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Factors Affecting Infertility in Women of Reproductive Age in the IVF Programme

ABSTRACT

Approximately 8-10% of couples are facing some kind of infertility problem. Infertility is the inability of a couple to achieve pregnancy over an average period of one year without using birth control means and while having normal sexual intercourse. Infertility is divided into primary and secondary infertility. The high percentage of female factors of reproductive age concerning infertility and the existing studies on infertility-related factors in women leads to the researcher's interest in studying the factors influencing infertility in women. This study is an observational descriptive-analytic with a chi-square design based on secondary data collected from medical records. The majority (37,6%) of infertile women in this study were within the 31-35 age group. Most of the infertile women are primary infertile type women (81%). Indications that cause infertility include an indication of tubal damage, uterine disorders of the endometrium, and ovulation problems. In this case, researchers used these three indications to examine infertility factors in women of reproductive age. Based on the study results, 25% of indications of tubes, 21.7% of endometrial indications, and indications of ovarian problems were calculated by looking at AMH (Anti Müllerian Hormone) and AFC (Antral Follicle Count) values. In this study, the researchers looked for a correlation between increasing age in reproductive women with increasing AMH and AFC levels. Based on random sampling, there was a significant correlation between the increasing reproductive age of women and decreasing AMH and AFC values in women of reproductive age who underwent therapy at Bunda International Clinic, Morula IVF Jakarta.

Keywords: Infertility, Women of Reproductive Age, AMH, AFC

Introduction

Every married couple in this world craves to have children, namely children. Children are the next generation of the nation. Producing a quality next generation of the nation is an extraordinary challenge; everything must be prepared. With pregnancy, husband and wife can provide the best for the next generation in their family. However, this hope could not be fulfilled for several married couples because of several problems, including difficulty getting pregnant.

Pregnancy is a process that can cause physiological and psychological changes in a woman's body, so some adjustments are needed for these changes. Early changes in pregnancy begin with the fertilization process [1]. When there is no fertilization between the sperm and the ovum at that time, we call it infertility [2].

Infertility is a condition where pregnancy does not occur in couples who have had sexual intercourse without regular use of contraception within one year [3]. Based on the 1996 household health survey in Indonesia, an estimated 3.5 million couples (7 million people) were infertile. They are called infertile because they haven't gotten pregnant after a year of marriage. Now, experts confirm that infertility rates have increased to 15-20 percent of around 50 million couples in Indonesia [4].

Based on the WHO report, globally, it is estimated that there are cases of

infertility in 8-10% of couples, which is around 50 million to 80 million couples. The definition of infertility used by WHO is a problem of the reproductive system, which is described as a failure to get pregnant after 12 months or more, having sexual intercourse at least 2-3 times a week regularly without using contraception [5]. In the United States, 5 million people experience infertility problems, while in Europe, the incidence reaches 14% [6]. Meanwhile, based on the 1996 household health survey in Indonesia, it is estimated that there are 3.5 million married couples who are infertile. Experts confirm that the infertility rate has reached 15-20% of around 50 million couples in Indonesia [7].

According to the cause of infertility, there are several treatment options related to the possibility of getting pregnant. Therapy can begin with examinations including length of the marriage, causes of fertility disorders, examinations and treatments performed, efforts to get previous pregnancies, and, what is equally important, the age of the husband and wife. The ideal age to get pregnant is 20-30 years. According to research by the Association of Indonesian Hospitals (PERSI) in Jakarta, 36% of infertility occurs in men, and 64% occurs in women. Other research shows that female infertility occurs around 15% in productive age (30-34 years), increases up to 30% in ages 35-39 years, and 64% in ages 40-44 years [8].

The World Health Organization (WHO) says that 36% of infertile couples are caused by abnormalities in men, while 64% are in women. It is experienced by 17% of couples who have been married for more than two years, have not experienced signs of pregnancy, and have never even been pregnant. WHO also estimates that around 50-80 million couples (1 out of 7 couples) have infertility problems, and every year there are around 2 million infertile couples [9].

Given the many factors that cause infertility, it is necessary to limit the problems in this study in the form of a) medical record data of women of reproductive age who underwent therapy in the last four years at BIC Morula IVF Jakarta; b) the group of women of reproductive age; c) infertility with indications of tubal damage; d) infertility with indications of disorders of the endometrium; and e) infertility with indications of disorders of the ovaries. The problem answered in this study is "What are the causes of female infertility at Bunda International Clinic (BIC), Morula IVF Jakarta?" the research aims to find out the factors that cause female infertility at Bunda International Clinic (BIC), Morula IVF Jakarta.

Literature Review

The physiological anatomy of the female reproductive system is divided into two parts, namely: the external female reproductive organs (external genital organs), which are located in the perineum, and the internal female reproductive organs, which are located in the pelvic cavity (internal genitalia organs) [10]. Oogenesis is the beginning of the ovulation process. Oogenesis is the process of forming an ovum in the ovaries, and in the ovaries, there are oogonia or ovarian cells. Oogonia are diploid with 46 chromosomes or 23 pairs of chromosomes. Oogonia will reproduce by mitosis to form primary oocytes. Then the primary oocyte undergoes meiosis I, producing a secondary oocyte and polar body I (primary polocyte). Next, the secondary oocyte continues the stage of meiosis II and produces one large cell called the ootid and one small cell called the second polar body (secondary polocyte). The first polar body also splits into two-second polar bodies. Finally, there are three polar bodies and one ootid, which will grow into an ovum from the oogenesis of every oogonium.

A normal menstrual function results from interactions between the hypothalamus, pituitary, and ovaries with associated changes in target tissues of the normal reproductive tract. The ovaries play an important role in this process, as they appear responsible for regulating cyclic changes and the length of the menstrual cycle. The ovaries produce steroid hormones, especially estrogen and progesterone. The ovarian follicles, which contain the developing ovum and the cells surrounding them, produce several different estrogens. The most influential ovarian estrogen is estradiol.

Estrogen is responsible for developing and maintaining the female reproductive organs and the secondary sexual characteristics associated with adult women. Estrogen plays an important role in breast development and in monthly cyclical changes in the uterus. Progesterone is also important in regulating the changes that occur in the uterus during the menstrual cycle. Progesterone is the most important hormone for preparing the endometrium, the mucous membrane lining the uterus, for the implantation of a fertilized ovum. If pregnancy occurs, progesterone secretion plays an important role in the placenta and in maintaining a normal pregnancy.

Menstruation accompanied by ovulation occurs every few months to 2-3 years after menarche, which takes place around the age of 17-18 years. By paying attention to the components that regulate menstruation, it can be revealed that any deviation from the system will occur in the general pattern of menstruation. Menstruation will generally occur every 28 days for \pm seven days. The bleeding time is around 3-5 days, with blood lost around 30-40 cc. Followed by a proliferative phase of about 6-8 days [11].

