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(REVIEW ARTICLE)

Multifactorial etiology of male and female infertility/ assisted reproductive technique

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Abstract

Introduction: Infertility defined as inability of female to conceive after 12 months (6 months for women above 35 years) of unguarded sexual coitus. It affected about 15% of new couples. Genetic causes contribute about 15-30% of male infertility. Also the infertility can be defined as inability to carry the gestation until giving birth of a live fetus. Infertility can be classified into primary and secondary infertility, also can be classified according to etiological cause into male and female infertility.

Conclusion: This review yield the importance of infertility as serious medical problem, affecting the partners life and focus on the important etiological factors affecting the fertile male or female as life style and smocking state in addition to aging, hormonal state, infections and systemic disease, also this review focus on the importance of assisted reproductive technique and its complication.

Keywords: Male infertility; Female infertility; Reproduction; ASTs; IUI

1. Introduction

Infertility defined as inability of female to conceive after 12 months (6 months for women above 35 years) of unguarded sexual coitus [1]. It affected about 15% of new couples [2]. Genetic causes contribute about 15-30% of male infertility [3]. Also the infertility can be defined as inability to carry the gestation until giving birth of a live fetus [4]. Infertility can be classified into primary and secondary infertility, primary infertility; couples that have been not conceiving previously while the secondary infertility; couples that have previous conception but fail to conceive once later [5]. The infertility also can be classified according to etiological cause into male and female infertility [6].

2. Male infertility

Male infertility is major and important medical issue, although; the exact etiological cause is poorly understood, but male infertility account for more than half of the infertile couple among the world [7]. Male infertility largely dependent on spermatogenesis and linear development of spermatozoa from spermatogonia that characterized by mitotic and meiotic division followed by chemical and functional differentiation until it reach full mature sperm [8]. Male infertility some time underestimated because of socioeconomic dilemmas, in addition to inaccurate sampling and analysis, it can potentiate the male anxiety about hegemonic masculinity, and can be associated with psychological rather than marital tension, risk of cancer development, decrease in quality of health and life [9]. The most acceptable diagnostic method for male infertility is quality of sperm, concentration and motility, though; there are some limitations, like ambiguous

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threshold value affecting the accuracy of sperm analysis [7]. The abnormal spermatozoal differentiation that contributed to male infertility includes total sperm absence or Azoospermia, low sperm count or oligospermia, abnormal sperm shape or teratozoospermia, abnormal sperm motility or asthenozoospermia [10].

2.1. Multifactorial etiology of male infertility

2.1.1. Anatomic-pathophysiological factors

Several factors (anatomical and pathophysiological) affected male infertility like sperm duct occlusion (either in vas deference or occlusion in epididymis), ejaculation abnormality, disease of the testis, genetic disorders, hormonal imbalance in addition to iatrogenic factors [7]. Oligospermia and Azoospermia are indication of duct occlusion that occurs in about 5% of infertile men [11]. About 2% of infertile cases have retrograde ejaculation or disturbed bladder sphincter that characterized by semen ejaculation pass retrogradly into bladder [12]. Also disturbance in endocrine hormones development and function caused infertility related to Hypothalamus-pituitary-testis through decrease sperm production by malfunctioning of sexual hormones [13]. Autoimmune disorders that release sperm antibody and varicocele that happened duo to enlargement of testicular veins also cause infertility [12]. Beside some pathogens like bacteria [14], virus like Zika virus [15] and STDs infection of reproductive organs in addition to urinary tract infection can cause infertility [16, 17].

2.1.2. Environmental cause

Pollution and several environmental causes can affect male fertility through epi\genomic way [18]. Occupational exposure to physical and chemical hazard that lead to male infertility and decrease sperm quality and motility [19, 20]. Sitting for long time, high temperature exposure (bakeries and metallurgical industries) also affects the men fertility [21].

The other environmental cause that affected male fertility; exposure to radiation from mobile phone and laptop, in addition to tight wearing underwear, exposure to high temperature like hot bath and sauna, also exposure to chemical that modulate the production of sex hormones like pesticide, bisphenol and dioxine [22].

2.1.3. Life style cause

The behavioral style of men affects its health like diet, exercise and consumption of alcohol and tobacco, these factors modified the male fertility. Obesity can alter male fertility by alteration of male sleeping, sexual attendance, sexual hormones profile, temperature of testis and semen quality and motility, so chance for nonviable gestation is high [23].

Oligo or Azoospermia also found in higher rate in both under and overweight in comparing to normal weight person, in obese patient there were decrease in sex hormones binding globulin that leads to hyperinsulinemia with increasing total estradiol level, while decreasing in weight associated with decreasing in DNA damage that lead to improve sperm quality and function [24].

High fat diet and high energy diet can induce male infertility by inducing intestinal dysbiosis through increasing blood endotoxin levels, inflammation and epididymitis in addition to deregulation of gene expression of the testicular gland [25, 26]. While poor diet can induce asthenozoospermia in contrast to balanced diet that improve sperm quality [26].

