



MINISTRY OF HEALTH
Quality and Service
Administration

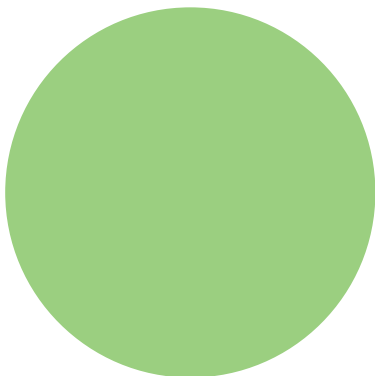
Guide to In-Vitro Fertilization in Israel



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Introduction

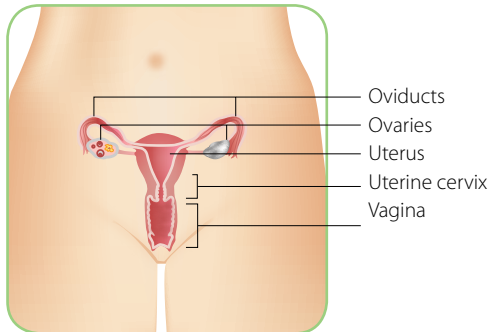
Introduction

The Natural Fertilization Process

During the natural fertilization process of a woman of childbearing age, a number of follicles develop in the ovary every month, due to hormonal activity of the pituitary gland and ovaries. The oocytes (eggs) are contained within these follicles. Usually, each month, a single follicle of all, reaches maturation. The mature oocyte is released into the oviduct (fallopian tube) in preparation for fertilization. This process is called ovulation. If no pregnancy develops, the oocyte will disintegrate, and the uterine mucosa (the endometrium), which had been preparing for pregnancy, will shed in the form of menstrual bleeding.

In order for fertilization to take place and an embryo to form, a spermatozoon (sperm cell) must fertilize the oocyte. The natural fertilization process takes place in the oviduct, when a single spermatozoon penetrates the envelope of the oocyte and activates a mechanism preventing other spermatozoa from penetrating. This ensures normal fertilization. The fertilized oocyte divides many times, forming many cells that form the developing embryo. At the same time, the embryo moves down the oviduct in the direction of the uterus, and about a week after fertilization, implants in the uterus and continues to develop.

Figure 1: Structure of the Female Reproductive System



In Vitro Fertilization

In vitro fertilization (IVF), also known as “test tube baby”, is used when a woman and/or man suffers from infertility, which can happen for a number of different reasons.

The medical definition of infertility is a couple that is unable to conceive after having had unprotected sexual intercourse for 12 months, and the woman is 35 years of age or younger. Over the age of 35, the timeframe for infertility is reduced to six months.

During the in vitro fertilization process, the oocyte is fertilized by the spermatozoon outside the woman's body, in laboratory conditions. The incubation of the fertilized oocytes is done in an incubator, in a petri dish with liquid containing substances vital for embryonic growth. Two to six days after fertilization, the embryos are transferred to the uterus, if and when the embryo is implanted, an ordinary pregnancy begins.

The Main Reasons for In Vitro Fertilization

Female Infertility (Approximately 40% of Cases):

- Mechanical disorders: obstruction of oviducts and/or lesions in the pelvis or around the oviducts, oophorectomy, endometriosis (cases in which it is possible to find uterine mucosa cells in other areas of the body) and so on.
- Hormonal deficiencies in ovulation.

The Woman's Age

- The woman's age has a pivotal effect on the number and quality of the oocytes and the chance of achieving pregnancy. Over the age of 35, the quality of oocytes decreases and the chances of pregnancy gradually decrease. The chances decrease significantly over the age of 38; over the age of 42, the chances are less than one percent.

Male Infertility (Approximately 40% of Cases)

- Poor sperm quality: oligospermia (low sperm cell count), spermatozoon immobility or low motility rates, or abnormal shape (morphological disorder).
- Lack of spermatozoa in the semen.

Unexplained Infertility (Approximately 20% of Cases):

There are also cases of unexplained infertility. When no reason for infertility is found, and the couple is still unable to achieve pregnancy using other treatments, doctors will usually be recommended that the couple undergo in vitro fertilization.



Combined reasons

Since Fertility is a unique field of medicine where usually two individuals with various degrees of fertility potential are involved, in many of the cases the reasons are a combination of female and male factors.

In Vitro Fertilization in Israel

In vitro fertilization treatments and associated processes in Israel are regulated by the Public Health Regulations (In Vitro Fertilization), 5747-1987. The regulations state that the fertilization treatments can only be conducted in an acknowledged/designated departments; for woman under medical care due to infertility or with the aim of maintaining fertility; and only after a doctor has decided that this process will advance her treatment.

In Israel, in vitro fertilization has been performed since 1980. This field has developed over the years, and the last decade has seen an increase in the number of fertilization treatments performed. Today, Israel has the highest number of fertility treatments by number of treatment cycles per capita.

Israel is the only country in the world that finances a large number of fertility treatment cycles. In vitro fertilization treatments are included in the health basket that the healthcare organizations are required to provide their members under the State Healthcare Insurance Law, 5754-1994. These treatments are given to people who wish to conceive their first and second children-couples who have no children from their current marriage and/or a woman without children interested in raising a single-parent family.

Treatment Restrictions: The treatment is given to women between the ages of 18-45 (Until the age of 45), and in cases of egg donation, up to the age of 54. Women who are 39 years old may undergo IVF treatments as a first option for fertility treatments, based on medical considerations. Women who have reached the age of 42 years will not undergo more than three consecutive treatment cycles in which they have not reached the stage of embryo transfer. This does not include the transfer of frozen embryos from previous treatments, regardless of the unit in which the treatment was performed.



At any age, after four consecutive treatment cycles which did not reach the stage of embryo transfer, or after eight treatment cycles (not including the transfer of frozen embryos) without a clinical pregnancy (clinical pregnancy diagnosed by demonstrating an embryonic pole in an US exam, including an ectopic pregnancy) the team providing the treatment, including a social worker, will conduct a session to discuss recommendations for continuing treatment. This discussion is the responsibility of the clinic where the last treatment cycle was conducted.

Additionally, these restrictions require the medical institution to conduct a **professional review** after eight failed treatment cycles in order to recommend further treatment, regardless of the insurer and their considerations. The medical institution can certainly recommend additional treatment cycles, based on the data found during the examination.

