



INFERTILITY SCREENING

Rizani Amran, Kms Yusuf Effendi, Iskandar Zulqarnain, Heriyadi Manan,
Fatimah Usman, M Komarul Hakim, Vicela Patricia, Selly Rizany, Anton Rama,
Achmad Fachroni¹

Obstetric and Gynecology Department, dr. Moh. Hoesin General Hospital /
Faculty of medicine, Universitas Sriwijaya Palembang, Indonesia

Email : vicelavirgynajan19@gmail.com

ABSTRACT

Infertility is a common condition caused by the female factor, male factor, or both. Infertility problems can have a significant impact on married couples who experience them. In addition to causing medical problems, infertility can also cause economic and psychological problems. Couples who experience infertility will undergo a long process of evaluation and treatment, where this process can be both physical and psychological for the infertile couple. The aim of this article is presenting a literature study on infertility screening. Infertility affects millions of people of reproductive age worldwide and impacts family and community life. Estimates suggest that between 48 million couples and 186 million people are living with infertility. Infertility occurs in 15% of couples. Female factors cause infertility in 50-70%, and malefactors are the cause of infertility in 40-50% of couples. Given the high prevalence of malefactors in infertility heterosexual couples, medical history and early evaluation of male partners are needed. Ovulation dysfunction was defined as a history of oligomenorrhea or amenorrhea, recurrent luteal progesterone levels of less than 3 ng/mL, or both. For many women, a menstrual history is sufficient to assess ovulatory function. The clinical history can be used to assess the ovulatory cycle as most women will have regular menstrual cycles every 25–35 days. Anovulation may be associated with obesity, hypothalamic and pituitary dysfunction, PCOS, and other etiologies. Polycystic ovary syndrome is the most common cause of ovulatory infertility. Women with PCOS who have been diagnosed are at increased risk of the metabolic syndrome associated with cardiovascular events and negatively impacting pregnancy.

Infertility is the failure of a couple to get pregnant for at least 12 months having regular sex without contraception, or also known as primary infertility. Secondary infertility is the inability of a person to have children or maintain a pregnancy. Idiopathic infertility refers to infertile couples who have undergone standard examinations, including ovulation tests, tubal patency, and semen analysis with normal results.

Keywords: Infertility, Screening.



INTRODUCTION

Infertility is a common condition found and caused by females, males, or both factors. Infertility problems can have a big impact on married couples with its problems. In addition to causing medical problems, infertility can cause economic and psychological problems. In the big picture, couples with infertility problems will undergo the long process of evaluation and treatment, which can cause physical and psychological burdens for infertile couples.¹

Primer infertility is the failure of a couple to get pregnant within 12 months of routinely having sexual intercourse without contraception.

Secondary infertility is an inability to have children or maintain a pregnancy. Infertility can also have no known cause, which is known as idiopathic infertility.¹

Many known causes can cause infertility, which consists of female factors and malefactors. Female factors are caused by ovulation disorders and tubal pelvic disorders. While malefactors are caused by urogenital disorders, urogenital tract infections, endocrine disorders, genetic disorders, and immunological factors.¹

Age also greatly affects the fertility of a woman. However, in men, an increase in age has not had a clear effect on fertility. Research in France reported that 65% of women aged 25 years would experience pregnancy at 6 months, and an accumulation of 85% of pregnancies will be obtained by the end of the first year. This means that if 100 couples try to conceive, 40 couples will not get pregnant after six months, and 15 couples will remain non-pregnant after a year. For couples aged 35 or older, the chances of getting pregnant are 60% in the first year and 85% in the second year. Approximately 15 percent still have not conceived after the 3rd year of marriage.¹ The aim of this article is presenting a literature study on infertility screening.

