

AMERICAN HOSPITAL ASSISTED REPRODUCTION UNIT ISTANBUL

You can trust us because we deliver!

Pregnancy rates equivalent to most successful centers around the globe!

One of the biggest IVF centers in the country!

More than 22 000 cycles performed over the last 18 years!

State-of-the-art technology!

ISO 9001 and Joint Commission International Accredited Embryology Laboratory!

Academic and Research Facilities!

(You can search us on the Medline, just enter Urman B (au))

WE OFFER AMONG MANY OTHERS:

Blastocyst transfer

Testicular sperm extraction

Assisted Hatching

Embryo Glue

Slow freezing and vitrification

Preimplantation Genetic Screening and Diagnosis

A BRIEF HISTORY OF THE AMERICAN HOSPITAL AND THE ASSISTED REPRODUCTION UNIT



American Hospital, located in the heart of Istanbul, is one of the oldest privately owned hospitals in the country. Admiral Bristol founded the hospital in 1921. It was governed by a board of directors in the United States until 1995, when Vehbi Koç Foundation bought the hospital and undertook an extensive renovation to bring it up to its current status. The hospital is a tertiary private care facility with 300 beds. Assisted Reproduction Unit was founded in 1996 and rapidly became one of the most successful centers in the country, performing over 1000 treatment cycles a year. We receive patients from all over the country and also from abroad. With the exception of gamete and embryo donation and sex selection, the services offered encompass all assisted reproduction and related procedures. Assisted Reproduc-

tion Unit boasts luxuriously decorated waiting areas, large operating rooms, and state-of-the-art embryology and andrology laboratories. A very experienced team of 8 gynecologists, 6 embryologist and embryology technicians and 1 andrologist operate the unit headed by Dr. Bülent Urman. Supporting personnel include geneticists, dieticians, psychologists, secretaries, and a very experienced nursing staff. Besides patient care, the American Hospital Assisted Reproduction Team has also been very active in research and has published over 100 articles and 170 abstracts in respected scientific journals. Clinicians and embryologist from the team have been invited to national and international meetings as guest speakers. Clinical Director of the IVF program Dr. Bülent Urman is the national representative to the European Society of Human Reproduction and Embryology (ESHRE) and the past president of the Turkish Society of Reproductive Medicine. Laboratory Director of the IVF program Bio. Başak Balaban is the national representative to the ESHRE, Past President of the ALPHA International Embryology Society, and the President of the Clinical Embryology Society of Turkey.

WHAT IS IN VITRO FERTILIZATION?

IVF treatment is a long and tedious procedure that necessitates commitment from both the couple and the team. Despite significant advances in the field, unfortunately not all couples are expected to conceive. Outcome of the treatment is directly related to woman's age and her ovarian reserve. For women who produce an adequate number of eggs and who are < 39 years old, the outlook is bright, as cumulative conception rates of 80% can be expected with 3 treatment cycles. That is to say approximately 80 couples out of 100 will conceive when 3 treatment cycles are undertaken. In women > 39 years old, particularly when the ovarian reserve is diminished, however, the outcome is bleak as cumulative conception rates will be in the range of 10-30%.

IVF treatment entails basically three steps that have been fairly standardized throughout the world. Treatment starts with stimulation of the ovaries to produce many eggs. The next step is egg collection and fertilization to produce embryos. After fertilization the embryos are kept in incubators for approximately 3-5 days after which they are transferred into the mother's womb. Pregnancy test will be performed 10-12 days after the transfer.

Despite standardization of treatment protocols there is a wide variation in pregnancy rates that basically stem from laboratory conditions, experience of the medical staff, and embryo transfer policy. In the past, IVF clinics have been pressurized from the patients and their competitors to increase the number of embryos transferred into the uterus. However, this has been associated with an alarming increase in multiple pregnancy rates. Regulatory bodies in most European countries and Australia issued imposing restrictions on the number of embryos that can be transferred to a patient. The most recent legislation in Turkey passed in 2010 allows only one embryo to be transferred for the first two treatment cycles in women < 35 years of age. The transfer of two embryos is allowed from the third cycle onwards in women < 35, and for all cycles in women > 35 years of age.