Data on In Vitro Fertilization in Israel

- **The number of in vitro fertilization units:** As of 2013, there are 24 IVF units available to the public, 38% are government owned, 29% are owned by Clalit Healthcare Services, 16% are publicly owned and the rest (17%) are privately owned.
- **The number of treatment cycles in in vitro fertilization:** In the last decade, there has been an increase in the number of in vitro fertilization treatments in Israel. In 2011, the number of treatment cycles was 38,284 compared to 18,011 cycles in 2000 (an increase by a factor of 2.1 in a decade). The rate of treatment cycles increased from 11.5 per 1,000 women of childbearing age (age 15-49) in 2000 to 20.7 per 1,000 women in 2011 – an 80% increase since the year 2000.
- **The average number of infants per birth after in vitro fertilization treatments:** On average, 1.2 live infants are born after in vitro fertilization treatments. This rate has been stable in the last decade (1.2-1.3), and shows that approximately 25% of pregnancies are multiple pregnancies.
- **Treatment Results:** treatment results indicate a stable trend in the last decade.
 - Embryos are transferred in most treatment cycles (women who have started treatment) (in 86%-90% of treatment cycles since 2011).
 - Approximately 25% of treatment cycles result in pregnancy, and nearly 20% result in the birth of an infant.



- About two thirds of all pregnancies following in vitro fertilization treatments result in birth (65%).
- The number of births after in vitro fertilization treatments has increased to 6,901 in 2011 compared to 3,546 in 2000.

To summarize: in the last decade, 15%-18% of all treatment cycles and 17%-20% of treatment cycles with embryo transfer resulted in the birth of an infant.

Preparation for Treatment

- According to the guidelines of the World Health Organization and the Ministry of Health, it is advisable for women at childbearing age, to consume 400 micrograms of folic acid each day. **The consumption of folic acid is particularly important in the three months prior to pregnancy and during the first three months of pregnancy**, as it significantly reduces (by up to 70%) the risk of neural tube defects in the fetus.
- According to Ministry of Health guidelines, patients must undergo the tests listed below prior to starting treatments. Most tests are valid for one year from the date they are performed.

The Women:

1. Blood type and RH (if unknown), complete blood count, coagulation functions.
2. Confirmation of rubella vaccination in vaccine records. If there is no documentation, the patient must receive two vaccine doses.
3. Lab tests for antibodies: CMV, syphilis, HIV, and hepatitis B and C.
4. A blood test for hormone profile, performed between days 2-5 of the menstrual cycle. The hormones prolactin, progesterone, TSH, E2, FSH, LH are tested to determine the initial hormone levels and to rule out other possible disorders.
5. A recent gynecological exam, including a PAP smear (of the uterine cervix) and breast exam by a doctor, mammography or breast ultrasound.
6. If imaging of the uterus by transvaginal ultrasound or uterus imaging (on day 11-13 of the menstrual cycle) or hysteroscopy (not mandatory) has been performed, the results must be brought.



7. It is advisable to perform genetic screening tests for hereditary diseases in advance.
8. For Women over the age of 40 an ECG study is recommended to undergo the results should be brought to the visit.

The Men:

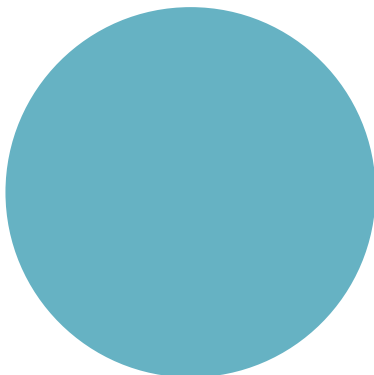
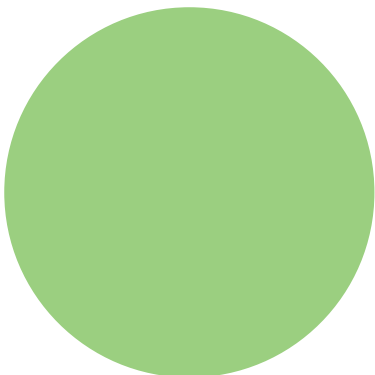
1. Sperm analysis (including morphology).
2. Blood test for hepatitis B and C antibodies.
3. Blood test for acquired immunodeficiency (HIV) antibodies.

Emotional and Mental Support

In vitro fertilization is a complex process in many aspects. Couples dealing with infertility must cope with physical, medical, ethical, financial, emotional and psychological problems. The need for fertility treatments may be interpreted as the shattering of the dream of parenthood. Fertility treatments themselves, which include hormone treatments, affect women physically and mentally. The loss of spontaneity in sexual intercourse, uncertainty, and cycles of hope and disappointment can affect the relationship and may result in stress and tension during a time when support is most needed.

The in vitro fertilization unit team is at your disposal. The team will provide assistance throughout the entire process and will recommend medical and nursing support frameworks. Some of the in vitro fertilization units in hospitals have a social worker or psychologist who can provide assistance to the couple. In units where this service is unavailable, hospital or community services can substitute. Some units have support groups for women or couples undergoing fertility treatments. Find out what options are available to you at the unit providing you care.





The First Meeting at the Unit

The First Meeting at the Unit

The first meeting at the unit is usually longer than usual and includes a discussion with the doctor, a discussion with the nurse, and a comprehensive explanation of the personal treatment plan established for the couple or patients.

What Should You Bring to the First Meeting?

1. Come with your partner or another companion.
2. A "Form no. 17" in accordance with the requirements of the unit.
3. A referral letter from the attending doctor or a summary letter on previous treatments, if conducted.
4. Approval for in vitro fertilization treatments (committee approval).
5. An identity card and a photocopy of the identity card (including appendix) of both partners.
6. Partners that are not married according to the entry on their identity card must bring a notarized agreement that has been performed and signed between them.
7. Single Mothers: Confirmation that a file was opened a file at the sperm bank
9. The results of all the required tests prior to in vitro fertilization treatment, as discussed in the preparations for the treatment section.
10. Patients who are under medical follow up owing to any health disorders must bring a letter from their attending doctor.

Upon arriving at the unit, go to the reception desk in order to open a medical file. As a rule, it is preferable to complete all of the tests listed before coming to the first meeting however, you must come to the scheduled meeting even if you have not performed all of the tests yet.

The Meeting

During the meeting, you will be asked to give personal and medical information, including your general health status, previous hospitalizations and operations, regular medication, cigarette use, use of other addictive

substances, and information on the medical history of your immediate family. You will also be asked to give details about any previous pregnancies, treatments were necessary for achieving pregnancy, whether there any complications during pregnancy, and how each pregnancy ended. You will be asked to show the results of all tests you performed as discussed in the **preparations for treatment** section. Based on the results of these tests, and your medical history, the team will make a diagnosis, and the doctors will give you a personalized treatment plan . Afterwards, you will receive a detailed explanation of your treatment plan.

Summary of the Treatment Stages

In vitro fertilization treatment includes a number of stages that will be described briefly. The stages will be discussed later in the booklet.