DISCUSSION

Definition

Infertility is the failure of a couple to get pregnant for at least 12 months of having regular sexual intercourse without contraception or also known as primary infertility. Secondary infertility is the inability to have children or maintain a pregnancy. In women over 35 years old, evaluation and treatment can be done after six months of marriage. Idiopathic infertility refers to infertile couples who have undergone standard examinations, including ovulation tests, tubal patency, and semen analysis with normal results. Fecundity is a woman's ability to get pregnant. Data from studies that have been conducted on the population shows the probability of a woman getting pregnant each



month is about 20-25%. In women aged 40, immediate evaluation and treatment are required. In addition, evaluation and treatment should be done if a woman has a condition that can cause infertility.^{1,2}

Epidemiology

Infertility affects millions of people of reproductive age worldwide and impacts family and community life. Estimation suggests that globally, between 48 million couples and 186 million people are living with infertility. Infertility occurs in 15% of couples. In couples, 50-70% are female factors, and malefactors cause 40-50%. Given the high prevalence of malefactors in infertility of heterosexual couples, medical history and early evaluation of male partners are needed.

Tabel 1.1. Persentase perempuan yang mengalami infertilitas primer

Negara	Total								Standar
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	25-49	Umur
Bangladesh	u	U	U	U	U	U	u	u	U
Kamboja	6.8	30.8	24.0	7.3	12.3	5.0	10.2	6.7	-3.5
India	u	U	U	U	U	U	u	u	U
Indonesia	4.5	21.3	16.8	4.9	8.2	3.3	3.5	6.0	2.5
Kazakhstan	3.1	10.0	6.9	3.0	4.8	1.8	2.6	3.7	1.1
Nepal	u	U	U	U	U	U	u	u	U
Filipina	u	U	U	U	U	U	u	u	U
Turkmenistan	3.1	43.7	40.6	3.7	9.2	5.5	3.1	4.5	1.4
Uzbekistan	1.2	9.3	8.1	1.3	2.1	0.8	0.9	1.7	0.8
Vietnam	U	U	U	U	U	U	u	u	U
Rata-rata			19.4			2.9			1.4

U : Data tidak diketahui

The prevalence of idiopathic infertility varies between 22-28%. Recent studies have shown that among couples visiting fertility clinics, 21% of women are under 35 years of age, and 26% of women are over 35 years of age.¹

Etiology

Ovulation dysfunction was defined as a history of oligomenorrhea or amenorrhea, recurrent luteal progesterone levels of less than 3 ng/mL, or both. For many women, a menstrual history is sufficient to assess ovulatory function. The clinical history can be



used to assess the ovulatory cycle because most women will have regular menstrual cycles every 25–35 days with symptoms of molimina.²

Anovulation may be associated with obesity, hypothalamic and pituitary dysfunction, PCOS, and other etiologies. Polycystic ovary syndrome is the most common cause of ovulatory infertility. Women with PCOS who have been diagnosed are at increased risk of the metabolic syndrome associated with cardiovascular events and adversely affecting pregnancy. All women with diagnosed PCOS should be screened for metabolic syndrome with measurements of waist circumference, blood pressure, fasting blood sugar, and glucose tolerance tests. Thyroid disease and hyperprolactinemia can cause ovulatory dysfunction, ranging from inadequate luteal oligo-ovulation to amenorrhea. Serum thyrotropin should be measured in women with ovulatory dysfunction, infertile women, or those with signs of thyroid disease. Serum prolactin should be measured in infertile women with irregular menstruation or other signs such as symptoms of hyperprolactinemia.¹

Risk Factors

Several factors related to infertility and suggestions for examination includes:^{1,2}

