

**ORIGINAL RESEARCH****Factors in infertility score on referral and non-referral cases who underwent In Vitro Fertilization (IVF) treatment at a fertility clinic in Surabaya, Indonesia**Nadhif Rashesa Brahmana<sup>1</sup>, Ashon Sa'adi<sup>2</sup>, Rina Yudiwati<sup>3</sup><sup>1</sup>Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, <sup>2</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, <sup>3</sup>Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.**ABSTRACT**

**Objectives:** To examine the factors used in infertility score on referral and non-referral cases who underwent IVF treatment at Fertility Clinic of Graha Amerta, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2014-2016

**Materials and Methods:** This research was a descriptive analytic retrospective study using secondary data from medical records at Fertility Clinic of Graha Amerta in 2014-2016. With a total sampling technique, total of 342 referral and non-referral infertility cases were obtained. The variables of this study were the factors used in infertility score.

**Results:** From total of 342 cases, 44% had a wife's age in the range of 30-35 years, 80.1% had an infertile duration of  $\geq 3$  years, and 54.7% had one type of pelvic pain, 68.4% still had regular menstrual cycles, and about 76% did not have a history of pelvic infection. On sperm analysis factor, there were 27.5% of men who fell into the severe category according to infertility score. There was a significant difference from the duration of infertility and sperm morphology in referral and non-referral cases.

**Conclusion:** Infertility score can be useful because each case has its own infertility factors with different degrees of severity, which leads to infertility.

**Keywords:** Infertility; infertility score; In Vitro Fertilization (IVF); maternal health.

**ABSTRAK**

**Tujuan:** Mengkaji gambaran faktor dalam skor infertilitas pada kasus rujukan dan non rujukan yang menjalani tindakan IVF di Klinik Fertilitas Graha Amerta RSUD Dr. Soetomo, Surabaya, Indonesia, periode 2014-2016.

**Bahan dan Metode:** Penelitian ini merupakan deskriptif analitik retrospektif dengan menggunakan data sekunder dari rekam medis di Klinik Fertilitas Graha Amerta tahun 2014-2016. Dengan teknik total sampling didapatkan total 342 kasus infertilitas rujukan dan non rujukan. Variabel penelitian ini adalah faktor-faktor yang dipakai dalam skor infertilitas

**Hasil:** Dari total 342 kasus, sebanyak 44% memiliki umur istri dalam rentang 30-35 tahun, 80.1% memiliki lama infertil  $\geq 3$  tahun, dan 54.7% memiliki satu macam nyeri, 68.4% masih mempunyai siklus haid teratur dan sekitar 76% kasus tidak memiliki riwayat infeksi panggul. Pada faktor analisa sperma, didapatkan 27.5% dari pria yang masuk dalam kategori berat menurut skor infertilitas. Didapatkan perbedaan yang signifikan dari lama menikah dan morfologi sperma pada kasus rujukan dan non-rujukan.

**Simpulan:** Skor infertilitas dapat bermanfaat karena setiap kasus memiliki faktor infertilitasnya masing-masing dan dengan derajat keparahan yang berbeda-beda sehingga menyebabkan terjadinya infertilitas.

**Kata kunci:** Infertilitas; skor infertilitas; Fertilisasi In Vitro (FIV); kesehatan ibu.

**\*Correspondence:** Nadhif Rashesa Brahmana, Medical Program, Faculty of Medicine, Universitas Airlangga, Jalan Prof Dr Moestopo 47, Surabaya 60131, Indonesia. E-mail: nadhifrb@gmail.com

- pISSN:0854-0381 • eISSN: 2598-1013 • doi: <http://dx.doi.org/10.20473/mog.V30I22022.58-65>
- Maj Obs Gin. 2022;30:58-65 • Received 15 Nov 2021 • Revised 3 Mar 2022 • Accepted 18 Mar 2022 • Published 1 Aug 2022
- Open access under CC-BY-NC-SA license • Available at <https://e-journal.unair.ac.id/MOG/>

## INTRODUCTION

Infertility is a complex problem that can often be found especially in married couples who desire to have children. It can have a big impact on many aspects of our lives, such as medically, psychologically, or even economically. It is necessary to know that there are actually many factors from both partners that can affect this condition. The incidence of infertility also increases over time. In 2010, it was estimated about 48.5 million couples around the world has infertility, of which 14.4 million of them came from Asia.<sup>1</sup> Likewise in Indonesia, it was stated the incidence rate of infertility in Indonesia is around 10-22% of the total reproductive age couples.<sup>2</sup>

There are also several obstacles of treating infertility in Indonesia, such as its vast and archipelagic geographic condition, the lack of health service capabilities and the uneven distribution of socioeconomic, educational and cultural conditions. Therefore, a fast, structured, and targeted infertility service system is needed. If they're late to be treated, it will increase the likelihood of complications in infertile patients, especially those related to their aging process.