- 1. Hormone treatment for ovarian stimulation:** Hormonal drugs are given to stimulate the ovaries, which will produce a large number of follicles containing oocytes. At this stage, ultrasound exams and blood tests are conducted to track the follicles growing in the ovaries. When the ovarian follicles reach the appropriate size based on the ultrasound image, and the hormone level in the blood test is suitable for the number of follicles, you will be given an injection for the final maturation of the oocytes. About 34-36 hours after the injection, oocytes will be retrieved via aspiration.
- 2. Oocyte retrieval and sperm provision:** Oocytes are retrieved from the ovaries via aspiration in an operating room located near the fertilization laboratory. The process is usually done under general anesthesia and using a transvaginal ultrasound to guide the needle. During the retrieval process, the follicles in the ovaries are punctured and the follicular fluid with the oocytes is aspirated. The procedure involves discomfort, requiring recovery, as is standard following anesthesia. On that day, the man will be asked to give sperm to the laboratory for to be used to fertilize the retrieved oocytes or frozen sperm will be thawed.
- 3. The fertilization process in the laboratory:** After the retrieval, the oocytes are transferred to the laboratory and put on petri dishes containing a culture medium. At the same time, the sperm sample undergoes careful preparation. At this stage, the team decides which method of fertilization will be used based on the quality of the sperm (ordinary fertilization or micromanipulation – explanation is brought later in this booklet). Afterwards, the spermatozoa and the oocytes are co-incubated

to induce fertilization. Once fertilization occurs, the early stages the embryonic development are tracked. Tracking the fertilized oocytes in the laboratory lasts 2-6 days (usually 2-3 days).

- 4. Transfer of the fertilized oocytes (embryos) to the uterus:** The embryos are transferred to the uterus by inserting a very thin tube into the uterine cervix and injecting the embryos into the lumen (cavity) of the uterus. The process is simple, painless and does not require anesthesia. The decision of the embryo transfer date and the number of embryos that are transferred is based on the quality of the embryos and other medical considerations, such as the woman's age and the number of treatments she has already undergone. The embryos remaining in the laboratory will be frozen for future use, but only if the quality of the embryos is sufficient for freezing.
- 5. Hormonal support:** After the embryos are transferred to the uterus, you will be given hormonal drugs to support the implantation of the embryos in the uterus and the developing pregnancy.
- 6. Blood test for pregnancy:** 14-16 days after oocyte retrieval, you will perform a pregnancy test. If pregnancy is achieved, you will have to continue the supportive hormonal therapy, and you will be asked come to the clinic or hospital for blood tests and ultrasonography to ensure normal fetal development. If pregnancy is not achieved, an appointment will be scheduled for you for an additional treatment cycle.

Failure to achieve pregnancy is likely to cause grief, disappointment, and emotional difficulty. Do not hesitate to take advantage the emotional support offered by the unit!

Establishing the Treatment Protocol

To improve the chances of pregnancy and produce a number of oocytes without endangering the patient, the team establishes a personal treatment plan and hormonal therapy protocol, which includes various combinations of drugs and doses, for each patient. There are a number of main treatment protocols (details on which are provided in the section **hormonal therapy for ovarian stimulation**). Although the treatment is complex and involves taking of a number of different drugs, most patients get through the process without any complications. However, each woman responds and reacts to the treatment differently. These reactions are unpredictable, and may even vary

between different treatment cycles. Therefore, blood tests and ultrasound imaging are used to closely follow-up with the patient. Feel free to ask any questions you may have throughout the treatment stages and follow-up.

The Odds of Treatment Success

The odds of the treatment succeeding depend on a number of factors, including the woman's age, cause of infertility, sperm and oocyte quality, previous treatments, course of previous pregnancies, and more. Based on the above, the doctor can estimate the chances of the treatment cycle succeeding. For the general success rate of in vitro fertilization treatments in Israel, see the **data on in vitro fertilization in Israel** section above.

Side Effects and Complications

Like any other medical procedure, in vitro fertilization treatment also involves risks and complications, although most of these are rare. The most complications are ovarian hyperstimulation (mild, moderate or severe), risks related to anesthesia, ovarian bleeding, ovarian cysts, infection or inflammation, risks related to multiple pregnancy and others. See the **risks and side effects of hormonal therapy** section for details on the risks and side effects.

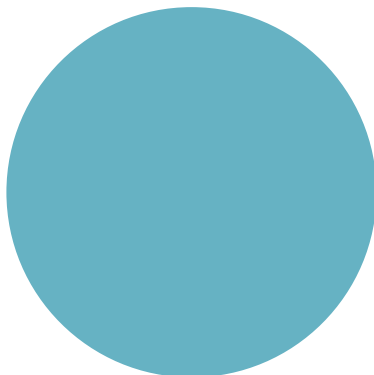
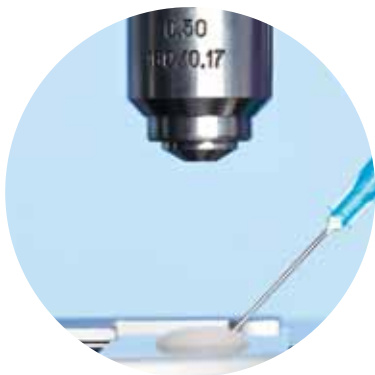
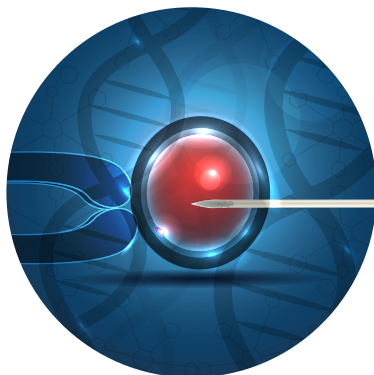
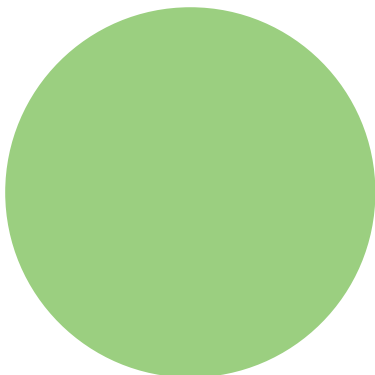
The Meeting with the Nurse

After you receive a detailed explanation from the doctor and all of your questions are answered, you will be asked to sign IVF treatment consent forms. The doctor will forward all of the details of your personalized treatment plan to the nurse, and you will be referred to her for further guidance. The nurse will introduce the rest of the team and give you a tour of the unit, including the treatment room, the ultrasound room, the recovery room, and the room/s in which the oocytes are retrieved and the embryos are transferred into the uterus. She will go over the treatment protocol with you and emphasizing the different treatment stages, the medications you will be taking during each stage, the side effects and how to minimize them, how to administer and store the medication, and to whom to direct your questions when the unit is not open.

