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Intrinsic fertility of human oocytes

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Objective: To study the intrinsic fertility of the human oocyte.
Design: A large retrospective study of natural cycle single embryo transfer (ET) IVF cycles.
Setting: Private IVF clinic, university, and private hospital.
Patient(s): Patients were enrolled consecutively over an 8-year period in a single ET natural cycle protocol.
Intervention(s): A total of 13,949 oocyte retrievals with natural IVF single ET. Software package R (version 3.2.5) was used for statistical calculations.
Main Outcome Measure(s): Live baby rate per oocyte according to age.
Result(s): A total of 14,185 natural cycle oocytes resulted in 1,913 live babies from single ET. The number of oocytes required to make one live baby in this large series varied with the age of the female partner. For those under 35, the live baby born per oocyte was 26%. For over age 42 it decreased to 1%. These results fit very robustly with a logistic function curve, which is at first steady (horizontal), followed by a linear decline after age 35 with a 10% loss every year until age 43, and then a flattening out (horizontal) by age 44.
Conclusion(s): The intrinsic fertility per oocyte in natural cycle is far greater than reported in hyperstimulated cycles, varying robustly from 26% to 4% with age from <35 to 42 years. The curve is relatively flat until age 34, and then declines rapidly 10% per year thereafter. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Intrinsic fertility, human oocyte, natural cycle, single embryo transfer, age

The first successful human IVF was performed with natural cycle and single embryo transferred by Steptoe and Edwards in 1978 (1). Subsequently, ovarian hyperstimulation has been used to produce multiple oocytes and thus improve the pregnancy rate. It is generally accepted now that IVF requires ovarian hyperstimulation to produce many oocytes to increase pregnancy and live baby rate per egg retrieval (2–6). However, the pregnancy and live baby rate per egg rather than per cycle, that is, the average number of oocytes required to produce a baby, is a metric that in a natural cycle would give us the intrinsic fertility of the human egg without hormonal manipulation and without the confusion of statistically trying to account for untransferred frozen embryos (7, 8). Ovarian hyperstimulation in previous studies has been found to yield a live baby rate per oocyte of only about 4%–6%, and so on average more than 20–25 oocytes would be required to produce a single live baby, indicating an enormous oocyte wastage (7). However, there is a statistical problem with such a calculation. If there are untransferred remaining embryos (and there usually are), then it is impossible to determine the actual live baby rate per oocyte unless one "guesses" what the live baby rate would be from those untransferred embryos. Otherwise, the live baby rate per egg would be understated, and the number of eggs required to produce a baby would be overstated.

We originally wished to investigate the possibility of lessening IVF cost and morbidity with the recruitment of fewer oocytes, using natural cycles. That issue is still open to clinical debate. However, the main interest that evolved out of this study has become simply to answer the question, what is the baseline live baby rate per oocyte in an unstimulated cycle exclusively with single ET (the intrinsic fertility rate of the human egg), with no leftover frozen untransferred embryos? And by inference, what might be the limit of pregnancy expectation in any given month of unprotected intercourse?

MATERIALS AND METHODS

This retrospective cohort study involved routine consecutive nondonor natural IVF cycles at the Kato Ladies Clinic in Tokyo, Japan. The study was approved by the Institutional Review Board, and

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written informed consent was obtained from all patients. In a natural cycle single ET IVF program, 13,949 oocyte retrievals (ORs) yielded 14,819 oocytes (Table 1). Eliminating the occasional cycles with a leftover untransferred frozen embryo, a total of 14,185 oocytes were obtained from 13,386 cycles (Table 1). Note that even in a natural cycle, there will be occasional cases where more than one egg is retrieved "like in real life." All transfers were single embryo only. Results were divided into detailed subgroups by female age, whether fresh or frozen, and whether intracytoplasmic sperm injection (ICSI) or conventional IVF, detailing ET rate, cleavage rate, and blastocyst rate. There was no selection process. This was a uniformly Japanese population. Furthermore, pregnancy rates and live baby rates per egg were compared for blastocyst- versus cleavage-stage transfer and fresh versus frozen transfer, to determine whether there was any significant difference. This natural cycle protocol with single ET with no leftover frozen embryos would be appropriate as the best (if possible) estimate of the intrinsic fertility of the human oocyte. An oocyte was defined as a cumulus oocyte complex because in conventional IVF one does not determine whether it is a mature or immature oocyte.

