

MALE FERTILITY, SPERM TESTING,
AND SPERM FREEZING

The Future of the Fatherhood Industry

2019

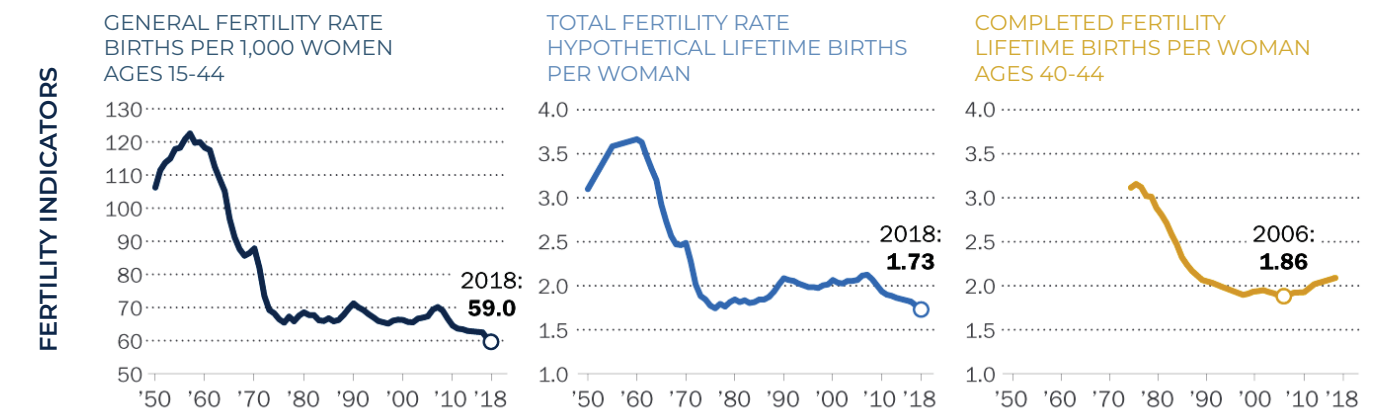
 **LEGACY**

Fertility Rates Worldwide Have Dropped 50%

For a population to remain stable from one generation to the next, the *replacement rate* is 2.1 children/women. Globally, that rate has declined from ~5 children per women in the 1960s, to just 2.43 in 2017 .

The CDC noted in July 2019 that the US fertility rate fell to an ‘all-time low’ of 1.72 children per women. Meanwhile, England saw its lowest birthrate since records began, down almost 50% since its peak in 1947. Western Europe has the lowest total fertility rate in the world, at just 1.6 children/woman.

U.S. fertility hit all-time low in 2018 ... and 2006



It's Not You, It's Median

The increased age of men and women in heterosexual relationships has a **compounding, negative effect on their ability to have children.**

Since the 1970s,

- The median age has increased **10 years**, from 28.1 to 38.2
- The median age of marriage has increased **6.5 years** for men, from 23 to 29.5
- The median age of marriage has increased **6.6 years** for women, from 20.8 to 27.4

In fact, for the first time, more women are giving birth in the 30-34 age range than in the 25-29 age range. This signals a significant shift in how men and women think about family planning today.

Fertility is not a “Women’s Issue”

Because infertility is such a hidden topic, most aren’t aware of how prevalent it is. **About 1 in 7 couples are infertile.**

- Within 6 months, 20-35% of couples fail to conceive
- Within 12 months, approximately 15% of couples fail to conceive
- Infertility is defined as “the inability to conceive after 12 months of unprotected intercourse”, or just 6 months if the women is over 35

Despite preconceptions, **men are equally likely to be the cause of infertility as women.** About 1/3rd of infertility is caused by the man, about 1/3rd of infertility is caused by the woman, and in the remaining cases, it is caused by both, or is unexplained.

The Male Fertility Crisis



Male Fertility Has Declined 50%-60%

In the summer of 2017, a meta-analysis of 185 studies was released; it showed that in the past 40 years, sperm counts in the Western world declined **59.3% while sperm concentration dropped 52.4%**. On average, sperm count is dropping 1% every year, with no evidence of levelling off.