The nurse will instruct you on how to inject the medications on your own. You will receive a referral for a visit to the nurse at your regular clinic so that you can practice injecting yourself, or initial training can be arranged for you at the unit. The nurse will measure your blood pressure, height, and weight.

At this same time, you may also meet with the social worker.

In general, during treatment, it is advisable to maintain an ordinary routine, including sexual intercourse. This can help you get through the process in a more pleasant and calm manner. It is important for you to know that the attending doctor, the medical staff, and the service providers are committed to maintaining your privacy and confidentiality in all matters relating to the treatment and outcomes. Treatment details will be given to a third party only with the consent and signature of both partners, together and individually. At the end of the treatment, you will receive a letter summarizing the details of the treatment. The letter can be used for any medical appointment, if required.



Hormonal Therapy for Ovarian Stimulation

Hormonal Therapy for Ovarian Stimulation

The Purpose of the Treatment

The oocytes develop and mature in the ovary inside small structures called follicles. Every month, a group of follicles develop and compete over the possibility to ovulate. Out of this group, one (or two) leading follicle(s) develops and reaches ovulation, while the remaining follicles disintegrate. The hormone therapy initiated during in vitro fertilization is intended to stimulate the growth of a number of follicles simultaneously. The use of hormonal drugs prevents the disintegration of the additional follicles, thereby increasing the chance of retrieving more oocytes.

The Course of the Hormonal Therapy

The treatment includes administration of hormonal injections. The treatment protocol is specifically chosen for each woman, based on her personal details: age, weight, hormonal profile, previous response to ovulation stimulation protocols, and more. Similarly, the drug dosage is adjusted for each woman since every woman responds differently to the treatments. To stimulate the growth of a number of follicles simultaneously, and to prevent the natural ovulation process, different combinations of a range of hormonal agents are used.

Follicle growth stimulation: Is achieved using drugs containing a hormone called FSH – follicle stimulating hormone. This hormone contributes directly to the growth of follicles and the development of oocytes in the ovaries (usually 5 to 15 oocytes). Drugs based on this hormone are referred to as gonadotropins, and they are produced in two ways: (1) from a biological source – extracted from the urine of postmenopausal women, which contains high concentrations of FSH, or (2) FSH agents that are known as recombinant agents, produced in the laboratory using genetic engineering methods. The hormonal therapy is usually administered as daily subcutaneous injections into the abdomen, arm or thigh. There is also an agent that contains a weekly dose of the hormone. As mentioned earlier, the medical staff will instruct you on how to perform injections

An additional hormone sometimes administered as an adjunct to FSH is the hormone LH – luteinizing hormone, also a gonadotropin. The LH hormone can help stimulate the ovary in the follicles recruitment process. Some of the agents contain FSH and LH separately, while others contain mixtures of both of these hormones at different ratios.

In certain cases, tablets called Ikaclomin/Clomiphene are used to induce ovulation. These tablets stimulate the secretion of LH and FSH hormones from the pituitary gland which causes growth and maturation of follicles. However, these tablets are usually used as an initial treatment in fertility clinics to stimulate ovulation in women who do not regularly ovulate, or who suffer from infertility for an unknown reason, and they are usually less effective than injections.

Prevention of unexpected ovulation before oocyte retrieval: Is achieved by using drugs which contain analogs ? (derivatives) of GnRH (agonist or antagonist type) hormone. Normally, this hormone is responsible for the release of the LH, and FSH

gonadotropins, but by some changes to it is structured the region in the pituitary gland responsible for ovulation is temporarily blocked. This way, this hormone contributes to prevention of early ovulation and allows for full maturation of the oocyte. These drugs are administered via nasal spray several times a day, daily injections, or a one-time long-term injection.

The Treatment Protocol

The treatment protocol is personalized for each woman, but as a rule there are a number of main protocol types. These main protocols combine the two drug groups differently, and over different periods of time for in vitro fertilization treatment:

- 1. Long treatment protocol:** This protocol is considered long due to the length of time over which the drugs are administered – three to four weeks. During the first stage, the hormonal pathway from the pituitary gland to the ovaries is suppressed, preventing ovulation of the follicles prior the retrieval procedure. This stage lasts at least two weeks, and is reached with the help of GnRH agonist drugs. To verify that the hormonal axis is suppressed, a blood test is performed for estrogen (E2) and progesterone (P) and the size of the follicles in the ovaries is assessed. The second stage, follicle growth stimulation, is done simultaneously, by administrating

gonadotropins at the same time. The dose and duration of treatment depend on the ovarian response. When follicles reach maturity based on their size in an ultrasound (a diameter of more than 17 mm) and blood estrogen levels, an hCG hormone injection is administered. This injection is meant to complete the oocyte maturation process and prepares the follicles for oocyte retrieval. The retrieval procedure is usually performed 34-36 hours after the injection of hCG. The long protocol may be started at two points during the woman's menstrual cycle: at the beginning of menstruation or on the 21st day of the previous menstrual cycle, i.e. about a week before menstruation.

- 2. A short treatment protocol with an antagonist:** For this treatment protocol, the sequence of administration of the different drugs is reversed. The treatment starts during the first days of the menstrual cycle, as in the short protocol, but here it begins with stimulation of follicle growth using gonadotropins without an agonist. Once an ovarian response is identified according to the development of the follicles and a rise in estrogen values, the injections of the GnRH antagonist are added until mature follicles are achieved. In a "fixed antagonist protocol" the antagonist injection is added on a pre-determined day of the stimulation (usually day 6) When the follicles mature, the injection of hCG is administered, like the long protocol. In the short protocol, the doctor will choose in certain cases to prepare the follicles for retrieval not using an agent containing hCG, but with a GnRH agonist such as Decapeptyl.
- 3. Short treatment protocol with an agonist:** In this protocol, the duration of administration of the drugs is shorter – about two weeks – from which it gets its name. The treatment begins on the second or third day of the menstrual cycle. A GnRH agonist is administered first, and a day or two later the gonadotropin drugs are combined. The follow up of the development of follicles and the timing of administration of the hCG injection for preparing the follicles for retrieval of oocytes are performed in a manner similar to the long protocol.

