Aims and scope
Yeungnam University Journal of Medicine (Yeungnam Univ J Med, YUJM, eISSN 2384-0293, https://www.e-yujm.org), the official publication of the Yeungnam University College of Medicine, is an international, peer-reviewed, and open access journal in the medical field.

YUJM aims to communicate new medical information to medical personnel, and to facilitate the development of medicine and the propagation of medical knowledge by publishing high quality evidence-based articles. It covers all fields of medical science, including clinical research and basic medical science.

YUJM publishes original articles, case reports, review articles, and editorials. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and for the communication of valuable information about all fields of medicine.

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First step to international journal by indexing PMC and DOAJ

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The Yeungnam University Journal of Medicine (YUJM) was first published in December 1984 as the official journal of the Yeungnam University College of Medicine. It is an international, peer-reviewed, and open access journal. The aim of YUJM is to communicate new medical information to the medical personnel and facilitate the development of medicine through propagation of medical knowledge by publishing high quality evidence-based articles. It has been published in English since 2018.

YUJM has been indexed in both the Directory of Open Access Journals (DOAJ; June 2019) and PubMed Central (PMC; October 2019). It has been available for journal article search through PubMed since the publication of volume 35, issue 1, 2018. The significance of YUJM being indexed in DOAJ and PMC is as follows: firstly, it has advanced to an international-level journal; secondly, it can be easily searched in PubMed; and lastly, journal citations will increase because they are available online to be read and used readily. To promote YUJM to SCOPUS and SCIE-indexed journals, the efforts toward maintaining the high scientific standard of the journal need to be continued; additionally, there is a need to increase the critical mass and standard of content.

Finally, I would like to express my sincere thanks to the former editor-in-chiefs, members of the editorial board, reviewers, manuscript editors, and publishers for their utmost devotion to the success of YUJM. In particular, I deeply appreciate all authors of the articles for their support and contribution. I hope that the readers and researchers will share their valuable thoughts and experiences, and recent information in the field of medical science.

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No potential conflict of interest relevant to this article was reported.

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Drug-induced liver injury (DILI), including herbal and dietary supplement hepatotoxicity, is often passed lightly; however, it can lead to the requirement of a liver transplant or may even cause death because of liver failure. Recently, the American College of Gastroenterology, Chinese Society of Hepatology and European Association for the Study of the Liver guidelines for the diagnosis and treatment of DILI have been established, and they will be helpful for guiding clinical treatment decisions. Roussel Uclaf Causality Assessment Method scoring is the most commonly used method to diagnose DILI; however, it has some limitations, such as poor validity and reproducibility. Recently, studies on new biomarkers have been actively carried out, which will help diagnose DILI and predict the prognosis of DILI. It is expected that the development of new therapies such as autophagy inducers and various other technologies of the fourth industrial revolution will be applicable to DILI research.

Keywords: Diagnosis; Drug-induced liver injury; Herb; Management

Introduction

In a narrow sense, drug-induced liver injury (DILI) deals with liver injury caused only by drugs. Herb-induced liver injury can be described as hepatotoxicity caused by herbal medicines other than drugs, but it is named herbal and dietary supplement (HDS) hepatotoxicity as a comprehensive concept that includes herbal medicine, health food, and folk remedies. In general, DILI is a liver injury caused by over-the-counter drugs, herbal medicines, health foods, folk remedies, and environmental hormones, as well as by a wide range of prescription drugs including HDS.

Although DILI is a concern in several clinical fields, it is often overlooked. DILI can progress into a chronic liver injury that lasts more than six months and can reach hepatic failure, which requires liver transplantation, or death [1-4].

Further, DILI not only hurts the health of the patient, but also has very serious personal, social, and national problems, including the financial burden of payment for treatment, loss of insurance finances, distrust of prescription doctors, medical disputes surrounding compensation issues, and the withdrawal of drugs developed by investing enormous amounts of time and money from the market [5,6].

Therefore, basic knowledge and recent research trends about DILI are introduced.

Guidelines for drug-induced liver injury

In 2014, the American College of Gastroenterology (ACG) first established the ACG guideline, a diagnostic and treatment guideline for the idiosyncratic DILI [7]. It presents an evidence-based approach for the diagnosis and management of DILI with special emphasis on DILI caused by HDS and DILI occurring in individuals with underlying liver disease. In 2017, the Chinese Society of Hepatology (CSH) established the CSH guideline, a diagnosis and treatment guideline for DILI that covers 16 evidence-based recommendations on diagnosis, differential diagnosis, treatment, and prevention of DILI [8]. Recently, the 2019 European Association for the Study of the Liver guideline presenting the available
evidence on risk factors, diagnosis, management, and risk minimization strategies for DILI was also established [9].

**Online information resource on drug-induced liver injury**

The liver disease research branch of the National Institute of Diabetes and Digestive and Kidney disease, in collaboration with the National Library of Medicine and Drug-Induced Liver Injury Network (DILIN), has developed an online resource for information on DILI resulting from prescription and over-the-counter drugs as well as from complementary and alternative medicines such as HDS. The web-based resource called “LiverTox,” provides up-to-date, accurate, and easy-to-access information about the diagnosis, cause, prevalence, pattern, and management of DILI (http://livertox.nih.gov). China also provides a web-based resource called “Hepatox” on DILI (http://hepatox.org); however, it is not very helpful as it is only in Mandarin.

**Definition of drug-induced liver injury and categorization according to R-ratio**

DILI is defined as a liver injury caused by various drugs, herbs, or other xenobiotics leading to abnormalities in liver function. Terms such as hepatitis, liver cirrhosis, and liver necrosis should be used only to support liver biopsy findings; the term liver injury should be used if biochemical abnormalities are present and a liver biopsy has not been conducted. Clinical chemistry criteria for DILI is defined as elevation of the alanine aminotransferase (ALT) or the aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN) without symptoms, or rise of alkaline phosphate (ALP) > 2 × ULN or rise of bilirubin > 2 × ULN with any rise of AST and ALT, or rise of AST or ALT < 5 ULN with symptoms [10,11].

If liver injury recovers within 6 months, it is called acute liver injury (ALI), and if it persists for more than 6 months, it is said to be a chronic liver injury. ALI accounts for most cases of DILI and it is divided into hepatocellular, cholestatic, and mixed types based on the R-ratio. The R-ratio is calculated by dividing ALT by ALP, using multiples of ULN for both values. R-ratios of > 5 define hepatocellular; < 2, cholestatic; and between 2 and 5, a mixed pattern of enzymes [12].

**Spectrum of drug-induced liver injury**

The DILI spectrum is variable and broad; in most cases, hepatocytes are damaged, but cholangiocytes, stellate cells, and sinusoidal endothelial cells can also be damaged, and several other types of cells can also be damaged simultaneously. DILI can manifest itself as almost any kind of liver disease, from acute hepatitis to chronic hepatitis, fatty liver or steatohepatitis, vascular damage, liver cirrhosis, and even hepatic tumors (Fig. 1) [13,14].

**Incidence of drug-induced liver injury**

It is reported that the annual incidence of DILI is between 10 and 15 per 10,000 to 100,000 persons [15,16]. However, the actual incidence is estimated to be higher because diagnosis is not easy, and it is often disregarded unintentionally and is therefore not reported in the literature. A prospective study on DILI conducted in Korea estimated that 12 out of every 100,000 persons are admitted to university hospitals per year (data for 2005–2007) [17].

**Diagnosis of drug-induced liver injury**

1. **History taking**

   The most important factor for the diagnosis of DILI is careful history taking because DILI is a diagnosis of exclusion. The history of drug administration and the onset and progression of liver biochemical abnormalities must be accurate.

2. **Roussel Uclaf Causality Assessment Method**

   The Roussel Uclaf Causality Assessment Method (RUCAM) is a diagnostic tool that makes a probabilistic decision using a scorecard divided into 7 categories. The total scores ranges from less than 0 to 14, and the final score is interpreted as follows: highly probable (> 8), probable (6–8), possible (3–5), unlikely (1–2), or excluded (< 0) (Table 1) [18]. Currently, scores are conveniently calculated using the website (http://www.pmidcalc.org/?sid = 8229110&newtest = Y). Further, RUCAM can be easily used in clinical fields; however, in the case of liver transplantation for hepatic failure and HDS hepatotoxicity caused by Chinese medicine, health food, and folk remedies, the RUCAM scores may be low. In addition, the reproducibility of scoring is low [19].

3. **Drug-Induced Liver Injury Network expert opinion**

   DILIN is a network of US experts who have been conducting DILI-related research since 2004 [20]. The probability of DILI is divided into 5 categories: definite (95% or more), high likely (75%–95%), probable (50%–74%), possibly (25%–49%), and unlikely (25% or less) (Table 2) [21]. Three DILIN experts take a decision based on data recorded for more than 6 months. There is a limitation where only DILIN experts can make decisions; however, there is a high reproducibility advantage over the RUCAM scoring.
Hepatocyte
Acute hepatic injury
Acute hepatitis
Cholestatic injury
Mixed patterns
Acute steatosis
Extrahepatic manifestations
Chronic hepatic injury
Chronic hepatitis
Chronic steatosis
Steatohepatitis
Phospholipidosis
Chronic cholestasis
Chronic intrahepatic cholestasis
Granulomatous hepatitis
Neoplasia
Hepatic adenoma
Angiosarcoma
Hepatocellular carcinoma

Cholangiocyte
Cholestasis
Cholestatic injury
Vanishing bile duct syndrome
Biliary sclerosis
Cholangitis
Acute cholangitis
Chronic cholangitis
Sclerosing cholangitis

Stellate cell
Fibrosis
Perisinusoidal fibrosis
Cirrhosis

Endothelial cell
Vascular disease
Hepatic vein thrombosis
Sinusoidal obstruction syndrome
Peliosis hepatitis

Subclinical
Drug

Fig. 1. Spectrum of drug-induced liver injury. The spectrum of drug-induced liver injury is variable and broad from asymptomatic to liver failure. Drugs can damage not only hepatocytes but also cholangiocytes, stellate cells, sinusoidal endothelial cells, and they can cause acute hepatitis, chronic hepatitis, granulomatous hepatitis, neoplasia, cholestasis, cholangitis, vascular disease, and fibrosis.

Table 1. Roussel Uclaf Causality Assessment Method scale

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
<th>Likelihood (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly probable</td>
<td>&gt; 8</td>
<td>&gt; 75</td>
<td>Highly probable, including &quot;highly likely&quot; and &quot;definite.&quot; The evidence for the drug causing the injury is beyond a reasonable doubt, clear, and convincing</td>
</tr>
<tr>
<td>Probable</td>
<td>6–8</td>
<td>50–74</td>
<td>The preponderance of the evidence supports the link between the drug and the liver injury</td>
</tr>
<tr>
<td>Possible</td>
<td>3–5</td>
<td>25–49</td>
<td>The evidence for the drug causing the injury is equivocal but present</td>
</tr>
<tr>
<td>Unlikely</td>
<td>1–3</td>
<td>&lt; 25</td>
<td>There is evidence that an etiological factor other than a drug caused the injury</td>
</tr>
<tr>
<td>Excluded</td>
<td>&lt; 1</td>
<td>0</td>
<td>Causes could be excluded</td>
</tr>
</tbody>
</table>

Table 2. Drug-induced Liver Injury Network scale

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
<th>Likelihood (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>1</td>
<td>&gt; 95</td>
<td>The evidence for the drug causing the injury is beyond a reasonable doubt</td>
</tr>
<tr>
<td>Highly likely</td>
<td>2</td>
<td>75–95</td>
<td>The evidence for the drug causing the injury is clear and convincing but not definite</td>
</tr>
<tr>
<td>Probable</td>
<td>3</td>
<td>50–74</td>
<td>The preponderance of the evidence supports the link between the drug and the liver injury</td>
</tr>
<tr>
<td>Possible</td>
<td>4</td>
<td>25–49</td>
<td>The evidence for the drug causing the injury is equivocal but present</td>
</tr>
<tr>
<td>Unlikely</td>
<td>5</td>
<td>&lt; 25</td>
<td>There is evidence that an etiological factor other than a drug caused the injury</td>
</tr>
<tr>
<td>Not applicable</td>
<td>0</td>
<td>0</td>
<td>Key elements of the drug exposure history, initial presentation, alternative diagnoses, and/or diagnostic evaluation prevent one from determining a causality score</td>
</tr>
</tbody>
</table>
4. Liver biopsy

Although there are no characteristic pathological indicators for DILI, sometimes characteristic pathological findings based on the drug may appear, and this can help identify other liver diseases and the severity of liver injury. According to the ACG guideline, a liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated. Moreover, a liver biopsy may be considered if the liver biochemistries continues to increase or the liver function deteriorates despite the interruption of a suspected drug; if the peak ALT level has not dropped by >50% at 30–60 days after onset in cases of hepatocellular DILI; if the peak ALP level has not dropped by >50% at 180 days in the cases of cholestatic DILI despite stopping the suspected offending agent; in cases of DILI where continued use or re-exposure to the implicated agent is expected; or if liver biochemistry abnormalities persist beyond 180 days in the evaluation for the presence of chronic liver diseases and chronic DILI [7].

5. Biomarkers

Recently, there has been a growing interest in finding biomarkers that predict the occurrence of DILI, accurately diagnose it, and predict a poor prognosis. Biomarker candidates such as glutamate dehydrogenase, high-mobility group box 1, and keratin-18 have been found [22], and DILI studies using micro-ribonucleic acid, high throughput proteomics, genomics, and metabolomics have been attempted [23,24].

Mechanisms of drug-induced liver injury

Traditionally, DILI has been reported to be caused by intrinsic and idiosyncratic reactions, and sometimes, both may occur together. Intrinsic liver injury is dose dependent and predictable. On the other hand, idiosyncratic liver injury is divided into immunologic and metabolic idiosyncratic reactions regardless of dose, and it is unpredictable.

However, Lammert et al. [25] reported the relationship between the daily dose of oral medications and idiosyncratic DILI. Higher daily doses ( > 50 mg/day) were associated with serious hepatic events such as liver failure, liver transplantation, and death, but there was no association with lower daily doses ( < 10 mg.). Thus, dosage also appears to play a role in idiosyncratic liver injury. The traditional mechanism identified only the upstream of the mechanism of intrinsic and idiosyncratic reactions that cause liver injury. The current concepts of mechanisms in DILI focused not only on the upstream but also on the downstream. In other words, the hepatocyte injury mechanism is divided into 3 stages: hepatocyte injury (first stage), mitochondria permeability transition (second stage) belonging to downstream, and hepatocyte death (last stage) (Fig. 2) [26]. The initial hepatocyte injury caused by the drug does not uniformly progress to the third stage, but the injured hepatocyte may be recovered with the defense and regeneration ability of the patient. In addition, various environmental and genetic factors are involved in each stage, and the degree of individual liver injury is different.

In addition to hepatocellular injury caused by drugs, drug-induced cholestasis is also important (Fig. 3). There are 3 triggering factors that induce cholestasis, including effects on drug transporters, various hepatocellular changes, and altered bile canalicular dynamics [27]. The function of membrane drug transporters involved is inhibited, resulting in cholestasis. In addition, the drug metabolite that exits through the canalicular membrane damages the cholangiocyte, causing cholestasis. Liver injury may be exacerbated as the accumulation of drugs in the liver via enterohepatic circulation or cholehepatic shunt.

In addition, liver injury may be further exacerbated by transmitting hepatic injury and inflammatory signals to neighboring cells through other gap junctions, and the liver injury may be targeted to non-parenchymal cells other than hepatocytes and cholangiocytes [28].

Individual differences in drug-induced liver injury

Some people suffer liver injuries and others do not because every individual has different susceptibility to drugs. The risk factors for DILI can be divided into genetic factors and environmental factors [29,30]. Genetic factors include mutations in the cytochromes P450 enzyme, the expression of transport proteins and nuclear receptors, and changes in the levels of immune components. Environmental factors include old age, female gender, drug combination, previous drug adverse reactions, nutritional status, pregnancy, alcohol consumption, inflammation, and existing diseases (Table 3). The important fact is that the different risk factors are involved in different three-step model concepts that describe the changed liver injury mechanism. Changes in gut microbiota affect the drug metabolism and immune system, and it is interesting that it is one of the risk factors of DILI [31].

Drug-induced liver injury in patients with pre-existing liver disease

There is much debate over whether DILI occurs more frequently in patients with pre-existing liver diseases than in normal people.
Fig. 2. Mechanism of drug-induced liver injury. The hepatocyte injury mechanism is divided into three stages: (1) first stage (initial hepatocellular injury); initial injury is exerted through direct cell stress, direct mitochondrial inhibition, and/or specific immune reactions; (2) second stage (mitochondrial permeability transition); initial injury can lead to MPT. Direct cell stress causes MPT via the intrinsic pathway, and (3) final stage (hepatocyte death); MPT leads to necrosis or apoptosis depending on the availability of ATP, which is not uniformly progressive from the initial hepatocyte injury to the third stage, and damaged hepatocytes can be recovered depending on their defense and regeneration ability. Various environmental factors and genetic factors are involved in each step, and the degree of individual liver injury is different. MTP, mitochondrial permeability transition; ATP, adenosine triphosphate; CYP, cytochrome P450; NAT2, N-acetyltransferase 2; GST, glutathione S-transferase; UGT2B7, glycosyltransferase 2B7; BSEP, bile salt export pump; MDR3, multidrug resistance protein 3; MRP2, multidrug resistance-associated protein 2; OATP, organic-anion-transporting polypeptide; PXR, pregnane X receptor; CAR, constitutive androstane receptor; HLA, human leukocyte antigen; IL, interleukin; TNF-α, tumor necrosis factor-alpha; SOD2, superoxide dismutase 2; Nrf2, nuclear factor erythroid 2-related factor 2; GSH, glutathione S-transferase; EtOH, ethanol.

There are several exceptions, but they are not more frequent. However, it is known that DILI is more critical and has a higher mortality rate in patients with pre-existing liver diseases [32,33].

**Predictive model of progression to acute liver failure**

DILI is usually reversible and considered benign; however, it sometimes progresses to hepatic failure, requiring liver transplantation or causing death. According to Hyman Zimmerman’s Hy’s law, the hepatocellular type of DILI is known to have a mortality rate of over 10% if accompanied by jaundice [34,35]. Hy’s law is known to have a high specificity (0.92) but a low sensitivity (0.68) for the prediction of acute liver failure (ALF) [36].

A new index predicting ALF in DILI has been recently proposed by Robles-Diaz et al. [37], which integrates Hy’s law with the new R-ratio (nR) and demonstrates a sensitivity of 90% and a specificity of 63%. The nR is calculated as (the highest AST or

https://doi.org/10.12701/yujm.2019.00297
Fig. 3. Different mechanism of drug-induced cholestasis. Drug-induced cholestasis is caused by the degradation of the expression and function of the transport protein due to the environmental factors that directly inhibit the function of the transport protein and the genetic variation of the transport protein. In addition, the drug metabolite that exits through the canalicular membrane damages cholangiocyte, causing cholestasis. A liver injury may be exacerbated by drug accumulation in the liver via drug reabsorption through enterohepatic or cholehepatic circulation. Directly inhibition of BSEP function is cis-inhibition, whereas indirectly inhibition of BSEP function from the canalicular lumen is trans-inhibition. OATP, organic-anion-transporting polypeptide; MRP2, multidrug resistance-associated protein 2; BSEP, bile salt export pump; MDR3, multidrug resistance protein 3.
ALT/ULN)/(ALP/ULN); AST is substituted for ALT, if the AST yields a greater R-ratio.

Recently, a drug-induced liver toxicity ALF score (DrILTTox ALF Score) was developed to predict the progression of liver failure in DILI [36]. Scoring is based on platelet counts and total bilirubin (TB) \[\text{DrILTTox ALF Score} = -0.00691292 \times \text{platelet count} + 0.19091500 \times \text{TB} \text{(per mg/dL)}\]. Although the specificity (0.76) was slightly lower, the sensitivity (0.91) was higher than those of Hy’s law criteria. The risk of liver failure becomes higher as the platelet count decreases and TB increases.

### Herbal and dietary supplement hepatotoxicity

HDS include herbs or other plant materials, vitamins, and minerals. The incidence of HDS hepatotoxicity is increasing compared to that in the past [38]. In general, it is estimated that HDS hepatotoxicity is actually more likely to occur because it is not easy to diagnose, it is often missed if the symptoms are overlooked, and often, the cases are not reported in the literature in addition to inadequate treatment for the patient. It is difficult to detect the toxic substances contained in the herb itself, unlike the commercial medicines whose causative substances are clearly defined, and it is difficult to prove causal relationships between the herb-specific components and the liver injury. Since the herb is a mixture of various substances, it is difficult to know which ingredient causes the liver injury. It can be contaminated with microorganisms or fungi during distribution or storage, or the liver injury may be caused by herb denaturation. It should be noted that there may also be liver injury caused by impurities, heavy metal contamination, or illegal incorporation of drugs into the herb (Fig. 4).