“ This study is an urgent wake-up call for researchers and health authorities around the world to investigate the causes of the sharp ongoing drop in sperm count. ” – Dr. Hagai Levine

This matters because sperm count and concentration are related to both time to pregnancy and pregnancy rates and are predictors of conception. This marked a defining moment in the fertility world, proving that men were a part of the fertility equation and needed a solution to test, improve, and even freeze their sperm at a young age.

What's Causing the Decline?

Chemicals: The authors of that same study found that the sperm count decline was less significant in non-Western countries, suggesting that some of the decline could be attributed to chemicals found in our lives, like BPA's and phthalates, which are found in plastics.

Notably, dogs living in human households have faced a similar decline, decreasing 30% over a 26 year period. A 2016 study published in Nature suggested the presence of environmental chemicals may have caused that decline.

Cell-phone radiation: The jury is out on this one, although the Legacy team is paying close attention. The Guardian posted a damning report suggesting the industry is “orchestrating a global PR campaign aimed at misleading not only journalists, but also consumers and policymakers about the actual science concerning mobile phone radiation.” Just one week later in a subsequent article, David Grimes argued that the research was misrepresented.

“ The leading hypothesis is that there has been a vast increase in the number and volume of chemicals that have entered the environment during the last 50 years. ”

– Dr. Jorge Chavarro, Harvard Medical School

Lifestyle factors: As a society, we are eating more, drinking more, sitting more, and exercising less. These general factors are making us less healthy, and by extension, less fertile. Even the prevalence of mobile and laptop screens at night can negatively affect sperm production by disrupting the circadian rhythm, which is detrimental to sperm production. Because fertility is closely correlated with overall health, many techniques to improve your health will also improve your fertility.

“ The genetic quality of sperm from younger men, in terms of new mutations, is generally much better than that of older men. ”

– Dr. Allan Pacey

Legacy recently conducted a survey of over 411 men and women aged 21-35.



Over 85% had some awareness that sperm quality has declined in the past 40 years, but less than 50% were somewhat or very concerned about the decline



Almost 70% did not know that age impacted sperm health, and only 10% of respondents were concerned about the impact of aging on their sperm



About 50% of respondents were concerned about the fact that 1 in 7 couples will face infertility



Only half of the respondents were somewhat concerned or very concerned about the generational sperm decline

There is a lot of work to be done to change the conversation around fertility and demonstrate that sperm quality will impact both parties when trying to conceive.

The Genetic Risks of Older Fathers

A recent study of Icelandic men, published in Nature, showed that a **man transmits 2 additional mutations to his child each year he gets older.**

While women are born with their eggs, men continuously produce sperm using a process that is not perfect at copying DNA. As a result, sperm cells divide more frequently, with each division creating the potential for mutation. In fact, fathers pass on **4 times as many new genetic mutations as mothers.**

A comprehensive assessment of parental age and psychiatric disorders showed that “the offspring of older fathers were at an increased risk of schizophrenia and related disorders, mental retardation, and autism spectrum disorders.”

The Size of Your Risk Matters

In March 2019, the New York Times reported that since the 1970s, the percentage of births to fathers aged 40 or older in the US has doubled, and by 2015 they accounted for 9% of births.

A 2018 study of more than 40.5 million births in the United States revealed that, with advanced paternal age (45+) relative to ages 25-34, a baby could potentially face risks including:

- 41% more likely to have low birth weight
- 34% more likely for the mother to develop gestational diabetes
- 18% more likely to have seizures
- 15% more likely to have a low Apgar score (measures health of newborns against mortality)
- 14% more likely to be born prematurely

A rigorous study of over 130,000 men also found that fathers over **40 were six times as likely to have children with Autism Spectrum Disorder (ASD)**

Why Test Your Sperm?

Sperm & the SATs

Getting a sperm analysis is like taking a standardized test: while your scores will cluster around an average, there is a degree of variability from one sample to the next.