Follow Up and Monitoring

The follow up of the process of ovarian stimulation and the monitoring of the development of follicles is carried out, as set forth, using transvaginal ultrasound studies and frequent blood tests. For this purpose, you will be summoned for a checkup every few days (the checkup will be carried out at the IVF unit or alternatively at a clinic near your home). In the transvaginal

ultrasound study, the follicles developing in the ovaries will be counted and measured and the thickness of the endometrium will be measured. In the blood sample, the level of hormones secreted by the follicles, estrogen and progesterone, will be tested. There is a reason to track the level of LH too. It is important to make sure that the response to the treatment is not weaker than desired, and at the same time, an over response must be prevented. Therefore, the process is closely monitored by the attending medical staff, which regulates the duration of the treatment and the doses of the drugs according to the results of the tests, with the aim of achieving an optimal response.

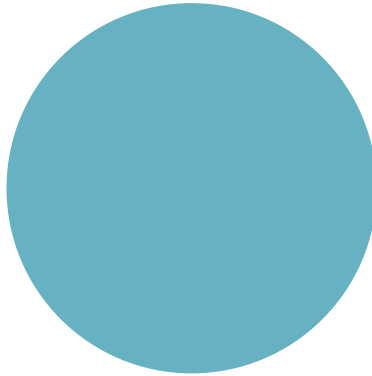
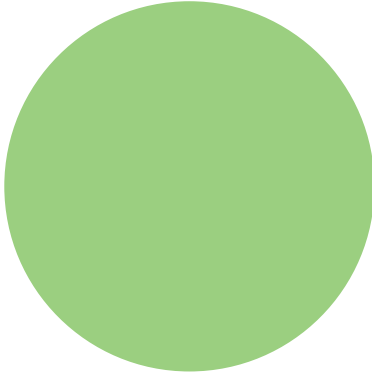
Risks and Side Effects of Hormonal Therapy

Like any medical procedure, in vitro fertilization treatments also involve risks and complications, although most of them are rare.

- 1. Ovarian hyperstimulation syndrome:** a complication of ovulation induction/controlled ovarian hyperstimulation treatment that features a significant enlargement of the ovaries and the passage to and accumulation of fluids in various cavities in the body. Mild ovarian hyperstimulation (which is the most common) manifests in abdominal swelling, abdominal pain, enlarged ovaries and mild accumulation of fluids in the abdomen. The effects usually resolve a few days after retrieving the oocytes by resting and profuse drinking, but if pregnancy is achieved, they may last longer. When the hyperstimulation is moderate, there may be nausea, vomiting, diarrhea and highly concentrated blood. In severe ovarian hyperstimulation there is a chance of effusions (fluid) in the lungs thrombi and emboli, in rare cases, heart and/or kidney failure may occur. While severe hyperstimulation is rare, it requires hospitalization when it occurs.
- 2. HyperSensitivity to hormonal agents:** Such hypersensitivity is rare, but in any case of an adverse effect, you should present yourself to the attending physician immediately.
- 3. Multiple pregnancy:** The rate of multiple pregnancies after hormonal treatments and after in vitro fertilization treatments is relatively high. As a rule, multiple pregnancy is defined as a high risk pregnancy for the mother and the fetuses alike, due to the concern of premature delivery, or birth of preterm infants, resulting in the delivery of unhealthy children. therefore, before the embryos are transferred, a discussion will be held and a recommendation will be given concerning the number of embryos

to transfer, considering the risks and the guidelines of the Ministry of Health.

4. **Additional complications:** No causality has been proved until today between an increase in frequency of ovarian cancer, endometrial cancer or breast cancer and hormonal therapy for stimulation of ovulation.



Oocyte Retrieval and Sperm Preparation

Oocyte Retrieval and Sperm Preparation

Admission of the Female Patient

On the day of retrieval, after office admission and review of the “hitchaivut” form, the nurse will admit you, identify you by name and an identity card and will apply a wristband with your identifying information. She will ask you about your allergy to any drugs, the day and time of administration of the hCG injection, and will check that you have been fasting for at least six hours before the anesthesia. She will take your vital signs and make sure that you are not wearing any jewels, dentures, contact lenses, etc. In addition, the nurse will make sure that your partner (if you are not using a sperm donation) has provided sperm for the laboratory as required. As driving after oocyte retrieval is prohibited, it is important for you to come with a companion.

Sperm Preparation

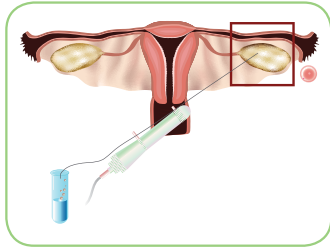
The man may provide sperm in the morning of the retrieval in a room that is designated for this purpose at the unit or bring the sperm from home in a sterile beaker. A liquid lubricant (soap, cream or gel) should not be used when giving sperm, because these substances may damage the spermatozoa. In addition, the sperm should not be heated or cooled. If there is a known difficulty in giving sperm upon demand, sperm may be frozen in advance in the laboratory as a backup for the retrieval day. At the unit, the man will be identified and his sperm will be received and transferred to the laboratory for further care.

The Preparations before Oocyte Retrieval

A nurse will ask you to empty your bladder before the procedure she will then accompany you to the bed and explain the surrounding instruments to you and. The anesthesiologist and the gynecologist who will be performing the retrieval will talk to you and examine you, and after that you shall be asked to sign a consent form for the procedure and anesthesia.

The Retrieval Procedure

The general anesthesia is short and usually lasts 10 to 20 minutes, during which you will receive liquid transfusion. The follicle retrieval is performed using a needle that is attached to an ordinary transvaginal ultrasound probe. The doctor will aspirate the follicles in the ovary while tracking the procedure using the ultrasound transducer. The needle will aspirate the follicular fluid containing the oocytes into a test tube that has a label containing your personal information\ on it. The test tube will be transferred to a laboratory that is near the operating room.



