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Egg Freezing and the Biological Clock

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There are seemingly endless—and conflicting—statistics quoted regarding fertility and how hard (or easy) it might be for a woman to get pregnant. But like most statistics, the key to their real meaning can only be found in context. For example: asking the question "How hard is it to get into law school?" isn't really helpful, and can't be answered intelligently, without the relevant context (GPA, LSAT score, etc). When it comes to fertility, that important context is *age*.

When seen through the lens of age, infertility is actually a universal disease, with 100% prevalence, affecting every single woman—eventually. Simply put, every woman has a certain population of healthy eggs, and as she ages, this group of eggs declines in number and, eventually, runs out. It's not a question of *who* might be impacted or *if* they will be; it's simply a question of *when*.

While almost all women have a general awareness that having children is easier when "younger" compared with "older," most women have never been provided a detailed understanding of this topic. How old is "old"? What *exactly* happens inside a woman's body to make it more difficult to get pregnant? How does this relate to risk of miscarriage? What about Down syndrome or other genetic problems? And finally: how can a better understanding of the biological clock be harnessed to help do something about it?

The goal of this white paper is to capture the most up-to-date scientific understanding of the biological clock, one that sits at the intersection of reproductive biology, genetics, and assisted reproductive technology. By laying bare the inner workings of the biological clock, it should become clear why egg freezing is an option that more young women should consider as a way to effectively manage their reproductive choices.

What is the Biological Clock?

There is no question that a woman's ability to conceive, her "fertility potential," is the collective product of an interplay of many factors, of which the egg is just one. But the availability of healthy eggs always serves as the starting point of a woman's ability to conceive, and is the factor that underlies all other variables. Why? Because *every* woman's fertility potential is limited, to some extent, by the **quantity** and **quality** of her eggs. In the past few decades, the scientific understanding of human reproductive biology has demonstrated that there are two parallel degenerative processes—quantity and quality—that are linked to the "biological clock." Let's explore them in depth, one at a time.

Quantity

All women are born with a finite number of eggs; this is the group of eggs from which a woman "draws" for the duration of her reproductive lifespan. (While some recent research has suggested the possibility of stem cells in the ovary that are capable of replenishing the egg supply, these results are quite controversial and are not clinically relevant, at least not now.)

The most commonly cited statistics regarding egg quantity, endorsed by the American College of Obstetricians and Gynecologists (ACOG) as well as the American Society for Reproductive Medicine (ASRM), describes a typical woman having 1–2 million eggs at birth, 300,000–500,000 at puberty, 25,000 at age 37, and 1,000 at age 51, the average age of menopause in the US.[1]

And recently, a highly sophisticated and impressive analysis used data from eight different studies spanning almost 60 years of research to create a robust mathematical model of egg supply. This analysis found that an average woman has just about 300,000 ovarian follicles per ovary at birth; this reserve declines to about 65,000 (22% remaining) follicles by age 25, 36,000 (12%) at age 30, 16,000 (5%) at age 35, 9,000 (3%) at age 40, and 3,000 (1%) or less by age 45.[2]

Age	Egg supply remaining
Puberty	50%
25	22%
30	12%
35	5%
40	3%
45	1%

It is important to note that these numbers are averages; there is a very wide range of egg supply for any individual woman at a given age. For example, in the combined analysis, while the *average* number of follicles per ovary is 300,000 at birth, this number can range from as high as 2.5 million or as low as 35,000 per ovary in any individual woman.

So how can a woman know where she stands when it comes to her egg quantity? In the past couple of decades, several approaches have been developed, focused primarily on reproductive hormone testing and ultrasound imaging of the ovaries. Most experts would agree that the single most informative data point is a hormone called Anti-Müllerian Hormone, or AMH. The AMH level is a direct reflection of the population of eggs remaining.

