CHAPTER-2

SCIENTIFIC ASPECTS OF SURROGACY

2.1 Overview of the Surrogacy Process

There are two types of surrogacy—traditional surrogacy and gestational surrogacy. In traditional surrogacy, a surrogate mother is artificially inseminated, either by the intended father or an anonymous donor, and carries the baby to term. The child is thereby genetically related to both the surrogate mother, who provides the egg, and the intended father or anonymous donor.\(^1\)

In gestational surrogacy, an egg is removed from the intended mother or an anonymous donor and fertilized with the sperm of the intended father or anonymous donor. The fertilized egg, or embryo, is then transferred to a surrogate who carries the baby to term. The child is thereby genetically related to the woman who donated the egg and the intended father or sperm donor, but not the surrogate. Some lesbian couples find gestational surrogacy attractive because it permits one woman to contribute her egg and the other to carry the child.

Traditional surrogacy is more controversial than gestational surrogacy, in large part because the biological relationship between the surrogate and the child often complicates the facts of the case if parental rights or the validity of the surrogacy agreement are challenged. As a result, most states prohibit traditional surrogacy agreements. Additionally, many states that permit surrogacy agreements prohibit compensation beyond the payment of medical and legal expenses incurred as a result of the surrogacy agreement.

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### 2.2 Finding a Surrogate

Sometimes a family member or friend offers to be a surrogate. This can greatly reduce the cost of surrogacy. However, because not everyone knows a woman in a position to volunteer to be a surrogate, most people find a surrogate through other means.

There are many full-service agencies/firms that will match intended parents to surrogates. When choosing an agency, it is imperative to research the agency’s history. Important questions to ask include how fees are determined and how surrogates are screened. If possible, it is often helpful to speak to former clients of the agency.

A selection of sample questions that parents should ask includes:

- Is the agency responsive to clients? For example, are they prompt in returning calls and e-mails?
- Is there more than one person who can respond if the parents’ primary contact is away or busy?
- Does the firm operate as a team?
- Regarding screening of potential surrogates:
  - Do they meet the surrogate in person?
  - Do they evaluate her home environment or is the screening limited solely to a telephone or office interview?
- Do they do reference checks?
- Do they routinely do criminal background checks?
- What kind of information do they obtain about the surrogate candidate’s prior pregnancies to minimize the risk that this will be a high-risk pregnancy?

Some parents choose to search for a surrogate independently. In this case, it is of the utmost importance that both intended parents and surrogates obtain legal advice before making any agreements or signing any contracts. A clear contract can prevent many potential conflicts during the process. Intended parents should also research a potential surrogate’s history to make sure that there is no cause for concern. Additionally, many states that allow gestational...
surrogacy prohibit traditional surrogacy and/or compensated surrogacy agreements as a caution against perceived coercion.

2.3 Surrogacy Qualifications

Most surrogacy agencies and fertility clinics require surrogates to meet the following general qualifications:

A. Be in good physical and mental health;

b. Have carried and delivered at least one child;

c. Have had pregnancies that were all free of complications and were full term;

d. Be less than 43 years of age (some clinics will accept older woman in certain circumstances; others have younger age cut-offs for all surrogates);

e. Be in a stable living situation; and

f. Not smoke or abuse alcohol.

2.4 The Process, Step by Step

There are many steps to becoming a surrogate mother in our surrogate program. They may vary slightly based on location, physician, and needs of the surrogate mother and intended parents. Below you’ll find a general framework of what to expect as a surrogate mother. And remember, we will be there walking you through each step as you progress through the process to make becoming a surrogate mother as easy as possible.

2.4.1 Step One: The Surrogate Mother Application and Evaluation Process

• Begin by filling out the online surrogate mother application. This application asks about your lifestyle, pregnancy, medical, and work history. It is crucial that you complete the application thoroughly and
honestly so that we may get to know you and match you with appropriate intended parents.

- If your application is accepted, you will receive a call from our surrogacy coordinator who will gather more information about you and your family.
- At this point, we ask for relevant surrogacy information such as medical records from all previous pregnancies.

2.4.2 Step Two: Matching Surrogate Mother with Intended Parents

Once you are accepted into our surrogate mother program, we will provide you with information about the intended parents so that all parties can mutually select who they would like to work with. Once everyone feels comfortable with the profile selection, the surrogacy coordinator will arrange a meeting between all parties to discuss the partnership and expectations. This is one of the most important, crucial, and reaffirming steps in the surrogacy journey—establishing a connection between the surrogate and hopeful intended parents.

2.4.3 Step Three: Surrogate Mother Medical Work Up

You will be meeting at the IVF clinic with the intended parents’ physician, who will speak with you in detail and perform a surrogacy information assessment. The work up varies from clinic to clinic but will often include:

- Vaginal ultrasound (a probe is inserted into the vagina enabling the technician to look at your uterus for polyps, scar tissue, and lining thickness)
- Physical and pap smear
- Hysteroscopy- A procedure where a small camera is placed in the uterus to look at the uterine cavity
- Medical instruction of the IVF cycle, injections, medication use, and embryo transfer
2.4.4 Step Four: Surrogate Mother IVF Cycle

The IVF nurse will give you full instructions and details about the medications needed, the medical protocol, any restrictions, and expectations. In preparation for your uterus to receive embryos created by the couple:

- You will most likely be asked to take estrogen and progesterone in patch, pill, suppository, or injection form. You may also be asked to take a birth control pill to regulate and synch your menstrual cycle with the intended mom or egg donor.
- You will have your blood drawn and ultrasounds regularly to monitor the progress of the cycle.
- You will have an embryo transfer where a small catheter is inserted into your vagina and through to your uterus. The embryos will be placed through the catheter and into the uterus for anticipated implantation.

2.4.5 Step Five: Surrogate Mother Pregnancy and Delivery

This pregnancy may be different from your own pregnancies in that it is conceived via In Vitro Fertilization and requires a little more early attention than your past pregnancies.

- You may be asked to have your blood drawn, ultrasounds, or other procedures far more regularly than with “natural” pregnancies.
- There is a possibility of multiples that may require additional office visits, bed rest, or other monitoring.
- This pregnancy is shared with the loving intended parents, and therefore there requires ongoing communication about the developing fetus, your health status, needs for support, or other matters.
- You will be participating in support groups that are offered in person and on-line in order to assure that all of your questions are answered and that you have support from other surrogate moms.
• Delivery is a very special time for all involved. Our mental health professional will meet with both the gestational carrier and the intended parents to create a birth plan that will attempt to meet everyone’s needs.2

2.5 FERTILITY TREATMENT OPTIONS

2.5.1 *In vitro fertilization (IVF)* 3: Eggs are removed from the ovaries and fertilized with sperm in a laboratory dish before being placed in the woman’s womb. IVF literally means ‘fertilization in glass’, giving us the familiar term ‘test tube baby’.

2.5.2 *Intra-cytoplasmic sperm injection (ICSI)*: ICSI involves injecting a single sperm directly into an egg in order to fertilize it. The fertilized egg (embryo) is then transferred to the woman’s womb.

2.5.3 *Intra Uterine insemination (IUI)*: Before fertility treatment, the best quality sperm are selected. They are then inserted into the womb at the woman’s most fertile time, when an ovary releases an egg (ovulation).

2.5.4 *Donor insemination (DI)*: Sperm that has been screened for sexually transmitted diseases and some genetic disorders from a donor is used to fertilize a patient’s egg. DI is IUI (intrauterine insemination) with donor sperm.

2.5.5 *Embryo testing*: Testing that enables people with a specific inherited condition in their family to avoid passing on this condition to their children. Includes PGD, PGS and sex selection. Testing can also be carried out to find a tissue match for an existing sick sibling (PTT).

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2.5.6 Gamete intra-fallopian transfer (GIFT): Eggs are removed from the ovaries and the healthiest are selected and placed together with sperm in the woman’s fallopian tubes. Fertilization therefore takes place in the body, as it would if conception had occurred naturally.

2.5.7 In Vitro Maturation (IVM): Eggs are removed from the ovaries and are collected when they are still immature. They are then matured in the laboratory before being fertilized. This means that the woman does not need to take as many drugs before the eggs can be collected as she might if using conventional IVF, when mature eggs are collected.

2.5.8 Reproductive immunology: Reproductive immunology is a service offered by a few fertility clinics in the UK. It includes a range of tests and treatment to do with the patient’s immune system in pregnancy.

2.5.9 Surrogacy: Surrogacy is when another woman carries and gives birth to a baby for you.

2.5.10 Fertility drugs: If you aren’t ovulating properly (producing and releasing an egg each month), fertility drugs – which trigger egg production in much the same way as your body’s own hormones – can help.

2.5.11 Surgery: Sterilization can sometimes be reversed, fallopian tubes can be unblocked using keyhole surgery and, for men, sperm can be retrieved surgically for use in fertility treatment.
2.6 Available Programs for Intended Parents

2.6.1 Unlimited IVF Plan

Circle Surrogacy has an exclusive arrangement to offer Circle’s intended parents the only Unlimited IVF plan in existence that promises continuing IVFs until you have a baby for the low price of $33,750. This is an all inclusive financial package for all procedures involved in IVF, whether fresh or frozen cycle, all medications, all standard screening tests, all lab fees done at PFCLA, etc. The only limitations on the program are that the donating woman must be under 30 and the Intended Parents must agree to implant 2 embryos per cycle.

2.6.2 Gestational Surrogacy

The Gestational Surrogacy using Intended Parent Eggs program is designed for intended parents who have the ability to provide all of the needed biology to create embryos but require the assistance of a gestational surrogate. Circle staff assists you in the selection of an IVF center if you are not already established with a medical team. You are then matched with a gestational surrogate that meets your legal, psychological and emotional needs.

2.6.3 Gestational Surrogacy using Your Own Egg Donor

Many times, intended parents (IPs) begin a gestational surrogacy process needing a surrogate and an egg donor; however they have a family member or friend that is willing to be their donor.

In this situation, intended parents can begin their journey with Circle by connecting with an IVF center and asking Circle to match them with a gestational surrogate that meets their legal, psychological and emotional needs. Circle staff provides screening, coordination, and contracts for your donor during the process.

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2.6.4 Gestational Surrogacy with Egg Donation

Intended parents often have the need for both a gestational surrogate and an egg donor. In the Gestational Surrogacy with Egg Donation program, Circle Surrogacy staff coordinates a surrogacy journey that allows you to work with the IVF clinic of your choice. If you are not already connected with an IVF clinic, Circle staff can make recommendations and provide you with personal introductions. Once established with an IVF clinic, Circle staff helps you to select an egg donor from our network of egg donor agencies and clinics. Once you have selected an egg donor, you are matched with a gestational surrogate that meets your legal, psychological and emotional needs.

2.6.5 Frozen Egg Bank Program

One of Circle’s lower cost options is the Frozen Egg Bank program. When you need donor eggs, whether or not you need a surrogate, the Frozen Egg Bank allows you to select from eggs that have already been frozen from fully screened egg donors and are ready to use in an IVF cycle.

2.6.6 Circle Egg Donation

For intended parents who do not require a gestational surrogate but need the assistance of an egg donor, Circle Surrogacy’s access to over 1,000 egg donors can help you find the donor that meets your unique requirements. Speak to a member from Circle’s staff to discuss the differences between known and anonymous donors; first time donors, donors with proven fertility and proven donors. Understanding your options and making a selection can be an overwhelming prospect. At Circle Surrogacy, we aim to make that choice easier for you.
2.7 Egg Donation

2.7.1 What is Egg Donation?  
In egg donation, eggs are borrowed from a young woman (less than 33 yrs of age) called the donor, with her consent. These eggs are then fertilized with the sperms of the husband of the recipient woman and the resultant embryo (the earliest form of the baby), is inserted into the womb of the recipient. The success rate of this procedure is in the region of 30 to 40%. In fact, many women till the age of 50-55 have become pregnant by this technique. You will be surprised that the oldest woman pregnant by this procedure is 69 year old, residing in Italy. At Babies and Us, the oldest woman who has conceived with this technique is 62 years of age. This is probably the oldest woman to have become pregnant, in India.

Infertility India is an anonymous egg donation centre that provides personal attention and support to both egg donor and recipient. Check the online information about Egg Donation Clinic, Egg Donation & Egg Donation Centre in India.

2.7.2 Who can qualify for Egg Donation?
A. In this day and age more and more career oriented women are getting married late in life. By the time they start planning to have children; they are nearing the fourth decade of their life (40 years). Fortunately, at this age, many women can conceive naturally. However nearly 10 to 15% women fail to conceive within a year's time. These women who are more than 37-40 years of age then resort to treatment of infertility by their gynecologist. If they still do not become pregnant they take help of newer technologies like IVF - In Vitro Fertilization (test-tube baby) or ICSI - Intra Cytoplasmic Sperm Injection. Women after the age of 40 tend to have fewer eggs in their ovaries or the quality of the eggs they produce may be poor.

Thus, even new technologies like IVF and ICSI may not ensure a successful pregnancy. Furthermore, after the age of 40 to 42, many women stop producing eggs as they enter the stage of per menopause (decreased periods) or menopause (stoppage of periods). Till now, such women could only have a baby through the wonderful route of adoption. However, in the last ten years, a new technique of egg donation has come as a blessing to many such women.

B. In India, preference is given to younger couples to adopt children. Couples over the age of 45 can adopt, but find it difficult to do so, because of Governmental preference for younger parents. Such couples can tremendously benefit by egg donation.

C. Egg donation can also be performed on women who have had multiple cycles of test-tube baby (IVF or ICSI) and have still failed to conceive and become pregnant.

D. Besides elderly or menopausal women, egg donation can be done in younger women whose ovaries have prematurely failed or in young women who have undergone radiation or chemotherapy for cancer. Radiation or chemotherapy destroys the eggs and hence these women have a failure of their ovaries.

E. Egg donation is also used in patients who are carrying major chromosomal defects so that they do not pass the genetic defect to their children.

F. Patients suffering from severe Tuberculosis and severe Endometriosis6 may also produce poor quality eggs and hence can be treated by egg donation.

2.7.3 How are the Donors screened?

Generally, eggs are borrowed from healthy women less than 30-35 years of age and who are not suffering from any illness or genetic disorders. These young women, also called donors, are specially screened for AIDS and Hepatitis. Their family history is taken, to rule out any genetic problems. The donor can be married or unmarried. However, married donors with children would be preferable, primarily because they will have established their ability to bear children.

2.7.4 How is the procedure done?

The staff will coordinate the cycles of the donor and recipient to accomplish a fresh embryo transfer whenever possible. Synchronization of cycles includes using a series of medications to facilitate a hospitable uterine environment for the transfer of embryos. During egg donation, the donor is given injections to produce many eggs. When these eggs are ripe, she is given a short anesthesia and the eggs are removed from inside the vagina without giving a cut on the abdomen. The donor can return home three to four hours after the procedure. The eggs are then fertilized with the recipient's husband's sperms in the laboratory, either by IVF or ICSI and kept in the incubator for two days.

In case the recipient's husband's sperm is of poor quality; the eggs can be fertilized by the technique of Intra Cytoplasmic Sperm Injection (ICSI). Two days later, a four-celled embryo is formed. Three days later, an eight-celled embryo is formed or five days later a multi-celled Blastocyst is formed. This embryo (small baby) is then transferred back to the womb either at the four cell, eight cells or the Blastocyst stage. 30 to 40% of such women will become pregnant. In case they fail to become pregnant they can have a repeat egg donation cycle. Many women undergo two to four cycles and achieve their goal of a child.

