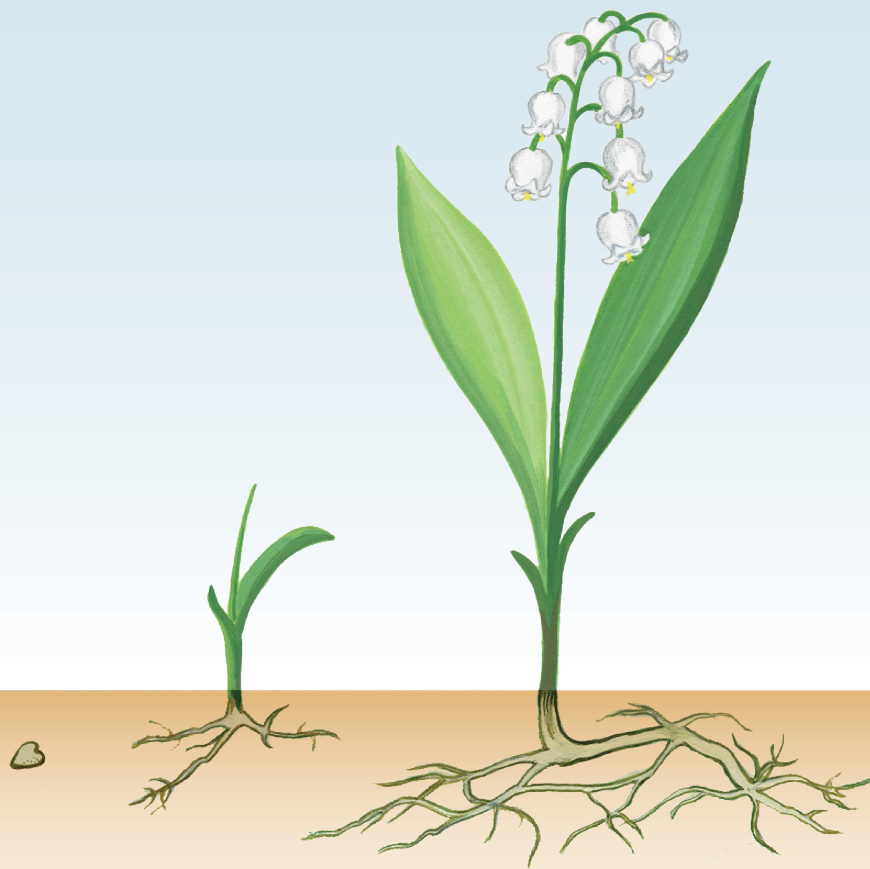


A Practical Guide to Fertility and IVF



*Helping You to Tackle Infertility
and Quickly Navigate the World of
Human-Assisted Reproductive Technologies*

—— First Edition ——

Paolo Rinaudo, MD, PhD

A Practical Guide to Fertility and IVF: Helping You to Tackle Infertility and Quickly Navigate the World of Human Assisted Reproductive Technologies © 2016
by Paolo Rinaudo, MD PhD

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This book is dedicated to the many patients who struggle, often for a long time, with infertility.

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Introduction

μέγα βιβλίον μέγα κακόν, (mega biblion, mega kakon: big book, big evil)

Callimachus 310/301–240 BCE

The primary goal of this booklet is to educate¹ and inform individuals who want to build a family with medical help.² The secondary goal is to provide information in a fast and efficient manner. The booklet contains “pearls” and recommendations on how to better face the challenges of infertility and how to quickly understand the complex world of assisted reproductive technologies (ART).

This booklet therefore is NOT meant to be a comprehensive guide on infertility. There are indeed plenty of authoritative (and lengthy) books about infertility available both for the medical professional or the general public (see suggested reading section).

¹ Because the goal is to teach and inform, there is abundant use of footnotes, for interested readers.

² Many couple consulting this booklet will be affected by infertility, i.e. the inability to conceive after one year of unprotected intercourse.

Chapter 1

How to Find the Best Fertility Center for You

Finding the best doctor for you is one of the critical aspects of any fertility treatment.

If possible, you should aim to find a fertility center with 1) high success rates, 2) good volume, and 3) is close to home/work (for convenience). Once you have chosen a center, I would find the doctor in that center with bedside manners that most suite you.

1. Quality of the Center

Fortunately for patients in the US, there is a relatively objective way to understand the quality of IVF centers. The Society of Assisted Reproductive Technologies (SART, www.sart.org) provides the success rates per age group of IVF clinics³ in the USA. This data is freely available online and can be used to compare different clinics. I would suggest choosing a clinic with high pregnancy rates for your age group.

The best parameters to compare are:⁴

1. The live birth rate per fresh⁵ cycle

This number represents the chances, in your age group, of delivering a child after one treatment when the embryos are not frozen.⁶

2. The multiple rate per fresh cycle

A few very important points:

³ Only a very small percentage (e.g. 6% in 2013) of clinics do not report data to SART.

⁴ See **Figure 10** at the end as an example

⁵ Many abbreviations and concepts, like “fresh” cycle, are explained in an appendix at the end of the book.

⁶ It is generally believed that chances are approximately the same in the first, second and third fresh IVF cycle. Starting from the fourth IVF fresh cycle, the chance of getting pregnant is usually lower. This is secondary to the fact that a group of patients, unfortunately, will never get pregnant, for unknown reasons.

- Because different types of patients access different clinics,⁷ and different clinics might select patients differently,⁸ it is difficult, if not impossible, to exactly compare one clinic to the other.
- I would not use a center that does not report data to SART.⁹
- SART data, when published, is two years old.¹⁰ Therefore, the clinic might have made significant changes and use new protocols; thus the current success rate might be different from the one published.
- The increase in use of Preimplantation Genetic Screening results in many patients having embryos tested but not transferred.¹¹ Patients undergoing PGS are not included in the live birth rate per cycle statistics.

Other methods you can use to choose a clinic are by word of mouth from friends and social media.¹²

2. Volume of the Clinic

Ideally you should aim to use a clinic that performs more than a certain number of cycles¹³ (250 or more) per year.

3. Geographical Convenience

Since you might have to visit your clinic multiple times (even daily for three to five days), finding an easy to access clinic might be one of the key parameters to base your choice on.

4. University or Private Practices

⁷ For example, certain centers or universities often accept patients with very complex medical problems that are not accepted in other clinics.

⁸ Certain clinics might exclude patients with low ovarian reserves.

⁹ If the center that you want to use does not report the success statistics to SART, you should ask your doctor why the clinic's data is not publically available via SART. You should be convinced with the answer.

¹⁰ The lag in data publication is secondary to bureaucratic needs and the way that the live birth rate is reported: If an embryo transfer is performed on the last day of the year, a child will be born nine months later. Further, the patient needs to communicate to the clinic the outcome of the birth—hence the delay in reporting.

¹¹ It takes several days to get the results back from the genetic test—hence, embryos need to be frozen and not transferred.

¹² There are new websites that promise to share the experience of patients with doctors.

¹³ Many doctors will have very different opinions about this minimal number. The concept is simple: too few cases could indicate that the procedures are not standard and not done routinely. There is also the possibility of too many cycles: very busy clinics can give off an impersonal feeling.

I believe this is a less important factor, after the prior three items have been satisfied. A university-based program usually guarantees that the physicians are highly skilled and undergo continuous training. In addition, several university programs have ongoing studies, and the medications may be provided at a discount. On the other hand, university programs may lack the personal feel of a private practice.

5. Personality of the Doctor

All of us have different needs: there is not a single doctor with bedside manners that would satisfy every patient. You might want to meet several doctors in the same practice and find the one that is most appropriate for your needs. Since ovulation can occur on any day of the week, it is likely that you will be treated by various doctors in the team (depending on who is on call). Therefore, it is important to choose the doctor whose team you feel good about as a whole.

6. Waiting time

Some clinics will require a significant waiting time to schedule an initial visit. Then, after the initial visit, several diagnostic tests¹⁴ must be performed prior to starting the actual stimulation with medications. If the waiting time is too long (many months) it might be wiser to find a different clinic.

¹⁴ This waiting time cannot be eliminated. Obtaining test results is critical to maximize success and avoid errors.

Chapter 2

The Menstrual Cycle and Some Terminology

It is critical to understand a few basic physiologic and anatomical concepts. Your doctor will routinely use several technical terms.

The Menstrual Cycle

The menstrual cycle lasts approximately 28 days (**Figure 1**) and it is divided into two parts based on the moment of ovulation.¹⁵ The time before ovulation is called the FOLLICULAR phase¹⁶ and the part following ovulation is called the LUTEAL phase.¹⁷

In a non-stimulated menstrual cycle only one egg¹⁸ is released. With the use of fertility medications two or more eggs are often released or collected.

Regarding the anatomical structures involved, we have a few important players (**Figure 2**):

- the hypophysis (also called pituitary) gland, which releases FSH and LH
- the ovary that responds to FSH and LH and produces estrogen during the follicular phase and both estrogen and progesterone during the luteal phase
- The endometrium, or lining of the uterus, which responds to levels of estrogen and progesterone and changes its shape and appearance during stimulation

¹⁵ Ovulation refers to release of the egg.

¹⁶ Because this is when the follicle (i.e. the anatomical structure that houses the egg) grows

¹⁷ It is called luteum because the follicle after ovulation becomes yellow ("*luteum*" means yellow in Latin). The corpus luteum will start secreting progesterone.

¹⁸ Occasionally (and more commonly in women over 35, when FSH is physiologically increased) an ovary may release two eggs—hence, the possibility of fraternal or non-identical twins. On the contrary identical twins occur when a single fertilized egg (therefore with the same genetic material) divides in two.

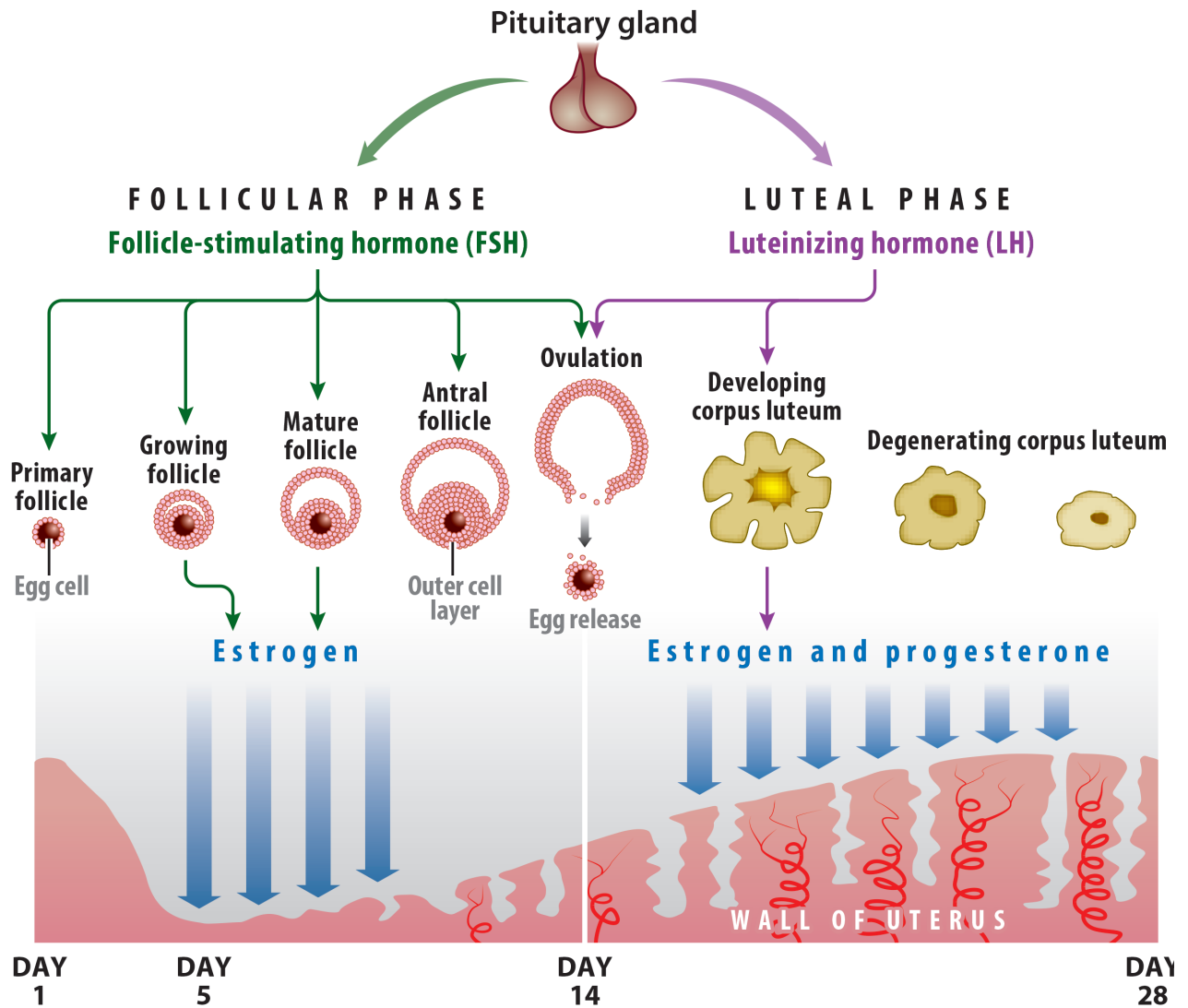


Figure 1: The Menstrual Cycle

The menstrual cycle lasts on average 28 days, but can vary from as little as 21 days to as long as 35 days. Every month the female body prepares for pregnancy, aided by a stunningly orchestrated sequence of hormonal secretions from the pituitary gland and mediated by well-regulated feedback mechanisms.