Similar to that for the liver injury caused by commercial drugs, RUCAM scoring is applied to diagnose HDS hepatotoxicity. However, it is necessary to adjust the RUCAM for HDS hepatotoxicity [39,40] because there are few reports of HDS hepatotoxicity, and thus, the results tend to be lower than the actual RUCAM scores; further, the time between the termination of herb administration and symptom development is often long as low concentrations of plants are often taken over a long period of time.

Interestingly, Suh et al. [41] showed that psychological factors that present vulnerability to the temptation to use alternative medicines such as herbs and plant preparations are important for understanding toxic liver injury. Therefore, the treatment of toxic liver injury itself is important. However, to prevent toxic liver injury and recurrence, it is necessary to implement an active strategy to understand and improve anxiety and depression faced by the patient.

### Treatment of drug-induced liver injury

Stopping the suspected drugs is key to treatment. Other treatments involve the administration of N-acetyl cysteine (NAC) and steroids, and liver transplantation are considered when hepatic failure occurs.

#### 1. Stopping the suspected drug

Follow-ups are necessary after stopping not only the suspected drug but also herbal medicines, plant preparations, and health food. Depending on when the drug is discontinued, the severity of the liver injury can vary; therefore, the drug should be stopped as early as possible. Since such liver injuries are reversible to normal state, it is necessary to repeat liver function tests after stopping the medication. In some cases, even if the drug is discontinued, it may not immediately improve the liver condition and the liver injury may continue; therefore, careful follow-ups must be performed. It is very difficult to assess if the drug should be continued if there is a rise in hepatic enzymes in the liver function test during the course of the treatment. Further, if the suspected causative drug is important for the control of the underlying disease, the balance between the risk of progression of the underlying disease after drug withdrawal and the risk of exacerbation of liver damage due to the continued administration of potentially related drugs should be considered. According to the “stop rule” for new drugs developed by the US Food and Drug Administration (FDA) [42], the guidelines are based on AST, ALT, and TB, and the medication being administered should be immediately stopped when any of the following results are obtained: (1) ALT or AST > 8 \times ULN; (2) ALT or AST remains > 5 \times ULN over 2 weeks; (3) ALT or AST > 3 \times ULN & TB > 2 \times ULN or international normalized ratio (INR) > 1.5; (4) ALT or AST > 3 \times ULN with symptoms (e.g., fatigue, nausea and vomiting, right upper quadrant pain, fever, and rash) or eosinophilia. Therefore, it is acceptable to follow the FDA “stop rule” in clinical practice.

#### 2. Specific treatment

Although no specific therapies are available for DILI, NAC (IV infusion, 50–150 mg/kg/day) may be administered for at least 3 days in patients with early or sub-ALF [43-45]; it is not recommended for children with severe DILI as it can lead to ALF. Several studies have shown that steroids can prove effective; however, there have been some debates on the efficacy of corticosteroid in treating patients with DILI [46,47]. In the case of immunological or autoimmune hepatitis-like DILI, the administration of glucocorticoid may be considered.
3. Re-administration of suspected drugs
Although there is controversy regarding the unconditional re-administration of all suspected drugs that cause DILI, care should be taken because re-administration of immunoallergic reacting drugs may cause more serious liver damage than before.

4. Liver transplantation
Liver transplantation should be considered if the liver function deteriorates and is concomitant with coagulopathy and encephalopathy [48]. Survival is less than 20% if liver transplantation is not performed in drug-induced ALF caused by a hypersensitivity reaction. The recommendations of Kings’ College on indications for liver transplantation due to drug-induced liver failure as follows: In case of acetaminophen-induced liver failure, liver transplantation is required when the arterial blood pH is < 7.3, regardless of encephalopathy grade, or if grade III or IV encephalopathy and an INR > 6.5 and a serum creatinine > 3.4 mg/dL. Liver transplantation is required for liver failure caused by non-acetaminophen drugs as follows: patients with prothrombin time (PT) > 100 s (INR > 6.5) (with or without encephalopathy, regardless of grade) or who satisfy any 3 of the following criteria: (1) age < 10 or > 40 years of age; (2) etiology: non-A/non-B hepatitis, drug-induced; (3) duration of jaundice to hepatic encephalopathy > 7 days; (4) PT > 50 s (INR > 3.5); or (5) serum bilirubin level > 17 mg/dL ( > 300 μmol/dL) [49,50].

5. New treatments for drug-induced liver injury
Many studies have been actively pursued to develop therapeutic agents aimed at nuclear receptors in DILI [51,52]. The activation of constitutive androstane receptor (CAR) and pregnane X receptor (PXR) exacerbates hepatotoxicity by acetaminophen [53,54]. Thus, compounds that inhibit CAR and PXR may be beneficial.

Fig. 4. Risk factors contributing to hepatotoxicity of herbal remedies. There are many causative factors for herb-induced liver injury such as the misidentification of the plant, mislabeling of the final product, unstandardized dose, plant-specific toxic substances, various ingredients, denaturalization during inadequate storage, illegal drug incorporation, contamination of the plant by various chemicals, heavy metals, microorganisms, individual difference due to genetic or environmental factors, and herb-drug interactions.
for the treatment of hepatic damage induced by acetaminophen. Farnesoid X receptor (FXR) plays an important role in the regulation of bile acid synthesis and metabolism. Thus, FXR agonists such as obeticholic acid have been considered as promising targets for the treatment of cholestatic disorders involving drug-induced cholestasis.

Autophagy refers to the activity in which a cell obtains energy by dissolving its protein or removing unnecessary cell components when it becomes nutrient deficient. Recently, studies on autophagy have been actively conducted in various areas such as cancer, diabetes, infectious diseases, and Crohn’s disease. For DILI, a new therapeutic approach is being attempted to reduce the liver injury by controlling autophagy [55]. Acetaminophen overdose results in hepatic necrosis caused by mitochondrial damage. The activation of autophagy degrades the damaged cytoplasmic proteins, which allows cells to survive without cell necrosis. While liver injury is prevented by the administration of rapamycin (autophagy inducer), 3-methyladenine, or chloroquine (autophagy inhibitor), they have been shown to decrease liver injury. Further, it is expected that several new treatments, including autophagy induction, will be developed and applied to the treatment of DILI in clinical practice.

Drug-induced liver injury and the fourth industrial revolution

DILI has also been actively researched by applying various new technologies of the fourth industrial revolution. Recently, organ-on-a-chip (OOC) such as liver, lung, heart, nerve, and skin have been developed [56,57]. OOC is a technique that imitates the mechanical and physiological cellular responses as well as the functions and characteristics of the organs by culturing cells that constitute a living OOC on which electronic circuits are placed. The OOC is worth using as a model for drug development and toxicity assessment. A liver-on-a-chip can be used to evaluate the toxicity of a drug without animal testing [58]. In addition, it is reported that deep learning using artificial intelligence can predict the occurrence of DILI [59]. It is expected that research using various technologies of the fourth industrial revolution will help predict the side effects and drug–drug interactions in advance through “In-Silico,” a computer virtual test using biological big data [60,61].

Conclusion

DILI is a problem that can be encountered in clinical settings, and clinicians should therefore have appropriate knowledge and diagnosis and treatment skills. We hope that various biomarkers to accurately diagnose and predict the prognosis of DILI will be developed and used conveniently, and various new technologies of the fourth industrial revolution will be developed and applied to DILI.

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Conflicts of interest

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Maturity-onset diabetes of the young (MODY) is a clinically heterogeneous group of monogenic disorders characterized by β-cell dysfunction. MODY accounts for between 2% and 5% of all diabetes cases, and distinguishing it from type 1 or type 2 diabetes is a diagnostic challenge. Recently, MODY-causing mutations have been identified in 14 different genes. Sanger DNA sequencing is the gold standard for identifying the mutations in MODY-related genes, and may facilitate the diagnosis. Despite the lower frequency among diabetes mellitus cases, a correct genetic diagnosis of MODY is important for optimizing treatment strategies. There is a discrepancy in the disease-causing locus between the Asian and Caucasian patients with MODY. Furthermore, the prevalence of the disease in Asian populations remains to be studied. In this review, the current understanding of MODY is summarized and the Asian studies of MODY are discussed in detail.

Keywords: Diabetes mellitus; Genes; Genetic testing; Maturity-onset diabetes of the young

Introduction

Monogenic diabetes is caused by mutations in one of the genes that control insulin levels [1,2]. Forms of monogenic diabetes include neonatal diabetes, maternally inherited diabetes with deafness and genetic syndromes, such as Bardet-Biedl syndrome, and Wolfram syndrome; however, maturity-onset diabetes of the young (MODY) and neonatal diabetes are the most common. MODY was first described in 1974 by Tattersall [3] as a mild familial diabetes with dominant mode of inheritance. MODY is a clinically heterogeneous group of monogenic diabetes mellitus characterized by β-cell dysfunction. The diagnostic criteria reported in 2008 include onset before 25 years of age in at least one of the family members, β-cell dysfunction without autoantibodies, and family history of autosomal dominant diabetes for at least two generations [4]. In the 1990s, molecular methods for the diagnosis of MODY were introduced, after which the mutations associated with the disease were identified. To date, MODY-associated mutations have been reported in 14 different genes (Table 1) [5-10]. MODY is the most common type of monogenic diabetes and comprises between 2% to 5% of all diabetes cases in Europe [11,12]. Among these genes, mutations in HNF1A, GCK, HNF4A, and HNF1B are the underlying cause in more than 95% cases of MODY; the other mutations are rare in the Caucasian population [12-14]. There is a discrepancy in the disease-causing locus between the Caucasian and Asian patients with MODY. Moreover, the exact prevalence of the disease in the Asian population has not been reported. This review summarizes the current understanding of MODY and discusses the Asian studies of the disease.

MODY2 (GCK-MODY)

Glucokinase (GCK) is a major enzyme in glucose metabolism, which catalyzes the conversion of glucose to glucose-6 phosphate,
and thus, controls glucose-mediated insulin secretion. Until 2009, more than 600 mutations in GCK had been identified in over 1,400 families [15]. The inactivating heterozygous mutations in GCK elevate the glucose threshold for insulin secretion resulting in mild fasting hyperglycemia (5.6–8.0 mmol/L, glycosylated hemoglobin range of 5.6%–7.3%) [16]. Mutations in GCK are some of the most common causes of MODY, and affect 32% of the total number of patients with MODY in the United Kingdom [17]. Patients with GCK-MODY are usually asymptomatic; hence, the majority are diagnosed through routine examination, such as urine glucose screening at school or during pregnancy. Mutations in GCK were found in 40%–50% of incidental hyperglycemia cases in children; therefore, the prevalence of GCK-MODY is high in countries where the school glucose screening test is performed [18,19]. However, only 2.5% of 40 studies of MODY and early onset type 2 diabetes in Korea reported GCK mutations [20]. This implies that there might be a discrepancy between the Caucasian and Asian patients. The clinical manifestations of GCK-MODY may be mild and non-progressive as long-term complications rarely develop despite chronic mild hyperglycemia. Therefore, patients with this mutation usually do not require treatment, except during pregnancy [21].

**MODY3 (HNF1A-MODY)**

Hepatocyte nuclear factor 1a (HNF1A) is a transcription factor expressed in various organs, such as the pancreas, kidney, liver, and intestine. *HNF1A* knockout mice develop diabetes due to impaired glucose-induced insulin secretion [22,23]. Prevalence of this mutation is the highest in Europe, North America, and Asia [17,20,24]. Over 400 different *HNF1A* mutations have been identified in approximately 1,200 families; among these, a mutation in exon 4 of the gene (P291fsinsC) is the most frequently observed [25,26]. These mutations alter the expression of proteins related to glucose transport, such as glucose transporters, as well as that of key enzymes involved in mitochondrial glucose metabolism. In *HNF1A*-knockout mice, reduced β-cell proliferation and increased apoptosis leads to a progressive decline in β-cell function [27]. *HNF1A* mutations have high penetrance, with almost 63% of their carriers developing diabetes by the age of 25, and almost 96% by the age of 55 [28]. Since *HNF1A* is also expressed in tissues other than the pancreas, patients with *HNF1A*-MODY can display extra-pancreatic manifestations such as glycosuria, which can develop even before the onset of diabetes because of a low renal threshold for glucose [29]. Hyperglycemia induced by heterozygous *HNF1A* mutations might be deteriorating and progressive.
and the risk of developing long-term complications in HNF1A-MODY is similar to that in type 1 and type 2 diabetes [30]. Therefore, rigorous glucose control is needed in these patients.

Patients with HNF1A-MODY show marked sensitivity to the oral hypoglycemic agent sulfonylurea, which elicits a five-fold greater response than metformin although the two agents show similar efficacy in type 2 diabetes [31]. Consequently, many patients with HNF1A-MODY achieve better glycemic control with sulfonylurea than with insulin treatment [32,33]. Therefore, low-dose sulfonylurea should be considered the first-line treatment for HNF1A-MODY, although some patients might need additional insulin therapy as the diabetes progresses [34].

**MODY1 (HNF4A-MODY)**

HNF4A is a transcription factor primarily expressed in the liver and, to a lesser extent, in the kidney and pancreas. HNF4A regulates the transcription of genes involved in glucose transport and metabolism [35]. Mutations in the HNF4A gene are uncommon and account for only approximately 3%–5% of all MODY cases; more than 100 HNF4A mutations have been identified in 173 families [25,36]. Patients with heterozygous HNF4A mutations display progressive β-cell dysfunction similar to that observed in patients with HNF1A mutations. Fetal heterozygous HNF4A mutation results in diazoxide-responsive form of neonatal hyperinsulinemic hypoglycemia and subsequent macrosomia [31]. Therefore, close monitoring of the baby of an affected mother is recommended. The hyperinsulinemia usually resolves during infancy and the insulin production gradually decreases leading to the development of diabetes in adolescence [24]. Unlike HNF1A-MODY, HNF4A-MODY is not associated with glycosuria. Instead, low levels of apolipoproteins (apoAII, apoCIII, and apoB) can be a clue to diagnosing this subtype [37]. HNF4A-MODY is characterized by sensitivity to sulfonylureas similar to that of HNF1A-MODY; therefore, low-dose sulfonylurea is recommended as the first-line treatment [31].

**MODY5 (HNF1B-MODY)**

HNF1B is a transcription factor associated with early organogenesis of the pancreas, kidney, liver, lungs, gut, and genito-urinary tract [38]. Patients with HNF1B mutations develop abnormalities in all these organs; however, renal manifestations, such as renal cysts, renal dysplasia, renal tract malformations, and familial hypoplastic glomerulocystic kidney disease, are the most common [39,40]. The association of renal cysts and diabetes mellitus with mutations in the HNF1B gene is termed the renal cysts and diabetes syndrome. Renal dysfunction is usually developed by the age of 45, and approximately 50% of the patients progress to end-stage renal failure requiring renal replacement therapy without diabetic renal disease [41]. Therefore, carriers of HNF1B mutations should be monitored for the development of diabetes and non-diabetic nephropathy. Diabetes associated with MODY5 develops in adolescence or early adulthood and presents with hepatic insulin resistance before progressing to insulin-dependent status due to pancreatic hypoplasia. HNF1B mutations can reduce the birth weight by up to 900 g [42,43]. In contrast to patients with MODY3, those with MODY5 progress to insulin-dependent status and do not respond to sulfonylurea; therefore, they usually require early insulin therapy. Patients with HNF1B mutations manifest highly variable phenotypes, which might even differ between family members carrying the same mutation. Hence, patients with HNF1B-MODY should seek endocrinology, as well as nephrology, urology, and gynecology consultation.

**MODY4 (IPF1-MODY)**

Insulin promoter factor 1 (IPF1) is a transcription factor that regulates β-cell development and insulin expression in pancreatic islets, and has roles similar to those of the HNF family of transcription factors [44,45]. IPF1-MODY was first discovered in 1997 and is a very rare subtype of MODY [46]. Heterozygous mutation in the IPF1 gene causes β-cell dysfunction and MODY, while homozygous mutation in the IPF1 gene results in neonatal diabetes [47].

**MODY6 (NEUROD1-MODY)**

NEUROD1 encodes neurogenic differentiation 1, a basic helix-loop transcription factor involved in the development of endocrine cell lineage as well as neuronal development. Although heterozygous mutations in NEUROD1 result in MODY, homozygous mutations cause a novel syndrome of permanent neonatal diabetes and neurological abnormalities [48].

**MODY7 (KLF11-MODY)**

The Krüppel-like factor (KLF) 11 gene is located on chromosome 2 and encodes a zinc-finger transcription factor. Mutations in KLF11 cause β-cell dysfunction by modulating the expression of free radical scavengers. Two rare variants of KLF11 that impair its transcriptional activity (Ala347Ser and Thr220Met) were identified in families with early-onset type 2 diabetes [49].
MODY8 (CEL-MODY)

The CEL gene encodes the bile salt-stimulated lipase, a major component of the pancreatic juice that is secreted by the pancreas into the digestive tract. The enzyme aids in the digestion of cholesterol and lipid-soluble vitamins, ester hydrolysis, and absorption of dietary fat from the intestine. In 2006, a heterozygous mutation in the CEL gene was identified in two families [50]. Exocrine pancreatic dysfunction (defined by fecal elastase deficiency) and β-cell failure were found in a patient with single-base deletion in CEL. To date, heterozygous mutations in CEL have only been identified in three families [51].

MODY9 (PAX4-MODY)

PAX4 is a homeodomain transcription factor that plays a central role in β-cell development and function [52]. Two variants of PAX4 (R164W and IVS7-1G > A) were identified in two Thai probands [53].

MODY10 (INS-MODY)

Dominant misfolding mutations in the INS gene are a common cause of isolated permanent neonatal diabetes; however, the age at which the disease develops can vary [54]. These mutations cause a severe folding defect, unfolded protein response, and β-cell apoptosis.

MODY11 (BLK-MODY)

B-lymphocyte kinase (BLK) is a nonreceptor tyrosine-kinase from the Src family of proto-oncogenes. It is expressed in β-cells where it promotes insulin synthesis and secretion by up-regulating the transcription factors PDX1 and NKX6.1 [55]. These transcription factors enhance pancreatic β-cell mass. Decreased BLK activity reduces the insulin content and renders the β-cells less responsive to glucose, leading to decreased insulin secretion and, eventually, diabetes.

MODY12 (ABCC8-MODY)

The ABCC8 gene encodes the sulfonylurea receptor 1 (SUR1) subunit of the pancreatic β-cell ATP-sensitive potassium channel (K_ATP), which directly regulates insulin release. Recessive loss-of-function mutations in ABCC8 lead to the development of congenital hypoglycemic hyperinsulinism (CHI) [56], while dominantly inherited ABCC8 mutations may cause CHI with predisposition to insulin deficiency and diabetes later in life. Heterozygous activating mutations in ABCC8 cause MODY without a history of diabetes or hyperinsulinism in the neonatal period, and produce clinical manifestations similar to those of HNF1A/4A MODY [57]. Patients with mutations in ABCC8 respond to high-dose sulfonylurea therapy.

MODY13 (KCNJ11-MODY)

KCNJ11 encodes the Kir6.2 subunit of the hetero-octameric K_ATP channel, which is highly expressed in pancreatic β-cells. Homozygous or heterozygous mutations in this gene lead to the development of either transient or permanent neonatal diabetes within the first 6 months of life. Heterozygous KCNJ11 mutations were identified in 6 out of 96 families with early-onset type 2 diabetes [58]. Some of these carriers stopped the insulin therapy and switched to sulfonylurea.

MODY14 (APPL1-MODY)

APPL1 (adaptor protein, phosphotyrosine interaction, PH domain, and leucine zipper containing 1) is the most recently identified MODY-related gene (first reported in 2015). APPL1 is an anchor protein with multiple functional domains that interact with other proteins, including the key components of the insulin-signaling pathway. Two loss-of-function mutations in the APPL1 gene have been identified in 60 families through whole-exome sequencing [9].

Ways to avoid misdiagnosing patients with MODY

The diagnostic criteria for MODY are as follows: (1) presence of overt diabetes in at least three consecutive generations, with autosomal dominant mode of inheritance, (2) at least one family member diagnosed with diabetes before the age of 25, (3) absence of β-cell autoantibodies, and (4) relatively preserved endogenous insulin secretion with a serum C-peptide level of > 0.6 ng/mL. These diagnostic criteria can help discriminate MODY from type 1 and type 2 diabetes. Nevertheless, distinguishing MODY from type 1 or type 2 diabetes at presentation is often challenging [24,59,60].