To overcome this, an instrument was made by a professor of Obstetrics and Gynecology from Airlangga University, which can help medical personnel to detect infertility quickly, namely through the scoring system of infertile patients. This infertility score can be used as an initial screening, making it easier for health workers in their work field to differentiate which infertile couples are classified as mild, moderate, or severe, and also the appropriate level of health service for each score. The factors assessed in the score are a combination of female and male factors, including wife's age, menstrual cycle, sperm analysis, and others.<sup>3</sup> After counting the score, the next step is to the treatment itself, ranging from just giving information and education about fertility, until treatment that requires careful calculation and special skills, such as by in vitro fertilization (IVF).

Several studies on IVF have been conducted before, but there is not much about this infertility score, specifically discussing each factor that is being used in it. It's important to know more about these factors, so hopefully health workers can easily differentiate infertility cases, based on each factor that are being used. Therefore, the researcher wanted to know and study the description of the factors in the infertility score in referral and referral cases who underwent IVF at the Graha Amerta Fertility Clinic, Dr. Soetomo Hospital, Surabaya, for the period 2014-2016.

## MATERIALS AND METHODS

The design of this study was a descriptive analytical study, which is intended to provide a complete and clear picture of the variables to be studied. The data of this study is from secondary data, which was gained specifically from the medical record. Incomplete medical records were excluded from this study. This research was conducted in Graha Amerta Fertility Clinic, Dr. Soetomo General Academic Hospital, Surabaya, from January – June 2020. The population of this research is all infertile cases at Graha Amerta Fertility Clinic. Sample of the research is all infertile cases (referral and non-referral) who underwent IVF treatment at Graha Amerta Fertility Clinic. Incomplete medical records were excluded from this study. Total sampling method is used in this study.

Variables of this study are factors that are being used to calculate the infertility score, which are wife's age, duration of infertility, menstrual cycle, pelvic pain, history of pelvic infection and Intrauterine Device (IUD), and sperm analysis which include concentration, motility, and morphology of the sperm. The type of data used in this study is secondary data, which were obtained from the medical records of Graha Amerta Fertility Clinic. The data collected will be processed and analyzed by using SPSS software, then will be described in the discussion.

## RESULTS AND DISCUSSION

There were total of 342 infertility cases that were included in this study from all cases available from 2014-2016 at the Graha Amerta Fertility Clinic in Surabaya. Among those cases, there were 183 referral cases and 159 non-referral cases. [Table 1](#) shows the characteristics of those cases based on factors used to calculate the infertility score. Each factor has their own parameter or certain value that can later be categorized as mild, moderate, and severe. Most of the factors are from the women such as their age, menstrual cycle, and others. The only male factor is sperm analysis, which includes concentration, motility, and morphology of the sperm. The final result of the score is obtained after taking into account all factors from both women and men. Based on the result of this study, it was found that there are only two factors from the infertility score, which is significantly different between referral and non-referral cases, which are the duration of infertility ( $P = 0.014$ ) and the sperm morphology ( $P = 0.038$ ).

