# Instructions for assisted reproductive technology (ART)

* Please read this explanation sheet carefully and try to acquire some preliminary knowledge before starting treatment.
* Individual ART explanations by cultivators are also available (2,200 yen including tax, at own expense). Please join us.

## Assisted reproductive technology (ART)

It is a general term for infertility treatments such as in vitro fertilization, embryo transfer, microscopic fertilization, freezing and thawing embryo transfer.
Generally, if pregnancy cannot be achieved in any other way, these methods will be applied.
The treatments in our hospital are provided is as follows.

(1) Ovulation induction (the ovaries are stimulated by hormone preparations, and multiple eggs are developed)
② Egg retrieval (eggs just before ovulation are collected from the ovaries)
③ In vitro fertilization and microinsemination (using the partner's sperm to create a fertilized egg)
④ embryo culture (fertilized eggs are cultured in an incubator)
⑤ embrio-freezing (freezing and preserving well-growing embrio)
⑥Fresh embrio Transplantation(Only those who wish will be transplanted to the cycle in which the eggs were collected.)
(7) Thawing embrio transplantation (Thawing and transplanting frozen cells in a cycle different from the cycle in which the eggs were retrieved)

## (1) Ovulation induction (promotion of follicle development)

In order to improve the pregnancy rate of ART, it is important to obtain multiple eggs in a single egg retrieval. Since natural cycle grow only 1 egg, it is necessary to perform ovulation induction with hormone preparations in order to obtain multiple eggs. There are following two main induction methods that we use. In addition, the induction method and drug dosage differ depending on age and ovarian reserve (AMH value).

### □ GnRH antagonist method

Applications: People with good ovarian response, young people
Advantages: Potentially higher number of eggs retrieved
From around the 3rd day of menstruation, either HMG or FSH is injected to develop follicles.
When the follicle diameter exceeds 16 mm, GnRH antagonist is injected to suppress ovulation.
When the follicle diameter exceeds 20 mm, either injection of HCG or nasal instillation of GnRH agonist is applied and egg retrieval is performed 34 - 36 hours later.

### □ Low stimulus cycle method

Applications: People with poor ovarian response, older people
Advantages: less frequent ovarian hyperstimulation syndrome
Clomid is taken daily from around the third day of menstruation, and a small amount of HMG or FSH is injected to develop follicles.
When the follicle diameter exceeds 16 mm, inject a GnRH antagonist formulation to suppress ovulation.
When the follicle diameter exceeded 20 mm, HCG injection or nasal GnRH agonist applied, and egg retrieval is performed 34 - 36 hours later.

Drugs used

Follicle development...Clomid, HMG (HMG), FSH (RECOBEL, Gonalef)
Ovulation suppression: GnRH antagonist (Cetrotide, Ganirest),
GnRH agonist (Bucererin, Suprecure)
Ovulation promotion: HCG (HCG, Ovidrel), GnRH agonist (Bucerelin, Sprecure)

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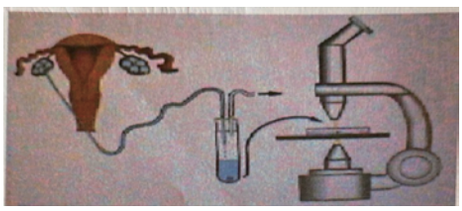
## ② Egg collection

Egg retrieval is performed using painkillers or anesthesia. Ultrasound is used to monitor the area around the ovaries, and follicles within the ovaries are punctured through the vaginal wall using a long needle. After the puncture, the follicular fluid inside the follicle is aspirated, and the embryologist collects the oocytes from this follicular fluid.
Eggs after egg collection are immediately transferred to the culture medium and cultured in a culture device called an incubator (37° C, 5% 02, 6% C02 environment).
After egg collection, you will rest and go home after a doctor's examination. Hormone supplementation will be performed from the day after the egg retrieval until the day of examination five days later in order to prepare the environment for implantation of the embryo.

*There are cases where egg collection cannot be performed due to poor follicle development or ovulation before egg collection.
*In some cases, even one egg may not be obtained after egg retrieval.



## ③ In vitro fertilization (insemination/IV F) and microinsemination (ICSI)

The history of natural pregnancies in the past and the condition of the partner's sperm determine whether to perform IVF or ICSI. For this reason, those who need it will be asked to undergo a fertility test by the day before egg collection. Even if in vitro fertilization is scheduled, ICSI may be performed in a hurry due to the partner's sperm condition on the day of egg collection, the doctor's judgment, or the patient's request.

The results of in vitro fertilization and microinsemination at our hospital (2021) are as follows.

| | in vitro fertilization | microinsemination |
|---|---|---|
| Normal fertilization rate | 77.0% | 79.7% |
| Abnormal fertilization rate (polyspermy, etc.) | 13.2% | 1.2% |
| Denaturation rate | 0.0% | 6.5% |
| Blastocyst arrival rate per fertilization | 55.4% | 53.3% |
| Good blastocyst rate per fertilization | 13.7% | 18.0% |

*There are individual differences in results.
*There are cases where not all eggs are fertilized, or even if fertilized, they may not be transplanted or frozen.