Various algorithms have been developed to identify diabetic patients who should undergo genetic testing for MODY. Shields et al. [61] proposed a clinical prediction model to distinguish MODY from type 1 and type 2 diabetes. According to the model, patients with MODY have lower HbA1c levels than those with
type 1 diabetes. Further, compared to type 1 diabetics, patients with MODY tend to have an older age at diagnosis and higher probability of being female and having a parent with diabetes. Compared to type 2 diabetics, patients with MODY tend to have a lower body mass index, lower HbA1c level, younger age at diagnosis, higher probability of being female and having a parent with diabetes, and lower probability of prior treatment with oral hypoglycemic agents or insulin. Although this model calculates a standardized probability of being diagnosed with MODY, it is important to bear in mind that the clinical manifestations of MODY may vary.

Sanger DNA sequencing, which is the gold standard for identifying mutations in MODY-related genes, might improve the chances of a correct diagnosis. However, genetic testing for MODY is expensive and may only be offered in specialist centers. Therefore, considerable efforts have been made to identify non-genetic biomarkers to facilitate the differential diagnosis of MODY. Persistent postprandial C-peptide level, which is measured in a spot urine sample, can discriminate HNF1/4A-MODY from type 1 diabetes [62]. Moreover, compared to type 2 diabetics, patients with HNF1A-MODY tend to have a lower level of high-sensitive C-reactive protein [63]. A proposed diagnostic algorithm for the identification of diabetic patients who might benefit from MODY genetic testing is presented in Fig. 1.

**Conclusion**

The genetic etiology and pathophysiology of MODY have been widely researched. The biosynthesis and secretion of insulin from pancreatic beta cells are changed at various stages depending on the specific gene mutations (Fig. 2). In a recent study from Korea, 109 patients with clinically suspected MODY underwent targeted panel sequencing. The diagnosis was confirmed in 23 patients (21.1%) [64]. The diagnostic rate was similar to that in a large study on monogenic diabetes performed in the United Kingdom (27%) [14]. In the latter study, molecular genetic testing confirmed a diagnosis of GCK-MODY, i.e. the most common subtype of MODY, in 50% of the patients. This result was in agree-
ment with that of studies in the Caucasian population [65,66]. In contrast, in a China-based study, HNF1A-MODY and GCK-MODY comprised only 9% and 1% of the total tested cases, respectively [67]. These results were similar to those obtained in Japanese studies [68-70]. A possible explanation for these discrepancies is that a large proportion of the MODY cases in China have defects in unknown MODY genes [67]. The studies from Korea, Japan, and China suggest that East Asia has a high prevalence of a not yet identified form of diabetes, i.e., ‘MODY X’ [64,67-72]. Next generation sequencing is one of the most powerful tools to discover unknown genetic defects [71,73], and attempts to identify new causative gene variants in MODY using whole-exome sequencing have been undertaken in Korea [72].

MODY is estimated to be the cause of 2%–5% of diabetes cases in Europe [11,12]. Owing to the increase in molecular genetic testing, the frequency of its detection has increased worldwide. Correct molecular diagnosis can help to ensure that patients with MODY receive optimal treatment. Metabolic profiling can also be an important diagnostic tool in patients with MODY.

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**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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There has been a growing concern and subsequent interest surrounding numerous reproductive toxic agents found in various working and non-working environments. Meanwhile, there have been many efforts in medical fields such as toxicology and epidemiology applying experimental studies to elucidate reproductive toxic agents' characterization and health effects. However, there remains insufficient research data and inadequate evidence in humans. Adverse reproductive outcomes vary from transient, moderate health effects to severely detrimental consequences, such as permanent infertility or childhood cancer of one's offspring. Furthermore, upon exposure to toxic agents, the latent period before reproductive health effects are observed is relatively short compared to other occupational diseases (e.g., occupational cancer); instant action is required once exposure to reproductive toxic agents is detected. Therefore, it is very important for workers and healthcare professionals to know about the reproductive toxic agents they are likely to be exposed to. In this review, we discuss the general epidemiology of reproductive health in Korea, and the information regarding these reproductive toxic agents.

Keywords: Abortion; Hazardous substances; Occupational diseases; Reproductive health

Introduction

Reproductive toxic agents are generally defined as materials that may adversely affect human reproductive function, fertility, or fetal development and growth [1]. It includes chemical, physical, environmental, and emotional factors like shift work, overwork, or stress. Reproductive toxicity encompasses adverse reproductive health outcomes in both men and women caused by exposure to such agents. Changes in reproductive systems, fertility, and adverse pregnancy outcomes can be caused by reproductive toxicity [2]. There are well established data regarding chemicals hazardous to reproductive health, but there are still unknown latent hazards; especially for commercial chemical products that are considered as trade secrets. Moreover, there are fewer human epidemiological data than animal experimental data, which makes it more difficult to interpret their real-world health effects [3]. For these reasons, it is hard to assess how many risks are there in workplaces, how many workers are exposed to hazards, and which agents are concerned.

Knowing this, the observed low birth rate and fertility problems are of severe concern in Korea. In 2018, the total fertility rate (TFR) of Korea was 0.98, one of the world’s lowest [4]. Moreover, in 2014, approximately 208,000 patients were diagnosed with fertility related problems, rising to 229,000 in 2018 according to Korean National Health Insurance (NHI) data [5]. Among these figures, the proportion of men increased notably from 22.7% in 2014 to 34.0% in 2018. These data raise concerns about the various reproductive toxic agents that the working population can be exposed to in their work environments, concerning men as well as women. In other words, reproductive toxicity is a health
risk factor for all, and is a very damaging occupational health and safety issue, as it can cause problems for the next generation, in the form of fetal malformation and childhood cancers. However, current regulation regarding reproductive health is insufficient and unclear. Although the dangers are mentioned in the Material Safety Data Sheets available at the workplace, detailing whether the material is a reproductive toxicant (Fig. 1) [6], it is very difficult for the average worker to know the exact hazards and toxicological properties of the chemical. In addition, general physicians are equally unable to discern the full details of various reproductive toxicity agents unless they are related. In some cases, furthermore, the patient's occupational history is missed, and important information is sometimes overlooked. This review aims to (1) introduce the reproductive health-related epidemiology of Korea, (2) discuss several reproductive toxic agents that are widely recognized but as yet not evaluated, and (3) discuss cases of occupational disease caused by reproductive toxic agents in Korea.

**Epidemiological perspective of reproductive health in Korea**

Since 2012, the number of births and TFR in Korea has been declining to its lowest level each year. In 2012, the number of births was about 485,000 and TFR 1.30. In 2017, the number of births was 358,000 and TFR 1.05, falling to the lowest level in the world [7]. According to a 2018 Korean survey of 11,000 women between the ages of 15 and 49, there was an average of 2.2 pregnancies per woman. Among them 1.7 live births, 0.3 spontaneous abortions, and 0.2 artificial abortions, with negative pregnancy outcomes totaling 14.3% [7].

It is not easy to identify a clear causal relationship here, as factors affecting pregnancy and childbirth are numerous, taking into account such influences as age, smoking, drinking, general health, and socioeconomic status, as well as occupational environmental factors [1]. The incidence rate of adverse pregnancy outcomes, including miscarriage, vary from study to study, with reports of up to a 40% rate of miscarriage including unrecognized abortions [8].

According to the 2018 Korean Statistical Information Service, women’s working rate continues to increase to 52.9%, and the working population of women also continues to increase (Fig. 2) [9]. Accordingly, research on the work environment in relation to women’s reproductive health has also been paid due attention. Concerns have been raised about reproductive health disorders such as miscarriages, menstrual abnormalities, and infertility among women workers in some industries. A study based on NHI health insurance data analyzing about 430,000 pregnancies in 2013, showed working women's odds ratio (OR) for miscarriage is 1.26 (95% confidence interval [CI], 1.23–1.28), statistically higher than non-working women. In addition, this high OR for miscarriage was represented within several major industries in which many women workers were involved (1) business facilities management and business support services (OR, 1.47; 95% CI, 1.38–1.57); (2) manufacturing (OR, 1.35; 95% CI, 1.31–1.39); (3) human health and social work activities (OR, 1.33; 95% CI, 1.29–1.37); (4) wholesale and retail trade (OR, 1.29; 95% CI, 1.25–1.34); and (5) professional, scientific, and technical activities (OR, 1.29; 95% CI, 1.22–1.35) [10].

According to a report published by the Korea Occupational Safety and Health Agency in 2014, a survey of all manufacturing companies having five workers or more showed that 1,284 workplaces dealt with reproductive toxicity category 1A substances and employed 107,741 workers, those with 1B substances had 157,294 employees at 1,153 workplaces [11,12]. Reproductive toxicity category 2 substances were handled by 206,359 workers in 1,750 workplaces. Among them, 15,449 workers (14.3%), 19,150 workers (12.1%), and 17,682 workers (8.6%) were directly exposed (Table 1). By exposure factor, the total number of women workers exposed to chemical/physical factors was 33,828, which is 6.78% of the 499,194 of women workers in manufacturing. Among the physical factors, the number of women workers exposed to high temperatures was 7,025, 20.77% of the total number of women workers experiencing this exposure, 5,855 (6.42%) experienced cold temperatures, and 2,173 (6.42%) were exposed to ionizing radiation. The chemical factor of toluene exposure

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**Fig. 1.** The symbol for carcinogenicity, mutagenicity or reproductive toxicity based on globally harmonized system (GHS). Reprinted from Occupational Safety and Health Administration [6].

https://doi.org/10.12701/yujm.2019.00416
counted 4,920 women, accounting for 14.54% of the total number of women workers experiencing this exposure. Hexane (n-hexane) was 3,315 (9.8%), 1,900 for 2-ethoxy-ethanol (5.62%), 1,833 for N,N-dimethylacetamide (5.42%), 1,806 for carbon monoxide (5.34%), and 1,633 for lead (4.83%). In particular, the proportion of workers exposed to lead or carbon monoxide, which belong to reproductive toxicity 1A, was 20.3% of

16,833 total women workers exposed to chemical reproductive toxicity factors [12].

In the non-manufacturing workplace sample of the survey, the number of women workers at risk of exposure to reproductive toxic agents was 3,415; 2.43% of the 140,147 women workers in the sample survey. Ionizing radiation was experienced by 1,550 of the women (45.39%). Those exposed to cold, toluene, and lead numbered 1,431 (41.90%), 137 (4.01%), and 44 (1.29%), respectively [12].

The legal management and regulation on reproductive toxic agents in Korea consist of the Ministry of Employment and Labor’s Industrial Safety and Health Act and the Ministry of Environment’s Hazardous Chemical Substance Management Act. Article 39 of the Occupational Safety and Health Act notes that “The Minister of Employment and Labor shall classify and manage chemicals and physical factors that cause workers’ health hazards according to the classification standards prescribed by the Ordinance of Employment and Labor”. In addition, Appendix I of the “Standards for Classification and Labeling of Chemical Substances and Safety Data Sheets” is defined based on epidemiological data (Table 2) [11].

Although the details of the Labor Standards Act are partially revised as necessary, the ‘Regulations on Prohibited Substances

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**Table 1.** The numbers of workplaces and working populations using reproductive toxic chemicals, 2014

<table>
<thead>
<tr>
<th>Category</th>
<th>1A&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1B&lt;sup&gt;b&lt;/sup&gt;</th>
<th>2&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workplace</td>
<td>1,284</td>
<td>1,153</td>
<td>1,750</td>
</tr>
<tr>
<td>Total worker</td>
<td>107,741</td>
<td>157,294</td>
<td>206,359</td>
</tr>
<tr>
<td>Exposed worker (%)</td>
<td>15,449 (14.3)</td>
<td>19,150 (12.1)</td>
<td>17,682 (8.6)</td>
</tr>
<tr>
<td>Man</td>
<td>9,231</td>
<td>12,554</td>
<td>9,833</td>
</tr>
<tr>
<td>Woman</td>
<td>6,218</td>
<td>6,596</td>
<td>7,849</td>
</tr>
</tbody>
</table>

Modified from Korea Occupational Safety and Health Agency [11].

<sup>a</sup>It is known to have produced an adverse effect on reproductive ability or capacity or on development in humans, largely based on evidence from human studies.

<sup>b</sup>It is presumed to produce an adverse effect on reproductive ability or capacity or on development in humans, largely based on evidence from experimental animals.

<sup>c</sup>This category includes substances for which there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on reproductive ability or capacity or on development.

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**Fig. 2.** The population of working women and woman’s working rate of Korea from 2009 to 2018. Source from the Korean Statistical Information Service [9].
and Occupations, etc. for Pregnant Women,’ which is presented as an appendix in the Act, was revised in November 2001, and has not been revised since. Therefore, there is an immediate and ongoing need to diversify management methods for workers and update management and inventory of reproductive toxicity-related chemicals.

The United States’ National Institute of Occupational Safety and Health (NIOSH) publishes the NIOSH Pocket Guide to Chemical Hazards (NPG) to provide workers, employers, and health and safety professionals with information on hazardous chemicals handled at work. A total of 49 reproductive toxicity factors are mentioned in the NPG [13]. Meanwhile, the French National Institute of Research and Safety; Institut National de Recherche et de Sécurité (INRS) publishes “DEMETER,” a medical assessment of occupational chemicals on the INRS web page [14]. The goal of this document is to help occupational physicians assess the reproductive toxicity of chemicals encountered in the workplace. DEMETER consists of a factsheet prepared by a group of toxicologists led by the INRS Medical Research Department, which provides information on 179 chemicals as of July 2017. Of these, 61 are highlighted for their reproductive toxicity. As such, the difference between Korean and foreign standards needs to be continually improved by amending relevant laws in consideration of the domestic reality and situation. According to a study in Korea, bisphenol A has a large amount of domestic consumption and distribution which is not yet regulated, calling for instant amendment of the relevant Act [15].

Reproductive toxic agents in females

There are six components for normal gestation and reproduction: (1) fertility, (2) conception, (3) implantation and preclinical gestation, (4) clinical pregnancy and fetal development, (5) birth, and (6) postnatal development. Fertility factors include the neuro-endocrine gonadal axis, oocyte development and ovulation, and anatomical integrity for passage of sperm and eggs [16]. Adverse effects on one or more of these three factors may act as a reproductive toxicity factor. As a result, various effects can be caused such as decreased fertility, infertility, spontaneous abortion, fetal growth retardation, premature birth, and birth defects.

General risk factors for miscarriage are a maternal age of over 35 years of age, previous history of miscarriage, gravida, smoking, drinking, and drug use. In addition to these, miscarriage can be induced by exposure to teratogens, mutagens or infections, and anatomical abnormalities of the maternal uterus. Therefore, those factors should be considered simultaneously when evaluating occupational and environmental reproductive hazards [17,18].

### Table 2. Reproductive toxic chemicals in the Occupational Safety and Health Act of Korea

<table>
<thead>
<tr>
<th>Category</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Lead and inorganic compounds, as Pb</td>
</tr>
<tr>
<td></td>
<td>2-Bromopropane</td>
</tr>
<tr>
<td></td>
<td>Lead arsenate, as Pb(AsO4)2</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td></td>
<td>Lead chromate as Cr</td>
</tr>
<tr>
<td></td>
<td>Lead chromate as Ni</td>
</tr>
<tr>
<td>1B</td>
<td>Nickel carbonyl, as Ni</td>
</tr>
<tr>
<td></td>
<td>Nitrobenzene</td>
</tr>
<tr>
<td></td>
<td>N,N-Dimethyl acetamide</td>
</tr>
<tr>
<td></td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td></td>
<td>Di-n-butyl phthalate</td>
</tr>
<tr>
<td></td>
<td>2-Methoxyethanol</td>
</tr>
<tr>
<td></td>
<td>Benomyl</td>
</tr>
<tr>
<td></td>
<td>Benzo(a)pyrene</td>
</tr>
<tr>
<td></td>
<td>Borates tetrasodium salts (anhydrous)</td>
</tr>
<tr>
<td></td>
<td>Borates tetrasodium salts (pentahydrate)</td>
</tr>
<tr>
<td></td>
<td>Borates tetrasodium salts (decahydrate)</td>
</tr>
<tr>
<td></td>
<td>1-bromopropane</td>
</tr>
<tr>
<td></td>
<td>Boron oxide</td>
</tr>
<tr>
<td></td>
<td>Elemental and inorganic forms of mercury (all forms except aryl and alkyl compounds)</td>
</tr>
<tr>
<td></td>
<td>2-Ethoxyethanol</td>
</tr>
<tr>
<td></td>
<td>2-Ethoxycarbonyl acetate</td>
</tr>
<tr>
<td></td>
<td>Ethylene glycol methyl ether acetate</td>
</tr>
<tr>
<td></td>
<td>2,3-Epoxy-1-propanol</td>
</tr>
<tr>
<td></td>
<td>Vanadium pentoxide (respirable fraction or fume; inhalable fraction)</td>
</tr>
<tr>
<td></td>
<td>1,2,3-Trichloropropane</td>
</tr>
<tr>
<td></td>
<td>Formamide</td>
</tr>
<tr>
<td>2</td>
<td>n-Hexane</td>
</tr>
<tr>
<td></td>
<td>Nitrotoluene(o-,m-,p-isomers)</td>
</tr>
<tr>
<td></td>
<td>Dinitrotoluene</td>
</tr>
<tr>
<td></td>
<td>Methyl isocyanate</td>
</tr>
<tr>
<td></td>
<td>Cyclohexylamine</td>
</tr>
<tr>
<td></td>
<td>3-Amino-1,2,4-triazole (or Amitrole)</td>
</tr>
<tr>
<td></td>
<td>Acrylamide (inhaled fraction and vapor)</td>
</tr>
<tr>
<td></td>
<td>Allyl glycidyl ether</td>
</tr>
<tr>
<td></td>
<td>Carbon disulfide</td>
</tr>
<tr>
<td></td>
<td>Cadmium and compounds, as Cd (respirable fraction)</td>
</tr>
<tr>
<td></td>
<td>Chloroform</td>
</tr>
<tr>
<td></td>
<td>Toluene</td>
</tr>
<tr>
<td></td>
<td>Phenylylethylamine</td>
</tr>
<tr>
<td></td>
<td>Piperazine dihydrochloride</td>
</tr>
<tr>
<td></td>
<td>2-Hexanone</td>
</tr>
</tbody>
</table>

Effects on or via lactation

decrease in fertility in women is associated with genetic abnormalities, endocrine abnormalities, anatomical abnormalities, reproductive toxicity agents, and maternal age. Several epidemiological studies have reported nitrous oxide, formaldehyde, toluene, 2-bromopropane, and nighttime work as factors that reduce fertility in women [19-23].

Among them, there is relatively strong evidence of reproductive toxicity in ionizing radiation, mercury, lead, polychlorinated biphenyls (PCBs), and anesthetic gases. Factors known to cause spontaneous abortion include antineoplastic agents, anesthetic gases, and ethylene oxide, all of which are likely to be encountered by healthcare workers [24-26]. Workers in many industrial fields are working night shifts, including healthcare workers. Night shift work is also known as a major cause of spontaneous abortion, and the link with night shift work is supported by many epidemiological studies. Therefore, night shift work for pregnant women should be carried out carefully, taking into account the health status of women workers and workplace conditions [23,27].

Many studies have mentioned the relationship between the use of organic solvents and rates of spontaneous abortion. Since the 1980s, laboratory workers have been recognized to have an increased risk of adverse pregnancy outcomes, and organic solvents such as perchloroethylene (PCE), methylene chloride, toluene xylene, and glycol ether, turn out to have strong causation. Women workers working in dry cleaning and pharmaceutical companies are shown to be exposed to similar situations [28]. In addition, among the women workers in computer chip and semiconductor production jobs, there was more of a tendency to experience miscarriage in the workers who handled ethylene glycol ether [29]. Many epidemiological studies have suggested a strong correlation between spontaneous abortion and PCEs. Also, reports of increased risk of spontaneous abortion in dry-cleaning workers and PCE poisoning from rice-oil contamination in Japan and Taiwan are representative cases of reproductive toxic hazards [30,31].