The menstrual phase is the most obvious, characterized by expulsing of the remaining endometrium from the vagina. When the corpus luteum in the ovary degenerates because fertilization and implantation of the ovum do not occur, blood levels of estrogen and progesterone drop sharply. Because the effect of estrogen and progesterone is to prepare the endometrium for implantation of the ovum. The decrease in ovarian hormone levels also stimulates the release of a uterine prostaglandin which causes endometrial blood vessel vasoconstriction and inhibits blood flow so that a decrease in O₂ delivery causes the death of the endometrium and its blood vessels so that bleeding occurs. The average blood loss during one menstruation is 50-150 mL [12].

The Fallopian tube is an oviduct that originates like the uterus from the Müllerian duct. The average length of the tube is 11-14 cm. The part in the uterus wall is called the pars interstitialis; lateral to it (3-6 cm), there is the pars isthmica which is still narrow (4-10 mm in diameter) and has an open end resembling an anemone called the infundibulum. The outside of the tube is covered by the visceral peritoneum, which is part of the broad ligament. The muscles in the tube wall consist of (outside to inside) longitudinal and circular muscles [13].

Fertility is the function of a couple being able to become pregnant and give birth to live children. Primary infertility is a married couple who have never been pregnant even though they have intercourse (2-3 times a week) for one year without protection [14]. Primary infertility means that a couple has never had children after one year of having sex 2-3 times per week without using any form of contraception. Secondary infertility means that a couple has had children before, but after one year of having sex 2-3 times per week without using any form of contraception, they have not had any more children [15].

As many as 60 - 70% of married couples will have children in their first marriage year. As many as 20% will have children in the second year of marriage, and as many as

10-20% will have children in the third year or more or will never have children. Couples who are considered infertile can, in fact, only have wives who experience problems or only husbands who experience problems [16]. An increase in the number of cases of primary infertility coincides with a decrease in secondary infertility due to the postponement of plans to have children [17].

Secondary infertility is when a couple has been pregnant before but cannot get pregnant again even though they have had regular intercourse for one year without protection [18]. To produce children, a husband and wife must be fertile. The following are fertility requirements for both men and women. Requirements for women: a) have a hypothalamic and anterior pituitary neuroendocrine system and ovaries capable of producing eggs (ovulation) regularly (every four to six weeks); b) have fallopian tubes (at least one) that are normally open to carry eggs and sperm; c) has a uterus that develops and maintains a sudden fertilized egg (embryo) until it reaches maturity; d) have external genital organs (vaginal introitus, cervix) that are capable of receiving sperm during intercourse; and e) have sufficient production of sex hormones (estrogen and progesterone) from the ovaries to maintain sex so that the placenta takes over these functions [19].

The factors that affect a woman's reproductive ability are age, frequency of intercourse, and time/during intercourse. Inappropriate intercourse time will affect the success of pregnancy. Pre-ovulation intercourse is the key to increasing the chances of pregnancy. Spermatozoa can live up to 72 hours or more in the female genital tract while waiting for the ovum to be fertilized. The ovum has a shorter lifespan if it is not fertilized within 12 hours [20].

Pregnancy is the fertilization or union of spermatozoa and ovum (conception), followed by nidation or implantation. Counted from the time of fertilization until the birth of the baby, a normal pregnancy usually lasts for 40 weeks [21]. The gestational age is divided into three trimesters, each lasting a few weeks. Trimester 1 for 12 weeks, trimester 2 for 15 weeks (week 13 to 27 weeks), and trimester 3 for 13 weeks (week 28 to week 40) [22]. Problems in pregnancy can occur if one or both of the male and female reproductive organs are impaired. If this happens, then conception will be difficult.

The frequency of women with impaired fecundity increases from 2% at the age of 15-19 years, 7% at the age of 20-24 years, 15% at the age of 30-34 years, and 28% at the age of >35 years [23]. As a woman ages during her reproductive period, her fertility and fecundity decrease. This decrease in reproductive ability is a picture of ovarian aging, which is characterized by a reduced number of follicles which results in compromises in gametogenesis and endocrine function of the ovaries.

The decline in fertility is due to increasing age in this case, and our focus is on the reproductive age of women, namely 25-45 years. The process occurs gradually, starting around the age of 24-25 years, declining rapidly at the age of 35 years to 40 years. The reduction in female fecundity is 3% per year for all women but can be as high as 9% in women with unexplained infertility >30 years of age. Infertility is a condition where pregnancy does not occur in couples who have had sexual intercourse without regular use of contraception within one year [3]. Infertility is considered primary infertility if the husband and wife have previously never experienced pregnancy. Meanwhile, it is said to be secondary infertility if a married couple fails to get pregnant after one year after delivery or after an abortion without using any contraception. Infertility can be caused by either the wife or the husband. Conditions

that cause infertility from wife factors 65%, husband factors 20% [24]. Factors that cause infertility in women.

In all embryos, there are two primitive duct systems: Wolffian ducts and Müllerian ducts. In the male fetus, the reproductive tract develops from the Wolffian ducts, and the Müller ducts degenerate, while in the female fetus, the Müller ducts differentiate into the reproductive tract, and the Wolffian ducts regress. Under the influence of AMH formed in Sertoli cells, the Müllerian ducts descend in male fetuses to inhibit the Mullerian ducts in male fetuses, leading to normal male genital development [25]. In women, at the start of puberty AMH, like inhibin B, is formed by the granulosa cells of the maturing ovarian follicle. AMH is a biological regulator of folliculogenesis and primordial follicular rupture. It reduces the conversion rate of the follicle from the primordial to the growth stage and regulates follicular growth by inhibiting the conversion of FSH from early to late stages.

AMH is an ideal marker of functional ovarian reserve because it is formed only by primary follicles, which have the potential to cause maturation, and secondary follicles. Thus there is a very good correlation between rum AMH levels and the number of follicles capable of fertilizing and, thus, the functional reserve of the ovary. In women over 30 and especially those over 35 years, AMH can be used as a screening test to assess fertility status [26].

Research Method

This research uses a descriptive-analytic research method. This study describes the factors that cause infertility at various women ages by taking medical record data for the last four years at Bunda International Clinic, Morula IVF Jakarta. The data obtained in this study will be processed and analyzed descriptively based on the number of cases obtained from medical records according to the variables to be studied. This type of research also used bivariate analysis with a descriptive-analytic design, namely by measuring the independent variables (free) consisting of the age group of reproductive women with the dependent variable, namely infertility with indications of tubal damage, disorders of the uterus (endometrium), levels of Anti Mullerian Hormone (AMH).), and Antral Follicle Count (AFC). The population in this study were women of reproductive age who would take part in therapy at BIC Morula IVF from January 2014 - July 2017. The sample or sample was a subunit of the population considered by researchers to represent the target population (Danim, 2003). The samples in this study were women of reproductive age who underwent therapy at BIC Morula IVF Jakarta from January 2014 to July 2017.

