Global leader in Assisted Reproductive Technology (ART) in Medical Korea
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1. Assisted Reproductive Technology (ART) in Korea

1) The history of ART development in Korea

Assisted reproductive technology (ART) such as in vitro fertilization (IVF) and embryo transfer (ET) has been essential in the treatment of infertility. IVF involves a sequence of highly coordinated steps beginning with controlled ovarian hyperstimulation with exogenous gonadotropins, followed by retrieval of oocytes from the ovaries under the guidance of transvaginal ultrasonography, fertilization in the laboratory, and transcervical transfer of selected embryos into the uterine cavity. The world’s first IVF-ET baby was born in 1978 based on the technique developed by Dr. Robert Edwards and Dr. Patrick Steptoe. In Korea, the first IVF baby was reported in 1985 by Prof. Chang Yoon Seok at Seoul National University Hospital, then, Korea was recorded as the 10th country succeeded in live birth from IVF in the world.

1978  The first IVF baby in the world
1985  The first IVF baby in Korea
1987  Transvaginal ultrasound for oocyte retrieval (TV-OPU)
1988  The first baby from frozen embryo
1989  Selective fetal reduction, Surrogacy pregnancy
1991  The first baby from immature oocyte in the world
1996  The first pregnancy in non-obstructive azoospermia (NOA) using TESE
1999  Embryonal Germ line stem cell was established
2000  The first pregnancy achieved by PGD from a patient with SMA
2005  Oocyte cryopreservation using slush nitrogen
2014  The world’s first pregnancy resulting in live birth by using frozen oocyte previously vitrified in 2003 (in cancer survivor)
By the birth of Louise Brown on 1978, the world celebrated the start of a new era of assisted human reproductive technology (ART). The first frozen embryo were born in 1988 at Cheil General Hospital and Women’s Healthcare center in Seoul. Transvaginal ultrasound for oocyte retrieval (TV-OPU) were introduced in 1987. In 1989, successful pregnancy was achieved by using surrogacy, and multifetal pregnancy reduction (MFFPR) to reduce the number of pregnancy was done in the same year as well.

In 1990, intra-cytoplasmic sperm injection (ICSI) for fertilizing oocytes was introduced. The first baby in the world following IVF using immature oocyte was successful in 1991 at CHA hospital in Seoul. Testicular sperm extraction (TESE) was introduced, and first pregnancy in non-obstructive azoospermia (NOA) using TESE were successful in 1996. Embryonal Germ line stem cell was established in 1999 at MizMedi Hospital in Seoul.

Preimplantation genetic diagnosis (PGD) team in Cheil General Hospital and Women’s Healthcare center reported the first pregnancy achieved by PGD from a patient with spinal muscular atrophy (SMA) in 2000. The introduction of a new effective method, slush nitrogen, for oocyte cryopreservation was in 2005. The world’s first pregnancy resulting in live birth by using frozen oocyte previously vitrified in 2003 and live birth in cancer patients by using frozen oocyte was successful in 2014.

The Korean Society for Infertility was established in 24 July 1972 and official journal, Korean Journal of Infertility was published in December 1974. The society was renamed as Korean Society for Reproductive Medicine in 2007, and the official journal was republished as Clinical and Experimental Reproductive Medicine (CERM) since 2011. Thereafter, societies associated reproductive medicine were established; The Korean Society for Assisted Reproduction in 2003, Korean Society for Fertility Preservation in 2013 and Korean Society for Reproductive Immunology in 2015. The Korean Association of Clinical Embryologist was established in 2013.

2) Statistics of ART in Korea

Infertility is generally defined as one year of unprotected intercourse without contraception. Approximately 85–90% of healthy young couples conceive within 1 year, most within 6 months. Infertility therefore affects approximately 10–15% of couples and is an important part of the practice of many clinicians. Over the more than 40 years since the first IVF baby was born, ART has been greatly developed and expanded, resulted in millions of births worldwide, and now accounts for 1–3% of all births in the U.S. and Europe. IVF was firstly developed as a method to overcome infertility resulting from irreparable tubal disease, but now is applied much more broadly for the treatment of almost all causes of infertility (Figure 1). IVF is most clearly indicated when infertility results from one or more causes having no other effective treatment; severe tubal disease relating to previous infection or advanced endometriosis and severe male factor infertility are the most obvious examples. Also, maternal and paternal advanced age is becoming the most common indication of IVF these days.

At present over 150 clinics were registered as IVF center in Korea on nationwide.

![Figure 1. Causes of Infertility(Speroff 8 eds.)](image)

![Figure 2. Increased numbers of ART cycles by Reimbursement Program in Korea(Ministry of Health and Welfare 2017)](image)

![Figure 3. Increased numbers of Thawed-Embryo Transfer cycles in Korea(Ministry of Health and Welfare 2017)](image)
Accurate and complete reporting of ART success rates is complicated. Clinics may have differences in patient selection, treatment approaches, and cycle reporting practices which may inflate or lower pregnancy rates relative to another clinic.

According to a report by the International Committee for Monitoring Assisted Reproductive Technologies, the pregnancy rate per egg collection in 2010 was 42.8% in the United States, 31.5% in Sweden, 31.1% in Britain, 28.6% in Norway, 26.2% in Australia and Belgium, 26.0% in Denmark, 25.4% and Korea, and the lowest in Japan (9.3%). (S. Dyer et al., Hum Reprod 2016) Korean IVF outcomes were not inferior to the European countries in worldwide report.

In Korea, the total clinical pregnancy rate per embryo transfer supported by reimbursement program in 2015 is 36.0% (4,193 cases of the 11,596 cases, Figure 5). The pregnancy rate per fresh embryo transfer was 34.1% (10,297 cases) out of 29,515 cases, the clinical pregnancy rate among frozen-thawed embryos was 40.6%. Frozen embryo transfer is more effective than fresh embryo transfer maintaining higher pregnancy rate. The reason for the high rate is that since the embryos in good condition were selected and frozen and transferred especially in frozen embryo transfer. Also elevated supraphysiological estradiol level during controlled ovarian hyperstimulation may affect the derangement of endometrium.

Patients undergoing in vitro fertilization (IVF) are rapidly aging worldwide. Also there was a strict regulation of the number of transferred embryo(s) from 2015 in Korea. The total clinical pregnancy rates in Korea (Figure 5) was stable or slightly decreasing trend that was likely shown to US or UK (Figure 4.a). The increase of frozen thawed ET cycles having higher pregnancy rates showed highly qualified IVF technology in Korea (Ministry of Health and Welfare 2017). The success rate of pregnancy is high through intensive treatment especially in patients with repeated IVF failures and the advanced maternal age. In the elder patients, clinical pregnancy rates was about 16-19% during the last 5 years (Figure 6). It was good results compared to SART report (6.2% from 8372 cycles started).

Figure 4

a. ART live birth rates with fresh embryos created from autologous oocytes.
   The figure demonstrates stable or slightly decreasing live birth rates in most regions. Increasing live birth rates are noted in continental Europe while most pronounced decreases are noted in Japan and in Canada after 2009.

b. ART live birth rates with frozen-thawed embryos created from autologous oocytes.
   The figure demonstrates improving live birth rates in frozen-thawed cycles in all regions. Data is reported per initiated cycles for all regions except Latin America which reports data per embryo transfer and Europe which reports data per thawing procedure (Reprod Biol Endocrinol 2017).
3) Reimbursement program of ART treatment

Due to the social phenomenon of late marriage and childbearing age, the number of infertile couples is continuously increasing, and social and national responsibility are also becoming important. The law, Bioethics and Safety Act was established in 2004, which deal with the matters of bioethics and governing laws and regulations for biotechnology in reproductive medicine. Through the 1980s and 1990s, the number of babies born was in the 600,000 and 700,000 range, but in the 2000s, this began to sharply decrease to about 400,000. Now Korea’s birthrate remained the lowest among OECD countries. Based on 2015 data, the country’s birthrate, or the average number of babies that a woman is projected to have during her lifetime, was 1.24, well below the OECD average of 1.68. It dropped to 1.17 in 2016, down 0.7 from the previous year. This was the lowest figure since 1.15 of 2009.

The Korean government has implemented reimbursement program for the cost of in vitro fertilization (IVF) treatment of women who want to have children since 2006 and a program for the cost of intrauterine insemination (IUI) treatment in 2010. As of June 2015, the number of designated institutions for in vitro fertilization was 152, 34.5% higher than 113 in 2006, and 389 designated artificial insemination institutes increased by 13.7% from 342 in 2010. The number of IVF conducted by reimbursement program was a total of 47,886 cases in 2015. The performance of the treatment increased as 16.9% by 6,920 cases from 40,966 cases in 2014. The rapid increase in total budget of reimbursement correlated well with the number of baby births from ART (19,736 births in 2016, Figure 7).

Figure 7. Total ART budgets (x1,000 won, left) and the number of births (number, right) by Reimbursement Program in Korea (2006~2016, Ministry of Health and Welfare 2017)

<table>
<thead>
<tr>
<th>Year</th>
<th>Contents</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Law of Bioethics &amp; Safety, Define IVF Purposes, Designate IVF Center to make embryo creation</td>
<td>Ministry of Health and Welfare (Personnel, Infrastructure)</td>
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<tr>
<td>2005</td>
<td>Development Guideline of IVF indication under IVF center-regulation: Medical Guideline of IVF</td>
<td>IVF centers</td>
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<tr>
<td>2006</td>
<td>Reimbursement program for IVF &amp; (Medical indication and Guideline of IVF should be kept.)</td>
<td>Ministry of Health and Welfare (국민건강증진기금)</td>
</tr>
<tr>
<td>2008</td>
<td>Development of Korean Guideline to restrict the Number of Transferred Embryo based on American Society for Reproductive Medicine (ASRM) guideline</td>
<td>Ministry of Health and Welfare</td>
</tr>
<tr>
<td>2010</td>
<td>Reimbursement program for IUI Medical Guideline of IUI</td>
<td>Ministry of Health and Welfare (국민건강증진기금)</td>
</tr>
<tr>
<td>2015</td>
<td>Revised Korean Guideline about regulation the Number of Transferred Embryo strictly and prerequisites of IVF centers and Medical Guideline of IUI/IVF</td>
<td>Ministry of Health and Welfare</td>
</tr>
<tr>
<td>2017</td>
<td>National Health Insurance Service Act; covers IVF and IUI</td>
<td>Ministry of Health and Welfare</td>
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Table 1. Developmental History of the Quality Control of ART in Korea

Policy for ART Reimbursement Program in Korea (2017. Oct.)
Criteria for subject:
- Legal marital status
- Women ≤ 44 year old
- Korean nationality for at least one of the couple
- National Health Insurance subscription
- A diagnostic certificate by infertility specialist

IVF Centers
- Designated by the Minister of Health and Welfare
- Government-sponsored In Vitro Fertilization designation center

*** 3 IUI cycles and 4 IVF-ET fresh cycles and 3 frozen T-ET cycles are reimbursed ***

The criteria for the number of transferred embryos have been implemented since 2008 in Korea. In case of poor condition, up to 5 embryos could be allowed. But there was no correlation between the number of transferred embryos and pregnancy rates, so higher number of transferred embryos could increase side effects such as multiple pregnancy. In October 2015, the government revised the guidelines to further protect the health of women and fetuses and to further limit the number of embryos that can be transferred to the age of women in terms of bioethics. In the case of women under 35 years of age, the number of embryos can be up to two, and for women over 35 years old whose fertility abruptly decreases, so that only a maximum of 3 of cleavage stage embryos are permitted in revised guidelines. The number of blastocyst should be 1 for under 35 years of age, and 1 or 2 for over 35 years of age.

| The maximum number of transferred embryos: Revision Oct. 2015. |
|---------------------|---------------------|---------------------|
| Age (yr)            | Day 5~6             | Day 2~4             |
|                     | Blastocyst          | Cleavage stage embryo |
| C35                 | 1                   | 2                   |
| ≥35                 | 2                   | 3                   |
4) Infrastructure of the treatment of infertility

The world-class fertility treatment options includes experienced and comprehensively skilled team of experts providing a full range of care to the patient seeking ART. Top-quality medical staffs and updated embryo culture system and embryology skill will be the key to IVF success. And well educated international coordinator should be in place to connect the patient with medical staffs on-line and off-line.