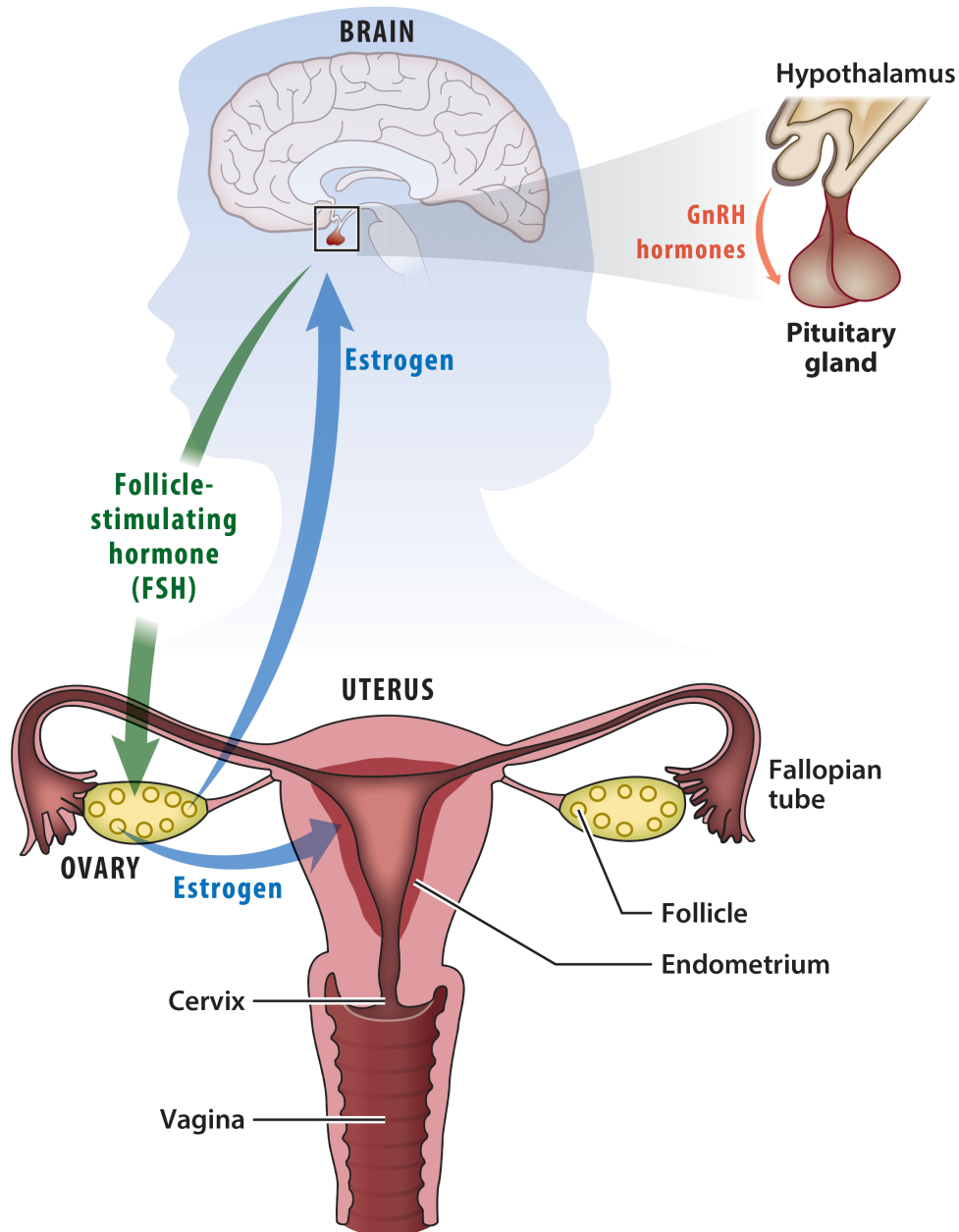


Figure 2: Anatomy and Hormonal Activity

In the brain, the hypothalamus makes hormones (GnRH) that induce secretion of other hormones such as FSH (and LH) from the pituitary glands. These hormones travel through the blood and act on the follicles—the anatomical structure that houses the egg, represented in the ovary as the circle. Follicles then produce estrogen (and progesterone in the luteal phase) to regulate the development of the uterine lining (called “endometrium”) and further regulate the secretion of hormones from the brain.

Chapter 3

Decline of Fertility with Age in Women¹⁹

Changes in lifestyle have led to postponement of family-building in the Western world. Overall, the average age of first-time mothers increased 3.6 years from 21.4 to 25.0 years old between 1970 and 2006.²⁰

Unfortunately biology does not reflect our different social needs.²¹ Fertility in women²² decreases as age increases (**Figure 3**).

The reason for the decrease in fertility with increase in women's age is two-fold. First, there is a decline in the quality of the eggs, manifested by an increase in chromosomal errors. If an embryo is chromosomally abnormal it will not implant (most common scenario) or could result in a pregnancy with a genetic condition like Down Syndrome. Second, there is a decline of the number of eggs (quantity). This is important since your doctor might not be able to make many eggs grow with medications, hence a reduced chance of pregnancy.

For a healthy woman in her 20s, the chances of conceiving each month are approximately 25%. But by the time a woman is 40 years old, the chances of conception are 10% or less.²³

Increased age at conception is probably the one key factor responsible for decreasing fertility in the Western world.

¹⁹ There are obviously multiple additional reasons why fertility can be diminished. See appendix.

²⁰ From 1970 to 2006 the proportion of first births to women aged 35 years and over increased nearly eight times.

²¹ There is an exciting possibility that one day new oocytes or sperm might be generated from stem cells present in the ovary or testicle. As of 2015, this topic and the possibility of generating new eggs are highly controversial.

²² In males, fertility is maintained until older ages, although a modest decline is also observed.

²³ According to one study (Menken, 1986), if we consider healthy women aged 20–24 as having “100% fertility,” fertility decreased on average 6% for women 25–29; 14% in women aged 30–35; 31% for women 35–39; in the next age group fertility is much lower and can be close to zero percent.

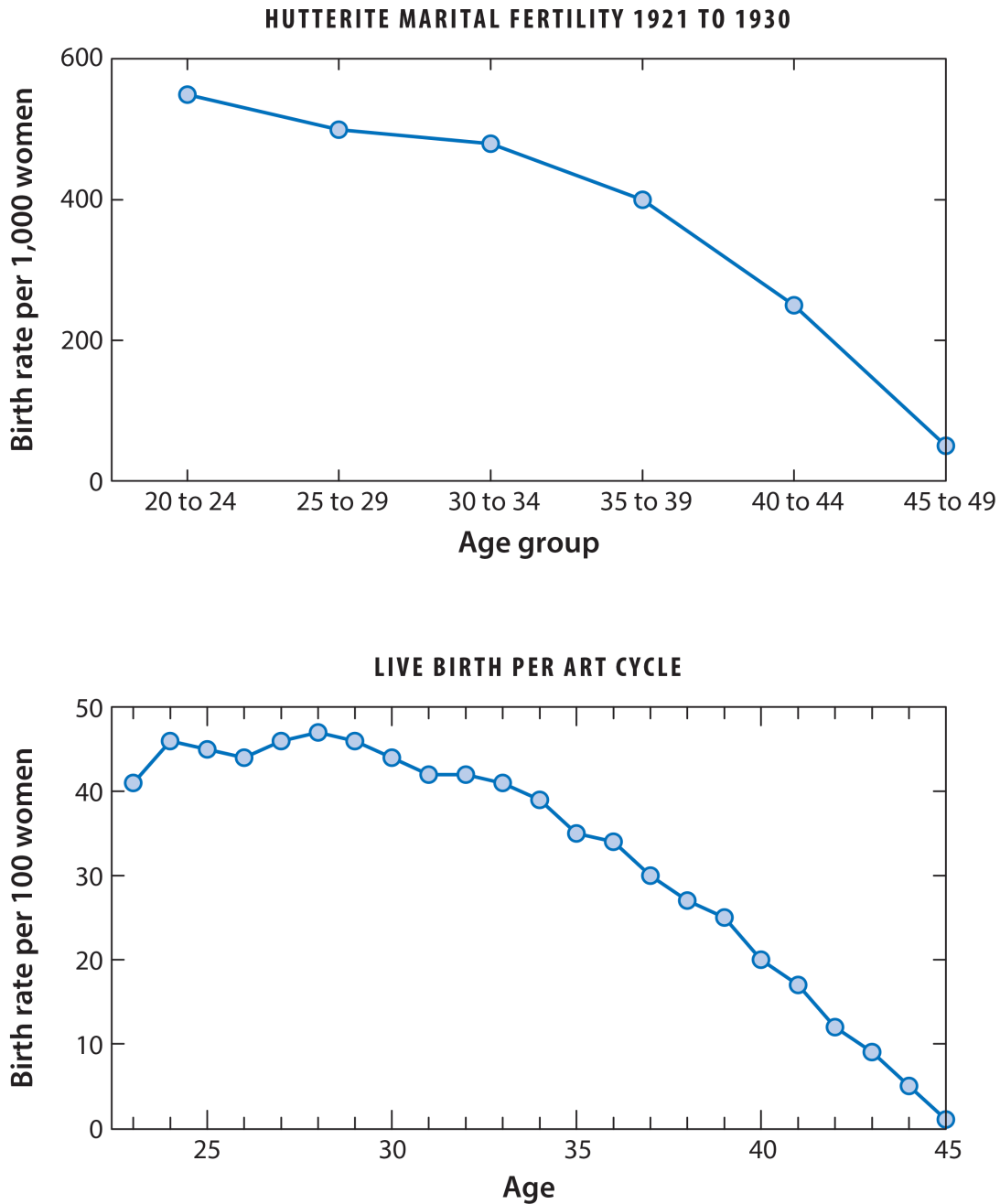


Figure 3: Decline of Fertility with Age.

Top panel shows how live birth rate declines with increasing maternal age in Hutterites couples, in women that are having regular intercourse and that, for religious reasons, never used contraception (data is from Menken, 1986). Bottom panel shows how live birth rate after one fresh cycle declines with increasing maternal age in couples using Assisted Reproductive Technologies (data is from US SART data set in 2013).

Chapter 4

Tests for Fertility

Seeing a fertility doctor²⁴ is a key aspect of your evaluation and should be your immediate priority.

Among the different tests²⁵ available, these are the key ones:

1. Analysis of Ovarian Reserve

Assessment of the ovarian reserve is a method used to understand how many eggs (i.e. the “quantity” of eggs) are present.²⁶ There are three methods currently in use:

a. Anti Mullerian Hormone (AMH)

The granulosa cells of the ovary produce the hormone AMH. A simple blood test can be performed at any time during the menstrual cycle to measure this hormone. The higher the AMH levels the more eggs are present. (**Figure 4**)

b. Antral Follicular Count

Your fertility doctor can perform a transvaginal ultrasound and count how many antral follicles (**Figure 5**) are present. The higher the number of follicles the better, since there are more chances to generate a healthy embryo with the ability to grow.

²⁴ Fertility doctors are obstetrician/gynecologists who spend three additional years of training to become Reproductive Endocrinologists. While an obstetrician/gynecologist can easily perform the initial steps of diagnosis, I would certainly not delay a visit to a subspecialist.

²⁵ Additional tests could be requested.

²⁶ As of 2015, there is no accepted and validated method to evaluate the quality of the eggs, i.e. to understand if the eggs present have a real chance of generating a live birth.

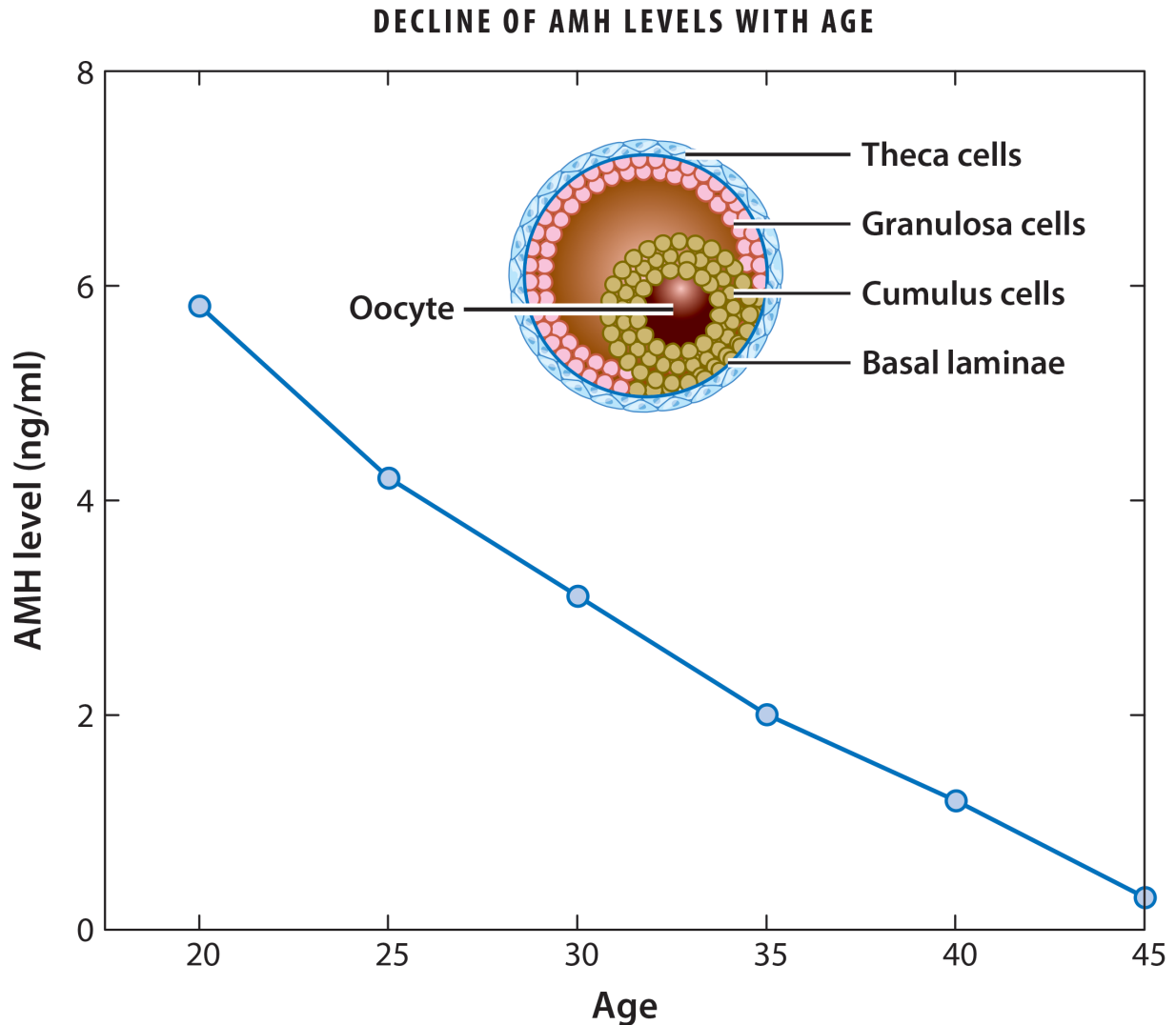


Figure 4: Decline of Antimullerian Hormone (AMH) with Increasing Female Age

*Detail: The follicle is the structure that houses the egg, composed of one oocyte plus specialized granulosa cells and theca cells. The granulosa cells produce AMH. As the **graph** shows, the higher the AMH level the higher the number of follicles (and therefore eggs) existent. AMH levels are higher in younger women; in menopause (the time when the period has stopped) AMH is not detectable.*