[Sperm freezing]

If semen cannot be collected on the day of egg collection due to the absence of a partner, sperm will be frozen in advance, and microinsemination using frozen sperm will be performed on the day of egg collection. However, prior application is required for sperm freezing. If you are interested, please consult the staff as soon as possible.

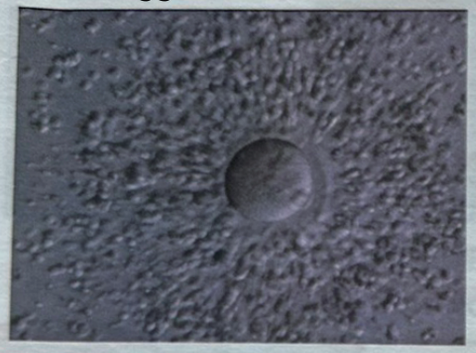
[Split method]

If the sperm condition is good and many eggs are obtained in the first egg collection, we will propose a split method in which half of the eggs will be in vitro fertilized and the other half will be micro-insemination. If there is fertilization failure, it cannot be fertilized by IVF, so ICSI can be performed on half of the cases. A separate fee (see price list) will be incurred if the split method is used.

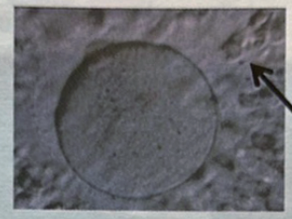
## ④ Embryo culture fertilization, process of embryo development

egg collected date

eggs collected



in vitro fertilization

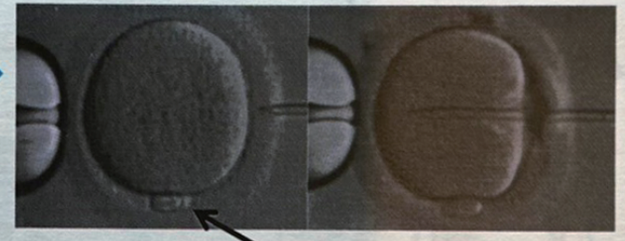


sperm

The collected eggs and prepared sperm are cultured together. Fertilization occurs when a sperm with good motility penetrates the egg

Since the collected oocytes are surrounded by cumulus cells, it is difficult to judge whether they are mature or not.

microinseminatio

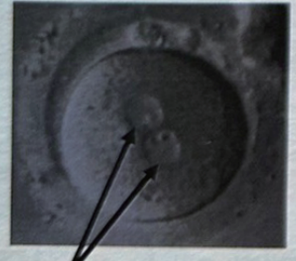


polar body

The cumulus cells are peeled off, and microinsemination is performed only on mature eggs (with polar bodies). Only one of the adjusted sperm with good motility and morphology is injected into the egg.

### 1st Day

pronucleus confirmed



pronucleus

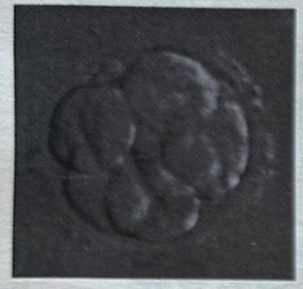
Normal fertilization is determined when one oocyte-derived pronucleus and one sperm-derived pronucleus can be observed.
If 3 or more pronuclei can be observed, it is judged as abnormal fertilization and the culture is stopped.

### 2nd Day

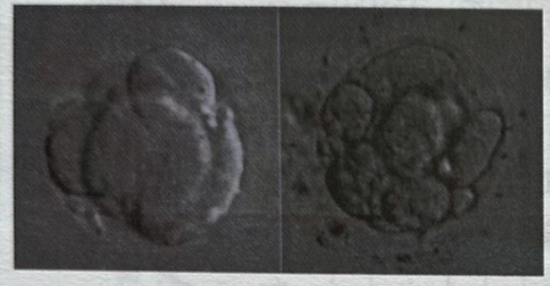
2-4 cell stage

## 3rd Day

6-8 cell stage



良好胚

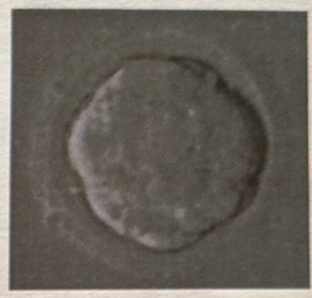


不良胚

Each cell (blastomere) is evenly sized and less fragmented (cell fragments produced during cell division) is called the better embryo.

## 4th Day

Morula



The blastomeres unite to form a mulberry-like embryo.