We begin with a detailed, thorough evaluation of a patient and their partner for the causes of their infertility or especially recurrent IVF failures or habitual abortion with recommendations for treatment using the most advanced technology. The infertility specialist will discuss with patients to understand the current status of them, and they will be guided through out the journey of getting better IVF results. The Korean IVF Program does not stay in the domestic clinical development, is also continuously evolving. In the research activities, a continuous paper presentation has been made in the international journals. In addition, several IVF centers also offer education program for the demand of the foreign doctors who want to visit Korea. Although there are differences among institutions, we also have programs to help organize long-term and short-term training, providing opportunities to participate in medical care as well as updated in-vitro culture systems.

Clinical observership program

- **Medical Korea Academy ; Government financial support program**

Korea has accomplished world class medical skills, want to share them and give a chance of education. Thesedays mutual exchange of clinicians is actively proceeded mainly in Asian coutries- Russia, Uzbekistan, China, Japan, Mongolia, etc.

Especially, Korean government[Korea Health Industry Development Institute] has run an financial support program- Medical Korea Academy. Every year about 20 clinicians are selected. As of 2017, they will be provided with

- A roundtrip airfare up to KRW1,000,000 [Extra cost will not be supported.]
- Hostel-level accommodation up to KRW60,000/day [Extra cost will not be supported.]
- KRW30,000 of daily expense [Weekend and holidays excluded]
- International Student Insurance [The least coverage]

- **MizMedi Hospital (Seoul)** : over 100 clinicians from China, Japan, Russia, Kazakhstan, Indonesia, Vietnam, UAE
- **Russia**
- **Indonesia**
- **Vietnam**
- **Japan**
- **UAE**
- **China**
- **CHA Gangnam Medical Center** : about 20 clinicians
5) Training ART medical staffs

- Required medical education

1) Graduation of College of medicine(6 years of education including premedical 2-year-course) or Graduation of University for 4 years (as a premedical course)

2) College of medicine for 4 years in accordance with the university affiliated with the hospital to obtain the opportunity to apply to the medical doctor certificate.

3) Internship at a general hospital(one year)

4) Residency program in the Department of Gynecology and Obstetrics and Endocrinology(4 years)

5) Clinical fellowship program(1–2 years)

<table>
<thead>
<tr>
<th>Course</th>
<th>Status</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>University (premedical)</td>
<td>Student</td>
<td>2–4 years</td>
</tr>
<tr>
<td>University/College of Medicine</td>
<td>Student</td>
<td>4 years</td>
</tr>
<tr>
<td>Internship</td>
<td>Medical doctor</td>
<td>1 year</td>
</tr>
<tr>
<td>Resident (Obstetrics &amp; Gynecology)</td>
<td>Medical doctor</td>
<td>4 years</td>
</tr>
<tr>
<td>Fellowship</td>
<td>Clinical staff</td>
<td>1–2 years</td>
</tr>
</tbody>
</table>

It takes 12-15 years of training courses to achieve the knowledge and skills dealing with infertility and ART treatment in Korea. Many academic societies and study groups on reproductive endocrinology and infertility science are actively conducting research into the topic. Physicians in Korea needed to improve the level of infertility treatment by improving their clinical skills, providing treatment in order to improve ART outcomes at a larger number of institutions, innovating new treatment methods, and conducting further research on ART. Many medical researchers and clinicians trained abroad to learn theories, techniques, and ethical considerations of ART.

- Academic achievement of Korea.

Korea shows steady excellent achievement in clinical as well as academic field. Searching in the Pubmed using infertility related MESH terms(e.g. infertility, IVF, ICSI, IUI, PCOS, fertility preservation), you can find that abundant papers of Korea not inferior to other countries. This graph shows that steady increase in published papers. Total 72 papers were published in 2010 and total 131 papers were published in 2016 - more than twice as many publications have been published over the past six years.

Better clinical outcomes come from the experimental research and many interests in new techniques. Thus, such an effort and result promise the brighter future of clinical achievement of Korea.

- CL Hospital (Gwangju) : about 40 clinicians from Mongolia, Russia, Uzbekistan
1) In Vitro Maturation-IVF [using immature oocyte-In Vitro Fertilization(IVM-IVF)]

I. Introduction

IVM refers to aspiration and in vitro maturation of immature oocytes from small antral follicles at the stage prior to selection and dominance. In this infertility treatment, immature oocytes are retrieved from the unstimulated or minimally stimulated ovaries and matured in a maturation medium supplemented with follicular fluid and gonadotropins. The nuclear status of the oocytes is evaluated every three hours up to the end of the culture and fertilized in vitro. The embryos are then transferred into intrauterine cavity.

IVM of rabbit oocytes was first described in 1935, and IVM of human oocytes was first reported in 1965. CHA fertility center in Korea has reported the first successful pregnancy and delivery after IVM-IVF-ET(embryo transfer) in 1989. Since IVM procedure can reduce potential adverse effects of controlled ovarian hyperstimulation(COH), the application of IVM for polycystic ovary syndrome(PCOS) patients has been described in 1994. Recently, IVM has become an alternative option to be considered for patients with PCOS, a risk of developing ovarian hyperstimulation syndrome(OHSS), estrogen-sensitive diseases/cancers, and/or for fertility preservation. PCOS is one of the endocrine disorders causing ovarian dysfunction in women in the reproductive phase of life. Patients with PCOS are more likely to develop OHSS, even with the minimal ovarian stimulation. A risk of OHSS has been characterized by the presence of multiple luteinized cysts within the ovaries leading to ovarian enlargement and secondary complications such as abdominal bloating, distention or ascites. In severe forms of OHSS, life-threatening complications including pleural or pericardial effusion, adult respiratory distress syndrome, thromboembolic events, myocardial or cerebral infarctions and even death may occur. Patients can benefit from IVM procedure reducing the risk of OHSS, avoiding potential side effects of COH using gonadotropic releasing hormone and gonadotropins and reducing the cost for COH.

II. IVM

(1) IVM procedure:

Figure 8. IVM procedure

Immature oocytes are retrieved from unstimulated or minimally stimulated ovaries. Retrieved oocytes are cultured for 24 hours in in vitro maturation medium and ICSI(intracytoplasmic sperm injection) is performed. ICSI is an injection of a single healthy selected sperm directly through the oolemma(zona pellucida) and into the inner part of the oocyte by micromanipulation under a microscope. Fertilized embryo(s) is transferred after 72 hours of culture. ICSI technique is performed for male patient with a low sperm count and poor sperm quality, obstructive or non-obstructive azoospermia where it cannot be resolved by a surgical correction, ejaculation disorder caused by spinal cord injury or other urethral obstruction, oocyte fertilization after IVM procedure and preimplantation genetic diagnosis(PGD).

Figure 9. ICSI procedure

(2) Korea as a pioneer in the field of IVM:

In 1989, for the first time in the world, CHA fertility center in Korea succeeded in pregnancy and delivery after in vitro maturation and fertilization of human follicular oocytes collected from non-stimulated cycles with winning of prize paper award from American Fertility Society(Figure 10). In 1996, for the second time in the world, successful pregnancy and delivery was reported after in vitro maturation and fertilization of immature oocytes of patients with PCOS.
(3) Pregnancy outcome after IVM

Births following IVM-IVF have been estimated to be more than 2,500 by 2012. Previous studies have reported that the success rate of IVM is suboptimal than conventional IVF; however, IVM does not increase the adverse perinatal outcomes. In 2005, at the report of the obstetric outcomes of patients with PCOS treated by IVM and IVF-ET, it revealed that IVM and IVF-ET does not adversely affect the abortion rate, gestational age and birth weight of delivered infants, or the rate of pregnancy complications. Considering that the best way to treat PCOS in assisted reproductive technology(ART) is to maximize pregnancy outcomes without the risk of OHSS, IVM-IVF can be a safe and efficient alternative ART treatment when the patients are properly selected.

(4) Improvement of IVM outcomes

IVM protocol and technology have been continued to improve since the first IVM-induced pregnancy in 1989. Many fertility centers in Korea continuously have focused on developing culture media and improving the culture conditions for oocyte in vitro maturation. In 2013, CHA fertility center has reported that melatonin supplementation in IVM media improves implantation rates of IVM-IVF ET for PCOS patients. Implantation and clinical pregnancy rates were significantly increased in oocytes cultured in IVM media supplemented with melatonin. It has been suggested that the addition of melatonin to the maturation medium appears to have positive effects on the clinical outcomes of IVM.

2) Cryopreservation & Fertility Preservation

I. Introduction

Cryopreservation is a technique used to freeze and then thaw oocytes, embryos and sperms for use in vitro fertilization(IVF) treatment. For many patients, unfertilized oocyte or embryo cryopreservation can be an essential part of the IVF fertility treatment process. Through cryopreservation, fertilized dividing embryos or unfertilized oocytes can be preserved for future use. With the availability of frozen oocytes and embryos, women don’t need to undergo stimulation by gonadotropin drugs to transfer embryos during an infertility treatment cycle. Furthermore, when sperms are collected during ejaculation or microsurgery, and frozen for a subsequent IVF cycle, additional ejaculation or surgery may be avoided.

There are many benefits of oocyte and embryo cryopreservation. In case of being used as part of the IVF treatment process, cryopreservation can increase the pregnancy rate for many patients when is compared with fresh embryo transfer cycle. Cryopreservation also allows couples to continue to undergo IVF treatments whenever years later, from the same group of oocytes originally recovered for treatment.

In Korea, cryopreservation is also widely used as an important part of IVF treatment. The survival rate of frozen oocytes and embryos after thawing is over 95%, and the pregnancy rate is increasing now by using frozen-thawed embryo transfer IVF cycles in Korea. Korea has been the pioneer in the field of reproductive medicine using cryopreservation techniques such as vitrification for over 20 years introducing cutting-edge technology after year and bringing hope and new life into the homes of countless families.