Medical record data for women of reproductive age who underwent treatment at BIC Morula IVF Jakarta from January 2014 to July 2017 had a history of systemic disorders such as Hyperthyroidism and DM. To determine the size of the sample using the Slovin formula (Sevilla et al., 1960: 182), for sampling from a total of 5005 medical record data, the data was taken randomly (random sampling), and 364 data were taken according to the calculation of the Slovin formula, the data was taken randomized with multiples of 13. In this study, all data were collected using the medical records of infertile female patients (secondary data), which included: a) Requesting permission to conduct research with a letter of recommendation from the campus; b) an Explanation regarding the intent and purpose of conducting research; and c) Coordination with the medical record unit at BIC (Bunda International Clinic), Morula IVF, Jakarta. The data obtained from the data collection process will be described in tabular form and analyzed

descriptively based on the number of cases obtained in the medical record according to the variables studied. The research results will then be presented in the form of tables and graphs, which will then be explained in narrative form. It is a frequency analysis to determine the frequency distribution and percentage of the independent and dependent variables. In univariate analysis, the age groups of reproductive women, infertility indicated by tubal, infertility indicated by disorders of the uterus (endometrium), and infertility indicated by problems with the ovaries were analyzed by looking at AMH and AFC levels. Bivariate analysis was carried out to analyze two variables that were thought to be related. The bivariate analysis analyzed the relationship between the age group of reproductive women with tubal infertility indications, infertility indications of disorders of the uterus (endometrium), and infertility indications of ovarian problems by looking at AMH and AFC levels. To analyze the relationship between these variables using the Chi-Square test. Based on the statistical test results, the null hypothesis and alternative hypothesis can be determined.

Result and Discussion

The data collected is secondary data. The data was taken directly from the medical record section of Bunda International Clinic, Morula IVF Jakarta. The data taken is medical record data for all infertile women aged 25 to 45 who participated in the in vitro fertilization program at BIC Morula IVF Jakarta from January 2014 to July 2017. The amount of data obtained was 364 data. Data were tested using the SPSS program with univariate analysis and bivariate analysis. In Univariate analysis, the authors described the frequency distribution of each variable.

Table 1. Frequency Distribution of Reproductive Women Age Groups

Age Group	Female	
	N	Percentage
25-30 years	35	9,6
31-35 years	137	37,6
36-40 years	112	30,8
41-45 years	80	22
Total	364	100

In this study, it was found that the majority of reproductive women who were infertile were in the age group 31-35 years (37.6)%.

Table 2. Distribution of Infertility Types

Types of Infertility (P/S)	N	Percentage
Primary	295	81
Secondary	69	19
Total	364	100

From the above data, it can be seen that most types of infertility are primary infertility (81%).

Table 3. Distribution of Tubal Indications

Indications of Tubal Damage	N	Percentage
There is tubal damage	91	25
There is no tubal damage	273	75

Total	364	100
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The data above shows that most of the intertality factors with indications of tubal disorders are absent (75%).

Table 4. Distribution of Endometrial Indications

Indications for Endometrial Disorders	N	Percentage
There is no indication of endometrial disorders	285	78,3
There is an indication of endometrial disorders	79	21,7
Total	364	100

The above data shows that most intertality factors with indications of abnormal uterus disorders (endometrium) do not exist (78.3%).

Table 5. Distribution of Unexplained Indications

Indications cannot be Explained	N	Percentage
There is no indication	324	89
There is indication	40	11
Total	364	100

The above data shows that most of the Intertality with Indication factors, which cannot be explained by the majority (89%), do not exist.

Table 6. AMH Values in Women

<i>Anti Mullerian Hormone</i>	N	Percentage
>0,1 Fertil	330	90,7
< 0,1 reduced fertile	34	9,3
<0,025 Infertil	0	0
Total	364	100

Dari data di atas dapat diketahui bahwa sebagian besar faktor Intertilitas dengan nilai Anti Mullerian Hormone <0,1 yang menunjukkan bahwa wanita reproduktif dalam keadaan fertil.

Table 7. Distribusi Nilai Hitung Folikel Antral

Antral Follicle Count	N	Percentage
> 20 High follicle	10	2,7
15-20 ideal follicle	16	4,4
10-14 normal follicle	97	26,6
< 10 low follicle	241	66,2
Total	364	100

The above data shows that most of the Intertality factors with Antral Follicle Count values <10 indicate that reproductive women have the lowest levels of AFC.

Table 8 : Correlation between Reproductive Women's Age and Tubal Indications on Infertility Factors

Chi-Square Test

Value	df	Asymptotic Significance(2-sided)
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Pearson Chi-square	6.424 ^a	3	0.93
Likelihood Ratio	6.520	3	0.89
Linear-by-Linear Association	3.454	1	0.63
N of Valid Cases	364		

The table shows the relationship between the two variables, namely the age group of reproductive women and infertility factors with indications of tubal damage. Based on the Asymptotic Significance test, results show that there is no significant relationship between the two variables because the coefficient p is $0.093 > 0.05$. Based on the statistical test results above, then H_0 is accepted, and H_a is rejected.

Table 9 : Relationship between Reproductive Women's Age and Indications of Endometrial Disorders in Infertility Factors

Chi-Square Test

S	Value	df	Asymptotic Significance(2-sided)
Pearson Chi-square	2.950 ^a	3	.399
Likelihood Ratio	3.115	3	.374
Linear-by-Linear Association	2.044	1	.153
N of Valid Cases	364		

The results of the above study show a relationship between two variables, namely the age group of reproductive women and infertility factors with indications of endometrial disorders. Based on the Asymptotic Significance test, results show that there is no significant relationship between the two variables because the coefficient p is $0.339 > 0.05$. Based on the statistical test results above, H_0 is accepted, and H_a is rejected.

Table 10 : Relation between Reproductive Female Age and Anti-Mullerian Hormone Levels

Chi-Square Test

	Value	Df	Asymptotic Significance(2-sided)
Pearson Chi-square	12.055 ^a	3	.007
Likelihood Ratio	12.556	3	.006
Linear-by-Linear Association	6.231	1	.013
N of Valid Cases	364		

The results of the research above show a relationship between two variables, namely the age group of reproductive women and infertility factors with indications of Anti-Mullerian Hormone levels. Based on the Asymptotic Significance test, results show that there is a significant relationship between the two variables because the coefficient p is $0.007 < 0.05$. Based on the statistical test results above, then H_a is accepted, and H_0 is rejected.

Table 11 : Relation between Reproductive Female Age and Antral Follicle Count Level

Chi-Square Test

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-square	29.282 ^a	9	.001
Likelihood Ratio	30.612	9	.000
Linear-by-Linear Association	24.998	1	.000
N of Valid Cases	364		

The results of the research above show the relationship between the two variables, namely the age group of reproductive women and infertility factors with an antral follicle count indication. Based on the Asymptotic Significance test, results show that there is a significant relationship between the two variables because the coefficient p is $0.001 < 0.05$. Based on the statistical test results above, then H_a is accepted, and H_o is rejected.

This study used 364 secondary data based on the sample calculated in chapter 3. The results showed the frequency distribution of women of reproductive age, the majority aged 31-35 years (37.6%). In general, the age range of 31-35 is the age of women at 5-6 years of marriage. Most types of infertility experienced by this age group were primary infertility (81%).

Primary infertility is a couple who have never had children after one year of having sex 2-3 times a week without using contraception. Infertility is a problem for married couples. One partner cannot be said to be infertile because it is possible that one or both of them are subfertile or sterile.