## 5th Day

Blastocyst (Blasto)
(Some embryos reach day 6/day 7)

inner cell mass

outer cell layer

Blasto1

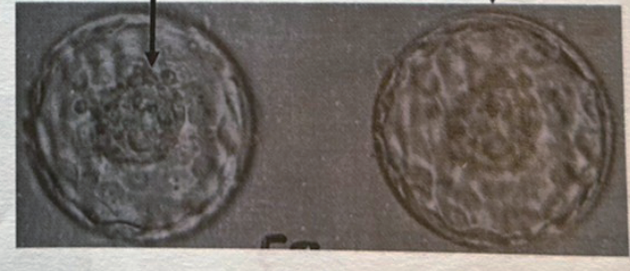
early blastocyst

Blasto2

blastocyst

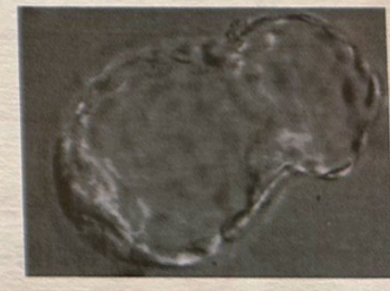
Blasto3

complete blastocyst



Blasto4

expanded blastocyst



Blasto5

Hatching mesblastocyst

When it becomes a blastocyst, the blastocyst cavity is formed, and the cells that become the fetus (inner cell mass) and the cells that become the placenta (outer cell layer) are produced. As development progresses, the blastocyst cavity enlarges and eventually cells hatch from the zona pellucida and implant in the endometrium.

# Embryo evaluation method

Embryos can be graded according to their division stage (when they are divided into blastomeres) and when they have grown into blastocysts.

## period of division

### Grade 1(G1)

Even blastomeres and no fragmentation

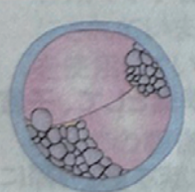
### Grade 2(G2)

Even blastomeres and less than 10% fragmentation

### Grade 3(G3)

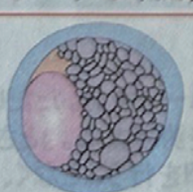
Uneven penalties with less than 10% fragmentation

### Grade 4(G4)



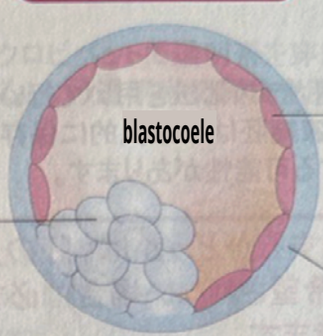
Uneven penalties with 10-50% fragmentation

### グレード 5 (G5)



Irregular blastomere with >50% fragmentation

## blastocyst

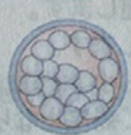



Evaluation of blastocysts is performed by combining the following three points

Blastocyst (4 A A) ①②③

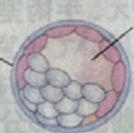
① Growth conditions (1~6)
② State of inner cell mass (A~C)
③ State of outer cell layer (A~C)

**Blasto1** early blastocyst



Blastocoele is less than half of the embryo

**Blasto2** blastocyst

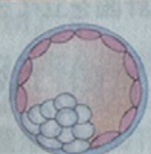



Blastocoele is more than half of the embryo

**Blasto3** complete blastocyst

Blastocoel fills the embryo

**Blasto4** Expanded blastocyst

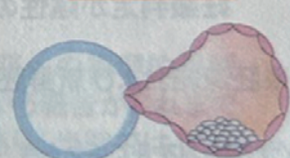


Embryo expands itself

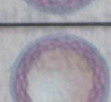
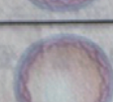
**Blasto5** Mid-hatching blastocyst

Starts hatching

**Blasto6** Post-hatch blastocyst



Embryo escapes from the zona pellucida

| | | outer cell layer | | |
|---|---|---|---|---|
| | | A: Tight and many cells | 8: Sparse and little cells | c： very few cells |
| inner cell mass | A: Tight and many cells |  |  |  |
| | 8: Sparse and little cells |  |  |  |
| | c ：very few cells |  |  |  |

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5th day after egg collection (5th day if it is a non-consultation day)
At 14:00, the doctor will explain the culture results and which embryos should be freshly transferred or frozen. If you are not going to have a fresh embryo transfer, you will be sent home on this day with only an explanation.

## ⑤ Embryo freezing

Embryo freezing is a method of freezing and preserving well-developed embryos obtained by in vitro fertil - ization and microinsemination. By freezing well-developed embryos that have not undergone fresh embryo transfer, it is possible to repeat the transfer by thawing the frozen embryos without having to perform egg retrieval again in the next cycle. This is called a thawed embryo transfer.

## Method

Embryo freezing is performed using the ultra-rapid vitrification method and the frozen embryos are stored in liquid nitrogen. The quality of embryos does not deteriorate over time during storage, and frozen embry - os can be stored semi-permanently. However, freezing injury may occur after thawing depending on the quality of the embryos before freezing.
Whether or not to freeze the embryo will be determined comprehensively by our hospital based on the de -

Whether or not to freeze the embryo will be determined comprehensively by our hospital based on the developmental status of the embryo and the patient's wishes. If you do not wish to have the em - bryos frozen, please be sure to let us know in advance. If there is no offer, it will be considered as ap - proved.

cost
If embryo freezing is performed, an embryo freezing fee (see price list) will be charged for each egg re - trieval cycle. The storage period for frozen embryos is calculated from the date of embryo freezing.
One year. It is possible to extend the storage period by one year every year.