Furthermore, studies on physical activity, heavy lifting [32], and subjective psychological stress [33] have been reported in clinical guidelines as reproductive toxic agents. Physical stress, such as heavy lifting, prolonged standing, and repeated bending of the waist may also act as a detrimental factor, mainly associated with preterm delivery, low birth weight, and spontaneous abortion. For this reason, pregnant women in their first trimester are recommended against the above operations in Korea and the United States. Reproductive toxic agents with epidemiological evidence and their toxic outcomes are noted in Table 3 [34]. Some of the mechanisms of each reproductive toxicity factor is known, but most are unknown. Ethylene glycol ethers are known to cause reproductive toxicity by breaking the gap junctions of cells [28,35]. Some substances, such as cadmium, act as an asphyxiant or placental toxin [36]. Lead and organic mercury’s toxic effects directly affect the fetus [37–39]. More research in this area is needed because understanding the mechanisms is essential to

<table>
<thead>
<tr>
<th>Type of exposure</th>
<th>Observed effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spontaneous abortion Birth defect</td>
</tr>
<tr>
<td>Anesthetic gases</td>
<td>X X</td>
</tr>
<tr>
<td>Antineoplastic drugs</td>
<td>X X</td>
</tr>
<tr>
<td>Arsenic</td>
<td>X X</td>
</tr>
<tr>
<td>Cadmium</td>
<td>X X</td>
</tr>
<tr>
<td>Carbon disulfide</td>
<td>X X</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>X X</td>
</tr>
<tr>
<td>Dichlorodiphenyltrichloroethane</td>
<td>X X</td>
</tr>
<tr>
<td>Electromagnetic field</td>
<td>X X</td>
</tr>
<tr>
<td>Ethylene glycol ether</td>
<td>X</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>X</td>
</tr>
<tr>
<td>Lead</td>
<td>X</td>
</tr>
<tr>
<td>Mercury</td>
<td>X X</td>
</tr>
<tr>
<td>Pesticides</td>
<td>X X</td>
</tr>
<tr>
<td>Radiation, ionizing</td>
<td>X X</td>
</tr>
<tr>
<td>Solvents, organic</td>
<td>X X</td>
</tr>
<tr>
<td>Tobacco smoke</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 3. Female reproductive hazards

Modified from LaDou and Harrison [34] with permission of McGraw-Hill.

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prevent negative health effects from these reproductive toxicity agents.

**Reproductive toxic agents in males**

The mechanism by which reproductive toxins produce their effect is very complex, but usually occurs during absorption, distribution, metabolism, excretion, and repair. In other words, the toxic factor enters the body and disrupts the material transfer, energy transfer, and information transfer between cells; preventing cells, organs, and systems from functioning normally. In fact, most of the toxins go through this process, where gonads, hypothalamus, testis, and epididymis are the target organs when reproductive toxicity factors affect men\(^{[40,41]}\). These effects result in diminished spermatogenesis in the testicles or, more seriously, apoptosis of germ cells.

Three systems are required for normal male fecundity: (1) the hypothalamic-pituitary-gonadal (HPG) endocrine axis, (2) spermatogenesis of the testes, (3) the accessory gland and transport system of the genitalia\(^{[42]}\). As with women, factors affecting any of these three factors can act as reproductive toxicity factors, with HPG endocrine axis or spermatogenesis being the primary target. Adverse health effects of reproductive toxicity that may occur in men include decreased libido, erectile dysfunction, and sperm-related problems (e.g., oligospermia, azoospermia, teratospermia, and asthenospermia)\(^{[43]}\). When evaluating reproductive toxic agents in men, their age, medical history, medication, and smoking history should be considered. Consideration should also be given to environmental factors that they may be incidentally exposed to (e.g., solvents, pesticides, heat, ionizing radiation, etc.). Most reproductive toxic agents in women can also cause reproductive toxicity in men, and agents with relatively strong epidemiological evidence include 1,2-dibromo-3-chloropropane (DBCP), ionizing radiation, and lead (Table 4)\(^{[44]}\).

DBCP caused the first known case of male reproductive toxicity due to exposure in the working environment. It has been known to cause reproductive toxicity and developmental disorders in animals, causing oligospermia and testicular atrophy. Male workers exposed to DBCP during the chemical manufacturing process similarly showed testicular toxicity in proportion to the exposure dose\(^{[45,46]}\). Workers exposed to high doses of DBCP had damage to spermatogonia and irreversible azoospermia\(^{[47]}\).

Occupational and environmental exposure to lead and its adverse health effects have been studied for a long time, and as such, the epidemiological evidence has been well established. The risk of reproductive toxicity from lead has become known, with case

<table>
<thead>
<tr>
<th>Table 4. Male reproductive hazards(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of exposure</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Lead</td>
</tr>
<tr>
<td>Dibromochloropropane</td>
</tr>
<tr>
<td>Carbaryl (sevin)</td>
</tr>
<tr>
<td>Toluenediamine and dinitrotoluene</td>
</tr>
<tr>
<td>Ethylene dibromide</td>
</tr>
<tr>
<td>Plastic production (styrene and acetone)</td>
</tr>
<tr>
<td>Ethylene glycol monoethyl ether</td>
</tr>
<tr>
<td>Welding</td>
</tr>
<tr>
<td>Perchloroethylene</td>
</tr>
<tr>
<td>Mercury vapor</td>
</tr>
<tr>
<td>Heat</td>
</tr>
<tr>
<td>Military radar</td>
</tr>
<tr>
<td>Kepone(^b)</td>
</tr>
<tr>
<td>Bromine vapor(^b)</td>
</tr>
<tr>
<td>Radiation(^c) (chemobyl)</td>
</tr>
<tr>
<td>Carbon disulfide</td>
</tr>
<tr>
<td>2,4-Dichlorophenoxyacetic acid</td>
</tr>
</tbody>
</table>

Modified from The National Institute for Occupational Safety and Health\(^{[44]}\).

\(^a\)Studies to date show that some men experience the adverse health effects listed here from workplace exposures. However, these effects may not occur in every worker. The amount of time a worker is exposed, the amount of hazard to which he is exposed, and other personal factors may all determine whether an individual is affected.

\(^b\)Workers were exposed to high levels as a result of a workplace accident.

https://doi.org/10.12701/yujm.2019.00416
reports of decreased fertility after inhalation of lead fuel, followed by case reports of sperm abnormalities in lead-exposed workers [48]. Lead is also known to be a risk factor for prostate cancer, along with cadmium, requiring careful protection and caution from male workers [49]. The toxicity of 2-Bromopropane is known to be directly affects spermatogonia. In addition, PCBs, dioxins, and pesticides are known to act as endocrine disruptors in men, causing reproductive toxicity [50]. A characteristic case of oligospermia was caused by endocrine disruptors in male workers exposed to kepone at a pesticide factory in the USA [51].

Cases of adverse reproductive outcomes caused by occupational exposure

1. Adverse reproductive health outcomes among workers exposed to 2-bromopropano [22,52]

In 1996, an electronics company reported a group of workers’ amenorrhea symptoms when a new solvent, Solvent 5200, was introduced as a replacement for Freon. Sixteen of the 25 women workers complained of amenorrhea, and ten of the 16 women also had hot flash symptoms. None had experienced any previous health problems before the wash solution was introduced. Follicle-stimulating hormone and luteinizing hormone levels were elevated in these women. In eight men workers, two had azoospermia and four had oligospermia or a decreased sperm count. They were all workers in the tactile switch assembly process and the new solvent’s contents were shown to contain 97.4% 2-bromopropane. This case provides an epidemiological evidence for toxicity of 2-bromopropane, which induces germ-cell failure and bone marrow suppression.

2. Spontaneous abortions and congenital heart defects in Jeju Medical Center nurses

From 2009 to 2010, in the Jeju Medical Center, nine out of 27 pregnancies (33.3%) terminated with miscarriage, and congenital heart defects occurred in four out of 18 births [53]. It is already known that abortions are higher than the general population among healthcare workers, but in this case, the abortions occurred over a short period of time, and the congenital heart defects observed made the cases a subject for investigation. Investigations have not confirmed the definitive epidemiological cause for the miscarriages and abnormalities, but may have been due to an excessive workload, night work, stresses including job instability, and drug grinding operations (including FDA X grades) during pregnancy. Through this case, the widely known poor reproductive health situation of health workers is demonstrated, and it remains the case that legal interpretation is needed to determine whether compensation for occupational diseases covers not only workers but also maternally-dependent fetuses. Although reports of heart disease caused by occupational exposure of the fetus’s parents mainly refer to organic solvents [54], there are no related reports for causing congenital heart defects in children born to healthcare workers, which indeed calls for further research.

3. Azoospermia in a non-destructive test worker

A case of azoospermia was reported in a male worker who performed a non-destructive test (NDT) to inspect a pipe for cracks with X-ray equipment [55]. The 39-year-old male worker had carried out NDTs for about eight years and had no children after marriage, diagnosed with azoospermia. According to the thermoluminescent dosimeter used by the radiation worker, the worker was found to have experienced cumulative doses below the limit dose, but was suspected to have been exposed to far more radiation. Since he rarely wore the device due to fear of being excluded from work if the dose was exceeded, the cumulative dose could not be confirmed. Instead, the cumulative dose was estimated to be 1.926 Gy due to the level of inducer of azoospermia by fluorescence by in situ hybridization translocation assay. Indeed, a case of azoospermia caused by ionizing radiation, a reproductive toxicity factor, is the first case in Korea to be compensated as an occupational disease.

Conclusion

Since most occupational diseases do not differ in symptoms and disease trajectory from non-occupational diseases, history taking, including detailed occupational history, job, and work environment, is very important for patients in clinical practice. In addition to the above case reports, there were more diseases caused by unknown reproductive toxicity factors that the patient or physician could not recognize. There are many factors to be considered and asked along with the individual’s past medical history and underlying disease, but sometimes, these are easily overlooked in actual clinical practice [56,57]. If a patient experiences fertility problems, or is planning to conceive, those questions are essential: “What do you do for a living (including present and in the past)?” and “What materials do you handle or are you exposed to in your working environment?” In addition, questions should include the patient’s work schedule, whether they wear protective equipment, and the risk factors of the workplace where workers are particularly concerned.

At present, the framework of related laws is relatively well established in Korea, but there is still a need to improve the system by reflecting the ever-changing ideas of evidence-based medicine.
Beyond simply minimizing and blocking the exposure of reproductive toxicity factors, customized precautions for vulnerable groups are needed. For example, it is well known that the first trimester, a critical period of organogenesis during a woman’s pregnancy, is a particularly important and vulnerable period, and extra maternity protection for women workers during this time will be needed. Many women workers benefit from the maternity protection time system introduced in 2012 and the restriction on night work for pregnant women, but it is also true that for some occupations, workers cannot easily utilize this system. There is also an urgent need to care for workers who are trying to, or are likely to get pregnant, or those who are visiting a fertility clinic. These precautions will mainly be for women workers but should include measures for men.

Acknowledgments

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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18. Weiss JL, Malone FD, Vidaver J, Ball RH, Nyberg DA, Com-


Nasal tip plasty using three-dimensional printed polycaprolactone (Smart Ball®)

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²Bora Plastic and Reconstructive Surgery Clinic, Ansan, Korea

Background: Rhinoplasty is one of the most commonly performed cosmetic surgery procedures. Most Asians desire elevation of their relatively flat nasal dorsum and tip to make them appear more prominent. This study introduces a simple method of nasal tip plasty using three-dimensional (3D)-printed polycaprolactone (PCL) (Smart Ball®), which provides the required length and volume for this purpose and enables the creation of a nasal tip of the desired shape in a safe and simple manner.

Methods: Between September 2014 and May 2017, 22 patients participated in a survey to assess postoperative satisfaction levels. Additionally, three plastic surgeons compared patients’ pre- and 1-year postoperative photographs to evaluate the results. All patients underwent 2- to 4-year postoperative follow-up.

Results: Levels of subjective satisfaction among patients were 3.59, 3.50, 3.82, 3.73, 3.55, and 3.82 for each of the 6 categories evaluated, with a mean of 3.67/4 points, indicating high satisfaction levels. The mean plastic surgeon-reported score for the 22 patients was 4.47/5 points, which also indicates highly successful outcomes. Postoperative nasal tip rotation and tip projection were ideal in most patients.

Conclusion: Our novel method using 3D-printed PCL (Smart Ball®) provides the optimal length and volume required for nasal tip plasty and enables the creation of a nasal tip of the desired shape, in a safe and simple manner. An advantage of our method is that it retains the original nasal structure in contrast to structural changes observed with the use of conventional methods.

Keywords: Bioprinting; Plastic surgery; Polycaprolactone; Rhinoplasty

Introduction

Rhinoplasty is one of the most common plastic surgery procedures performed globally; however, the methods that are applicable to or successful in White patients may be unsatisfactory among Asians. This is on account of the differences between Asians and Caucasians with regard to their expectations of surgical outcomes and the distinctive nasal structures of these races, which require different approaches to rhinoplasty [1].

Modern nasal plastic surgery methods used in Asians have evolved with the help of advanced concepts and techniques introduced in the West, owing to greater academic exchanges between the East and the West and better access to articles published in international journals (Fig. 1).

Correction of a deviated nose and unaesthetic nasal shapes requires the application of methods developed by Western medicine; however, performing elaborate surgical procedures is challenging secondary to the anatomical differences between Asian and Cau-
Polycaprolactone (PCL) is a synthetic biodegradable aliphatic polyester that undergoes hydrolytic degradation in humans. The end products of PCL degradation do not include harmful elements, such as boron or chlorine. Therefore, PCL is approved by the United States Food and Drug Administration for use in humans owing to its high biocompatibility and safety [2].

Rhinoplasty is usually performed in patients with a deviated nasal septum, a wide lobule with columellar retraction, and deficient nasal tip projection (NTP). In this study, we discuss the successful outcomes of a novel rhinoplasty technique using three-dimensional (3D)-printed PCL (Smart Ball®), which increases the length and volume of the nasal tip and enables the creation of a nasal tip of the desired shape, in a safe and simple manner.

Materials and methods

1. Ethics statement
This study was approved by the Institutional Review Board of Pusan National University Hospital (IRB No. K-2019-32819369). All patients provided written informed consent for the use and publication of their photographs.

2. Patients
This study included 22 patients who underwent nasal tip plasty with 3D-printed PCL between September 2014 and May 2017. Patients who had previously undergone invasive nasal plastic surgery were excluded.

Postoperative results were evaluated based on the following data: (1) a postoperative patient satisfaction survey, (2) objective evaluation of plastic surgeon-reported scores obtained 1 year postoperatively, and (3) measurement of the degree of nasal tip rotation and tip projection.

1) Patient survey as a measure of subjective levels of satisfaction
The Rhinoplasty Outcome Evaluation questionnaire (Fig. 2) was distributed to all patients included in the study [3]. Patients responded to 6 questions, and each question was answered on a scale from 0 (lowest satisfaction) to 4 (high satisfaction).

2) Evaluation by plastic surgeons
Surgical outcomes were evaluated by 3 board-certified plastic surgeons who compared patients’ pre- and 1-year postoperative photographs. Outcomes were expressed as a score rated on a scale of 1 to 5 as follows: highly successful (5 points), moderately successful (4 points), successful (3 points), somewhat successful (2 points), and unsuccessful (1 point).

3) Measurement of the degree of nasal tip rotation and tip projection
Pre- and postoperative photographs obtained in 22 patients were analyzed with regard to the nasolabial angle, columellar lobular angle, and NTP. The nasolabial angle is the angle between a line drawn through the anterior and posterior ends of the nostril and the vertical facial plane (Fig. 3A) [4]. The columellar-lobular angle is formed at the junction of the columella and the infratip lobule and represents the junction of the middle and medial crura (Fig. 3B). Tip projection is defined as the distance from the alar...
Rhinoplasty outcomes evaluation (ROE)

This questionnaire is designed to assist your surgeon in determining the best patient outcomes following rhinoplasty surgery. Your comments are confidential and may be used to refine surgical procedures for future patients. Please circle the number that best characterizes your current opinion regarding the following questions:

1. How well do you like the appearance of your nose?
   - Not at all: 0
   - Somewhat: 1
   - Moderately: 2
   - Very much: 3
   - Completely: 4

2. How well are you able to breathe through your nose?
   - Not at all: 0
   - Somewhat: 1
   - Moderately: 2
   - Very much: 3
   - Completely: 4

3. How much do you feel your friends and loved ones like your nose?
   - Not at all: 0
   - Somewhat: 1
   - Moderately: 2
   - Very much: 3
   - Completely: 4

4. Do you think your current nasal appearance limits you social or professional activities?
   - Always: 0
   - Usually: 1
   - Sometimes: 2
   - Rarely: 3
   - Never: 4

5. How confident are you that your nasal appearance is the best that it can be?
   - Not at all: 0
   - Somewhat: 1
   - Moderately: 2
   - Very much: 3
   - Completely: 4

6. Would you like to surgically alter the appearance or function of your nose?
   - Definitely: 0
   - Most likely: 1
   - Possibly: 2
   - Probably not: 3
   - No: 4

**Fig. 2.** The Rhinoplasty Outcomes Evaluation survey administered to patients.

**Fig. 3.** Measurement of the degree of nasal tip rotation and tip projection. (A) Nasolabial angle. (B) Columellar-lobular angle. (C) Tip projection.
3. Surgical procedure

Surgical draping of the facial area was performed using the standard method followed in clinical practice. Subsequently, we marked the area where we planned to insert the 3D-printed PCL (Smart Ball®) (Fig. 4). It is important to remember that in addition to achieving a sharp nasal tip, the tip should be in the correct position, because following this procedure, the nose may appear slightly longer or shorter.

All procedures were performed under local anesthesia. After the creation of an infra-cartilaginous incision (Fig. 5), curved or straight Metzenbaum scissors were used for dissection. If dissection is performed too close to the skin, the implant or the thick cartilage remains in continuous contact with the thin skin, thereby affecting the blood circulation and causing skin discoloration and/or thinning, which may complicate the surgery. Therefore, careful dissection is important to avoid close contact between the implant and the skin.

Careful dissection of skin is warranted to prevent injury to the alar cartilage. Dissection of the perichondrium from cartilage is not required. The alar cartilage is smaller and thinner in Asians than in Caucasians; therefore, injury to this structure is more likely to cause delayed nasal deformity. We trimmed the Smart Ball® to the appropriate size, threaded it through the bottom of the Smart Ball® and fixed the implant. The Smart Ball® is relatively soft and easy to manipulate with surgical instruments. Therefore, it is recommended that the size of the Smart Ball® be adjusted depending on the shape of the patient’s nasal tip and cartilage size (Fig. 6).

When preparing the Smart Ball® before insertion, its front side should be wrapped with conchal cartilage or AlloDerm with sutures if necessary. After fixing the Smart Ball® onto the alar cartilage, the upper layer of skin is temporarily closed to confirm the nasal tip shape and is subsequently reopened to check correct positioning (whether the Smart Ball® is tilted toward any particular side) and whether the suture ends are protruding through the incision (Fig. 7).

**Fig. 4.** Preoperative markings in the area of implant insertion. Three-quarter view.

**Fig. 5.** Photograph shows an infra-cartilaginous incision.

**Fig. 6.** (A) Measurement of the size of Smart Ball® after trimming it to the appropriate size. (B) Fixation of the Smart Ball® implant using a suture and cutting the remaining suture before insertion.
The incision may be sutured with the same material that is used for conventional augmentation rhinoplasty, and absorbable or nonabsorbable sutures are acceptable. This technique is associated with minimal postoperative edema; therefore, application of a light dressing over 3 days postoperatively is sufficient.

**Results**

Of the 22 patients included in the study, 6 were men and 16 were women. All patients underwent 2- to 4-year postoperative follow-up (mean 36 months).

1. **Patient survey as a measure of subjective levels of satisfaction**

Surveys performed in the 22 patients who underwent this procedure indicated excellent postoperative satisfaction, with a mean score of 3.67 (Table 1).

2. **Evaluation by plastic surgeons**

Comparative evaluation of patients’ pre- and postoperative photographs performed by 3 plastic surgeons indicated successful outcomes in all 22 patients included in the study, with a mean score of 4.48 (Table 2).

3. **Measurement of the degree of nasal tip rotation and tip projection**

Pre- and postoperative photographs obtained in 22 patients were analyzed with regard to measurements of the nasolabial angle, columellar lobular angle, and tip projection (Table 3).

Notably, 95°–100° and 45° are considered ideal measurements for the nasolabial and columellar lobular angles, respectively. Tip projection is considered normal if 50%–60% of the nasal tip lies anterior to the vertical line adjacent to the most prominently projecting portion of the upper lip. Postoperative values were close to normal values in most patients. Slight cephalic rotation of the nasal tip was associated with high satisfaction levels, particularly in women.

1) **Case 1**

A 42-year-old woman underwent nasal tip plasty with 3D-printed PCL (Smart Ball®) for correction of ptosis of the nasal tip. We observed high levels of patient satisfaction and successful functional outcomes without any complications.