American Hospital Assisted Reproduction Unit has been first in the country to incorporate into routine practice procedures such as embryo freezing, blastocyst transfer, PGD, assisted hatching, embryo glue, and vitrification. We have broad experience in dealing with couples with poor prognosis (age > 39, less than optimal quality embryos, poor ovarian reserve and previous multiple failed treatments). Third party reproduction that entails the use of donated gametes is not allowed in Turkey.

BEFORE YOU COME

Long Agonist Protocol

1. Stop smoking if you are a smoker.
2. Start using Folic acid pills 0.4 mg/day.
3. Start birth control pills on the third day of your menstrual bleeding.
4. Start Synarel nasal spray (1 puff-two times a day) on the 20th day of your bleeding. Alternatively you can use daily Leuprolide acetate (LA) injections (10 U/day subcutaneously).
5. Keep on using the Synarel nasal spray/LA subcutaneous injections until you come to the clinic.
6. We will perform an ultrasound examination and start stimulating your ovaries when you come to Istanbul. Treatment may be initiated any time within the first 10 days of your menstrual bleeding.

Short Antagonist Protocol

1. Stop smoking if you are a smoker.
2. Start using Folic acid pills 0.4 mg/day.
3. Come to the clinic directly on the second day of your cycle.
4. We will perform an ultrasound examination and start stimulating your ovaries when you come to Istanbul. Treatment may be initiated if certain conditions are met such as the absence of cysts and the presence of a thin endometrium.
5. In women planned to be treated with the antagonist protocol there is a 10-15% risk of not being able to initiate the treatment due to the presence of functional ovarian cysts or a early growing follicle that will suppress the stimulation of other follicles.

STIMULATION OF THE OVARIES

For IVF/ICSI treatment to be successful the ovaries should be stimulated to produce more than a single egg. In order to achieve this goal potent drugs called gonadotropins are administered in a controlled manner. Gonadotropins are self administered as most of the medications used today can be administered subcutaneously.

How is the treatment started?

An ultrasound examination is performed when the patient arrives in Istanbul. This examination should coincide with the third to fifth day of the cycle if a long protocol (the nasal sniff or subcutaneously administered Leuprolide acetate) or the second day of the cycle if a short antagonist protocol has been planned. If you don't have any cysts and the inner lining of the uterus is thin, then treatment is initiated. You may need to have a blood test to check for your estrogen levels if your doctor finds this necessary.

How long does the treatment last?

The treatment usually lasts for 10-12 days. During this phase you will be asked to come for periodic ultrasound examinations. The frequency of these examinations will increase as the treatment progresses. When the eggs appear to be mature, a final injection will be given at a specific time and the eggs are collected after approximately 36 hours.

How much medication am I going use?

The amount of medication used to stimulate the ovaries depends on the age of the woman and her ovarian reserve. While younger women with normal ovarian reserve use lesser amounts, older women and women with diminished ovarian reserve need higher doses to stimulate the ovaries. Variation in drug dosage may be up to two-fold.

Can my treatment be cancelled?

If there is inadequate response from the ovaries (poor response) meaning that the ovaries did not produce enough eggs to be successful, then the treatment may be cancelled and reinitiated with another protocol. Sometimes only one egg gains dominance and prevents other eggs from growing (asynchronous growth). This is another reason for canceling the treatment. When too many eggs are stimulated (hyper response), it may result in ovarian hyper stimulation syndrome if the treatment is continued. There are several options that may be exercised in this case.

EGG COLLECTION

Egg collection is a procedure whereby matured eggs are retrieved by ultrasound. Under the guidance of the transvaginal ultrasound probe, a thin needle is introduced from the vagina into the ovaries, and follicles that harbor the eggs are aspirated. This aspirate is sent to the embryology laboratory and the egg is identified in the fluid.



What should I do prior to egg collection?

These are summarized in the egg collection information leaflet.

Is egg collection a painful procedure? Do I need anesthesia?

Egg collection is relatively well-tolerated and can be undertaken with intravenous sedation and local anesthesia. However, if the ovaries are difficult to access your doctor may advise you to have general anesthesia. This will be discussed with you prior to the procedure.

Are there any complications associated with egg collection?