Table 1. Infertile cases characteristics based on factors in infertility score

Characteristics based on the Infertility Score	Number of referral cases (%)	Number of non-referral cases (%)	Total cases (%)
<b>Wife's age</b>			
< 30 years	45 (24.6)	43 (27)	88 (25.7)
30-35 years	86 (47)	64 (40.3)	150 (43.9)
> 35 years	52 (28.4)	52 (32.7)	104 (30.4)
<b>Duration of infertility</b>			
1-2 years	11 (6)	14 (8.8)	25 (7.3)
> 2 years	15 (8.2)	28 (17.6)	43 (12.6)
≥ 3 years	157 (85.8)	117 (73.6)	274 (80.1)
<b>Menstrual cycle</b>			
Normal	119 (65)	115 (72.3)	234 (68.4)
Oligomenorrhea	61 (33.3)	42 (26.4)	103 (30.1)
Amenorrhea	3 (1.6)	2 (1.3)	5 (1.5)
<b>Pelvic pain</b>			
Negative	89 (48.6)	71 (44.7)	160 (46.8)
1 type of pain	93 (50.8)	87 (54.7)	180 (52.6)
≥ 2 types of pain/adnexal mass	1 (0.5)	1 (0.6)	2 (0.6)
<b>History of pelvic infection &amp; IUD</b>			
Negative	142 (77.6)	118 (74.2)	260 (76)
Once/IUD	34 (18.6)	36 (22.6)	70 (20.5)
≥ 2 times	7 (3.8)	5 (3.1)	12 (3.5)
<b>Sperm concentration</b>			
≥ 20 million/ml	141 (77)	137 (86.2)	278 (81.3)
10-20 million/ml	14 (7.7)	5 (3.1)	19 (5.6)
< 10 million/ml	28 (15.3)	17 (10.7)	45 (13.2)
<b>Sperm motility (a+b)</b>			
≥ 50 %	131 (71.6)	129 (81.1)	260 (76)
25-50 %	16 (8.7)	6 (3.8)	22 (6.4)
< 25 %	36 (19.7)	24 (15.1)	60 (17.5)
<b>Sperm morphology (normal)</b>			
≥ 15 %	122 (66.7)	125 (78.6)	247 (72.2)
5-15 %	24 (13.1)	16 (10.1)	40 (11.7)
< 5 %	37 (20.2)	18 (11.3)	55 (16.1)

### Wife's age

Wife's age is the first factor in infertility score. From the analysis, it was found that from all 342 infertile cases, most of them are 30-35 years old, which is 150 women (43.9%), followed by 104 women (30.4%) who are more than 35 years old and 88 women (25.7%) who are less than 30 years old. When viewed based on the type of referral, the results of the Chi-square statistical test showed that there was no significant difference between the ages of the wives of referral and non-referral cases ( $P = 0.450$ ). From the data obtained, it is true that the age of the wife in referral and non-referral cases is not much different, most of them are 30-35 years old, which is in the moderate category according to infertility score.

This study is similar to several studies that have been conducted before. A study in 2015 at the fertility clinic of Putri Hospital, Surabaya, found that, out of 83

infertile cases, more than half (57.8%) were between 26-35 years old.<sup>4</sup> Another study on a total of 212 infertile women in three different fertility clinics in three major cities of Indonesia (Jakarta, Surabaya, Bali) found 40% of those aged 30-35 years.<sup>5</sup>

Infertility is closely related to age, especially in women or wives. According to theory, as a woman gets older her fertility will decrease due to several reasons. Unlike men, who will continue to produce sperm throughout their lives, women are born with all the follicles they will have throughout their lives, so it can be said that the number will only gradually decrease as they get older. At birth there are about 1 million follicles, at puberty it will decrease to about 300 thousand follicles, and among them only about 300 will be released at ovulation during their reproductive period.

The quality of the ova also decreases with age. An important change in the quality of the ovum is the

frequency of the genetic abnormality of aneuploidy, which is an insufficient or too many chromosome counts in the ovum. This will decrease the likelihood that women can get pregnant and also increases the likelihood of miscarriage in older women.<sup>6</sup> It is also said that women's fecundity decreases gradually but significantly starting from the age of 32 years and decreases more rapidly after the age of 37 years. This is due to the decreasing quality of the ovum and also, with age, the risk of diseases that can affect fertility, such as leiomyoma, tubal disease, and endometriosis also increases.<sup>7</sup> The trend of infertility cases where many are found at the productive age (<35 years) is not only because the physiology of the body decreases with age, but is also influenced by several other factors such as lifestyle, behavior, level of stress, diet, work and daily activities. It can also have effect to the body as a whole and to fertility conditions.

### Duration of infertility

The second factor in infertility score, which is the duration of infertility, also plays a big role in determining the degree of infertility. From the analysis, it was found that from all 342 cases, most of them have been infertile for three years or more, which is 274 cases (80.1%), and only 25 cases (7.3%) that have duration of 1-2 year. There was also found one case with the duration of 20 years.