Vitrification(rapid freezing) is the newest technique for freezing eggs or embryos used in IVF treatment. The latest advances in vitrification technology have allowed frozen embryos to have better survival, especially for embryos cultured in media or conditions that are not ideal. Furthermore, vitrification allows for faster freezing rates compared to traditional freezing techniques, reducing the risk of cryopreservation damage.
success rates to be almost as high as using fresh embryos. The fertility centers in Korea have used the vitrification technique for cryopreservation from about 20 years ago, and have higher survival rate of frozed oocytes, embryos and sperms, and higher pregnancy rate in IVF treatment cycles.

II. Cryopreservation

(1) Oocyte cryopreservation

(1-1) For infertility patients

Korea is in a leading position in the field of cryopreservation technology. In 1998, CHA Fertility Center first reported the efficiency of rapid freezing technology (vitrification) of oocytes in the world, and live births after vitrification of oocytes in a stimulated in vitro fertilization-embryo transfer program.

To improve the viability and quality of oocytes after vitrification, CHA Fertility Center also reported the new type of vitrification vehicle and mediator, gold grid and slush-liquid nitrogen (S-LN2), applied in order to elevate cooling speed for reducing ice crystal formation in 2005. Gold grid provides extremely high heat conductivity. And by applying negative pressure with a vacuum, LN2 can freeze and convert into a slush state. Slush-LN2 has a lower internal temperature of -201°C without vaporization. Since it may offer high-speed cooling rates, it may be possible to increase the survival rate as well as other characteristics. In fact, a higher cooling rate resulting from the use of gold grid and slush-LN2 is beneficial for the survival and fertilization of human mature oocytes after vitrification. Therefore, this modified vitrification system is a promising technique to effectively reserve human oocytes in Korea.

II. Cryopreservation

(1) Oocyte cryopreservation

(1-2) For cancer patients

Advances in cancer detection and treatment have resulted in an increasing amount of long-term survivors who are left to deal with the adverse effects of their treatments. Fortunately, progress in fertility preservation technologies has been paralleling the trend in improving cancer outcomes. Because of the variations in type and dose of chemotherapy or radiation, the type of cancer, the time available before treatment initiation, and the patient’s age and partner status, each case is unique and requires a different strategy for fertility preservation. Chemotherapy and radiation treatments for cancer and other serious illnesses can affect reproductive health. Therefore, fertility preservation, such as oocyte cryopreservation, may also be used to prevent infertility before cancer treatments.

In 2010, CHA Fertility Center reported a successful pregnancy and delivery of chronic myeloid leukemia patient using vitrified-warmed oocytes which were stored over 9 years after BMT for chronic myeloid leukemia (CML) conditioning with high-dose cyclophosphamide and fractional total body irradiation. And many fertility centers in Korea have been using the cryopreservation technique for fertility preservation of cancer patients.

Figure 13. Slush Nitrogen vitrification protocol

Figure 14. Successful pregnancy of chronic myeloid leukemia patient using vitrified-warmed oocytes

Patient diagnosed with CML in 2001, at the age of 22

Oocytes frozen before the start of chemotherapy

Whole-body irradiation and bone marrow transplantation

Menopause, hormone therapy to maintain uterine function

Complete remission announced in 2006

Marriage in 2009

IVF conducted with previously frozen oocytes in 2010

2 embryos cultured and transferred in uterus

Baby born in July 2011

“First birth with previously stored oocyte at CHA Fertility Center; successful thawing of frozen oocyte; 9-year record for storage of oocyte”
(2) Embryo cryopreservation

(2-1) For infertility patients

(2-1-1) Cryo-storage of surplus embryos after embryo transfer for the next use

(2-1-2) Embryo freezing for women who are at a high risk of developing severe ovarian hyperstimulation syndrome following ovarian stimulation

(2-2) For cancer patients

Embryo freezing before cancer treatments for a married woman diagnosed with cancer

(3) Sperm and testicular tissue cryopreservation for infertility patients

(3-1) Sperm [semen] Freezing

It is applied when semen collection is not available on the day of IVF or IUI treatment and when the patient is at a high risk of losing testicular function following cancer chemotherapy or radiotherapy.

(3-2) Testicular tissue Freezing

After surgical retrieval methods (TESE, PESA and MESA of obstructive azoospermia) were performed to collect sperm, surplus testicular cells or tissues are cryo-storaged for the next use.

III. Social Oocyte Banking [freezing] for single women

Technological advances now in Korea allow women to preserve their fertility potential by freezing and storing their oocytes. There are two reasons why women may choose to freeze their eggs. The first is for health reasons; in particular, for women who wish to preserve their fertility before undergoing cancer treatment. The second is for personal and social reasons as many women delay starting a family beyond their most fertile years, which increases the risk of age-related infertility.

3) Blastocyst Transfer

There are two possibilities for embryo transfer in IVF: either a cleavage-state embryo or a blastocyst embryo can be transferred. Although the first human birth after IVF resulted from transfer of a blastocyst, most transfers since then have involved earlier cleavage-stage embryos (day 2 or 3 after fertilization). The main reason is the lack of culture media that could reliably sustain embryos during the compaction (morula) and blastocyst stages of development. However, the identification of key regulators and a greater understanding of the changing physiological requirements of growing embryos have developed “sequential” media which vary according to the stage of embryo development. Pre-compaction embryos prefer pyruvate rather than glucose as a nutrient and non-essential amino acids that are found in higher concentrations in the fallopian tube (where fertilization takes place in natural pregnancies), and post-compaction embryos favor glucose and essential amino acids that are found in higher concentrations in the uterus (where the embryo moves before implantation in the endometrium).

Figure 15. The blastocyst structure

Figure 16. Stages of human pre-implantation embryo development

Recently, pregnancy rates from frozen oocytes are the same as those from fresh oocyte cycles in Korea. This success has led to increased the trend of social oocyte freezing because women want the opportunity to safely defer and delay motherhood until the right time or the perfect partner arrives in Korea.

Nowadays, the cases of social freezing are also increasing very rapidly every year in Korea. Many fertility centers in Korea have the best advanced storage system for oocyte freezing which can make no physical damage on oocytes during long-term storage by using liquid-nitrogen vapor.
When a human egg is fertilized, it forms an embryo, which then divides and grows from one cell into a ball of more than 200 cells, called a blastocyst. The fertilized egg becomes a blastocyst, an embryo with a fluid-containing sac in the central part of the cell mass, which divides 5 days after in vitro fertilization. Between 5 and 7 days after fertilization, the healthy blastocyst gradually expands and hatches out of the zona pellucida, adheres to the endometrium within 24 hours and proceeds to infiltrate. The blastocyst begins to differentiate further. After implantation, the trophectoderm develops into the placenta, and the inner cell mass in the center of the blastocyst develops into the fetus. Extended culture and blastocyst transfer offer several potential advantages over the transfer of cleavage-stage embryos.

Advantages of Blastocyst Transfer

1. Synchronization
The time of embryo entry into the endometrial cavity is naturally the timing of blastocyst development, and blastocyst transfer has the advantage of attempting implantation when embryo developmental stage and female endometrial maturity stage coincide. The environment of the fallopian tube and the endometrium is slightly different, so that a cleavage stage embryo can get metabolic stress if it is transferred into the uterine cavity early.

2. Embryo Selection
Cleavage stage embryos, with 2 to 8 blastomeres, are at the developmental stage when the embryonic genome transcription begins, so the growth ability is not yet revealed and it is difficult to select which embryo will have the highest chance of success. A better assessment of true viability is possible after activation of the embryonic genome. Therefore, it is possible to select better embryos at the blastocyst stage by activating the genome of the embryo. This explains the higher implantation rates after blastocyst transfer as opposed to cleavage-stage embryos. Blastocyst culture and transfer will be the most effective means of being able to transfer a single embryo while maintaining high pregnancy rates, as it is evident that blastocyst scoring is highly predictive of implantation potential and successful pregnancy.

3. (or) PGD/PGS
Extended culture to blastocysts provides the opportunity to perform trophectoderm biopsy for preimplantation genetic diagnosis (PGD)/preimplantation genetic screening (PGS), when it is indicated.

4. Higher implantation rates
With higher implantation rates, allowing the transfer of fewer embryos, the risk for multiple pregnancies is decreased.

Nine of the 18 trials included in the analysis compared outcomes in a good prognosis population (as defined by age, number of previous failed cycles, response to ovarian stimulation, and quality of embryos). Among these, clinical pregnancy rates achieved with cleavage-stage embryo and blastocyst transfer were not different (1,315 patients, OR = 1.21, CI 0.96–1.51), but live birth rates were significantly higher with blastocyst transfer in fresh cycles. Although there is a benefit favouring blastocyst transfer in fresh cycles, it remains unclear whether the day of transfer impacts on cumulative live birth and pregnancy rates (Cochrane Database Syst Rev, 2016).

Not all have embraced the trend to wider use of extended culture, which also has at least two potential disadvantages: Embryos of lesser quality that may implant if transferred on day 3 may fail to reach the blastocyst stage in vitro, increasing the risk there may be no embryos for transfer.

4) Preimplantation Genetic Diagnosis/ Preimplantation Genetic Screening

I. Preimplantation genetic diagnosis (PGD)

Every parent hopes to have a healthy child. Although most babies are born healthy, genetic diseases are not uncommon. In fact, a significant proportion of childhood birth defects or adult onset chronic illnesses are due to genetic conditions. Increased risk for a fetal genetic abnormality may be due to family history of a hereditary disease, advanced maternal age during pregnancy, exposure to medications or environmental hazards, or other factors. Cheil General Hospital & Woman’s Health care center offers an exceptional range of genetic services. Genetic services assists people who seek answers about the usefulness of genetic testing during their family planning: before conception, during IVF treatments, in an ongoing pregnancy, or when they are seeking to understand pregnancy losses or recurrent miscarriages.

What is PGD?
Pre-implantation genetic diagnosis (PGD) refers to the genetic test on cells removed from embryos (embryos prior to implantation, and sometimes even of oocytes prior to fertilization), to help select the best embryo[s] for pregnancy or to be free of a genetic disease. PGD thus is an adjunct to assisted reproductive technology, and requires in vitro fertilization (IVF) to obtain oocytes or embryos for evaluation. PGD is an option not to transmission of genetic diseases or recurrent miscarriages in a similar fashion to prenatal diagnosis. When used to screen for a specific genetic disease, its main advantage is to avoid selective pregnancy termination of affected fetus. PGD helps these couples identify embryos carrying a genetic disease or a chromosome abnormality, thus avoiding diseased offspring.

Who should consider PGD?
PGD may be considered in all IVF cycles. PGD can potentially be used to select embryos to be without a genetic disorder, to have increased chances of successful pregnancy, to match a sibling in HLA type in order to be a donor, to have less cancer predisposition, and for sex selection. In addition, this includes women who have had several miscarriages, or who have had a prior pregnancy with a chromosome abnormality. However, those who might benefit most from this test are couples at increased risk for chromosome abnormalities or specific genetic diseases. If a person carries a rearrangement of the chromosomes, PGD can identify which embryos have a normal amount of chromosomal material. When there is a chance to have a child affected with a specific genetic disease, PGD can be designed to identify which embryos are affected, unaffected, or a carrier (if applicable) for that disease. Then, only embryos without the disease are transferred to the uterus to attempt pregnancy.