The results showed that women of reproductive age with indications of infertility with tubal damage had a small frequency of 25%, as well as infertility with indications of disorders of the endometrium, which had a frequency of 21.7%. Examination of the uterus (including the cervix and uterine cavity) – the tubes and peritoneum are usually performed as a unit. The peritoneal uterine tubal factor accounts for 30% of infertility [27].

Some of the recommended examinations for examining uterine, tubal, and peritoneal factors are transvaginal ultrasound and laparoscopy. Transvaginal ultrasound can accurately identify pelvic anatomy. Ultrasound can evaluate pelvic pathologies such as endometriosis, polyps, and ovarian or adnexal abnormalities.

Nargund recommends a "one-stop fertility diagnosis" with ultrasound as follows:

Uterus:

Position, mobility

Long dimensions (normal length: 75 mm)

Anomaly

Mioma/ademiosis (assessment by dopple).

Investigation of the uterine cavity with "Somo Contrast Salpingo Hysterography" (SCSH).

Endometrial uterine blood flow:

Thickness(>7mm)

Volumes (>2ml)

Morphology (Triple layer)

Doppler assessment

Ovary:

Mordology

Position and mobility

Volume (>3ml) and number of antral follicles (>6)

Stromal blood volume and flow

Cysts (endometriomas, dermoids)

Doppler assessment of cysts

Dominant follicle and blood flow (PSV)

Tube:
 Sonocontrast salpingo hysteroGRAPHY
 Hydrosalpinx
 Kavum
 Douglasi
 Free liquid
 Mass.

Besides tubal and endometrial indications, ovarian function assessment also plays an important role in female infertility. The quantity and quality of eggs generally decreases in women in their early 30s and decreases significantly in their late 30s and will decrease even more drastically in their early 40s. Every woman is born with a gift of 1-2 million primordial follicles, and starting at menarche, primordial follicles decrease to around 300,000-500,000 grains. Every time menstruation occurs, there will be a reduction in the number of follicles until finally approaching, menopause. And during the 35-40 years of the reproductive period, it is estimated that 400-500 ovulations will occur, with an estimated average loss of 1000 oocytes per ovulation episode. Although the average age of menopause reaches 51 years, there are individual variations regarding the age between 40 -60 years. So ovarian age generally parallels the woman's chronological age.

The research results found that the frequency distribution of Anti Mullerian Hormone in women tends to be in the fertile phase (90.7%). AMH is an ideal marker of functional ovarian reserve because it is formed only by primary follicles, which have the potential to cause maturation, and secondary follicles. Thus there is a very good correlation between AMH and the number of capable follicles and, thus, functional ovarian reserve.

According to bioscientie, AMH levels decrease steadily with age, corresponding to loss of ovarian functional reserve; a significant decrease is very likely to occur earlier than a clear rise in FSH. A decreased AMH level indicates a limited reserve of ovarian function and a poor response to ovarian stimulation. AMH concentration must be determined before treatment in assisted reproductive technology (TRB), namely In Vitro Fertilization. It allows treatment to be tailored to each individual. With AMH levels $<0.025 \mu\text{g/l}$, the patient is already in the infertile phase. With AMH levels $<0.1 \mu\text{g/l}$, IVF treatment is no longer recommended due to decreased fertility in these women. With AMH levels $<0.5 \mu\text{g/l}$, a maximum of 2 oocytes can generally be obtained by stimulation with increasing doses of rFSH. While women with AMH values $>0.1 \mu\text{g/l}$ are in the fertile phase.

This study found that the majority (90.7%) of reproductive-age women had good AMH values of $>0.1 \mu\text{g/l}$. It is because the age group of women aged 31-35 years still have good oocytes even though they are in the process of decreasing. There are about 400-500 ovulations, with an estimated average loss of 1000 oocytes per ovulatory episode. It indicates that the age range of women 31-35 years still has functional ovarian reserves formed by primary follicles, which have the potential to cause maturation, secondary follicles, and functional ovarian reserves.

Evaluation of ovarian function can also be seen from the antral follicle count. Antral follicles are tiny, measuring 2 - 8 mm, that can be seen in the ovaries using transvaginal ultrasound. Antral follicles are also known as resting

follicles. These follicles are seen early in the menstrual cycle, and their number can predict the number of primordial follicles in the ovary. The number of antral follicles of the two ovaries <10 follicles indicates a group of poor responses in the superovulation program, groups of 10-14 follicles include normal responses, groups of 15-20 follicles include ideal responses, and above 20 follicles are called excessive responses (Halim et al., 2006). The age of the mother is very important to know because, with increasing age, it is more difficult to have children. Aged 20 - 24 years, female fertility reaches 100%; for ages 30 - 34 years, female fertility is 85%; for ages 35 - 39 years, fertility remains 60%; for ages 40 - 44 years, female fertility remains 25%, and ages 50 - 59 years female fertility already 0% (Baziad, 2008). The average woman will experience a decrease in fertility at the age of 37.5 years [28]. Fertility decreases with increasing age due to a decrease in the number of primordial follicles. Acceleration of follicular loss occurs around the age of 37 years and is followed by menopause 10-12 years later. As assessed by transvaginal ultrasound, the number of antral follicles >2 mm decreased by 60% between the ages of 22 and 42. The quantity and quality of eggs generally decline from 30 and decrease dramatically in the early 40s. In general, the number of antral follicles is inversely related to age. Fecundity disorders increased from 2% at the age of 15-19 years, 7% at the age of 20-24 years, 15% at the age of 30-34 years, and 28% at the age of > 35 years.

Antral follicle count as an easy and non-invasive way to provide important information about the ovarian response [29]. Based on the results found in these data, the majority (66.2%) of women of reproductive age have a very low antral follicle count, namely <10 follicles, following the theory in CHAPTER II that a woman's age greatly influences the number of antral follicles which plays an important role in reducing ovarian response to gonadotropin stimulation, especially in vitro fertilization programs. It also supports the concept of a decreased number of primordial follicles developing into small antral follicles. It was further reported that decreased AFC was also associated with a decrease in the number of oocytes obtained.

Conclusion

Based on the results of research conducted based on medical record data at BIC Morula IVF, conclusions can be drawn, namely: a) The reproductive age group of women undergoing therapy at BIC Morula IVF is mostly in the age group of 31-35 years; b) Most types of infertility are primary infertility, so the percentage of indications of tubal damage, endometrial disorders, and ovarian problems is not as high as types of primary infertility; c) There is a relationship between a woman's age and anti-Mullerian hormone levels in women; d) There is a relationship between a woman's age and Antral Follicle Count. Thus, it is necessary to carry out further research on the same problem, and in more depth, even to the biomolecular stage, to obtain even better results.