To avoid any confusion for interpreting the results per oocyte, the 13,386 ORs involving 14,185 oocytes in which there were no remaining untransferred embryos were analyzed to determine the number of eggs required to produce a single pregnancy and a single live baby.

In our natural cycle protocol, the only pharmaceutical intervention was final oocyte maturation with a GnRH agonist (9, 10). Cycles were monitored by transvaginal ultrasonography, as well as measurements of serum E_2, LH, and P, which occurred from day 8 to 12. OR was scheduled when the leading follicle reached 18 mm in diameter with a concomitant serum E_2 level $\geq$250 pg/mL. Ovulation was triggered with the GnRH agonist busereline (600 μg; Suprecure, Aventis Pharma) administered in a nasal spray, followed by OR 32–35 hours later. OR was performed using a 21-gauge needle (Kitazato Medical). P supplementation was routinely used for all fresh and for all frozen ETs.

TABLE 1

Oocyte retrievals in natural cycles.

Age group (y)	Patients	OR cycles	Oocytes	Oocytes per OR
A. Before subtraction of patients with leftover frozen embryos				
<35 (21–34)	3,457	2,911	3,075	1.1 ± 0.3
35–37	3,726	3,115	3,269	1.0 ± 0.2
38–40	2,788	2,519	2,647	1.1 ± 0.2
41–42	1,652	1,737	1,865	1.1 ± 0.3
>42 (43–54)	2,400	3,667	3,963	1.1 ± 0.3
Total ≤42	11,623	10,282	10,856	1.1 ± 0.3
Total	14,023	13,949	14,819	1.1 ± 0.3
B. After subtraction of patients with leftover frozen embryos				
<35 (21–34)	2,582	2,860	2,991	1.1 ± 0.3
35–37	2,810	3,030	3,176	1.0 ± 0.2
38–40	2,035	2,334	2,449	1.1 ± 0.2
41–2	1,261	1,650	1,772	1.1 ± 0.3
>42 (43–54)	1,731	3,512	3,797	1.1 ± 0.3
Total ≤42	8,688	9,874	10,388	1.1 ± 0.3
Total	10,419	13,386	14,185	1.1 ± 0.3

Note: Values presented as n or mean ± SD, unless stated otherwise. OR = oocyte retrievals.

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ICSI was performed when less than a total of 100,000 morphologically normal motile sperm were available post-wash. Fertilized two-pronucleate zygotes were cultured individually in 20 μL of cleavage-stage medium (Sage) for 2 or 3 days, and blastocyst culture was also performed using commercially available media (Quinn's Advantage; Sage). All the embryos were cultured at 37°C under a gas phase of 5% O_2, 5% CO_2, and 90% N_2 with full humidity in water jacket small multigas incubators (Astec). Blastocyst culture, elective vitrification, and subsequent frozen-thawed ET were performed routinely. Embryos that appeared to have good quality were transferred at cleavage stage. Others were cultured to blastocyst. If a patient had poor endometrium, or slowly developing blastocysts, or if there was simply a scheduling preference, the embryos or blastocysts were cryopreserved. Whether it was a cleavage-stage transfer or blastocyst, only one embryo was transferred. A single embryo was transferred, and only cycles in which there were no remaining frozen embryos are included in the calculations of pregnancies and live baby rate per oocyte. Since this was natural cycle, almost all cycles involved only one egg and one embryo, although a very small number yielded two oocytes and two embryos, and they were excluded, as mentioned previously.