2) **Case 2**

A 27-year-old woman underwent nasal tip plasty with 3D-printed

![Fig. 7. Photographs obtained immediately after insertion of the Smart Ball® implant. Three-quarter view.](https://doi.org/10.12701/yujm.2019.00290)

### Table 1. Patient satisfaction scores

<table>
<thead>
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<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (mean ± SD)</td>
<td>3.59 ± 0.73</td>
<td>3.50 ± 0.60</td>
<td>3.82 ± 0.50</td>
<td>3.73 ± 0.55</td>
<td>3.55 ± 0.51</td>
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<tr>
<td>Total average</td>
<td>3.67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation.

### Table 2. Plastic surgeons’ scores for the outcomes of surgery

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<tr>
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<tr>
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</tr>
<tr>
<td>21</td>
<td>4.67</td>
</tr>
<tr>
<td>22</td>
<td>4.67</td>
</tr>
</tbody>
</table>

Total average (mean ± SD) 4.49 ± 0.41

SD, standard deviation.
Table 3. The preoperative and postoperative measurements of patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Nasolabial angle (°)</th>
<th>Columellar-lobular angle (°)</th>
<th>Tip projection (%)</th>
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<tr>
<td></td>
<td>PreOP</td>
<td>PostOP</td>
<td>PreOP</td>
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<tr>
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<tr>
<td>22</td>
<td>88.00</td>
<td>92.00</td>
<td>45.00</td>
</tr>
</tbody>
</table>

Total average (mean ± SD) 84.03 ± 7.12 90.75 ± 6.30 40.84 ± 3.41 43.88 ± 2.52 39.10 ± 9.42 47.61 ± 8.10

OP, operation; SD, standard deviation.

PCL (Smart Ball®) for a deviated nose and tip ptosis. She complained of nasal tip pinching on the 3rd postoperative day, which resolved 1 month postoperatively, and she reported no other complaints. No complications such as infection or warping occurred postoperatively, and the patient was satisfied with the cosmetic outcome (Fig. 8).

Discussion

Adjusting the nasal tip is the most challenging task during nasal plastic surgery, because the shape of the tip significantly varies among individuals. Therefore, it is difficult to contour the nasal tip to ensure an aesthetically attractive appearance and perform a procedure that suits the needs of each patient. Creation of an aesthetically attractive nasal tip requires accurate measurements to evaluate the existing nasal contour to determine the optimal procedure and materials for the purpose.

Structural changes in the nasal contour and incision and suturing of these tissues commonly require the open approach, involving a columellar incision. This method is associated with longer operation and incision healing times and/or permanent scars, as well as prolonged edema of the nasal tip. Manipulation of a wider area predisposes to structural or functional adverse effects. In contrast, the closed approach is not associated with any visible scar formation. Additionally, because a smaller area is dissected, the operation time is shorter and patients develop lesser edema.

The 3D-printed PCL is a ball-shaped prosthesis that serves as a biological scaffold that allows the growth of tissues within the tiny holes of the scaffold without interfering with blood circulation and therefore enhances the volume of the nasal tip [3,5]. Complete absorption of PCL occurs in approximately 36 months; however, no study has reported long-term follow-up of > 2 years. Our study is important because our patients underwent long-term follow-up over at least 2 years (mean 36 months) to evaluate the stability of NTP even after PCL absorption.

A limitation of this technique is that it warrants consistent and long-term postoperative follow-up over the course of 4–5 years, because the shape of the PCL-based implant and its orientation with respect to the surrounding cartilage and soft tissues can be altered following absorption of PCL and replacement by autolo-

https://doi.org/10.12701/yujm.2019.00290
Large-scale studies are warranted in future to confirm the generalizability of this technique. Research in this field is ongoing to obtain more data.

The use of a foreign-body artificial implant for nasal tip contouring increases the risk of complications during long-term follow-up. Following implant fixation, the nasal tip is subjected to high pressure, and this is the point where most complications occur in Asians undergoing rhinoplasty. Complications such as thinning of skin and soft tissue, erythema, or inflammation did not occur in any patient in our study.

Previous studies have reported that prostheses made of PCL are structurally complete and can withstand significant dynamic stress [6]. Studies that have reported several-year follow-up in patients receiving PCL prostheses have shown no differences between these patients and those who underwent autologous chondrocyte implantation. Moreover, it has been proved that the me-

Fig. 8. Representative case of a patient (case 1) show an excellent surgical outcome. Preoperative (A, C, E) and 14-month postoperative (B, D, F) photographs of a 27-year-old woman who underwent nasal tip plasty using Smart Ball® for nasal tip ptosis.
Mechanical properties of the PCL prostheses correspond to those of cartilage and therefore, this material does not cause skin contraction or permanent scarring, indicating long-term maintenance of the shape of the nasal tip achieved postoperatively [7].

We emphasize that the 3D-printed PCL (Smart Ball®) technique will significantly benefit patients undergoing nasal tip plasty, because it is a safe procedure that achieves the desired length and volume of the nasal tip without affecting the blood circulation of skin and does not require excessive manipulation.

Acknowledgments

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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References

Correlation between anterior thigh pain and morphometric mismatch of femoral stem

Haksun Chung, So Hak Chung

Department of Orthopaedic Surgery, Kosin University College of Medicine, Busan, Korea

Background: Postoperative pain occurring after hip arthroplasty has become common since the expanded use of cementless femoral stems. The characteristic pain develop in the anterolateral thigh area. This study aimed to predict anterior thigh pain based on the measurements of postoperative anteroposterior (AP) and lateral (Lat) radiographs of the hip joint.

Methods: The present study included 26 patients (29 hips) who underwent total hip replacement or bipolar hemiarthroplasty between March 2010 and May 2016, whose complete clinical information was available. AP and Lat radiographs of the affected hip were taken on the day of surgery and 1 and 6 months postoperatively. Patients with improper radiographs were excluded. The distance from the femoral stem to the nearest cortical bone in the distal region of the stem was measured. The patient group with a visual analog scale (VAS) score of ≥6 points was designated as patients with anterior thigh pain.

Results: Sex, age, weight, height, body mass index, and bone mineral density in the lumbar spine and femur did not have a significant effect on postoperative VAS scores (p>0.05). Presence of contact between the femoral stem and cortical bone was associated with postoperative anterior thigh pain.

Conclusion: Hip AP and Lat radiographs are usually taken to confirm fixation and alignment of the femoral stem after hip arthroplasty. The measurement method introduced in this study can be utilized for predicting anterior thigh pain after hip arthroplasty.

Keywords: Hemiarthroplasty; Pain; Postoperative; Total hip replacement

Introduction

Thigh pain after hip arthroplasty typically appears in the anterior thigh. Such pain reportedly occurs in approximately 3%–25% of cases and is more common in cases that used a cementless rather than a cemented stem [1-8]. Especially in cementless technique, initial stability is vital for biologic fixation. However, when initial stability is not achieved, a loose prosthesis might initiate pain. Anterior thigh pain after hip arthroplasty is also associated with femoral stem size, use of cement, femoral stem design and material, femoral stem instability, and loosening and disharmony in flexural strength between the bone and femoral stem [4,8-15]. It is believed that cancellous bone and type-C nerve fibers that accompany blood vessels within the bone unit may be associated with postoperative anterior thigh pain by responding to changes in pressure and local extension [16]. The purpose of the present study was to predict anterior thigh pain based on measurements of the postoperative anteroposterior (AP) and lateral (Lat) radiographs of the hip joint.

Materials and methods

1. Ethics statement

We conducted this study in compliance with the principle of the
Declaration of Helsinki. The design and protocol of this retrospective study were approved by the Institutional Review Board of Kosin Gospel Hospital (IRB No. 2017-12-011). Since this was a retrospective study, the requirement for informed consent was waived.

2. Subjects
The present study retrospectively included 26 patients (29 hips) who underwent hip arthroplasty between March 2010 and May 2016, with their complete clinical information available. There were 14 patients (16 hips) who underwent total hip arthroplasty and 12 patients (13 hips) who underwent bipolar hip arthroplasty. Preoperative diagnoses included avascular necrosis of the femoral head (n = 14), femoral neck fracture (n = 10), intertrochanteric fracture (n = 2), solitary myeloma (n = 1), synovial sarcoma (n = 1) and secondary coxarthrosis (n = 1); avascular necrosis of the femoral head was the most common diagnosis (Table 1).

The femoral stem used in surgery consisted of the Bencox® (Corentec, Seoul, Korea) ID stem proximal fit and filled cementless femoral stem. We included patients who were operated on with only Bencox® ID stem and excluded other stems.

Patients with improper radiographs were excluded. Patients with distal anterior or Lat thigh pain, extending beyond the groin area, were considered to have anterior thigh pain, while patients with posterior thigh pain or gluteal pain were excluded from the experimental group.

3. Surgical methods and postoperative care
The same surgeon performed all surgeries using a modified Hardinge approach. The femoral stem was inserted using the press-fit technique based on preoperative templating and an intraoperative decision by the surgeon. In total hip replacement arthroplasty cases, the press-fit technique was also used for the acetabular implant, while additional screw fixation was used on all patients.

The prophylactic intravenous antibiotic was administered preoperatively to all 26 patients, while low-molecular-weight heparin was used as per standard postoperative protocol to prevent thrombosis. Quadriceps contraction training was implemented from the first day and partial weight-bearing walking exercise using a walker was implemented within postoperative 1 week. Total weight-bearing was allowed for all patients within 2 weeks postoperatively.

4. Clinical evaluation
For the investigation of anterior thigh pain, pre and postoperative visual analog scales (VAS; preoperative and postoperative 1 and 6 months) were used. Investigated factors include the final follow-up period, sex, age, type of implant, disease, and distance between the femoral stem and cortical bone.

Postoperative physical examination referenced the definition suggested by Barrack et al. [1] for the diagnosis of anterior thigh pain. Patients with distal anterior or lateral thigh pain, more than in the groin area, were considered to have anterior thigh pain, while patients with posterior thigh pain or gluteal pain were excluded from the experimental group. Also, patients with radiating pain extending to the calf or foot were excluded from the experimental group.

The patient group with VAS score of ≥ 6 points postoperatively was designated as the ‘patients with pain’ group, while the group with VAS score of ≤ 5 points postoperatively was designated as the ‘patients without pain’ group. The ‘patients with pain’ group included 13 hips (10 patients), with VAS scores of 6 points for 6 hips, 7 points for 2 hips, and 8 points for 5 hips. The ‘patients without pain’ group included 16 hips (16 patients), with all hips having a VAS score of 1 point.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Thigh pain</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Patient</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>12 (14 hips)</td>
<td>8 (57.14)</td>
<td>6 (42.86)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>14 (15 hips)</td>
<td>8 (53.33)</td>
<td>7 (46.66)</td>
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<tr>
<td>Age (yr)</td>
<td>61.59 ± 16.33</td>
<td>63.31 ± 4.46</td>
<td>59.46 ± 4.08</td>
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<tr>
<td>Weight (kg)</td>
<td>63.77 ± 10.23</td>
<td>63.61 ± 2.13</td>
<td>63.96 ± 4.43</td>
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</tr>
<tr>
<td>Height (cm)</td>
<td>162.39 ± 8.29</td>
<td>164.19 ± 2.53</td>
<td>160.19 ± 1.34</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>24.20 ± 3.69</td>
<td>23.57 ± 0.54</td>
<td>24.98 ± 1.38</td>
<td></td>
</tr>
<tr>
<td>BMD (lumbar spine)</td>
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<td>-1.28 ± 0.52</td>
<td>-0.9 ± 0.55</td>
<td></td>
</tr>
<tr>
<td>BMD (femur)</td>
<td>-1.63 ± 1.41</td>
<td>-1.78 ± 0.36</td>
<td>-1.41 ± 0.54</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation. BMI, body mass index; BMD, bone mineral density.
5. Radiological evaluation
We have taken an AP hip radiograph (standard total hip) to include images of both sides of the hip on the same film that project towards the middle of the line connecting the upper symphysis pubis and anterior-superior iliac spine. Both patellae were faced forward and lower extremities were internally rotated by 15°–20° to accommodate femoral anteversion. To obtain the affected hip Lat radiographs (hip joint axial), the patient was turned onto the affected hip at least 45° with a hip flexion angle of 90° and internal rotation angle of 45° in a supine position. Images were then taken vertically from the groin region.

For evaluation of fixation and alignment between the femoral stem and acetabular implant, hip AP and affected hip Lat radiographs were acquired from all patients on the day of surgery and at 1 and 6 months postoperatively. For confirmation of contact, the shortest distance from the femoral stem to the nearest cortical bone was measured. Since there was no admissible definition of measurement for the contact between femoral stem and cortex, we measured the gap in the distal region of the stem to the cortical bone in AP and axial view (Fig. 1). Three orthopedic specialists independently interpreted the radiographs. This study statistically analyzed the average value of the three specialists’ measurements.

6. Statistical analysis
We conducted statistical analysis with Student t-test, logistic regression and linear mixed-effects regression.

Kolmogorov-Smirnov test was done to confirm the normality of the data. With log-transformation, normality of data was established. Student t-test was used for a grid search to find out the cut-off value of stem to femoral distance (Table 2). Logistic regression was used for risk factor analysis. A p-value of less than 0.05 was considered to be statistically significant (Table 3). To investigate the association between anterior thigh pain and stem to cortex distance, linear-mixed effects regression was used for repeated

![Fig. 1.](https://doi.org/10.12701/yujm.2019.00325)
measured data (Table 4). IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA) was used for all statistical calculations.

**Results**

All patients were reviewed for at least 2 years. The median period of follow-up was 4 years. The patient population included 12 males (14 hips) and 14 females (15 hips). At the time of surgery, the median age was 63 years (range, 25–86 years); median weight 67.0 kg (range, 42.0–81.0 kg); median height 161.7 cm (range, 143.0–179.0 cm); and median body mass index (BMI) 23.9 (range, 15.8–31.6). In addition, median bone mineral density (BMD) T-score was -1.4 (range, -3.5–3.8) in the lumbar spine (L-spine) and -1.7 (range, -3.5–0.8) in the femur (Table 1).

Thirteen hips with anterior thigh pain had a median value of the stem to cortex distance of 0.65 mm (range, 0.32–1.01 mm) in

Table 2. Cut-off value of stem to femoral distance (Student t-test)

<table>
<thead>
<tr>
<th>Cut-off (mm)</th>
<th>0 mo</th>
<th>1 mo</th>
<th>6 mo</th>
</tr>
</thead>
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<tr>
<td>0.5</td>
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<td>0.7358</td>
<td>0.0839</td>
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<td>0.6</td>
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<td>0.0365</td>
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<td>0.0250</td>
<td>0.5624</td>
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<td>1.5</td>
<td>0.1429</td>
<td>0.7305</td>
<td>0.1292</td>
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</table>

*p*-value for association test of contact on log-transformed VAS for each cut-off value.

VAS, visual analogue scale.

Table 3. Logistic regression for risk factor analysis

<table>
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<tr>
<th>Independent variable</th>
<th>Beta</th>
<th>Standard error</th>
<th>Wald statistic</th>
<th>p-value</th>
<th>OR</th>
<th>CI for OR</th>
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<td></td>
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<td>Lower bound</td>
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<td>0.748</td>
<td>0.042</td>
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<td>0.024</td>
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<td>0.523</td>
<td>0.985</td>
<td>0.941</td>
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<td>Weight</td>
<td>0.003</td>
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<td>0.009</td>
<td>0.926</td>
<td>1.003</td>
<td>0.933</td>
</tr>
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<td>Height</td>
<td>-0.064</td>
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<td>1.633</td>
<td>0.201</td>
<td>0.938</td>
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<td>1.049</td>
<td>0.306</td>
<td>1.118</td>
<td>0.903</td>
</tr>
<tr>
<td>BMD (lumbar spine)</td>
<td>0.130</td>
<td>0.253</td>
<td>0.262</td>
<td>0.609</td>
<td>1.138</td>
<td>0.693</td>
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<tr>
<td>BMD (femur)</td>
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<td>0.317</td>
<td>0.386</td>
<td>0.535</td>
<td>1.218</td>
<td>0.654</td>
</tr>
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</table>

Stem to cortex distance (mm)

<p>| | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<td>&lt; 0.001</td>
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<td>7.306</td>
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</table>

Dependant variable: existence of anterior thigh pain (patients=1, control=0).

OR, odds ratio; CI, confidence interval; BMI, body mass index; BMD, bone mineral density.

Table 4. Linear-mixed model to analyze association between anterior thigh pain and stem to cortex distance

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Beta</th>
<th>Standard error</th>
<th>t-value</th>
<th>p-value</th>
<th>CI</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Constant</td>
<td>0.6107</td>
<td>0.4598</td>
<td>1.328</td>
<td>0.0938</td>
<td>-0.3029</td>
<td>1.5243</td>
<td></td>
</tr>
<tr>
<td>Stem to cortex distance</td>
<td>-0.5992</td>
<td>0.1289</td>
<td>-4.6490</td>
<td>&lt; 0.001</td>
<td>-0.8570</td>
<td>-0.3414</td>
<td></td>
</tr>
</tbody>
</table>

Dependent variable: logVAS. Random effect: measuring time.

CI, confidence interval; VAS, visual analogue scale.
the AP view and 0.72 mm (range, 0.41–1.77 mm) in the Lat view postoperatively (Table 5). Sixteen hips without pain had a median value of 1.65 mm (range, 0.51–2.94 mm) in the AP view and 1.82 mm (range, 0.96–4.72 mm) in the Lat view, postoperatively (Table 5). Radiolucent line around the stem were not visible in the radiographs of all patients. The cut-off value for the stem to cortex distance was chosen as 0.8 mm, which is statistically significant in Student t-test (Table 2). There was no statistically significant association between anterior thigh pain and patient’s sex, age, weight, height, BMI, and L-spine and femoral BMD T-score ($p > 0.05$; Table 3). Since the association of stem to cortex distance on logVAS is strongly negative, it was shown that thigh pain after hip arthroplasty diminished over time (Table 3, $p < 0.05$). Presence of contact between the femoral stem and cortical bone (stem to cortex distance < 0.8 mm) was associated with postoperative anterior thigh pain (Tables 3, 4).

**Discussion**

Thigh pain after hip arthroplasty typically appears in the anterior thigh. Barrack et al. [1] reported that such pain reportedly occurs in up to 40% of cases. The percentage of symptomatic patients in this study is higher than that in other reports and a small number of cases is the potential reason for this. Since the 1970s, various fixation methods using cementless implants have been introduced. These implants have shown better biocompatibility than those used in cement-based fixation methods and have been preferred over implants that use cement because of their advantage of secondary fixation to prevent contact between the implant and bone [18]. However, postoperative anterior thigh pain was repeatedly reported to be more common with cementless than with cemented stems [2,4-7,17].

The exact significance and cause of thigh pain after hip arthroplasty have not been identified. Since operational goals include the elimination of pain, stable fixation of the femoral stem, recovery of biomechanical function and restoration of the femoral shape [19], anterior thigh pain can be viewed as an essential factor that can diminish postoperative patient satisfaction.

Hedley et al. [20] described thigh pain that appears after cementless hip arthroplasty as a benign complication that appears in the early stage after surgery and dissipates naturally, whereas Campbell et al. [4] reported it to be an unusual and dangerous sign of an unstable femoral stem, indicating failure in biomechanical fixation. While some papers have reported anterior thigh pain in association with the instability of the implant and fixation failure [4,15], others have reported that severe anterior thigh pain may be found among patients who underwent hip arthroplasty using a cementless femoral stem despite firm fixation, proper

---

**Table 3.** Distance in 0, 1, and 6 months

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>0 (AP)</th>
<th>0 (Lat)</th>
<th>1 (AP)</th>
<th>1 (Lat)</th>
<th>6 (AP)</th>
<th>6 (Lat)</th>
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<tr>
<td>1</td>
<td>0.64</td>
<td>1.77</td>
<td>0.72</td>
<td>1.72</td>
<td>0.72</td>
<td>1.65</td>
</tr>
<tr>
<td>2</td>
<td>1.01</td>
<td>0.68</td>
<td>0.92</td>
<td>0.66</td>
<td>0.93</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>0.80</td>
<td>0.51</td>
<td>0.87</td>
<td>0.36</td>
<td>0.82</td>
<td>0.49</td>
</tr>
<tr>
<td>4</td>
<td>0.66</td>
<td>0.72</td>
<td>0.56</td>
<td>0.68</td>
<td>0.52</td>
<td>0.52</td>
</tr>
<tr>
<td>5</td>
<td>0.96</td>
<td>0.72</td>
<td>1.01</td>
<td>0.45</td>
<td>0.89</td>
<td>0.62</td>
</tr>
<tr>
<td>6</td>
<td>0.32</td>
<td>0.51</td>
<td>0.32</td>
<td>0.45</td>
<td>0.28</td>
<td>0.50</td>
</tr>
<tr>
<td>7</td>
<td>0.51</td>
<td>0.72</td>
<td>0.42</td>
<td>0.63</td>
<td>0.49</td>
<td>0.65</td>
</tr>
<tr>
<td>8</td>
<td>0.64</td>
<td>0.41</td>
<td>0.58</td>
<td>0.36</td>
<td>0.52</td>
<td>0.28</td>
</tr>
<tr>
<td>9</td>
<td>0.80</td>
<td>0.78</td>
<td>0.82</td>
<td>0.84</td>
<td>0.88</td>
<td>1.01</td>
</tr>
<tr>
<td>10</td>
<td>0.64</td>
<td>0.80</td>
<td>0.58</td>
<td>0.71</td>
<td>0.44</td>
<td>0.62</td>
</tr>
<tr>
<td>11</td>
<td>0.66</td>
<td>0.97</td>
<td>0.54</td>
<td>0.84</td>
<td>0.39</td>
<td>1.02</td>
</tr>
<tr>
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<tr>
<td>13</td>
<td>0.48</td>
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<td>0.43</td>
<td>0.32</td>
<td>0.36</td>
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<tr>
<td>14</td>
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<td>0.82</td>
<td>0.84</td>
<td>0.88</td>
<td>1.01</td>
</tr>
<tr>
<td>15</td>
<td>0.64</td>
<td>0.80</td>
<td>0.58</td>
<td>0.71</td>
<td>0.44</td>
<td>0.62</td>
</tr>
<tr>
<td>16</td>
<td>0.66</td>
<td>0.97</td>
<td>0.54</td>
<td>0.84</td>
<td>0.39</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Values are presented as stem to cortex distance (mm). AP, anteroposterior; Lat, lateral.