In one recent study looking at AMH levels in almost 3,000 reproductive-aged women, the median AMH levels were 5.4 ng/ml at age 25, 3.5 ng/ml at age 30 (35% reduction relative to age 25), 2.3 ng/ml at age 35 (57% reduction), 1.3 ng/ml at age 40 (76% reduction), and 0.7 ng/ml at age >43 (87% reduction).[3]

Age	AMH level (ng/ml)
25	5.4
30	3.5
35	2.3
40	1.3
>43	.07

Confirming the idea of averages rather than universal values, in this study too, there was a wide variation of AMH results: 10% of women at age 40 had an AMH of 3.7 or higher (similar to the average 30-year-old), but 10% of women at age 30 had an AMH of 1.2 or lower (similar to the average 42-year-old!).

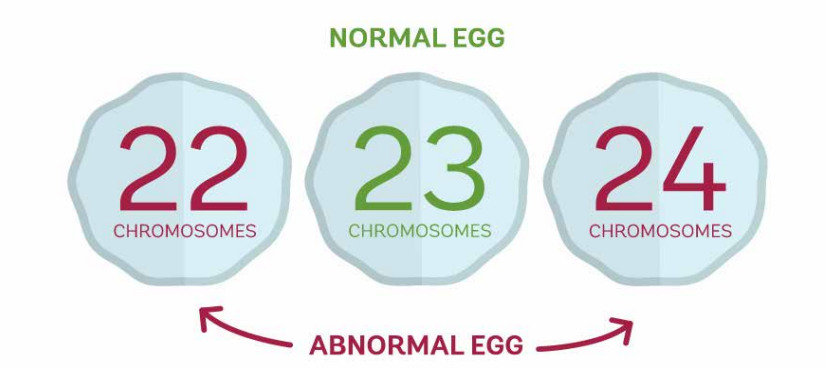
Quality

While the reduction in quantity of eggs is a hugely powerful driver of the biological clock, it is only half of the story. The decline in **quality** of eggs with age is equally powerful, and as we will see below, egg quality is actually the *primary* driver of the decline in natural fertility with age.

Eggs and sperm (together known as germ cells, or gametes) are biologically unique, fundamentally different from other cells in the body. Gametes contain only one half of the genetic material relative to all other cells, since their role is to combine with a gamete of the opposite sex (via fertilization) to re-assemble a full genetic complement for a new human being.

Gametes themselves are created via a process of cell division that results in a splitting of the genetic material, called meiosis. Unlike sperm cells, which are produced on an ongoing basis throughout a man's life, eggs are formed during a process of meiosis that's initiated before birth and is completed for each egg, one by one, at the time the eggs are ovulated. This happens throughout the woman's reproductive life—sometimes as many as 50 years after the eggs were first created!

But the process of meiosis is imprecise, and errors in the splitting and distribution of the genetic material occur with an increasing frequency as the egg (or more simply put, the woman herself) gets older. These errors in the distribution of genetic material are called aneuploidy—having too much or too little genetic material.



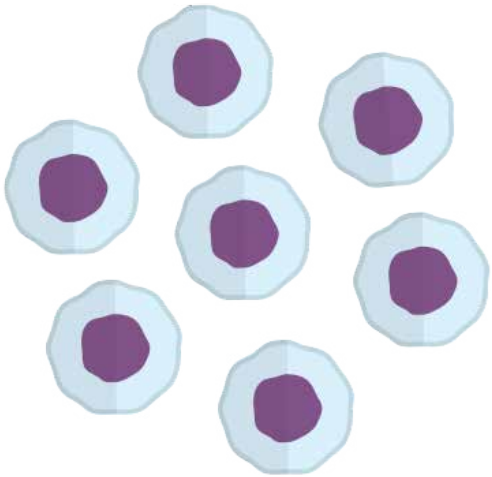
The concept of egg quality is often perceived to be some amorphous parameter of how generally healthy the egg is, ranging on a spectrum from "very healthy" at young ages to "not very healthy" at older ages. It is also commonly thought that maintaining a healthy lifestyle will at least partially or indirectly preserve egg quality. But the best science demonstrates that this paradigm for egg quality is incorrect. The reality is that egg quality is actually a binary issue. There are only two possibilities for any individual egg: either "normal" (having the right amount of genetic material, also called euploid) or "abnormal" (aneuploid); when it comes to egg quality, there is no spectrum of "very healthy" vs. "pretty healthy" vs. "not so healthy."