Embryo/Blastocyst Vitrification, Thawing Protocol, and ET

All embryos and blastocysts that were cryopreserved used the Cryotop vitrification method as described elsewhere (Kitazato Medical) (9–12). Thawing of the vitrified embryo consisted of an ultraquick warming in a 37°C thawing solution, and then cryoprotectants were completely diluted in washing steps; 99% of the cryopreserved embryos survived the thaw. Both fresh and frozen transfers were used to determine total live births per ET and per oocyte. A total of 6,983 transfers were performed. The majority of transfers were fresh (5,833 vs. 1,150), and the division between ICSI and conventional IVF was 4,006 ICSI, versus 2,977 conventional IVF.

Statistical Analysis

The primary data of live baby per oocyte were approximated with a logistic curve $r = 1/(a + \exp[b(t - c)])$, where r is live baby rate per oocyte and t is age in years. The coefficients were evaluated using the gradient method as implemented in statistical package R (ver. 3.2.5). The secondary data of pregnancy and live baby rate per transfer using ICSI or conventional IVF or fresh versus frozen transfer were analyzed with the chi-square test. It was important to evaluate whether there were differences between fresh or frozen transfer, between cleavage-stage transfer or blastocyst transfer, and between pregnancy and live baby rate per oocyte according to age. Very few patients underwent more than one (OR) cycle (1.3 OR cycles per patient), because if they failed natural cycle, they would usually undergo mild stimulation IVF for the subsequent cycle.

RESULTS

Outcomes Evaluation and Potential Confounders

For all ages, 13,386 successful ORs yielded 14,185 oocytes (Table 2). In the composite age group ≤42 years, only 9,874 successful ORs were performed, yielding 10,388 oocytes, with 2,127 pregnancies (fetal heart beat [FHB], 20.5%) and 1,874 live births (live baby born [LBB], 18.0%). The number of natural cycle retrievals yielding oocytes was of course higher than the number of transfers: 47.1% of ORs (6,983/14,819) resulted in an ET, 49.2% of oocytes (6,983/14,185) resulted in an ET, and 52.1% of successful retrievals (6,983/13,386) resulted in a transfer. For fresh ETs in this overall group, 36.1% became pregnant and 31.9% achieved live births. There was no significant difference between fresh and frozen transfers. There was also no significant difference between ICSI and regular IVF (Table 2). These results allowed us to group all cases simply by pregnancy rate per oocyte by age and compare cleavage-stage transfer to blastocyst transfer. The pregnancy rate per ET was not, however, the primary outcome of interest (44% for women <35, 17% for women 41–42, and 6% for >42).

The primary outcome of interest was live baby rate per oocyte (Table 3). For women ≤42 years, the overall live baby rate per oocyte was 18%, which translated into an estimated 5.5 oocytes needed to produce one baby. For women 42 years of age, every oocyte would have a 4% chance of becoming a baby, which means that for a 42-year-old woman it would require 22.7 rather than 5.5 eggs to produce a baby. The drop in intrinsic fertility per oocyte is summarized remarkably robustly in a logistic curve (Fig. 1). It requires six eggs at age 38 to make a baby, by age 40 it requires 10.9 eggs, and by age 42 it requires 22.7 eggs. There is at first a steady (almost horizontal) maintenance of fertility per oocyte, followed after age 34 with a sharp linear decline until age 43, when approximately 10% of fertility is lost every year. This decline slows down after age 43, with only 3% of original fertility remaining at age 45.