Distance in 0, 1, and 6 months in patients with thigh pain. Distance in 0, 1, and 6 months in patients without thigh pain.

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https://doi.org/10.12701/yujm.2019.00325
alignment and proper implant size [8,13].

The exact etiology of anterior thigh pain that appears in patients with stable implant fixation remains unclear. The most widely recognized hypothesis attributes the cause to an abnormally high level of bone stress at the femoral stem tip; such abnormal bone stress was reported to have been caused by disharmony in flexural strength between the cortical bone and femoral stem [2,10,12,14].

Namba et al. [12] studied femoral stress at the femoral stem tip in association with various factors and stated that the directionality of the femoral stem might explain why postoperative thigh pain appears mostly in the anterior area. Vresilovic et al. [14] investigated the effects of femoral stem size on the prevalence of postoperative anterior thigh pain and reported that an increase in stem size usually resulted in increased pain. As the stem size increases, the cross-sectional size increases, which causes an increase in flexural strength [21]. This can cause a sudden shift in the femoral stem tip during hip joint movement.

Directionality and cross-sectional area of the femoral stem mentioned in preceding studies can be viewed with contact with cortical bone at the femoral stem tip, which may be associated with nociceptors in the endosteum of cortical bone and the presence of unmyelinated type-C nerve fibers within the Haversian canal [16,22].

Limitations in the present study included the following: first, if radiographs were taken with a slight rotation, it might cause an error in measurement. We tried to prevent this problem by taking an accurate AP and axial view. Second, since only AP and Lat radiographs were acquired, the distance between the femoral stem and cortical bone was not measured from various angles. Third, the number of cases is small compared to that of other studies. Fourth, the age and diagnosis of patients are heterogeneous. Since computed tomography examination presents limitations from a cost-effectiveness aspect, a plain radiograph is preferred for routine examination for checking fixation and alignment of femoral stem after hip arthroplasty. The plain radiograph is low-cost and could be routinely performed after hip arthroplasty. We believe that the method used in the present study was meaningful since it can be used to predict anterior thigh pain with plain radiography. According to our study, if stem to cortical distance is smaller than 0.8 mm in the distal region of the stem, the possibility of anterior thigh pain after hip arthroplasty can be expected.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

References


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Clinical factors that affect the pregnancy rate in frozen-thawed embryo transfer in the freeze-all policy

Seo Yoon Hwang, Eun Hye Jeon, Seung Chul Kim, Jong Kil Joo

Department of Obstetrics and Gynecology, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Korea

Background: This study was conducted to analyze clinical factors that can affect pregnancy rates in normal responders undergoing the freeze-all policy in in vitro fertilization.

Methods: We evaluated 153 embryo transfer cycles in 89 infertile women with normal response to controlled ovarian stimulation (COS). After COS, all embryos were cultured to the blastocyst stage, and good quality blastocysts were vitrified for elective frozen-thawed embryo transfer (FET). Clinical variables associated with COS and the results of COS and culture, including the number of retrieved oocytes, fertilized oocytes, and frozen blastocysts were compared between the pregnant group and the non-pregnant group.

Results: After a single cycle of COS for each patient, 52 patients became pregnant while 37 did not. Significant differences were observed in the number of matured oocytes, fertilized oocytes, and transferred embryos. The number of frozen blastocysts in the pregnant group was almost twice that in the non-pregnant group (5.6 ± 3.1 vs. 2.8 ± 1.9, p < 0.001). The area under the receiver operating characteristic curve for the 4 frozen blastocysts was 0.801 in the pregnant group.

Conclusion: In the freeze-all policy, the number of matured oocytes, number of fertilized oocytes, and number of frozen blastocysts might be predictive factors for pregnancy.

Keywords: Blastocyst; Embryo transfer; In vitro fertilization; Pregnancy
rate in the FET cycle are unclear. Therefore, it is important to predict the possibility of acquisition of good quality embryos and the pregnancy rates of the FET cycle.

In a recent study, characteristics of high-quality embryos, endometrial preparation protocol, number of transferred embryos, and body mass index of the patients independently affected the live birth rate in FET [5]. However, in case of the freeze-all policy, all embryos are frozen and fresh embryo transfer is not performed. Hence, the parameters primarily related with the pregnancy rate are unclear.

In this study, we analyzed the differences in various clinical parameters in the freeze-all policy between the pregnant group and the non-pregnant group through a single cycle of controlled ovarian stimulation (COS) composed of 3 cycles of FET.

Materials and methods

1. Ethics statement

The present study was approved by the Institutional Review Committee of Pusan National University Hospital (IRB No. H-1908-021-082). Eighty-nine infertile women qualified as normal responders were recruited for this study and provided informed consent. The informed consent included the benefits and the threats of the freeze-all policy.

2. Patients

This study was retrospectively conducted from January 2015 to December 2016 at the Infertility Center, Pusan National University Hospital. A normal responder was defined as having the following criteria: (1) age < 40 years, (2) follicle stimulating hormone level < 12 mIU/mL at cycle day 2 or 3 and, (3) anti-Müllerian hormone level > 1 ng/mL. Patients having inappropriate endometrium for implantation, which included conditions such as endometrial synchieae, unresponsive thin endometrium, or abnormal anatomy of the uterine cavity, were excluded. After infertility workups, endometrial and/or tubal corrective surgeries were performed after COS and before FET in indicated cases. This study was conducted through a single cycle of COS composed of 3 cycles of FET.

3. Preparing the blastocyst and the endometrium for frozen-thawed embryo transfer

We adopted the routine protocol of our clinics for COS, the blastocyst culture, and the preparation of the endometrium [6]. The infertile women individually received the GnRH antagonist protocol or the GnRH agonist long protocol. For triggering, human chorionic gonadotropin (hCG) (Ovidrel 5,000–10,000 IU; Merck Serono, Geneva, Switzerland) or a GnRH agonist (decapetly 0.2 mg; Ferring, Saint-Prex, Switzerland) was used. All fertilized embryos were cultured to the blastocyst stage in sequential G1/G2 media (Vitrolife, Gothenburg, Sweden). Good quality embryos having appropriate morphology of the trophectoderm and inner cell mass and fewer fragmentations of blastomeres were selected and vitrified for elective FET. Two to 3 months after the oocyte pick up, oral estradiol valerate was administered in gradually increasing quantity for endometrial preparation (progynova 2–6 mg/day; Bayer Schering Pharma, Berlin, Germany) after pituitary luteal down-regulation with preliminary GnRH agonist (lucrin, 0.1 mg/day; Abbott, Chicago, IL, USA). At menstrual day 15, endometrial thickness (EMT) was evaluated. In cases with EMT over 7–8 mm, vaginal progesterone gel (Crinone 90 mg/day; Merck Serono) and oral estradiol valerate were administered for inducing the secretory phase of the endometrium. In cases where EMT did not reach 7 mm, oral estradiol valerate was administered continuously and EMT was rechecked later. Vaginal progesterone was administered after EMT was confirmed to be suitable. Blastocysts were warmed and transferred under transabdominal ultrasound guidance using a soft embryo transfer catheter (Cook Medical, Spencer, IN, USA).

4. Outcome measures and following procedures

Twelve days after the embryo transfer, serum β-hCG was checked for confirmation of pregnancy. Progesterone support was continued until 10 gestational weeks in women who conceived. In the non-pregnant group, a second embryo transfer or a second COS cycle was conducted (Fig. 1).

5. Statistical analyses

All patients were retrospectively divided into the pregnant and the non-pregnant groups after FET. The variables under study were compared between the two groups by Wilcoxon rank sum test for independent samples using PASW version 18.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as mean ± standard deviation unless specified otherwise. The value of p < 0.05 was considered statistically significant.

Results

In this study, we analyzed the difference in various clinical parameters in the freeze-all policy between the pregnant group and the non-pregnant group through a single cycle of COS composed of 3 cycles of FET.

Totally, 153 FETs were carried out in 89 patients (Fig. 1). Patient characteristics and outcomes of COS are presented in Table 1. After
In this study, 153 embryo transfer cycles in 89 infertile women were analyzed. The second FET cycle was conducted in 50 patients and the third FET cycle was conducted in 14 patients. In case of no remnant frozen embryos, a second COS was started. FET, frozen-thawed embryo transfer; COS, controlled ovarian stimulation.

The first FET cycle, 35 patients (39.3%) became pregnant. Table 2 shows the comparison of parameters between the pregnant group and the non-pregnant group after the first FET cycle. Significant differences were observed in the number of matured oocytes, the number of fertilized oocytes, the number of frozen blastocysts, and the number of transferred embryos between the two groups. Among the 35 pregnant patients, 2 patients (5.7%) had a spontaneous abortion and 2 patients (5.7%) experienced chemical pregnancy. The second FET cycle was carried out in 50 patients. Fourteen patients (28.0%) became pregnant after the second cycle. Among these 14 pregnant patients, 3 patients (21.4%) experienced chemical pregnancy and 1 patient (7.1%) was diagnosed with a missed abortion.

Table 3 shows the comparison of parameters between the pregnant group and the non-pregnant group after all FET cycles. Through a single cycle of COS that consisted of 3 cycle of FET, 52 patients became pregnant, while 37 patients did not become pregnant. Significant differences were observed in the number of matured oocytes, the number of fertilized oocytes, the number of frozen blastocysts, and the number of transferred embryos. In particular, the number of frozen blastocysts in the pregnant group was almost twice that in the non-pregnant group (5.6 ± 3.1 vs. 2.8 ± 1.9, \( p < 0.001 \)).

Fig. 2 shows the area under curve (AUC) of the receiver operating characteristic (ROC) curve for the number of matured oocytes, fertilized oocytes, and frozen blastocysts in the cumulative pregnancy cycle (Fig. 2A) and in the pregnancy cycle after the first FET (Fig. 2B). The AUC of the ROC curve in the cumulative pregnancy group was 0.801 for the 4 frozen blastocysts (95% confidence interval [CI], 0.625–0.819), 0.713 for the 13 fertilized oocytes (95% CI, 0.540–0.747), and 0.710 for the 8 matured oocytes (95% CI, 0.525–0.733) (Fig. 2A). The AUC of the ROC curve in the pregnancy group after the first FET cycle was 0.730 for the 4 frozen blastocysts (95% CI, 0.588–0.788), 0.649 for the
13 fertilized oocytes (95% CI, 0.548–0.753), and 0.634 for the 14 matured oocytes (95% CI, 0.524–0.733) (Fig. 2B). The AUC of the ROC curve for the 4 frozen blastocysts was 0.801 in the pregnant group.

**Discussion**

This study was conducted to investigate the factors that affect the pregnancy rates of the FET cycle in the freeze-all policy. We analyzed the difference in various clinical parameters in the freeze-all policy between the pregnant group and the non-pregnant group through a single cycle of COS composed of 3 cycles of FET. And carried out the freeze-all policy in the normal responders after informed consent was obtained from the patients. Currently, FET is being performed in extra frozen embryos due to the legislation changes such as medical insurance coverage in South Korea.

Introduction of vitrification and development of GnRH antagonist protocol are the foundations of the freeze-all policy. Vitrification as a method of cryopreservation of embryos improved the survival rate of thawing embryos. By using GnRH agonist triggering in the GnRH antagonist protocol, the ovarian hyperstimulation syndrome (OHSS) risk is almost removed from the assisted reproductive technology procedure [3].

### Table 1. Patients characteristics and COS outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Age (yr)</td>
<td>33.6 ± 3.6</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>22.9 ± 3.7</td>
</tr>
<tr>
<td>Primary infertility</td>
<td>52 (58.4)</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>37 (41.6)</td>
</tr>
<tr>
<td>Duration of infertility (mo)</td>
<td>47.1 ± 30.5</td>
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<td>Basic laboratory findings</td>
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</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>6.9 ± 4.6</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>8.1 ± 13.8</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>15.9 ± 9.4</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>5.2 ± 4.1</td>
</tr>
<tr>
<td>COS outcomes</td>
<td></td>
</tr>
<tr>
<td>Total dose of FSH (IU)</td>
<td>3,056.0 ± 1,102.9</td>
</tr>
<tr>
<td>Total dose of LH (IU)</td>
<td>1,229.8 ± 1,178.3</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>14.1 ± 6.9</td>
</tr>
<tr>
<td>Oocytes matured</td>
<td>11.4 ± 6.1</td>
</tr>
<tr>
<td>Oocytes fertilized</td>
<td>10.3 ± 5.6</td>
</tr>
<tr>
<td>Blastocysts frozen</td>
<td>4.4 ± 3.0</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation. COS, controlled ovarian stimulation; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-Müllerian hormone.

### Table 2. Clinical and COS parameters according to pregnancy or not after first FET

<table>
<thead>
<tr>
<th>Clinical and COS parameter</th>
<th>Pregnant group (n = 35)</th>
<th>Non-pregnant group (n = 54)</th>
<th>p-value</th>
</tr>
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<tr>
<td>Primary infertility</td>
<td>18 (51.4)</td>
<td>34 (63.0)</td>
<td>0.105a</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>17 (48.6)</td>
<td>20 (37.0)</td>
<td>0.960</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33.5 ± 3.4</td>
<td>33.7 ± 3.8</td>
<td>0.987</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>22.4 ± 3.2</td>
<td>23.1 ± 3.9</td>
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<tr>
<td>Duration of infertility (mo)</td>
<td>40.5 ± 28.6</td>
<td>51.3 ± 31.2</td>
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<td>Basic laboratory findings</td>
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</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>7.0 ± 4.5</td>
<td>6.8 ± 4.7</td>
<td>0.564</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>8.5 ± 15.7</td>
<td>7.9 ± 12.6</td>
<td>0.253</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>16.6 ± 11.6</td>
<td>15.5 ± 7.7</td>
<td>0.920</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>4.7 ± 3.5</td>
<td>5.65 ± 4.6</td>
<td>0.591</td>
</tr>
<tr>
<td>COS outcomes</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total dose of FSH (IU)</td>
<td>3,034.3 ± 1,198.8</td>
<td>3,070.0 ± 1,102.2</td>
<td>0.468</td>
</tr>
<tr>
<td>Total dose of LH (IU)</td>
<td>1,125.0 ± 865.5</td>
<td>1,295.6 ± 1,342.0</td>
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</tr>
<tr>
<td>Oocytes retrieved</td>
<td>15.6 ± 7.1</td>
<td>13.1 ± 6.7</td>
<td>0.107</td>
</tr>
<tr>
<td>Oocytes matured</td>
<td>13.1 ± 6.6</td>
<td>10.3 ± 5.5</td>
<td>0.037</td>
</tr>
<tr>
<td>Oocytes fertilized</td>
<td>12.1 ± 6.4</td>
<td>9.1 ± 4.8</td>
<td>0.020</td>
</tr>
<tr>
<td>Blastocysts frozen</td>
<td>6.1 ± 3.5</td>
<td>3.4 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blastocysts transferred</td>
<td>2.1 ± 0.1</td>
<td>1.7 ± 0.1</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation. COS, controlled ovarian stimulation; FET, frozen embryo transfer; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-Müllerian hormone.

Wilcoxon rank sum test. "Fisher exact test.
### Table 3. Clinical and COS parameters according to pregnancy or not after all FET

<table>
<thead>
<tr>
<th>Clinical and COS parameter</th>
<th>Pregnant group (n = 52)</th>
<th>Non-pregnant group (n = 37)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary infertility</td>
<td>30 (57.7)</td>
<td>22 (59.5)</td>
<td>0.784&lt;sup&gt;α&lt;/sup&gt;</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>22 (42.3)</td>
<td>15 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33.3 ± 3.4</td>
<td>34.0 ± 3.9</td>
<td>0.677</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>22.9 ± 4.0</td>
<td>22.8 ± 3.1</td>
<td>0.836</td>
</tr>
<tr>
<td>Duration of infertility (mo)</td>
<td>44.3 ± 29.6</td>
<td>51.1 ± 31.7</td>
<td>0.339</td>
</tr>
<tr>
<td><strong>Basic laboratory findings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>7.1 ± 4.4</td>
<td>6.6 ± 5.0</td>
<td>0.307</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>8.1 ± 14.3</td>
<td>8.1 ± 13.3</td>
<td>0.245</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>16.3 ± 10.1</td>
<td>15.3 ± 8.3</td>
<td>0.666</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>5.4 ± 4.1</td>
<td>4.9 ± 4.3</td>
<td>0.439</td>
</tr>
<tr>
<td><strong>COS outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose of FSH (IU)</td>
<td>3,008.2 ± 948.6</td>
<td>3,123.1 ± 1,300.4</td>
<td>0.767</td>
</tr>
<tr>
<td>Total dose of LH (IU)</td>
<td>1,109.4 ± 946.0</td>
<td>1,995.0 ± 1,436.1</td>
<td>0.857</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>15.4 ± 6.8</td>
<td>12.3 ± 6.7</td>
<td>0.031</td>
</tr>
<tr>
<td>Oocytes matured</td>
<td>12.9 ± 6.1</td>
<td>9.2 ± 5.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Oocytes fertilized</td>
<td>11.8 ± 5.8</td>
<td>8.2 ± 4.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Blastocysts frozen</td>
<td>5.6 ± 3.1</td>
<td>2.8 ± 1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blastocysts transferred</td>
<td>2.0 ± 0.5</td>
<td>1.7 ± 0.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean±standard deviation.

COS, controlled ovarian stimulation; FET, frozen embryo transfer; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-Müllerian hormone.

Wilcoxon rank sum test. <sup>α</sup>Fisher exact test.

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**Fig. 2.** ROC curve of the cumulative pregnancy group (A) and the pregnancy group after the first frozen embryo transfer (B). (A) AUC of the ROC curve of the cumulative pregnancy group: 0.801 for the 4 frozen blastocysts (95% CI, 0.625–0.819), 0.713 for the 13 fertilized oocytes (95% CI, 0.540–0.747), and 0.710 for the 8 matured oocytes (95% CI, 0.525–0.733). (B) AUC of the ROC curve of the pregnancy group for the first frozen embryo transfer: 0.730 for the 4 frozen blastocysts (95% CI, 0.588–0.788), 0.649 for the 13 fertilized oocytes (95% CI, 0.548–0.753), and 0.634 for the 14 matured oocytes (95% CI, 0.524–0.733). ROC, receiver operating characteristic; AUC, area under curve; CI, confidence interval.
Apart from the decreased risk of OHSS, the freeze-all policy has several strengths. A meta-analysis comparing the fresh transfers and the FET cycles showed significantly higher implantation rates and clinical and ongoing pregnancy rates in the FET cycles [7]. The suggested mechanisms for the poor clinical outcomes in the fresh cycles are abnormal hormonal milieu and the suboptimal endometrial development in the COS cycles [4]. Moreover, the rate of ectopic pregnancy is reduced [8,9] and better perinatal outcomes have been reported in FET cycles [10,11].

However, there are several critical opinions about the freeze-all policy. A meta-analysis about the results of the freeze-all policy included only three small studies and the total number of patients included in the analysis was only 633 [12]. The studies included in this meta-analysis were highly heterogeneous in terms of the types of patients and some of the technical aspects [12]. To confirm the advantages of the freeze-all policy, further large-scale research with homogeneous criteria is needed.