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UNDER PEER REVIEW

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Journal Name:	International Journal of TROPICAL DISEASE & Health
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Department, University & Country	K. J. Somaiya College of Nursing, India

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Name:	Kavitha Bakshi
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Review Form 1.7

Journal Name:	International Journal of TROPICAL DISEASE & Health
Manuscript Number:	Ms_IJTDH_95634
Title of the Manuscript:	Factors Affecting Infertility in Women of Reproductive Age in the IVF Programme
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Reviewer Details:

Name:	F. D. Haleemah Olalere
Department, University & Country	Lagos State University College of Medicine, Nigeria

Factors Affecting Infertility in Women of Reproductive Age in the IVF Programme

ABSTRACT

Approximately 8-10% of couples are facing some kind of infertility problem. Infertility is defined as a couple's inability to achieve pregnancy over an average of one year without using birth control methods and while engaging in normal sexual intercourse. Primary and secondary infertility are the two types of infertility. The high percentage of female reproductive age factors influencing infertility, as well as existing studies on infertility-related factors in women, piques the researcher's interest in studying the factors that influence infertility in women. This study is an observational descriptive-analytic with a chi-square design based on secondary data collected from medical records. The majority (37,6%) of infertile women in this study were within the 31-35 age group. Most of the infertile women are primary infertile type women (81%). Indications that cause infertility include an indication of tubal damage, uterine disorders of the endometrium, and ovulation problems. In this case, researchers used these three indications to examine infertility factors in women of reproductive age. Based on the study results, 25% of indications of tubes, 21.7% of endometrial indications, and indications of ovarian problems were calculated by looking at AMH (Anti Müllerian Hormone) and AFC (Antral Follicle Count) values. In this study, the researchers looked for a correlation between increasing age in reproductive women with increasing AMH and AFC levels. Based on random sampling, there was a significant correlation between the increasing reproductive age of women and decreasing AMH and AFC values in women of reproductive age who underwent therapy at Bunda International Clinic, Morula IVF Jakarta.

Keywords: Infertility, Women of Reproductive Age, AMH, AFC

Introduction

Every married couple in this world craves to have children, namely children. Children are the next generation of the nation. Producing a quality next generation of the nation is an extraordinary challenge; everything must be prepared. With pregnancy, husband and wife can provide the best for the next generation in their family. However, this hope could not be fulfilled for several married couples because of several problems, including difficulty getting pregnant.

Pregnancy is a process that can cause physiological and psychological changes in a woman's body, so some adjustments are needed for these changes. Early changes in pregnancy begin with the fertilization process [1]. When there is no fertilization between the sperm and the ovum at that time, we call it infertility [2].

Infertility is a condition where pregnancy does not occur in couples who have had sexual intercourse without regular use of contraception within one year [3]. Based on the 1996 household health survey in Indonesia, an estimated 3.5 million couples (7 million people) were infertile. They are called infertile because they haven't gotten pregnant after a year of marriage. Now, experts confirm that infertility rates have increased to 15-20 percent of around 50 million couples in Indonesia [4].

Based on the WHO report, globally, it is estimated that there are cases of

infertility in 8-10% of couples, which is around 50 million to 80 million couples. The definition of infertility used by WHO is a problem of the reproductive system, which is described as a failure to get pregnant after 12 months or more, having sexual intercourse at least 2-3 times a week regularly without using contraception [5]. In the United States, 5 million people experience infertility problems, while in Europe, the incidence reaches 14% [6]. Meanwhile, based on the 1996 household health survey in Indonesia, it is estimated that there are 3.5 million married couples who are infertile. Experts confirm that the infertility rate has reached 15-20% of around 50 million couples in Indonesia [7].

According to the cause of infertility, there are several treatment options related to the possibility of getting pregnant. Therapy can begin with examinations including length of the marriage, causes of fertility disorders, examinations and treatments performed, efforts to get previous pregnancies, and, what is equally important, the age of the husband and wife. The ideal age to get pregnant is 20-30 years. According to research by the Association of Indonesian Hospitals (PERSI) in Jakarta, 36% of infertility occurs in men, and 64% occurs in women. Other research shows that female infertility occurs around 15% in productive age (30-34 years), increases up to 30% in ages 35-39 years, and 64% in ages 40-44 years [8].

The World Health Organization (WHO) says that 36% of infertile couples are caused by abnormalities in men, while 64% are in women. It is experienced by 17% of couples who have been married for more than two years, have not experienced signs of pregnancy, and have never even been pregnant. WHO also estimates that around 50-80 million couples (1 out of 7 couples) have infertility problems, and every year there are around 2 million infertile couples [9].

Given the many factors that cause infertility, it is necessary to limit the problems in this study in the form of a) medical record data of women of reproductive age who underwent therapy in the last four years at BIC Morula IVF Jakarta; b) the group of women of reproductive age; c) infertility with indications of tubal damage; d) infertility with indications of disorders of the endometrium; and e) infertility with indications of disorders of the ovaries. The problem answered in this study is "What are the causes of female infertility at Bunda International Clinic (BIC), Morula IVF Jakarta?" the research aims to find out the factors that cause female infertility at Bunda International Clinic (BIC), Morula IVF Jakarta.

Literature Review

The physiological anatomy of the female reproductive system is divided into two parts, namely: the external female reproductive organs (external genital organs), which are located in the perineum, and the internal female reproductive organs, which are located in the pelvic cavity (internal genitalia organs) [10]. Oogenesis is the beginning of the ovulation process. Oogenesis is the process of forming an ovum in the ovaries, and in the ovaries, there are oogonia or ovarian cells. Oogonia are diploid with 46 chromosomes or 23 pairs of chromosomes. Oogonia will reproduce by mitosis to form primary oocytes. Then the primary oocyte undergoes meiosis I, producing a secondary oocyte and polar body I (primary polocyte). Next, the secondary oocyte continues the stage of meiosis II and produces one large cell called the ootid and one small cell called the second polar body (secondary polocyte). The first polar body also splits into two-second polar bodies. Finally, there are three polar bodies and one ootid, which will grow into an ovum from the oogenesis of every oogonium.

A normal menstrual function results from interactions between the hypothalamus, pituitary, and ovaries with associated changes in target tissues of the normal reproductive tract. The ovaries play an important role in this process, as they appear responsible for regulating cyclic changes and the length of the menstrual cycle. The ovaries produce steroid hormones, especially estrogen and progesterone. The ovarian follicles, which contain the developing ovum and the cells surrounding them, produce several different estrogens. The most influential ovarian estrogen is estradiol.

Estrogen is responsible for developing and maintaining the female reproductive organs and the secondary sexual characteristics associated with adult women. Estrogen plays an important role in breast development and in monthly cyclical changes in the uterus. Progesterone is also important in regulating the changes that occur in the uterus during the menstrual cycle. Progesterone is the most important hormone for preparing the endometrium, the mucous membrane lining the uterus, for the implantation of a fertilized ovum. If pregnancy occurs, progesterone secretion plays an important role in the placenta and in maintaining a normal pregnancy.

Menstruation accompanied by ovulation occurs every few months to 2-3 years after menarche, which takes place around the age of 17-18 years. By paying attention to the components that regulate menstruation, it can be revealed that any deviation from the system will occur in the general pattern of menstruation. Menstruation will generally occur every 28 days for \pm seven days. The bleeding time is around 3-5 days, with blood lost around 30-40 cc. Followed by a proliferative phase of about 6-8 days [11].