The duration of infertility is high in relation to the first factor, which is wife's age. The longer the duration of infertility in women, the more their age will be. One study suggests that the length of marriage affects the causes of infertility. In couples with length of marriage less than five years, the causes of PCOS and tubal factors due to sexually transmitted diseases are common. Whereas in couples with a length of marriage more than five years, what is often encountered is idiopathic infertility and male infertility. This is related to the increasing age of both partner which results in decreased quality and quantity of both ovum and sperm.<sup>8</sup>

This duration of infertility factor is also important to be considered in treating infertility. It has been said that the age of the woman and the duration of infertility are important factors in determining specific therapy for partners, where the age of more than 35 years and also long duration of infertility are suitable candidates for IVF treatment.<sup>9</sup>

When viewed based on the type of referral or non-referral cases, there was a significant difference between the duration of infertility for referral and non-referral cases ( $P = 0.014$ ). Duration of  $\geq 3$  years, which is the

severe category according to infertility score, was more prevalent in referral cases (85.8%). Meanwhile, the duration of 1-2 years, or the mild category according to the infertility score, was found more in non-referral cases (8.8%). This difference could happen due to the referral cases usually tend to have more complicated conditions than non-referral cases, which may result in longer or shorter duration of infertility.

### Menstrual cycle

Menstrual cycle was chosen as the third factor in infertility score because of its high relation to ovulation disorders, which may affect fertility. From the analysis, it was found that from all 324 cases, 234 of them (68.4%) still have a regular or normal menstrual cycle, and only five cases (1.5%) have amenorrhea. When viewed based on the type of referral or non-referral case, there was no significant difference between the menstrual cycle for referral and non-referral cases ( $P = 0.350$ ), most of them still have regular menstrual cycles, which is in the mild category according to the infertility score.

The average duration of a menstrual cycle is 28 days, with the most common occurring between 25-30 days. If the menstrual cycle is more than 35 days, it is called oligomenorrhea. And if there is no menstruation after three or more cycle, it is called amenorrhea.<sup>3</sup> Irregular menstrual cycles often occur when women are in the early and late stages of reproductive age (menarche and menopause) due to anovulation and inadequate follicular development.

Several studies also found an association between menstrual cycle duration and fecundity. A study stated that short menstrual cycles, menarche at a young age, and heavy menstrual bleeding are associated with reduced fecundity. So in this case it indicates that the characteristics of the menstrual cycle can be used as a marker of potential fertility in those planning a pregnancy.<sup>10</sup> Apart from physiological factors, irregular menstrual cycles can also be caused by lifestyle. A study conducted in Korea found that factors such as stress, obesity, and smoking were significantly associated with menstrual irregularities in premenopausal women, which can lead to infertility itself.<sup>11</sup>

### Pelvic pain

Pelvic pain is the fourth factor that is used to calculate the infertility score. Based on the analysis of frequency distribution, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that out of a total of 342 cases, 180 cases (52.6%) had one type of pain, 160 cases (46.8%) no

pain, and only two cases (0.6%) had  $\geq 2$  kinds of pain/adnexal mass. When viewed based on the type of referral or non-referral cases, the results of the Chi-square statistical test showed that there was no significant difference between pelvic pain in referral and non-referral cases ( $P = 0.762$ ), both of them mostly have one kind of pain, which is in the moderate category according to the infertility score.

In calculating the infertility score, types of pelvic pain include menstrual pain, intercourse pain, and spontaneous pelvic pain. According to research by Samsulhadi, these three types of pain are the clinical effects of endometriosis in general. Endometriosis has an incidence of 10% in the general population, and about 50% in infertile women.<sup>3</sup>

Endometriosis is closely related to infertility and fecundity. The prevalence of endometriosis increases dramatically to 25-50% in infertile women. The fecundity rate in women with endometriosis is estimated to be 2-10% wherein normal women the range is 15-20%.<sup>12</sup> Endometriosis is also associated with the management of infertility, one of which is IVF. Several studies have described the relationship of endometriosis with the outcome of IVF, where the pregnancy rate that can be obtained from IVF is inversely related to the severity of the endometriosis.<sup>13</sup>