After the Retrieval

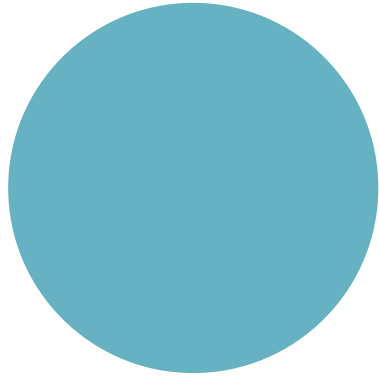
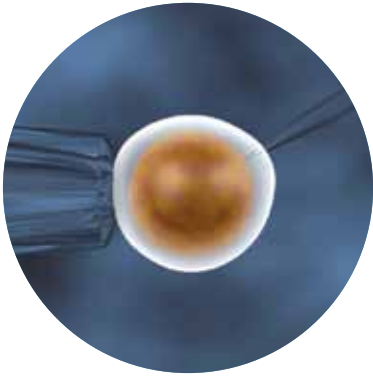
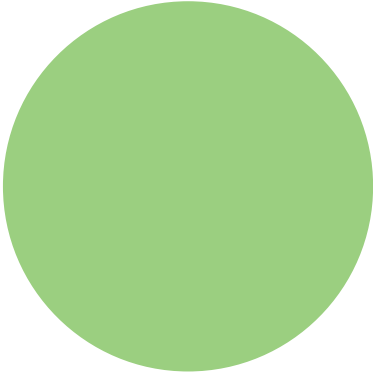
When you wake up, you will be in a bed, under the observation of the recovery nursing staff. The number of oocytes that were retrieved will be recorded in your medical chart. You will be connected to a monitor that measures your blood pressure and heart rate and you will have an oxygen mask for the first few minutes and an intravenous fluid transfusion. The recovery process lasts an hour or two. During this time, your vital signs will be taken and your condition will be tracked. If you feel pain, you will receive painkillers as necessary. Later, a nurse will help you get out of bed. It is important for you to empty your bladder and drink. 2-4 hours later, an anesthesiologist and a gynecologist will examine you, make sure that you have recovered, will discharge you and give you a discharge letter.

The nurse will discharge you after you eat a light snack, drink and dress yourself unassisted. She will make sure that a companion is with you. The anesthetics are cleared from the body over a course of 24 hours and there is a tendency to fall asleep, so additional rest is recommended. You will receive an explanation on the continued medication and what to do if pain or bleeding appears, and an explanation on the process of transfer of the embryos. You will also receive written directions on the preparations for the transfer of the embryos.

The day after the retrieval, you will be given information on the fertilization of the oocytes and the estimated transfer date (some units call the woman and in others, the woman calls and identifies herself using a code).

Risks and Side Effects in Oocyte Retrieval

- 1. The anesthesia risk:** The risk is very low. Oocyte retrieval is usually performed under general anesthesia, but this is a mild, simple anesthesia that does not necessitate intubation. The anesthesiologist will examine you before the procedure and make sure that the anesthesia is carried out in the safest manner.
- 2. Ovarian bleeding or rupture:** The puncture of the ovaries for aspiration of oocytes is carried out under ultrasound guidance, but despite this, the puncture very rarely causes excessive bleeding that necessitates an operation. As a rule, ovarian bleeding or rupture are very rare events.
- 3. Infection and inflammation:** May occur at the puncture site. To avoid this, the aspiration is performed under sterile conditions in an operating room. In certain cases, the doctor will recommend administration of antibiotics.



The Fertilization Process in the Laboratory

The Fertilization Process in the Laboratory

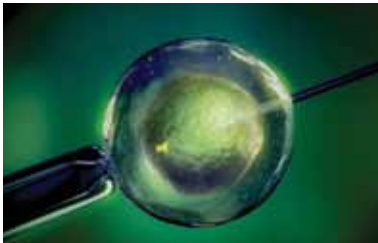
In the laboratory, the sperm and oocytes are identified by two embryologist or two staff members, to ensure that the sperm and oocyte originate from the two partners. Work in the laboratory occurs under sterile conditions in accordance with the procedures of the Ministry of Health. The embryologists find the oocytes in the follicular fluid and transfer them to dishes containing a suitable culture for growing embryos.

Manner of Performance of Fertilization

As mentioned, on the day of oocyte retrieval, your male partner will provide a sperm sample in a sterile beaker. The sperm will be examined under a microscope to assess its condition and quality, and it will be undergo a preparation process in the laboratory. In the laboratory, a decision will be made, according to the quality and quantity of the sperm, on the method by which the fertilization will be performed. There are two main methods for fertilization:

- **Insemination:** If the sperm is in a good condition, the laboratory calculates the number of spermatozoa that must be added to the culture of each oocyte, and the sperm is added after it is processed and count. This way, the fertilization process, in which just one spermatozoon penetrates an oocyte, is performed on the growth culture without further intervention.
- **Micromanipulation (ICSI):** Is performed in cases where the spermatozoon is of poor quality or quantity, or when the sperm appears to be normal but fertilization was not achieved in a previous treatment. Micromanipulation

Micromanipulation



Insemination



is also used in cases in which preimplantation genetic diagnosis is needed (see below). Using this method, the oocytes and spermatozoa are put in an injection dish under a microscope and an embryologist finds a spermatozoon that is intended for injection. The embryologist aspirates a single spermatozoon into a thin glass needle and injects it directly into a single oocyte, and repeats the process with a single spermatozoon that is injected into each mature oocyte. The oocytes into which a spermatozoon has been injected are transferred to an incubator for incubation.

A certain proportion of men who present for treatment have no sperm at all in their semen (azoospermia). In about 30%-40% of these cases, spermatozoa may be found in a sample from the testis (TESE) that is taken under local or general anesthesia. It is possible for spermatozoa that are found using this method to be sparse, and in some cases immotile. In these cases too, the spermatozoa are injected directly into the oocytes using the micromanipulation technique, and the fertilization rates are usually high.

It is important to know that irrespective of fertilization method, not all oocytes may be fertilized.

The Oocyte after Fertilization

After fertilization, the oocytes will be transferred to an incubator for further development. After a day, each separate oocyte will be inspected to see which of them has been successfully fertilized. The occurrence of fertilization may be identified under a microscope by the presence of two pro-nuclei in the oocyte, one originating from the oocyte and the other from the fertilizing spermatozoon.

The Number and Quality of Fertilized Oocytes

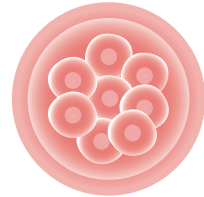
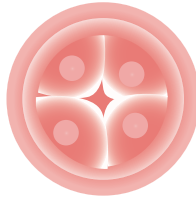
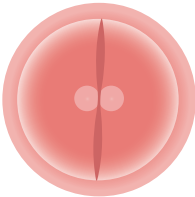
The fertilized oocytes (zygotes) usually start a process of cell division: ideally into 4 cells on the day after fertilization and into 8 cells one day later. The fertilized oocytes are inspected each day under a microscope and are graded by cell division rate, form of division and symmetry, and by the number of cell fragments observed. In some of the units, this procedure is performed automatically, without taking the fertilized eggs out of the incubator, using a camera that sends data to a computer (embryoscope). The best quality fertilized oocytes, according to set criteria, are transferred to the uterus, and if good quality fertilized oocytes are left over, they are frozen. If pregnancy is not achieved or if the partners are interested in another child, the frozen

fertilized oocytes may be thawed. See the section **freezing of fertilized oocytes** for further details.