The menstrual phase is the most obvious, characterized by expelling of the remaining endometrium from the vagina. When the corpus luteum in the ovary degenerates because fertilization and implantation of the ovum do not occur, blood levels of estrogen and progesterone drop sharply. Because the effect of estrogen and progesterone is to prepare the endometrium for implantation of the ovum. The decrease in ovarian hormone levels also stimulates the release of a uterine prostaglandin which causes endometrial blood vessel vasoconstriction and inhibits blood flow so that a decrease in O₂ delivery causes the death of the endometrium and its blood vessels so that bleeding occurs. The average blood loss during one menstruation is 50-150 mL [12].

The Fallopian tube is an oviduct that originates like the uterus from the Müllerian duct. The average length of the tube is 11-14 cm. The part in the uterus wall is called the pars interstitialis; lateral to it (3-6 cm), there is the pars isthmica which is still narrow (4-10 mm in diameter) and has an open end resembling an anemone called the infundibulum. The outside of the tube is covered by the visceral peritoneum, which is part of the broad ligament. The muscles in the tube wall consist of (outside to inside) longitudinal and circular muscles [13].

Fertility is the function of a couple being able to become pregnant and give birth to live children. Primary infertility is a married couple who have never been pregnant even though they have intercourse (2-3 times a week) for one year without protection [14]. Primary infertility means that a couple has never had children after one year of having sex 2-3 times per week without using any form of contraception. Secondary infertility means that a couple has had children before, but after one year of having sex 2-3 times per week without using any form of contraception, they have not had any more children [15].

As many as 60 - 70% of married couples will have children in their first marriage year. As many as 20% will have children in the second year of marriage, and as many as

10-20% will have children in the third year or more or will never have children. Couples who are considered infertile can, in fact, only have wives who experience problems or only husbands who experience problems [16]. An increase in the number of cases of primary infertility coincides with a decrease in secondary infertility due to the postponement of plans to have children [17].

Secondary infertility is when a couple has been pregnant before but cannot get pregnant again even though they have had regular intercourse for one year without protection [18]. To produce children, a husband and wife must be fertile. The following are fertility requirements for both men and women. Requirements for women: a) have a hypothalamic and anterior pituitary neuroendocrine system and ovaries capable of producing eggs (ovulation) regularly (every four to six weeks); b) have fallopian tubes (at least one) that are normally open to carry eggs and sperm; c) has a uterus that develops and maintains a sudden fertilized egg (embryo) until it reaches maturity; d) have external genital organs (vaginal introitus, cervix) that are capable of receiving sperm during intercourse; and e) have sufficient production of sex hormones (estrogen and progesterone) from the ovaries to maintain sex so that the placenta takes over these functions [19].

The factors that affect a woman's reproductive ability are age, frequency of intercourse, and time/during intercourse. Inappropriate intercourse time will affect the success of pregnancy. Pre-ovulation intercourse is the key to increasing the chances of pregnancy. Spermatozoa can live up to 72 hours or more in the female genital tract while waiting for the ovum to be fertilized. The ovum has a shorter lifespan if it is not fertilized within 12 hours [20].

Pregnancy is the fertilization or union of spermatozoa and ovum (conception), followed by nidation or implantation. Counted from the time of fertilization until the birth of the baby, a normal pregnancy usually lasts for 40 weeks [21]. The gestational age is divided into three trimesters, each lasting a few weeks. Trimester 1 for 12 weeks, trimester 2 for 15 weeks (week 13 to 27 weeks), and trimester 3 for 13 weeks (week 28 to week 40) [22]. Problems in pregnancy can occur if one or both of the male and female reproductive organs are impaired. If this happens, then conception will be difficult.

The frequency of women with impaired fecundity increases from 2% at the age of 15-19 years, 7% at the age of 20-24 years, 15% at the age of 30-34 years, and 28% at the age of >35 years [23]. As a woman ages during her reproductive period, her fertility and fecundity decrease. This decrease in reproductive ability is a picture of ovarian aging, which is characterized by a reduced number of follicles which results in compromises in gametogenesis and endocrine function of the ovaries.

The decline in fertility is due to increasing age in this case, and our focus is on the reproductive age of women, namely 25-45 years. The process occurs gradually, starting around the age of 24-25 years, declining rapidly at the age of 35 years to 40 years. The reduction in female fecundity is 3% per year for all women but can be as high as 9% in women with unexplained infertility >30 years of age. Infertility is a condition where pregnancy does not occur in couples who have had sexual intercourse without regular use of contraception within one year [3]. Infertility is considered primary infertility if the husband and wife have previously never experienced pregnancy. Meanwhile, it is said to be secondary infertility if a married couple fails to get pregnant after one year after delivery or after an abortion without using any contraception. Infertility can be caused by either the wife or the husband. Conditions

that cause infertility from wife factors 65%, husband factors 20% [24]. Factors that cause infertility in women.

In all embryos, there are two primitive duct systems: Wolffian ducts and Müllerian ducts. In the male fetus, the reproductive tract develops from the Wolffian ducts, and the Müllerian ducts degenerate, while in the female fetus, the Müllerian ducts differentiate into the reproductive tract, and the Wolffian ducts regress. Under the influence of AMH formed in Sertoli cells, the Müllerian ducts descend in male fetuses to inhibit the Müllerian ducts in male fetuses, leading to normal male genital development [25]. In women, at the start of puberty AMH, like inhibin B, is formed by the granulosa cells of the maturing ovarian follicle. AMH is a biological regulator of folliculogenesis and primordial follicular rupture. It reduces the conversion rate of the follicle from the primordial to the growth stage and regulates follicular growth by inhibiting the conversion of FSH from early to late stages.

AMH is an ideal marker of functional ovarian reserve because it is formed only by primary follicles, which have the potential to cause maturation, and secondary follicles. Thus there is a very good correlation between rum AMH levels and the number of follicles capable of fertilizing and, thus, the functional reserve of the ovary. In women over 30 and especially those over 35 years, AMH can be used as a screening test to assess fertility status [26].

METHODOLOGY

This research uses a descriptive-analytic research method. This study describes the factors that cause infertility at various women ages by taking medical record data for the last four years at Bunda International Clinic, Morula IVF Jakarta. The data obtained in this study will be processed and analyzed descriptively based on the number of cases obtained from medical records according to the variables to be studied. This type of research also used bivariate analysis with a descriptive-analytic design, namely by measuring the independent variables (free) consisting of the age group of reproductive women with the dependent variable, namely infertility with indications of tubal damage, disorders of the uterus (endometrium), levels of Anti Mullerian Hormone (AMH), and Antral Follicle Count (AFC). The population in this study were women of reproductive age who would take part in therapy at BIC Morula IVF from January 2014 - July 2017. The sample or sample was a subunit of the population considered by researchers to represent the target population (Danim, 2003). The samples in this study were women of reproductive age who underwent therapy at BIC Morula IVF Jakarta from January 2014 to July 2017.