Furthermore: when we talk about a woman's egg quality in general, we are talking about the expected percentage of her total population of eggs that are normal. For better or worse, this is purely a function of age, as we described above. Young women have mostly normal eggs (though they already have plenty of abnormal ones), and older women have mostly abnormal eggs (though they still have some normal ones). And importantly: **in stark contrast to the "wide range of normal" we see when it comes to egg quantity, the impact of age on egg quality is consistent and universal**. In other words: women in their 20s will have mostly normal eggs, even if they are not healthy people in general (smokers, overweight, etc). And women in their 40s will have mostly abnormal eggs—no matter how healthy a lifestyle they maintain.

The most direct and convincing evidence of the correlation between age and aneuploidy comes from the in vitro fertilization (IVF) lab, where this subject can be studied in a controlled environment under the microscope. In the largest study of its kind published to date, over 15,000 fertilized eggs (embryos) were tested for aneuploidy, and the frequency of aneuploidy was correlated with the age of the woman producing the egg. In this study, about 25% of embryos created by women aged 25–30 were genetically abnormal; this percentage gradually increased to 35% in women age 31–35, 45% in women ages 35–37, 60% in women 38–40, 80% in women ages 41–43, and over 80–90% abnormal in women age 44 and older.[4]

Ages	Number of genetically abnormal embryos
25–30	25%
31–35	35%
35–37	45%
38–40	60%
41–43	80%
≥44	≥80–90%

One Egg Per Month



Women are naturally hormonally programmed to allow just one egg to grow, mature, and be released ("ovulated") each month. That one egg represents the one chance for pregnancy that exists in that particular menstrual cycle. It's important to note that this "one egg per month" rule is true regardless of whether a woman is younger and/or has a very robust egg supply, or is older and/or has a low egg supply. Without the influence of fertility medications, women routinely get one egg to work with every month—no more, no less. (This system starts to fail when the ovarian reserve is almost completely depleted, at which point the system of regular ovulation falters, leading to irregular menses).

It's equally important to re-emphasize that any individual egg—regardless of the age of the woman—is either normal or abnormal; and a normal egg from a 40-year-old woman is expected to perform similarly to a normal egg from a 25-year-old woman. The difference between the egg quality of the 25-year-old vs the 40-year-old is just a matter of the *statistical likelihood* of any given egg being normal.

It might seem obvious, but it is worth stating explicitly, that an abnormal egg does not provide the potential for conceiving a healthy pregnancy. So what happens to all the unhealthy eggs?

- **Absence of pregnancy**: Failure of fertilization—or fertilization with failed implantation (attachment to the womb)—both lead to absence of pregnancy. This represents the vast majority of unhealthy eggs.

- **Miscarriage**: In a minority of cases there will be successful implantation—and therefore pregnancy—but shortly thereafter, programmed cessation of fetal development will occur, clinically manifesting as miscarriage.

- **Genetically abnormal pregnancy**: In the least common scenario, successful implantation and continued development of an abnormal fetus will occur, clinically manifesting as a genetically abnormal pregnancy. The most common outcome of this is Down syndrome (formally known as trisomy 21), in which there are three copies of chromosome #21 as opposed to the normal two.

Putting It All Together

Now that we've clearly defined the parallel "gears" of the biological clock—egg quantity and egg quality—we can use those principles to understand more precisely how and why it becomes increasingly difficult for a woman to conceive a healthy pregnancy with increasing age. By integrating those concepts with the "one egg per month" rule, we can now reach the following conclusions that represent the fundamental ideas of the biological clock:

1. Natural fertility declines with age.

The chance of achieving pregnancy in any given month is directly and inextricably tied to the likelihood that the one egg which is ovulated—selected biologically at random—will be genetically normal. If the egg is abnormal, the most likely outcome will be absence of pregnancy (either from failure to fertilize or failure to implant). It should be clear then that older women—who have a higher percentage of abnormal eggs—will have a decreased chance of pregnancy per month relative to a younger woman.