PGD is available for a large number of monogenic disorders—that is, disorders due to a single gene only (autosomal recessive, autosomal dominant or X-linked)—or of chromosomal structural aberrations (such as a balanced translocation). The most frequently diagnosed autosomal recessive disorders are cystic fibrosis, Beta-thalassemia, sickle cell disease and spinal muscular atrophy type 1. The most common dominant diseases are myotonic dystrophy, Huntington’s disease and Charcot–Marie–Tooth disease; and in the case of the X-linked diseases, most of the cycles are performed for fragile X syndrome, haemophilia A and Duchenne muscular dystrophy.

Work-flow Process of PGD

PGD for a specific genetic disease is a specialized test that has to be adapted to work on a small amount of DNA from biopsied embryos. The tests are developed individually for each family based on their history, prior testing results, and family studies. Prior to the initial IVF
cycle, the PGD Laboratory would need a blood sample from the couple themselves and may request blood from family members as well. Once the test has been designed and optimized for that couple, the PGD laboratory will be able to run the analysis on embryos from one or more than one IVF cycle, as needed.

The test is designed to identify the presence or absence of the specific gene mutation(s) that cause the disease in that family. In addition, linked markers (unique DNA identifiers near the mutation(s)) are identified in the family studies ahead of time. Embryos are also tested for the markers, and it is this combination of both a mutation test as well as linked markers that results in a robust PGD test with high accuracy. It is this combination of both mutation testing and markers that also separates the PGD Laboratory at IVF center of Cheil general Hospital from other laboratories offering PGD.

**What are the PGD steps during the IVF cycle?**

After embryos are created in the laboratory, they are grown for three to five days. On day three or on day five, the biopsy for PGD is done on all appropriately developing embryos (Figure 17). Biopsy involves removing a few cells from embryo or the trophectoderm at this stage of development. The embryos are stored while genetic material inside the removed cells is tested for abnormalities.

**Figure 17. Blastomere biopsy vs trophectoderm biopsy for PGD/PGS**

Is biopsy and PGD safe? Yes. Data from many years of PGD in animals and thousands of live births in humans indicate that PGD does not lead to an increase in birth defects over that of the general population. In embryos where chromosomal microarray testing is performed, one can expect fewer pregnancies with chromosomal disorders since most chromosomal abnormalities are identified prior to transfer of the embryos to the uterus. Removal of a few of the cells of the early embryo does not alter the ability of that embryo to develop into a complete, normal pregnancy.

**II. Preimplantation genetic screening (PGS); Aneuploidy Screening**

The object of PGS is to have increased chances of successful pregnancy in repeated implantation failure or women who have had several miscarriages, or who have had a prior pregnancy with a chromosome abnormality. Aneuploidy screening reduces the chance that a transferred embryo has a chromosome abnormality. The most common chromosome abnormalities in miscarriages include: trisomy (three copies of a chromosome) or monosomy (one copy of a chromosome) for chromosomes 13, 15, 16, 18, 21, or 22; triploidy (three copies of all the chromosomes); and abnormalities of the sex chromosomes.

Approximately three out of four (75%) embryos created by IVF will not be capable of producing a live born child. Some will fail to implant in the uterus, while others will implant but be unable to carry out early embryonic development. Finally, as in natural pregnancy, approximately 15%-20% of conceptions will be lost as a clinical miscarriage. While there are many reasons for the failure of an embryo to make a baby, the single most important factor is an abnormality of the chromosomes. Similarly, for most couples, a significant number of the embryos created by IVF will have chromosome abnormalities. The exact percentage of chromosomally abnormal embryos that each couple produces is related to many factors including maternal age, number of failed IVF cycles, and the type of sperm used.

Embryos created in an IVF cycle are cultured in the laboratory for three days. By this time they contain approximately eight cells. Each embryo at this point is called a blastomere. Embryos with normal development on day three will have one or two cells removed for testing in a procedure called a biopsy. The embryos are placed under a powerful microscope and a laser is used to create a tiny opening in the zona pellucida, a tough outer membrane holding the embryo together. One or two cells are then removed out (Figure 17).

PGD testing is different than most genetic testing since it is done on only one or two embryonic cells and is completed within 48 hours for a fresh embryo transfer by day five. Since standard chromosome analysis takes several days, a different method called fluorescence in-situ hybridization (FISH) is performed.

Each chromosome has unique areas of DNA present only on that chromosome. A small DNA probe is used to recognize these unique patterns and fluoresce, or light up, when it attaches to the chromosome. Each probe shines light in a different color, allowing several chromosomes to be tested at the same time. This technique is called FISH. Our Laboratory uses FISH for chromosomes 13, 16, 18, 21, X, and Y because these are the chromosomes that are most commonly abnormal. A normal cell should show two FISH signals (or lights) for each of the numbered chromosomes, and either two X signals for a female or one X and one Y signal for a male. There are only five different colors that can be used, so most tests are done in two parts. The first five chromosomes are tested, those probes are washed off and then the remaining chromosomes are tested. The washing process can affect the integrity of each chromosome, therefore, a maximum of two cycles of FISH are used per cell. For this reason, every chromosome cannot be tested.

**PGS: 24 Chromosome Microarray/ Next Generation Sequencing (NGS)**

24 Chromosome Microarray is a genetic test on embryos to screen for common chromosome abnormalities as well as the X and Y chromosomes. This test can identify if an embryo has extra or missing chromosomes, which is called aneuploidy. Only embryos with the correct number of chromosomes are selected for transfer into the woman’s uterus. It is known that one of the major causes (60-70%) of failed implantation and early miscarriage is extra or missing chromosomes in the embryo. By selecting the best embryos for transfer, this testing may decrease the miscarriage rate or increase the implantation rate.

**Figure 18. Developmental history of PGS**
5) Time-lapse Embryo monitoring system

I. Time-lapse Embryo Incubator

Time-lapse embryo monitoring system is a revolutionary device used to screen embryos in several in vitro fertilization centers in the United States and Europe. The principle of this device is that the embryo is not exposed to the outside of the incubator until the day of embryo transfer, but the image of all embryos is visualized and then the best embryo is selected using a special program. By using these advanced technologies, clinician can minimize the number of transferred embryos and at the same time improve the pregnancy rate. For example, embryos are cultured in EmbryoScope™, data is obtained from each embryo, and the embryo is selected using the data. In this way, if the embryo is selected and transferred and the pregnancy is succeeded, the pregnancy success data can be supplemented by retrospective analysis in addition to each IVF center’s embryo screening selection criteria.

What is conventional in-vitro fertilization?

When you undergo routine in-vitro fertilization (IVF) or an intra-cytoplasmic sperm injection (ICSI) cycle, your embryos will be kept in an incubator with strictly controlled environment. Conventionally, during incubation, the embryos must be taken out from the incubator periodically to check its development under a microscope. After checking, the embryos must be returned to the incubator as quickly as possible to avoid any potential damages such as shift of temperature or PH. This procedure is often done daily during the days of culturing, in order to assess the embryo quality and select the best embryos to be transferred.

II. Time-lapse Advantages

1. Ensuring optimal embryo development: EmbryoScope is the world’s most used time-lapse system for observation of embryo development, while maintaining stable embryo culture conditions. It has been used in more than 300,000 patient treatments since 2009. At the heart of the system is the EmbryoScope incubator which ensures stable incubation while automatically taking images of the developing embryos at defined intervals. This information is transferred to the ES server so that the information can be accessed from conveniently accessed computer stations.

2. Improved basis for embryo selection: The EmbryoViewer software has been developed with input from leading embryologists around the world and includes all the tools needed to register embryo development, analyse the data and provide a ranking of embryo development potential.

3. Safe and secure embryo handling: The specially designed and patented EmbryoSlide culture dish allows safe handling and optimal microscopy & image acquisition of embryos.

4. Documented improvement in clinical outcome: A prospective randomized control trial comparing culture and selection using the EmbryoScope time-lapse system to traditional culture and evaluation documented a relative increase in ongoing pregnancy rate of 23% while early pregnancy loss was reduced by 36%. For this study, the Compare and Select feature of the EmbryoViewer software was used to input a selection model based on analysis of embryo development parameters previously identified at the clinic. (Rubio et al. 2014 Fertility and Sterility)

Figure 19. Time-lapse helps you overcome the catch 22 in IVF: The observational dilemma or catch 22, in IVF is that you want as much information as possible about the developing embryos to be able to select the best to transfer, or deselect those with a lower implantation potential. On the other hand you want to avoid disturbing the embryos by taking them out from the incubator for evaluation. Access to time-lapse technology in the IVF lab allows you to leave the embryos in the incubator while a camera continuously takes images of the whole embryo development. These images are put together into a film, which gives unlimited possibilities to evaluate embryos without any handling stress.

Proven clinical benefits of Time-lapse Embryo Incubator

- Reduced pregnancy loss
- Improved implantation rate
- Shorter time to pregnancy
The comparison of embryo culture condition in EmbryoScope or Standard incubator by clinical outcome: The rate of blastocyst development was significantly increased in EmbryoScope than in Standard Incubator. The results were higher in clinical pregnancy and implantation rate in EmbryoScope than in Standard Incubator, but it is not significant. Even though the number is limited, it showed the EmbryoScope is stable to culture for embryo. [ASPIRE, 2014]

**Time-lapse enabled analysis - Improved embryo selection criteria**

- Continue monitoring all embryos - incubation without damage in a stable environment
- Flexible working environment - Flexible choice of working time
- Objective Data from quantifying subjective judgment about embryo development
- Retrospective Data Analysis - Better embryo prediction based on retrospective data analysis
- Technology enabling single embryo transfer

**Figure 22. Various Time-lapse embryo monitoring systems**

6) Treatment of Male Infertility

**I. Male infertility**

Approximately 15% of couples cannot conceive a child after 1 year of regular, unprotected intercourse. Male factor as the single cause of infertility is contributory in 30% to 40% of couples. For the treatment of male subfertility, the causative factor remains unknown in 40% of men presenting with a male factor. However, most causes of male infertility are treatable and the goal of many treatments is to restore the ability to conceive naturally. The dramatic recent improvements in the management of male infertility are largely contributable to improved surgical techniques and assisted reproductive technology (ART). Specifically, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) allow us to overcome even the most severe defects in spermatogenesis in which only a few are available. These advances have also added important reproductive options for men with non-obstructive azospermia (NOA), or testicular failure.

**II. Surgically correctable cause of male infertility**

1) Varicocele

Varicoceles are present in 15% of normal male population and in approximately 40% of men with infertility. The association between male subfertility and varicocele is unknown, but many studies showed that semen improvement is usually observed after surgical correction. Varicocele repair may be considered as the primary treatment option when a man with a varicocele has suboptimal semen quality and the female partner does not present any additional infertility factor.