There may be some pain after the procedure but this usually resolves with simple analgesics. The doctor or the nurse coordinator will prescribe you medications that you will use after egg collection. Complications that arise after egg collection are usually of infectious nature but they are very uncommon (1/3000-1/4500 cases). There may be slight vaginal bleeding that is self-limited. If the bleeding is severe please contact your doctor or the nurse coordinator.



How are my eggs going to be fertilized?

This depends on the reason why you are not getting pregnant. If there is male factor infertility then microinjection (ICSI) is required. This is a procedure whereby a single sperm is injected into the egg using an instrument called micromanipulator. If infertility is due female factors, classical IVF is done where sperm at a certain concentration are added to the culture medium containing the eggs. Sperm fertilizes the egg in a natural manner.



Where are my embryos going to be stored until the day of transfer?

We keep the embryos inside incubators. Incubators are temperature and pH controlled environments that mimic the human body. Each couples' embryos are allocated a special compartment in the incubator.

EMBRYO TRANSFER



Embryos are transferred into the uterus usually between 2 and 5 days after egg collection. During the time they spend out of the body they are kept in culture medium in incubators that mimic the fallopian tubes. Embryo transfer is simple procedure that is done without anesthesia or sedation. The embryos are loaded into a plastic catheter that is then introduced into the uterus via the cervical canal. The number of embryos transferred depends on the age of the woman, previous failed treatment attempts and embryo quality. Turkish IVF legislation mandates the transfer of a single embryo in the first two attempts in women < 35 and two embryos thereafter. Two embryos can be transferred to women > 35 years of age. The transfer of more than two embryos is not allowed under any circumstances.

EMBRYO FREEZING



After the transfer there are usually excess embryos that can be frozen for later use. Only embryos that are of good quality are suitable for freezing. In Turkey, according to regulations embryos can be stored for 5 years. Embryo freezing does not harm the embryo. We currently prefer vitrification over slow freezing, as the former is associated with higher survival rates after thawing and higher pregnancy rates after transfer. There are over 700.000 babies worldwide that were born after the transfer of frozen-thawed embryos. American Hospital of Istanbul has a very successful embryo-freezing program. Our pregnancy rates for frozen-thawed embryo transfers are approximately equal to fresh transfers. A

couple can elect to have their frozen embryos thawed after an unsuccessful attempt or after delivering a baby. Preparation for frozen embryo transfer is a relatively simple procedure that entails stimulation of the inner lining of the uterus with orally used medications.

SPERM RETRIEVAL IN AZOSPERMIC SUBJECTS

In men who have no spermatozoa in the ejaculate, sperm need to be retrieved either from the epididymis or the testes. When the etiology of azospermia is obstructive (blockage to the canals that bring the spermatozoa from the testes to the ejaculate) sperm can be retrieved from the epididymis using a needle aspiration technique. In men with azospermia due to defective sperm production, sperm can be obtained from the testes, usually with an open surgical procedure. Both procedures are performed under general anesthesia. While sperm can be retrieved in almost 100% of subjects with obstructive azospermia, only 40-50% of the subjects will yield viable spermatozoa. Azospermia may be associated with certain genetic disorders. There may be mutations in the cystic fibrosis gene in men with obstructive azospermia. Chromosomal abnormalities and Y-chromosome micro deletions may be associated with nonobstructive azospermia. It is advised that genetic testing be undertaken in all men with azospermia.

PREIMPLANTATION GENETIC SCREENING AND DIAGNOSIS

Preimplantation genetic diagnosis (PGD) is a procedure whereby a single cell is removed from the embryo on day 3 to perform genetic testing. PGD can detect certain chromosomal abnormalities (i.e. trisomies, monosomies, translocations, etc.) and single gene defects (i.e. thalassemia, fragile X syndrome, etc.) and can also be performed for HLA typing. Full scopes of PGD services are provided in the American Hospital. Please contact your doctor for your specific condition.

Recently CGH using microarrays have been introduced to our PGS for aneuploidy (preimplantation genetic screening) program. The embryo is usually biopsied at the blastocyst stage (day 5) and array CGH is used to screen for anomalies of all chromosomes. This technique is superior to classical PGS where only 5-9 chromosomes can be screened. Array CGH increases the possibility to detect embryos harboring chromosomal errors that may not be visible to classical PGS. The embryos are usually frozen and healthy embryos are transferred later in an artificial cycle.