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2.7.5 Who can be a Donor?

A. As easy as the method may sound, the biggest problem faced by both doctors and patients is the availability and source of egg donors. Ideally, the best donor would be her own sister or near relative from her side (not from husband's blood relative). However, in this day and age of small nuclear families many times it is difficult to get such donors. Furthermore, it is very important that if there is a sister donating eggs, there should be a very good mental understanding between the sisters. The donor is not anonymous in this case and thus many a time there are possibilities of inter-personal conflicts arising when the child becomes older. We also accept recipients who have identified their own non anonymous donors.

B. The other and the most acceptable donor would be a voluntary unrelated donor. There are a lot of women who may just out of altruistic (philosophical) reasons donate eggs to women who are suffering from the trauma of infertility. It is important to popularize such egg donation. However, even in an advanced society like Britain's, there is a great dearth of voluntary egg donors, in spite of extensive advertisement in the press. By voluntary egg donation, we mean donation of the eggs by the donor without expecting any monetary or other reward in return.

C. The third area, which can be a source of donors can be a paid donor. You may be surprised that this is legal in USA and young college girls are paid as much as US$6,000 for donating their eggs. But in a protestant society like Britain's, this form of donation is considered illegal and unethical. Even in the Indian society, where there is no law on egg donation at present, such kind of paid donation may not be socially and culturally acceptable. Clinics in India do not practice paid donation. Recently the Govt. of India has appointed Indian Council of Medical Research to legalize infertility practice in this country including that of egg donation, embryo donation, semen donation & surrogacy. The ICMR has legalized paid egg donation and surrogacy. In all the groups of related, voluntary or paid donors, there is a certain degree of risk the donor is exposed to. The donor is given multiple injections to produce eggs, as well as a shot anesthetic. She is also exposed to the risk of surgical egg removal.
D. Hence, there evolved a new concept of shared egg donation which started in Britain but is now popular in the USA and also in India. There are many young women who are infertile due to other reasons and who also need the procedure of IVF or ICSI. However, they cannot afford to spend money for these procedures. Many of these women produce 8 to 10 eggs during their treatment. These patients are asked to share some of their extra eggs with the recipient. This is done by taking the informed consent of the young woman. In return, a part of the expense of medical treatment of the young woman is borne by the recipient. Thus, both the donor as well as the recipient who need IVF is benefited, without any extra amount of risk to the donor. The anonymity of both-the donor and the recipient- is maintained so that they don't know each other. With the help of this technique, many young women who cannot afford IVF can mother a child. The same goes for elderly women who can afford IVF and can have a child. The process of egg sharing is an excellent example of symbiotic relationship between women, one with a physical need and one with a monetary need, with the ultimate common goal of bearing a child. It is a safe, effective, successful, legal, ethical and socially acceptable method of advanced reproductive technology.

2.7.6 What is the age limit of the recipient?

In general, any woman with a medical or genetic indication for using an egg donor can be a recipient, if there are no medical contraindications to pregnancy. Our current age limit is 55 years. The decision to utilize donor eggs is made in association with staff and consultants. If a male factor exists, donor egg with ICSI is also available. Generally a psychiatrist and a physician would assess a recipient. This is done to gauge the mental and physical fitness of the patient. This analysis is very important to withstand the pressures of childbirth.

2.7.7 What is the background of Recipients? The patients hail from all over the country. They are from different walks of life. Our unit facilities are also utilized by NRI patients (Non Resident Indians) from USA, UK, Africa, Middle East, Sri Lanka & Far East (Singapore). Some patients from other nationalities who hail from Asian countries...
2.8 IVF - In Vitro Fertilization (IVF)

2.8.1 What is IVF?

In vitro fertilization (IVF) literally means ‘fertilization in glass’ giving us the familiar term ‘test tube baby’.

During the IVF process, eggs are removed from the ovaries and fertilized with sperm in the laboratory.

The fertilized egg (embryo) is later placed in the woman’s womb. In 1977, Steptoe and Edwards successfully carried out a pioneering conception which resulted in the birth of the world's first baby to be conceived by IVF, Louise Brown on 25 July 1978, in Oldham General Hospital, Greater Manchester, UK.

The second successful birth of a test tube baby occurred in India just 67 days after Louise Brown was born. The girl, named Durga was created by Subhash Mukhopadhyay, a physician and researcher from Kolkata.

2.8.2 For whom this IVF is?

A clinic may recommend IVF as the best treatment option if:

- One have been diagnosed with unexplained infertility
- Ones fallopian tubes are blocked
- One have been unsuccessful with other techniques like using fertility drugs or intrauterine insemination (IUI)
If there is a minor degree of male sub fertility - more severe problems are treated with intra-cytoplasmic sperm injection (ICSI).

2.8.3 How does IVF work?

IVF techniques can differ from clinic to clinic, often depending on your individual circumstances.

A typical IVF treatment may involve:

2.8.3.1 for women:

Step 1. Suppressing the natural monthly hormone cycle

- As a first step of the IVF process one may be given a drug to suppress her natural cycle.
- Treatment is given either as a daily injection (which is normally self-administered unless one is not able to do this herself) or a nasal spray. This continues for about two weeks.

Step 2. Boosting the egg supply

- After the natural cycle is suppressed if one is given a fertility hormone called FSH (or Follicle Stimulating Hormone). This is usually taken as a daily injection for around 12 days.
- This hormone will increase the number of eggs you produce - meaning that more eggs can be fertilized. With more fertilized eggs, the clinic has a greater choice of embryos to use in your treatment.

Step 3. Checking on progress

- Throughout the drug treatment, the clinic will monitor your progress. This is done by vaginal ultrasound scans and, possibly, blood tests.
- 34–38 hours before your eggs are due to be collected you have a hormone injection to help your eggs mature.
Step 4. Collecting the eggs

- In the IVF process eggs are usually collected by ultrasound guidance under sedation. This involves a needle being inserted into the scanning probe and into each ovary.
- The eggs are, in turn, collected through the needle.
- Cramping and a small amount of vaginal bleeding can occur after the procedure.

Step 5. Fertilizing the eggs

Figure-2.2

- Ones eggs are mixed with partner’s or the donor’s sperm and cultured in the laboratory for 16–20 hours. They are then checked to see if any have fertilized.
- Those that have been fertilized (now called embryos) are grown in the laboratory incubator for another one - two days before being checked again. The best one or two embryos will then be chosen for transfer.
- After egg collection, you are given medication to help prepare the lining of the womb for embryo transfer. This is given as pessaries, injection or gel.

Step 6. Embryo transfer

- For women under the age of 40, one or two embryos can be transferred. If women are 40, or over, a maximum of three can be used.
- The number of embryos is restricted because of the risks associated with multiple births. Remaining
embryos may be frozen for future IVF attempts, if they are suitable.

**Step 7. Other treatments**

- Some clinics may also offer blastocyst transfer, where the fertilized eggs are left to mature for five to six days and then transferred.
- For information about embryo transfer, and the different methods used see:
  1. Embryo transfer
  2. Blastocyst transfer
  3. Assisted hatching

### 2.8.3.2 for Men:

**Step 1. Collecting sperm**

- Around the time one’s partner’s eggs are collected, man is asked to produce a fresh sample of sperm.
- This is stored for a short time before the sperm are washed and spun at a high speed. This is so the healthiest and most active sperm can be selected.
- If one is using donated sperm, it is removed from frozen storage, thawed and prepared in the same way.

### 2.8.4 IVF - Get started

**Figure-2.3**

- If a woman is having problems getting pregnant, her first call should be to her GP. They will look at your medical history, give her a
physical examination and may recommend some tests or lifestyle changes.

- Her GP can also refer her to see a specialist at her local hospital or fertility clinic.

- **What to expect at the fertility clinic?**
  - When at the fertility clinic, her full fertility history will be taken and an examination carried out.
  - It may be that there are simple treatments that can be offered before in vitro fertilization (IVF) needs to be considered.
  - If IVF is indicated, your specialist will be able to refer her to an appropriate assisted conception unit.

- **What to expect at the assisted conception unit**
  - Be prepared to answer questions on her medical and social history. This allows the clinic to assess the impact of a potential birth on both the baby and on any other children she may have.
  - Once she is accepted for treatment, blood tests will be taken from both she, and if applicable, her partner. These include tests for HIV and Hepatitis B & C and she will be screened to ensure that you are immune to Rubella (German measles).
  - Her hormone profile will be also assessed. This is done via a blood sample taken early in the menstrual cycle to see if there is likely to be any difficulty in obtaining eggs and to detect any hormone imbalance.
  - Her clinician will then discuss your treatment plan with her in full.
  - She will also need to sign forms that consent to the use and/or storage of her sperm, eggs or embryos and consent to the disclosure of identifying information.
  - Counseling is always available and can be particularly helpful while going through this process.
2.8.5 IVF - Chance of success

- A woman’s ability to conceive a child reduces with age. If she is using her own eggs, on average, the younger she is the higher her chances of success.
- In 2010 (the year for which the most recent data is available) women having in vitro fertilization (IVF) using fresh embryos created with their own fresh eggs, the percentage of cycles started that resulted in a live birth (national averages) was:
  - 32.2% for women aged under 35
  - 27.7% for women aged between 35–37
  - 20.8% for women aged between 38–39
  - 13.6% for women aged between 40–42
  - 5.0% for women aged between 43–44
  - 1.9% for women aged 45 and over
- Please note that IVF and intra-cytoplasm sperm injection (ICSI) success are very similar and as such are no longer presented separately. The above results are for both IVF and ICSI together

2.8.6 IVF - The risks

A clinic will discuss the risks of in vitro fertilization (IVF) with woman before she begins treatment. It is very important that she is fully aware of all the potential problems involved.

2.8.6.1 Drug reaction

A mild reaction to fertility drugs may involve hot flushes, feeling down or irritable, headaches and restlessness. Symptoms usually disappear after a short time but if they do not, a woman should see a doctor as soon as possible.

2.8.6.2 Fertility drugs

- Ovarian hyper-stimulation syndrome (OHSS)
- OHSS can be a dangerous over-reaction to fertility drugs used to stimulate egg production. It can cause symptoms such as a swollen stomach, stomach pains, nausea and vomiting.
- If women start to experience any of these symptoms she must contact your doctor immediately.

2.8.6.3 Risks of fertility treatment: Miscarriage

Although the risk of a miscarriage after IVF is no higher than after a natural conception, nor is the risk lower.

- Her clinic will arrange an early pregnancy ultrasound scan if she conceives after IVF. This is to check that the pregnancy is not likely to miscarry. The scan is usually done about two weeks after the positive pregnancy test.

2.8.6.4 Ectopic pregnancy

- When an embryo develops in your fallopian tube rather than her womb, the pregnancy is said to be ectopic.
- An ectopic pregnancy can still occur after IVF. Ectopic pregnancy can cause vaginal bleeding, low pregnancy hormone levels and miscarriage.
- Hormone tests and scans are used to detect ectopic pregnancies and she should tell her doctor about any vaginal bleeding or stomach pain.

2.8.6.5 Multiple births

- Having a multiple birth (twins, triplets or more) is the single greatest health risk associated with fertility treatment.
- Her clinic should discuss this risk with her when deciding how many embryos to transfer in your treatment.
2.8.7 IVF treatment options

It is worth exploring the various in vitro fertilization (IVF) treatment options to ensure that you understand what is available:

2.8.7.1 Natural cycle IVF

Natural cycle IVF involves collecting and fertilizing the one egg that you release during your normal monthly cycle. No fertility drugs are used in this treatment.

- **What is natural cycle IVF?**
  - Natural cycle IVF involves collecting and fertilizing the one egg that you release during your normal monthly cycle. No fertility drugs are used in this treatment.

- **Is natural cycle IVF for me?**
  - It may be worth discussing this treatment option with your clinician if your periods are fairly regular and you are ovulating normally, but:
  - you are unable to take fertility drugs (for example, cancer patients or those whose clinician has suggested that they are at risk of OHSS – ovarian hyper-stimulation – a dangerous over-reaction to fertility drugs)
  - Because for personal or religious beliefs you do not wish to have surplus eggs or embryos destroyed or stored.

- **How does natural cycle IVF work?**
  - The treatment is the same as conventional IVF, but without the fertility drugs that are used to stop natural egg production and hormones that boost the supply of eggs.
  - As your ovaries aren’t being artificially stimulated, you don’t need to rest as you would after conventional IVF.
- If your treatment is unsuccessful, you can try again sooner if you wish.

- **What is my chance of having a baby with natural cycle IVF?**
  - Live birth rates are lower per treatment cycle than with conventional (stimulated) IVF. Because this treatment does not rely on any artificial aids, much depends on your individual circumstances. You may not produce an egg, it may not be collected at the right time or it may not develop into an embryo.
  - In the year from 01/01/2008 - 31/12/2008, for women receiving natural cycle IVF using fresh embryos created with their own eggs, the percentage of cycles that resulted in a live birth (National Averages) was:
    - **(1/26) for women aged under 35**
    - **(1/21) for women aged between 35-37**
    - **(0/34) for women aged between 38-39**
    - **1.3% (1/77) for women aged between 40-42**
    - **(0/25) for women aged between 43-44**
    - **(0/2) for women aged over 44**
    - **Percentages are not calculated where there are less than 50 cycles. Figures given in brackets are (cycles resulting in a live birth / all cycles started).**

- **What are the risks of natural cycle IVF?**
  - The risks with natural cycle IVF are lower than those with conventional IVF. Natural cycle IVF avoids the side effects of fertility drugs and you are less likely to have twins or triplets.
2.8.7.2 Mild stimulation IVF

With mild stimulation IVF, the woman is either given a lower dose of fertility drugs or is given them over a shorter period than with conventional IVF.

- **What is mild stimulation IVF?**
  With mild stimulation IVF you are either given a lower dose of fertility drugs or are given them over a shorter period than with conventional in vitro fertilization (IVF).

- **Is mild stimulation IVF for a woman?**
  Your clinic may recommend mild stimulation IVF if there is particular concern about possible adverse reactions to fertility drugs.

- **How does mild stimulation IVF work?**
  Mild stimulation IVF is similar to conventional IVF but with the following variations: a lower dose of fertility drugs is taken for a shorter period of time the fertility drugs taken do not suppress your natural cycle, unlike conventional IVF. This shortens the length of drug treatment by about two weeks and avoids menopausal side effects because lower doses of drugs are used, fewer eggs may be available for collection any embryos of suitable quality that are not used in treatment may be frozen and stored for your future use because fewer fertility drugs are used, if your treatment is unsuccessful, you may not have to wait as long to undergo further treatment.

- **What is IVF and how does it work?**
  What is my chance of having a baby with mild stimulation IVF?
  Not much data is available on mild stimulation IVF but as fewer eggs are available, your chances of having a baby may be lower than with conventional IVF.
• **What are the risks of this treatment?**
  The types of risks with mild stimulation IVF are similar to those with conventional IVF but are significantly reduced because smaller quantities of fertility drugs are used.

2.8.8 **Monitoring of embryo development:**

• To select the best embryo and to avoid early miscarriages.

• To make infertility treatment absolutely transparent (following the progress of embryo development on-line and exact analysis of developmental processes).

• IVF – in vitro fertilization, i.e. spontaneous fertilization

  During IVF eggs are placed together with washed spermatozoa\(^8\) and fertilization occurs spontaneously, similarly like in the oviducts of the mother.