Varicocele repair can reverse a pathologic condition and halt further damage to testicular function, and improve spermatogenesis. Pregnancy rate at 1yr after correction of varicocele...
were comparable for open inguinal, laparoscopic, and subinguinal microscopic varicocelectomy. Preferred approaches of most experts are microsurgical inguinal and subinguinal operations. The advantages of microsurgical techniques are the reliable identification and preservation of arterial and lymphatic vessels, while reducing the risk for persistence or recurrence of varicocele. The application of microsurgical techniques to varicocele repair has resulted in a substantial reduction in the incidence of hydrocele formation because the lymphatic vessels can be more easily identified and preserved.

Varicoceles are found in 4.3% to 13.3% of men with azoospermia or severe oligospermia and can result in sperm in the ejaculate of azoospermic men when severe hypospermatogenesis or maturation arrest spermatid stage is present. Varicocele repair in patients with NOA can result in motile sperm in the ejaculate and even spontaneous pregnancy. Motile sperm from the ejaculate can be used for IVF without the need for surgical retrieval. Therefore, varicocelectomy offers patients with NOA an opportunity to have sperm for undergoing ICSI in their ejaculate and even the possibility of natural conception.

Treatment strategies for male infertility have changed dramatically over the past decade. These advances are largely attributable to microsurgical varicocelectomy and microsurgical techniques for surgical sperm retrieval and ART specifically ICSI. Microsurgical varicocelectomy significantly increased the sperm retrieval rate in patients with clinical varicocele and NOA.

Figure 23. Microsurgical Varicocelectomy

[2-2] Vasoepididymostomy

Approximately 20% of men visiting for infertility are azoospermia. Of these patients, about 40% have post-testicular obstruction. Obstructive azoospermia(OA) is the absence of both spermatozoa and spermatogenic cells in semen and post-ejaculate urine due to the bilateral obstruction of the epididymis or the seminal or ejaculatory ducts. OA may result from epididymal, vasal or ejaculatory duct abnormalities. Epididymal obstruction is the most common cause of OA, affecting 30-67% of obstructive azoospermic men with normal testicular spermatogenesis. Epididymal obstruction may be caused by infection, trauma, or epididymal blowout breakage after vasectomy. Microsurgical reconstruction remains the safest and most cost-effective treatment option for OA patients.

With microsurgical technique, restoration of patency can be achieved in 70-90% of patients, although restoration of fertility is achieved only in 50%. Surgically success rate was dependent on pre- and intraoperative variables of individual patients. Success rate of unilateral vasoepididymostomy is low, bilateral surgery is likely to enhance the overall patency rate. In some reports, vasoepididymostomy site was associated with patency rate. Sperm retrieval and cryopreservation during an operation is recommended for surgical and pregnancy failure, in men undergoing vasoepididymostomy. Intraoperative sperm cryopreservation in men undergoing vasoepididymostomy will maximize the postoperative fertility options.

III. Surgically uncorrectable male infertility (including testicular failure)

Nonobstructive azoospermia(NOAs) is the most challenging type, but no specific treatment was available previously. With the advent of ICSI in conjunction with sperm retrieval via testicular sperm extraction(TESE), many of nonobstructive azoospermic patients are able to father own babies. Also, TESE/ICSI is successful in intervention in Klinefelter syndrome(KS). KS is the most common sex chromosome abnormality in males. It affects approximately in 500 newborn boys and accounts for up to 11% of azoospermic men. The clinical feature of KS gynecomastia, small testis and azoospermia. In the past, men with azoospermia were classified as infertile, and a sperm donor was initially considered one of the best options for conceiving. Currently, microsurgical TESE is an advanced type of TESE that applies microsurgical techniques.

Microsurgical TESE is an effective sperm retrieval from men with NOA for ICSI. The procedure is performed through a very small incision in the midline of the scrotum. Surgeon open the testicles through this incision and look under a high power, operating microscope (at 20-25X magnification) for seminiferous tubules that are swollen and contain sperm. The...
advantages of this technique are minimally invasive technique, removal of minimal amount of testicular tissue and minimalizing negative impact on testicular function. Microsurgical TESE is more effective in men with NOA than conventional TESE. In the study to assess and compare the outcomes of testicular sperm extraction (TESE)-intracytoplasmic sperm injection (ICSI) using spermatozoa from fresh and frozen testicular tissue from men with subgroups of non-obstructive azoospermia (NOA). No significant differences were observed in spermatozoa retrieved from frozen testicular tissue from NOA subgroups: hypospermatogenesis (HS), maturation arrest (MA), or Sertoli cell-only syndrome (SCO). Once spermatozoa have been successfully obtained, acceptable laboratory outcomes can be achieved for NOA, whether or not the spermatozoa are cryopreserved (Park et al., Syst Biol Reprod Med, 2015).

Treatment strategies for male infertility have changed as dramatically over the past decade. These advances are largely contributable to microsurgical varicocele repair, microsurgical reconstructive techniques, and microsurgical techniques for surgical sperm retrieval and ART specifically ICSI.

Figure 25. Microsurgical TESE. arrow: exposed pink thickened seminiferous tubules, isolated regions of spermatogenesis within the testis (Kim et al., Korean J Urol. 2008)

7) Reproductive Surgery: Importance of reproductive surgery in infertile patients

(1) Laparoscopy

A. Endometriosis: Endometriosis exists as ovarian cysts and causes adhesion of pelvic organs, thus impairing normal anatomy and degrading ovarian function. Without proper surgery, the disease is likely to recur and reduces the pregnancy rate. Thus, after conserving the normal ovarian tissue and normal anatomical structure by a skilled surgeon and right after that getting assisted reproductive procedure expect temporary pregnancy with high pregnancy rate.

B. Hydrosalpinx: Hydrosalpinx is a one of the common cause of female infertility. In women with hydrosalpinx, lower implantation and pregnancy rates have been reported because of inflammatory factors in the fluid. Therefore, surgical treatment for hydrosalpinx prior to in-vitro fertilization is recommended. Removal of hydrosalpinx (Salpingectomy) improves pregnancy rate by up to twice.

C. Myoma (Uterine fibroid): Myoma is the most common benign tumor in women in their thirties. Depending on the location and size of myoma, there are various symptoms. Myomas especially close to the endometrium so that compress endometrial cavity could interfere with the implantation. In case of that, laparoscopic surgery which could minimize endometrial damage is needed.

(2) Hysteroscopy

A. Polyp: Endometrial polyp usually there is no symptoms. However, endometrial polyps in the uterus can cause infertility and miscarriage. In the past, polyps were often removed by doing a D&C. Now a hysteroscopy is the best method, because polyps can be removed under vision so that preventing unnecessary endometrial damage.

B. Intrauterine adhesion: Women previously received multiple D&C (including artificial abortion) or had endometrial inflammation may have intrauterine adhesion. The fibrotic band interferes implantation and reduces menstrual amount. Hysteroscopic uterine adhesion removal (synchiliolysis) should be done.

C. Myoma: As mentioned above, myoma that occupied endometrial cavity, called submucosal myoma, should be removed before in-vitro fertilization. Although hysteroscopic myomectomy is a simple and common surgery in OBGYN, in order to minimize endometrial damage, it is better to find a skilled surgeon.

Figure 26. Cumulative intrauterine pregnancy rate in the 12 months after laparoscopy in women with endometriosis from near 0% up to 40%.

Figure 27. Laproscopic myomectomy – myoma removed from uterus with intact endometrium (left), after uterine suture (right)

Figure 28. Hysteroscopic myomectomy – Before surgery (left), After surgery (right)
A. History of reproductive laparoscopy

In 1910, Jacobaeus of Sweden first observed the human abdominal cavity as a cystoscope and called it laparoscopy. It was the first laparoscopy in OBGYN field. In 1973, laparoscopic salpingectomy was performed for the first time by Shapiro and Alder et al. It has been used for therapeutic purposes as well as for diagnostic purposes. In 1977, surgical treatment of several gynecologic diseases was initiated by Semm and Mettler in Germany. After then, laparoscopic surgery was replaced by many gynecologic surgeries that rely on past laparotomy due to advances in optical technology and the rapid development of various laparoscopic devices. And its application range is widening from fine reproductive surgery to cancer treatment. (Korean J. Obs. & Gyn. 2003)

B. History of reproductive laparoscopy in Korea

Since the first laparoscopic tubal ligation in Korea in 1973, laparoscopic surgery has started. Even in the light of world-wide laparoscopic history, it has actively introduced advanced technology at a very early stage. It was already reported that more than 20,000 cases of laparoscopy were performed in a single center in 2005. At present, most of the pelvic masses like myomas and endometriosis are treated by laparoscopic surgery, not laparotomy. In 1988, the Korean Obstetrics and Gynecology Society was established and supported not only academic activities but also excellent academic achievement. In 2007, the world leading group of single port assisted laparoscope and robotic laparoscopes were presented with global guidelines and possesses advanced technology that is recognized as a standard textbook method.

C. Single port assisted laparoscopic surgery

Classical laparoscopy is a method of performing 3 to 4 incisions per 1 cm in the umbilicus and lower abdomen. Laparoscopic surgery significantly reduced scar and recovery time compared to laparotomy. In a single port assisted laparoscopic surgery, about 2 centimeter single incision is made in the umbilicus. Since the incision is localized to the umbilicus, it not only has a high cosmetic satisfaction but also is effective in reducing postoperative pain.

Given that most of the patients undergoing reproductive surgery are young women, a single port assisted laparoscopic surgery with excellent cosmetic effect and low cost should be actively considered.

D. Robotic surgery

Laparoscopy has lots of advantages of quick recovery, less blood loss, and lower risk of post-operative adhesion band formation, which could itself cause infertility. However, there are some cases that should get laparotomy, due to the limited range of motion of the instruments. The robotic surgery has been FDA approved for gynecologic surgeries since 2005, and has recently become a useful reproductive surgeon. This surgical approach combines the advantages of laparoscopy, but overcome the limitation with the full range of motion that may not have been accomplished with traditional laparoscopy. There are many centers that has Robotic surgery systems and skillful surgeons in Korea.

Figure 29. A single port assisted laparoscopic surgery

Figure 30. Umbilical wound after applying skin adhesive; there is little scarring and no need to remove the surgical thread

Figure 31. This graph shows that single port surgery proportion has increased during recent 10 years in a single tertiary center. (Graph provided by pf. TJ Kim in SMC)

Figure 32. Graph showing increased numbers of Robotic surgery in Korea
E. Fertility sparing surgery in cancer patient

The incidence of malignant tumors such as endometrial cancer, cervical cancer, and ovarian cancer is increasing in young women. Any woman who considers pregnancy and childbirth in the future should undergo surgery to preserve as much fertility as possible.

Korea has lots of experienced surgeons for laparoscopic removal of malignant tumors, and research and efforts are being actively carried out in surgery to preserve fertility in young women.

In the cervical cancer patients, successful pregnant cases have been reported in removing the cervix with the tumor instead of removing the entire uterus. In the early ovarian cancer or borderline malignant patients, the incidence of complete remission of the disease after the removal of one ovary or only tumor tissue and success in pregnancy is reported to be close to 80% before resection of the entire bilateral ovary. The latest method of transplanting ovarian tissue into the abdominal cavity by cryopreservation is also carried out in some hospitals experimentally.