### History of pelvic infection & IUD

It's the last women factor that is used to calculate the infertility score. Based on the analysis, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that, out of a total of 342 cases, most of them had no history of pelvic pain or IUD, which is 260 cases (76%), and only a small proportion had a history of  $\geq 2$  times, which is only 12 cases (3.5%). When viewed based on the type of referral or non-referral cases, the results of the Chi-square statistical test showed that there was no significant difference between the history of pelvic infection and IUD in referral and non-referral cases ( $P = 0.629$ ). From the data obtained, both of them mostly have no history of pelvic infection or IUD use, which is in the mild category according to the infertility score.

According to the literature by Samsulhadi, history of pelvic infection and IUD are related to the tubes and peritoneum, where residual defects after pelvic infection and also a history of IUD use can cause abnormalities in the tubes and peritoneum.<sup>3</sup> A history of pelvic infection is often referred to as Pelvic Inflammatory Disease (PID), which is defined as inflammation of the female genital tract due to infection. The effect of PID on fertility can be very significant, with several studies

showing a 5-fold increase in infertility in women with a history of PID. Not only that, PID can also lead to ectopic pregnancy due to damage to the fallopian tubes.<sup>14</sup>

The intrauterine device (IUD) also has a value in the infertility score, where patients who have a history of IUD use will be included in the moderate category. This is because the IUD can also cause pelvic infections.<sup>3</sup> Based on a study from the WHO, it was found that the risk of PID from IUD users is low, but the incidence of PID that increases during the first month indicates that infection may be due to the insertion process of the IUD itself.<sup>15</sup>

### Sperm analysis

It is the last and also the only male-acquired factor in the infertility score. The European Association of Urology (EAU) states there are several things that can cause infertility in men, including congenital, acquired, or idiopathic factors. To date, several methods have been found to assess male infertility, including semen/sperm analysis, hormonal tests, and testicular biopsy. Sperm analysis includes both macroscopic and microscopic examinations. The examination can be carried out from the first five minutes and if the sample is frozen it can be done at a later date. Microscopic counts were performed manually under a microscope with a magnification of 200-400 x. After that, observations were made on volume, concentration, motility, and others.<sup>16</sup>

### Sperm concentration

Based on the analysis of frequency distribution, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that of a total of 342 cases, most of them had a concentration of  $\geq 20$  million/ml, namely 278 people (81.3%), followed by concentration  $<10$  million/ml for 45 people (13.2%), and a concentration of 10-20 million/ml for 19 people (5.6%). When viewed based on the type of referral or non-referral cases, the results of the Chi-square statistical test showed that there was no significant difference between the sperm concentration of referral and non-referral cases ( $P = 0.069$ ). From the data obtained, both of them mostly have sperm concentrations of  $\geq 20$  million/ml, which is in the mild category according to the infertility score.

The WHO states that the standard reference value for sperm concentration is  $\geq 15$  million/ml. If it is lower than this value, it is called oligozoospermia, and if there is no sperm in the ejaculate, it is called azoospermia. A study says that 90% of male infertility is related to



sperm count, and there is a positive relationship between abnormal semen parameters and sperm count.<sup>17</sup> A decrease in sperm concentration/number is found in many cases of infertility, especially those caused by male factors. A 2013 study was conducted on a total of 396 men who came to a fertility clinic in Lahore, Pakistan. The results found that as many as 44 people (11.1%) experienced oligozoospermia and 59 people (14.9%) experienced azoospermia.<sup>18</sup>

### Sperm motility

Based on the analysis of frequency distribution, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that, out of a total of 342 cases, most had  $\geq 50\%$  progressive motile sperm, namely 260 people (76%), followed by those who had  $<25\%$  of progressive motile sperm, which is 60 people (17.5%), and the rest had 25-50% progressive motile sperm, namely as many as 22 people (6.4%). When viewed based on the type of referral or non-referral case, the results of the Chi-square statistical test showed that there was no significant difference between sperm motility in referral and non-referral cases ( $P = 0.071$ ). From the data obtained, both of them mostly have  $\geq 50\%$  progressive motile sperm, which is included in the mild category according to the infertility score.