## ⑥ Fresh embryo transfer

① After visiting the hospital, do not go to the restroom, but wait while drinking a drink and collect about 70% of the small amount of urine.
(2) Those who have accumulated will change into surgical gowns and perform transplantation in the oper - ating room.
(3) In transplantation, the embryo is injected into the uterus using a thin catheter.
(4) After the transplantation is completed, a urinary catheter is used to remove the small amount of urine that has accumulated.
⑤ Move to bed on a stretcher, rest for about 10 minutes, and then clean up.
After the transplant, hormone replacement is given for 2 weeks to maintain the pregnancy. Please rest in peace during this time.
(6) A pregnancy test is performed 2 weeks after transplantation. Please be sure to visit the hospital.
*Even if you are bleeding, there is a possibility that you are pregnant. Do not interrupt hormone replace - ment.
*Contraceptives should be used for 2 weeks before and after the transplant. There is a risk of multiple pregnancies.
⑧ If the pregnancy test is positive, a prenatal checkup will be performed every week, and you will be transferred to a maternity hospital at around 12 weeks of pregnancy.
If the pregnancy test is negative, we will plan the next transfer or egg retrieval.

*Oocytes and embryos not subjected to embryo freezing or fresh embryo transfer will be discarded after culturing.

## ⑦ Thawed embryo transfer

The thawed embryo transfer will be performed after the cycle following the cycle in which the egg retriev - al was performed. In the transplant cycle, as a preparation for the transplant, hormone replacement is performed for 20 days until the transplant day to thicken the uterine lining and prepare the implantation environment.
On the day of transplantation, the frozen embryos are thawed using the rapid thawing method and cul - tured for half a day to a day to check for freezing injury. Frozen embryos may be additionally thawed at this time if necessary. If there are no problems with the thawed embryos, the embryo transfer will be car - ried out as scheduled.
*Transplantation may be canceled if the thawed embryo is morphologically determined to be dead.
Transfer is the same as ⑥ fresh embryo transfer.

## Significance of Embryo Freezing/Thawing Embryo Transfer

According to the Japan Society of Obstetrics and Gynecology, ``In principle, embryos to be transferred in assisted reproductive technology should be single. 2 embryo transfers are permitted." Therefore, by freez - ing well-developed embryos that have not undergone fresh embryo transfer, there is no need to perform egg collection again.
It is possible to aim for pregnancy by repeating the de-embryo transfer. In addition, it is said that a satis - factory pregnancy rate cannot always be obtained with a fresh embryo transfer because the body during the cycle of egg collection is affected by ovulation-inducing hormones.



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## About options

### Assisted Hatching (AH)

The expanded blastocyst hatches (hatches) from the zona pellucida and becomes pregnant when it attaches to the endometrium ready for implantation. However, if the zona pellucida is thick or hard, it is thought that embryo hatching (hatching) is not performed well, resulting in implantation failure. Therefore, in order to assist hatching (hatching) of the embryo, a cut is made in advance in the zona pellucida of the embryo to be transferred. This is called assisted hatching. At our hospital, assited hatching is done by using a micropipette to pierce the zona pellucida toward the gap between the zona pellucida and the cells of the fixed embryo, and then rub the fixing pipettes together to incise a part of the zona pellucida.

### Application of Assisted Hatching (AH)

1. Repeated ART unsuccessful cases: cases in which implantation does not occur despite repeated embryo transfer for no particular reason
2. Elderly cases
3. Patients with thin endometrium
4. Embryos with thick or hard zona pellucida, embryos with developmental delay, embryos with fragments, etc.
5. When qualitative abnormalities such as hardening of the zona pellucida are observed

Conference report

- Implantation rate increases by artificially manipulating the zona pellucida and performing a treatment that assists the hatching of the embryo.

### High-concentration hyaluronic acid-containing medium (UTM)

The high-concentration hyaluronic acid-containing culture medium is a culture medium for transplantation rich in hyaluronic acid, and it improves the pregnancy rate and miscarriage rate by physically protecting the embryo and promoting the implantation of the embryo to the uterine lining. So far there have been reports of a decline. There are products such as UTM and bryo Glue for high-concentration hyaluronic acid-containing culture solutions, and we use UTM at our clinic.

Conference report

- Significantly increase the pregnancy rate in repeat failure cases and elderly cases
  Can increase pregnancy rates in fresh and thawed embryo transfer cycles
  On the contrary, there is also a report that there is no significant difference in the pregnancy rate and miscarriage rate and there is no effect.

## Option application method

If you wish, you need to submit an application form. Please submit what you filled out in advance.

Assisted hatching (AH): 11,000 yen including tax 3,000 yen when insurance is applied

<Fresh Embryo Transfer>

Please submit it at the treatment room on the day of the ovulation day.