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\(^8\) Developmental sperm contributions: fertilization and beyond Gerardo Barroso, M.D., M.Sc.a, Carlos Valdespin, M.D.a, Eva Vega, M.Sc.a, Ruben Kershenovich, M.D.a, Rosaura Avila, B.Sc.a, Conrado Avendaño, M.D.b, Sergio Oehninger, M.D., Ph.D.b. FertStert, Volume 92, Issue 3, Pages 835-848 (September 2009)
A disadvantage of this method is the low fertilization rate mainly in cases when the partner’s sperm is low-quality. Often fertilization is unsuccessful even though the sperm is assessed as good-quality in a semen analysis. Sometimes polyspermy occurs, when more than one sperm fertilize an egg – the resulting embryos are abnormal (have more chromosomes than normal) and so are rejected.

…to be on the safe side… especially in your first treatment cycle, when you don’t know yet whether your sperm can fertilize the eggs, have a part of the oocytes fertilized using ICSI, even though your semen analysis results state “normospermy”…

By this you lower the risk of canceling the cycle due to absence of fertilization to a minimum.

**Figure-2.4 ICSI – intra cytoplasmic sperm injection**

During ICSI one sperm is injected directly into the egg cytoplasm using an apparatus that transforms imperfect hand movements into fine and precise movements of micromanipulation tools.

This method is used in the following cases:
Abnormal semen analysis findings i.e. low sperm concentration or a high level of abnormal sperm with low motility,

Fertilization using sperm surgically extracted from testicles or the epididymis (using MESA/TESE techniques)

Failure to spontaneously fertilize in the previous cycle even though semen analysis results are positive

PICSI technique improves pregnancy rates and reduces the number of IVF miscarriages.

In the ICSI procedure, an individual sperm is selected and injected into an oocyte. Until now, the only technique available to embryologists to select the sperm has been visual observation. Using PICSI procedure we are able to determine sperm selection in much the same way it happens in human biology.

Sperms are placed in PICSI dish containing samples of hyaluronan hydrogel. Hyaluronan is a naturally occurring bio-polymer found in all human cells, including the gel layer surrounding the oocyte.

Mature, biochemically competent sperm bind to the hyaluronan where they can be isolated by the embryologist and used for ICSI. This procedure mimics a key step in the natural fertilization process, the binding of mature sperm to the oocyte complex. As a result, the selected sperm is essentially the same as one that would be successful in the natural reproductive process.

The research proved that hyaluronan-bound PICSI-selected sperm are, in the vast majority of cases, more mature, exhibit less DNA damage, and have fewer chromosomal aneuploidies.

The PICSI method to be a biologically more natural and effective form of fertilization in comparison to ICSI, because only those sperm are chosen for fertilization that are able to form a bond with the oocyte cumulus complex, i.e. only mature sperm are selected...

This method is suitable for everyone but highly recommend it especially in the following cases:

- Previous total failure or low fertilization even after ICSI
• Low embryo quality or their failure to develop
• Repeated abortions

2.8.8.1 What is intra-cytoplasmic sperm injection (ICSI) and how does it work?

Intra-cytoplasmic sperm injection (ICSI) involves injecting a single sperm directly into an egg in order to fertilize it. The fertilized egg (embryo) is then transferred to the woman’s womb.

The major development of ICSI means that as long as some sperm can be obtained (even in very low numbers), fertilization is possible.

2.8.8.2 Is ICSI for woman?

ICSI is often recommended if:

• the male partner has a very low sperm count other problems with the sperm have been identified, such as poor morphology (abnormally shaped) and/or poor motility (poor swimmers)
• at previous attempts at in vitro fertilization (IVF) there was either failure of fertilization or an unexpectedly low fertilization rate
• the male partner has had a vasectomy and sperm have been collected from the testicles or epididymis (sperm reservoir)
• other situations where the sperm count is zero and donor insemination is not wanted
• the male partner does not ejaculate any sperm but sperm have been collected from the testicles
The male partner has had problems obtaining an erection and ejaculating. This includes men with spinal cord injuries, diabetes and other disorders.

2.8.8.3 How does ICSI work?

The procedure for ICSI is similar to that for IVF, but instead of fertilization taking place in a dish, the embryologist selects sperm from the sample and a single sperm is injected directly into each egg.

**For women**

**Step 1.** She takes fertility drugs to stimulate her ovaries to produce more eggs, as for IVF.

**Step 2.** The eggs are then collected and each egg is injected with a single sperm from her partner or a donor. After two to three days in the laboratory, those that are fertilized are transferred to her womb in the same way as for conventional IVF.

Any suitable remaining embryos can be frozen for future use.

**Step 3.** Some clinics may also offer blastocyst transfer, where the fertilized eggs are left to mature for five to six days and then transferred.

**Step 4.** After the treatment, her clinic will arrange a date with her for her pregnancy test.

**For men**
Step 1. An embryologist will examine his sperm under a microscope and decide whether ICSI could increase his chances of fathering a baby.

Step 2. The next step depends on whether he is able to provide sperm without medical intervention:

If he can, he produces a fresh sperm sample on the same day as his partner’s eggs are collected.

–Or–

- Sperm can be collected directly from the epididymis (a narrow tube inside the scrotum, where sperm are stored and matured) using a type of fine syringe. This is known as ‘percutaneous epididymal sperm aspiration’ or PESA.
- Sperm can also be retrieved from the testicles, a process known as ‘testicular sperm aspiration’ or TESA.
- It is also possible to remove tiny quantities of testicular tissue from which sperm can be extracted. This procedure is called ‘testicular sperm extraction’ or TESE.

Step 3. A single sperm is injected into each egg. This does not mean that the egg is fertilized, but ICSI now gives an opportunity for that complex process to commence. ICSI is not a guarantee that fertilization will take place.

Step 4. Subsequently one - three of the best quality embryos are transferred to the womb.

- **In case of zero sperm count:**

  If a Man has a zero sperm count (other than caused by vasectomy), the chances of retrieving sperm surgically by PESA, TESA or TESE may be very low or at least uncertain.

  In this situation, consider having a surgical retrieval such as a ‘dummy run’ and store any sperm that are obtained. If no sperm are
retrieved the options of having Donor insemination (DI) or In vitro fertilization (IVF) with donor sperm can be considered instead.

**Noninvasive embryo imaging with detection of abnormal divisions leading to aneuploidy.**

Objective and non-invasive imaging of embryo characteristics allows detection of abnormal cleavages leading to the occurrence of chromosomal mal segregation which are a major cause of spontaneous miscarriage or birth defects.

Scanning and analyzing embryo development is a breakthrough approach in assessing human embryos in a culture medium. It is performed by a computer which continuously monitors the embryo’s development.

The embryos are not disturbed during their extra-corporeal development by constant examinations as the entire monitoring process happens behind closed doors of the incubator. Subsequent analysis is based on acquired digital records. The developmental abilities of human embryos can be predicted by measurement of their cell cycles. Continuous non-invasive embryo monitoring allows an exact measurement of these phases of human embryo development. The duration of the first 4 inter phases and synchrony of the daughter cells cleavages are expressed in Embryo Cleavage Rating (ECR) and correspond with regular ooplasmic, metabolites, and organelles distribution and with embryonic genome activation (EGA).

**PGD/PGS – Preimplantation Genetic Diagnosis/ Preimpl. Genetic Screening and ANEULOIDY PREDICTION**

**PGD – Preimplantation Genetic Diagnosis** is indicated in the cases of genetically transmitted diseases.

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Preimplantation Genetic Screening is indicated if meiotic errors are expected therefore, PGS is offered in the cases of advanced maternal age and severe male factor infertilities for example after TESE – surgical spermatozoa retrieval from testes.

Noninvasive aneuploidy prediction using continuous monitoring is used for elimination of embryonal chromosomal anomalies all the embryos determined for aneuploidy screening by PGS undergoes embryo monitoring and the cleavage analysis to avoid misdiagnosis due to the cell mosaicism.

1. All the embryos determined for aneuploidy screening by PGS undergo embryo monitoring and the cleavage analysis to avoid misdiagnosis due to the cell mosaicism.

2. Only morphologically normal 3 days old embryos(having 8 cells) are used for PGD/PGS biopsy procedure

2.8.8.4 What is pre-implantation genetic testing?

- Pre-implantation genetic testing involves carrying out tests on embryos created through in vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) to detect certain inherited conditions or abnormalities.
- This helps to ensure that only unaffected embryos are selected before they are transferred to the womb.
- Conventional pre-natal tests for genetic diseases cannot be carried out until the 12th week of pregnancy.
• Testing embryos before they are implanted could help avoid miscarriage or could help her and her partner to avoid having to make the difficult decision about whether to risk getting pregnant or whether to have an abortion.

2.8.8.5 Pre-implantation genetic testing options:

• Pre-implantation genetic screening (PGS)
• Pre-implantation genetic diagnosis (PGD)
• Pre-implantation tissue typing (‘savior siblings’)

2.8.8.5.1 What is PGD?

Pre-implantation genetic diagnosis (PGD) is a technique that enables people with a specific inherited condition in their family to avoid passing it on to their children. It involves checking the genes of embryos created through IVF for this genetic condition.

• **PGD - Genetic testing of the embryos may be recommended if:**
  • She have had a number of abortions because your baby had a genetic condition
  • She already have a child with a serious genetic condition
  • She has a family history of a serious genetic condition.

• **Which genetic conditions can be tested for during PGD?**

  PGD can be used to test for over 100 genetic conditions. To see the types of conditions that may be tested for, see the HFEA’s list of PGD conditions:

  If a condition is not on the list, a clinic can submit an application to add it to the list.

• **PGD application process**

  The HFEA must agree that a particular genetic condition is sufficiently serious before clinics are permitted to test for that condition using pre implantation genetic diagnosis (PGD). Even if
the HFEA approves the genetic condition for testing, clinics must make their own judgment on whether PGD is the appropriate treatment for a particular patient. In doing this, they will use the guidance contained in the HFEA’s Code of Practice. This guidance requires them to take into account the view of that patient of the seriousness of the condition to be avoided.

- **Code of Practice - Guidance on embryo testing**
  
  PGD is an area of medicine that is rapidly developing, so new tests often become available. If a condition is not approved by the HFEA, we recommend getting in touch with a licensed PGD clinic to see whether they are prepared to make an application for that condition to be approved.

- **Which clinics can carry out PGD?**
  
  A clinic must have a license from the HFEA to carry out PGD testing. The license allows the clinic to test for any condition or combination of conditions that appear on the HFEA’s list of PGD conditions. Some clinics will have particular experience of testing for some conditions.

- **What are the risks of PGD?**
  
  Most of the risks involved in PGD treatment are similar to those for conventional IVF.

  With PGD, there is also the possibility that:

  - some embryos may be damaged by the process of cell removal
  - testing may not be 100% reliable or conclusive.

  The procedure for PGD is likely to be as follows:

  **Step 1.** She undergoes normal in vitro fertilization (IVF) treatment to collect and fertilize her eggs.

  **Step 2.** The embryo is grown in the laboratory for two - three days until the cells have divided and the embryo consists of around eight cells.
Step 3. A trained embryologist removes one or two of the cells (blastomeres) from the embryo.

Step 4. The cells are tested to see if the embryo from which they were removed contains the gene that causes the genetic condition in the family.

Step 5. Embryos unaffected by the condition are transferred to the womb to allow them to develop.

Step 6. Any suitable remaining unaffected embryos can be frozen for later use. Those embryos that are affected by the condition are allowed to perish.

Step 7. About two weeks after the embryo transfer, the woman is given a pregnancy blood test.

- **Trophectoderm biopsy**
  - It is possible that, instead of removing and testing one or two cells from a 2-3 day old embryo, some centers may allow the embryo to develop to 5-6 days, when there are 100-150 cells.
  - At this stage, cells within an embryo have separated into two types: cells which will form the fetus (inner cell mass) and cells which will form the placenta (trophectoderm).
  - More cells can be removed at this stage (from the trophectoderm) without compromising the viability of the embryo, possibly leading to a more accurate test.

- **What is the chance of having a baby with PGD?**
  
  It is difficult to assess success rates for PGD because there is currently little data available. Most women use this treatment not because they have fertility problems but because they want to avoid having a child with a genetic disease.

As with most fertility treatments, success depends on many factors, including the woman’s age and whether a cause of infertility has been identified.
Sometimes no embryos are suitable for transfer to the womb, for reasons including: not enough eggs are produced or fertilized in the first place removing the cells to be analyzed damages the embryos all the embryos are affected by the genetic disease.

In 2010 (the year for which the most recent data is available) 311 women received 383 cycles of PGD. This resulted in 121 live births (live birth rate of 31.6% per cycle started).

- **starting the process**

If a woman considering this treatment, she should talk to her GP to go through the options available, Her GP can also refer her to see a specialist at her local hospital or fertility clinic.

Access a list of Genetic Centers and Services in your area by visiting the Genetic Interest Group website.

- **Sex selection**

Some genetic diseases only affect one sex rather than the other. Examples include Duchenne muscular dystrophy, which affects boys but not girls. (Girls may still ‘carry’ the gene for the disease but they will not suffer from it). In these sorts of cases, the embryo is tested to find out its sex and only embryos of the non-affected sex are transferred to the womb. In the UK, sex selection is only allowed to avoid having a child with a serious medical condition; it is illegal to carry out sex selection for social reasons (e.g. for family ‘balancing’).

- **How does sex selection work?**

The procedure for carrying out sex selection is likely to be as follows:

**Step 1**: You undergo normal IVF treatment to collect and fertilize your eggs.

**Step 2**: The embryo is grown in the laboratory for a number of days.
Step 3: A trained embryologist removes a number of cells from the embryo.

Step 4: The chromosomes are examined to identify which embryos are male and which are female.

Step 5: One, two or three of the embryos of the appropriate sex are transferred to the womb so that they can develop. Any remaining embryos of the appropriate sex can be frozen for later use.

However, embryos that have been biopsied may not be suitable for cryopreservation and use in subsequent treatment cycles.

Step 6: The embryos of the different sex are allowed to perish or may be used for research or training (with your consent).

- **What are the risks of sex selection?**
  Most of the risks involved in sex selection treatment are similar to those for conventional in vitro fertilization (IVF). For more information, see:

  - **IVF - what are the risks?**
    With sex selection, there is also the possibility that:
    - some embryos may be damaged by the process of testing
    - no embryos are suitable for transfer to the womb after sex selection (i.e. all embryos are of the sex being selected against)
    - the test is not 100% reliable.
    - New genetic testing techniques
    - Some scientists are developing genetic tests that look for the specific genes that cause sex-linked disorders, such as Duchenne muscular dystrophy or Hemophilia A.
    - This means that as well as selecting all female embryos, you may also be able to select male embryos that do not carry the gene for the disease.

  - **PGD conditions licensed by the HFEA**
Pre-implantation genetic diagnosis (PGD) is a technique that enables people with a specific inherited condition in their family to avoid passing it on to their children. It involves checking the genes of embryos created through IVF for this genetic condition.

Before PGD clinics are permitted to test for a condition or combination of conditions, the HFEA must first agree that the condition they want to test for is sufficiently serious. This list of conditions is those that the HFEA has so far agreed that it is acceptable for clinics to use PGD to test for.

- **What is an OMIM\(^{10}\) number?**

  OMIM stands for ‘Online Mendelian Inheritance in Man.’ An OMIM number is a way of cataloguing human genes and genetic conditions.

  The HFEA, when approving genetic conditions for PGD, asks clinics to provide the relevant OMIM number for that condition. This ensures that the HFEA, the clinic, and any prospective patients can be clear about the conditions which have been approved for PGD.