There are some obstacles to the adaptation of the freeze-all policy to the real clinical practice. The policy needs changes in the current IVF practice and optimization of the cryopreservation techniques [4]. In an institute having suboptimal culture techniques, the possibility of cancellation of embryo transfer after COS would be increased. To apply the freeze-all policy to general infertility clinics, it has to be preceded by quality control of the culture technique. After quality control, the strengths of the freeze-all policy, such as better pregnancy rates and lower ectopic pregnancy rates, could be achieved, particularly in normal responders. Moreover, the freeze-all policy is a cost-effective strategy when compared to the fresh embryo transfer [13]. Thus, if adequate number of oocytes or embryos were retrieved, the freeze-all policy is a better option than the fresh embryo transfer in normal responders.

In this study, the AUC of the ROC curve was 0.801 for cumulative pregnancy group when the cut-off value of the number of frozen blastocysts was 4. To the best of our knowledge, there has been no report suggesting the cut-off value for the freeze-all policy as a predictive parameter for pregnancy.

The outcomes of IVF could be different in low or poor responders. Roque et al. [14] reported that the freeze-all policy may be related to better IVF outcomes in normal responders, but these potential advantages decrease with worsening ovarian response. In patients with 4–9 oocytes retrieved, the implantation rate and the ongoing pregnancy rate showed no difference between the fresh embryo transfer and the FET group. Meanwhile, patients with 10–15 retrieved oocytes showed significant differences in the implantation rate and the ongoing pregnancy rate between the fresh transfer group and the FET group. The FET group showed better outcomes (implantation rate of 30.1% in the FET group and 22.1% in the fresh embryo transfer, \( p = 0.028 \); ongoing pregnancy rate of 47% in the FET group and 34% in the fresh embryo transfer, \( p = 0.021 \)). Moreover, in poor responders, cycle cancellation rates could be increased.

On the contrary, the strengths of the freeze-all policy such as better pregnancy rates and perinatal outcomes and lesser ectopic pregnancy rates might also be similar for the poor responders. In case of the poor responders who need uterine surgery for improving the possibility of implantation, the freeze-all policy could avoid unnecessary operation. Usually, in older age groups, increased incidence of benign uterine disease is observed and the chances of poor response to COS are increased. If an adequate number of embryos could be obtained, gynecologic operation could be conducted after freezing all the embryos. In case of failure to obtain adequate embryos, benign uterine disease could be managed by other treatment modalities. The freeze-all policy is also suitable for pre-implantation genetic testing, which is applied more commonly in the older age group. Hence, the freeze-all policy could have several advantages in normal as well as poor responders.

This study suggested a cut-off value of the number of oocytes and blastocysts for the pregnant group in the freeze-all policy. However, there are critical limitations to this study. The number of patients included in this study was relatively small, and the study was carried out retrospectively. The possible causes of repeated implantation failure, such as intrauterine adhesion and thin endometrium were considered in the exclusion criteria. However, the factors associated with immunologic or thrombotic tendencies were not included in the screening. In addition, a dramatic decrease was observed in the pregnancy rates in the second cycle of FET. This finding may be because the embryos with poorer quality than those from the first cycle had been transferred. Only the good quality embryos were frozen according to the morphological criteria. However, the quality of the embryos in the same grade of the morphological criteria may vary. All embryos were cultured to the blastocyst stage at our center. Hence, information about the prediction of pregnancy in day 3 embryo transfer could not be obtained.

Despite these limitations, this study might provide significant information about the predictive value of clinical parameters and results of COS for pregnancy rates in the freeze-all policy.

In this study, we confirmed that the number of matured oocytes, fertilized oocytes, and frozen blastocysts might be predictive factors for pregnancy in the freeze-all policy.

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Community-acquired *Achromobacter xylosoxidans* infection presenting as a cavitary lung disease in an immunocompetent patient

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*Achromobacter xylosoxidans* is a gram-negative bacterium that can oxidize xylose. It is commonly found in contaminated soil and water but does not normally infect immunocompetent humans. We report a case of a cavitary lung lesion associated with community-acquired *A. xylosoxidans* infection, which mimicked pulmonary tuberculosis or lung cancer in an immunocompetent man. The patient was hospitalized due to hemoptysis, and chest computed tomography (CT) revealed a cavitary lesion in the superior segment of the left lower lobe. We performed bronchoscopy and bronchial washing, and subsequent bacterial cultures excluded pulmonary tuberculosis and identified *A. xylosoxidans*. We performed antibiotic sensitivity testing and treated the patient with a 6-week course of amoxicillin/clavulanate. After 2 months, follow-up chest CT revealed complete resolution of the cavitary lesion.

**Keywords:** Achromobacter xylosoxidans; Cavity; Hemoptysis; Immunocompetence; Pneumonia

**Introduc**

*Achromobacter xylosoxidans* is a gram-negative bacillus that can easily oxidize xylose. It is distributed in polluted environments (e.g., soil and water) and rarely infects human beings. However, *A. xylosoxidans* can opportunistically infect immune-deficient patients with various conditions, such as tumors, hematological disorders, organ transplantation, and acquired immune deficiency syndrome [1].

In Korea, cavitary lung lesions are typically observed in cases of lung cancer, pulmonary tuberculosis, bacterial pneumonia, and fungal lung infections. Furthermore, Yang et al. [2] reported that pulmonary tuberculosis is the most common cause of cavitary lung lesions, and most Korean clinicians primarily suspect pulmonary tuberculosis in these cases. Two cases of community-acquired *A. xylosoxidans* infection were reported by Lee et al. [3] in Korea. The patients were in the elderly age-group, and a single cavitary lung lesion was not observed in all patients [3]. Moreover, in our Korean medical literature search for cases of community-acquired *A. xylosoxidans* infection presenting as a cavitary lung lesion in an immunocompetent patient, no cases were found. Therefore, we report a case of hemoptysis (without immunodeficiency or chronic disorders) in a middle-aged man who was hospitalized for a single cavitary lung lesion in the superior segment of the left lower lobe. We suspected pulmonary tuberculosis because of its prevalence in Korea but detected *A. xylosoxidans* in bacterial testing and successfully treated the patient with targeted antibiotics.
Case

A 46-year-old man was hospitalized for hemoptysis, with no other symptoms, such as fever, weight loss, or thoracic wall pain. He had a smoking history of 30 pack-years but had never been diagnosed with immunodeficiency or chronic disorders and had not visited a medical institution for the past 12 months. The patient was an office worker, but he went camping. Chest radiography revealed a cavitary lung lesion in the left lung (Fig. 1), and chest computed tomography (CT) revealed a smooth internal margin of a cavitary mass (approximate size, 2.4 cm) with surrounding reticulonodular opacities in the superior segment of the left lower lobe. We did not detect mediastinal lymph node enlargement or pleural effusion (Fig. 2).

Laboratory testing revealed a white blood cell count of 12,690/\text{mm}^3 (range, 3,900–11,000/\text{mm}^3), hemoglobin level of 15.4 g/dL (range, 13–18 g/dL), platelet count of 275,000/\text{mm}^3 (range, 140,000–440,000/\text{mm}^3), and C-reactive protein level of 4.40 mg/dL (range, ≤ 0.3 mg/dL). Biochemical testing revealed a total protein level of 7.1 g/dL (range, 6.6–8.8 g/dL), albumin level of 4.3 g/dL (range, 3.5–5.2 g/dL), aspartate transaminase level of 32 IU/L (range, 0–40 IU/L), alanine transaminase level of 34 IU/L (range, 0–41 IU/L), blood urea nitrogen level of 10 mg/dL (range, 6–20 mg/dL), and creatinine level of 1.16 mg/dL (range, 0.7–1.2 mg/dL). Immunological testing was negative for human immunodeficiency virus. We performed bronchoscopy to detect the lesion and obtain a specimen. Bronchoscopy revealed mild stenosis due to mucosal edematous changes in the lateralis bronchus orifice of the superior segment of the left lower lobe (Fig. 3). We attempted bronchial washing with a physiological salt solution. The acid-fast bacilli testing and cytopathological testing of the wash specimen revealed no specific findings, with negative polymerase chain reaction results for *Mycobacterium tuberculosis* and nontuberculous mycobacteria.

However, gram-negative identification of the wash specimen using Vitek® 2 (bioMérieux, Marcy-l’Étoile, France) revealed the presence of gram-negative *A. xylosoxidans*. Therefore, we per-

Fig. 1. Chest radiography reveals a cavitary lesion (arrow) in the left lung.

Fig. 2. Chest computed tomography reveals a smooth internal margin of a cavitary mass (approximate size, 2.4 cm) with surrounding reticulonodular opacities (arrow) in the superior segment of the left lower lobe.

Fig. 3. Bronchoscopy reveals mild stenosis (arrow) in the lateralis bronchus orifice of the superior segment of the left lower lobe.

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formed antibiotic sensitivity testing based on the Clinical & Laboratory Standards Institute criteria, which revealed sensitivity to amoxicillin/clavulanate, piperacillin/tazobactam, ceftazidime, imipenem, and trimethoprim/sulfamethoxazole and resistance to the other tested antibiotics (Table 1). We administered a 6-week outpatient course of amoxicillin/clavulanate. Follow-up chest CT at 2 months revealed no cavitary lung lesions (Fig. 4). In addition, the acid-fast bacilli testing of the follow-up bronchial wash specimen did not detect *M. tuberculosis* or nontuberculous mycobacteria.

**Discussion**

*A. xylosoxidans* was described by Yabuuchi and Oyama [4] in 1971 after isolation from ear discharge in patients with chronic otitis media and was included in the *Alcaligenaceae* family. It is an aerobic, motile, non-fermenting, gram-negative bacillus, which is catalase- and oxidase-positive. It is similar to the strains of *Pseudomonas* but has peritrichous rods [1]. It is ubiquitous in aqueous environments and has been found in well water, tap water, and swimming pools. It is a prevalent nosocomial colonizer that has been isolated from multiple aqueous solutions used in healthcare settings, such as non-bacteriostatic saline, dialysis solutions, contact lens solutions, CT contrast solutions, ultrasound gel, and chlorhexidine gluconate solutions. Moreover, it colonizes fomites, such as mechanical ventilators, neonatal incubators, intravenous catheters, epidural catheters, and urinary catheters [5]. *A. xylosoxidans* infection typically presents with non-specific symptoms, and the bacteria have been isolated from multiple sources in patients, including blood, cerebrospinal fluid, sputum, skin, ear discharge, wounds, abscesses, bones, joints, endocardium, ascites fluid, corneal scrapings, and vitreous humor fluid [1,5]. However, *A. xylosoxidans* generally has low virulence and is typically isolated in cases of hospital-acquired infections that affect patients with hematological or oncological disorders (30%), cardiac diseases (21%), or immunosuppression (27%) [5]. In the United States of America, *A. xylosoxidans* infection is relatively common among patients with cystic fibrosis (CF) [6], and recently, attention has been focused on *A. xylosoxidans* and *Pseudomonas* as the etiological agent in cases of chronic respiratory inflammation. In patients with CF, *A. xylosoxidans* is detected in approximately 5.3% of the cases, and misdiagnosis is common because of its resemblance to *Pseudomonas*. Therefore, accurate bacterial and antibiotic sensitivity testing are important for identification and adequate treatment [6,7].

In adults, cavitary lung diseases are typically associated with malignant tumors and infective disorders [2,8,9], and the disorder can be differentiated based on the lesion’s thickness and location, characteristics of the inner margin, and patient’s age. For example, cavity-forming carcinoma commonly has a smooth or irregular inner margin, and cavity-forming abscesses commonly have a rough inner margin. Furthermore, approximately 95% of the lesions with maximal wall thickness > 15 mm are malignant, and most lesions with maximal wall thickness < 4 mm are benign [8]. In the present case, the lesion exhibited a smooth inner margin, and the maximum thickness was 7.8 mm.
Tuberculosis is the predominant infectious cause of cavitary lung lesions in Korea and predominantly occurs in patients aged < 50 years [8]. Furthermore, autoimmune and vascular disorders can cause cavitary lung diseases [2,9]. However, in patients with pulmonary tuberculosis, the presence of pulmonary cavitary lesions is associated with M. tuberculosis infection or reactivation. Moreover, the cavity’s thickness is not useful in detecting pulmonary tuberculosis in cases of Mycobacteria infection, which can make the diagnosis difficult [2]. Therefore, bronchoscopy is typically needed to exclude malignancy (e.g., bronchial cancer or other bronchial diseases) in patients who are hospitalized for hemoptysis and have a smoking history [10]. This approach can also facilitate the immediate treatment of active bleeding, detection of intrabronchial lesions missed on radiological imaging (e.g., radiography or chest CT), and other testing (e.g., biopsy or bronchial washing). In the present case, the patient had a smoking history, which is a risk factor for malignancy; therefore, we performed chest CT and bronchoscopy to evaluate the cause of the hemoptysis. Chest CT revealed a smooth internal margin of a cavitary mass (approximate size, 2.4 cm), suggesting pulmonary tuberculosis or malignancy, which are the most common causes of cavitary lung lesions in Korean men aged < 50 years. However, culturing of the bronchial wash fluid revealed A. xylosoxidans.

Claassen et al. [5] experienced a similar case (73-year-old man with a smoking history of 30 pack-years and moderate chronic obstructive pulmonary disease) with lung lesions (maximum size, 13 mm) and performed wedge resection because of the possibility of malignancy but isolated A. xylosoxidans from the surgical specimen. The authors provided 18 months of antibiotic treatment (levofloxacin, amoxicillin/clavulanate, doxycycline, and azithromycin), but lesion growth and multiplication led them to perform surgical resection [5]. Previous studies have indicated that A. xylosoxidans is resistant to aminoglycosides and rifampin but sensitive to imipenem, ceftazidime, β-lactamase inhibitor combinations, and trimethoprim/sulfamethoxazole. However, there are no accurate criteria for antibiotic sensitivity testing, and the existing data have been provided through a few in vivo experiments [7,11]. Nevertheless, the sensitivity results from the present case were similar to the results from previous experiments (Table 1).

In Korea, Lee et al. [3] reported 2 cases of pulmonary infection due to A. xylosoxidans in immunocompetent patients. One patient presented with a mass-like lesion suspected of lung cancer, and the other patient presented with pneumonia and para-pneumonic pleural effusion. In both cases, A. xylosoxidans was confirmed on culture of bronchial washing solution with bronchoscopy, as in our case. Our patient was relatively young and had a single cavitary lesion. The symptoms were clinically mild, and outpatient treatment was provided without hospitalization. However, the patients reported by Lee et al. [3] were the elderly and needed hospitalization due to relatively severe clinical conditions.

Infective disease or malignancy is typically suspected in cases of cavitary lung lesions detected using on radiography, and pulmonary tuberculosis testing is often performed in Korea (especially in cases of hemoptysis). However, these conditions must be differentiated based on the lesion’s radiographic shape, size, and location; more extensive testing may be needed to confirm the shape of the lesion and specific disease (e.g., pulmonary tuberculosis or bacterial/fungal infection). Herein, we reported a 46-year-old man hospitalized for hemoptysis (with no history of chronic disorders or recent hospital visits). We suspected pulmonary tuberculosis, based on the lesion’s radiographic shape and location, but culture of the bronchial wash fluid was negative for pulmonary tuberculosis and positive for A. xylosoxidans. Therefore, based on the antibiotic susceptibility results, we successfully treated the patient with an outpatient course of amoxicillin/clavulanate.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article were reported.

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Hemoptysis is a major reason for emergency department (ED) visits. Catamenial hemoptysis (CH), a rare condition of thoracic endometriosis, can cause recurrent hemoptysis but is difficult to diagnose in the ED due to the scarcity of cases and nonspecific clinical findings. We report a case of a 26-year-old woman who presented to the ED with recurrent hemoptysis since 2 years without a definite cause. Her vital signs and blood test findings were unremarkable. Chest computed tomography (CT) did not show any specific lesions other than a non-specific ground-glass opacity pattern in her right lung. She was on day 4 of her menstrual cycle and her hemoptysis frequently occurred during menstruation. Although there was no histological confirmation, based on her history of hemoptysis during menstruation and no other cause of the hemoptysis, the patient was tentatively diagnosed with CH and was administered gonadotropin-releasing hormone. She had no recurrence of hemoptysis for 3 months. While CH is difficult to diagnose in the ED, the patient's recurrent hemoptysis related to menstruation was a clue to the presence of CH. Therefore, physicians should determine the relationship between hemoptysis and menstruation for women of childbearing age presenting with repeated hemoptysis without a definite cause.

Keywords: Emergency; Endometriosis; Hemoptysis; Menstrual cycle; Menstruation

**Introduction**

Hemoptysis is a common respiratory symptom occurring in 7%–15% of patients with respiratory disease [1]. Pulmonary tuberculosis, bronchiectasis, lung cancer, and bronchitis are the most common causes of hemoptysis. In addition, while approximately 40 other conditions can cause hemoptysis, the cause cannot be identified in about 30% of cases [2]. Massive hemoptysis, defined as bleeding of more than 100 mL at one time or more than 400–600 mL in 24 hours, is associated with high mortality but occurs in only 1.5% of cases. Most hemoptysis cases do not present a life-threatening situation and usually resolve within 24 hours. However, hemoptysis is a major cause of emergency department (ED) visits because its occurrence is anxiety-inducing for both patients and caregivers [3]. Because recurrent hemoptysis lowers patient quality of life and causes anxiety, ED visits increase in patients searching for the cause of their hemoptysis. Here, we present a case of a young woman who presented with recurrent hemoptysis for 2 years without a definite cause.

**Case**

A 26-year-old woman visited our ED for 2 days with recurrent hemoptysis. The woman produced blood-tinged sputum and the frequency of hemoptysis had increased gradually over 2 days. Her first hemoptysis event had occurred 2 years prior. The hemoptysis
stopped without any special treatment but had recurred every 2–4 months. When hemoptysis had recurred 5 months prior, the patient had again visited the hospital. While her chest radiograph was unremarkable, chest computed tomography (CT) showed a lesion with a focal ground-glass opacity (GGO) pattern in her right lung (Fig. 1A). No abnormal findings were found in other examinations, including bronchoscopy. Her tuberculin test was negative. The hemoptysis improved after 2 days and the GGO-pattern lesion disappeared on follow-up CT. She had a 2 pack-year smoking history. The patient had no other known disease or family history. She was married but had never given birth. There was no history of pelvic surgery. Her menarche began at 14 years and her menstrual period was regular but with mild dysmenorrhea.

On presentation, the patient’s blood pressure was 124/83 mmHg, pulse rate was 76 beats/min, oxygen saturation was 98%, and she was afebrile. Her lung auscultation was clear. The laboratory results included a hemoglobin concentration of 10.9 g/dL and platelet count of 373 K/μL. Her prothrombin/activated partial thromboplastin times were normal, at 13.4/30.8 seconds. Serum profiles including blood chemistry, electrolyte, and liver and renal function tests were normal. The serum levels of tumor markers such as cancer antigen 125 (CA 125) were not evaluated. Her urine was red in color. Chest radiographs were unremarkable. CT chest scans showed a focal GGO pattern in the right lower lung field in the same location as the lesion observed 5 months prior (Fig. 1B). While investigating the cause of her red-colored urine, we learned that the patient was on day 4 of her menstrual cycle and that her hemoptysis frequently occurred during menstruation. Based on her history of frequent hemoptysis during menstruation with no other cause of hemoptysis, she was tentatively diagnosed with catamenial hemoptysis (CH). The patient was referred to a gynecologist for pelvic examinations, with no remarkable findings from ultrasonography or pelvic examination. Video-assisted thoracoscopic surgery (VATS) was planned for histological confirmation. However, she was reluctant to agree to surgical resection for diagnosis. The gynecologist administered gonadotropin-releasing hormone (GnRH, 3.75 mg Leuplin DPS®) subcutaneously for control of her recurrent hemoptysis. She visited the gynecological clinic and additionally received GnRH injection once monthly for 3 months, during which time there was no recurrence of hemoptysis.

Discussion

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity. Endometriosis is estimated to affect 3%–10% of fertile and 2%–5% of post-menopausal women. It is usually confined to the pelvis and rarely occurs in extra-pelvic areas. Thoracic endometriosis syndrome (TES) refers to the various clinical and radiological manifestations associated with the deposition of endometrial tissue in the lung parenchyma, pleura, diaphragm, and/or tracheobronchial tree. The incidence of TES is very rare. Nearly all cases have been reported through case reports and small retrospective series [4,5]. The four main types of TES are catamenial pneumothorax, catamenial hemothorax, CH, and lung nodules. Of these, CH is an extremely rare manifestation, occurring in 7% of all TES cases [6].