・Please bring the fee on the day of transplantation (5th or 4th day after egg collection)

・If a fresh embryo transfer is carried out, the fee will be settled.

<Thawed Embryo Transfer>

Please submit it at the reception on the 7th and 8th day of the thawed embryo transfer schedule.

・The fee will be settled on the day of transplantation.

High-concentration hyaluronic acid-containing culture medium (UTM): 11,000 yen including tax 3,000 yen when insurance is applied

<Thawed Embryo Transfer>

Please submit it at the reception on the 7th and 8th day of the thawed embryo transfer schedule.

・The fee will be settled on the day of transplantation.

Notes

□ Application for the option is for each transplantation.

□If you did not perform a mouth transplant, please apply again next time.

□If the application is delayed, the option cannot be accepted.

□ You cannot apply for UTM with a fresh embryo transfer.

□ Even if you are planning a fresh embryo transfer, the transfer may be canceled in the following cases.

・A transferable embryo could not be obtained

- Bleeding on the day of transplantation

・There is a risk of ovarian hyperstimulation syndrome

・ Failure to use prescription drugs as planned, etc…

□Even if you are planning a mouth-melted embryo transfer, the transfer may be canceled in the following cases.

・Difference in hormone secretion due to spontaneous ovulation

- Bleeding on the day of transplantation

・ Poor development of thawed embryos

・ Failure to use prescription drugs as planned, etc…

□ If the transplantation is canceled after the AH or UTM application, or if the transplantation is not covered by insurance, the cost will not be covered by insurance and will be borne by the patient.

□Unused UTMs due to withdrawal of application or cancellation of transplantation cannot be used for the next transplantation due to expiration date.

□If there is bleeding on the day of the mouth transplant, please contact the culturist by email from our hospital website by 7:30 in the morning.
After checking with the doctor, we will contact you by phone.

## Tracking record of our hospital

You can see from here



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# Adjunctive therapy

At our hospital, we use a variety of supplementary treatments to promote ART.

## Sun Beamer (Far Infrared Therapy)

By irradiating the same wavelength as the wavelength emitted from the human body, it has the effect of warming the deep part of the body in a short time. By improving ovarian blood flow and uterine blood flow with this irradiation, the quality of eggs is poor. I will try to fix the problem you mentioned.
How to use / Treatment can be started at any time. The exposure time is ☒☒ minutes per time, and the sunpemer is applied over thin clothing, and is performed at least twice a week for three months. (About ☒☒☒ yen per session) Rental is also available, so you can do it every day at home. Please see a nurse.

## DHEA

It is an anti-aging supplement. It has been noted that oral administration of DHEA improved responsiveness in patients with decreased ovarian reserve, who were unable to collect eggs due to poor ovarian response even after ovulation induction. Directions for use: Take ☒ tablets daily. It is said that taking it for more than ☒ months is effective.

## Interpunch: MACH (Macrophage activating Chinese mixed herbs)

This herbal preparation consists of ☒ types of herbal medicines that have an interferon-inducing effect: pumpkin, psyllium, gold and silver flowers, and safflower.
It has been reported that in cases where it is difficult to get pregnant even after repeated in vitro fertilization and micro-insemination due to the inability to obtain good embryos, the rate of obtaining good embryos increases and pregnancy occurs after oral administration of MACH and egg collection. We have introduced MACH at our hospital, and we are realizing its effectiveness. Directions: Dietary supplement to be taken with water or lukewarm water, ☒ sachets daily.

## AglyMax-S (Dr.AglyMax-S): Daidzein-rich aglycon isoflavone

An isoflavone that has been shown to be effective against menopausal disorders. A fermented soybean germ extract extracted and concentrated as aglycon-type isoflavones. It is a nutritional supplement that has been processed so that isoflavones can be absorbed more efficiently than ingested directly from soybeans. Oral administration of this will increase the secretion of leukemia inhibitory factor (LIF) and transforming growth factor-β (TGF-β), which are essential for pregnancy and implantation. These factors promote the endometrium to become a membrane called the decidua that provides nutrients to the fertilized egg, and work to create an environment that makes it difficult for the decidua to come off and allows the fertilized egg to easily implant. The results of this research have been published in an authoritative British journal of endocrinology and have attracted attention. Directions: Take ☒ tablets daily from the first day of the thawed embryo transfer cycle until the pregnancy test date.

## prescription drug

**Julina Tablets/Premarin**

Used for hormone replacement cycles in thawed embryo transfer.
Side effects may include severe headache, cholestasis jaundice, pruritus, and thrombosis.

### estrana tape

Used for hormone replacement cycles in thawed embryo transfer.
Anaphylaxis, venous thromboembolism and thrombophlebitis may occur as side effects. In rare cases, contact dermatitis, irregular bleeding, withdrawal bleeding, and breast engorgement may occur.

### Lutinus Vaginal Tablets

Used for hormone replacement cycles in fresh and thawed embryo transfers.
Side effects may include dizziness, nausea, irregular bleeding, headache, and acne.
*Drugs once prescribed cannot be refunded for any reason.