Figure 1 is a graphic logistic model that fits very well this very large amount of data on live baby rate per oocyte that is summarized in Table 3. The formula for this model is $r = 1/(a + \exp[b(\mathrm{t} - \mathrm{c})])$, where r is the live baby rate per oocyte and t is the age. The coefficients were calculated using the gradient method in statistical package R (version 3.2.5). All coefficients are significant: $a = 3.625 \pm 0.0784$, $b = 0.519 \pm 0.0404$, $c = 36.122 \pm 0.286$. This model explains virtually all observed variation in the live baby per oocyte rate, and the adjusted R^2 is 99%. The details of every single age group, under 30 and up to 50 for every year, upon which the model was based can be found in Supplemental Table 1. Supplemental Table 2 compares not just live baby rate per egg for all eggs, but also compares the live baby rate per egg by age for those who had cleavage-stage or blastocyst-stage transfers. There was only a minor difference in LBB per egg for cleavage versus

TABLE 2

LBB fresh versus frozen, ICSI versus IVF, overall results (before subtraction of cases with leftover frozen embryos).

	Fresh					Vitrified/thawed					Total	
Patient category	Transfers	CP	FHB	LBB	Pregnancy rate, % (FHB/ET)	Transfers	CP	FHB	LBB	Pregnancy rate, % (FHB/ET)	FHB	LBB
<35 (21–34)												
Total	1,693	811	756	707	44.7[a]	225	112	99	88	44.0[b]	855	795
IVF	797	421	390	375	48.9	98	53	45	39	45.9	435	414
ICSI	896	390	366	332	40.8	127	59	54	49	42.5	420	381
35–37												
Total	1,780	728	666	598	37.4[a]	250	112	98	90	39.2[b]	764	688
IVF	839	368	341	306	40.6	106	53	44	39	41.5	385	345
ICSI	941	360	325	292	34.5	144	59	54	51	37.5	379	343
38–40												
Total	1,099	378	323	254	29.4[a]	206	82	66	54	32.0[b]	389	308
IVF	526	195	164	124	31.2	62	25	20	15	32.3	184	139
ICSI	573	183	159	130	27.7	144	57	46	39	31.9	205	169
41–42												
Total	528	119	94	67	17.8[a]	200	58	43	33	21.5[b]	137	100
IVF	229	49	39	28	17.0	74	22	17	13	23.0	56	41
ICSI	299	70	55	39	18.4	126	36	26	20	20.6	81	59
Total ≤42												
Total	5,100	2,036	1,839	1,626	36.1[a,c]	881	364	306	265	34.7[c]	2,145	1,891
IVF	2,391	1,033	934	833	39.1	340	153	126	106	37.1	1,060	939
ICSI	2,709	1,003	905	793	33.4	541	211	180	159	33.3	1,085	952
>42 (43–54)												
Total	733	63	45	26	6.1[a,d]	269	43	27	13	10.0[b,d]	72	39
IVF	211	18	11	6	5.2	35	8	3	1	8.6	14	7
ICSI	522	45	34	20	6.5	234	35	24	12	10.3	58	32

Note: Values presented as n or percent, unless stated otherwise. CP = clinical pregnancy; ET = embryo transfer; FHB = fetal heart beat; ICSI = intracytomplasmic sperm injection; IVF = in vitro fertilization; LBB = live baby born.

[a] $P < .001$ across five age subgroups (χ^2). $P < .001$ for trend.

[b] $P < .001$ across five age subgroups (χ^2). $P < .001$ for trend.

[c] $P = .45$ comparing pregnancy per ET between fresh and frozen transfers among women ≤42 years (χ^2).

[d] $P = .03$ comparing pregnancy per ET between fresh and frozen transfers among women >42 years (χ^2).

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TABLE 3

Pregnancy and live baby rate per oocyte (eliminating cycles where there were "leftover" untransferred frozen embryos).