While specific statistics on the correlation between age and natural fertility are not easy to obtain—especially from contemporary societies where contraceptive use is widespread—the most comprehensive analysis of this subject available combined data spanning four centuries (1600–1950) from seven different populations worldwide. Those groups were selected as they rarely practiced contraception, premarital sexual activity was rare, and they kept accurate birth records. In the combined analysis, the risk of childlessness was 6% for women who married at age 20–24, 9% at ages 25–29, 16% at ages 30–34, 30% at ages 35–39, and 64% for those who married at ages 40–44.[5]

Contemporary data, the most comprehensive of which is published by the National Center for Health Statistics (part of the Centers for Disease Control), strongly confirms this trend. Data from almost 23,000 women in the US gathered 2006–2010 shows the incidence of impaired fecundity (defined as "physical difficulties getting pregnant or carrying a pregnancy to live birth") amongst women who have never been pregnant before to be 6% at ages 15–24, 14% at ages 25–29, 17% at ages 30–34, 27% at ages 35–39, and 30% at ages 40–44.[6]

Another contemporary study compiled data from women aged 30–44 trying to conceive between 2008–2015. In this study, for women who have never been pregnant before, the average chance of pregnancy per cycle was 17–19% for women ages 30–33, decreasing to 11–12% per cycle for ages 34–37, 5% per cycle at ages 38–39, and just 3% per cycle at ages 40–44.[7]

2. Miscarriages and genetically abnormal pregnancies increase with age.

The increasing percentage of abnormal eggs as a woman gets older, translating into an increasing likelihood that the randomly selected "egg of the month" will be abnormal, leads to a higher likelihood that in the event pregnancy *does* occur, the outcome will be a miscarriage or genetically abnormal pregnancy.

One large study analyzed over 1.2 million pregnancies in Denmark over a 15-year period. The incidence of miscarriage was approximately 11% for women ages 20–24, 12% for women ages 25–29, 15% for women ages 30–34, 25% for women ages 35–39, 51% for women ages 40–44, and 93% for women age 45 or older.[8] **Importantly, numerous studies have demonstrated that the majority of miscarriages are caused by genetic abnormalities in the fetus**.[9, 10]

With regard to genetically abnormal pregnancies, like those that result in Down syndrome, the dramatic association with increasing maternal age has been consistently reported as early as the 1930s.[11] The American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine's most recent Practice Bulletin on this subject cites data demonstrating that compared to the risk of genetically abnormal pregnancy at age 25 (which is 1 in 475), the risk increases almost three-fold by age 35 (1 in 178), eight-fold by age 40 (1 in 62, or nearly 1 in 6), and twenty-six-fold by age 45 (1 in 18, or more than 1 in 5).[12]