Medical record data for women of reproductive age who underwent treatment at BIC Morula IVF Jakarta from January 2014 to July 2017 had a history of systemic disorders such as Hyperthyroidism and DM. To determine the size of the sample using the Slovin formula (Sevilla et al., 1960: 182), for sampling from a total of 5005 medical record data, the data was taken randomly (random sampling), and 364 data were taken according to the calculation of the Slovin formula, the data was taken randomized with multiples of 13. In this study, all data were collected using the medical records of infertile female patients (secondary data), which included: a) Requesting permission to conduct research with a letter of recommendation from the campus; b) an Explanation regarding the intent and purpose of conducting research; and c) Coordination with the medical record unit at BIC (Bunda International Clinic), Morula IVF, Jakarta. The data obtained from the data collection process will be described in tabular form and analyzed

descriptively based on the number of cases obtained in the medical record according to the variables studied. The research results will then be presented in the form of tables and graphs, which will then be explained in narrative form. It is a frequency analysis to determine the frequency distribution and percentage of the independent and dependent variables. In univariate analysis, the age groups of reproductive women, infertility indicated by tubal, infertility indicated by disorders of the uterus (endometrium), and infertility indicated by problems with the ovaries were analyzed by looking at AMH and AFC levels. Bivariate analysis was carried out to analyze two variables that were thought to be related. The bivariate analysis analyzed the relationship between the age group of reproductive women with tubal infertility indications, infertility indications of disorders of the uterus (endometrium), and infertility indications of ovarian problems by looking at AMH and AFC levels. To analyze the relationship between these variables using the Chi-Square test. Based on the statistical test results, the null hypothesis and alternative hypothesis can be determined.

Result and Discussion

The data collected is secondary data. The data was taken directly from the medical record section of Bunda International Clinic, Morula IVF Jakarta. The data taken is medical record data for all infertile women aged 25 to 45 who participated in the in vitro fertilization program at BIC Morula IVF Jakarta from January 2014 to July 2017. The amount of data obtained was 364 data. Data were tested using the SPSS program with univariate analysis and bivariate analysis. In Univariate analysis, the authors described the frequency distribution of each variable.

Table 1. Frequency Distribution of Reproductive Women Age Groups

Age Group	Female	
	N	Percentage
25-30 years	35	9,6
31-35 years	137	37,6
36-40 years	112	30,8
41-45 years	80	22
Total	364	100

In this study, it was found that the majority of reproductive women who were infertile were in the age group 31-35 years (37.6)%.

Table 2. Distribution of Infertility Types

Types of Infertility (P/S)	N	Percentage
Primary	295	81
Secondary	69	19
Total	364	100

From the above data, it can be seen that most types of infertility are primary infertility (81%).

Table 3. Distribution of Tubal Indications

Indications of Tubal Damage	N	Percentage
There is tubal damage	91	25
There is no tubal damage	273	75

Total	364	100
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The data above shows that most of the intertality factors with indications of tubal disorders are absent (75%).

Table 4. Distribution of Endometrial Indications

Indications for Endometrial Disorders	N	Percentage
There is no indication of endometrial disorders	285	78,3
There is an indication of endometrial disorders	79	21,7
Total	364	100

The above data shows that most intertality factors with indications of abnormal uterus disorders (endometrium) do not exist (78.3%).

Table 5. Distribution of Unexplained Indications

Indications cannot be Explained	N	Percentage
There is no indication	324	89
There is indication	40	11
Total	364	100

The above data shows that most of the Intertality with Indication factors, which cannot be explained by the majority (89%), do not exist.

Table 6. AMH Values in Women

<i>Anti Mullerian Hormone</i>	N	Percentage
>0,1 Fertil	330	90,7
< 0,1 reduced fertile	34	9,3
<0,025 Infertil	0	0
Total	364	100

Dari data di atas dapat diketahui bahwa sebagian besar faktor Intertilitas dengan nilai Anti Mullerian Hormone <0,1 yang menunjukkan bahwa wanita reproduktif dalam keadaan fertil.

Table 7. Distribusi Nilai Hitung Folikel Antral

Antral Follicle Count	N	Percentage
> 20 High follicle	10	2,7
15-20 ideal follicle	16	4,4
10-14 normal follicle	97	26,6
< 10 low follicle	241	66,2
Total	364	100

The above data shows that most of the Intertality factors with Antral Follicle Count values <10 indicate that reproductive women have the lowest levels of AFC.

Table 8 : Correlation between Reproductive Women's Age and Tubal Indications on Infertility Factors

Chi-Square Test

Value	df	Asymptotic Significance(2-sided)
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Pearson Chi-square	6.424 ^a	3	0.93
Likelihood Ratio	6.520	3	0.89
Linear-by-Linear Association	3.454	1	0.63
N of Valid Cases	364		

The table shows the relationship between the two variables, namely the age group of reproductive women and infertility factors with indications of tubal damage. Based on the Asymptotic Significance test, results show that there is no significant relationship between the two variables because the coefficient p is $0.093 > 0.05$. Based on the statistical test results above, then H_0 is accepted, and H_a is rejected.

Table 9 : Relationship between Reproductive Women's Age and Indications of Endometrial Disorders in Infertility Factors

Chi-Square Test

S	Value	df	Asymptotic Significance(2-sided)
Pearson Chi-square	2.950 ^a	3	.399
Likelihood Ratio	3.115	3	.374
Linear-by-Linear Association	2.044	1	.153
N of Valid Cases	364		

The results of the above study show a relationship between two variables, namely the age group of reproductive women and infertility factors with indications of endometrial disorders. Based on the Asymptotic Significance test, results show that there is no significant relationship between the two variables because the coefficient p is $0.339 > 0.05$. Based on the statistical test results above, H_0 is accepted, and H_a is rejected.

Table 10 : Relation between Reproductive Female Age and Anti-Mullerian Hormone Levels

Chi-Square Test

	Value	Df	Asymptotic Significance(2-sided)
Pearson Chi-square	12.055 ^a	3	.007
Likelihood Ratio	12.556	3	.006
Linear-by-Linear Association	6.231	1	.013
N of Valid Cases	364		

The results of the research above show a relationship between two variables, namely the age group of reproductive women and infertility factors with indications of Anti-Mullerian Hormone levels. Based on the Asymptotic Significance test, results show that there is a significant relationship between the two variables because the coefficient p is $0.007 < 0.05$. Based on the statistical test results above, then H_a is accepted, and H_0 is rejected.

Table 11 : Relation between Reproductive Female Age and Antral Follicle Count Level

Chi-Square Test

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-square	29.282 ^a	9	.001
Likelihood Ratio	30.612	9	.000
Linear-by-Linear Association	24.998	1	.000
N of Valid Cases	364		

The results of the research above show the relationship between the two variables, namely the age group of reproductive women and infertility factors with an antral follicle count indication. Based on the Asymptotic Significance test, results show that there is a significant relationship between the two variables because the coefficient p is $0.001 < 0.05$. Based on the statistical test results above, then H_a is accepted, and H_o is rejected.