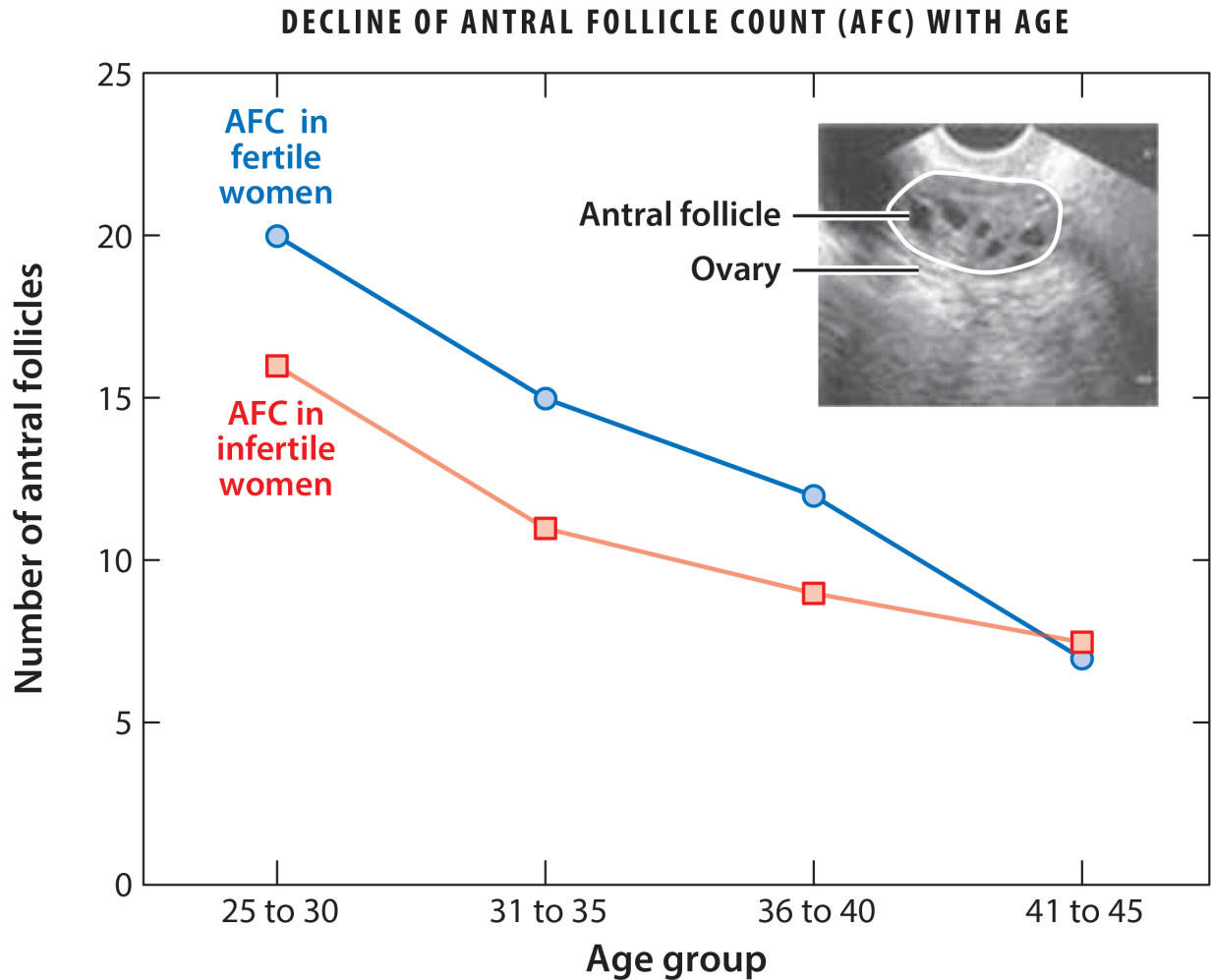


Figure 5: Decline of Antral Follicles with Increasing Female Age

*Antral follicles are small in size (two to ten mm) but can be easily measured via ultrasound in the vagina. The **insert** shows an ovary (the darker grey structure) with follicles (the dark circles). In this example there are six follicles, making the antral follicular count—AFC—six for this ovary. The light gray color surrounding the ovary indicates other abdominal organs such as intestines.*

The graph shows how the AFC declines with advancing female age. Note that fertile women have slightly more antral follicles than women who visit an infertility clinic for evaluation after one year of attempting to conceive.

c. Level of FSH/Estradiol on the Third Day of the Cycle

The pituitary gland (located in the center of your brain, **Figure 2**) produces the Follicular Stimulating Hormone (FSH). This hormone is responsible for allowing the growth of one follicle from the ovary every month. In response to FSH, the ovary produces estradiol (E2).²⁷ The higher the level of FSH on the third day of the menstrual cycle²⁸ the lower the ovarian reserve (i.e. number of eggs) is.

2. Semen Analysis (SA)²⁹

Analyzing sperm production entails a microscopic analysis of the ejaculate, performed three to five days after the last ejaculation.³⁰ Sperm count involves³¹ evaluation of:

1. The volume
2. The count (normal: greater than 15 million/ml)
 - a. If there are less than 15 million sperm the diagnosis is of oligospermia (oligo: few in Greek)³²
 - b. If there are no sperm the condition is called azospermia (the absence of spermatozoa)
3. The motility (normal: 50% or more motile sperms)³³
 - a. If the motility is below the threshold of normalcy the diagnosis is of asthenospermia (asthenos: weak!)
4. The shape (or “morphology” in medical terms) (normal: at least 5% of sperm with normal shape)
 - a. According to the 2010 WHO criteria, the test is done using the so-called Kruger criteria. If the presence of normal sperm is below the

²⁷ It is important to check E2 to assess how reliable the FSH test is. If E2 levels are too high (greater than 50 or 80 picograms/ml, according to some doctors), the FSH test will be erroneously low and therefore the FSH test will not be reliable. Instead, if the E2 is normal or low, the FSH test is reliable.

²⁸ It can also be done on the second day of the menstrual cycle (cycle day two).

²⁹ Male factor infertility is responsible for 25–50% cases of infertility.

³⁰ If semen analysis is done fewer than two days from the last ejaculate, the volume, count and motility of spermatozoa will be lower. If the semen analysis is done after more than five days, the parameters might be inaccurately high or the number of dead spermatozoa increased.

³¹ According to the 2010 World Health Organization (WHO 5th edition) criteria.

³² Some doctors still use the threshold of 20 million from the 1999 WHO criteria.

³³ Given that there are millions of sperm it is normal to have up to 50% of sperm that are unable to move!

minimal number (4%) the condition is called teratospermia³⁴ (teratos: monster)

One essential concept regarding sperm analysis is the total motile count (TMC).³⁵ The total number of mobile spermatozoa present in the ejaculate is important. Based on the TMC, the doctor might decide what kind of treatment is needed, i.e. if intrauterine insemination is possible, or if IVF is required.

3. Patency of the Fallopian Tubes

To be sure that the fallopian tubes are open, your doctor will most likely order a test called a **Hysterosalpingogram (HSG)**.

The hysterosalpingogram involves 1) injecting a dye inside the uterus and 2) performing an X-ray to document passage of the dye from the uterus to the tubes to the inside of the abdomen. If the tubes³⁶ are open, it is possible to proceed with ovulation induction (OI) + placing the sperm inside the uterus (by a process called uterine insemination or IUI). If the tubes are blocked, the next step³⁷ is ART.

A less used alternative to HSG is a procedure called sonohysterography (SHG). This test involves 1) injection of fluid (watery solution with “bubbles”) into the uterus and 2) a transvaginal ultrasound to see if the fluid goes from the uterus into the abdominal cavity, indicating that the fallopian tubes are not blocked.³⁸

³⁴ It is believed that sperm with abnormal shape are unable, or less likely, to fertilize.

³⁵ There are really two types of TMC: 1) the TMC in the native sperm count, after ejaculation—this parameter guides the doctor in deciding, from the initial visit, if IUI is possible or if IVF is immediately indicated; 2) the TMC present after washing the sperm and prior to insemination (sometimes called the inseminating sperm count). Value below 5 million are unlikely to be successful and therefore the doctor might decide after few IUIs that it is time for IVF.

³⁶ If only one tube is open, many doctors still perform ovulation induction and IUI. There might be increased risk of ectopic pregnancy.

³⁷ In the past, surgical correction was attempted. This is much less common today, although still possible in selected cases.

³⁸ The SHG is used less because it is newer (therefore less doctors are trained in it) and because it is more difficult to obtain a full evaluation of each portion of the fallopian tubes.

Chapter 5

Type of Treatments Available

*Primum non nocere** (First, do not harm)

*Attributed to Hippocrates of Cos (460–370 BC), considered the Father of medicine.

Several different types of treatment are available. A general principle is that treatments should initially be gentler and if necessary become more aggressive over time. Your doctor will be instrumental in recommending a course of action³⁹.

Of note, many treatment strategies can be thought of as additional diagnostic steps. For example, during stimulation with hormones, you will not only use a form of treatment but also learn about how your ovary responds to medications. Or, during IVF, you will learn if there is a problem with fertilization or early embryo development. And as long as we adapt to the new facts, then there is a real positive gain in information and learning.

1. Diagnostic Tests

After all the diagnostic tests have been performed, treatment begins. It is important to emphasize the importance of completing a full work-up prior to treatment. Many couples are eager to start treatment immediately. However, not performing the right test at the proper time could lead to error and problems later on.

2. Intra-uterine insemination (IUI)

For many couples, the usual first step is to start with ovulation induction with intrauterine insemination (IUI).⁴⁰ Ovulation induction can be done with one of two oral medications, Clomid or Letrozole. Your doctor will decide how many cycles you will need (usually one to six).

³⁹ There is obviously a very large permutation of treatment modalities that are possible. Your doctor will find the one that is ideal for you. Below are some generalizations only.

⁴⁰ There are many situations where ovulation induction alone or IUI alone will be done. However, for many couples, the combination of ovulation induction and IUI is the most common scenario.

If unsuccessful, some couples will use gonadotropins (i.e. drugs containing analogues of the hormones FSH and LH) and IUI (usually from one to four cycles).

3. IVF Fresh Cycle

IVF is not often the first line of treatment.⁴¹ After a certain number of unsuccessful OI, your doctor may propose that you undergo IVF. This is an important choice, since the cost can be substantially higher than the other procedures, to the order of \$15,000–20,000 US dollars in 2015.

A typical IVF cycle (**Figure 6 and Figure 7**) lasts approximately two months. There is a preparatory month,⁴² followed by the actual stimulation.

There is no theoretical limit to how many cycles of IVF can be performed. You and your doctor need to thoroughly discuss the outcome of each cycle and decide if it is reasonable or not to proceed with additional treatments.

4. Frozen Embryo Transfer

If frozen embryos were generated in a prior IVF cycles, the embryos can be transferred without needing to stimulate the growth of follicles, and only preparing the lining of the uterus (the endometrium) to accept the embryo. The process of frozen embryo transfer can be done in two different ways that are equally successful:

- a. A natural frozen cycle: the frozen embryo (or embryos) will be thawed and transferred at the exact time when the embryo would implant in a natural cycle. Since the ovary produces all of the hormones that are needed to sustain pregnancy, your doctor will have to monitor your natural cycle and decide when to transfer the embryo(s) based on your timing of ovulation. The advantage of this method is that no medications are used. The disadvantage is that ovulation occurs predictably only in 70–80% of cases, and therefore there is a possibility that the transfer will not be done if the doctor is not absolutely sure that timing is correct. Also, there is the need for multiple visits to the clinic to assess when ovulation occurs. Given that

⁴¹ For some patients, based on age and medical conditions, IVF may well be the first option.

⁴² Studies show that the preparatory month is critical for increasing success, i.e. it usually cannot be skipped.

ovulatory dysfunction can occur at age 38 and over, this method is usually reserved for patients without ovulatory problems and who are younger than 38.