Fig. 1. Chest CT scan performed during menstruation. (A) A GGO lesion (arrow) is visible in the right lower lung field on chest CT performed 5 months prior. (B) A similar GGO lesion (arrow) is also visible in the same position in chest CT performed in the emergency department for hemoptysis. CT, computed tomography; GGO, ground-glass opacity.
CH was first reported by Lattes et al. in 1956 and approximately 74 cases have been reported in the English literature since that time [7]. Unlike other forms of TES, pleuritic chest pain is not a common clinical presentation and symptoms may not occur with every menstrual cycle [8]. Fatal hemoptysis from CH has not yet been reported but it may cause life-threatening asphyxiation. Recent studies have reported massive hemoptysis requiring bronchial embolization in CH [9,10]. In addition, recurrent hemoptysis by CH can reduce the quality of life of patients due to the associated respiratory symptoms and anxiety. Therefore, early recognition of CH has significance for patients. However, CH is not easy to diagnose because of the limited number of cases and its nonspecific physical examination, laboratory, and imaging findings. Auscultation is generally unremarkable and chest radiography and CT findings are nonspecific. Increased serum CA 125 levels have been reported, but only in patients with concurrent pelvic endometriosis [11]. Histologically, pulmonary endometriosis can be diagnosed when endometrial tissue is found in the lung parenchyma. Because most pathological lesions are located around the lung parenchyma, the role of bronchoscopy in diagnosis is limited [12]. Currently, VATS, which can directly observe the lung parenchyma, is the preferred method for histologic diagnosis; however, this method is invasive and can lead to complications [8]. CH is diagnosed by identification of the characteristic cyclic hemoptysis associated with menstruation after excluding other pulmonary causes of hemoptysis, for which treatment can be started on that basis [3]. Chest CT scans in CH often show nonspecific findings such as ill- or well-defined opacities, nodules, thin-walled cavities, bullous formations, and GGO patterns [13,14]. Although the results are nonspecific, a comparison of serial CT scans not only helps in the detection of CH but also in determining the underlying causes of the hemoptysis [9,15]. Pelvic endometriosis may help clinicians to suspect CH; however, TES is not always accompanied by pelvic endometriosis. While 50%–85% of women diagnosed with TES have concomitant pelvic endometriosis, the incidence of TES in women with pelvic endometriosis is unknown [16].

CH can be treated medically or surgically; however, there are no clear treatment guidelines. Hormone therapy, including GnRH, oral contraceptives, progesterone drugs, and danazol, is commonly used for the treatment of CH. Our patient had no hemoptysis recurrence for 3 months with GnRH; however, long-term follow-up was not performed. With medical treatment alone, hemoptysis in CH recurs in up to 50% of patients [16]. Considering the pathogenesis of TES, inhibiting estrogen stimulation by removing endometrial tissue is reasonable and recent studies support the efficacy of combined surgical and medical therapy [8,17].

In conclusion, despite recent advances in diagnostic techniques, CH is not easy to diagnose in the ED due to the scarcity of cases and its nonspecific examination results. However, recurrent hemoptysis due to CH causes not only patient anxiety and discomfort but may also cause asphyxia or massive hemoptysis. When ruling out the common causes of hemoptysis, identification of the relationship between hemoptysis and menstruation is helpful for the diagnosis of CH. Therefore, physicians should assess this relationship in women of childbearing age presenting with repeated hemoptysis without a definite cause.

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Conflicts of interest
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Purulent pericarditis: subdiaphragmatic supplicative focus

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Introduction

Purulent pericarditis is defined as a localized pericardial infection with gross pus formation in the pericardial space. Although purulent pericarditis is now rare in the antibiotic era, if it is not diagnosed quickly, it may be life-threatening. We describe a rare case of purulent pericarditis that originated from a subdiaphragmatic supplicative focus in an immunocompromised host.

Case

A 53-year-old man was admitted to the emergency department with drowsiness. He was a heavy alcoholic and had a past medical history of diabetes and chronic hepatitis C (CHC). One month previously, he underwent surgery for peritonitis, which was related to a suspected perforation of a sigmoid colon diverticulum. The surgeon performed a segmental resection of the sigmoid colon, but could not detect any definite perforation site during the operation. The initial blood pressure was 80/50 mmHg, and body temperature 36°C. The laboratory findings revealed a white blood cell (WBC) count of 13,980/µL, hemoglobin of 7.8 g/dL, platelet count of 214 K/µL, and elevated creatinine of 5.85 mg/dL, C-reactive protein of 24.6 mg/dL (range, < 0.5 mg/dL), and procalcitonin of 31.9 ng/mL (range, < 0.5 ng/mL). An arterial blood gas analysis on a 2 L/min oxygen supplement via a nasal cannula revealed the following: pH 7.371, partial pressure of carbon dioxide of 16.8 mmHg, partial pressure of oxygen 189 mmHg, HCO₃⁻ 9.5 mmol/L, and oxygen saturation 99.5%. A chest X-ray revealed an enlarged cardiac silhouette with pulmonary edema (Fig. 1A). Non-contrast chest computed tomography (CT) revealed large pericardial and pleural effusions (Fig. 1B, 1C), and echocardiography revealed a large pericardial effusion with non-homogeneous echogenicity (Fig. 1D). In view of the septic condition, an emergency pericardiocentesis via a subxiphoid approach was performed with drainage (500 mL) of pus (Fig. 2). The patient's
blood and pericardial fluid were collected for cultures and he was started on intravenous (IV) vancomycin and meropenem. The pericardial fluid analysis revealed a WBC count of 400,000/µL (polymorphonuclear leucocytes 65%), glucose of 2 mg/dL, adenosine deaminase of 270.5 IU/L, and lactate dehydrogenase of 29,632 IU/L. A Gram stain of the pericardial fluid revealed Gram-negative rods ( >30 per oil immersion field), and the acid-fast bacilli stain was negative. Cytology of the pericardial fluid was negative for the presence of atypical or malignant cells. On the 6th hospital day, the culture from the pericardial effusion grew extended-spectrum β-lactamase negative Escherichia coli. The blood cultures were negative. Follow-up echocardiography on the
11th hospital day revealed a pericardial adhesion and thickening with a constrictive physiology (29% respiratory variation of the mitral E wave velocity and septal bouncing motion).

His clinical symptoms and laboratory findings gradually improved with continuous renal replacement therapy, and IV meropenem was continued for 3 weeks. A contrast abdominal CT scan, performed on the 9th hospital day, showed a segmental wall thickening of the rectosigmoid junction with adjacent free air, which was suspected of being a rectal malignancy with a microperforation (Fig. 3). The carcinoembryonic antigen level was 13.8 ng/mL (range, <10 ng/mL). The fever subsided on the 9th hospital day, and he was discharged without any abdominal symptoms on the 19th hospital day. He was transferred to the department of colorectal surgery, and underwent an open low anterior resection operation for rectosigmoid lesions. A direct invasion of the main colorectal mass into the adjacent tissue was detected during the operation, and a biopsy confirmed the adenocarcinoma. A follow-up echocardiography 6 months later revealed a slightly improved pericardial adhesion and thickening without an effusion.

Discussion

Purulent pericarditis is relatively uncommon in the antibiotic era, and occurs in less than 1% of patients presenting with acute pericarditis [1]. In the pre-antibiotic era, the major cause of purulent pericarditis was a primary infectious disease, such as pneumonia [2]. However, the predisposing factors have since changed to pre-existing pericardial diseases, alcohol abuse, immunosuppression, surgery, and trauma [3]. Our patient was also an immunocompromised host with several predisposing factors such as alcohol abuse, diabetes, CHC, current abdominal surgery, and malignancy.

There are several mechanisms by which purulent pericarditis can develop: a direct spread of a thoracic infectious focus [4], hematogenous spread [5], and very rarely as an extension from a
subdiaphragmatic suppurative focus [6]. Further, few strains of bacteria causing pericarditis have been identified. Streptococcal pneumonia [7] has been reported to be associated with respiratory infections or to occur after respiratory procedures. Purulent pericarditis caused by an intraperitoneal infection, such as Salmonella enteritis, has also been reported in an immunosuppressed host [8]. The purulent pericarditis in this patient was presumed to have developed due to bacterial seeding of a subdiaphragmatic focus, considering a current history of peritonitis surgery, pericardial fluid culture of E. coli, and colorectal malignancy with a suspected microperforation.

The cause of purulent pericarditis should also be considered to originate from a subphrenic focus if the patient has not had a recent respiratory tract infection. In this case, the Gram-negative strains could be covered by a broad spectrum antibiotic because the Gram stain was confirmed early. Therefore, a detailed medical history including one of recent infection needs to be elicited.

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Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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References
Whole lung lavage using a rapid infusion system to treat a patient with pulmonary alveolar proteinosis

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Whole lung lavage (WLL) is a therapeutic procedure to remove accumulated material by infusing and draining the lungs with lavage fluid. This procedure has been regarded as the current standard of care to treat pulmonary alveolar proteinosis. However, the WLL protocol has not yet been standardized and the technique has been refined and modified a number of times. A rapid infusion system is a device used to infuse blood or other fluids at precise rates and normothermic conditions. This device is not typically used in WLL, which relies on the passive infusion of fluids using the gravitational force. However, in this study we performed WLL using a rapid infusion system, since we aimed to take advantage of its shorter operation time and greater degree of control over fluid volume and temperature. The patient's symptoms improved without the occurrence of any complications.

Keywords: General anesthesia; Infusion pump; Lung lavage; Pulmonary alveolar proteinosis

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare disorder that is characterized by accumulation of lipoproteinaceous material within alveoli, which impairs gaseous exchange and leads to progressive respiratory insufficiency [1]. PAP prevalence has been estimated to be in 0.37/100,000 individuals [2]. Lipoproteinaceous material typically accumulate within the alveoli due to the impaired surfactant catabolism of alveolar macrophage [3]. Whole lung lavage (WLL) is widely practiced and currently used as a standard of care to physically remove the lipoproteinaceous material from the affected lung [4]. Recently, it has become common knowledge that the autoantibodies or abnormalities of granulocyte macrophage colony-stimulating factor (GM-CSF) is one of the major causes of PAP, which may be ameliorated by a medical treatment to supplement GM-CSF.

Of these treatment modalities, WLL is typically performed with the passive infusion of lavage fluid using the gravitational force. However, in a number of cases WLL was performed with a rapid infusion system [5], which is advantageous considering the fact that it can be used to adjust the volume of infused fluid while regulating the pressure applied during infusion. Additionally, it can heat the infusion fluid to help maintain the body temperature. We have focused on these advantages of a rapid infusion system and have reported here that a rapid infusion system was safely used in WLL.

Case

The patient provided written informed consent for publication of the research details and clinical images.

A 46-year-old man 166 cm tall and weighing 67 kg, presented
with symptoms of dyspnea after exercise for 5 months, but did not undergo treatment for the same. He had a history of smoking 20-packs of cigarettes per year without an underlying diseases. One week before visiting our hospital, he was treated with pneumonia specific antibiotics and steroids in another hospital. However, there was no improvement in his symptoms, following which he visited our hospital. He underwent a high-resolution computed tomography (HRCT) and transbronchial lung biopsy, all of which were consistent with the diagnosis of PAP. An HRCT of the chest revealed a ground glass opacity and an irregular crazy paving appearance in the left upper and right upper and lower lung fields (Fig. 1). On histopathologic pulmonary biopsy, no malignant cells were found, but the presence of amorphous proteinaceous substances in the lung alveoli was confirmed (Fig. 2).

At the time of diagnosis, arterial blood gas (ABG) analysis under room air revealed severe hypoxemia with pH 7.45, arterial partial pressure of carbon dioxide (PaCO₂) 36.5 mmHg, arterial partial pressure of oxygen (PaO₂) 48.7 mmHg, bicarbonate (HCO₃⁻) 25.1 mEq/L, arterial saturation of oxygen (SaO₂) 86.6% (Table 1) and an alveolar arterial gradient 55.4 mmHg. Pulmonary function tests revealed a normal but decreased lung diffusing capacity, with a forced vital capacity (FVC) of 4.08 L (95% of predicted value), a forced expiratory volume in 1 second (FEV₁) of 3.16 L (96% of predicted value), a ratio of FEV₁/FVC 77%, and diffusing capacity of the lungs for carbon monoxide of 57% of predicted value. We decided to perform therapeutic WLL considering the lack of improvement in the patient's clinical symptoms and hypoxemia. Based on the radiographic findings, we decided to first lavage the right lung, which seemed to be affected to a greater degree.

We administered oxygen (6 L/min) via a nasal cannula. The patient had entered the operation room while appearing to be mentally alert and subsequently, electrodes from an electrocardiogram, pulse oximeter, noninvasive blood pressure (BP) monitor, and bispectral index (BIS) monitor were attached to the patient. The radial artery catheter was placed under local anesthesia to

![Fig. 1. Pre-whole lung lavage HRCT findings. HRCT scan shows ground glass opacities and crazy paving pattern.](image1)

![Fig. 2. Transbronchial lung biopsy specimen from right lower lobe shows intraalveolar pinkish proteinaceous material (arrows), consistent with pulmonary alveolar proteinosis (hematoxylin and eosin stain, ×400).](image2)

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<th>Table 1. Arterial blood gas analysis</th>
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<td><strong>FiO₂, fraction of inspired oxygen; PaCO₂, arterial partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen; HCO₃⁻, bicarbonate; SaO₂, arterial saturation of oxygen.</strong></td>
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**Arterial blood gas analysis was done under O₂ 6 L/min via nasal prongs before induction of anesthesia.**
moved into a supine position and was transferred to the intensive care unit (ICU) after exchanging a double-lumen endotracheal tube for a single lumen endotracheal tube.

In the ICU, the patient was provided to ensure pressure controlled mechanical ventilation with the pressure of 14 mmHg, an inhaled oxygen concentration of 0.45 and respiratory rate of 18 breaths/min. ABG analysis revealed pH 7.41, PaCO\(_2\) 32.0 mmHg, PaO\(_2\) 103.0 mmHg, HCO\(_3^-\) 20.3 mEq/L, and SaO\(_2\) 98% (Table 1). The patient was extubated 4 hours after ICU admission, and pulse oxygen saturation was maintained at 95% or more under administration of oxygen (4 L/min) via a nasal cannula. Four days later, the left lung was treated with the same procedure. After the clinical symptoms improved, he was discharged after 1 week. ABG analysis that was performed right before the patient’s discharge revealed pH 7.39, PaCO\(_2\) 38.7 mmHg, PaO\(_2\) 87.2 mmHg, HCO\(_3^-\) 22.8 mEq/L, and SaO\(_2\) 96.1% (Table 1).

**Discussion**

PAP was first described by Rosen et al. [6] in 1958, since the accumulation of lipoproteinaceous material in the alveoli lead to nonspecific symptoms such as cough, hypoxemia, and dyspnea. Histopathologic examination reveals that presence of lipoproteinaceous material in the alveoli. Radiographic appearance of PAP are extensive bilateral infiltration on chest radiograph and ground-glass opacifications which is commonly referred to as crazy paving on computed tomography images. However, there is often a dissociation between the extent of radiographic abnormalities and severity of the symptoms and physical findings [1], and variable/ nonspecific clinical symptoms delay PAP diagnosis [7]. PAP has been classified into three types according to the developmental

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**Fig. 3.** Left lateral decubitus position (lavage side up) and application of a Y-connector attached to the double lumen endotracheal tube.
mechanism: congenital, idiopathic, and secondary. Idiopathic PAP mentioned in this study is considered to represent approximately 90% of PAP cases. According to Inoue et al. [8] in 2008, the male to female ratio was 2.1:1, the median age at diagnosis was 51 years, and a history of smoking occurred in 56%.

The pathogenesis of PAP has remained unclear for several decades after its first report. However, a report in 1994 that used knockout mice which were deficient in GM-CSF gene demonstrated similar pulmonary pathology as human PAP and subsequently provided a fresh perspective on the causes of the disease [9]. PAP results from an accumulation of surfactant that appeared to occur due to impaired clearance and not its overproduction [10]. In addition, autoantibody against GM-CSF was found to be present in all specimens of bronchoalveolar lavage fluid obtained from 11 idiopathic PAP patients [11]. Therefore, it is now accepted that dysfunction of alveolar macrophages caused by abnormalities of GM-CSF due to autoantibodies leads to the condition of idiopathic PAP. This finding has been associated with medical treatment modalities that include exogenous GM-CSF [12].

These novel therapeutic modalities for PAP have prompted the necessity of evaluating the efficacy of WLL, which was presented by Ramirez et al. [13] in 1963 as the primary treatment modality. According to a study by Gay et al. [14] in 2017, the effectiveness of WLL was demonstrated by the improvement of short-term clinical symptoms, including arterial partial pressure oxygen after lavage although the application of the WLL technique was variable. The use of exogenous GM-CSF supplementation as the first line of therapeutic intervention has its limitations due to a lack of placebo-controlled randomized trials with large sample sizes [15]. Additionally, randomized trials that have compared WLL with exogenous GM-CSF supplementation therapies have not yet been performed [15]. Therefore, we decided to perform WLL first.

The primary indications for WLL include decreased pulmonary function, decreased arterial oxygen saturation at rest, and abnormal radiographic findings. All of these were present in this case [16]. Complications that may occur during WLL are fever, hypoxemia, pneumonia, and pneumothorax, all of which were absent in this case. Due to a lack of a standardized protocol, there are various aspects of the procedure which function under the premise of physically removing the accumulated lipoproteinaceous material by washing the alveoli. However, in most institutions, lavage is performed under general anesthesia with lung isolation [17]. There are several variations considering the anesthetic maintenance agent, the choice of lung to be lavaged, the patient’s position at the time of lavage, the volume of lavage fluid, and the method of chest percussion [16].

Here, the right lung appeared to be in a poorer condition on the radiographic findings was lavaged first, and left lung lavage was followed after 4 days. The patient was positioned in the lateral decubitus position and manual chest percussions were performed by an assistant during the lavage. Infusing fluid by gravity is widely selected method among institutions. However, we adopted a rapid infusion system which has an advantage of shortening lavage time and maintaining constant temperature and pressure; furthermore, decreases labor intensity by reducing the need for fluid replacement, controlling accurate infusion rate in real time, and measuring the amount of infused fluid accurately [18]. Although it was possible to perform bilateral sequential lung lavage in one session, we performed a single lung lavage in one session. Since this was the first time that we adopted a rapid infusion system for WLL, we had to consider possible adverse effect of using a rapid infusion system for WLL.

Possible adverse effect of using a rapid infusion system could be caused by barotrauma. Observing the infusing pressure in real time seemed to be helpful. In practice, it is recommended to use a liquid bag placed 50 cm above the thoracic cavity [17], for which the pressure would be equal to 36.78 mmHg. The average pressure observed in this case was 22 mmHg at the time of infusion (Fig. 4). Barotrauma caused by a rapid infusion system was not observed in clinical and radiological aspects. The use of a rapid infusion system resulted in a shorter procedural time than other cases which used similar amount of fluid [19].

There is no consensus regarding the total volume of infusion in WLL, and it varied significantly 5–40 liters of saline [16]. Most institutions repeat the infusion and drainage until the effluent is relatively clear by visual inspection. In a previous case of using a

![Fig. 4. Intraoperative monitored vital sign denoted as 'central venous pressure' (arrow) shows pressure of injected fluid to the right lung.](https://doi.org/10.12701/yujm.2019.00360)
rapid infusion system for WLL, 8.5–16 liters of normal saline was used [5]. In our opinion, a rapid infusion system will help to shorten operation time when relatively large volume of infusion is needed. However, further reports and studies are needed to establish the cutoff volume of infusion in using a rapid infusion system for WLL.

In this case, the discordance of the volume of infusion and drainage might suggest leakage into the contralateral lung. However, it was our understanding that leakage did not occur in regards of not quantifying the amount of last aspiration fluid, achieving successful lung isolation; furthermore, there was no evidence or suspicion of leakage, which presented by a desaturation on the monitoring equipment. In addition, there were no post procedural complications such as respiratory insufficiency and hypoxemia, which might occur when the fluid had leaked [20]. The average pressure at the time of infusion was low when using a rapid infusion system; however, it should be considered that there is a possibility of using high pressure since the difference in pressure depends on the characteristics of the rapid infusion system.

WLL is performed as the main treatment modality for PAP, but the treatment method needs to be standardized and various methods are used. In conclusion, we successfully performed WLL with a rapid infusion system which has several advantages such as: shortening the lavage time, maintaining constant temperature and pressure without adverse effects caused by barotrauma.

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**Conflicts of interest**
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