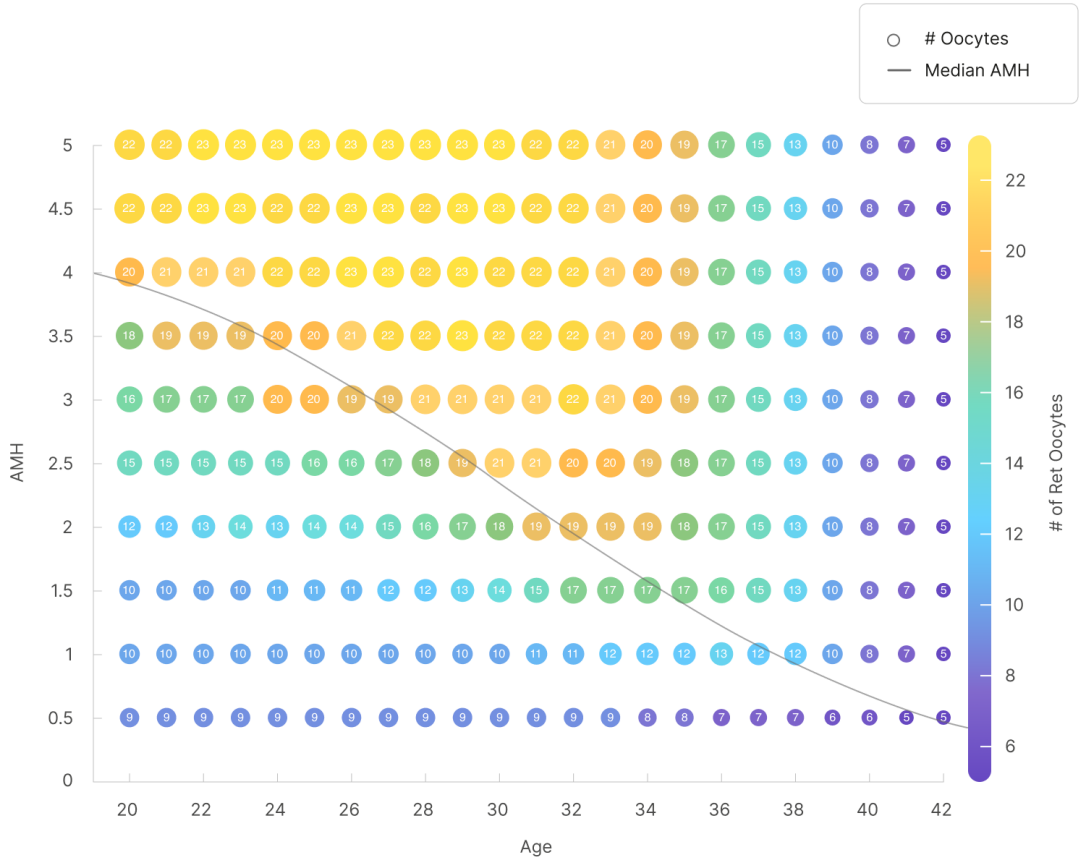

Figure 4: Impact of AMH on the number of predicted retrieved oocytes expected by age.

E. Version 1.0 Limitations and future prospects

- Some of the data behind the literature on IVF is from patients suffering from infertility, while the intended use of this calculator is for women wishing to undergo planned OC to extend their fertility window. This is fundamentally a different subset of patients, and published data may therefore not be a true reflection of these women's IVF outcomes.
- This calculator was programmed using data predominantly from the United States and Spain based literature and limited by the number of factors included. More data points can have an impact on women's fertility as shown in the existing literature. The results of this calculator version may therefore be less accurate for other populations.
- Different controlled ovarian stimulation protocols may alter the expected number of retrieved oocytes, oocyte maturity or oocyte quality. This version of the calculator doesn't account for these differences and further research is needed to give more accurate predictions depending on hormonal protocol.
- Validation of large cohort clinical data of planned OC cycles and their followed outcomes after thawing cycles is needed to evaluate this algorithm better.
- In the future when more clinical data will be collected and analyzed, when a consensus can be determined on the likely impact of additional factors, or when the intended use of the calculator is updated, the algorithm and/or the factors included may vary in subsequent versions.

F. References

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