- **Can’t find the condition you are looking for?**

  If the condition you are looking for does not appear on this list, it may be because the condition is not yet approved or it was approved after this webpage was last updated. We update this page as soon as possible after a new condition is approved. PGD is an area of medicine that is rapidly developing, and new tests often become available. If a condition does not appear on this list, we recommend getting in touch with a licensed PGD clinic.

\(^{10}\) OMIM  National Center for Biotechnology information retrieved from URL: http://www.ncbi.nlm.nih.gov/omim 05-Apr-16 6:15:05 PM
• **PGD conditions awaiting consideration**

Pre implantation genetic diagnosis (PGD) is a technique that enables people with a specific inherited condition in their family to avoid passing it on to their children. It involves checking the genes of embryos created through IVF for this genetic condition.

If a clinic wishes to use Pre implantation genetic diagnosis (PGD) to test for a new genetic condition, then it must apply to the HFEA for permission.

• **PGD conditions licensed by the HFEA**

The following conditions are those which the HFEA is considering to allow clinics to use PGD to test for:

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\textsuperscript{11} Online Mendelian Inheritance in Man, OMIM (TM), McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), World Wide Web
2.8.8.5.2 Pre-implantation genetic screening (PGS)

PGS (also known as aneuploidy screening) involves checking the chromosomes of embryos conceived by in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) for common abnormalities. This avoids having abnormal embryos transferred to the womb during IVF or ICSI.

Chromosomal abnormalities are a major cause of the failure of embryos to implant, and of miscarriages. They can also cause conditions such as Down’s syndrome.

- **PGS may recommend genetic screening of embryos, particularly if:**
  - Woman is over 35 and have a higher risk of having a baby with a chromosome problem (such as Down’s syndrome)
  - Woman have a family history of chromosome problems
  - Woman have a history of recurrent miscarriages
  - Woman have had several unsuccessful cycles of IVF where embryos have been transferred
  - Her partner’s sperm is known to be at high risk of having chromosome problems.

- **How does PGS work?**

  The procedure for PGS is likely to be as follows:

  **Step 1.** She undergoes normal IVF treatment to collect and fertilize your eggs.

  **Step 2.** The embryo is grown in the laboratory for two - three days until the cells have divided and the embryo consists of about eight cells.

  **Step 3.** A trained embryologist removes one or two of the cells (blastomeres) from the embryo.

  **Step 4.** The chromosomes are examined to see how many there are and whether they are normal.
Step 5. One, two or three of the embryos without abnormal numbers of chromosomes are transferred to the womb so that they can develop. Any remaining unaffected embryos can be frozen for later use.

However, embryos that have been biopsied may not be suitable for cryopreservation and use in subsequent treatment cycles.

Step 6. Those embryos that had abnormal chromosomes are allowed to perish or may be used for research (with your consent).

- Possible variations to this procedure: Testing at five – six days
  It is possible that instead of removing and testing one or two cells from a two – three day old embryo, some centers may allow the embryo to develop to five - six days, when there are 100-150 cells. Cells can be removed at this stage without compromising the viability of the embryo, possibly leading to a more accurate test. Alternatively some centers may test eggs for chromosomal abnormalities before they are used to create embryos. Polar bodies (small cells extruded by eggs as they mature) can be extracted and tested.

- Comparative Genomic Hybridization (CGH)
  A small number of clinics are now using a procedure called comparative genomic hybridization (CGH) which allows centers to test for abnormalities in all 23 chromosomes.

  These abnormalities may or may not be of biological significance, but their presence will lower the chance of finding suitable embryos for transfer.

- What is my chance of having a baby with PGS?
  Because a large proportion of patients who receive PGS are older patients, patients with a history of miscarriages or other indications and also because many of the embryos produced are not suitable for transfer to the womb, the success rate varies considerably depending on the patient’s individual circumstances.
The average success rate for PGS treatment in the UK for in the year from 01/01/2008 - 31/12/2008 is:

- **(2/7)** for women aged under 35
- **(2/15)** for women aged between 35-37
- **(7/25)** for women aged between 38-39
- **(12/42)** for women aged between 40-42
- **(1/29)** for women aged between 43-44
- **(0/12)** for women aged over 44

**Percentages are not calculated where there are less than 50 cycles. Figures given in brackets are (cycles resulting in a live birth / all cycles started).**

Various studies have questioned whether or not PGS is effective at increasing the chance of having a live birth. There is a lack of evidence that having a treatment cycle with PGS will increase her chances of having a baby compared to having a treatment cycle without PGS.

More robust randomized controlled trials are needed before a decision can be made either way.

Centers are required to validate the use of PGS (i.e. demonstrate there is evidence) for each category of patients they offer it to (e.g. advanced maternal age, recurrent implantation failure, recurrent pregnancy loss and male factor infertility).

**What are the risks of PGS?**

Some of the risks involved in PGS treatment are similar to those for conventional IVF.

Other problems unique to PGS treatment include:

- some embryos may be damaged by the process of cell removal
- possibility that no embryos are suitable for transfer to the womb after PGS.
• It is important to understand that there is no guarantee against a miscarriage occurring even though PGS has been carried out prior to embryo transfer.

• Mosaic embryos

PGS relies on the theory that all the cells in a human embryo are chromosomally identical, so that if she examines one cell from an embryo, it will show whether or not all the other cells have a chromosomal abnormality.

However, research has shown that in some embryos (known as mosaic embryos), the cells are not chromosomally identical. As a result, many such embryos will be discarded that are in fact capable of producing a normal pregnancy.

2.8.8.5.3 Pre-implantation tissue typing ('savior siblings')

Figure-2.8

• What is pre-implantation tissue typing?

For children with life limiting blood disorders such as Beta Thalassaemia, Fanconi’s Anaemia and Diamond Blackfan Anaemia, one of the best available treatments is a transfusion of stem cells from cord blood provided by a tissue-matched donor. Pre implantation tissue typing (PTT) offers parents the chance of conceiving a child who is a tissue match with their older sibling.

A tissue matched donor who is a close relative of the recipient often means that treatment of the blood disorder is more likely to be successful than treatment using a tissue matched unrelated donor.
In the media, those born following this procedure have sometimes been referred to as ‘savior siblings’.

- **How does pre implantation tissue typing work?**
  - PTT uses the same technique as pre implantation genetic diagnosis (PGD), but involves testing the tissue type of the embryo.
  - In many cases, the condition the existing child suffers from is heritable, meaning it can be passed from generation to generation. In these cases, parents can use PTT with a PGD step, to ensure they have a child who is not only a tissue donor for the older sibling, but is also born free from the condition.
  - In some cases the condition can occur where there is no genetic history in the family. An example of this is Diamond Blackfan Anaemia. In such cases, tissue typing can be carried out without the additional PGD step.

- **Is pre implantation tissue typing for her family?**
  She should talk to her child’s treating clinician about whether PTT is an appropriate option for her.

- **PTT may be suggested as an option if:**
  - Her child has a life limiting blood disorder that can only be treated through a donation from a compatible donor
  - There are no closely related compatible donors available in her family, and her clinician has established that an unrelated donation from a tissue bank would not be suitable
  - The condition her child suffers from has an established genetic basis, and she additionally want to ensure that any future children you have do not also inherit the condition.
• Which conditions can be tested for using pre implantation tissue typing?
  So far, 10 conditions have been licensed by the HFEA\textsuperscript{12} for particular families in the UK. These include Diamond Blackfan Anaemia, Beta and Alpha Thalassaemia, Fanconi’s Anaemia, and Aplastic Anaemia.

  See a complete list of licensed conditions (the conditions for which pre implantation tissue typing has been previously licensed are noted with an asterisk):

  ▪ Licensed PGD conditions
    Though these conditions have been licensed for use in particular cases of pre implantation tissue typing, each subsequent case must still be approved by the HFEA. Her PGD clinician will manage this process for her.

  ▪ Which clinics carry out PGD?
    Clinics licensed to carry out PGD may also carry out preimplantation tissue typing. Not all PGD clinics, however, will offer this treatment. Some clinics will have particular experience of testing for some conditions.

• What are the risks of pre implantation tissue typing?
  The risks of pre implantation tissue typing are similar to the risks of IVF, and PGD. There is also the risk that the donation does not successfully treat the child. One should speak to her treating clinician about the potential risks.

\textsuperscript{12} “IVF treatment options” retrieved from http://www.hfea.gov.uk/ivf-treatments.html on 05-Apr-16 6:27:56 PM
• **What is the chance of having a baby with pre implantation tissue typing?**
  
  - It is difficult to assess reliable success rates for PTT because there is very little data available.
  - In the case of PTT the numbers of cycles every year are even smaller than for PGD, making it more difficult to assess the chances of success.
  - As with most fertility treatment, success will depend on many factors, including the woman’s age and whether a form of infertility has been identified.
  - The measure of success for PTT will not only be the birth of a baby free from the condition, but whether a transfusion of stem cells from that baby will help to treat the older sibling. Data regarding the success of this kind of treatment also remains very limited, and we strongly recommend you speak to your child’s treating clinician about your chances of success.

• **Patient support groups**
  
  Many people find it helps to speak with those who have gone through similar experiences. There are patient support groups for people with children suffering from some of the conditions for which PTT may be an option:

2.8.9 **Blastocyst transfer**

- **Extended embryo culture to blastocyst stage**

  Extended embryo culture is a term used to describe the embryo remaining in a culture medium from the third day after fertilization onwards. Its advantage is that it provides the possibility to judge the embryo’s development and morphological characteristics.

  Permanent monitoring of the embryo’s development provides us with much more information about the dynamics of cell division and very often the healthiest embryos suitable for transfer are known already at day 2 of culturing.
Culture duration is also influenced by the following factors:

1) Endometrial development (growth of uterine lining)

2) Possible occurrence of hyper-stimulation syndrome

3) Time necessary for genetic screening of biopsy cells during PGD/PGS

With blastocyst transfer, embryos are cultured in the laboratory incubator to the blastocyst stage before they are transferred to the womb.

- **What is blastocyst transfer?**
  - A blastocyst is an embryo that has developed for five to six days after fertilization.
  - With blastocyst transfer, embryos are cultured in the laboratory incubator to the blastocyst stage before they are transferred to the womb.
  - At this time, one or two of the best quality blastocysts are selected and then implanted into the woman’s womb. A blastocyst must successfully attach itself to the wall of the womb for a woman to become pregnant.

- **Is blastocyst transfer for a woman?**
  - Many clinics are now offering blastocyst transfer as a means of improving chances of pregnancy after single embryo transfer. This is particularly useful for younger women with a good prognosis for pregnancy from in vitro fertilization (IVF).
  - Her doctor may also suggest her try blastocyst transfer if she has produced good quality embryos in a previous IVF cycle but they failed to implant in the womb.
  - It is not normally recommended if she produce fewer than normal healthy eggs.

- **How does blastocyst transfer work?**
  The procedure for blastocyst transfer is similar to that for normal embryo transfer, but instead of being implanted into the
womb after two or three days, the embryos are allowed to develop for five to six days before transfer.

- **What are the risks of blastocyst transfer?**
  - Not all embryos will develop to produce blastocysts in the laboratory. Embryos can stop developing at the four-cell stage (day two) and progress no further.
  - The embryologist may advise your consultant that in your case it is safer to consider a day two-three embryo transfer than risk having no blastocyst to transfer on day five-six.
  - As with normal embryo transfer, due to the risks of a multiple birth if more than one blastocyst is transferred, you may want to consider single blastocyst transfer.

- **Disruption of the outer embryo layer, this helps implantation of the embryo in the uterus**

  On the 5th or 6th day of its development, the embryo leaves its protective outer layer (zona pellucid), which among other things has protected it till now from extra-corporeal manipulation. This process of breaking out or “hatching” is necessary for the embryo to establish contact with uterus cells in which it becomes implanted. Some embryos are not able to undergo this process and they remain lodged in the zona pellucid. This is why scientists have come up the assisted hatching (AH) technique. Using this technique the zona pellucid is breached in one place using micromanipulation tools, this helps the embryo when hatching out of its layer. Although today there are many varying opinions about AH, it is generally believed that healthy embryos are not affected by this technique. Patients should not overrate the effectiveness of AH.

  “Assisted hatching only if repeated failed implantation has occurred and it is also recommend combining it with PICS and extended embryo culture”
Vitrification method for freezing of embryos
Preserving embryos for use at a later time

There are many reasons why to freeze embryos when undergoing infertility treatment, the most common ones are:

1) Preserving surplus embryos (not used for embryo transfer) in the given cycle

2) Freezing all embryos in these cases:
   - Risk of hyper-stimulation syndrome
   - Inadequate growth of uterine lining
   - Medical finding on the reproductive organs which prevents the creation of conditions necessary for embryo implantation
   - Other acute diseases that are incompatible with pregnancy

During your first visit it is recommend freezing the partner’s spermatozoa. For fertilization used stored sample.

There is no waiting list for egg donation

Only use eggs from healthy young donors and never use surplus eggs from patients. The donors undergo hormone screening, an ultrasound examination, psychological screening and repeated tests for sexually transmitted diseases (HIV, HBsAg, HCV, syphilis). They also undergo karyotype screening and genetic screening to reveal the presence of CFTR gene mutations which cause cystic fibrosis. Donors are usually university students or young mothers on maternity leave. None of them are treated for infertility and egg donation is their free choice. Czech law states that egg donation is anonymous.

It is not possible for the donor to know the identity of the recipient or vice-versa.

It is however possible to choose a donor with certain specific characteristics such as height, weight, hair, and eye color. It is also
possible to choose a donor with the same blood group like the recipient.

- **Sperm donation**
  
  Sperm donation involves using semen from an appropriately screened man (donor). The semen is used to fertilize eggs during assisted reproductive treatment

- **Embryo Donation**
  
  In embryo donation program, embryos that have been created using donated eggs and donated spermatozoa.

### 2.8.10 MEDICAL

#### 2.8.10.1 What medical procedures is involved?\(^{13}\)

In many respects, a Gestational Surrogacy is no different from any other pregnancy with one important exception: the process used to achieve the pregnancy. The pregnancy will be achieved by IVF or *in vitro* fertilization, which simply describes a procedure in which eggs are fertilized outside the body to create Embryos that are then transferred back into the uterus. Because you will not be the Egg Donor, you will only undergo the second half of IVF. To this end, you will be given a combination of medications designed to both stop your own ovulation and to synchronize your cycle with that of the woman who will donate the eggs. Sometimes, the Intended Mother will be the Egg Donor, while other times the Egg Donor will be a separate individual altogether.

Typically, these synchronizing medications are administered by small injections, often in combination with birth control pills. Next, you will be prescribed hormones to cause the lining of your uterus to thicken in preparation for the Embryo transfer.

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\(^{13}\) “In Vitro Fertilization (IVF): One of the Effective and Safest Medical Procedure” retrieved from http://www.meditourcz.com/medicalprocedure/ivf-fertilization/ on date 05-Apr-16 6:33:34 PM
These hormones are typically administered either by patches or oral pills (or sometimes both). Finally, you will be prescribed still another hormone to prevent your body from rejecting the Embryo (and then Fetus).

These hormones are administered either by intramuscular injections or by a combination of oral pills and suppositories. The Embryo transfer itself is not painful but rather is performed as a simple outpatient procedure in which the cervix is opened with a speculum (similar to that used in a Pap smear) and the Embryos are placed directly into the uterus. Once pregnant, you will be asked to continue the hormones until a viable heartbeat is detected on an ultrasound.