OUTCOME OF IVF PREGNANCIES

Approximately 80% of pregnancies achieved via IVF/ICSI carry to term and result in delivery of healthy baby/s. Delivered infants were shown to be normal when compared with infants that were naturally conceived. Only certain subsets of IVF babies (those that were conceived with the use testicular spermatozoa) may carry sex chromosome abnormalities detectable by amniocentesis or alternatively with PGD. In all other instances, long term follow-up of infants showed normal motor, neurological and behavioral development.

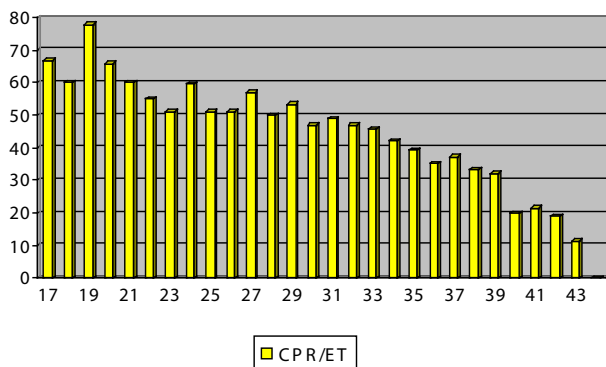
LONG TERM CONSEQUENCES OF IVF TREATMENT

Ovarian stimulation has been linked to an increased risk of ovarian and breast cancer. However, none have been proven beyond doubt. As infertility itself has been reported to be a risk factor for both malignancies it is still unknown whether some of the reported increased risks are associated with the treatment or infertility itself. Studies and long term follow-up of the patients are still ongoing. In the mean time women who received IVF treatment but failed to conceive are advised to have their annual gynecologic check-ups and yearly mammograms (depending on their age).

SUCCESS RATES OF IVF IN THE AMERICAN HOSPITAL

Success depends on woman's age and, if present, previous failed IVF/ICSI attempts. IVF is most successful in women < 35 years of age. In this age group pregnancy rates may be as high as 40% with a single and 55% with a double embryo transfer. However, pregnancy rates start to decline after 35 and more so after 39. Theoretically a chance of conception beyond the age 45 is zero. The graphic below displays the clinical pregnancy rate (ultrasound visible pregnancy sac) per embryo transfer in the American Hospital of Istanbul.

Clinical Pregnancy Rates according to woman's age



SERVICES PROVIDED IN THE ASSISTED REPRODUCTION UNIT OF THE AMERICAN HOSPITAL*

Controlled ovarian stimulation and patient follow-up with serial hormone measurements and ultrasonography

Transvaginal egg retrieval

Fertilization by IVF or ICSI

Laser Assisted Hatching

Blastocyst transfer

Embryo Glue

Embryo freezing on day 3 or day 5 (slow freezing and vitrification)

Testicular sperm retrieval in azospermic patients (needle and open biopsy)

Sperm freezing and testicular tissue freezing

Array CGH for aneuploidy screening

PGD for single gene defects

PGD for molecular disorders

PGD for HLA typing

SERVICES THAT WE ARE UNABLE TO PROVIDE

Oocyte and sperm donation

Embryo donation

Surrogacy

Sex selection

* These services are provided all year round including national and international holidays.

PRE IVF TESTING

FEMALE

Hematology

Complete Blood Count

Blood Group

Hormones

Prolactin, TSH, T4, AMH

Immunology

Rubella IgG

HBSAg

HCV

HIV

VDRL

Biochemistry

Fasting Glucose

Creatinine

BUN

ALT

AST

MALE

HBSAg

HIV

HCV

VDRL

Semen analysis

REQUIRED DOCUMENTS

- Marriage Certificate
- Valid I.D. or passport
- Photographs of the husband and wife
- Summary of previous treatments

REASONS FOR CANCELLATION OF TREATMENT

Your treatment may be cancelled for several reasons:

1. The ovaries may respond inadequately and the treatment is cancelled prior to egg retrieval.
2. Despite the presence of follicles no eggs may be retrieved. There are two reasons for this. First follicles may contain no eggs (empty follicle syndrome). This is seen in < 1% of the patients. Next, the follicles may prematurely rupture prior to egg retrieval procedure. This is seen in 3-5% of the patients depending on the stimulation protocol.
3. The eggs may not fertilize. This is very rare in the microinjection era. However in approximately 2-5% of the patients no fertilization may be seen due to abnormal eggs.
4. Fertilized eggs may not cleave. This is also very rare and due to abnormal eggs.
5. Azospermic husband may not yield spermatozoa to needle aspiration or open biopsy. In this case the treatment is cancelled prior to egg retrieval.
6. No normal embryos may be found, if PGD is performed. In this case embryo transfer is not performed.