The classification of sperm motility according to the WHO is progressive motility, non-progressive motility, and also non-motile. Progressive motile sperm can move actively (linear or circular) regardless of the speed. Meanwhile, non-progressive motile sperm has a movement pattern but there is no progression, such as moving only in a small circle, or only movement in the flagellum is observed. It is said that non-motile sperm do not get any movement at all. The WHO also sets the lowest reference value for progressive motile total sperm, which is 32%, if less than that it is called asthenozoospermia.<sup>16</sup>

A study says that motile spermatozoa tend to make propulsive, linear and progressive movements when penetrating the cervical border. Therefore, several specific movement attributes (speed, straightness and amplitude of sperm head movement) assisted by other sperm analysis criteria (concentration and morphology) are characteristics of sperm quality that can facilitate the penetration process.<sup>19</sup> This is supported by other studies which say that the concentration of motile sperm is the most significant parameter to predict the likelihood of fertilization. Several factors that can affect sperm motility include oxidative stress, mitochondrial disorders, male age, and certain proteins.<sup>20</sup>

### Sperm morphology

Based on the analysis of frequency distribution, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that out of a total of 342 cases, most of them had  $\geq 15\%$  normal morphological sperm, namely 247 people (72.2%), followed by those 55 people (16.1%) who had  $<5\%$  normal morphological sperm, and 40 people (11.7%) who had 5-15% normal morphological sperm.

The WHO states that the lowest standard reference value for sperm morphology (normal) is 4%, and if less then it is called teratozoospermia. In the process of analyzing sperm morphology, the semen sample obtained was stained first and then observed with a 1000x magnification using immersion oil.<sup>16</sup> The cause of abnormalities in sperm morphology is still not known with certainty, but some sperm morphological abnormalities can be related to abnormalities in their function such as chromatin condensation, abnormalities in acrosome reactions, and disturbances in tail motility. There are also some disorders associated with genetic abnormalities such as globozoospermia, sperm macrocephaly syndrome, and others.<sup>21</sup>

When viewed based on the type of referral or non-referral cases, the results of the Chi-square statistical test showed that there was a significant difference between sperm morphology in referral and non-referral cases ( $P = 0.038$ ). Normal morphological sperm of  $<5\%$ , or severe category according to the infertility score, was more common in referral cases (20.2%). Meanwhile, normal morphological sperm of  $\geq 15\%$ , or the mild category according to the infertility score, was more common in non-referral cases (78.6%).

### CONCLUSION

This study shows that there are many factors from both men and women that can affect fertility. The result of this study suggests that the degree of severity of each factor varies widely among those cases. Some factors can be used to identify infertile patients. It was found that the duration of infertility and sperm morphology were significantly different between referral and non-referral cases. Therefore, this infertility score can be useful as an initial screening, by calculating some important infertility factor from both partners, and it also helps doctors and general practitioners to decide whether to treat them or to refer them to the gynecologist for further management. It is also necessary for health workers to provide information and education about infertility for couples, so that they are

more aware of their respective reproductive health conditions.

## DISCLOSURES

### Acknowledgment

The authors thank all the staff of the Faculty of Medicine, Universitas Airlangga, who gave permission and helped facilitate this research, and to all staff of the medical records section at the Fertility Clinic of Graha Amerta, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, who gave help to obtain the data for this research.

### Conflict of Interest

The authors declare there is no conflict of interest.

### Funding Disclosure

This research has received no external funding.