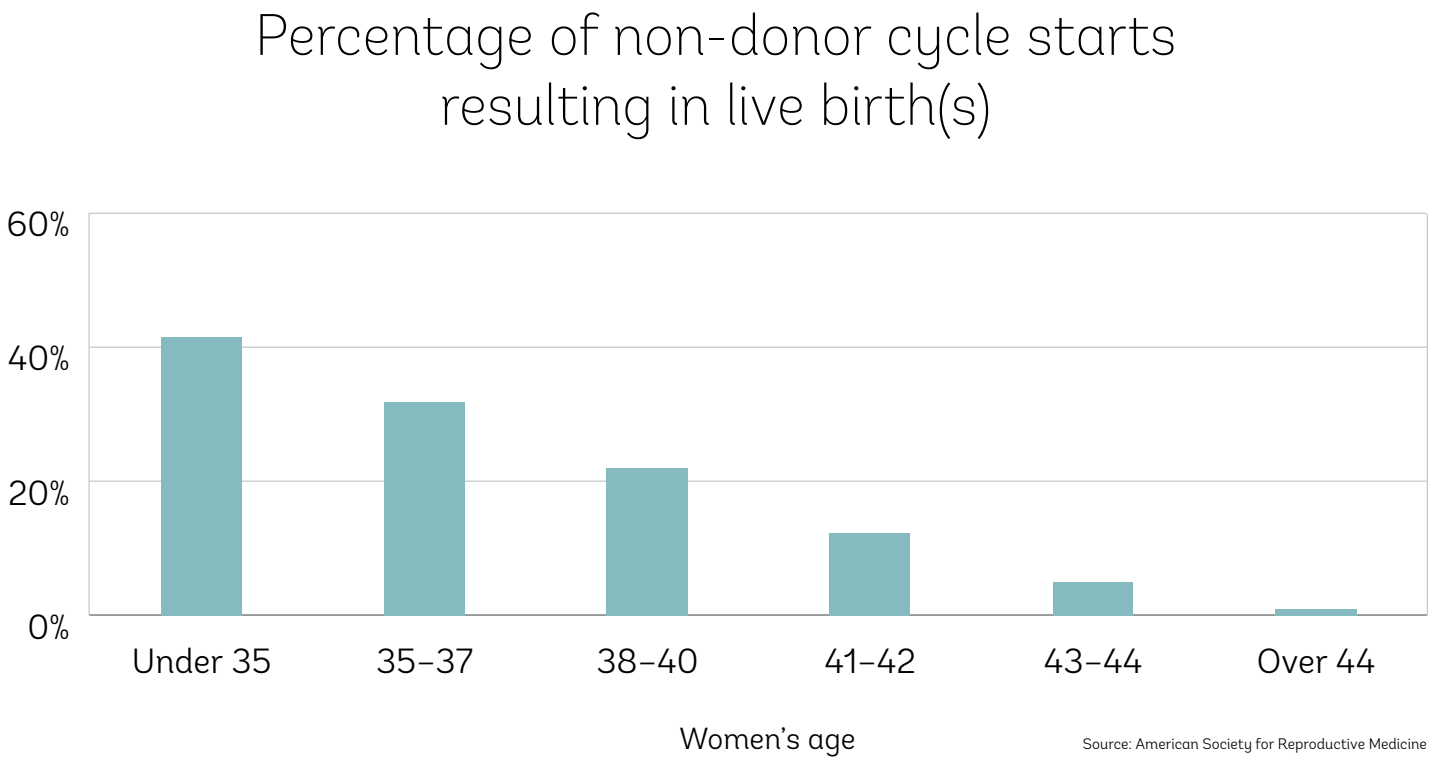
Age	Risk of genetically abnormal pregnancy
25	1 in 475
35	1 in 178
40	1 in 62
45	1 in 18

What About IVF?

Many women have a general understanding of the challenges of achieving a healthy pregnancy naturally at an older age, but are under the impression that women who have difficulties conceiving can, if necessary, rely on fertility treatments such as IVF to "rescue" their reproductive options.

Unfortunately, this just isn't the reality. While fertility treatments can dramatically improve the chances for an infertile woman or couple to conceive a child, with IVF being the most powerful fertility treatment available, even IVF is not an effective treatment for infertility due to "reproductive aging."

National statistics on all IVF performed in the US are tracked by the Centers for Disease Control and Prevention (CDC) as well as the Society for Assisted Reproductive Technology (SART), and the results are published annually online. According to SART's 2014 statistics (the most recent available), just over 101,000 IVF cycles were initiated in 2014. For women 34 or younger, the chance of a live birth resulting from an IVF attempt was 49%; this fell to 38% for ages 35–37, 24% at ages 38–40, 12% at ages 41–42, and just 4% at age 43 or older.[13] In other words, for women younger than age 35, the chance of IVF success was 1 in 2, whereas for women 43 or older, the chance was 1 in 25! Clearly, IVF does not represent a reliable back-up plan for women who defer childbearing to their late 30s or 40s.