Figure-2.9 Schematic of IVF within Tracytoplasmic Sperm Injection.

*In vitro fertilization* (IVF) is a process by which an egg is fertilized by sperm outside the body: *in vitro*. IVF is a major treatment for infertility when other methods of assisted reproductive technology have failed. The process involves monitoring and stimulating a woman's ovulatory process, removing ovum or ova (egg or eggs) from the woman's ovaries and letting sperm fertilize them in a fluid medium in a laboratory. The fertilized egg (zygote) is cultured for 2–6 days in a growth medium and is then transferred to the mother's uterus with the intention of establishing a successful pregnancy. The first successful birth of a "test tube baby", Louise Brown, occurred in 1978. Louise Brown was born as a result of natural cycle IVF where no stimulation was made. Robert G. Edwards, the physiologist who developed the treatment, was awarded the Nobel Prize in Physiology or Medicine in 2010.
The term *in vitro*, from the Latin meaning *in glass*, is used, because early biological experiments involving cultivation of tissues outside the living organism from which they came, were carried out in glass containers such as *beakers, test tubes, or petri dishes*. Today, the term *in vitro* is used to refer to any biological procedure that is performed outside the organism it would normally be occurring in, to distinguish it from an *in vivo* procedure, where the tissue remains inside the living organism within which it is normally found. A colloquial term for babies conceived as the result of IVF, "test tube babies", refers to the tube-shaped containers of glass or plastic resin, called *test tubes that* are commonly used in chemistry labs and biology labs. However, *in vitro* fertilization is usually performed in the shallower containers called Petri dishes. One IVF method, antiligious endometrial co culture, is actually performed on organic material, but is still considered *in vitro*.

### 2.8.10.2 Indications

IVF may be used to overcome female infertility where it is due to problems with the fallopian tubes, making fertilization *in vivo* difficult. It can also assist in male infertility, in those cases where there is a defect in sperm quality; in such cases intracytoplasmic sperm injection (ICSI) may be used, where a sperm cell is injected directly into the egg cell. This is used when sperm have difficulty penetrating the egg, and in these cases the partner's or a donor's sperm may be used. ICSI is also used when sperm numbers are very low. When indicated, the use of ICSI has been found to increase the success rates of IVF.

According to NICE guidelines, IVF is indicated in unexplained infertility for women that have not conceived after 2 years of regular unprotected sexual intercourse.

For IVF to be successful it typically requires healthy ova, sperm that can fertilize, and a uterus that can maintain a pregnancy. Due to the costs of the procedure, IVF is generally attempted only after less expensive options have failed.

IVF is also indicated in cases where any of its expansions is of interest, that is, a procedure that is usually not necessary for the IVF procedure itself,
but would be virtually impossible or technically difficult to perform without concomitantly performing methods of IVF. Such expansions include pre implantation genetic diagnosis (PGD) to rule out presence of genetic disorders, as well as egg donation or surrogacy where the woman providing the egg isn’t the same who will carry the pregnancy to term.

2.8.10.3 Method

Theoretically, *in vitro* fertilization could be performed by collecting the contents from a woman's fallopian tubes or uterus after natural ovulation, mixing it with semen, and reinserting into the uterus. However, without additional techniques, the chances of pregnancy would be extremely small. Such additional techniques that are routinely used in IVF include ovarian hyper stimulation to retrieve multiple eggs, ultrasound-guided trans vaginal oocyte retrieval directly from the ovaries, egg and sperm preparation, as well as culture and selection of resultant embryos before embryo transfer back into the uterus.

2.8.10.3.1 Ovarian hyper stimulation

Ovarian hyper stimulation is the stimulation to induce development of multiple follicles of the ovaries. It should start with response prediction by e.g. age, antral follicle count and level of anti-Müllerian hormone.\textsuperscript{14} The resulting prediction of e.g. poor or hyper-response to ovarian hyper stimulation determines the protocol and dosage for ovarian hyperstimulation.\textsuperscript{15}

Ovarian hyper stimulation also includes suppression of spontaneous ovulation, for which two main methods are available: Using a (usually longer) GnRH agonist protocol or a (usually shorter) GnRH antagonist protocol.


\textsuperscript{15} Natural cycle IVF at the Human Fertilization and Embryology Authority homepage.
In a standard long GnRH agonist protocol the day when hyper stimulation treatment is started and the expected day of later oocyte retrieval can be chosen to conform to personal choice, while in a GnRH antagonist protocol it must be adapted to the spontaneous onset of the previous menstruation. On the other hand, the GnRH antagonist protocol has a lower (or even eliminated) risk of ovarian hyper stimulation syndrome (OHSS), which is a life-threatening complication. For the ovarian hyper stimulation in itself injectable gonadotropins (usually FSH analogues) are generally used under close monitoring. Such monitoring frequently checks the estradiol level and, by means of gynecologic ultrasonography, follicular growth. Typically approximately 10 days of injections will be necessary.

2.8.10.3.2 Natural and mild IVF

There are two methods of natural cycle IVF:  

IVF using no drugs for ovarian hyper stimulation, while drugs for ovulation suppression may still be used.

IVF using ovarian hyper stimulation, including gonadotropins, but with a GnRH antagonist protocol so that the cycle initiates from natural mechanisms.

IVF using no drugs for ovarian hyper stimulation was the method for the conception of Louise Brown. This method can be successfully used when women want to avoid taking ovarian stimulating drugs with its associated side-effects. HFEA has estimated the live birth rate to be approximately 1.3% per IVF cycle using no hyper stimulation drugs for women aged between 40–42.

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Mild IVF is a method where a small dose of ovarian stimulating drugs are used for a short duration during a woman’s natural cycle aimed at producing 2–7 eggs and creating healthy embryos. This method appears to be an advance in the field to reduce complications and side-effects for women and it is aimed at quality, and not quantity of eggs and embryos. One study comparing a mild treatment (mild ovarian stimulation with GnRH antagonist co-treatment combined with single embryo transfer) to a standard treatment (stimulation with a GnRH agonist long-protocol and transfer of two embryos) came to the result that the proportions of cumulative pregnancies that resulted in term live birth after 1 year were 43.4% with mild treatment and 44.7% with standard treatment. Mild IVF can be cheaper than conventional IVF and with a significantly reduced risk of multiple gestation and OHSS.

### 2.8.10.3.3 Final maturation and egg retrieval

When the ovarian follicles have reached a certain degree of development, induction of final oocyte maturation is performed, generally by an injection of human chorionic gonadotropin (hCG). Commonly, this is known as the "trigger shot."\(^{18}\) hCG acts as an analogue of luteinizing hormone, and ovulation would occur between 38 and 40 hours after a single HCG injection,\(^{19}\) but the egg retrieval is performed at a time usually between 34 and 36 hours after hCG injection, that is, just prior to when the follicles would rupture. This avails for scheduling the egg retrieval procedure at a time where the eggs are fully mature. HCG injection confers a risk of ovarian hyperstimulation syndrome. Using a GnRH agonist instead of hCG eliminates the risk of ovarian hyperstimulation syndrome, but with a delivery rate of approximately 6% less than with hCG.

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2.8.10.3.4 Egg retrieval

The eggs are retrieved from the patient using a transvaginal technique called transvaginal oocyte retrieval, involving an ultrasound-guided needle piercing the vaginal wall to reach the ovaries. Through this needle follicles can be aspirated, and the follicular fluid is passed to an embryologist to identify ova. It is common to remove between ten and thirty eggs. The retrieval procedure usually takes between 20 to 40 minutes, depending on the number of mature follicles, and is usually done under conscious sedation or general anesthesia.

2.8.10.3.5 Egg and sperm preparation

In the laboratory, the identified eggs are stripped of surrounding cells and prepared for fertilization. An oocyte selection may be performed prior to fertilization to select eggs with optimal chances of successful pregnancy. In the meantime, semen is prepared for fertilization by removing inactive cells and seminal fluid in a process called sperm washing. If semen is being provided by a sperm donor, it will usually have been prepared for treatment before being frozen and quarantined, and it will be thawed ready for use.

2.8.10.3.6 Co-incubation

The sperm and the egg are incubated together at a ratio of about 75,000:1 in a culture media in order for the actual fertilization to take place. A review in 2013 came to the result that a duration of this co-incubation of about 1 to 4 hours results in significantly higher pregnancy rates than 16 to 24 hours.\(^\text{20}\) In most cases, the egg will be fertilized during co-incubation and will show two pronuclei. In certain situations, such as low sperm count or motility, a single sperm may be injected directly into the egg using intracytoplasmic sperm injection (ICSI). The fertilized egg is passed to a special growth medium and left for about 48 hours until the egg consists of six to eight cells.

In gamete intra fallopian transfer, eggs are removed from the woman and placed in one of the fallopian tubes, along with the man's sperm. This allows fertilization to take place inside the woman's body. Therefore, this variation is actually an in vivo fertilization, not an in vitro fertilization.

2.8.10.3.7 Embryo culture

Typically, embryos are cultured until having reached the 6 to 8 cell stage three days after retrieval. In many Canadian, American and Australian programme, however, embryos are placed into an extended culture system with a transfer done at the blastocyst stage at around five days after retrieval, especially if many good-quality embryos are still available on day 3.

Blastocyst stage transfers have been shown to result in higher pregnancy rates.\textsuperscript{21} In Europe, transfers after 2 days are common.

2.8.10.3.8 Embryo selection

Laboratories have developed grading methods to judge oocyte and embryo quality. In order to optimize pregnancy rates, there is significant evidence that a morphological scoring system is the best strategy for the selection of embryos.\textsuperscript{22} Since 2009 where the first time-lapse microscopy system for IVF was approved for clinical use,\textsuperscript{23} morphokinetic scoring systems has shown to improve to pregnancy rates further.


\textsuperscript{22} "Unisense FertiliTech A/S Receives CE Mark of Approval for EmbryoScope(TM) Embryo Monitoring System".

2.8.10.3.9 Embryo transfer

Embryos are failed by the embryologist based on the amount of cells, evenness of growth and degree of fragmentation. The number to be transferred depends on the number available, the age of the woman and other health and diagnostic factors. In countries such as Canada, the UK, Australia and New Zealand, a maximum of two embryos are transferred except in unusual circumstances. In the UK and according to HFEA regulations, a woman over 40 may have up to three embryos transferred, whereas in the USA, younger women may have many embryos transferred based on individual fertility diagnosis. Most clinics and country regulatory bodies seek to minimize the risk of pregnancies carrying multiples, as it is not uncommon for more implantations to take than desired. The embryos judged to be the "best" are transferred to the patient's uterus through a thin, plastic catheter, which goes through her vagina and cervix. Several embryos may be passed into the uterus to improve chances of implantation and pregnancy.24

Embryo transfer takes place after eggs have been collected and fertilized in the laboratory. Depending on your situation between one and three of the best quality embryos are selected and then transferred to the woman’s womb.

---

2.8.10.3.10 What is embryo transfer?

Embryo transfer takes place after eggs have been collected and fertilized in the laboratory. Depending on her situation between one and three of the best quality embryos are selected and then transferred to the woman’s womb. An embryo must successfully attach itself to the wall of the womb for pregnancy to begin.

a) How does embryo transfer work?

The exact procedure for embryo transfer depends on the clinic she chooses. A typical procedure may involve the following:

**Step 1.**

- Two to three days after the eggs are fertilized, the best quality embryos are selected to be transferred to her womb.
- If a woman is under the age of 40, one or two embryos can be replaced.
- If she is 40 or over, a maximum of three embryos can be used (unless she is using donated eggs, when the maximum is two because these eggs will be from donors who are not older than 35).
- If she has good quality embryos, those that are not transferred can be frozen. Some clinics may also offer blastocyst transfer, where embryos are transferred five to six days after fertilization.
Step 2.

- The doctor or nurse doing the embryo transfer inserts a speculum into your vagina. This is the same procedure as a cervical smear test where the speculum is used to keep your vagina’s wall apart.
- A fine tube (catheter) is passed through the cervix, normally using ultrasound guidance. The embryos are passed down the tube into the womb.
- This is normally a pain-free procedure and usually no sedation is necessary, but you may experience a little discomfort because you need a full bladder if ultrasound is used.

Step 3.

- It is generally recommended that she lead a gentle lifestyle during the few days after embryo transfer.

Step 4.

- About two weeks after the embryo transfer, a woman will be given a pregnancy blood test. If it is positive, she will have a scan about two weeks later.

New technique - Metabolomics

- Researchers are currently developing a new method of embryo selection – Metabolomics. The method could potentially be used to identify embryos with the best chance of implantation.
- Metabolomics involves taking a sample of the fluid (culture media) from the dish an embryo is developing in and testing it for levels of certain molecules (metabolites).
- Researchers are establishing which molecules, and levels of these molecules, corresponds to the most viable embryos.

b) What are the risks of embryo transfer?
There are no significant risks relating to the embryo transfer process itself.

If a woman have never had a baby or if the canal of the cervix has not been assessed before the in vitro fertilization (IVF) cycle was started, there can occasionally be difficulties in passing the embryo transfer catheter through the cervix.

While it is possible to stretch the cervical canal at the time of transfer, her specialist might prefer to avoid such interventions at this time.

In extreme cases, her specialist may decide that it is in her best interests to delay the embryo transfer and freeze all suitable embryos until after the cervix has been stretched.

There are significant risks if more than one embryo is transferred: she may want to consider single embryo transfer.

c) What are my chances of getting pregnant after embryo transfer?

Female fertility diminishes with age, so if she is using her own eggs, on average, the younger she is, the higher her chances of success.

In the year 2011 (the year for which the most recent data is available) for women receiving stimulated IVF using fresh embryos created with their own eggs, the percentage of cycles reaching embryo transfer that resulted in a pregnancy (national average) was:

- 40.6% for women aged under 35
- 35.5% for women aged between 35-37
- 28.1% for women aged between 38-39
- 21.2% for women aged between 40-42
- 11.2% for women aged between 43-44
- 3.4% (0/81) for women aged 45 and over
2.8.10.3.4 Assisted hatching

It has been suggested that making a hole in or thinning this outer layer may help embryos to ‘hatch’, increasing the chances of the woman becoming pregnant in some cases.

2.8.10.3.4.1 How does assisted hatching work?

- Before an embryo can attach to the wall of the womb, it has to break out or ‘hatch’ from its outer layer called the zona pellucida.
- It has been suggested that making a hole in or thinning this outer layer may help embryos to ‘hatch’, increasing the chances of the woman becoming pregnant in some cases.
- However, assisted hatching does not improve the quality of embryos.
- The NHS guidelines on fertility, issued by NICE (the National Institute for Health and Clinical Excellence), say: ‘Assisted hatching is not recommended because it has not been shown to improve pregnancy rates.’
- The guidelines also mention that further research is needed to find out whether assisted hatching can have an effect on live birth rates and to examine the consequences for children born as a result of this procedure.

2.8.10.3.4.2 What is Assisted Hatching?

Assisted hatching is done while the embryo is in the laboratory.

Before being transferred back to the womb a hole is made in the outer layer of the embryo or it is thinned, using acid, laser or mechanical methods.

A typical procedure is:

**Step 1.** On day three of embryo development, the embryologist uses either weak acid in a fine glass
pipette, a micro laser or a micro tool to thin or cut a hole in the outer layer of the embryo.

**Step 2.** If weak acid was used, the embryo is washed to prevent further damage.

**Step 3.** Because assisted hatching thins or makes a hole in the protective outer layer around the embryo, the woman may be given antibiotics to prevent infection.