1. Tubal Factors

From studies that have been done, endometriosis is present in 25%-50% of women, and 30% to 50% experience infertility. The hypothesis that explains endometriosis can cause infertility or decreased fecundity is still unclear, but there are several mechanisms in endometriosis, such as adhesions and pelvic anatomical distortion, that can lead to decreased fertility rates. Pelvic attachment in endometriosis can interfere with the release of oocytes from the ovary and inhibit oocyte capture and transport. The classification of tubal damage are:¹

a. Light/Grade 1

Proximal tubal occlusion without fibrosis or distal tubal occlusion without distension, mucosa looks good, light attachment (perituba-ovarian)

b. Medium/Grade 2

Unilateral severe tubal damage

c. Severe/Grade 3

Severe bilateral tubal damage Extensive tubal fibrosis

Tubal distention > 1.5 cm

The mucosa looks abnormal

Bilateral tubal occlusion

Heavy and broad attachment



Hysterosalpingography (HSG), a procedure used to view the uterus and fallopian tubes by injecting radiopaque contrast through the cervix during fluoroscopy, is commonly used to assess tubal patency. Proximal and distal tubal occlusion, peri tubal adhesions, and salpingitis isthmica nodosa can be seen on HSG examination. The positive and negative predictive values of HSG for assessing tubal patency have been estimated at 38% and 94%, respectively.

Sonohysterography is the ultrasonographic visualization of the uterus and adnexa with fluid infusion through a transcervical catheter. An extension of sonohysterography, hysterosalpingo contrast sonography, is used to determine tubal patency with the use of fluids through a transcervical catheter. This technique often uses a collagen trust with air bubbles to aid in identifying the tube, which is usually not visible on ultrasound.

2. Uterine factors

Uterine factors associated with infertility are material endopolyps, synechiae, Müllerian anomalies, and leiomyomas. By using sonohysterography, the uterine cavity can be easily identified, and abnormalities such as endometrial polyps, submucosal fibroids, and intrauterine adhesions can be seen using sonohysterography.²

Sonohysterography has a sensitivity and specificity of 91% and 84%, respectively, for detecting intrauterine structures that may have polyps or leiomyomas.

Transvaginal ultrasound helps in the detection of uterine leiomyomas affecting the uterine cavity. The size, number, and location of uterine leiomyomas can be determined by sonohysterography, which can help in planning fertility treatments for the uterus.

Ultrasonography (USG) improves the early detection of Müllerian anomalies with the same accuracy as pelvic magnetic resonance imaging. Direct visualization of the uterine cavity by hysteroscopy provides the most definitive results for diagnosing endometrial polyps, uterine synechiae, and submucosa.

Hysteroscopy is indicated to confirm and treat intracavitary lesions detected by other imaging studies. Hysterosalpingography has limitations in identifying masses or adhesions of the uterine cavity because it does not have a radio-opaque structure. The sensitivity of HSG for polypoid lesions of the uterine cavity is only 50%. The Mullerian anomaly can be detected by HSG, although other imaging modalities are needed to differentiate and confirm the final diagnosis. Magnetic resonance imaging and three-dimensional ultrasonography can help diagnose Mullerian Anomaly.²

3. Male Infertility Factors

Male factors cause infertility in 40-50% of couples considering the high prevalence of male factors in infertility in heterosexual couples. Male fertility can decrease as a result of:¹

a) Congenital or acquired urogenital disorders



- b) Urogenital tract infection
- c) Elevated scrotal temperature (eg, due to varicocele)
- d) Endocrine disorders
- e) Genetic disorders
- f) Immunological factors

A basic medical history and evaluation of the male partner should be carried out early on. Minimal evaluation of the male partner includes reproductive history and sperm analysis. Men who are suspected of being infertile should undergo a medical examination in the form of a semen analysis or refer the patient to a specialist. Semen analysis is a quantitative microscopic evaluation of sperm parameters. Perform a semen analysis examination; there are two to five days of abstinence to get optimal results. Ideally, the sample is obtained during masturbation and examined in the laboratory.

Sperm collection at home is possible if the sample is stored at room or body temperature within 1 hour. Abnormalities in semen analysis should be re-examined and further investigated.