- b. A medicated frozen cycle: in this case, the doctor will give you medications, including estrogen and progesterone, to medically prepare the endometrium to accept an embryo. The advantage of this method is that there is a greater than 95% chance that the transfer will occur at the proper time, selected by you and your doctor based on your schedule. Further, only one visit is usually needed to ensure that the endometrium is ready to accept the embryo(s). The disadvantage is that medications need to be taken. The whole process (from the start of taking the medications to the actual embryo transfer) is five to six weeks long.

5. Egg Donation

Often the decline of fertility with age will mean that no more eggs are realistically available and that your chances of pregnancy are so low that it might not be reasonable to continue to use your own eggs. Fortunately, in the US, is possible to use eggs donated anonymously by young women. Egg donations represent an excellent opportunity with very high pregnancy rates.⁴³

⁴³ Importantly it is the *egg* age that determines pregnancy success. Stated in other words, if an egg from a 20-year-old woman is used to produce an embryo, and the resulting embryo is transferred to a recipient who is 20, 30, 40 or 50 years old, the pregnancy rate is roughly the same!!

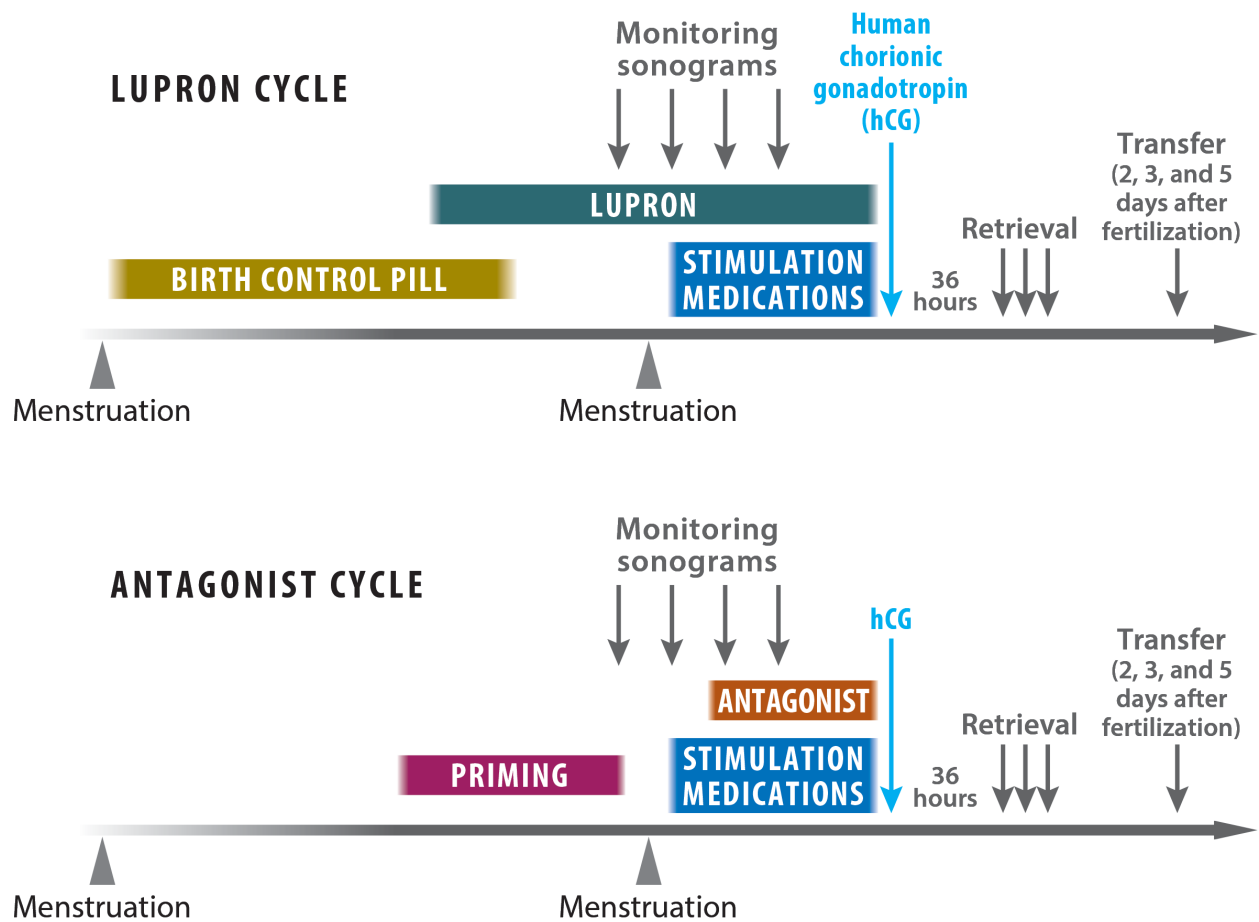


Figure 6: Examples of Stimulation Protocols

Stimulation protocols for in vitro fertilization will last two months—a preparatory month followed by a stimulation month.

*The Lupron cycle is one of the most commonly used protocols—see **top** panel. In the preparatory month, birth control pills are taken for two to three weeks, followed by Lupron injections to prevent ovulation. At the beginning of the new menstrual cycle, gonadotropins (FSH) are given daily for approximately ten days (8–14, usually). These medications make the follicles grow. When the largest follicles (called “dominant” follicles) are 18–20 mm in diameter, an injection of HCG is given to induce ovulation. Egg retrieval is performed 36 hours later.*

*The **bottom** panel is an example of the antagonist cycle⁴⁴ without birth control but with priming. Your doctor could choose this protocol if the ovarian reserve is lower. The stimulation component of the cycle is very similar to a Lupron protocol. The main differences from Lupron protocols are: 1) the lack of use of birth control, 2) the use of estrogen or progesterone for a few days in the luteal phase of the preparatory month (so-called “priming,” to synchronize the growth of the follicles) and 3) the use of an antagonist medication (GnRH-a) to prevent ovulation during the stimulatory portion of the cycle.*

⁴⁴ Antagonist cycles can also be done with birth control pills.

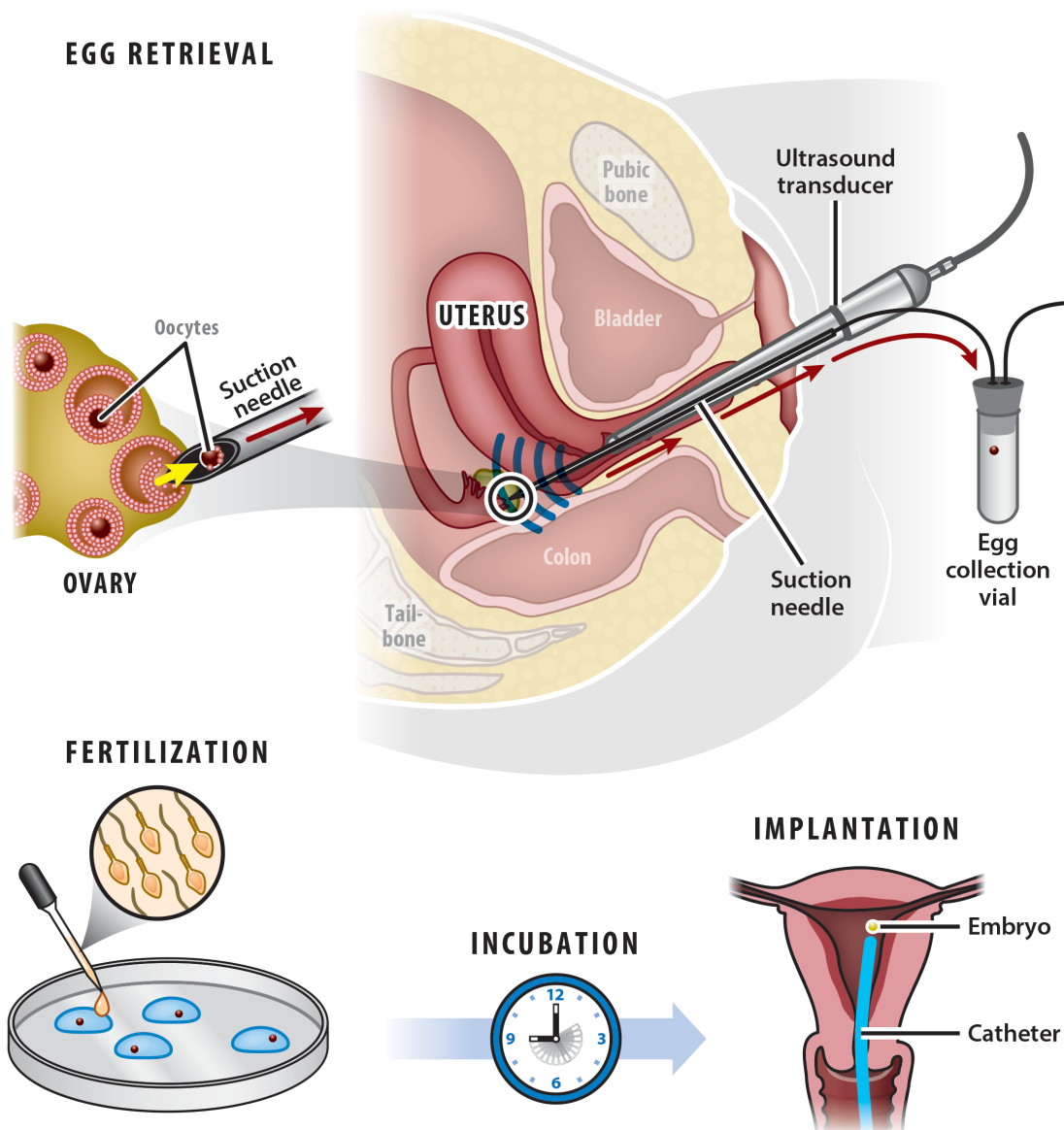


Figure 7: The IVF Procedure

The process of egg retrieval is performed in an operating room under mild anesthesia. The eggs are retrieved with a suction needle inserted via the vagina into the follicles of the ovary under ultrasound guidance. The retrieved eggs are examined by the embryologist and fertilized with sperm—either by adding a sperm solution to the egg (standard IVF) or by injecting a single moving sperm into the egg (intracytoplasmic sperm injection or ICSI). ICSI is done when the sperm count is not normal. The resulting embryos are allowed to grow (usually for two, three or five days) and then transferred into the uterus with a small soft catheter.

Chapter 6

What to Expect During Treatment

Once treatment begins, it is important to be prepared for the many challenges that lie ahead.

1. Medically

From a medical standpoint, treatment will occur during the follicular phase of the cycle. The following can be expected (**Figure 6 and 7**):

1. Several visits with your doctor for the performance of an ultrasound to observe follicular growth. Women undergoing IVF will need an average of six to seven visits,⁴⁵ while women undergoing IUI treatment only require one to three visits. Each visit is relatively brief and can last as little as five minutes.
2. Plan to take medications at approximately the same time every day. Some injections (not all!) can be combined in a single syringe. Be sure to discuss the details of the medications you are taking with your nurse.
3. The process of removal of the eggs (a.k.a. egg retrieval or ovum pick up, **Figure 7**). The procedure will last approximately 20–40 minutes. More often⁴⁶ than not, it is done with mild anesthesia (a.k.a. “conscious sedation”)—you will not be intubated (i.e. breathing will occur normally), but several medications will be given so that there is no pain and no memory of the actual procedure.
4. The process of intrauterine insemination or embryo transfer. From a technical standpoint the procedure requires you to be positioned as for a pap smear. A very small catheter will then be introduced into the uterus and either concentrated spermatozoa or embryos will be released into the uterine cavity.⁴⁷
5. Waiting phase. Following this active phase of treatment, there are two weeks of time in which we need to wait for results!

⁴⁵ Women undergoing IVF will often have blood taken to measure estradiol levels.

⁴⁶ Occasionally, it is done without anesthesia!

⁴⁷ A very common worry is that embryos or sperm may “fall out” of the uterus. This does not occur!

6. During the luteal phase of the cycle, progesterone is usually administered to sustain the possible pregnancy. Progesterone can be administered vaginally or intramuscularly. Your doctor will explain which formulation is preferred in your specific case.

2. Emotionally

All couples undergoing fertility treatment experience high levels of stress. The good news is that having a high level of stress or anxiety will NOT decrease your chances of getting pregnant! Not surprisingly, the second phase of the cycle (the “waiting phase” or luteal phase), although less intensive⁴⁸ from a treatment standpoint, is the most challenging phase of the cycle, since the expectations are high! If successful, the joy will be great. However, the arrival of a new menstrual period is often overwhelming—every new menstrual cycle is often associated with a new grieving experience, in which loss is experienced anew. Hence the recurring (monthly) phenomenon of grieving has led to comparing fertility treatment to an emotional roller coaster, in which high expectation and profound despair often occur within brief intervals.

The best advice is to focus on the action plan during the first phase (treatment phase) of the cycle and then pay particular attention to your emotional needs during the second phase of the cycle (see chapter 7 for tips).

3. Expectation of Success

It is important to know the chances of success that your doctor has given you, so that you can have clear expectations. Please ask your doctor to be as specific and clear as possible. The table below offers some general numbers.

⁴⁸ Many women (always in the case of IVF treatment) will need to take Progesterone supplementation during this phase.

Chances of pregnancy, per month, for selected groups of patients in which the woman is over 35 years old	
Condition	Chances
Couples not affected by fertility problems	20-25%
Single intercourse	8%
Couples with unexplained infertility ⁴⁹	3%
Clomid and IUI for couples with unexplained infertility	10-12%
Injectable IUI for couples with unexplained infertility	12-15%
IVF ⁵⁰	46%

4. Risks

There is no medical treatment without side effects.