### 2.8.10.3.4..3 What is my chance of having a baby with assisted hatching?

- Some clinicians believe that the use of assisted hatching results in higher pregnancy rates in selected cases. For example, it has been noted that in the older woman the zona pellucida around the embryo can appear to be thickened. The making of a ‘weak point’ in the zona may help implantation.
- Others feel that there is no convincing evidence that it helps to improve chances of pregnancy.
- If your clinic suggests this treatment, talk it through with them, asking why they are recommending it and what the benefits will be. You should also ask for any written information they may have on this treatment.
- Female fertility diminishes with age, so if you are using your own eggs, on average, the younger you are, the higher your chances of success.
- In the year from 01/01/2008 - 31/12/2008, for women receiving assisted hatching with stimulated IVF or ICSI using fresh embryos created with their own eggs, the percentage of cycles started that resulted in a live birth is:
- 37.2% (35/94) for women aged under 35
- 25.9% (28/108) for women aged between 35-37
- 21.2% (43/203) for women aged between 38-39
- 14.2% (35/246) for women aged between 40-42
- 1.6% (1/16) for women aged between 43-44
- **(0/13)** for women aged over 44

** Percentages are not calculated where there are less than 50 cycles. Figures given in brackets are (cycles resulting in a live birth / all cycles started).

**2.8.10.3.4.4 What are the risks of assisted hatching?**

Current research suggests that this treatment is no more likely to cause an abnormality to the baby than IVF without assisted hatching. As it is only the outer layer that is affected by this procedure, the embryo should remain unharmed.

There is always some risk of damage with any procedure of this type.

If you have more than one embryo transferred, this may increase the risk of multiple births.
2.9 Adjunctive medication

Luteal support is the administration of medication, generally progesterone, progestin or GnH agonists, to increase the success rate of implantation and early embryogenesis, thereby complementing and/or supporting the function of the corpus luteum. The live birth rate is significantly higher with progesterone for luteal support in IVF cycles with or without intracytoplasmic sperm injection (ICSI). Co-treatment with GnRH\textsuperscript{25} agonists further improves outcomes by a live birth rate RD of +16\% (95\% confidence interval +10 to +22\%). On the other hand, growth hormone or aspirin as adjunctive medication in IVF have no evidence of overall benefit.

2.10. Success rates

IVF success rates are the percentage of all IVF procedures which result in a favorable outcome. Depending on the type of calculation used, this outcome may represent the number of confirmed pregnancies, called the pregnancy rate or number of live births, called the live birth rate.

Due to advancement in reproductive technology, the IVF success rates are substantially better today than they were just a few years ago. The most current data available in the United States a 2009 summary compiled by the Society for Reproductive Medicine which reports the average national IVF success rates per age group using non-donor eggs (see table below).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pregnancy Rate</th>
<th>Live Birth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>47.6</td>
<td>41.4</td>
</tr>
<tr>
<td>35-37</td>
<td>38.9</td>
<td>31.7</td>
</tr>
<tr>
<td>38-40</td>
<td>30.1</td>
<td>22.3</td>
</tr>
<tr>
<td>41-42</td>
<td>20.5</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Table-2.2

The live birth rates using donor eggs are also given by the SART and include all age groups using either fresh or thawed eggs.

<table>
<thead>
<tr>
<th>Donor Egg Type</th>
<th>Live Birth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh</td>
<td>55.1</td>
</tr>
<tr>
<td>Thawed</td>
<td>33.8</td>
</tr>
</tbody>
</table>

Table-2.3

In 2006, Canadian clinics reported an average pregnancy rate of 35%. A French study estimated that 66% of patients starting IVF treatment
finally succeed in having a child (40% during the IVF treatment at the center and 26% after IVF discontinuation). Achievement of having a child after IVF discontinuation was mainly due to adoption (46%) or spontaneous pregnancy (42%).

2.10.1 Live birth rate.

The live birth rate is the percentage of all IVF cycles that lead to a live birth. This rate does not include miscarriage or stillbirth and multiple-order births such as twins and triplets are counted as one pregnancy. In 2006, Canadian clinics reported a live birth rate of 27%. Birth rates in younger patients were slightly higher, with a success rate of 35.3% for those 21 and younger, the youngest group evaluated. Success rates for older patients were also lower and decrease with age, with 37-year-olds at 27.4% and no live births for those older than 48, the oldest group evaluated. Some clinics exceeded these rates, but it is impossible to determine if that is due to superior technique or patient selection, because it is possible to artificially increase success rates by refusing to accept the most difficult patients or by steering them into oocyte donation cycles (which are compiled separately). Further, pregnancy rates can be increased by the placement of several embryos at the risk of increasing the chance for multiples.

Because not each IVF cycle that is started will lead to oocyte retrieval or embryo transfer, reports of live birth rates need to specify the denominator, namely IVF cycles started, IVF retrievals, or embryo transfers.

The Society for Assisted Reproductive Technology (SART) summarized 2008-9 success rates for US clinics for fresh embryo cycles that did not involve donor eggs and gave live birth rates by the age of the prospective mother, with a peak at 41.3% per cycle started and 47.3% per embryo transfer for patients under 35 years of age.

References:

IVF attempts in multiple cycles result in increased cumulative live birth rates. Depending on the demographic group, one study reported 45% to 53% for three attempts, and 51% to 71% to 80% for six attempts.

2.10.2 Pregnancy rate.

Pregnancy rate may be defined in various ways. In the United States, the pregnancy rate used by the Society for Assisted Reproductive Technology and the Centers for Disease Control (and appearing in the table in the Success Rates section above) is based on fetal heart motion observed in ultrasound examinations.

2.10.3 Success or failure factors

The main potential factors that influence pregnancy (and live birth) rates in IVF have been suggested to be maternal age, duration of infertility or sub fertility, bFSH and number of oocytes, all reflecting ovarian function. Optimal woman’s age is 23–39 years at time of treatment.

2.10.3.1 Stress

In a 2005 Swedish study, 166 women were monitored starting one month before their IVF cycles, and the results showed no significant correlation between psychological stress and IVF outcome. The study concluded with the recommendation to clinics that it might be possible to reduce the stress experienced by IVF patients during the treatment procedure by informing them of those findings. While psychological stress experienced during a cycle might not influence an IVF outcome, it is possible that the experience of IVF can result in stress that leads to depression. The financial consequences alone of IVF can influence anxiety and become overwhelming. However, for many couples, the alternative is infertility, and the experience of infertility itself can also cause extreme stress and depression.
2.10.3.2 Biomarkers

Biomarkers that affect the pregnancy chances of IVF include:

- Antral follicle count, with higher count giving higher success rates.
- Anti-Müllerian hormone levels, with higher levels indicating higher pregnancy chances.
- Factors of semen quality for the sperm provider.
- Level of DNA fragmentation as measured e.g. by Comet assay, advanced maternal age and semen quality.
- Women with ovary-specific FMR1 genotypes including het-norm/low have significantly decreased pregnancy chances in IVF.

Progesterone elevation (PE) on the day of induction of final maturation is associated with lower pregnancy rates in IVF cycles in women undergoing ovarian stimulation using GnRH analogues and gonadotrophins. At this time, compared to a progesterone level below 0.8 ng/ml, a level between 0.8 and 1.1 ng/ml confers an odds ratio of pregnancy of approximately 0.8, and a level between 1.2 and 3.0 ng/ml confers an odds ratio of pregnancy of between 0.6 and 0.7. On the other hand, progesterone elevation does not seem to confer a decreased chance of pregnancy in frozen–thawed cycles and cycles with egg donation.

Characteristics of cells from the cumulus oophorus and the membrana granulosa, which are easily aspirated during oocyte retrieval. These cells are closely associated with the oocyte and share the same microenvironment, and the rate of expression of certain genes in such cells are associated with higher or lower pregnancy rate.
2.10.3.3 Other factors

Other determinants of outcome of IVF include:

- Tobacco smoking reduces the chances of IVF producing a live birth by 34% and increases the risk of an IVF pregnancy miscarrying by 30%.
- A body mass index (BMI) over 27 causes a 33% decrease in likelihood to have a live birth after the first cycle of IVF, compared to those with a BMI between 20 and 27.
- Also, pregnant women who are obese have higher rates of miscarriage, gestational diabetes, hypertension, thromboembolism and problems during delivery, as well as leading to an increased risk of fetal congenital abnormality. Ideal body mass index is 19–30.
- Salpingectomy or laparoscopic tubal occlusion before IVF treatment increases chances for women with hydrosalpinges.
- Success with previous pregnancy and/or live birth increases chances.
- Low alcohol/caffeine intake increases success rate.
- The number of embryos transferred in the treatment cycle.
- Embryo quality.
- Some studies also suggest the autoimmune disease may also play a role in decreasing IVF success rates by interfering with proper implantation of the embryo after transfer.
- Aspirin is sometimes prescribed to women for the purpose of increasing the chances of conception by IVF, but there is insufficient evidence to show that it actually works.
- A 2013 review and meta-analysis of randomised controlled trials of acupuncture as an adjuvant therapy in IVF found no overall benefit, and concluded that an apparent benefit detected in a subset of published trials where the control group (those not using acupuncture) experienced a lower than average rate of pregnancy requires further study, due to the possibility of publication bias and other factors.
- A Cochrane review came to the result that endometrial injury performed in the month prior to ovarian hyper stimulation appeared to increase both the live birth rate and clinical pregnancy rate in IVF compared with no endometrial injury. However, there was a lack of data reported on the rates of adverse outcomes such as miscarriage, multiple pregnancy, and pain and/or bleeding.

- For females, intake of antioxidants (such as N-acetyl-cysteine, melatonin, vitamin A, vitamin C, vitamin E, folic acid, myo-inositol, zinc or selenium have not been associated with a significantly increased live birth rate or clinical pregnancy rate in IVF according to Cochrane reviews. On the other hand, oral antioxidants given to the men in couples with male factor or unexplained sub fertility resulted in significantly higher live birth rate in IVF.

- A Cochrane review in 2013 came to the result that there is no evidence identified regarding the effect of pre-conception lifestyle advice on the chance of a live birth outcome.

2.10.3.4 Complications of the IVF procedure

2.10.3.4.1 Multiple births

The major complication of IVF is the risk of multiple births. This is directly related to the practice of transferring multiple embryos at embryo transfer. Multiple births are related to increased risk of pregnancy loss, obstetrical complications, prematurity, and neonatal morbidity with the potential for long term damage. Strict limits on the number of embryos that may be transferred have been enacted in some countries (e.g. Britain, Belgium) to reduce the risk of high-order multiples (triplets or more), but are not universally followed or accepted. Spontaneous splitting of embryos in the womb after transfer can occur, but this is rare and would lead to identical twins. A double blind, randomized study followed IVF pregnancies that resulted in 73 infants (33 boys and 40 girls) and reported that 8.7% of singleton infants and 54.2% of twins had a birth weight of < 2,500 grams (5.5 lb).
Recent evidence also suggests that singleton offspring after IVF is at higher risk for lower birth weight for unknown reasons.

2.10.3.4.2 Spread of infectious disease

By sperm washing, the risk that a chronic disease in the male providing the sperm would infect the female or offspring can be brought to negligible levels.

In males with hepatitis B, The Practice Committee of the American Society for Reproductive Medicine advises that sperm washing is not necessary in IVF to prevent transmission, unless the female partner has not been effectively vaccinated. In females with hepatitis B, the risk of vertical transmission during IVF is no different from the risk in spontaneous conception. However, there is not enough evidence to say that ICSI procedures are safe in females with hepatitis B in regard to vertical transmission to the offspring.

Regarding potential spread of HIV/AIDS, Japan's government prohibited the use of in vitro fertilization procedures for couples in which both partners are infected with HIV. Despite the fact that the ethics committees previously allowed the Ogikubo, Tokyo Hospital, to use in vitro fertilization for couples with HIV, the Ministry of Health, Labour and Welfare of Japan decided to block the practice. Hideji Hanabusa, the vice president of the Ogikubo Hospital, states that together with his colleagues, he managed to develop a method through which scientists are able to remove HIV from sperm.

2.10.3.4.3 Other risks to the egg provider/retriever

A risk of ovarian stimulation is the development of ovarian hyperstimulation syndrome, particularly if hCG is used for inducing final oocyte maturation. This results in swollen, painful ovaries. It occurs in 30% of patients. Mild cases can be treated with over the counter medications and cases can be resolved in the absence of pregnancy. In moderate cases, ovaries swell and fluid accumulated in the abdominal cavities and may have symptoms of heartburn, gas, nausea or loss of appetite. In severe cases patients
have sudden excess abdominal pain, nausea, vomiting and will result in hospitalization.

During egg retrieval, there’s a small chance of bleeding, infection, and damage to surrounding structures like bowel and bladder (transvaginal ultrasound aspiration) as well as difficulty in breathing, chest infection, allergic reactions to meds, or nerve damage (laparoscopy).

Ectopic pregnancy may also occur if a fertilized egg develops outside the uterus, usually in the fallopian tubes and requires immediate destruction of the foetus.

IVF does not seem to be associated with an elevated risk of cervical cancer, nor with ovarian cancer or endometrial cancer when neutralizing the confounder of infertility itself. Nor does it seem to impart any increased risk for breast cancer.

A negative pregnancy test after IVF is associated with an increased risk for depression in women, but not with any increased risk of developing anxiety disorders. Pregnancy test results do not seem to be a risk factor for depression or anxiety among men.

2.10.3.4.4 Birth defects

A review in 2013 came to the result that infants resulting from IVF (with or without ICSI) have a relative risk of birth defects of 1.32 (95% confidence interval 1.24–1.42) compared to naturally conceived infants. In 2008, an analysis of the data of the National Birth Defects Study in the US found that certain birth defects were significantly more common in infants conceived through IVF, notably septal heart defects, cleft lip with or without cleft palate, esophageal atresia, and anorectal atresia; the mechanism of causality is unclear. However, in a population-wide cohort study of 308,974 births (with 6163 using assisted reproductive technology and following children from birth to age five) researchers found: "The increased risk of birth defects associated with IVF was no longer significant after adjustment for parental factors." Parental factors included known independent risks for birth defects such as maternal age, smoking status, etc. Multivariate correction did
not remove the significance of the association of birth defects and ICSI (corrected odds ratio 1.57), although the authors speculate that underlying male infertility factors (which would be associated with the use of ICSI) may contribute to this observation and were not able to correct for these confounders. The authors also found that a history of infertility elevated risk itself in the absence of any treatment (odds ratio 1.29), consistent with a Danish national registry study and "...implicates patient factors in this increased risk." The authors of the Danish national registry study speculate: "...our results suggest that the reported increased prevalence of congenital malformations seen in singletons born after assisted reproductive technology is partly due to the underlying infertility or its determinants."