Quantity vs. Quality Revisited

We mentioned earlier that, regardless of a woman's egg supply, she will naturally ovulate exactly one egg per month—not more, not less. This is the reason that the decline in *natural* fertility is actually driven primarily by egg quality (i.e. the chance that this month's egg is a healthy one), not egg quantity.

The arena where egg quantity takes a much larger role is in assisted reproductive technology like IVF. Women with a low egg supply will produce fewer eggs during treatment, whereas women with a more robust egg supply will produce more eggs during treatment. This difference translates directly into chance of success—that is, the likelihood that IVF will result in a healthy baby.

For example, in one recent analysis of over 250,000 IVF attempts in the US, women who produced five or fewer eggs had a pregnancy rate of 17%; women who produced 6–10 eggs had a pregnancy rate of 32%; women with 11–15 eggs had a 39% pregnancy rate, and women who produced more than 15 eggs had a pregnancy rate between 40–45%.[14]

	Egg Quantity	Egg Quality
Variability amongst women at a given age	High	Low
Testing available for individual results	Yes (AMH, antral follicle count)	No
Affects natural fertility	Usually no	Universally yes
Affects IVF success	Yes	Yes
Affects egg freezing	Yes++	Yes

Scientific Advances: Reducing Age-Related Infertility by Freezing Younger Eggs

If you open a textbook of reproductive medicine and turn to the chapter on reproductive aging, the ultimate "treatment strategy" for older women is donor egg IVF. Donor egg IVF entails creating an embryo in the laboratory using an egg from a younger woman (the egg donor), and then transferring the resulting embryo into the older woman's womb. **In striking contrast to the dramatic relationship between age and IVF success mentioned above, donor egg IVF success remains effectively equal—regardless of the age of the woman trying to conceive—*as long as the egg is from a young woman.***

To wit: there were almost 20,000 IVF attempts in the US in 2013 using donor eggs; when the woman trying to conceive was 34 or younger, the chance of live birth was 46%. For women 35–37, the chance of live birth was exactly the same: 46%; it was essentially unchanged (45%) for women 38–40, and nearly equivalent (42%) for women 40 or older.[15]

This is where egg freezing enters the picture.

The downside of donor egg IVF is that while the older woman finds a wonderful opportunity to carry a pregnancy and become a biological mother, she will not be the *genetic* mother of her child. Without a time machine that could somehow obtain eggs from her "younger self," the genetic motherhood is unavailable.

But for women who freeze eggs at a younger age, they essentially prepare for the possibility of *becoming their own egg donor*. Cryopreserving eggs halts the process of metabolic and genetic deterioration, meaning that those eggs from her "younger self" will be available—if needed—at an older age. And therein lies their power.

How Many Eggs?

Just like with IVF, when it comes to egg freezing, we know that producing and freezing a larger number of eggs is *directly* associated with an increased chance of success. In one of the largest published studies analyzing outcomes from almost 1500 women who froze their eggs at age 35 or younger, the chance of live birth increased from 15% for women who froze just 5 eggs, to 61% for women who froze 10 eggs, and 85% for women who froze 15 or more eggs.[16]

Number of eggs frozen	Chance of live birth*
5	15%
10	61%
15	85%

*For women who froze their eggs at age 35 or younger.

So what's the takeaway?

We now understand the biological clock from a scientific perspective. We've examined the relationship between quantity and quality of eggs and a woman's age. We've demonstrated—through a review of the scientific literature—that a woman's natural fertility declines with age. We've explained that the older the woman, the greater the chance of a randomly selected egg being abnormal—making it increasingly difficult for a woman to conceive a healthy pregnancy as she gets older.

And, finally, we explored the way that egg cryopreservation (freezing) can allow a woman to preserve her young, healthy eggs for use later.

With this understanding in hand, the conclusion becomes clear: more young women should consider egg freezing as a way to effectively manage their reproductive choices.

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