Treatment for fertility is highly effective but has some side effects. For this reason, the validity of any treatment modality needs to be thoroughly investigated. Overall, fertility treatments are considered safe. Common risks include:

1. Multiple pregnancies:⁵¹ This is without a doubt the most frequent and potentially risky complication. Although twins are often desired and welcomed, a twin pregnancy is associated with a significant increase in risks, both for the mother⁵² and the fetuses.⁵³ Higher order multiple pregnancies (triplets or more) have even more risks. Given this, the decision to cancel a cycle if there are too many follicles (during an IUI cycle) or to transfer fewer embryos or just one (e.g. elective single emryo transfer or eSET) is a priority for the field.

⁴⁹ These are couples that have tried unsuccessfully to conceive for at least one year *and* all the fertility testing results are normal. In other words, these couple *can* conceive, although with significantly lower chances.

⁵⁰ Interestingly, the cause of infertility will not meaningfully change the chances of success with IVF. Stated in other words, if your infertility is caused by endometriosis or male factors, the chances of success with IVF are pretty much the same.

⁵¹ Nearly 30% of pregnancies following an IVF cycle are twins. Less than 1% are triplets (data as of 2013).

⁵² There is a small increase in incidence of diabetes during pregnancy (~6%) and hypertension during pregnancy (~10%) in mothers with twins, compared to in mothers who carry a singleton gestation (3 and 6% respectively).

⁵³ There is an increase risk of preterm birth in twin gestations (50% versus 10% in singleton gestation). Premature babies may be at higher risk for neurological and developmental problems. In addition, delivery of twins can be more risky and complicated.

2. Risk of cancer. Fortunately, this has not been shown to be significant.⁵⁴
3. Risks related to medications:
 - a. Bruising at the injection site is very common. Even if it occurs, the medications are absorbed properly.
 - b. Ovarian hyperstimulation syndrome (OHSS). This condition occurs more commonly in young women with numerous eggs. It is associated with fluid accumulation in the abdomen⁵⁵ and enlarged ovaries. It could require hospitalization and removal of fluid with a needle from the abdomen or vagina. It is a serious complication and your doctor might decide to cancel the cycle if the risk is significant. The chance of occurrence is 1% or less.
 - c. Follicular rupture or ovarian torsion (twisted ovary). Since there are many follicles, it is possible for one follicle to rupture or for the ovary itself to twist on its blood supply. These are rare complications (less than 1%) but potentially dangerous and can require surgical intervention.
4. Risk related to the egg retrieval procedure
 - a. Egg retrieval can be associated with risks of bleeding and infection. The occurrence of this is less than 1%.
5. Pregnancy abnormalities
 - a. IVF has been associated with a very small increased risk of preterm birth and low birth weight.
 - b. Ectopic pregnancy⁵⁶
 - c. Increased risk of malformation in the newborn.⁵⁷ Some studies indicate that the risk of malformation in IVF children is 4-5%, while it is 3-4% in the general population.
6. Long-term risk for children.⁵⁸ It is presently unknown if children conceived using fertility treatments might be predisposed to an increased incidence of glucose intolerance or diabetes and hypertension when adults.

⁵⁴ Overall, infertility *per se* (even without treatment) has been associated with an increased risk for certain cancers.

⁵⁵ Called "ascites." Sometimes there is also fluid accumulation in and around the lungs.

⁵⁶ The pregnancy is located outside of the uterus, most often in the fallopian tube.

⁵⁷ It is unknown if the increased risk is secondary to the fact that the patients are infertile or if the treatment itself can increase this risk.

⁵⁸ This is my particular area of investigation.

5. Cost and Expenses

The cost of infertility diagnosis, treatment and related medications can be very high. Some states (like Massachusetts and Rhode Island) have mandated insurance (i.e. insurance companies are mandated to cover fertility diagnosis and treatment for residents of these states).

There is an excellent website offered by Resolve that summarizes different financing options available to patients. Google the words: “Resolve” and “Infertility Financing Programs” and you should easily find direct access to this comprehensive page.

A general example of the cost is provided on the table below.

Procedure	Approximate cost per cycle⁵⁹
Clomid or Letrozole + IUI	\$1,000–1,500
Gonadotropins + IUI	\$2,000–5000
IVF fresh cycle	\$15,000–20,000
IVF frozen cycle ⁶⁰	\$ 3,000
Egg donation	\$25,000–30,000

⁵⁹ One treatment with fertility drugs lasts for one menstrual cycle. If the treatment needs to be repeated, the same cost will need to be paid again. These are indicative and very general prices as of 2015 in California, US. Prices might vary greatly based on your insurance, your geographical location and the specific treatments that you will be using.

⁶⁰ The cost is approximately the same for a natural frozen cycle (more ultrasound to do) and a medicated frozen cycle (cost of medications).

Chapter 7

How to Face the Emotional Roller Coaster

For a large number of individuals, having a family is a fundamental need.⁶¹ For those who so desire, the inability to procreate is undoubtedly one of the most difficult experiences in a person's life.⁶² The inability of Abraham and Sarah to have a child is well described in all the Abrahamic religions.⁶³ Here are some suggestions for how to counteract these difficult emotions:

1. The journey through the infertility treatment should be thought of like a marathon, rather than an Olympic 100 meter race

Often when individuals first meet with a fertility doctor they have already struggled with infertility for a certain amount of time. They are appropriately very eager to have a rapid resolution to their problem (“we wanted a baby yesterday!”). However, while few fortunate individuals will conceive rapidly, for some others it might take a longer time. It is therefore critical to have a resilient mindset and visualize a specific length of time in which a certain events will occur.

A good approach is to think: “in the next one or two years we are going to build a family.” You should try to focus on the bigger picture and try not to concentrate on every single menstrual cycle with its undeniable challenges. A menstrual cycle should not be thought of as a failure, but rather as one extra step toward an additional treatment strategy and further options.

⁶¹ There are a significant group of individuals who are very happy and actively choose not to procreate. The National Center of Health Statistics confirms that the percentage of American women of childbearing age who define themselves as voluntarily childless rose sharply in the 1990s—from 2.4 percent in 1982 to 6.6 percent in 1995.

⁶² It has been compared to having cancer.

⁶³ Abraham and Sarah could not conceive until Sarah was menopausal (Genesis 21:2).

2. Have a clear game plan, understanding what steps will be taken and when

It is very important to know exactly the steps that have to be taken to get pregnant. Usually, after the initial visit, there will be some tests that need to be done. The usual first step will be to use some oral medications together with intrauterine insemination (IUI). Clarify with your doctors how many cycles he/she is suggesting and why. Next you might move to IVF. If one cycle is not successful, plan to meet again with your doctor and evaluate if it makes sense to proceed with another IVF cycle or more cycles. Ask your doctor when it is time to move to egg donation or adoption.

An example of a timeline can be as follows:

1. After the initial visit there are multiple laboratory tests that need to be done. Usually it will take anywhere from four to ten weeks to do all the tests, depending on how fast you will be able to have the test done.
2. Only after all the tests are completed, the treatment can start. For example, you could do Clomid with IUI for two to six menstrual cycles.⁶⁴
3. After having tried treatment for two to six cycles, you will meet with your doctor to decide if a different treatment is needed.

3. Share your emotional needs with a companion or friend

Infertility is such an overwhelming feeling that many individuals prefer not to share this information with others. However, it is very important to find one or more friends with whom to vent and discuss these problems. Since infertility affects 15% of couples, chances are that one or more of your friends will have undergone some form of fertility treatment. These individuals will completely understand your needs and will be very eager to help.

⁶⁴ The number of cycles will be decided conjunctly with your doctor and it will be based on your diagnosis, age and ovarian reserve.

4. Use the resources of your fertility clinic

Many fertility clinics have a psychologist as a part of the team. Do not hesitate to contact this very important person. He/she is there to try to meet your emotional needs.

5. Your nurse is your ally

IVF nurses are highly trained professionals with a deep understanding of the process of IVF and are very aware of the emotional stress associated with fertility treatment. They can be your best ally. Since they will often be in contact with you, you can always ask for their suggestions and support.

6. Join an online group

There are several organizations devoted to helping infertility patients. See Appendix at the end.

7. Think about your significant other

If you are planning to have a family with a partner, be aware of the strain that infertility can cause to your significant other.⁶⁵ In addition to the sense of loss that affects you as an individual, your partner may be uniquely affected in ways that you might not have predicted. This can add to the difficulty of the moment.

Often, infertility is the first real trial for a couple. Always remember to communicate actively with your partner and reserve time for it. Consider meeting with a couples counselor.

8. Be generous with yourself

If you are undergoing fertility treatment do not be excessively strict with yourself. Consider taking time off for a nice mini vacation⁶⁶ (or longer if possible) to recharge yourself and your partner. Along the same lines, while a healthy diet is

⁶⁵ There is evidence that the quality of life is greatly diminished in couples who cannot conceive after fertility treatments. Many couples lose interest in the sexual relationship and sex becomes a “medical procedure with no enjoyment.” Women with unsuccessful fertility treatments are at higher risk of hospitalization for mental health disorders, alcohol and substance abuse. On the contrary, families who used ART and their children function well from a psychological perspective, indicating that the availability of these techniques provides significant psychological benefits to family, and therefore should be offered.

⁶⁶ Especially in the two weeks while waiting for the results!

recommended, I personally believe that an absolute strict dietary discipline is not necessary. For example it is OK to give an extra gift to yourself (a nice meal or a dessert of your choice—see chapter 8).

9. Consider joining an exercise or meditation class

Mild physical exercise and/or meditation are wonderful methods to relieve stress. Consider joining a gym to be involved in some form of physical activity. This can be an excellent way to relieve stress.

10. A word of caution: too much online information

While I am a firm believer that “knowledge is power,” too much unfiltered information may be detrimental, anxiety-provoking and ultimately counterproductive. Always rely on facts and evidence and your doctor’s expert opinion.

Chapter 8

Is it Possible to Increase Fertility and the Number of Eggs?

Diet, Exercise, Supplements and Acupuncture

A very common question is whether there are additional strategies that can increase the chances of getting pregnant?

Although the list of proposed compounds beneficial for fertility is ever increasing, the evidence-based⁶⁷ answer is: NOT really.

In fact, if you are not using illicit drugs, smoking or abusing alcohol, but eating a balanced diet, you are already doing very well.

1. Diet

Fertility rates in young couples all over the world, where there are very different types of diets and nutritional habits, ARE approximately the same. From this simple observation we can conclude that nutritional habits do not play a major role in enhancing fertility. A diet rich in vegetables and fruit is highly beneficial for general health and also for fertility. Increasing vegetable intake and decreasing processed food should be a priority for any family.

On the other hand, if you are overweight, a gentle⁶⁸ program for weight loss might be beneficial.

2. Exercise

Exercise has multiple additional benefits to physical well-being: the mental relaxation and mood enhancement achieved with exercise are a major plus of any type of physical activity. While physical activity can be continued during the initial phases of fertility treatment, it is generally recommended to decrease and stop

⁶⁷ There is a lot of talk about evidence-based medicine, i.e. medical decisions based only on well designed and conducted research. While there is an enormous amount of literature on nutrition and fertility, only a very minor subgroup of studies are appropriately designed, conducted and analyzed and pass the threshold of being evidence-based.

⁶⁸ A too rapid weight loss is NOT beneficial, as it might alter the quality of the eggs.

physical activity during the final phases⁶⁹ of hormone stimulation of an IVF cycle, since the ovaries are enlarged and there is a risk of follicular rupture or ovarian torsion (chapter 7). In addition, it is also recommended not to exercise⁷⁰ for few days after an embryo transfer procedure, to optimize implantation.

3. Supplements

First, the good news: folic acid has been clearly shown to be beneficial in pregnancy or preconception. Taking 400 micrograms of folic acid daily can decrease the incidence of neural tube defects and is recommended. In general, one prenatal vitamin a day contains the proper amount of folic acid and it is all that is recommended.

All other supplements have not yet been convincingly⁷¹ shown to be beneficial or to clearly and undoubtedly increase the pregnancy rate.

Here is a list of compounds that have been suggested to increase fertility or be beneficial for fertility, but have not yet passed the evidence-based threshold:

- a. Antioxidants, like vitamin C or E
- b. Coenzyme Q10 (CoQ10)
- c. Dehydroepiandrosterone sulfate (DHEAS)⁷²
- d. Herbal products⁷³

⁶⁹ The exact time to stop and resume physical activity will be clarified by your own doctor. The guiding principle is that you should do a little less than what your body is telling you it can do. Of note, the final phases of hormone stimulation are uncomfortable for many patients and there is really no desire or willingness to exercise during this time.

⁷⁰ This is another area where very different recommendations exist and studies are controversial. Importantly, randomized studies indicate that bed rest is NOT needed. However, what constitutes appropriate physical activity is not clear yet. Normal activity, like working in an office or spending relaxed time at home, is generally believed to be appropriate and safe.

⁷¹ Obviously we are all waiting for a compound that can increase fertility. If a new valid study is published we will be thrilled to recommend the compound.

⁷² This supplement is particularly controversial.

⁷³ A special note about herbs: Herbal products should be thought of as powerful medications, and indeed approximately 25% of our prescription medications are derived from plants (Farnsworth, 1976). The problems with herbal supplements for fertility are that 1) herbal products are a combination of multiple herbs, hence there are multiple active principles that could interact in unknown ways and further interact with fertility drugs used; 2) the quality control to make herbal products is not the same as the one for drugs, hence there are questions about safety. Overall, many fertility experts do not recommend the use herbal products together with fertility medications.