Age group (y)	Retrieval cycles	Oocytes	Total FHB	Total LBB	Oocytes/FHBs	Oocytes/LBBs	FHB/oocytes, %	LBB/oocytes, %
<35	2,860	2,991	845	785	3.54	3.81	28	26
35	953	994	267	244	3.72	4.07	26	24
36	994	1,035	248	218	4.17	4.75	23	21
37	1,083	1,147	250	226	4.59	5.08	21	19
38	781	819	170	138	4.82	5.93	20	16
39	773	815	110	90	7.41	9.06	13	11
40	780	815	102	75	7.99	10.87	12	9
41	830	888	84	59	10.57	15.05	9	6
42	820	884	51	39	17.33	22.67	5	4
≤42	9,874	10,388	2,127	1,874	4.88	5.54	20	18
>42 (43–54)	3,512	3,797	72	39	52.7	97.4	1	1
Total	13,386	14,185	2,199	1,913				

Note: Values presented as n or percent, unless stated otherwise. FHB = fetal heart beat; LBB = live baby born.

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blastocyst transfer, which is confounded by the fact that blastocyst culture was performed for the poorer quality cleavage-stage embryos. However, the difference was remarkably minor in live baby rate per oocyte cumulus oocyte complex, despite blastocysts being derived from poorer quality cleavage-stage embryos. However, for all transfers the basic integrity of this logistic curve was remarkably robust.

DISCUSSION

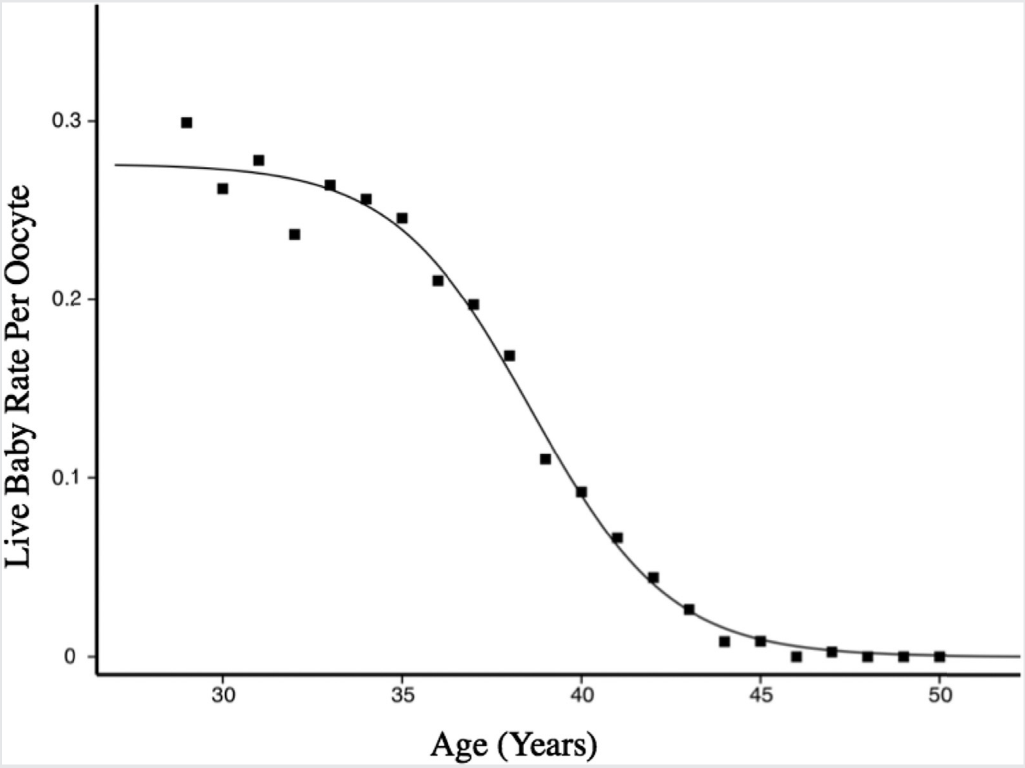
The present study investigated the viability of oocytes derived from human ovaries maintaining natural physiological function instead of undergoing hyperstimulation. The final net live baby rate per oocyte with natural cycle was inversely related to the woman's age in a very precise way when calculated for a large population of over 14,000 women. It is known that in ovarian hyperstimulation cycles, the vast majority of oocytes retrieved and the embryos transferred will not result in live births, even though many oocytes can be obtained (7, 8). This observational study accounted for confounders such as untransferred frozen embryos and the effect of hyperstimulation, and the results were remarkably robust. These findings suggest that the natural fertility of human oocytes is very low, even in women under 35 years of age, where it requires an average of 3.8 oocytes to make a baby for only a 26% live baby rate per oocyte. This correlates well with the impression of pregnancy rate per month (at least for the first few months) in fertile couples having regular unprotected intercourse (12–14). According to these data and this logistic model, fertility of the oocyte changes very little until age 34 (only 10% is lost over this whole time). However, a steep (close to linear) loss starts afterwards, with 20% lost by age 36 and 90% lost by age 42. Approximately 10% is lost every year between ages 34 and 42. This linear and steep decline slows down after age 43, with 3% remaining at age 45, 2% at age 46, and less than 1% of original oocyte potential remaining by the age of 47 (Fig. 1).