Further, sperm quality measures aren't perfectly predictive of fertility. While "a man with no sperm can't father a child through intercourse, researchers have found some men with relatively low sperm counts can conceive — and others with more abundant sperm can't".

A Sperm Analysis Should Test for These 4 factors:

1. **Volume:** How much semen is being produced?
2. **Count/Concentration:** Total Amount of Sperm (Count) and Sperm/mL (Concentration)
3. **Motility:** The percentage of moving sperm in a sample
4. **Morphology:** The percentage of sperm with normal size, shape, and appearance

In addition to other factors including but not limited to the presence of white blood cells.

Motility is critical for determining Total Motile Sperm Count (TMSC = Volume x Count x Motility), which is deemed by some specialists as the single most important factor in predicting a man's ability to conceive. A quality sperm analysis will include a motility test.

Of the 4, morphology is the most debated due to its limited specificity in the diagnosis of infertility. Nevertheless, abnormally shaped sperm can contain abnormal DNA, which can lead to genetic abnormalities in offspring, and morphology can highlight certain genetic disorders.

Notably, it is fairly normal for a man to be below the normal range for one or more of these factors. A recent study of 2,500 Swiss men between the ages of 18 and 22 found that almost two thirds (62%) had one or more factors below the normal ranges.

“Treat your body like a temple. Pretend you're training for a race. You need to take great care of yourself. Eat well. Sleep well. Reduce your stress. Exercise. Eat a heart-healthy diet. Your sperm count can be a biomarker of your health.”

— Dr. Paul Turek



The At-Home Option



Legacy's mail-in kit bridges both these worlds by providing men the privacy and comfort of producing a sample from home, clinical analysis at a leading andrology center, as well as provide men the option of freezing their sperm for future use.

Hospitals vs. Clinics vs. Mail-In vs. At-Home

The traditional option for men has been to book an appointment at a hospital or clinic, show up during working hours and answer a doctor or nurse's intimate questions about their sexual health. At that point, they are escorted to a small room with a small couch and pornographic materials intended to help a man masturbate and produce a sample in the clinic.

For most men, this process is suboptimal. And while advances in at-home testing have improved the quality of at-home sperm analysis, they cannot provide the level of detail – or technical know-how – that you can get at a fertility clinic.

The buffering medium

The Kit includes a buffering medium, which has a unique formula produced at the University of Illinois Chicago and serves as a preservative for sperm, effectively extending its life for 24 hours or longer with minimal reduction in quality.

For the purposes of analysis, there will be some decline in motility during transport due to the buffering medium, averaging about 10-15% depending on the quality of the sample, although for the purposes of analysis, the team can extrapolate initial motility based on hours in transit.

For the purposes of freezing, the percentage of motile sperm is less important as Intracytoplasmic Sperm Injection (ICSI) is used to identify a healthy, motile sperm that is selected and injected directly into eggs obtained via IVF.

How does the Legacy kit work?

Legacy's analysis is overseen by Dr. Gail Prins, who has deep expertise in the field of preserving sperm for transport and cryopreservation and is considered one of the pioneers of the industry.



When a client places an order for a Legacy Kit, it arrives the next morning, or on a date of their preference. They then produce the sample in the afternoon, and we arrange for it to be shipped overnight to our partner clinic, typically arriving within 18 hours. When it arrives at the clinic, the sample is tested, analyzed, and then frozen for future use.

For redundancy, once frozen the sample is divided into two geographies, and then further divided into two tanks within each geography.

The Legacy Advantage

Protecting Against Long Tail Risks

Any product that affects or preserves someone's fertility must be treated with the utmost responsibility. Legacy is FDA®-registered and focuses on its 3 core values of Privacy, Quality, and Security.

Privacy: Whether you are a Legacy customer is your decision to share, and your data should belong exclusively to you. We do not and will not sell your data. Our client list is undisclosed and discretion remains at the core of our values. Your data is stored on encrypted servers, shared via encrypted transmission devices, and is not shared with any third parties without expressed authorization in accordance with the strictest privacy laws.