**Figure 33. Successful pregnancy cases after ovarian conservation surgery in borderline ovarian tumor**

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<th>CE group (n=19)</th>
<th>P-value</th>
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<tr>
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<tr>
<td>Pregnancy rate (%)b</td>
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USO, unilateral salpingo-oophorectomy with or without contralateral ovarian cyst enucleation; CE, unilateral or bilateral cyst enucleation; ART, assisted reproductive technology.

*Achieved pregnancy: the number of patients who succeeded in becoming pregnant

bPregnancy rate: number achieved pregnancy/number attempted pregnancy. All four cases were cesarean section with fertility-sparing surgery.

**Why Korea?**

Korean infertility clinic and laparoscopic reproductive surgeons are very skillful and have abundant experience with high passion and interest in advanced medical technology. However, it costs very reasonable compared with North America and European countries. Getting reproductive surgery and procedure in Korea will be a best choice without regret.

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8) Treatment of Recurrent Miscarriage & Repeated IVF Failures

Better approach, Better outcome in Korea

Reproductive failure (Recurrent pregnancy loss and Repeated Implantation Failure)

(1) Definition
- Recurrent pregnancy loss: occurrence of two or more consecutive losses of clinically recognized pregnancies prior to the 20th week of gestation
- Repeated implantation failure: over two to three times of IVF failure in spite of good embryo transfer

(2) Etiology
- Chromosomal factor
  - Age, parental genetic disease
- Anatomical abnormality
  - Uterine anomaly

![Congenital Mullerian Anomalies](image)

- Normal Uterus
- Class I: Uterine Hypoplasia and/or agenesis
- Class II: unicornuate uterus
- Class III: Uterus Didelphys
- Class IV: Bicornuate uterus
- Class V: Septate uterus
- Class VI: Arcuate uterus
- Class VII: Diethylstilbestrol (DES) Drug Related

- Leiomyoma, adenomyosis, Endometrial polyps, Intrauterine adhesions etc.

- Immunologic factor
  - Autoimmune diseases
  - Antiphospholipid Antibody Syndrome
  - Abnormal immune cell proportion (NK cell activity and %, Th1/Th2 ratio etc.)

- Thrombotic factor
  - Inherited thrombophilia (Leiden Factor V etc.)
  - Thrombophilia and fibrinolytic factors (protein C and S activity, antithrombin III etc.)

- Endocrine factor
  - Thyroid autoantibodies and diseases
  - Diabetes, PolyCystic Ovarian Syndrome
  - Hyperprolactinemia
Every patient has been fully evaluated in Korea.

- Diagnostic Laparoscopy and Hysteroscopy
- Chromosome study
- Laboratory evaluation for Immunologic and Thrombotic factor

Patient-specific treatment by etiology

- Lifestyle modification and medical treatment.
- Laparoscopic or hysteroscopic surgery:
  - more conservative and fertility-preserving surgery
  - Laparoscopic myomectomy
  - Laparoscopic ovarian cystectomy
  - Hysteroscopic polypectomy and myomectomy
  - Hysteroscopic uterine synechiolysis
- Preimplantation Genetic Diagnosis or Screening.
- Treatment for Thrombophilia
  - Aspirin
  - Effective dose of Low Molecular Weight Heparin
- Immunologic treatment (Immunoglobulin G - IVIG)
  - Korea has the standard guideline for IVIG by the clinical evidence.
  - More effective in women with abnormal immune test, than unexplained group.

<table>
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<td></td>
<td>With autoimmunity</td>
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<td></td>
<td>Peripheral blood NK cell cytotoxicity</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood Th1/Th2 cytokine product ratio</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Total IVF(n)</th>
<th>Mean Age</th>
<th>Clinical Pregnancy Rate</th>
<th>RIF (≥ 3 MF failure)</th>
<th>Mean Age</th>
<th>Clinical Pregnancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>286</td>
<td>34.8</td>
<td>53.8%</td>
<td>207 (72.3%)</td>
<td>34.7</td>
<td>50%</td>
</tr>
<tr>
<td>2016</td>
<td>202</td>
<td>35.5</td>
<td>48.4%</td>
<td>136 (66.3%)</td>
<td>36.4</td>
<td>46%</td>
</tr>
</tbody>
</table>

- Over 81% of high live birth rate was reported in another Korean center after etiology-based treatment.

Good IVF outcomes of women with Repeated Implantation Failure in Korea

<table>
<thead>
<tr>
<th>Primary vs. secondary RPL</th>
<th>2 vs. ≥ 3RPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>63/145 (43.4)</td>
</tr>
<tr>
<td>Live birth</td>
<td>51/563 (81/0)</td>
</tr>
<tr>
<td>Gestational weeks</td>
<td>37.26±5.76</td>
</tr>
</tbody>
</table>

Approximately 70% of foreign IVF patients was RIF patients who had more than three failed IVF experiences. After the close investigation of the causes of their repeated implantation failure (RIF), RIF patients have shown high clinical pregnancy rates that was not significantly different from that of the whole IVF patients through an appropriate treatment.
3. Medical Korea

1) Why Korea?

(1) With the introduction of the latest technology and creative research, IVF technology is excellent and pregnancy rate is high.

The total clinical pregnancy through IVF (with fresh ET and frozen-thawed ET) is continuously sustained around 40% among the overall patients at the last several years. It is reputable statistics compared to the report of US or European countries. The numbers of time lapse embryo monitoring system and PGD/PGS are rapidly increased last several years. The strategies to select the best embryo to transfer are proceeded through non-invasive and/or invasive techniques.

(2) The success rate of pregnancy is high through intensive treatment especially in patients with repeated IVF failure and the advanced maternal age.

On this survey of the main IVF center’s outcome, the clinical pregnancy rates in the elderly women (over 42 years old) was shown 16~19%. It was rather high performance compared to SART report (positive pregnancy test: 9.3%, clinical pregnancy rate: 6.2%, over 42 years old patient).

(3) Many patients crossing borders to proceed ART in Korea

This survey demonstrated that 4667 OPU cycles, 3687 fresh ET cycles and 1134 T-ET cycles have been undergone for the foreign patients in the last 5 years.

(4) Highly qualified medical services: delicate care, transparent IVF cost

The cost per live birth was highest in the United States and United Kingdom ($41,132 and $40,364, respectively) and lowest in Scandinavia and Japan ($24,485 and $24,329, respectively, Fertil Steril. 2009). The cost per live birth in 2014 by Korean IVF Reimbursement Program was estimated $5,449.

(5) Provide donation and surrogate programs

Babies born through IVF procedure sponsored by Russia charity program [2017]

9) Third Party Reproduction

Although less commonly encountered, there are a number of other legitimate indications for IVF and related ART procedures.

Donor egg

The reproductive potential of some women is compromised because they do not produce eggs, produce low-grade eggs and/or embryos, or are carriers of a genetic condition. An option for these women is to undergo donor egg IVF, which is done in conjunction with IVF treatment. Treatment with egg donation involves a woman who serves as an egg donor and a woman who serves as the recipient. Donor Egg IVF can be used for women who have a healthy uterus, but who either have no eggs (women with early menopause or history of surgical removal) or eggs that have not responded to ovulation inducing medications or IVF. It is a process whereby the egg donor has eggs removed from her ovaries and then fertilized with sperm in our laboratory. The fertilized eggs (now embryos) are then transferred into the uterine cavity of the recipient woman for implantation and the establishment of pregnancy.

Donor sperm

is needed in • men whose sperm is unlikely to fertilize an egg • men who produce little or no sperm • men with a family history of genetic disease • men with past vasectomy or testicular failure • men undergoing treatment for cancer

Surrogacy

For women with normal ovaries but no functional uterus, due to a developmental anomaly (uterine anomaly), advanced disease (multiple myomas, severe intrauterine adhesions), or a previous hysterectomy, and for women with medical conditions that preclude pregnancy due to serious health risks, gestational surrogacy offers the opportunity to have their own genetic offspring.

Any patients who need to undergo third party reproduction, if it is indicated (pre-arrival counseling), are recommended to be accompanied by their own donor or surrogate. Each case will be reviewed through Institutional Review Board(IRB) belonged to the hospital before arrival.
(6) Closely connection with medical staffs before and after the procedure

(7) Environment is convenient and pleasant

2) Cases of infertile patients abroad

Case 1

The E** couple did not have their pregnancy for four years after marriage. In Mongolia, the medical facility for infertility treatment and the treatment were so bad at that time that they decided to visit ** Hospital in Korea where medical tourism was activated. During the medical examination, the adnexal adhesion of the uterus and the ovary was accompanied by severe endometriosis. After laparoscopic adhesiolysis, they received In Vitro Fertilization procedures twice in other hospitals, but the result was pregnancy failure.

She was disappointed to suffer a severe depression due to pregnancy failure, and she came to find the infertility Hospital in Vladivostok, Russia. However, the oocyte condition became worse than before, so she couldn’t have a pregnancy.

As a result of the repeated pregnancy failure, depression became worse and the fear of avoiding the interpersonal relationship was growing. Because of the fear of pregnancy failure and depression at the first visit ** Hospital, the patient’s distrust of the hospital and distrust of all medical care, the coordinator of foreign medical center had considerable difficulty. However, the coordinator understood the situation of the patient’s condition and depression, so all the staffs worked together to do their best. Those efforts allowed them to continue long-term care, medical treatment, and prescription for in vitro fertilization, and they were able to undergo oocyte retrieval and embryo transfer. Fortunately, she got pregnant and is now in a state of well-maintained pregnancy.

Case 2

The couple has been infertile for 9 years and has undergone cystectomy surgery to remove a tumor of the ovary. After ovarian function has been significantly reduced, the age of the ovary was revealed as 44 years old. The bilateral tubes are blocked, and corrective operation is inevitable, and her husband’s semen showed a marked decrease in mobility. As a matter of fact, I visited the Taniim Center in Mongolia and tried several ovulation induction and induction of natural ovulation but I could not even try to fertilize the egg because there was no egg collection at all. At CL Hospital, we tried to induce the ovarian hyperstimulation once, but there was no follicular maturation at all.

We decided to try the procedure through the egg donation program through medical consultation, and we have donated Mongolian donor. It is very difficult for Mongolians to obtain a visa to come to Korea, but with the help of the medical tourism visa program, they were able to come to Korea with difficulty during the three month stay. Through this process, the egg donor donated and the embryo was transferred, but the uterus was not implanted after the first freezing embryo transfer. During the short visa period it is difficult to try out the procedure according to the women’s menstrual cycle. After the first failure, I was forced to try within the remaining visa period. As a result, I was conceived and now I am pregnant well.

Case 3

The M couple from the United Arab Emirates suffered five pregnancies and five miscarriages starting in 2014, the fourth year of their marriage, and their pregnancy stopped at the gestational 10-weeks. I was diagnosed with a habitual abortion at a local hospital, got a test, tried to reduce my weight, took medication, but I was not pregnant. The couple was a series of heartbreaking and frustrated minds. The Arab couple decided to take a test tube baby procedure at a Korean hospital. From the far-off Middle East to South Korea, for the success of pregnancy, 8 months of steady treatment and 2 times of in vitro fertilization. And now I have been doing well of twin pregnancy with a 17-week gestation.