4. Acupuncture

Traditional Chinese Medicine (TCM) has a long and illustrious history of over 3000 years. I personally studied one year of acupuncture during medical school because I was so fascinated by its tradition, history and potential. Overall, it appears that acupuncture is safe and has beneficial effects on the general well being of patients. However, it is still unknown and unproven that its use increases pregnancy rates. Since we do not believe it is deleterious, patients who are drawn to acupuncture are free to use it.⁷⁴

5. Smoking, Drugs and Alcohol

Tobacco⁷⁵ or drug use (including light drugs, like marijuana) has a proven deleterious effect on fertility and should not be used.

While high alcohol use decreases fertility, low alcohol use (defined as less than 50 grams⁷⁶ per week) has not been associated with decreased fertility in the majority of studies. Importantly, alcohol should not be used while pregnant.

Caffeine and tea appear to be safe and can be consumed. Several studies suggest that less than 300 milligram a day⁷⁷ of caffeine, from any source, is safe.

6. Traveling during stimulation

It is possible to travel throughout the process. However it is not recommended to travel:

⁷⁴ As stated earlier, herbal supplements with acupuncture are NOT recommended.

⁷⁵ Tobacco use is associated with earlier menopause and decreased number of eggs produced.

⁷⁶ In the United States, a "standard" drink is any drink that contains about 0.6 fluid ounces or 14 grams of "pure" alcohol.

⁷⁷ An eight ounce (237ml) cup of coffee contains between 95–200 mg of caffeine and an eight-ounce cup of green tea 24–45mg. One Espresso, 47–75mg. A cola drink contains 38.9 mg of caffeine.

- from the positive pregnancy test until the first ultrasound (approximately two weeks). This is because the pregnancy could be in the wrong place (an ectopic pregnancy) or non viable. Both of these conditions require medical attention and could represent medical emergency.
- any time your doctor feels that you are unsafe to travel (for example because you have developed ovarian hyperstimulation syndrome).

Chapter 9

Thought-Provoking Decisions

Some decisions can be extremely challenging. Here are a few examples:

1. When to Stop Treatment or Change Treatment

Because of the significant physical, emotional and financial burden of fertility treatment, often it is very difficult to decide when to either change treatment strategy or when to completely stop trying to become pregnant. Your doctor is going to be your indispensable ally in this journey.

A particular discussion is needed for patients at the end of their fertility potential (**Figure 8**). Different fertility treatments offer different chances of pregnancy when fertility potential is normal or a little decreased. However, when there are few eggs, the differential advantage offered by a more aggressive treatment is not significant anymore, and it might make sense to reverse to less aggressive and less costly treatments, or simply try to get pregnant without medical help!

2. Egg Freezing

A major technical breakthrough has been the introduction of the technique of vitrification to freeze the oocytes.⁷⁸ Thanks to this technique, it is currently possible to freeze eggs and use them in a future time. This is very advantageous for anyone desiring to delay family building options for a different host of reasons (from studying to pursuing a career or simply because one is not ready).⁷⁹ At first thought, the decision would seem very easy, since it is like buying insurance for the future. However, there are several downsides: the procedure is 1) expensive,⁸⁰ 2) invasive⁸¹ and 3) will not lead to pregnancy in 100% of cases.⁸²

⁷⁸ Prior to the current vitrification or fast freezing procedure, there was the technique of slow freezing, used since the mid-1980s. This technique had a much lower success rate and many eggs would not survive the freezing-thawing process.

⁷⁹ There are very divergent opinions to the value of delaying having children. Some experts do not believe it to be valuable. See reading suggestions at the end.

⁸⁰ Approximately \$10,000 US in 2015.

⁸¹ The procedure requires taking medications and retrieving eggs. It can result in medical complications like ovarian hyperstimulation syndrome.

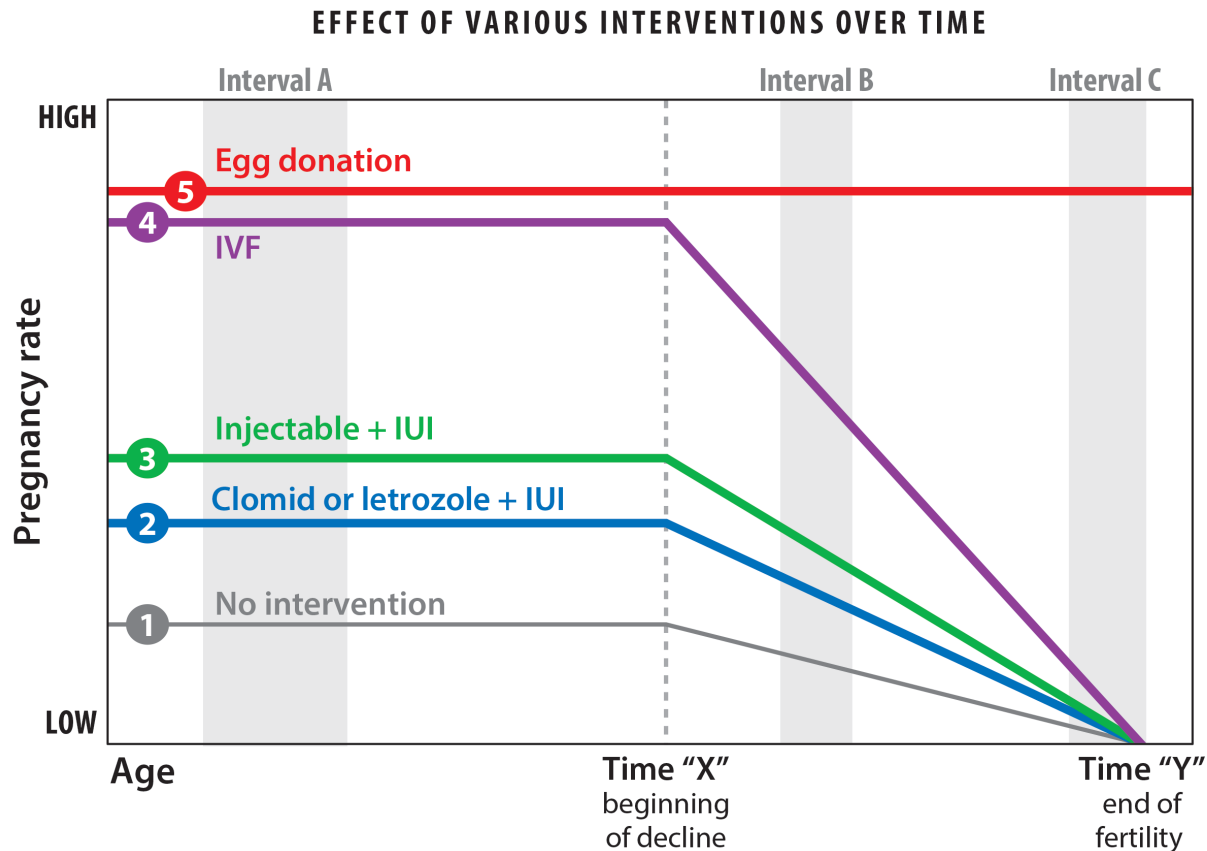


Figure 8: End of Treatment Decisions

The decision to end treatment is always extremely difficult. This graph might help in the decision.

First, the no intervention line (line 1) indicates that beginning at a certain age (indicated by the X shaded line) the ability to get pregnant declines over time (this age can vary between women, but usually corresponds to an age of 35 years). After a certain point, it is impossible to get pregnant because menopause occurs (all the eggs have been used—it is the absolute end point of natural fertility and occurs at an average age of 51 years). However, many years earlier (point Y on the graph), the actual ability to get pregnant diminishes. The age of the Y point varies between the ages of 40 to 45 years for different women.

Second, the different types of interventions (line 2 to 5) increase the chances of getting pregnant over time, compared to no intervention. However, no matter the

⁸² This is the major concern. If the use of the frozen eggs does not result in pregnancy, the only option for many women older than 42 will be the use of donor eggs.

types of interventions, after the age X, the success of each intervention will diminish.

These facts have important practical implications. If treatments done during the “time intervals” A or B (shaded areas) increase the chance of pregnancy, treatment done at interval C will not really be helpful, since the chance of pregnancy with each intervention is extremely low. Of note, the cost of IVF will be the same no matter the patient’s age, hence a less aggressive treatment might become cost-effective. Reaching period C would indicate that it is reasonable to quit aggressive and costly treatments.

Of note, the use of eggs donated by a younger woman (line 5) is associated with very high pregnancy rates no matter the age of the woman receiving the eggs (so-called “recipient”).⁸³ This is because while the ovary ages, the uterus maintains the ability to carry pregnancy until a more advanced age.

⁸³ There seems to be a very slight decrease (a few percentage points) in the pregnancy rate in older women.

In women less than 35 years old⁸⁴ every mature egg⁸⁵ has a 2–3% chance to result in the birth of a baby. To have a meaningful chance of pregnancy, it is suggested therefore to collect at least ten eggs.

3. Using Donor Gametes or a Gestational Carrier

The possibility of using spermatozoa or oocytes represents a wonderful opportunity for individuals who, for different reasons, cannot utilize their own gametes. Using donor eggs or donor sperm is associated with very high pregnancy rates. However, this technique is not available in many countries outside the US and can be expensive.

Understandably, many patients find it very hard to renounce passing on their genetic material. That is why it is very important to discuss this option with a professional or a psychologist who specializes in fertility.

Fortunately, published literature and my own experience suggest that couples that use donor gametes will make wonderful parents. Studies show that children born using donor eggs and sperm are very healthy, both from a physical and emotional perspective.

4. Adoption

Adoption is a wonderful opportunity to build a family and to help a child in need. Websites and information on family planning with adoption are in the Appendix section of this book.

5. Travelling to Other Countries to Have Medical Care

“Fertility tourism” (a.k.a. reproductive tourism), as it is often defined, is becoming a frequent phenomenon.⁸⁶ There are many reasons for its increase, but all are

⁸⁴ With increasing age there is a much faster decline in rate of success, and some experts believe that this procedure should not be offered to women over 40. Current statistics are not reliable enough to provide solid numbers for women that are aged 40 or more.

⁸⁵ A mature egg is defined as a metaphase II egg (MII) i.e. an egg that has entered metaphase of the second meiotic cycle. Only mature eggs can be fertilized. Eggs at retrieval can also be “immature: i.e. a germinal vesicle or metaphase I egg. These immature eggs cannot be fertilized by a sperm.

⁸⁶ Although exact statistics are difficult to find, it involves tens of thousands of couples annually. The global industry of commercial surrogacy (where women are paid to carry children) is worth nearly 6 billion US dollars (Deonandan, 2015).

basically secondary to: 1) legal unavailability of some services in certain countries, 2) differences in cost between countries and 3) different success rates of the same procedures in different countries.

Fortunately, in the US there is a wide availability of services and excellent success rates. Unfortunately the cost is often prohibitive.

There are few caveats that need to be taken into serious account when considering going to another country to receive medical care:

- If medical complications occur, it might be very difficult to receive proper medical treatment. Further, your insurance might not cover the services.
- Legal: there might be different laws regulating fertility treatments.
- Language and cultural barrier.

6. Performing Preimplantation Genetic Screening (PGS) of the Embryos

Advanced technology allows for screening the chromosomes of embryos. Since there is an increase in chromosomal errors in embryos originating from older women, the ability to find embryos without chromosomal errors offers the advantage of transferring only normal embryos with a higher chance to implant.⁸⁷

Incidence of Chromosomal Anomalies in Embryos According to Maternal Age	
Maternal Age	Chromosomal Anomalies
<35	30%
40	50%
45	95%

There is currently (2015) an intense debate over who should be offered PGS. Some providers believe that every patient should be offered this opportunity. Others

⁸⁷ Of note, the implantation rate of euploid embryos is only 50–60%. This means that 40–50% of chromosomally normal embryos tested by PGS will not implant.

believe that the technique could be damaging to the embryo,⁸⁸ is costly⁸⁹ and requires freezing the embryos.⁹⁰

I am a believer that PGS is an excellent choice for patients with

- A genetic disease that can be tested
- Recurrent pregnancy loss
- Recurrent IVF failure (if there are a high number of embryos to select from)

⁸⁸ The technique requires the embryos to grow to the blastocyst stage. If you have very few embryos, some doctors (I am one of those) prefer to transfer embryos earlier, at the cleavage stage, because they believe that embryos could grow in the mother but not in vitro (since the culture conditions are not ideal and not as good as the maternal uterus). Overall only 50% of embryos make it from the third to the fifth day of development.

⁸⁹ Approximately \$5,000 US.

⁹⁰ It takes often several days to obtain the result of PGS testing. The uterus will not be ready to accept an embryo so late, as the “window of implantation” has closed.

Appendix

Common abbreviations and definitions⁹¹

Doctors tend to use a large series of abbreviations. It is important to get familiar with the most common ones:

ART: Assisted Reproductive Technologies; this general term refers to any technology that requires the extraction of egg and sperm from the body.

Donor cycle: the use of eggs or sperm from another person (the donor). In the US, the donor can be anonymous. A large number of cases of egg and sperm donation are performed in the US. Oocyte and embryo donations now account for approximately 18% of in vitro fertilization births in the US.

Ectopic pregnancy: pregnancy resulting from an embryo implanting outside of the uterus, which is NOT conducive to live birth and may represent a medical emergency.

E₂ (estradiol): Estradiol is the female sex hormone and the most powerful type of estrogen.⁹²

Embryo transfer: The process of transferring an embryo into the uterus. It is done with a small catheter.

Fresh cycle: An IVF cycle in which embryos are immediately transferred and not frozen. As of 2015, this is one of the most common procedures.

FET or Frozen Embryo Transfer: a cycle that uses embryos formed in a prior cycle; the embryos were frozen and will be thawed immediately prior to the transfer process.

⁹¹ Not much different since the time of the Babel Tower, doctors often disagree on exactly what a definition should be. I used the most common definition, but you might find slightly different ones.