The limitations to these conclusions (aside from this just being a retrospective analysis) are the lesser amount of data for early ages under 29, so we cannot be absolutely certain that greater loss does not happen before 30 years of age. But the very robust logistic curve for the ages represented over 28 (which seems almost flat until age 34) suggests little loss during ages 20–34. But to be certain would require more data with natural cycles performed for women in their 20s. Also, it is not appropriate to make a conclusion about any clinical superiority of natural cycle to stimulated cycle IVF. Additionally, these 13,386 IVF cycles were sorted by the patient's "ID," and some patients underwent more than one cycle (1.3 OR cycles per patient). Nonetheless, this uniquely large series of natural cycle single ETs allows a convincing look at the intrinsic fertility of the human oocyte.

It is impossible to accurately calculate fertility (live baby or pregnancy) rate per oocyte if the IVF cycle is stimulated, if more than one embryo is transferred, or if there are remaining frozen or discarded embryos, which could have resulted in another pregnancy or a baby. It could be guessed what the additional number of babies would be from these unaccounted-for extra frozen embryos, or those cycles could be subtracted, as was done by Patrizio et al. (7). But the only way to be accurate is to rule out any untransferred embryos that resulted from the oocyte denominator, which is most reliable when there are very few extra frozen embryos, as in natural cycle single ET. Therefore, we have attempted to calculate the live baby rate per oocyte only in a very large number of natural cycles with no ovarian stimulation and single ET. To refine this estimate even further, the very few cycles in which there were "leftover" frozen embryos were removed from the calculation. In fact, this subtraction accounts for the small differences in the number of live babies in Table 2 versus Table 3.

For women age 37, there is still a 19% live baby rate per oocyte, for age 38, 16%, and for age 39, 11%, and so on. Thus, to estimate fertility or live baby rate per oocyte or the number of oocytes necessary to make a live baby cannot be done by lumping the patients into crude age groups. With this large amount of data, it is apparent that the fertility of the human oocyte is exquisitely sensitive to the very specific age of the woman. The logistic model, which fits the data very robustly, begins with little change at first, and then at

FIGURE 1



Fertility of the human oocyte related to age. We approximated the data with the simple logistic curve $r = 1/(a + \exp[b * (t - c)])$, where r is live baby rate per oocyte and t is age in years. The coefficients were evaluated using gradient method as implemented in statistical package R (version 3.2.5). The quality of the fit is very high and explains 99% of observed variation. The black squares depict empirical values (actual observations).

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some point (in this case age 34) begins a rapid linear descent; the system is then exhausted and stabilized at a very low level by age 44. The coefficients are very stable. Coefficient b ($b = 0.519$) characterizes the rate of decline. Coefficient a ($a = 3.625$) characterizes the early years. Initial fertility is $1/a$, arbitrarily set at age 20. Over age 45, fertility according to this model is nearing zero. There was actually one live baby at age 47 and six live babies at age 45. Thus, the intrinsic fertility of the human oocyte, based on natural cycle IVF, is exquisitely related to age and is predictable in a larger population by this simple logistic formula.