Case 4

One of the biggest worries of a couple living in Australia was that they did not have a child for four years. They went to the local obstetrics and gynecology department but it did not seem to have any effect. When he visited Korea in March this year, he heard a heartwarming message from his acquaintances. He contacted Korea *** Hospital International Clinic and received instructions for infertility treatment and came to Korea for examination procedure with his wife in May. After several weeks of treatment, the patient underwent an in vitro fertilization procedure, but the results failed. However, with the encouragement of the medical staff, he was willing to cooperate with the second attempt. When they visited the hospital a few weeks later, they were surprised, and they were informed of the positive results in the pregnancy test. The A couple are very proud of the fact that they are taking care for their health and that they will welcome a new family, and they are actively recommending Korean hospitals to their infertile friends.
Case 5

I am 41 years old Russian Yakuchia.

I have never been pregnant with my husband for 16 years, but I have done a lot of hard work and I have been treated at Moscow. However, my husband has male infertile problem, and I had laparoscopic surgery to remove ovarian nodules in Moscow from 2007 to 2009, and the ovarian function was reduced. In 2010, I received an in vitro fertilization procedure in St. Petersburg, but I was diagnosed that I could not get pregnant because of multiple myomas of my uterus, so they recommended me to use a surrogate mother as well as an egg donation. So I gave up and my friend sent me my test results by email to the coordinator in Korea.

However, the Korean Hospital *** suggested that she didn’t need to use a surrogate mother through the coordinator, and suggested that she come to Korea for an infertility test for an accurate diagnosis.

I was diagnosed in Korea in May 2015, and after many treatments, I cried with joy when I was told that I would try my best to have a success rate of at least 5% in *** teacher like God.

In July 2015, I came to Korea again and immediately after that, miraculous things happened. Since our daughters, our lives have become meaningful. Before that, both my husband and I were the only ones who lost their lives and a new life. Our daughter’s breathing proves that we are a family.

The child’s skirts, hairpins, and toys all over the place, our daughter’s nose cold, sleeping and our daughter’s crying and laughing sound filled every moment and our life turned into a happy color like a movie. We became parents. A miraculous thing happened to us that we could not dream about. We will live happily ever after moments. All of this seems to be due to the warm heart, touch and smile of the Korean teacher.

Thank you.

Case 6

My miraculous story was completed with the help of a Korean teacher and a coordinator team.

I regret now that my body and mind would not have suffered if I had known about Korean expertise five years ago.

Five years ago, she was told that she had no cause of infertility, but later she was taken to an emergency room with an extrauterine pregnancy and removed one of the fallopian tubes by laparoscopic surgery. Everything started from that work. After one year of surgery, she was told that there was a risk of another uterine pregnancy occurring in the other poor fallopian tube, and she had to remove one remaining fallopian tube. After that, ovarian nodules were generated and he was having a difficult time laparoscopically. Moreover, even my husband could not bear the fact that I was infertile and met another woman, and as a result, we became divorced. After all that, I finally got depressed. But everytime I was depressed, a friend helped me a lot and my friend was male infertility, so I comforted each other sore scars and finally I fell in love with each other.

As a result of in vitro fertilization in my hometown, I received a terrible diagnosis that I could get pregnant only after I got an egg donor. Then suddenly I learned about the success rate of the high examiners in Korea and I emailed the coordinator who posted the most warm testimonials. A month and a half later, we arrived in Seoul and arrived in a strange country. I was nervous but picked up in a good car and took me to a small, cozy hostel, which made my anxious mind disappear and gave me a sense of security. Having a sense of mental stability is very important for in vitro patients. The fact that we waited for us from the first moment seems to have comforted us.

I felt like going to a spa-therapy center rather than going to a hospital during my visit, so I was compared to my home hospital. Not only all of the nurses, but also my *** respect
At the end of ovulation induction, one oocyte was taken, and successfully fertilized and transferred. The precious one became my daughter. The teacher and coordinator seemed to be more delighted to my pregnancy than my relatives. In the end, I think this miracle happened because the true heart and expertise that they wanted to help me became one.

I am going to come back to Korea to pick up a younger brother of my daughter...I will come again, please wait.

---

Case 7

Good morning?

I have been married to my husband for 14 years. It was natural pregnancy in two years of marriage but it was ectopic pregnancy. In 2010, I received the first in vitro fertilization procedure in Russia and became pregnant with an ectopic pregnancy. At that time, both of the fallopian tubes were removed by laparoscopic surgery. Since then, I have not given up and have had more than five examinations, but all failed.

I thought I should go to a place with better technology, and I got to know Korea by the invitation of people around me. When I visited Korea for the first time in winter of 2014, my ovarian function was almost zero. I failed my first operation in Korea and received donation of eggs. I finally got pregnant and I was so happy to go back to Russia.

Unfortunately, it resulted a miscarriage after 25 weeks of pregnancy. I live in a Russian country where I could not keep my pregnancy, and I had to leave the baby without knowing the cause. It was around May of last year, and the cesarean section sent the baby, and the tears flowed.

The situation did not get better when I returned to Korea last winter after surgery. One side of the ovary was almost dry by long-term resection, and there was no fallopian tube, and there was a wound in the uterus when the cesarean section was performed as a miscarriage. Hormone levels were very low, and follicle stimulating hormone levels were also unstable. But my husband and I could not give up. We loved each other and could not abandon our desire to have our child. In the winter of that year, the embryos that had been frozen last time remained, and I received a test tube baby procedure again. And fail again. The second attempt was also a failure. I thought the frozen embryo was exhausted and I thought it was over. It was the coordinator who gave me the courage. I have had several sessions over the years and I have been very helpful with the coordinator. I was not only an interpreter but also a guest who cried and cried together and was more thankful than my family. I got a donor from Russia again, and I could not get the cycle, and the freezing embryo was not in good condition, so I could not transplant it and it failed again. I have been tired of my body and my heart by experiencing continued failure. My husband was working in Russia to earn a living expenses, and I had to stay in Korea apart from him. But my husband said it was hard, but there was no way to go back, so he decided to comfort me and again to find my way with my husband.

I went back to find the egg donor with the idea that it was the last, and the doctor recommended that I needed to ovulation induction while my possible donor could be ready. I thought it was unlikely, but I believed in my doctor. She understand my condition better than anyone else and I made myself a pregnant woman through uterine cervical surgery. After my abortion, my condition was getting worse and I could not dream. But I succeeded with my egg that I could not expect.

The first pregnancy test result is 109!!! The first ultrasound results are twins!!!

I do not know how to express my feelings and feelings, but I want to tell them to try and do not give up. I want to go to the end for happiness by giving strength without giving up others through my story which was really hard and difficult. The hard way is impossible by myself. In my case, I met a doctor with a great ability like a wizard and I firmly believed her words. I have walked together without giving up the hard way thanks to the care of everyone, including the coordinators who were very helpful, the hospital staff who had provided accommodation, transportation and documents during their stay in Korea. The last thing you want to say is to trust your doctor and believe in your strength and love! And I hope all couples find their happiness soon. Love each other! And be happy!
3) How to proceed IVF-ET in Korea?

(1) Pre-arrival Consultation

History taking, provision of medical records to review and advice to prepare during preconception period for enhancing fertility will be carried out before ART treatment.

History of marriage, pregnancy, menstrual pattern, infertility duration, previous operation history, previous ART treatment history, age, sex, body weight, and height will be recorded.

Patients are recommended to submit their medical records of ultrasonography, hysterosalpingography or pelvis CT scans (if applicable), and laboratory results (blood tests and urine tests) + past medical history, including malignancies, infections, hypertension, diabetes, etc. + Depending on the disease the patient is suffering from, additional general examinations may be carried out to identify the capability to conceive.

(2) Pre-arrival Preparation

Wife and spouse are recommended to prepare the mandatory official documents that proves their marital status. It is recommended to prepare documents for Marriage Certificate or Single certificate in embassy. Invitation letter should be provided before arrival (entrance to Korea) from the connected hospital.

(3) Post-arrival Process : Pretreatment preparation

Pretreatment testing will include blood work to determine hormone levels, blood tests required by Korean law (Act on Bioethics and Safety), a semen analysis (if applicable), and a uterine assessment. In order to have the optimal IVF outcome, physicians review patient’s medical history and the results of pretreatment testing before physicians decide on an individualized IVF protocol.

(4) Four Steps of IVF-ET

[1] Controlled Ovarian Stimulation (COS)
[3] In Vitro Fertilization (IVF) & Embryo Culture
[4] Embryo Transfer (ET)

[4-1] Controlled Ovarian Stimulation (COS): 8–14 days

An IVF cycle begins with ovarian stimulation and ultrasound monitoring. A baseline pelvic ultrasound will ensure a healthy starting point before initiating medication for the stimulation and assessment of egg production. The patient will take hormone injections to recruit multiple eggs from their ovaries. There are most popular protocols shown at the below (Figure 34-37).

During this time, follicular development and hormone levels will be monitored for appropriate growth for several days. Once follicles have reached the ideal size, they will be ready for egg retrieval. Approximately three to five monitoring visits will be conducted for ultrasounds and for the assessment of blood hormone levels in order to accurately monitor the follicular growth. GnRH antagonist protocol is the most common (Figure 36). Minimal stimulation protocol with oral medicine/ lower dose of gonadotropin for women with reduced ovarian reserve is increasing with the increment of the advanced aged female (Figure 37) and poor responder.

Transvaginal ultrasound-guided ovum pick-up was done usually under subconscious sedation. It is a procedure in which a long, thin needle is passed through the vaginal wall into the ovary. The physician aspirates the follicles from each ovary and the follicular fluid is collected in test tubes, where the embryologist carefully searches for the eggs. Injuries during this procedure are extremely rare. Limited bleeding from the ovaries may occur, but the need for transfusion is extremely rare. Infections following transvaginal egg retrieval are also possible, but are rare.

Figure 38. The procedures of IVF-ET, TVS of unstimulated ovary(A), enlarged several follicles in stimulated ovary(B), the process of ovum pick-up(C), aspirated mature oocyte(D), ICSI(F) or conventional insemination(E), 8 cell stage embryo(G), blastocyst(H), the process of embryo transfer(I).

[4-3] IVF & embryo culture at laboratory: 3–5 days

The eggs are cleaned, counted, and placed in an incubator. Later that day, the eggs are fertilized with sperm either by standard conventional insemination or Intracytoplasmic sperm injection(ICSI). During IVF, embryos are cultured for up to six days in a temperature-controlled incubator. Each day the embryos are evaluated for quality and development. This information is shared with the doctors to help determine the appropriate day for embryo transfer, which is typically performed on day three or day five of embryo culture or day six in the case of PGS/PGD. Embryologists will inform the patient each day to update on the embryo quality and to answer any questions they may have.

[4-4] Embryo Transfer (ET): 5–15 minutes

Embryos are typically transferred back to the uterus on day three, when the embryo is at a cleavage stage, or day five or six, when the embryo is at a blastocyst stage. This simple procedure usually requires no anesthesia. Doctor and embryologist will discuss the number of embryos to transfer that will provide the patient the highest probability of success and the lowest probability of high-order multiple births. The patient also will receive pictures of the embryos being transferred. The patient will relax in the room for a short period of time once the embryo transfer is complete. The transfer itself may cause mild irritation to the cervix or uterus.