⁹² The number 2 refers to the fact that there are two OH groups attached to the main molecule. The other types of estrogen are estrone (E1: one OH group!) or Estriol (E3: 3 OH groups).

Follicle: the anatomical structure that houses the egg.

Fresh (embryo) cycle: It is one IVF cycle in which eggs are collected, an embryo formed and then transferred. It is usually simply referred as a “fresh” cycle.

Frozen (embryo) cycle: It is one IVF cycle in which one or more frozen embryos, generated during a prior IVF cycle, are thawed and transferred to the uterus. This protocol is simpler and requires fewer medications than a fresh cycle. It is usually simply referred as a “frozen” cycle.

FSH: Follicular Stimulating Hormone. It is responsible for making follicles grow.

HCG: Human Chorionic Gonadotropin. This hormone is produced by the placenta⁹³ and it is therefore the hormone of pregnancy. It is often used to monitor the health of early pregnancy and to rule out an ectopic pregnancy. Because it has very similar function to LH, it is also used to induce ovulation!

HMG: Human Menopausal⁹⁴ Gonadotropin; it is a hormone that contains both FSH and LH and is used to induce follicular growth.

HSG: Hysterosalpingogram; this is a test often done to assess if the fallopian tubes are open, i.e. if they would allow egg and sperm to meet

ICSI: Intracytoplasmic Sperm Injection; the procedure performed to introduce a spermatozoon⁹⁵ inside of the egg, with a very small glass needle.

IUI: Intra-Uterine Insemination; the process of introducing a selected number of spermatozoa into the uterus.⁹⁶ The procedure is simple and requires introducing a catheter into the uterus and releasing the spermatozoa close to the end (“fundus”) of the uterus.

LH: Luteinizing Hormone. This hormone is responsible for inducing ovulation.⁹⁷

⁹³ Only in primates! Your cat and dog do not produce this hormone in pregnancy.

⁹⁴ In menopause there are very high levels of FSH and LH. This hormone was originally collected from the urine of post-menopausal women!

⁹⁵ The embryologist will choose a moving spermatozoon. This is the key requirement for the procedure.

⁹⁶ An important point: to be successful, there needs to be a minimal number of actively moving spermatozoa—usually at least 5 million.

⁹⁷ Many ovulation predictor kits are based on detecting this hormone in the urine.

OI: Ovulation Induction; using medications to induce ovulation. A closely related term is superovulation: using medications to induce growth of many follicles.

IVF: In Vitro⁹⁸ Fertilization. This indicates the actual process of fertilizing eggs in a dish, outside the body. The alternative way to fertilize eggs is ICSI.

REI or RE: Reproductive Endocrinologist and Infertility is your fertility doctor—an obstetrician and gynecologist who specialized for an additional three years (the so called “fellowship”) in the fertility field.⁹⁹

Less Common Abbreviations for Those Who May Be Curious

Gonadotropins: Drugs used to stimulate follicular growth. They include analogues of the hormones FSH and LH.

GIFT: Gamete Intra-Fallopian Transfer; the procedure to introduce egg and sperm into the fallopian tube. This procedure has only an historical value and is no longer performed. It requires performing a surgery (a laparoscopy) with full anesthesia.

OPK: Ovulation Predictor Kit; a kit used to detect ovulation. It measures the levels of the hormone LH in the urine.

NIFT: Non IVF Fertility Treatment; includes all the procedures used to enhance fertility that do not require removal of eggs and creation of embryos in vitro.

SART: Society of Assisted Reproductive Technologies; the professional organization that collects and publishes data on the success of IVF clinics.

SAS: Saline Sonogram or sonohysterogram; the ultrasound performed to assess if the cavity of the uterus is normal and does not have any lesions that could increase the risk of miscarriage

⁹⁸ *Vitro* in Latin means “glass.” The original procedure was performed in glass dishes. Now it is performed in plastic dishes.

⁹⁹ A note for patients having care in a university center: You might see Fellows performing part of your tests or caring for you. Of note, Fellows are fully trained Obstetrician-gynecologist that are legally able to deliver babies and perform advanced gynecologic surgeries, like hysterectomies, by themselves! Their training is superb. They were likely at the top of their class to be selected into a highly competitive REI fellowship program.

TMC: Total Motile Count; the total number of motile spermatozoa present at the time of ejaculation or at the time of intrauterine insemination.¹⁰⁰ It is an important number, since if it is less than 5 million the success of IUI is lower.

ZIFT: Zygote Intra-Fallopian Transfer; the procedure to introduce a fertilized egg (called a zygote) into the fallopian tubes. As for GIFT above, it has only an historical value.

Sperm-Related Abbreviations

Asteno spermia (“*Asteno*”: “tired” in Latin): The presence of fewer moving sperm than the standard threshold. Usually an ejaculate should have at least 50% spermatozoa with good motility.

AzospERMIA (“A zoo”: from the Greek “lack of”): Absence of sperm in the ejaculate.

Oligospermia: (“*Oligo*” from the Greek “few”): Sperm count below a defined threshold. Often it is considered to be less than 15 million spermatozoa per milliliter.

Teratospermia (“*teratos*” from the greek “monstrous”): Sperm with abnormal morphology (i.e. shape, form).

Surgical Techniques

MESA: Microsurgical Epididymal Sperm Aspiration; the removal of sperm from the epididymis. It is done with a microscope and sophisticated equipment.

PESA: Percutaneous Epididymal Sperm Aspiration; the removal of sperm from the epididymis (i.e. a sperm reservoir on top of the testicle). Can be done relatively easily with a syringe and a needle.

TESA: Testicular Sperm Aspiration; the removal of sperm from the testicle with a syringe and a needle.

¹⁰⁰ Some people call this parameter “inseminating motile count after washing.”

TESE and micro TESE: Testicular Sperm Extraction; the removal of sperm from the testicle. The micro TESE requires a microscope and sophisticated equipment.

Causes of Infertility

Figure 9 provides an overview of the most common causes of infertility.

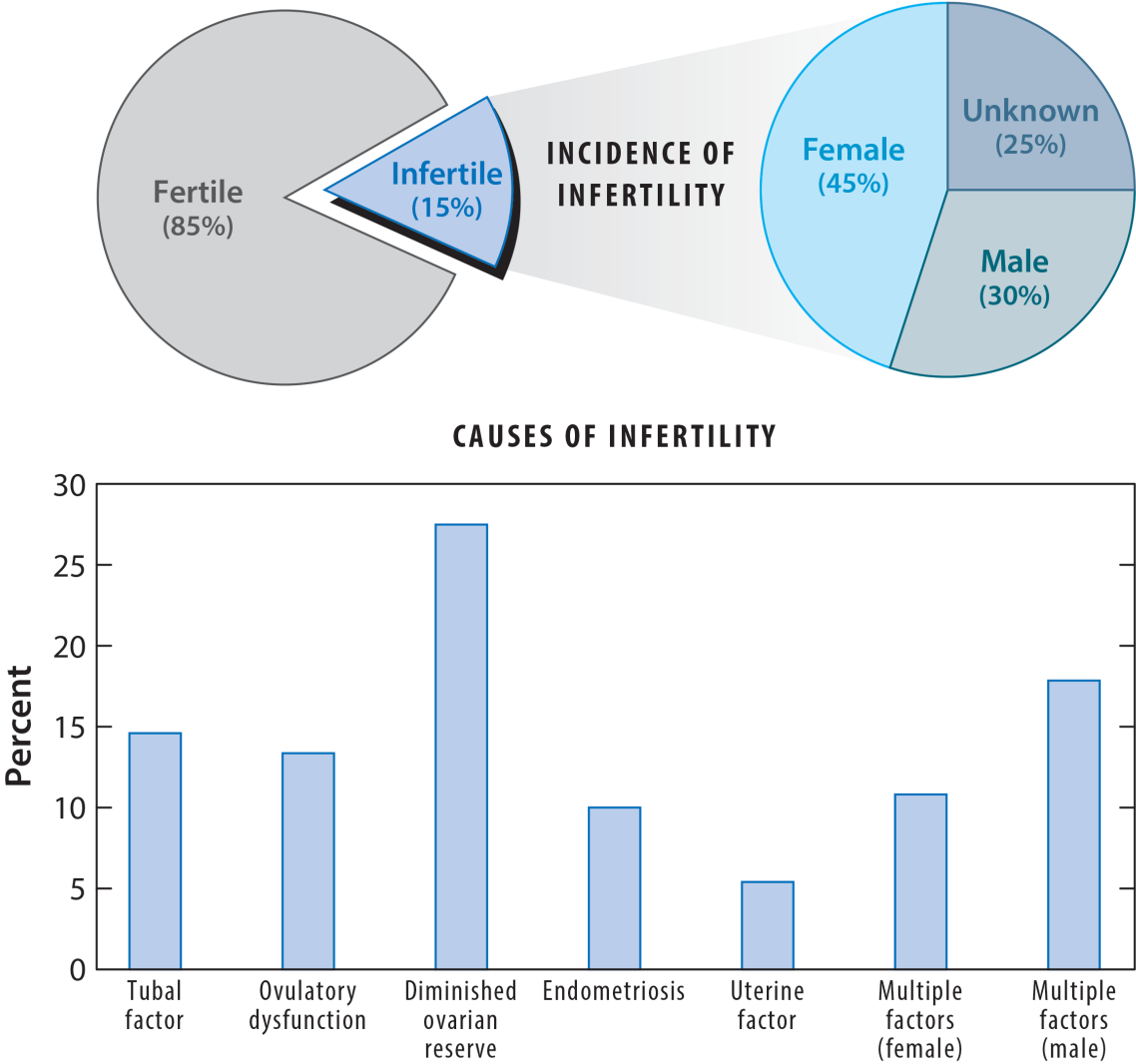


Figure 9: Causes of Infertility

*Top panel: Approximately one in seven couples are affected by infertility, i.e. the inability to conceive within a year. It can be broadly assumed that 45% of the causes are related to a female problem, 30% to a male problem and 25% are unexplained, i.e. all the test results are normal but still the couple cannot conceive. The **bar graph** shows a more detailed analysis of the reasons of female infertility. It is also common that more than one factor is responsible for the decrease in fertility, sometimes involving both a male and a female origin.*

SART Data

Figure 10 is a copy of the US national success rates of all IVF clinics that report data to SART (www.sart.org).

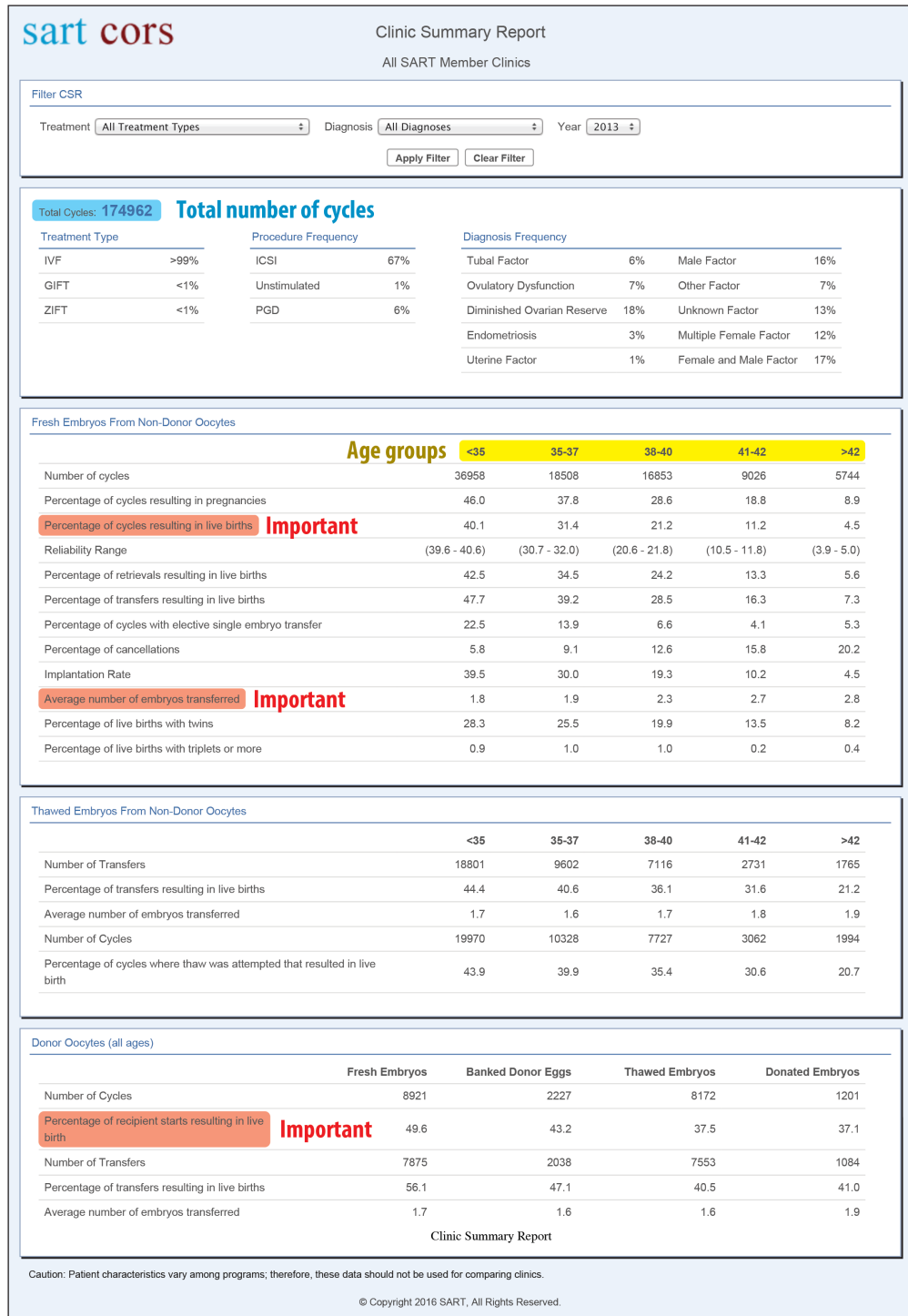


Figure 10: How to Read a SART Graph.