This study used 364 secondary data based on the sample calculated in chapter 3. The results showed the frequency distribution of women of reproductive age, the majority aged 31-35 years (37.6%). In general, the age range of 31-35 is the age of women at 5-6 years of marriage. Most types of infertility experienced by this age group were primary infertility (81%).

Primary infertility is a couple who have never had children after one year of having sex 2-3 times a week without using contraception. Infertility is a problem for married couples. One partner cannot be said to be infertile because it is possible that one or both of them are subfertile or sterile.

The results showed that women of reproductive age with indications of infertility with tubal damage had a small frequency of 25%, as well as infertility with indications of disorders of the endometrium, which had a frequency of 21.7%. Examination of the uterus (including the cervix and uterine cavity) – the tubes and peritoneum are usually performed as a unit. The peritoneal uterine tubal factor accounts for 30% of infertility [27].

Some of the recommended examinations for examining uterine, tubal, and peritoneal factors are transvaginal ultrasound and laparoscopy. Transvaginal ultrasound can accurately identify pelvic anatomy. Ultrasound can evaluate pelvic pathologies such as endometriosis, polyps, and ovarian or adnexal abnormalities.

Nargund recommends a "one-stop fertility diagnosis" with ultrasound as follows:

Uterus:

Position, mobility

Long dimensions (normal length: 75 mm)

Anomaly

Mioma/ademiosis (assessment by dopple).

Investigation of the uterine cavity with "Somo Contrast Salpingo Hysterography" (SCSH).

Endometrial uterine blood flow:

Thickness(>7mm)

Volumes (>2ml)

Morphology (Triple layer)

Doppler assessment

Ovary:

Mordology

Position and mobility

Volume (>3ml) and number of antral follicles (>6)

Stromal blood volume and flow

Cysts (endometriomas, dermoids)

Doppler assessment of cysts

Dominant follicle and blood flow (PSV)

Tube:
 Sonocontrast salpingo hysteroGRAPHY
 Hydrosalpinx
 Kavum
 Douglasi
 Free liquid
 Mass.

Besides tubal and endometrial indications, ovarian function assessment also plays an important role in female infertility. The quantity and quality of eggs generally decreases in women in their early 30s and decreases significantly in their late 30s and will decrease even more drastically in their early 40s. Every woman is born with a gift of 1-2 million primordial follicles, and starting at menarche, primordial follicles decrease to around 300,000-500,000 grains. Every time menstruation occurs, there will be a reduction in the number of follicles until finally approaching, menopause. And during the 35-40 years of the reproductive period, it is estimated that 400-500 ovulations will occur, with an estimated average loss of 1000 oocytes per ovulation episode. Although the average age of menopause reaches 51 years, there are individual variations regarding the age between 40 -60 years. So ovarian age generally parallels the woman's chronological age.

The research results found that the frequency distribution of Anti Mullerian Hormone in women tends to be in the fertile phase (90.7%). AMH is an ideal marker of functional ovarian reserve because it is formed only by primary follicles, which have the potential to cause maturation, and secondary follicles. Thus there is a very good correlation between AMH and the number of capable follicles and, thus, functional ovarian reserve.

According to bioscientie, AMH levels decrease steadily with age, corresponding to loss of ovarian functional reserve; a significant decrease is very likely to occur earlier than a clear rise in FSH. A decreased AMH level indicates a limited reserve of ovarian function and a poor response to ovarian stimulation. AMH concentration must be determined before treatment in assisted reproductive technology (TRB), namely In Vitro Fertilization. It allows treatment to be tailored to each individual. With AMH levels $<0.025 \mu\text{g/l}$, the patient is already in the infertile phase. With AMH levels $<0.1 \mu\text{g/l}$, IVF treatment is no longer recommended due to decreased fertility in these women. With AMH levels $<0.5 \mu\text{g/l}$, a maximum of 2 oocytes can generally be obtained by stimulation with increasing doses of rFSH. While women with AMH values $>0.1 \mu\text{g/l}$ are in the fertile phase.

This study found that the majority (90.7%) of reproductive-age women had good AMH values of $>0.1 \mu\text{g/l}$. It is because the age group of women aged 31-35 years still have good oocytes even though they are in the process of decreasing. There are about 400-500 ovulations, with an estimated average loss of 1000 oocytes per ovulatory episode. It indicates that the age range of women 31-35 years still has functional ovarian reserves formed by primary follicles, which have the potential to cause maturation, secondary follicles, and functional ovarian reserves.

Evaluation of ovarian function can also be seen from the antral follicle count. Antral follicles are tiny, measuring 2 - 8 mm, that can be seen in the ovaries using transvaginal ultrasound. Antral follicles are also known as resting

follicles. These follicles are seen early in the menstrual cycle, and their number can predict the number of primordial follicles in the ovary. The number of antral follicles of the two ovaries <10 follicles indicates a group of poor responses in the superovulation program, groups of 10-14 follicles include normal responses, groups of 15-20 follicles include ideal responses, and above 20 follicles are called excessive responses (Halim et al., 2006). The age of the mother is very important to know because, with increasing age, it is more difficult to have children. Aged 20 - 24 years, female fertility reaches 100%; for ages 30 - 34 years, female fertility is 85%; for ages 35 - 39 years, fertility remains 60%; for ages 40 - 44 years, female fertility remains 25%, and ages 50 - 59 years female fertility already 0% (Baziad, 2008). The average woman will experience a decrease in fertility at the age of 37.5 years [28]. Fertility decreases with increasing age due to a decrease in the number of primordial follicles. Acceleration of follicular loss occurs around the age of 37 years and is followed by menopause 10-12 years later. As assessed by transvaginal ultrasound, the number of antral follicles >2 mm decreased by 60% between the ages of 22 and 42. The quantity and quality of eggs generally decline from 30 and decrease dramatically in the early 40s. In general, the number of antral follicles is inversely related to age. Fecundity disorders increased from 2% at the age of 15-19 years, 7% at the age of 20-24 years, 15% at the age of 30-34 years, and 28% at the age of > 35 years.

Antral follicle count as an easy and non-invasive way to provide important information about the ovarian response [29]. Based on the results found in these data, the majority (66.2%) of women of reproductive age have a very low antral follicle count, namely <10 follicles, following the theory in CHAPTER II that a woman's age greatly influences the number of antral follicles which plays an important role in reducing ovarian response to gonadotropin stimulation, especially in vitro fertilization programs [30,31]. It also supports the concept of a decreased number of primordial follicles developing into small antral follicles. It was further reported that decreased AFC was also associated with a decrease in the number of oocytes obtained.

Conclusion

Based on the results of research conducted based on medical record data at BIC Morula IVF, conclusions can be drawn, namely: a) The reproductive age group of women undergoing therapy at BIC Morula IVF is mostly in the age group of 31-35 years; b) Most types of infertility are primary infertility, so the percentage of indications of tubal damage, endometrial disorders, and ovarian problems is not as high as types of primary infertility; c) There is a relationship between a woman's age and anti-Mullerian hormone levels in women; d) There is a relationship between a woman's age and Antral Follicle Count. Thus, it is necessary to carry out further research on the same problem, and in more depth, even to the biomolecular stage, to obtain even better results.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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