<table>
<thead>
<tr>
<th>IVF-ET Procedures</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Ovarian Stimulation (COS)</td>
<td>8 – 14 days Injection days</td>
</tr>
<tr>
<td>Transvaginal USG-guided Ovum Pick-Up (TV-OPU)</td>
<td>10–20 mins Sedation</td>
</tr>
<tr>
<td>In Vitro Fertilization (IVF) &amp; Embryo Culture</td>
<td>3–6 days Calls from Laboratory</td>
</tr>
<tr>
<td>Embryo Transfer (ET)</td>
<td>5–10 mins No sedation</td>
</tr>
<tr>
<td>Pregnancy test (9–11 days later)</td>
<td>5 mins Check serum hCG level</td>
</tr>
</tbody>
</table>

Pregnancy test

Pregnancy should be confirmed by the test of serum hCG level after 14 days of OPU.

Post ET follow up

Before then some patients can leave early to their home country, and report to us the result of their serum hCG level and the need to follow up the guideline of the hormonal treatment after pregnancy is confirmed.

+++ Necessary

When the patient visits the hospital for below symptoms after OPU
- abdominal pain or distension
- decreased urine output
- vaginal spotting or bleeding

+++ Necessary
With the steadily increasing IVF procedure, about 4.8% of all births in 2016 were born from Assisted Reproductive Technology (in vitro fertilization and intrauterine insemination). Approximately one out of 20 children in Korea today is born through ART. As of June 2015, the number of designated institutions for in vitro fertilization was 152, 34.5% higher than 113 in 2006 (97 IVF centers in 2009 at Figure 39). Korea has become known as a powerful fertility treatment country under the legislation on reproductive technology. With more and more people starting to have children later in life, an increasing number of couples are turning to medical support to conceive.

Table 3. Comparison with data from international registry

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IVF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycles with oocyte retrieval</td>
<td>9,474</td>
<td>91,182a)</td>
<td>115,875</td>
</tr>
<tr>
<td>Cycles with embryo transfer</td>
<td>8,360</td>
<td>84,039a)</td>
<td>101,809</td>
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<tr>
<td>CP</td>
<td>2,851</td>
<td>37,780a)</td>
<td></td>
</tr>
<tr>
<td>CP per retrieval (%)</td>
<td>30.1</td>
<td>41.4a)</td>
<td>28.5</td>
</tr>
<tr>
<td>CP per transfer (%)</td>
<td>34.1</td>
<td>45.0a)</td>
<td>32.5</td>
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<tr>
<td>Live birth per retrieval (%)</td>
<td>25.4</td>
<td>36.6a)</td>
<td>21.2</td>
</tr>
<tr>
<td><strong>ICSI</strong></td>
<td></td>
<td></td>
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<tr>
<td>Cycles with oocyte retrieval</td>
<td>11,575</td>
<td>-</td>
<td>267,661</td>
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<tr>
<td>Cycles with embryo transfer</td>
<td>11,283</td>
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<td>206,055</td>
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<tr>
<td>CP</td>
<td>2,211</td>
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<tr>
<td>CP per retrieval (%)</td>
<td>20.7</td>
<td>-</td>
<td>28.7</td>
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<tr>
<td>CP per transfer (%)</td>
<td>26.5</td>
<td>-</td>
<td>31.9</td>
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<tr>
<td>Live birth per retrieval (%)</td>
<td>24.1</td>
<td>-</td>
<td>20.4</td>
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<tr>
<td><strong>FER after IVF with/without ICSI</strong></td>
<td></td>
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<tr>
<td>Cycles with embryo transfer</td>
<td>5,704</td>
<td>26,069</td>
<td>73,024</td>
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<tr>
<td>CP</td>
<td>1,891</td>
<td>9,487</td>
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<tr>
<td>CP per transfer</td>
<td>33.7</td>
<td>36.4</td>
<td>19.3</td>
</tr>
<tr>
<td>Live birth per transfer</td>
<td>24.9</td>
<td>28.5</td>
<td>13.7</td>
</tr>
</tbody>
</table>

ART, assisted reproductive technology; ESHRE, European Society for Human Reproduction and Embryology; IVF, in vitro fertilization; CP, clinical pregnancy; ICSI, intracytoplasmic sperm injection; FER, frozen embryos replacement. a)Including ICSI.

Since October 2017, IVF centers in Korea are expected to have a more intense institutional control due to the more active IVF coverage policy of National Health Insurance.

<table>
<thead>
<tr>
<th>No.</th>
<th>Hospital Name</th>
<th>Address</th>
<th>Website</th>
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<tbody>
<tr>
<td>1</td>
<td>Ajou University Hospital</td>
<td>164, Worldcup-ro, Yeongtong-gu, Suwon, Gyeonggi-do</td>
<td>hosp.ajoumc.or.kr</td>
</tr>
<tr>
<td>2</td>
<td>Asan Medical Center</td>
<td>18, Olympic-ro 43-gil, Songpa-gu, Seoul</td>
<td>eng.ams.seoul.kr</td>
</tr>
<tr>
<td>3</td>
<td>Baby Eroom Women’s Clinic</td>
<td>25, Seomyeon-ro, Busan-ro, Busan (6F, Samhan Golden View)</td>
<td>baby.eroom.com</td>
</tr>
<tr>
<td>4</td>
<td>CHA Bundang Medical Center</td>
<td>19, Yatap-ro, Bundang-gu, Seongnam, Gyeonggi-do</td>
<td>bundang.chamc.co.kr/etn/</td>
</tr>
<tr>
<td>5</td>
<td>CHA Fertility Center Seoul Station</td>
<td>2F, 41A, Hangang-daero, Jung-gu, Seoul (Seoul Square, Namdaemun 5-ga)</td>
<td>seoul.chamc.co.kr</td>
</tr>
<tr>
<td>6</td>
<td>CHA Gangnam Medical Center</td>
<td>366, Noryeong-ro, Gangnam-gu, Seoul</td>
<td>gangnam.chamc.co.kr</td>
</tr>
<tr>
<td>7</td>
<td>Cheil Medical Center</td>
<td>17, Seoaro 1-gil, Jung-gu, Seoul</td>
<td><a href="http://www.chelmc.co.kr">www.chelmc.co.kr</a></td>
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<tr>
<td>8</td>
<td>CL Hospital</td>
<td>957, Miju-daero, Seo-gu, Gwangju-si</td>
<td><a href="http://www.clwhivf.com">www.clwhivf.com</a></td>
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<tr>
<td>9</td>
<td>Ewha Womans University Medical Center</td>
<td>1077, Anyangcheon-ro, Yangcheon-gu, Seoul</td>
<td><a href="http://www.eumc.ac.kr/mokdong">www.eumc.ac.kr/mokdong</a></td>
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<td>10</td>
<td>Good Moonhwa Hospital</td>
<td>179, Beenli-ro, Dong-gu, Busan</td>
<td><a href="http://www.moonhwa.or.kr">www.moonhwa.or.kr</a></td>
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<td>11</td>
<td>Keimyung University Dongsan Medical Center</td>
<td>56, Dalseong-ro, Jung-gu, Daegu</td>
<td><a href="http://www.dsmc.or.kr">www.dsmc.or.kr</a></td>
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<td>12</td>
<td>Korea University Anam Hospital</td>
<td>72, Inchon-ro, Seong</td>
<td><a href="http://www.anam.kumc.or.kr">www.anam.kumc.or.kr</a></td>
</tr>
<tr>
<td>13</td>
<td>Korea University Guro Hospital</td>
<td>146, Guroung-ro, Guro-gu, Seoul(Guro-dong)</td>
<td>guro.kumc.or.kr</td>
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<td>14</td>
<td>Maria Fertility Hospital</td>
<td>152, Song-ro, Songpa-gu, Seoul</td>
<td><a href="http://www.marianbaby.com">www.marianbaby.com</a></td>
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<td>15</td>
<td>Maria Fertility Hospital (Busan)</td>
<td>20, Cheonho-daero, Dongdaemun-gu, Seoul</td>
<td><a href="http://www.marianbaby.com">www.marianbaby.com</a></td>
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<td>16</td>
<td>Maria Fertility Hospital (Daegu)</td>
<td>7F and 8F, The Well Tower, 124, World Cup-daero, Yeoju-gu, Busan</td>
<td><a href="http://www.marianbaby.com">www.marianbaby.com</a></td>
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<td>17</td>
<td>Maria Fertility Hospital (Gangnam)</td>
<td>7F and 8F, Seocho-ro, Yongsan-gu, Busan</td>
<td><a href="http://www.marianbaby.com">www.marianbaby.com</a></td>
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<td>21</td>
<td>Pusan National University Hospital</td>
<td>101, Guryong-ro, Dongnae-gu, Busan</td>
<td><a href="http://www.pnuh.or.kr">www.pnuh.or.kr</a></td>
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<td>Premedi Women’s Clinic</td>
<td>790, Miju-daero, Seo-gu, Gwangju-si (Nogseong-dong)</td>
<td><a href="http://www.premedi.com">www.premedi.com</a></td>
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<td>Saewha Hospital</td>
<td>30, Minam-ro 132boen-gil, Dongnae-gu, Busan</td>
<td><a href="http://www.swmedi.com">www.swmedi.com</a></td>
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<tr>
<td>24</td>
<td>Samsung Medical Center</td>
<td>81, Guryong-ro, Gangnam-gu, Seoul</td>
<td>english.samsunghospital.com</td>
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<tr>
<td>25</td>
<td>Seoul National University Bundang Hospital</td>
<td>82, Gumi-ro 173boen-gil, Bundang-gu, Seongnam-gi, Gyeonggi-do</td>
<td><a href="http://www.snhub.org/index.do">www.snhub.org/index.do</a></td>
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<td>26</td>
<td>Seoul National University Hospital</td>
<td>771, Gyeongmae-daero, Nam-gu, Incheon-sil2-6F, Seoul Building, Juan-dong</td>
<td><a href="http://www.snuh.org/english">www.snuh.org/english</a></td>
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<tr>
<td>27</td>
<td>Seoul Women’s Hospital</td>
<td>771, Gyeongmae-daero, Nam-gu, Incheon-sil2-6F, Seoul Building, Juan-dong</td>
<td><a href="http://www.snuh.org/english">www.snuh.org/english</a></td>
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<tr>
<td>28</td>
<td>Seoul Women’s Hospital</td>
<td>3011-2, Withussol</td>
<td>bucheon.smh.co.kr</td>
</tr>
<tr>
<td>29</td>
<td>Yonsei University Gangnam Severance Hospital</td>
<td>50, Yonsei-ro, Seodaemun-gu, Seoul</td>
<td>yonsi.severance.com</td>
</tr>
<tr>
<td>30</td>
<td>Yonsei University Wonju Severance Christian Hospital</td>
<td>20, Ilnam-ro, Wonju, Gangwon-do, Seoul</td>
<td><a href="http://www.ywmc.or.kr">www.ywmc.or.kr</a></td>
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