Risk Factors

a. Lifestyle¹

Alcohol is said to have an impact on Leydig cell function by reducing testosterone synthesis and causing damage to the basement membrane. Excessive alcohol consumption can cause disturbances in the function of the hypothalamus and pituitary.

Cigarettes contain substances that are harmful to oocytes (causing oxidative damage to mitochondria), sperm (causing serious morphological damage), and embryos (causing miscarriage).

Consumption of caffeine (tea, coffee, soft drinks) does not affect infertility problems (Recommendation B)

Women who have a body mass index (BMI) of more than 29 tend to take longer to get pregnant. (Recommendation B)

Light-moderate exercise can increase fertility because it will increase blood flow and antioxidant status.

Excessive feelings of anxiety, guilt, and depression can be associated with infertility, but there are no adequate research results.

Excessive consumption of vitamin A in men can cause congenital abnormalities, including craniofacial, heart, thymus, and central nervous system.

Several antioxidants are known to improve the quality of sperm, including:



Vitamin C can be used to improve the quality of cement. Ubiquinone Q10 can improve sperm quality. Selenium and glutathione can increase sperm motility.

The combination of folic acid and zinc can improve sperm concentration and morphology. Cobalamin (Vit B12) is important in spermatogenesis

The use of drugs such as Spironolactone will impair testosterone and sperm production. Sulfasalazine can affect normal sperm development (can be replaced with mesalamine). Colchicine and allopurinol can cause a decrease in sperm to fertilize oocytes. The high doses of antibiotics; tetracycline, gentamicin, neomycin, erythromycin, and nitrofurantoin harm sperm motility and count. Cimetidine sometimes causes impotence and abnormal sperm. Cyclosporine can also reduce male fertility.

Research conducted in California found that consuming herbal medicines in minimal amounts, such as ginkgo Biloba, is suspected of inhibiting fertilization, altering sperm's genetic material, and reducing sperm viability.

Several occupations involve exposure to substances harmful to the fertility of both a woman and a man. At least 104,000 physical and chemical substances related to work have been identified, but their effect on fertility, 95%, have not been identified. Materials that have been identified that can affect fertility include heat, X-ray radiation, metals, and pesticides.

Diagnoses

History

The history may include:

- 1) Duration of infertility and outcome of previous therapy
- 2) Menstrual history (including age at menarche, cycle interval, length, and characteristics; the presence of molimina [mild premenstrual symptoms and changes]; and onset and severity of dysmenorrhea), signs of ovulation including positive ovulation test, changes in cervical mucus, or biphasic temperature body basal
- 3) Pregnancy history (gravidity, parity, gestational age, fertility treatment, pregnancy outcome, and related complications)
- 4) Previously used contraceptive methods
- 5) Coitus frequency and time
- 6) Sexual dysfunction
- 7) History of previous surgery (procedures, indications, and results) focusing on abdominal and pelvic surgical procedures
- 8) History of the previous hospitalization with serious illness or trauma
- 9) Gynecological history
- 10) Sexual history



- 11) Review of organ systems, including the history of thyroid disease, galactorrhea, hirsutism, pelvic or abdominal pain, and dyspareunia
- 12) History of abnormal cervical cancer screening and treatment
- 13) Medical history, with identification of allergies and potential teratogens
- 14) Family history of congenital disabilities, developmental delays, early menopause, or reproductive problems
- 15) Occupational history and environmental exposure to hazards
- 16) History of using nicotine products, alcohol, and illegal drugs

Targeted physical examination of the female partner is carried out focusing on vital signs and includes thyroid, breast, and pelvic examinations. Physical examinations that can be performed are as follows:

- 1) Body weight, body mass index, blood pressure, and pulse
- 2) The presence of enlarged thyroid and nodules
- 3) Breast secretion and its characteristics
- 4) Signs of androgen excess
- 5) Examination of the tanner stage on the breast, pubic hair, and axillary hair
- 6) Abnormalities of the vagina or cervix, presence of secretions, or discharge
- 7) Pelvic or abdominal pain, organ enlargement, or mass
- 8) Uterine size, shape, position, and mobility
- 9) Adnexal mass
- 10) Cul-de-sac mass or nodularity

Added evaluation for infertility etiology

Infertility tests include laboratory tests and imaging tests. For female partners, the test will focus on ovarian reserve, ovulatory function, and structural abnormalities. Specific fertility tests yield less significant results in identifying women who will and will not become pregnant, with the disadvantages outweighing the benefits (Box 1).