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## Measures to prevent fertilized eggs from being mixed up at our hospital

At our hospital, a specialized embryologist handles and manages your important fertilized eggs. In accordance with the safety manual, the transfer and manipulation of eggs and sperm are always double- and triple-checked by two or more embryologists, and measures are taken to prevent mix-ups.
However, if the semen sample is submitted without a name written on the container, it cannot be used from the viewpoint of preventing mix-ups.
Please be sure to check it yourself when you submit it. In order to prevent misunderstandings, we would appreciate your cooperation as it would not be possible without the cooperation of the patient.

## Things related to egg retrieval surgery

Complications associated with egg retrieval include bleeding, organ damage, infections, and side effects of anesthesia.

bleeding

Bleeding from the surface of the ovary due to follicular puncture is the most frequent, but usually stops bleeding spontaneously and does not lead to serious problems. However, if a large blood vessel is injured, intra-abdominal bleeding may occur, and if the amount is large, blood transfusion or laparotomy may be required to stop the bleeding. Immediately after egg retrieval, you will be examined and will be sent home after confirming that there are no abnormalities.

organ damage

In front of the uterus is the urinary bladder, behind it is the intestinal tract, and the ovaries are located between these organs. Egg retrieval is performed under ultrasound guidance, which can cause damage if the ovaries and these organs are adjacent. A puncture of the urinary bladder may cause blood in the urine, but is usually harmless. Intestinal puncture may cause peritonitis. After egg collection, you will be prescribed antibiotics, so be sure to take them. If you have persistent hematuria or abdominal pain with fever, please contact us.

anesthesia

In rare cases, hypotension and respiratory depression may occur when anesthesia is used during oocyte retrieval. In our clinic, we are working on these prevention by wearing various monitors.

allergy

Allergic reactions may occur with anesthetics and antibiotics.

If you have a history of allergies, please let us know in advance.

*Based on these, our hospital strives to ensure safety by conducting sufficient follow-up observations even after egg collection.

*Medical treatment and surgery are performed with care to avoid physical complications. In this treatment, there are complications that cannot be avoided even if there is no negligence. * It is not clear that repeated advanced reproductive medicine may have any effect on the body.

## **Ovarian Hyperstimulation Syndrome (OHSS)**

In the "spontaneous ovulation cycle", 1 (~2) follicles are formed in the ovary, but in the "stimulation cycle" using an ovulation inducer, multiple follicles are formed. It is not uncommon for 10 to 20 follicles to form when a strong injection is administered daily. "Ovarian hyperstimulation syndrome (OHSS)" is a pathological condition characterized by abdominal pain due to swelling of the ovaries due to numerous folliculogenesis and a feeling of abdominal pressure due to accompanying ascites. The severity of symptoms varies depending on the type and dosage of the drug, the patient's constitution (eg polycystic ovary syndrome), and drug sensitivity. OHSS gradually appears after administration of hCG preparations before egg retrieval, peaks about one week after egg retrieval, and suddenly improves before menstruation. However, if the pregnancy is successfully established, the pregnancy corpus luteum persists and the symptoms are said to be severe. Therefore, if OHSS is suspected in advance, the fertilized egg should be cryopreserved without transplantation in that cycle. do. OHSS is a symptom that about 5% of women who are undergoing ovulation induction are aware of, but most of them are mild and improve spontaneously. Caution should be exercised in severe cases (0.5%) such as large swollen ovaries accompanied by severe pain, ascites retention, and decreased urine output. In these cases, thrombosis and other complications may occur, and hospitalization may be required. If there are signs of OHSS, such as after oocyte retrieval, well-developed embryos are frozen rather than transferred. If you are undergoing ovulation induction and your doctor has pointed out the possibility of OHSS, please drink more water than usual and try to rest.

# multiple pregnancy

A report of the Japan Society of Obstetrics and Gynecology states, "In principle, a single embryo should be transferred in assisted reproductive technology. allows transfer of 2 embryos.", it is possible to transfer 2 embryos at a time (double transfer). However, even if only one embryo is transferred, monozygotic twins may occur, but if two embryos are transferred, the possibility of multiple pregnancies of twins or more increases. Many multiple pregnancies result in premature birth (twins: 42%, abortion: 85%) and may cause sequelae (twins: 4.7%, abortion: 3.5%). They also have serious perinatal problems, such as the onset of toxemia of pregnancy and 80% of cases requiring caesarean section. Considering the impact and burden on the mother's body during pregnancy and the various problems faced by premature babies (immature babies), multiple pregnancies cannot be welcomed lightly. In Europe and the United States, it is said that it can become a hotbed for infant abuse. In order to prevent multiple births, careful handling is required during embryo transfer.