Approximately 94% of the IVF centers report their IVF success rates¹⁰¹ to the Society of Assisted Reproductive Technologies reports every year (www.sart.org). This data is easily available for online view.

The table included represents the US data summary for 2013 (there is an approximate two year lag from the availability of data and reporting). You should go online and compare your desired clinic's statistics with the national statistics. If the clinic of your choice has a success rate close to the national average for your age group, you can be comfortable using it. If the success of the clinic that you are assessing is significantly lower than the national average, I would consider¹⁰² using a different clinic.

While there are multiple useful statistics, the key data points to focus on are the following:

- ***The total number of cycles performed at the specific clinic.*** *Too few cycles (and sometimes too many) might be a problem.*
- ***The age group.*** *You should focus on the success rate in your own age group.*
- ***Percentage of cycles resulting in live birth.*** *This represents the chance of having a child when you start one “fresh” cycle. For example, in 2013, in women who were 34 years old or younger, the chance of having a baby was 40.1%. In my mind this is the most important parameter—the pregnancy rate (row above) is higher, but this includes pregnancies that end up in miscarriage or are ectopic (outside of the uterus).*
- ***Percentage of live birth with twins.*** *This is also very important. Since twin gestations are more risky for both maternal and infant health, I would be wary of clinics that have both a very high live birth rate per cycle and a high twin rate.*
- ***Percentage of recipients¹⁰³ resulting in live birth.*** *This statistics refer to the chances of pregnancy while using donor eggs.*

¹⁰¹ There is no central reporting of success of ovulation induction and intrauterine insemination cycles.

¹⁰² Very important to remember that different clinics cannot really be compared. However, this provides a general guideline.

¹⁰³ Recipients are women who receive eggs from a younger woman (the egg donor).

Embryo Development

The process of embryo and fetal growth is incredibly beautiful and complex. It is also quite inefficient. In fact, on average:¹⁰⁴

- we obtain an egg from 80% of the follicles larger than 12 mm in the process of egg retrieval.
- 80% of the eggs are mature¹⁰⁵ and can accept a sperm.
- 80% of mature eggs fertilize (said in another way, 15–20% of oocytes fail to fertilize, even with ICSI).
- 40–75% of fertilized eggs grow to CD3 with a quality sufficient to transfer the embryo.¹⁰⁶
- 50% of embryos grow from CD3 to CD 5.
- Data from IVF suggest that even in the best prognosis patients, only 50% of embryos will attach to the uterus (the so called implantation¹⁰⁷ process). It is believed that a very common cause of lack of implantation is the presence of chromosomal anomalies in the embryo.
- With a positive pregnancy test, everything is the same as for a naturally conceived pregnancy!¹⁰⁸ Studies indicate that about 20 % of gestations end in miscarriage.¹⁰⁹ The risk of miscarriage is higher at the beginning of gestation. If a fetal heart rate is documented at eight to ten weeks of gestation, the risk of miscarriage is much lower, 5–10%.

Figure 11 shows pictures of embryo development during the preimplantation period.

¹⁰⁴ There is a big standard deviation. I have seen pregnancy in women who had only one follicle and not seen success in women with 30 or more follicles!

¹⁰⁵ Are arrested in the metaphase II of meiosis.

¹⁰⁶ Embryos that are of suboptimal quality do not have a chance to implant and therefore are not transferred.

¹⁰⁷ In older patients (with an age of 43 years or more) using their own eggs, the likelihood of an embryo implanting is less than 5%.

¹⁰⁸ Multiple gestations deserve careful monitoring.

¹⁰⁹ The miscarriage rate increases with age. In women 43 years or older, the miscarriage rate can be 50%.

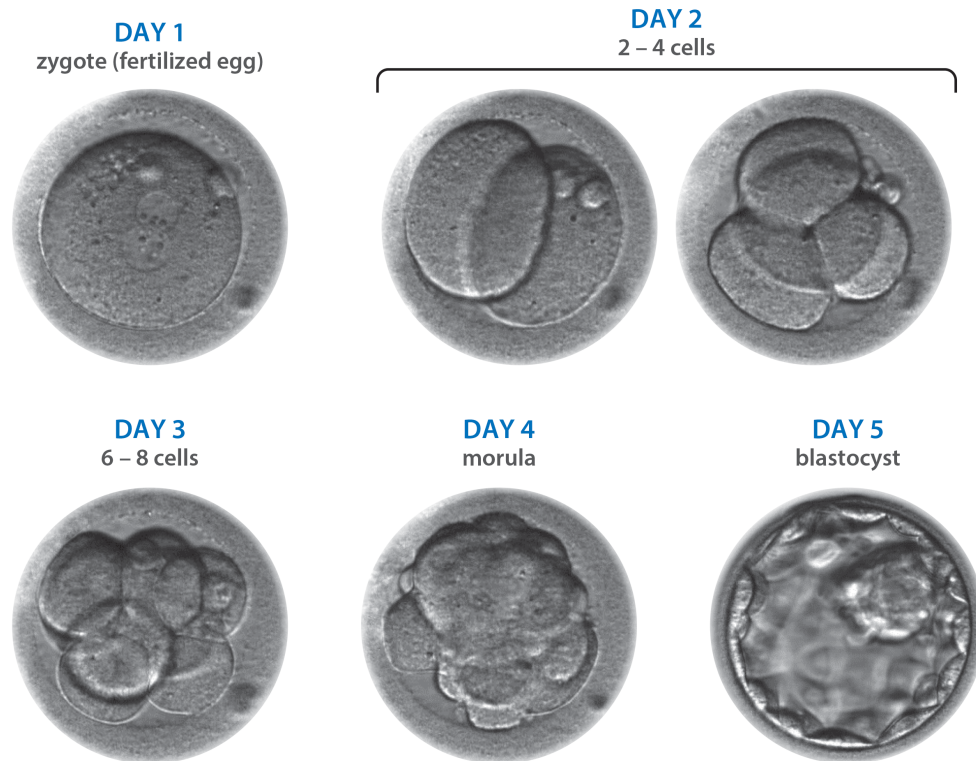


Figure 11: Embryonic Development

*The embryologist and your physician will identify the embryos that have the best chance of surviving. These embryos will either be transferred or frozen for future use. Some embryos will not divide properly and will not survive. The day after fertilization (**day one**) the embryo is called a zygote—the two circles at the center represent the paternal (slightly larger) and maternal nucleus, containing the chromosomes (the chromosomes contain the genetic material). On **day two**, the embryo has divided into two, three or four cells. On **day three** the embryo is usually six, seven or eight cells, sometimes more. On **day four** the embryo is called a morula. Embryos are not usually transferred on day four because all embryos look the same at this stage, hence it is not possible to recognize one that can survive from one that cannot. On **days five and six** the embryo has become a blastocyst with a cavity filled with fluid (the blastocoel), a group of cells that will form the embryo (the inner cell mass) and an external layer of cells that will form the placenta (called the trophoctodermal cells). Usually on day six the blastocysts start hatching—the process of exiting from the zona pellucida (a protective layer around the egg) to be ready to implant. The photo is a generous contribution by Dr. Danny Sakkas.*

Useful Books and Literature

Online Links

These excellent links are sponsored by professional societies in the US. The Society for Assisted Reproductive Technologies website provides pregnancy rate results for the great majority of clinics in the US.

www.asrm.org

www.iffs-reproduction.org/

www.sart.org

www.smru.org

For families and individuals interested in adoption:

www.adopting.org

<http://www.adoptionattorneys.org/>

For emotional support:

<http://www.drberman.org/hygeiafoundation>

www.fertilehope.org

www.resolve.org

For finding scientific articles of interest:

www.medlineplus.gov

www.scholar.google.com

Link with reviews of infertility books:

http://www.infertilitynetworkuk.com/information/book_reviews

General Books on Fertility Written for Patients

- *In Vitro Fertilization: The A.R.T. of Making Babies* (Assisted Reproductive Technology) by Geoffrey Sher and Virginia Marriage Davis, 2013
- *Taking Charge of Your Fertility, 10th Anniversary Edition: The Definitive Guide to Natural Birth Control, Pregnancy*, by Toni Weschler
- *What to Expect Before You're Expecting* Paperback – Black & White, May 15, 2009, by Heidi Murkoff (Author), Sharon Mazel (Contributor)

Books on Fertility Written for Health Professionals

- *Clinical Gynecologic Endocrinology and Infertility*, 2010 by Marc A. Fritz, MD and Leon Speroff, MD
- *Yen & Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management*, 2013 by Jerome F. Strauss III and Robert L. Barbieri

These two books are suggested for those truly interested in understanding the physiology of the menstrual cycle and the intricacies of the reproductive endocrinology world.

Articles on Specific Topics

The below articles are available for free in medical libraries. Often Google Scholar (<https://scholar.google.com/?hl=en>) will have several of these articles for free.

Egg Freezing

- **Cil AP, Bang H & Oktay K** 2013 Age-specific probability of live birth with oocyte cryopreservation: an individual patient data meta-analysis. *Fertil Steril* **100** 492–499 e493.
- **Goold I & Savulescu J** 2009 In favour of freezing eggs for non-medical reasons. *Bioethics* **23** 47–58.
- **Mertes H** 2015 Does company-sponsored egg freezing promote or confine women's reproductive autonomy? *J Assist Reprod Genet* **32** 1205–1209.
- **Mertes H & Pennings G** 2011 Social egg freezing: for better, not for worse. *Reprod Biomed Online* **23** 824–829.

Emotional Stress Experienced by Couples Undergoing Fertility Treatment

- **Baldur-Felskov B, Kjaer SK, Albieri V, Steding-Jessen M, Kjaer T, Johansen C, Dalton SO & Jensen A** 2013 Psychiatric disorders in women with fertility problems: results from a large Danish register-based cohort study. *Hum Reprod* **28** 683–690.
- **Barnes J, Sutcliffe AG, Kristoffersen I, Loft A, Wennerholm U, Tarlatzis BC, Kantaris X, Nekkebroeck J, Hagberg BS, Madsen SV & Bonduelle M** 2004 The influence of assisted reproduction on family functioning and children's socio-emotional development: results from a European study. *Hum Reprod* **19** 1480–1487.
- **Eugster A & Vingerhoets AJ** 1999 Psychological aspects of in vitro fertilization: a review. *Soc Sci Med* **48** 575–589.
- **Greil AL, McQuillan J, Lowry M & Shreffler KM** 2011 Infertility treatment and fertility-specific distress: A longitudinal analysis of a population-based sample of U.S. women. *Soc Sci Med* **73** 87–94.
- **Hogstrom L, Johansson M, Janson PO, Berg M, Francis J, Sogn J, Hellstrom AL & Adolfsson A** 2012 Quality of life after adopting compared with childbirth with or without assisted reproduction. *Acta Obstet Gynecol Scand* **91** 1077–1085.
- **Johansson M, Adolfsson A, Berg M, Francis J, Hogstrom L, Janson PO, Sogn J & Hellstrom AL** 2009 Quality of life for couples 4–5.5 years after unsuccessful IVF treatment. *Acta Obstet Gynecol Scand* **88** 291–300.
- **Lok IH, Lee DT, Cheung LP, Chung WS, Lo WK & Haines CJ** 2002 Psychiatric morbidity amongst infertile Chinese women undergoing treatment with assisted reproductive technology and the impact of treatment failure. *Gynecol Obstet Invest* **53** 195–199.
- **Verhaak CM, Smeenk JM, Evers AW, Kremer JA, Kraaijmaat FW & Braat DD** 2007 Women's emotional adjustment to IVF: a systematic review of 25 years of research. *Hum Reprod Update* **13** 27–36.

Fertility Financing Programs

- **Hawkins J. 2013** Selling ART: An empirical assessment of advertising on fertility clinics' Websites - *Ind. LJ*, - *HeinOnline*
- **Levens ED1, Richter KS, Levy MJ. 2013** Money-back guarantees. *Semin Reprod Med.* 31(3):198–203

Ovarian Reserve

- **Gleicher N, Weghofer A & Barad DH 2011** Defining ovarian reserve to better understand ovarian aging. *Reprod Biol Endocrinol* **9** 23.
This article is one of the best descriptions of ovarian reserve and ovarian aging.
- **Menken J, Trussell J & Larsen U 1986** Age and infertility. *Science* **233** 1389–1394.
This article analyzes fertility rate in multiple historical cohorts.

Reproductive Tourism

- **Deonandan R 2015** Recent trends in reproductive tourism and international surrogacy: ethical considerations and challenges for policy. *Risk Manag Healthc Policy* **8** 111–119.
- **Deonandan R, Green S & van Beinum A 2012** Ethical concerns for maternal surrogacy and reproductive tourism. *J Med Ethics* **38** 742–745.
- **Inhorn MC & Patrizio P 2009** Rethinking reproductive "tourism" as reproductive "exile." *Fertil Steril* **92** 904–906.
- **Inhorn MC & Patrizio P 2012** The global landscape of cross-border reproductive care: twenty key findings for the new millennium. *Curr Opin Obstet Gynecol* **24** 158–163.

Safety of Assisted Reproductive Technology

- **Feuer SK, Camarano L & Rinaudo PF 2013** ART and health: clinical outcomes and insights on molecular mechanisms from rodent studies. *Mol Hum Reprod* **19** 189–204.
- **Schultz RM & Williams CJ 2002** The science of ART. *Science* **296** 2188–2190.
- **Servick K 2014** 2014 Unsettled questions trail IVF's success. *Science* **345** 744–746.

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