While there may be other reasons for these tests to be performed, they are low-yielding for evaluating infertility. Imaging of the reproductive organs provides valuable information about conditions that affect fertility. Imaging modalities can detect tubal patency and pelvic pathology and assess ovarian reserve. Although there may be other reasons for this test, the test yields less significant results for evaluating infertility, so it should not be routinely examined. Imaging of the reproductive organs provides valuable information about conditions that affect fertility. Imaging modalities can detect tubal patency and pelvic pathology and assess ovarian reserve.



The reproductive potential of the ovary, called ovarian reserve, represents the number of oocytes available for potential fertilization at that time and can be assessed by serum tests or ultrasound. The presence of decreased ovarian reserve predicts the response to ovarian stimulation. The results of the ovarian reserve test should be considered in the context of the patient's age. Although there are no definitive criteria for decreased ovarian reserve, the following values can be considered consistent with reduced ovarian reserve:²

- Antimullerian hormone (AMH) levels less than 1 ng/mL
- The number of antral follicles is less than 5-7
- FSH hormone (follicle-stimulating hormone) more than 10 IU/L
- History of poor response to stimulation in vitro fertilization (less than four oocytes at the time of egg retrieval)

Ovarian reserve can be assessed by measuring estradiol and FSH between cycle days 2-5. FSH values greater than 10 IU/L may be associated with a less robust response to ovarian stimulation. Estradiol functions to assess the hormone FSH. Basal estradiol levels should usually be less than 60–80 pg/mL; Elevated estradiol levels may have a suppressive effect on FSH levels and indicate decreased ovarian reserve. Serum AMH is produced by the granulosa cells of the antral follicle to be a marker of other ovarian reserve serum. Because AMH levels are relatively stable throughout the menstrual cycle, they can be assessed every day. The antimullerian hormone is similar to antral follicle count in its ability to predict response to ovarian stimulation and pregnancy in infertile women.²

The ovarian reserve test is a good predictor of response to ovarian stimulation, but poor results do not necessarily predict the inability to achieve a live birth. If a woman has ovarian insufficiency or ovarian failure, or elevated FSH levels before the age of 40 years, fragile X carrier screening is recommended to determine the presence of FMR1 premutation.

Ultrasonographic assessment of the antral follicle count is determined by the number of follicles measuring 2-10 mm in both ovaries. The number of antral follicles is low when less than 5-7 follicles and is associated with a poor response to ovarian stimulation. However, the number of antral follicles is a relatively poor predictor of future ability to conceive. The number of antral follicles may be increased in women with polycystic ovary syndrome (PCOS) or in women with hypothalamic amenorrhea or those taking certain hormonal contraceptives.

Treatment for Infertility Case



Currently, the infertility referral system in Indonesia is still not well structured. Indonesia has a population of around 238 million, and an estimated prevalence of infertility is 2,647,695. The vast geographical conditions and the archipelago form of the country are challenges and obstacles in overcoming the problem of infertility in Indonesia. With uneven health service capabilities, uneven human resource capabilities, limited/uneven tools/technology, and diverse socio-economic, educational, and cultural conditions, and the complexity of infertility management, appropriate solutions are needed in the treatment of infertility. Therefore, a structured and directed infertility service system is needed, tiered infertility service units (primary, secondary, tertiary) and a referral system, cooperation or networking between service units, harmonious relationships between health workers and health services, health workers and married couples (couples), as well as health workers with the community. This condition requires clear job descriptions for each health service unit and health workers.¹