Normal fertilization

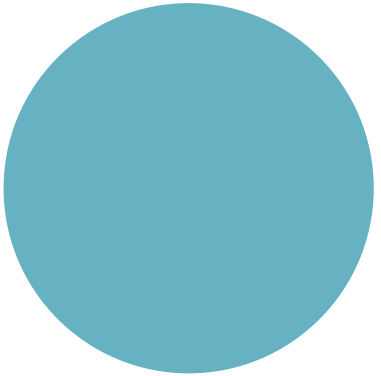
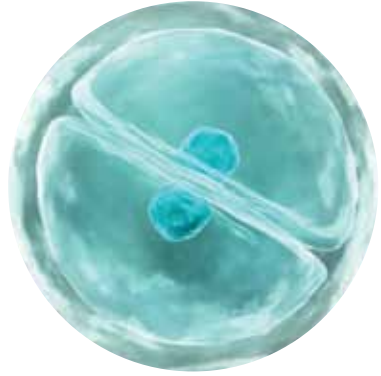
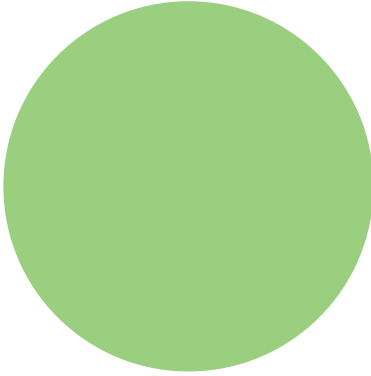
4 cell stage embryo

8 cell stage embryo



Preimplantation Genetic Diagnosis – PGD

Preimplantation genetic diagnosis – PGD – is conducted for couples who carry genetic diseases, with or without infertility, who have been identified in genetic screening tests or after the birth of a child who is affected by a genetic disease in the family. The genetic diagnosis is performed on the embryo approximately 3 days after the fertilization of the oocyte and before its implantation in the uterus. When the embryo consists of 6-10 cells, one or two cells are taken from it and the genetic test is performed. The embryo itself will continue to divide and develop normally after the extraction of the cell. After the test, genetically normal embryos are transferred to the uterus. The test is intended to reduce the need to terminate pregnancy in the case of an unborn child who is affected by a genetic disease.



Transfer of Fertilized Oocytes (Embryos) to the Uterus

Transfer of Fertilized Oocytes to the Uterus

Timing of transfer of Fertilized Oocytes to the Uterus

After the fertilization process in the laboratory, the development of the fertilized oocytes is tracked. Fertilized oocytes whose division and development process is normal are transferred to the uterus 2-6 days after fertilization. The fertilized oocytes are transferred to the uterus after division into 4-8 cells at least.

The Number of Fertilized Oocytes that Are Transferred to the Uterus

Before the transfer, you shall receive an explanation from the doctor and the embryology team on the number and quality of embryos that have been obtained. The doctor will discuss the number of embryos recommended to be transferred to the uterus with you. The recommendation is based on the quality of the fertilized oocytes, the woman's age and medical history, number of treatments undergone until today and the Ministry of Health guidelines on the subject. It must be remembered that the treatment in general and the number of fertilized oocytes transferred to the uterus in particular are unique to every woman and are based on all of the information that the medical team has gathered. Owing to the high risk of multiple pregnancies involving an increased risk to the unborn children and mother, the number of fertilized oocytes that are transferred to the uterus is limited to one to four. In any case, the decision on the maximum number is determined by professional decisions and is based on recommendations of the Israel Fertility Association on the subject.

The aim of the treatment is to ensure a pregnancy with a single embryo, as such a pregnancy has the best chances of ending successfully with a full term birth. For young women in the first cycle of treatment, it is advisable to transfer a single fertilized oocyte. The remaining fertilized oocytes that are of good quality (based on morphological criteria) may be frozen. Older patients with a history of recurrent failures are sometimes recommended to have more than one fertilized oocyte transferred to the uterus.

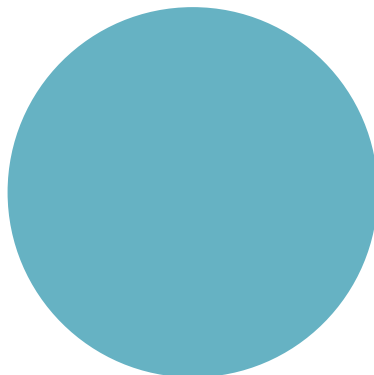
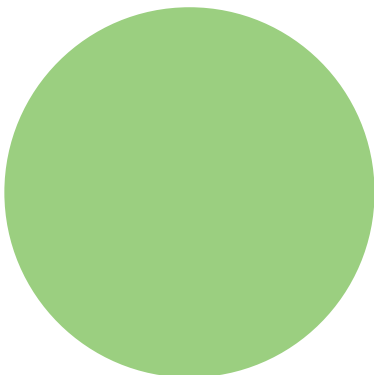
After the discussion and explanations, you shall both be asked to express your consent as to the number of fertilized oocytes that are to be transferred by signing a consent form. In the case of a single patient using a sperm donation, the patient only will be asked to sign the documents.

The Procedure for Transferring Fertilized Oocytes to the Uterus



Before the transfer of the fertilized oocytes to the uterus, an identification procedure is performed in which the name and identity number of the woman is checked against the information on the dish containing the embryos to be transferred. You will be asked to drink two to three cups of water so that your urinary bladder is full. A full bladder allows for better demonstration of the uterus by ultrasound transducer during the transfer of the fertilized oocytes and straightens the physiological angle between the uterine cervix and the uterus, thus facilitating the transfer procedure.

During the transfer, you will be asked to lie down in a manner that facilitates a gynecological examination. The fertilized oocyte will be aspirated into a thin tube that also contains a drop of the culture solution. Under ultrasound guidance, the thin tube containing the fertilized oocytes will be inserted into the lumen of the uterus, into which the embryo/s will be injected with the utmost care. After the procedure is over, the tube is routinely transferred for examination in the laboratory, to make sure that all of the fertilized oocytes have been released into the uterine lumen.



Hormonal Support

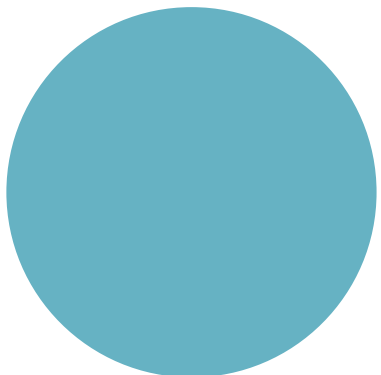
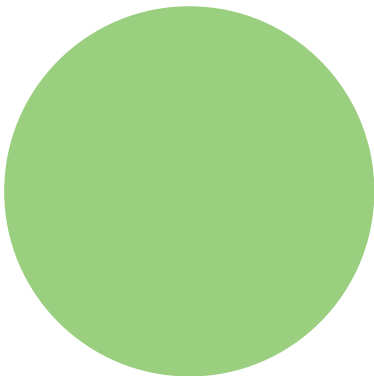
Hormonal Support

After the transfer of the embryos into the uterus, the patient can go back to ordinary life and daily activity, although it is advisable to reduce intensive physical activity until the date of the pregnancy test. There is no recommendation to stay in bed during this period, because it has not been proved that a prolonged bed rest affects the chances of pregnancy, and it may also burden the woman.