# miscarriage

Miscarriage occurs in about 10-15% of natural pregnancies, but the miscarriage rate in pregnancies caused by in vitro fertilization is higher than this (IVF Embryo Transfer: 23.1%, IVF Embryo Transfer: 26.8%, Thawed Embryos Transplantation: 25.4% Report of the Japan Society of Obstetrics and Gynecology 2019 grades). Causes of miscarriage are related to chromosomal abnormalities in gametes (eggs: 26%, sperm: 8%) or fertilized eggs (8%), maternal age and constitution, infections, uterine fibroids and endometriosis. It is said that there are The most frequent chromosomal abnormality (described later) is a natural selection, and it is thought that infants with weak vitality choose the path of miscarriage on their own. There is currently no way to prevent miscarriage, so we just have to wait and see.

A miscarriage breakdown is as follows:

(1) A urine test is positive for pregnancy, but the gestational sac cannot be confirmed (chemical pregnancy)

(2) A gestational sac was seen, but the fetal heartbeat could not be confirmed (5-7 week miscarriage)

(3) A heartbeat was confirmed once, but it cannot be confirmed afterwards (miscarriage after 7 weeks)

In the case of chemical pregnancy in (1), the pregnancy ends naturally with menstruation, but in the missed miscarriages in (2) and (3), treatment (abortion surgery: uterine cleaning) is required. After having an abortion, a period of contraception of about 3 months is generally required.

# chromosomal abnormalities, congenital anomalies

The miscarriage rate is said to be higher in pregnancies resulting from in vitro fertilization than in natural pregnancies (see above), but there is no significant difference in the rates of chromosomal abnormalities and congenital anomalies in miscarriages and offspring compared to natural pregnancies. Based on the many reports, gamete manipulation is considered to have no effect on the chromosomes of offspring. However, no definitive conclusions have yet been drawn on these matters.

In particular, we will have to wait for future tabulations regarding the impact on future generations, such as the next generation and the next generation.

There are two aspects to the effects of in vitro fertilization on the offspring.

(1) Effects of artificial manipulations such as in vitro culture and micromanipulation on fertilized eggs

Based on the above reports, it is considered that the "in vitro manipulation" of removing and culturing oocytes does not increase the number of chromosomal aberrations in fertilized eggs. In addition, when there is no chromosomal abnormality in the couple, it has been reported that there is no difference in the incidence of chromosomal aberrations in fertilized eggs between in vitro fertilization and microinsemination. It is possible.

(2) Effects caused by the characteristics of the population undergoing infertility treatment female factor

Chromosomal abnormalities in fertilized eggs increase with aging, and the rate of miscarriages and births of chromosomally abnormal babies increases accordingly (e.g. Down syndrome).

male factor

5.6% of patients with severe male infertility have chromosomal abnormalities, a higher frequency than 0.6% in the general population.

For this reason, there is concern that abnormalities in the offspring will increase if men with severe infertility factors are able to have children by performing microinsemination. In addition, since genes related to male sexual function are located on the Y chromosome, it has been pointed out that males with sex chromosome abnormalities may inherit male infertility if the offspring is a boy.

## ectopic pregnancy

Even if the embryo is transferred into the uterus, ectopic pregnancy may occur (in vitro fertilization embryo transfer: 1.1%, micro-insemination embryo transfer: 1.9%, thawed embryo transfer: 0.6% Report of the Japan Society of Obstetrics and Gynecology 2019 results). Embryos transplanted into the uterus are thought to return to the uterus after moving up the fallopian tubes without staying there, but if the fallopian tubes have transport problems, the fertilized egg may be trapped en route. It's going to be a floor in the place. Tubal infertility is associated with a higher risk, so the incidence differs between IVF and ICSI. 95% of ectopic pregnancies are “tubal pregnancy”, and more attention is required in cases of “tubal infertility”, “previous ectopic pregnancy”, and “previous chlamydia infection”. Simultaneous intrauterine pregnancy and ectopic pregnancy

It may be. There are two types of ectopic pregnancy: the abortion type and the ruptured type. The former may resolve spontaneously, but the latter causes intra-abdominal bleeding and requires additional intervention such as surgery. Early diagnosis is important because delayed detection can lead to serious complications. Even if bleeding occurs around the day of pregnancy determination after ART and it is judged that "menstruation has come", it is possible that an ectopic pregnancy has occurred, so be sure to see a doctor on the "diagnosis day".

## Responsibility for Storage and Response to Natural Disasters and Disasters

At our hospital, we properly lock our facilities and equipment, and take measures to prevent disasters such as power outages and earthquakes. I am taking full responsibility. However, in spite of this, if the facility or equipment is damaged due to force majeure due to various factors such as invasion, theft, natural disasters, etc., embryos being cultured or preserved

Frozen embryos in tubes can be damaged or lost. In this case, please understand that we cannot compensate for this loss. In addition, in the event of a disaster, please follow the instructions of our hospital regarding evacuation and other measures. In addition, if our hospital is closed, we will not be able to transfer or store frozen embryos or embryos in culture. In such a case, we will notify you in advance, and if you wish, at the patient's expense and responsibility

Punari. In such a case, we will inform you in advance, and if you wish, we can transfer the frozen embryos to the designated hospital.

In addition, in preparation for such cases, we have established a system that can introduce nearby ART specialist clinics. Thank you for your understanding and understanding.