### Author Contribution

All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

## REFERENCES

- Mascarenhas MN, Flaxman SR, Boerma T, et al. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med*. 2012;9(12):e1001356. doi: 10.1371/journal.pmed.1001356. Epub 2012 Dec 18. PMID: 23271957; PMCID: PMC3525527.
- Harzif AK, Santawi VPA, Wijaya S. Discrepancy in perception of infertility and attitude towards treatment options: Indonesian urban and rural area. *Reprod Health*. 2019;16(1):126. doi: 10.1186/s12978-019-0792-8. PMID: 31426818; PMCID: PMC6700767.
- Samsulhadi. Sistem rujukan kasus infertilitas (berdasarkan faktor risiko) [Infertility case referral system (based on the risk factors)]. *Indonesian Journal of Obstetrics and Gynecology*. 2007;31(1): 49-56.
- Sa'adah N, Purnomo W. Karakteristik dan perilaku berisiko pasangan infertil di Klinik Fertilitas dan Bayi Tabung Tiara Cita, Rumah Sakit Putri Surabaya [Characteristics and risky behavior of infertile couples]. *Jurnal Biometrika dan Kependudukan*. 2017;5(1): 61.
- Bennett LR, Wiweko B, Bell L, et al. Reproductive knowledge and patient education needs among Indonesian women infertility patients attending three fertility clinics. *Patient Educ Couns*. 2015;98(3):364-9. doi: 10.1016/j.pec.2014.11.016. Epub 2014 Nov 24. PMID: 25477052.
- Cimadomo D, Fabozzi G, Vaiarelli A, et al. Impact of maternal age on oocyte and embryo competence. *Front Endocrinol (Lausanne)*. 2018;9:327. doi: 10.3389/fendo.2018.00327. PMID: 30008696; PMCID: PMC6033961.
- American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee. Female age-related fertility decline. Committee Opinion No. 589. *Fertility and Sterility*. 2014;101(3): 633-4.
- Deshpande PS, Gupta AS. Causes and Prevalence of Factors Causing Infertility in a Public Health Facility. *J Hum Reprod Sci*. 2019;12(4):287-93. doi: 10.4103/jhrs.JHRS\_140\_18. Epub 2019 Dec 17. PMID: 32038077; PMCID: PMC6937760.
- Sadeghi MR. Unexplained infertility, the controversial matter in management of infertile couples. *J Reprod Infertil*. 2015;16(1):1-2. PMID: 25717428; PMCID: PMC4322174.
- Wesselink AK, Wise LA, Hatch EE, et al. Menstrual cycle characteristics and fecundability in a North American preconception cohort. *Ann Epidemiol*. 2016;26(7):482-7.e1. doi: 10.1016/j.annepidem.2016.05.006. Epub 2016 May 31. PMID: 27449569; PMCID: PMC4964792.
- Bae J, Park S, Kwon JW. Factors associated with menstrual cycle irregularity and menopause. *BMC Womens Health*. 2018;18(1):36. doi: 10.1186/s12905-018-0528-x. PMID: 29409520; PMCID: PMC5801702.
- Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am*. 2012;39(4):535-49. doi: 10.1016/j.ogc.2012.10.002. PMID: 23182559; PMCID: PMC3538128.
- Vassilopoulou L, Matalliotakis M, Zervou MI, et al. Endometriosis and in vitro fertilisation. *Exp Ther Med*. 2018;16(2):1043-51. doi: 10.3892/etm.2018.6307. Epub 2018 Jun 13. PMID: 30116357; PMCID: PMC6090275.
- Jennings LK, Krywko DM. Pelvic Inflammatory Disease. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2022 -. PMID: 29763134.
- Hubacher D. Intrauterine devices & infection: review of the literature. *Indian J Med Res*.

- 2014;140 Suppl(Suppl 1):S53-7. PMID: 25673543; PMCID: PMC4345753.
16. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: World Health Organization; 2010.p. 9-102
  17. Kumar N, Singh AK. Trends of male factor infertility, an important cause of infertility: A review of literature. *J Hum Reprod Sci.* 2015;8(4):191-6. doi: 10.4103/0974-1208.170370. PMID: 26752853; PMCID: PMC4691969.
  18. Butt F, Akram N. Semen analysis parameters: experiences and insight into male infertility at a tertiary care hospital in Punjab. *J Pak Med Assoc.* 2013;63(5):558-62. PMID: 23757979.
  19. Khatun A, Rahman MS, Pang MG. Clinical assessment of the male fertility. *Obstet Gynecol Sci.* 2018;61(2):179-91. doi: 10.5468/ogs.2018.61.2.179. Epub 2018 Mar 5. PMID: 29564308; PMCID: PMC5854897.
  20. Sati L, Huszar G. Sperm motility and viability: Overview of the cellular and physiological aspects that support these functions. *European Medical Journal.* 2015;1(1): 74-80.
  21. Gatimel N, Moreau J, Parinaud J, et al. Sperm morphology: assessment, pathophysiology, clinical relevance, and state of the art in 2017. *Andrology.* 2017;5(5):845-862. doi: 10.1111/andr.12389. Epub 2017 Jul 10. PMID: 28692759.