It is important to continue supportive hormonal therapy in accordance with the instructions of the attending doctor, until the results of the pregnancy test are received. The hormonal support is administered as a backup and adjunct to the hormones that the corpora lutea in the ovaries secrete. The function of the corpora lutea includes the production of the hormones estrogen and progesterone. These hormones support the endometrium (the mucosa of the uterus), thus assisting in the implantation of the embryos into the uterus.

There are many different hormonal combinations for supporting the endometrium and its suitability for implantation of the embryo, and the doctor will usually recommend continuing to take the agents after the pregnancy test date as well.

Discontinuation of hormonal support therapy will be according to the recommendation of the attending doctor.



Blood Test for Pregnancy

Blood Test for Pregnancy

As set forth, from the day on which the fertilized oocytes are transferred to the uterus, you will receive directions on continuing medication and the manner of taking the drugs, with the aim of supporting the implantation in the uterus and your pregnancy. It is important for you to make sure that you have suitable prescriptions for continuing the treatment. In any case, do not stop the medication without consulting your doctor.

The pregnancy test will usually be carried out 14-16 days after the date of retrieval of the oocytes. A blood pregnancy test is to be performed at the unit providing your care or at the community clinic near your home. It is not advisable to perform pregnancy tests before then, because at an earlier time you may receive a false positive answer, due to remains of the hormone hCG that was injected (this being a hormone that is secreted during pregnancy too). The laboratory result will be received on the same day and the department staff will inform you whether you are pregnant or not.

Positive Result

If the result is positive, you will have to continue the medication and set a date for reexamination and later another visit, which includes a blood test and ultrasound study, to make sure that the pregnancy is normal. On the 5th to 6th week of pregnancy, an amniotic sac will already be visible via US in the uterus, and in the 6th to 7th week an embryonic pulse may already be visible. The pregnancy followup at the unit will usually end in the 7th week of pregnancy, at which time you will be referred for further pregnancy follow up by your gynecologist.

Negative Result

If the result is negative, you will have to stop taking the medications and arrange for an appointment with the doctor for summarizing the current treatment cycle and planning another treatment cycle. Remember that failing to achieve pregnancy may involve a feeling of grief, disappointment and emotional difficulties. Do not hesitate to take advantage the emotional support that the unit offers you. If you have fertilized oocytes that have been frozen, you may plan the date of starting the treatment for their thawing with the doctor and unit staff.

Repeated Treatments

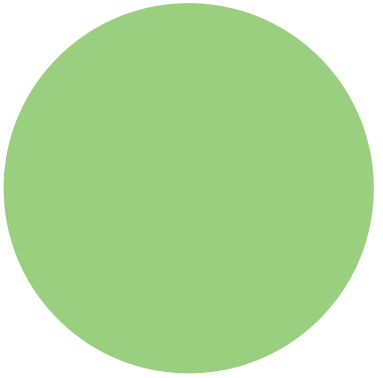
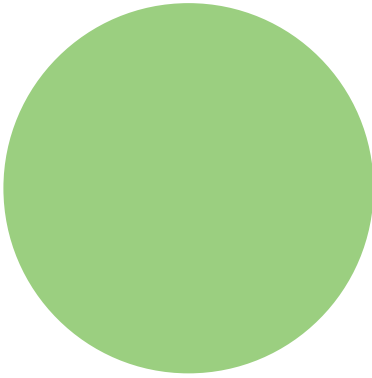
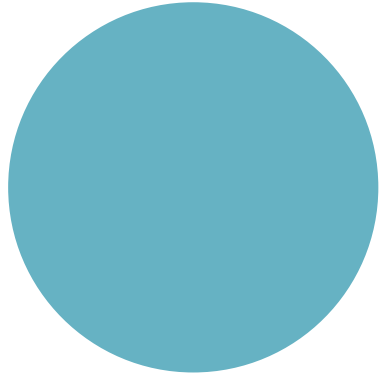
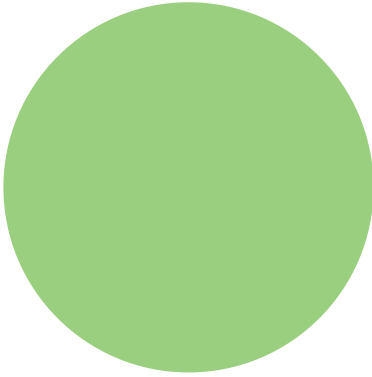
As mentioned, the State of Israel funds repeated in vitro fertilization treatments for its citizens up to the second child for women aged 18-45 (Until the age of 45). In vitro fertilization treatments are included in the healthcare services basket that the healthcare services are required to provide their members. Couples who have no mutual children from their current marriage and a woman without children who is interested in starting a single-parent family are also entitled to repeated treatments. Additionally, there are options through the complementary insurance programs offered by the various healthcare organizations that may cover additional coverage and it is worth checking out information on these options in advance.

Freezing of Fertilized Oocytes

As mentioned, controlled ovarian hyperstimulation causes the development of many follicles in the ovaries, which leads to the formation and retrieval of a number of oocytes, depending on the ovarian response. The improvement in fertilization methods and in embryo culture means that in many cycles of treatment, surplus embryos may be frozen. However, it has been found that only fertilized oocytes of good quality have a reasonable chance of surviving the freezing and thawing process, leading to pregnancy. Other reasons for freezing are diverse medical reasons, such as a fear of severe ovarian hyperstimulation that will harm the pregnancy, chemotherapy or radiotherapy due to a tumor or sudden disease of the woman.

According to Regulation 9 of the Public Health Regulations (In Vitro Fertilization), 5747-1987, and a Ministry of Health circular from 2008, "Guidelines for patients on use of **frozen fertilized oocytes** in in vitro fertilization units", the frozen fertilized eggs belong to both partners and may be kept in a deep freezing (in liquid nitrogen at a temperature of -196 degrees Celsius) for a period of five years at no cost. Later, by a written application by both partners or of the woman only, in the case of a sperm donation, they may be kept for five years longer subject to payment. The partners will declare what they intend to do after the first 5 years and will sign an appropriate form.

Good luck!



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