EGG COLLECTION INFORMATION LEAFLET

Your follicles have matured and you are ready for egg collection. Please be sure to adhere to the following:

You should have your hCG (Ovitrelle) injection IU on athours.

Please be present in the clinic on athours.

Be sure to come on an empty stomach. Do not eat or drink after midnight.

Your husband has to accompany you as he will be asked to present a semen sample that will be used to fertilize your eggs.

Egg collection can be performed under local or general anesthesia. Be sure to discuss this with your physician, as you will be asked which method you prefer.

WHAT TO DO AFTER EGG COLLECTION?

After your eggs are collected you will stay in the hospital for approximately 2 hours. You are allowed to lead your normal life after egg collection. There is no need to rest. It is advised that you refrain from intercourse. There may be slight bleeding in the form of spotting after the procedure. This should last no more than 24 hours.

The next day after egg collection please call the clinic and speak to one of our embryologists (Başak Balaban or Aycan Işıklar; +90 212 444 3 777/1620-1621). They will give you information regarding the number of fertilized eggs and the approximate day of embryo transfer.

Use the following medications as directed:

1. Crinone gel-once a day intravaginally in the morning. You can insert your first crinone when you arrive home after egg collection. Thereafter use the gel in the mornings.
2. Monodox tablet-twice a day on an empty stomach.
3. Prednol tablets-once a day with a full cup of milk. If you have gastric problems Prednol may not be suitable for you. Please inform your doctor.

There may be other medications that may be used specifically for you. Your doctor or the nurse coordinator will give information regarding these.

You can come to the embryo transfer on a full stomach. Embryo transfer is a simple procedure that will cause no or minimal pain. Please come for embryo transfer with a partially full bladder.

WHAT TO DO AFTER EMBRYO TRANSFER?

Congratulations!

You have successfully completed your treatment cycle.

Please adhere strictly to the schedule regarding medications that has been given to you by our nurse coordinator.

1. Use Crinone gel twice a day.
2. Continue using Monodox and Prednol until the tablets given to you are finished.
3. Your physician may have prescribed other medications specific for you. Please use them as instructed.

Strict bed rest has never been shown to increase the pregnancy rate in IVF. Therefore you can continue with your life as usual. It is advised that you refrain from intercourse and physical exercise. Travel via car or plane is permitted.

Pain in the groins can be encountered after embryo transfer. This does not imply that you will menstruate. Sometimes there may be slight spotting before the pregnancy test. This does not always mean that the treatment has failed.

Have a blood pregnancy test (β -hCG) done 12 days after embryo transfer and report the result to the nurse coordinator.

Telephone numbers to contact

Nurse Coordinator

IVF Clinic +90 212 444 3 777/1601

Dr. Bülent Urman

Professor and Head

Department of Obstetrics and Gynecology

Assisted Reproductive Unit

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AMERICAN HOSPITAL SERVICES

For the services below, please contact the American Hospital, International Patient Programs at **+90 212 444 3 777 (ext: 1279)** or e-mail: **international@vkfah.org**

- Appointment coordination and hospital admission assistance for routine and/or preventive medical care.
- Coordination of all patient appointments with specialists for consultations and medical procedures.
- Pre-assessment from physicians, second opinions and recommendations concerning treatment plans.
- Advance financial and billing arrangements, including detailed estimates.
- Billing arrangements, detailed estimates on financial information prior to admission.
- Hotel recommendations with special rates.
- Translation services organization.
- VIP Transfer services organization.

From initial inquires, questions and concerns about medical treatments to the follow-up of medical care after returning home, American Hospital staff members are here to assist patients during all phases of their care.