## About fees

In principle, it is covered by insurance, but if the wife's age is 43 years or older on the date of treatment start, it will not be covered by insurance. In addition, fees will be added according to the number of eggs obtained, the number of microinsemination, the number of cultures, and the number of embryos frozen. Please refer to the price list for details. Please note that treatment fees once paid cannot be refunded for any reason. Thank you for your understanding and understanding.

## counseling, second opinion

If you wish, you can receive counseling from doctors, reproductive medicine consultants, and embryo culture specialists. You can also get a second opinion from another doctor.

## Obligation to report treatment results to the Japan Society of Obstetrics and Gynecology and the Personal Information Protection Law

Since our hospital is registered as a medical institution for assisted reproductive technology registered by the Japan Society of Obstetrics and Gynecology, we are obligated to report treatment results to the society. In addition, the results of our hospital may be reported at academic conferences and in papers, and may be published on our website. In that case, we will use the information appropriately in accordance with the Personal Information Protection Law. Thank you for your understanding and understanding.

Relevant therapeutic actions are subject to the agreement of the physician and the patient. If you have any questions or requests, please feel free to contact us.

*If you have any questions, please call us from 9:00 to 12:00 and 14:00 to 16:00 on the day of treatment.



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# ☆ Egg retrieval cycle

| Billing date | Item | fee | | | |
|---|---|---|---|---|---|
| | | 1 | 2~5 | 6~9 | 10 or more |
| egg collection day | Egg collection preparation (egg collection stop) | 8,800 yen | | | |
| | analgesia by suppository *1 | 1,140 yen (about 1,100 yen) | | | |
| | Intravenous anesthesia *2 | 24,200 yen (about 4,600 yen) | | | |
| | General anesthesia *2 | 68,200 yen (about 20,500 yen) | | | |
| | Egg collection: | ¥35,200 (9,600 yen) | | | |
| | Number of acquired eggs | 26,400 yen (7,200 yen) | 39,600 yen (10,800 yen) | 60,500 yen (16,500 yen) | 79,200 yen (21,000 yen) |
| 5th day after egg collection or your next clinic visit | Hyaluronidase treatment (no mature eggs) | 14,300 yen | | | |
| | In vitro fertilization | 46,200 yen (12,600 yen) | | | |
| | Microinsemination (number of implementations) | 52,800 yen (14,400 yen) | 7 4,800 yen (20,400 yen) | 110,000 yen (30,000 yen) | 140,800yen (38,400) yen |
| | + Split addition | 23,100 yen (6,300 yen) | | | |
| | + Calcium ionophore | 11,000 yen (3,000 yen) | | | |
| | + Pentoxifylline | 11,000 yen | | | |
| | + use TESE sperm | 55,000 yen (15,000 yen) | | | |
| | Embryo/blastocyst culture (number of fertilized eggs) | 66,000 yen (18,000 yen) | 88,000 yen (24,000 yen) | 119,900 yen (32,700 yen) | 148,500yen (40,000)yen |
| | Fresh embryo transfer *2 | 82,500 yen (22,500 yen) | | | |
| | + Assisted hatching (hatching) | 11,000 yen (3,000 yen) | | | |
| Next time | Embryo freezing (number of implementations) | 55,000 yen (15,000 yen) | 77,000 yen (21,000 yen) | 112,200 yen (30,600 yen) | 143,000yen (39,000)yen |

*1: Includes disposable surgical gown fee (1,100 yen including tax) to prevent infectious diseases
*2: Includes disposable surgical gown and anesthesia mask fee (2,200 yen including tax) to prevent infectious diseases
○ Fee includes 10% consumption tax
○ The price in parentheses is the self-pay amount when insurance is applied
○In addition to the above, re-examination fees, examination fees, drug fees for ovulation induction, etc. will be charged.
○The fee once paid cannot be refunded under any circumstances.
○These are subject to change without notice. Please note

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## ☆ Thawed Embryo Transfer Cycle

| Billing date | Item | Price |
|---|---|---|
| Transplant date | Thawed embryo transfer* | 132,000 yen<br>(36,000 yen) |
| | + High-concentration hyaluronic acid-containing culture solution: (UTM) | 11,000 yen<br>(3,000 yen) |
| | + assisted hatching (AH) | 11,000 yen<br>(3,000 yen) |
| | Frozen embryo thawing fee (transfer cancellation) | 35,200 yen |

## ☆Others

| Billing date | Item: | Fee |
|---|---|---|
| | Sperm freezing | 22,000 yen |
| | Extension of frozen sperm storage period (1 month) | 4,400 yen |
| | Extension of frozen embryo storage period (1 year) | 77,000 yen<br>(10,500 yen) |

*Disposable surgical gowns (1,100 yen including tax) must be purchased separately to prevent infectious diseases.

○ Prices include 10% consumption tax

○ Fees in parentheses are self-pay amounts when insurance is applied

○ In addition to the above, re-examination fees, examination fees, and drug fees for hormone replacement will be charged.

○ Fees once paid cannot be refunded under any circumstances.

○ Please note： These are subject to change without notice.

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