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
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<tbody>
<tr>
<td>congenital anomalies</td>
<td>1.67</td>
<td>1.33–2.09</td>
</tr>
<tr>
<td>ante-partum haemorrhage</td>
<td>2.49</td>
<td>2.30–2.69</td>
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<tr>
<td>hypertensive disorders of pregnancy</td>
<td>1.49</td>
<td>1.39–1.59</td>
</tr>
<tr>
<td>preterm rupture of membranes</td>
<td>1.16</td>
<td>1.07–1.26</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>1.56</td>
<td>1.51–1.60</td>
</tr>
<tr>
<td>gestational diabetes</td>
<td>1.48</td>
<td>1.33–1.66</td>
</tr>
<tr>
<td>induction of labour</td>
<td>1.18</td>
<td>1.10–1.28</td>
</tr>
<tr>
<td>small for gestational age</td>
<td>1.39</td>
<td>1.27–1.53</td>
</tr>
<tr>
<td>preterm birth</td>
<td>1.54</td>
<td>1.47–1.62</td>
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</table>
Table 2.4

<table>
<thead>
<tr>
<th>Low birthweight</th>
<th>1.65</th>
<th>1.56–1.75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal mortality</td>
<td>1.87</td>
<td>1.48–2.37</td>
</tr>
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</table>

2.10.3.4.5 Other risks to the offspring

If the underlying infertility is related to abnormalities in spermatogenesis, it is plausible, but too early to examine that male offspring is at higher risk for sperm abnormalities.

IVF does not seem to confer any risks regarding cognitive development, school performance, social functioning and behavior. Also, IVF infants are known to be as securely attached to their parents as those who were naturally conceived, and IVF adolescents as are as well-adjusted as those who have been naturally conceived.

Limited long-term follow-up data suggest that IVF may be associated with an increased incidence of hypertension, impaired fasting glucose, increase in total body fat composition, advancement of bone age, subclinical thyroid disorder, early adulthood clinical depression and binge drinking in the offspring. It is not known, however, whether these potential associations are caused by the IVF procedure in itself, by adverse obstetric outcomes associated with IVF, by the genetic origin of the children or by yet unknown IVF-associated causes.

An IVF-associated incidence of cerebral palsy and neurodevelopmental delay are believed to be related to the confounders of prematurity and low birth weight. Similarly, an IVF associated incidence of autism and attention deficit disorder are believed to be related to confounders of maternal and obstetric factors.

Overall, IVF does not cause an increased risk of childhood cancer. Studies have shown a decrease in the risk of certain cancers and increased risks of certain others including retinoblastoma hepatoblastoma and rhabdomyosarcoma.
2.11 Expansions

There are various expansions or additional techniques that can be applied in IVF, which are usually not necessary for the IVF procedure itself, but would be virtually impossible or technically difficult to perform without concomitantly performing methods of IVF.

2.11.1 Pre implantation genetic screening or diagnosis (PGS or PGD)

Pre implantation genetic screening (PGS) or pre implantation genetic diagnosis (PGD) has been suggested to be able to be used in IVF to select an embryo that appears to have the greatest chances for successful pregnancy. However, a systematic review and meta-analysis of existing randomized controlled trials came to the result that there is no evidence of a beneficial effect of PGS as measured by live birth rate. On the contrary, for women of advanced maternal age, PGS significantly lowers the live birth rate. Technical drawbacks, such as the invasiveness of the biopsy, and non-representative samples because of mosaicism are the major underlying factors for inefficacy of PGS.

Still, as an expansion of IVF, patients who can benefit from PGS/PGD include:

- Couples who have a family history of inherited disease
- Couples who want to use gender selection to prevent a gender-linked disease
- Couples who already have a child with an incurable disease and need compatible cells from a second healthy child to cure the first, resulting in a "saviour sibling" that matches the sick child in HLA type.

PGS screens for numeral chromosomal abnormalities while PGD diagnosis the specific molecular defect of the inherited disease. In both PGS and PGD, individual cells from a pre-embryo, or preferably trophectoderm cells biopsied from ablastocyst, are analyzed during the IVF process. Before the transfer of a pre-embryo back to a woman's uterus, one or two cells are removed from the pre-embryos (8-cell stage), or preferably from a blastocyst. These cells are then evaluated for normality. Typically within one to two days, following
completion of the evaluation, only the normal pre-embryos are transferred back to the woman's uterus. Alternatively, a blastocyst can be cryopreserved via vitrification and transferred at a later date to the uterus. In addition, PGS can significantly reduce the risk of multiple pregnancies because fewer embryos, ideally just one, are needed for implantation.

2.11.2 Cryopreservation

Cryopreservation can be performed as oocyte cryopreservation before fertilization, or as embryo cryopreservation after fertilization.

The Rand Consulting Group has estimated there to be 400,000 frozen embryos in the United States. The advantage is that patients who fail to conceive may become pregnant using such embryos without having to go through a full IVF cycle. Or, if pregnancy occurred, they could return later for another pregnancy. Spare oocytes or embryos resulting from fertility treatments may be used for oocyte donation or embryo donation to another woman or couple, and embryos may be created, frozen and stored specifically for transfer and donation by using donor eggs and sperm. Also, oocyte cryopreservation can be used for women who are likely to lose their ovarian reserve due to undergoing chemotherapy.

The outcome from using cryopreserved embryos has uniformly been positive with no increase in birth defects or development abnormalities.

2.11.3 Other expansions

Intracytoplasmic sperm injection (ICSI) is where a single sperm is injected directly into an egg. Its main usage as an expansion of IVF is to overcome male infertility problems, although it may also be used where eggs cannot easily be penetrated by sperm, and occasionally in conjunction with sperm donation. It can be used in teratozoospermia, since once the egg is fertilized abnormal sperm morphology does not appear to influence blastocyst development or blastocyst morphology.

Additional methods of embryo profiling. For example, methods are emerging in making comprehensive analyses of up to
entire genomes, transcriptomes, proteomes and metabolomes which may be used to score embryos by comparing the patterns with ones that have previously been found among embryos in successful versus unsuccessful pregnancies.

Assisted zona hatching (AZH) can be performed shortly before the embryo is transferred to the uterus. A small opening is made in the outer layer surrounding the egg in order to help the embryo hatch out and aid in the implantation process of the growing embryo.

In egg donation and embryo donation, the resultant embryo after fertilization is inserted in another woman than the one providing the eggs. These are resources for women with no eggs due to surgery, chemotherapy, or genetic causes; or with poor egg quality, previously unsuccessful IVF cycles or advanced maternal age. In the egg donor process, eggs are retrieved from a donor's ovaries, fertilized in the laboratory with the sperm from the recipient's partner, and the resulting healthy embryos are returned to the recipient's uterus.

Embryo splitting can be used for twinning to increase the number of available embryos.

2.11.3.1 Leftover embryos or eggs

There may be leftover embryos or eggs from IVF procedures if the woman for whom they were originally created has successfully carried one or more pregnancies to term. With the woman's or couple's permission, these may be donated to help other women or couples as a means of third party reproduction.

In embryo donation, these extra embryos are given to other couples or women for transfer with the goal of producing a successful pregnancy. The resulting child is considered the child of the woman who carries it and gives birth, and not the child of the donor, the same as occurs with egg donation or sperm donation.
Typically, genetic parents donate the eggs to a fertility clinic or embryo bank where they are preserved by oocyte cryopreservation or embryo cryopreservation until a carrier is found for them. Typically the process of matching the embryo(s) with the prospective parents is conducted by the agency itself, at which time the clinic transfers ownership of the embryos to the prospective parents.

In the United States, women seeking to be an embryo recipient undergo infectious disease screening required by the U.S. Food and Drug Administration (FDA), and reproductive tests to determine the best placement location and cycle timing before the actual Embryo Transfer occurs. The amount of screening the embryo has already undergone is largely dependent on the genetic parents' own IVF clinic and process. The embryo recipient may elect to have her own embryologist conduct further testing.

Alternatives to donating unused embryos are destroying them (or having them implanted at a time where pregnancy is very unlikely), keeping them frozen indefinitely, or donating them for use in research (which results in their unavailability). Individual moral views on disposing leftover embryos may depend on personal views on the beginning of human personhood and definition and/or value of potential future persons and on the value that is given to fundamental research questions. Some people believe donation of leftover embryos for research is a good alternative to discarding the embryos when patients receive proper, honest and clear information about the research project, the procedures and the scientific values.
2.12 Ethics

2.12.1 Mix-ups

In a few cases, laboratory mix-ups (misidentified gametes, transfer of wrong embryos) have occurred, leading to legal action against the IVF provider and complex paternity suits. An example is the case of a woman in California who received the embryo of another couple and was notified of this mistake after the birth of her son. This has led to many authorities and individual clinics implementing procedures to minimize the risk of such mix-ups. The HFEA, for example, requires clinics to use a double witnessing system, where the identity of specimens is checked by two people at each point at which specimens are transferred. Alternatively, technological solutions are gaining favor, to reduce the manpower cost of manual double witnessing, and to further reduce the with uniquely numbered RFID tags which can be identified by readers connected to a computer. The computer tracks specimens throughout the process and alerts the embryologist if non-matching specimens are identified. Although the use of RFID tracking has expanded in the USA, it is still not widely adopted.

2.12.2 Pre implantation genetic diagnosis or screening

Another concern is that people will screen in or out for particular traits, using pre implantation genetic diagnosis or pre implantation genetic screening. For example, a deaf British couple, Tom and Paula Lichy, have petitioned to create a deaf baby using IVF. Some medical ethicists have been very critical of this approach. Jacob M. Appel wrote that "intentionally culling out blind or deaf embryos might prevent considerable future suffering, while a policy that allowed deaf or blind parents to select for such traits intentionally would be far more troublesome."

2.12.3 Profit desire of the industry

Many people do not oppose the IVF practice itself (i.e. the creating of a pregnancy through "artificial" ways) but are highly critical of the current state of the present day industry. Such individuals argue that the industry has
now become a multi-billion industry, which is widely unregulated and prone to serious abuses in the desire of practitioners to obtain profit. For instance, in 2008, a California physician transferred 12 embryos to a woman who gave birth to octuplets (see Suleman octuplets). This has made international news, and had led to accusations that many doctors are willing to seriously endanger the health and even life of women in order to gain money. Robert Winston, professor of fertility studies at Imperial College London, had called the industry "corrupt" and "greedy" saying that "One of the major problems facing us in healthcare is that IVF has become a massive commercial industry," and that "What has happened, of course, is that money is corrupting this whole technology", and accused authorities of failing to protect couples from exploitation "The regulatory authority has done a consistently bad job. It's not prevented the exploitation of women, it’s not put out very good information to couples, and it’s not limited the number of unscientific treatments people have access to". The IVF industry can thus be seen as an example of what social scientists are describing as an increasing trend towards a market-driven construction of health, medicine and the human body. The industry has been accused of making unscientific claims, and distorting facts relating to infertility, in particular through widely exaggerated claims about how common infertility is in society, in an attempt to get as many couples as possible and as soon as possible to try treatments (rather than trying to conceive naturally for a longer time). This risks removing infertility from its social context and reducing the experience to a simple biological malfunction, which not only can be treated through bio-medical procedures, but should be treated by them. Indeed, there are serious concerns about the overuse of treatments, for instance Dr. Sami David, a fertility specialist and one of the pioneers of the early days of the IVF treatments, has expressed disappointment over the current state of the industry, and said many procedures are unnecessary; he said: "It's being the first choice of treatment rather than the last choice. When it was first opening up in late 1970s, early 80s, it was meant to be the last resort. Now it's a first resort. I think that's an injustice to women. I also think it can harm women in the long run." IVF thus raises ethical issues concerning the abuse of bio-medical facts to ‘sell’ corrective procedures and treatments for conditions that deviate from a constructed ideal of the ‘healthy’ or
‘normal’ body i.e., fertile females and males with reproductive systems capable of co-producing offspring.

2.12.4 Pregnancy past menopause

Although menopause is a natural barrier to further conception, IVF has allowed women to be pregnant in their fifties and sixties. Women whose uterus has been appropriately prepared receive embryos that originated from an egg of an egg donor. Therefore, although these women do not have a genetic link with the child, they have an emotional link through pregnancy and childbirth. In many cases the genetic father of the child is the woman's partner. Even after menopause the uterus is fully capable of carrying out a pregnancy.

2.12.5 Same-sex couples, single and unmarried parents

A 2009 statement from the ASRM found no persuasive evidence that children are harmed or disadvantaged solely by being raised by single parents, unmarried parents, or homosexual parents. It did not support restricting access to assisted reproductive technologies on the basis of a prospective parent's marital status or sexual orientation.

Ethical concerns include reproductive rights, the welfare of offspring, nondiscrimination against unmarried individuals, homosexual, and professional autonomy.

A recent controversy in California focused on the question of whether physicians opposed to same-sex relationships should be required to perform IVF for a lesbian couple. Guadalupe T. Benitez, a lesbian medical assistant from San Diego, sued doctors Christine Brody and Douglas Fenton of the North Coast Women's Care Medical Group after Brody told her that she had "religious-based objections to treating her and homosexuals in general to help them conceive children by artificial insemination," and Fenton refused to authorize a refill of her prescription for the fertility drug Clomid on the same grounds. The California Medical Association had initially sided with Brody and Fenton, but the case, North Coast Women's Care Medical Group v. Superior Court, was decided unanimously by the California State Supreme Court in favor of Benitez on 19 August 2008.
Nadya Suleman came to international attention after having twelve embryos implanted, eight of which survived, resulting in eight newborns being added to her existing six-child family. The Medical Board of California sought to have fertility doctor Michael Kamrava, who treated Suleman, stripped of his license. State officials allege that performing Suleman's procedure is evidence of unreasonable judgment, substandard care, and a lack of concern for the eight children she would conceive and the six she was already struggling to rise. On 1 June 2011 the Medical Board issued a ruling that Kamrava's medical license be revoked effective 1 July 2011.

2.12.6 Anonymous donors

Some children conceived by IVF using anonymous donors report being troubled over not knowing about their donor parent as well any genetic relatives they may have and their family history.

Alana Stewart, who was conceived using donor sperm, began an online forum for donor children called AnonymousUS in 2010. The forum welcomes the viewpoints of anyone involved in the IVF process. Olivia Pratten, a donor-conceived Canadian, sued the province of British Columbia for access to records on her donor father's identity in 2008. “I’m not a treatment, I’m a person, and those records belong to me,” Pratten said. In May 2012, a court ruled in Pratten's favor, agreeing that the laws at the time discriminated against donor children and making anonymous sperm and egg donation in British Columbia illegal.

In the U.K., Sweden, Norway, Germany, Italy, New Zealand, and some Australian states, donors are not paid and cannot be anonymous.

In 2000, a web site called Donor Sibling Registry was created to help biological children with a common donor connect with each other.

In 2012, a documentary called Anonymous Father's Day was released that focuses on donor-conceived children.
2.12.7 Discarding unwanted embryos

During the selection and transfer phases many embryos may be discarded in favor of others. This selection may be based on criteria such as handicaps, genetic disorders, or even simply sex. This is a question of ethics as no consensus exists in science, religion, and philosophy on when during the development of a human embryo, it should be recognized as a new person. For those who believe that this is at the moment of conception, IVF becomes a moral question when multiple eggs are fertilized, begin development, and only a few are chosen for implantation.

If IVF were to involve the fertilization of only a single egg, or at least only an amount that will be implanted, then this would not be an issue. However, this has the chance of increasing costs dramatically as only a few eggs can be attempted at a time.