Stratification of the Infertility Referral System

The infertility referral system is divided into three levels: primary level services, secondary level services, and tertiary level services¹

1) Primary Infertility Service¹

Initial diagnostic activities for infertile couples at this level aim to determine the cause of infertility from both parties and whether the couple needs to receive services at a higher level of service. Patients will get a general and comprehensive picture of the pattern of infertility services. Counseling and support need to be provided to avoid anxiety for the patient and their partner. Primary level infertility services are usually given in the following conditions:

- Duration of infertility less than 24 months
- Female partner less than 30 years old
- There are no risk factors for pelvic pathology and male reproductive system abnormalities.
- Couples have been on therapy for less than four months without successful therapy.

2) Secondary Infertility Services¹

In certain conditions, patients will be referred to secondary infertility services.

- Age above 35 years, but the duration of infertility is not more than 36 months.
- Menstrual cycle disorders (amenorrhea or oligomenorrhea)
- Presence of galactorrhea
- Suspicion of thyroid dysfunction
- Presence of pelvic inflammatory disease
- Suspicion of endometriosis



- History of surgery in the pelvic area
- Symptoms of hirsutism
- Symptoms of obesity (BMI > 30) or malnutrition (BMI < 20)
- Ovulation disorders (progesterone levels < 30 nmol/l)
- Abnormalities in the external and internal genitalia
- Abnormalities in the results of sperm analysis (number, movement, and shape)
- There is a history of infection in the genitalia or systemic infection that can affect fertility
- History of urogenital surgery

3) Tertiary Level Infertility Services¹

Tertiary-level infertility services require special skills, including assisted reproductive technology actions that can only be performed at specialized infertility clinics. Infertility cases that can no longer be treated at the secondary level will be referred for tertiary level infertility services. Patient criteria:

- Spouse does not meet the qualifications of level I and II
- Possibility of Assisted Reproductive Technology (TRB)

The approach taken in infertility management is multidisciplinary, including obstetrics and gynecology, uro-andrology, psychology/psychiatry, nursing, and others, depending on the degree of difficulty causing infertility. Therefore, infertility services can be carried out in several levels (3 levels) of service based on the clinical competence of the service provider.

CONCLUSIONS

Infertility is the failure of a couple to get pregnant for at least 12 months having regular sex without contraception or also known as primary infertility. Secondary infertility is the inability of a person to have children or maintain a pregnancy. Idiopathic infertility refers to infertile couples who have undergone standard examinations, including ovulation tests, tubal patency, and semen analysis with normal results.

Estimation suggests that between 48 million couples and 186 million people are living with infertility globally. Infertility occurs in 15% of couples. Female factors cause infertility in 50-70%, and male factors are the cause of infertility in 40-50% of couples. The prevalence of idiopathic infertility varies between 22-28%.

The etiology of infertility consists of female factors and male factors. The female factor is caused by ovulation disorders and tubal and pelvic disorders. At the same time, the male factor is caused by urogenital disorders, urogenital tract infections, endocrine disorders, genetic disorders, and immunological factors.



The diagnosis can be made based on the history, clinical symptoms, and investigations. Physical examination includes an examination of body weight, body mass index, blood pressure, and pulse, as well as an examination of thyroid, breast, pelvis, signs of excess androgens, vaginal/cervical abnormalities, uterus, adnexal masses, cul-de-sac masses. Investigations that can be performed, are detection of tubal patency, pelvic pathology, assessment of ovarian reserve, and sperm analysis.

Infertility service systems must be structured and directed, tiered infertility service units (primary, secondary, tertiary) and referral systems, cooperation or networks between service units, harmonious relationships between health workers and health services, health workers, and married couples (newlyweds) as well as health workers with the community. This condition requires a clear job description for each health service unit and health worker.

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