The usual pregnancy rate per month in fertile couples with unprotected intercourse in the first few months of trying has been assumed to be about 20%–25% (12–15). Remarkably, that is indeed the pregnancy rate per oocyte that we found with oocytes from natural cycle IVF with single ET. The accepted average rate of live baby per oocyte for IVF has been about 4%–6% (7). From this natural cycle study the human oocyte without stimulation has a 26% fecundity rate for women $<$35 and 18% for $\leq$42. The live baby rates per oocyte from the literature were 5.5% for women under 35, 6.5%–7.6% for women 35–40, and 2.9% for women 41–42 (7). This is dramatically lower than the live baby rate per oocyte in our 14,185 natural cycles of IVF. This does not mean that natural cycle IVF is preferred, because the greater number of eggs in a stimulated cycle can compensate for a lower baby rate per egg. However, aggressive ovarian stimulation is likely to yield many oocytes that will not result in a live baby.

One might argue that the fertility of Japanese eggs might differ from other ethnic groups or races. However, registries show no difference in the quality of eggs from Japanese women compared with those from American women (16–18). In addition, it is well documented that the age of menopause and ovarian reserve does not differ for Japanese as opposed to other populations (19).

Previous reports by necessity were unclear on this metric, where the pregnancy or live baby rate per oocyte was based on ovarian stimulation IVF cycles, with leftover embryos, and thus a predictive model could not be developed and the live baby rate per oocyte might be underestimated (20–24). In frozen oocyte reports, it was assumed that about 6.5% of oocytes would result in a live baby, which would mean a woman would need about 32 oocytes frozen to be likely to have a baby and about 40 oocytes to have a 97.5% chance of having a baby. That is much less than what our report indicates to be the intrinsic fertility of the human oocyte, possibly indicating a negative effect of hyperstimulation. In the official American Society of Reproductive Medicine committee report of 2014, it is warned that fertility begins to decrease at age 32 and rapidly decreases at age 37. However, the basis of such a conclusion is only indirect, with no specific age-based model (25). The model we are presenting is a very specific and robust age-related model of the decline in the intrinsic fertility of the human egg, which correlates well with the general epidemiologic view of the decline in fertility of women as they age (12–15, 22).

Interestingly, the very act of IVF may increase the intrinsic fertility of the human oocyte, since live baby rate per oocyte declines little in our study until age 34, even though we suspect natural fertility does decrease in a woman's 20s. However, it is still safe to infer that the intrinsic fertility per oocyte, in the IVF model at least, does follow this robust logistic downward curve after age 34. It is interesting to note that, even though blastocyst transfers were derived from lesser quality cleavage-stage embryos, nonetheless blastocyst transfer was almost equivalent to cleavage-stage transfer pregnancy rate per egg. There is, of course, an increase in blastocyst aneuploidy with aging, similar to the decline in live baby rate per age (26). There is also a similar curve for the impact of age on live baby rates per embryo in stimulated cycles (27). However at age 40, 42% of human blastocysts are euploid. Yet at age 40 only 6% of human oocytes are capable of making a baby. At age 44, 12% of human blastocysts are euploid, but only 0.8% of human oocytes can make a baby. Therefore, aneuploidy alone cannot fully explain the intrinsic fertility of the human oocyte.

Conclusion

The results of natural cycle single embryo IVF transfer in a very large population allows an observation of the likely intrinsic fertility of the human oocyte. The extraordinary decline in pregnancy rate per oocyte related to age should encourage a wider awareness among women of the natural decline in fertility as their age increases, albeit at a time of their life when they still are young by modern standards. This study also validates that the most important cause of decreasing fertility after age 35 is the intrinsic fertility decline of the oocyte, which cannot explain the clinical decrease in fertility from the teen years to age 35 (12–14).

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