Quality: Our clients remain with us for decades, not months. We ensure deposits are stored under the most stringent requirements, including constant and precise temperature monitoring, natural disaster protection. Our partners have been carefully screened to meet the Legacy Standard and our work is overseen by a world-class advisory board of the leading male fertility experts.

Security: For many of our clients, physical security is paramount. We are the only company to implement Multi-Geography Cryogenic Storage (MGCS) to ensure redundancy. We also take extensive steps to ensure the security of your assets to the greatest extent possible, including 24/7 security. The exact storage location of your assets is only shared with you and individuals you authorize.

Why Freeze?

The benefits of sperm-freezing can last literally a lifetime; once a man tests and freezes his youngest and healthiest sperm, that sperm can be used years later in procedures such as IUI or IVF.

Scientists believe that sperm can be frozen indefinitely with no loss in quality.

In March 2019, scientists decided to un-freeze a ram's sperm that had been frozen back in 1968. Once thawed, the researchers were excited to see that "50 years of storage at -196C had seemingly no ill effects on the health of the sperm." The sperm was then used to artificially inseminate 56 ewes, 34 of which eventually gave birth. The pregnancy rate was 61%, which is almost on par with the 59% pregnancy rate for sperm that is frozen for just 1 year.

This research is also good news for humans as well. Cancer patients who may lose their fertility due to treatments now can be assured that if they freeze their sperm, they have a chance of fathering children later in life.

While our generation is facing an unprecedented decline in fertility, we also face an array of solutions to take reproductive health into our hands, and social norms around fertility are quickly changing.

Legacy aims to rebalance the responsibilities of family planning and change the outdated view that fertility is a "women's issue".

For men, our goal is to create a product that is so convenient, private, and affordable that it becomes a 'no-brainer' for every man to freeze his sperm when he reaches his 20s.

Legacy Aims to Change Views Around Fertility

Legacy's Advisory Board includes the following experts:



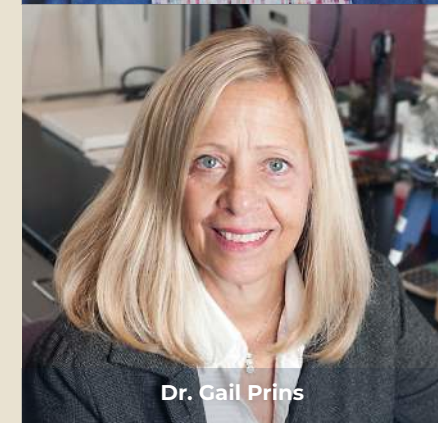
Dr. Marcia Inhorn



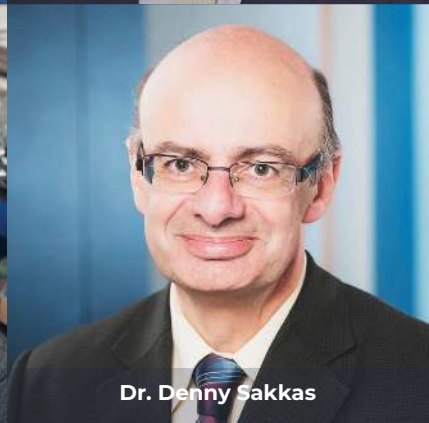
Dr. Francisco Arredondo



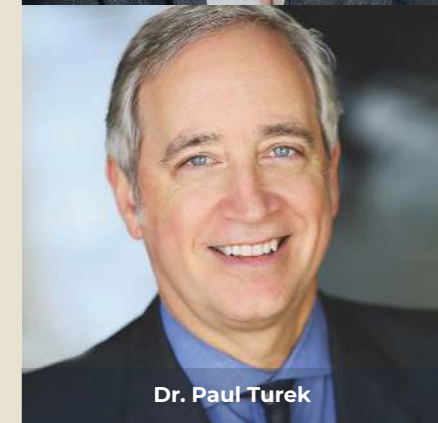
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