2.12.8 Religious response

The Roman Catholic Church opposes all kinds of assisted reproductive technology and artificial contraception, claiming they separate the procreative goal of marital sex from the goal of uniting married couples. The Roman Catholic Church permits the use of a small number of reproductive technologies and contraceptive methods like Natural family planning, which involves charting ovulation times. The church allows other forms of reproductive technologies that allow conception to take place from normative sexual intercourse, such as a fertility lubricant. Pope Benedict XVI has publicly re-emphasized the Catholic Church's opposition to in vitro fertilization, claiming it replaces love between a husband and wife. The Catechism of the Catholic Church claims that Natural law teaches that reproduction has an “inseparable connection” to sexual union of married couples. In addition, the church opposes IVF because it might cause disposal of embryos; in Catholicism, an embryo is viewed as an individual with a soul that must be treated as a person. The Catholic Church maintains that it is not objectively evil to be infertile, and advocates adoption as an option for such couples who still wish to have children.
Regarding the response to IVF of Islam, the conclusions of Gad El-Hak Ali Gad El-Hak’s ART\textsuperscript{31} fatwa include that:

IVF of an egg from the wife with the sperm of her husband and the transfer of the fertilized egg back to the uterus of the wife is allowed, provided that the procedure is indicated for a medical reason and is carried out by an expert physician. Since marriage is a contract between the wife and husband during the span of their marriage, no third party should intrude into the marital functions of sex and procreation. This means that a third party donor is not acceptable, whether he or she is providing sperm, eggs, embryos, or a uterus. The use of a third party is tantamount to zina, or adultery.

Within the Orthodox Jewish community the concept is debated as there is little precedent in traditional Jewish legal textual sources. Regarding laws of sexuality, religious challenges include masturbation (which may be regarded as “seed wasting”), laws related to sexual activity and menstruation (niddah) and the specific laws regarding intercourse. An additional major issue is that of establishing paternity and lineage. For a baby conceived naturally, the father’s identity is determined by a legal presumption (chazakah) of legitimacy: rov bi’ot achar ha’baal - a woman's sexual relations are assumed to be with her husband. Regarding an IVF child, this assumption does not exist and as such Rabbi Eliezer Waldenberg (among others) requires an outside supervisor to positively identify the father. Reform Judaism has generally approved in vitro fertilization.

2.12.9 Society and Culture

Many people of sub-Saharan Africa choose to foster their children to infertile women. IVF enables these infertile women to have their own children, which impose new ideals to a culture in which fostering children are seen as both natural and culturally important. Many infertile women are able to earn more respect in their society by taking care of the children of other mothers, and this may be lost if they choose to use IVF instead. As IVF is seen as unnatural, it may even hinder their societal position as opposed to making them equal with fertile women. It is also economically advantageous for infertile women to raise foster children as it gives these children greater ability to access resources that are important for their development and also aids the development of their society at large. If IVF becomes more popular without the birth rate decreasing, there could be more large family homes with fewer options to send their newborn children. This could result in an increase of orphaned children and/or a decrease in resources for the children of large families. This would ultimately stifle the children's and the community's growth.

2.12.10. Men and IVF

An underrepresented view, some argue, is the men’s experience of IVF. Research has shown that men largely view themselves as ‘passive’ contributors since they have ‘less physical involvement' in IVF treatment. Despite this, many men feel distressed after seeing the toll of hormonal injections and ongoing physical intervention on their partner. Fertility was found to be a significant factor in a man’s perception of his masculinity, driving many to keep the treatment a secret. In cases where the men did share that he and his partner were undergoing IVF, they reported to have been teased, mainly by other men, although some viewed this as an affirmation of support and friendship. For others, this led to feeling socially isolated. In comparison with women, men showed less deterioration in mental health in the years following a failed treatment. However many men did feel guilt, disappointment and inadequacy, stating that they were simply trying to provide an ‘emotional rock’ for their partners.
2.13. Availability and utilization

In the USA, overall availability of IVF in 2005 was 2.5 IVF physicians per 100,000 populations, and utilization was 236 IVF cycles per 100,000. Utilization highly increases with availability and IVF insurance coverage, and to a significant extent also with percentage of single persons and median income. In the USA 126 procedures are performed per million people per year. In the USA an average cycle, from egg retrieval to embryo implantation, costs $12,400, and insurance companies that do cover treatment, even partially, usually cap the number of cycles they pay for.

The cost of IVF rather reflects the costliness of the underlying healthcare system than the regulatory or funding environment, and ranges, on average for a standard IVF cycle and in 2006 United States dollars, between $12,500 in the United States to $4,000 in Japan. In Ireland, IVF costs around €4,000, with fertility drugs, if required, cost up to €3,000. The cost per live birth is highest in the United States ($41,000) and United Kingdom ($40,000) and lowest in Scandinavia and Japan (both around $24,500).32

Many fertility clinics in the United States limit the upper age at which women are eligible for IVF to 50 or 55 years. These cut-offs make it difficult for women older than fifty-five to utilize the procedure. In Australia, the average age of women undergoing ART treatment is 35.5 years among those using their own eggs (one in four being 40 or older) and 40.5 years among those using donated eggs. Israel has the highest rate of IVF in the world, with 1657 procedures performed per million people per year. The second highest rate is in Iceland, with 899 procedures per million people per year. Israel provides unlimited free in vitro procedures for its citizens for up to two children per woman less than 45 years of age. In other countries the coverage of such procedures is limited if it exists at all. The Israeli Health Ministry says it spends roughly $3450 per procedure.

These high costs keep IVF out of reach for many developing countries, but research by the Genk Institute for Fertility Technology, in Belgium, claim to have found a much lower cost methodology (about 90% reduction) with similar efficacy, which may be suitable for some fertility treatment.

### 2.14 Legal status

Government agencies in China passed bans on the use of IVF in 2003 by unmarried women or by couples with certain infectious diseases. Sunni Muslim nations generally allow IVF between married couples when conducted with their own respective sperm and eggs, but not with donor eggs from other couples. But Iran, which is Shi'a Muslim, has a more complex scheme. Iran bars sperm donation but allows donation of both fertilized and unfertilized eggs. Fertilized eggs are donated from married couples to other married couples, while unfertilized eggs are donated in the context of mut'ah or temporary marriage to the father. The nation of Costa Rica has a complete ban on all IVF technology, it having been ruled unconstitutional by the nation's Supreme Court because it "violated life." Costa Rica is the only country in the western hemisphere that forbids this technique. A law project sent reluctantly by the government of Pres. Laura Chinchilla was rejected at the Costa Rican parliament. President Chinchilla, whose strong Catholic views have won her to be named officially as Preferred Daughter of the Virgin Mary has not publicly stated her position on the question of in vitro fertilization. However, given the massive influence of the Catholic Church in her government any change in the status quo seems very unlikely. In spite of Costa Rican government and strong religious opposition, the Costa Rican ban on in vitro fertilization has been struck down by the Inter-American Court of Human Rights in a decision held on 20 December 2012. The court said in the ruling that a long-standing Costa Rican guarantee of protection for every human embryo violated the reproductive freedom of infertile couples because it prohibited them from using in-vitro fertilization, which often involves the disposal of embryos not implanted in a patient’s uterus. Federal regulations in the United States include screening requirements and restrictions on donations, but generally do not
affect sexually intimate partners. However, doctors may be required to provide treatments due to nondiscrimination laws, as for example in California.

All major restrictions on single but infertile women using IVF were lifted in Australia in 2002 after a final appeal to the Australian High Court was rejected on procedural grounds in the Leesa Meldrum case. A Victorian federal court had ruled in 2000 that the existing ban on all single women and lesbians using IVF constituted sex discrimination. Victoria’s government announced changes to its IVF law in 2007 eliminating remaining restrictions on fertile single women and lesbians, leaving South Australia as the only state maintaining them. The US state of Tennessee proposed a bill in 2009 that would have defined donor IVF as adoption. During the same session another bill proposed barring adoption from any unmarried and cohabitating couple, and activist groups stated that passing the first bill would effectively stop unmarried people from using IVF. Neither of these bills passed.

2.15 In vitro maturation (IVM)

In the IVM process, eggs are removed from the ovaries and are collected when they are still immature. They are then matured in the laboratory before being fertilized.

2.16 What is IUI?

Intrauterine insemination (IUI)\textsuperscript{33} involves a laboratory procedure to separate fast moving sperm from more sluggish or non-moving sperm. The fast moving sperm are then placed into the woman’s womb close to the time of ovulation when the egg is released from the ovary in the middle of the monthly cycle.

\textsuperscript{33} Godwin I. Meniru, Peter R. Brinsden, Ian L. Craft “A Handbook of Intrauterine Insemination”. Cambridge university press page no.2
2.16.1 IUI may recommend if

There is unexplained infertility

- There are ovulation problems
  - The male partner experiences impotence or premature ejaculation
  - A woman do not have any known fertility problems but may not have a male partner
- And are trying for a baby using donated sperm.

2.16.2 Patency health tests

- It is essential that her fallopian tubes are known to be open and healthy before the IUI process begins. A tubal patency test is usually carried out as part of her assessment by the fertility clinic.
- The typical method for assessing the health of her pelvis and the patency of her fallopian tubes is laparoscopy and dye testing.
- At laparoscopy a direct view of the pelvis is obtained by inserting a telescope into the abdomen.
- When the pelvis and tubes are healthy, dye passes freely through both tubes. There should be no adhesions present that might prevent an egg from having access to either tube from the ovaries. This is performed under a short general anesthetic.
- The test may show that a woman only have one open healthy tube although she may have both ovaries. IUI treatment can then only be carried out when there is evidence that ovulation is about to occur from the ovary that is on the same side as the open tube.
- The second essential requirement is that there is no significant problem with sperm numbers or sperm quality.

2.16.3 IUI options

If her clinic has recommended IUI treatment, she may want to discuss the following options with her clinician:
- **IUI with or without fertility drugs** – as IUI can be given with or without fertility drugs to boost egg production, you should discuss the risks involved in using fertility drugs and whether IUI without fertility drugs might be suitable for you.

- **IUI with partner’s sperm or donor sperm** – instead of using your partner’s sperm, if your partner is unable to provide sperm, or if you do not have a male partner, you may want to consider using donated sperm.

- **If IUI is unsuccessful** – you may want to talk to your clinician about other procedures such as in vitro fertilization (IVF).

### 2.16.4 How does IUI work?

**For women:**

**Step 1.** If she is not using fertility drugs IUI is done between day 12 and day 16 of her monthly cycle – with day one being the first day of your period. She is given blood or urine tests to identify when she is about to ovulate. Many clinics will provide her with an ovulation predictor kit to detect the hormone surge that signals imminent ovulation.

- or -

If she uses fertility drugs to stimulate ovulation, vaginal ultrasound scans are used to track the development of her eggs. As soon as an egg is mature, you are given a hormone injection to stimulate its release.

**Fertility drugs**

**Step 2.**

- The sperm are inserted 36 to 40 hours later. To do this, the doctor first inserts a speculum (a special instrument that keeps your vaginal walls apart) into your vagina (as for a cervical smear test).

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your vaginal walls apart) into your vagina (as for a cervical smear test).

- A small catheter (a soft, flexible tube) is then threaded into your womb via your cervix. The best quality sperm are selected and inserted through the catheter.
- The whole process takes just a few minutes and is usually a painless procedure but some women may experience a temporary, menstrual-like cramping.

**Step 3.** You may wish to rest for a short time before going home – ask your clinic what they recommend.

**For men:**

**Step 1.** He will be asked to produce a sperm sample on the day the treatment takes place.

**Step 2.** The sperm are washed to remove the fluid surrounding them and the rapidly moving sperm separated out.

**Step 3.** The rapidly moving sperm are placed in a small catheter (tube) to be inserted into the womb.
2.17 Donor insemination (DI)

2.17.1 What is DI?

Donor insemination (DI) uses sperm from a donor to help the woman become pregnant.

Sperm donors are screened for sexually transmitted diseases and some genetic disorders. In DI, sperm from the donor is placed into the neck of the womb (cervix) at the time when the woman ovulates.

DI - IUI uses intrauterine insemination with donor sperm.

Donor sperm can also be used for in vitro fertilization (IVF).

2.17.2 DI may recommend if:

- Her partner is unable to produce sperm
- Her partner’s sperm count or quality is so poor that it is unlikely to result in the conception of a baby, unless intra-cytoplasmic sperm injection (ICSI) is carried out
- Her partner has a high risk of passing on an inherited disease
- She does not have a male partner.

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34 Carol Frost Vercollone, Heidi Moss, Robert Moss, "The Choices and Challenges of Donor Insemination "AI books.co.in page no. 234
2.17.3 Counseling for DI patients and partners

- Counseling is regarded as being essential before DI treatment is offered to her.
- Try to talk to those who already have donor-conceived children. Whatever her situation, it can help her to talk through your feelings.

2.17.4 How does DI work?

For women:

Step 1. Before proceeding with donor insemination, a tubal patency test should be performed.

Step 2. Screening tests for blood group, HIV, hepatitis B & C, syphilis and gonorrhea will be carried out. In addition she will have screening to ensure that she is immune to Rubella (German Measles) and a full blood count will be performed. Her hormone profile will be assessed to determine any hormonal imbalance.

Step 3. The selection of a suitable donor is now carried out. Some assisted conception units run their own sperm banks and have a range of suitable donors available to you.

She is not obliged to accept the donor who is offered to her. If donor sperm are in short supply, she may have to wait for suitable sperm to become available.

Step 4. She and, if applicable, her partner, will both need to sign a consent form agreeing to insemination with donor sperm, as well as consent to the disclosure of information.

Step 5. She may be given fertility drugs to boost egg production.

Step 6. Her clinic will perform blood or urine tests to find out when she is at her most fertile. It is common to carry out ultrasound scanning to ensure that no more than two mature eggs are about to ovulate.
Step 7. The donated sperm are inserted into the womb using a procedure called intrauterine insemination (IUI). The procedure is normally painless, although a small proportion of women may experience temporary, menstrual-like cramping.

Step 8. A week after DI/IUI is performed, a blood sample may be taken to measure your progesterone hormone level to confirm that ovulation has occurred.

For men (sperm donors):

Step 1. If He has decided to become a sperm donor, contact a licensed clinic from the list held by the National Gamete Donation Trust who recruits sperm donors.

Step 2. At the clinic, He produces semen and blood samples for testing purposes.

He is tested to find out his blood group, karyotype (chromosome analysis), cystic fibrosis screening (as this is the most common inherited genetic disorder), HIV, Hepatitis B & C, syphilis, gonorrhea and CMV (cytomegalovirus).

Step 3. He is examined by a genito-urinary physician to ensure that there are no obvious signs of genital infection.

Step 4. He is asked to sign a form allowing the clinic to contact your GP to ask whether they consider his suitable as a donor.

Step 5. A member of staff explains the donation process and the legal aspects. Make sure he understands his rights and those of the recipient(s) and of any child born as a result of the treatment.

Step 6. If He is accepted as a donor, He will need to sign forms consenting to the storage and use of his samples. They are kept in storage for up to ten years, but He may specify a shorter time.

Notes are kept about his physical appearance and may be used to match your characteristics with the requirements of the recipients of his donated sperm.
If he wishes, he may also leave a short description of himself and his achievements and a goodwill message for any child who is born as a result of your donation.

**Step 7.** His details will be held on a register maintained. Note that a registered donor has no legal or financial responsibilities towards a child who is born as a result of his donation.

**Step 8.** He now produces sperm samples for storage and future donation. The clinic will have a private room where you can provide your samples - all samples for donation must be produced on the premises of the clinic. The samples are quarantined until cleared by negative HIV and Hepatitis B & C testing six months after production of the samples.

**Step 9.** He can continue to be used as a sperm donor for 10 separate families have resulted. Although you can specify a lower family limit if you wish.

If a woman has had a baby as a result of your sperm donation, she can request that some vials of your sperm (if available) are set aside for her future use, so that her baby can have a genetic brother or sister at a later date.

**Step 10.** He can withdraw consent to the usage of your sperm at any time. This can include the use of any embryos in storage that resulted from the fertilization of a recipient’s egg with your sperm.