2.1.4. Aging

The molecular mechanisms of male infertility due to aging are incompletely understood, but its multifactorial process that leads to weakness in cellular immunity and disturbance in sexual hormones production from reproductive system that leads potentially to late onset andropuase in male [27]. The andropuase duplicate the risk of male infertility and affect the seminal fluid factors like sperm motility and morphology, while the volume; the aging process have no explained reason of how it affect, also it had increased risk on pregnancy and on infancy by increasing risk of abortion and infancy complication like autism, low birth weight [27,28].

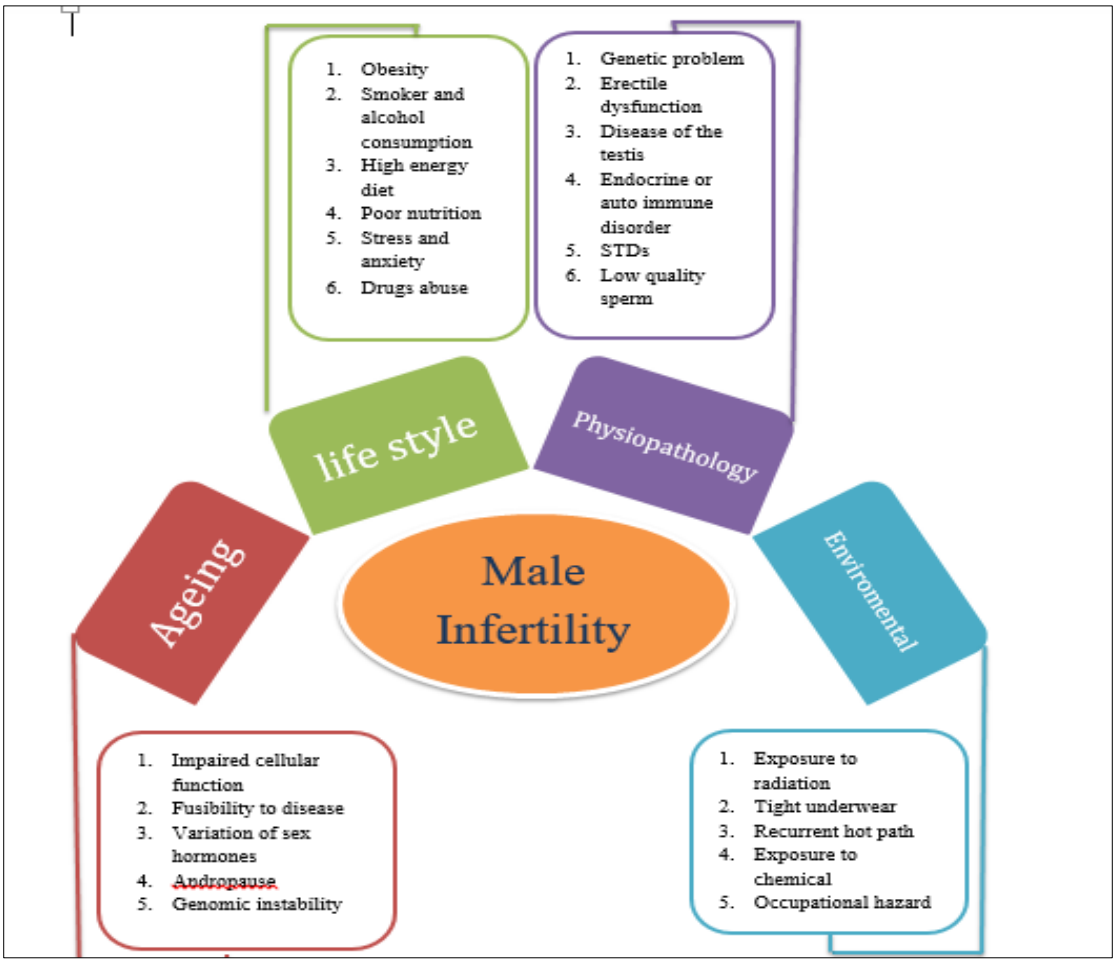

Figure 1 Etiological causes of male infertility

2.2. Male infertility markers

Many factors of given male infertility etiology can be interact, combination of several parameters are required to explains the molecular and pathophysiological reasons of male infertility like seminal fluid analysis, sperm morphology, mutation and so on, using these parameters can leads to more accurate diagnosis and effective therapies [7].

2.2.1. Seminal fluid analysis

The seminal fluid analysis and sperm morphology regarded primary morphological and physiochemical diagnostic test of male infertility, the WHO developed in 1980s a standardized laboratory technique to avoid the bias between laboratories and more recent update published in 2021s [29]. The parameters of semen analysis according to update to diagnose the male infertility are (i) liquefaction time should be 15-20 minutes at room temperature (ii) Viscosity (increased viscosity indicate prostatic malfunction) (iii) Volume (after 3-5 abstinence the volume should be 1.5-6 ml, no more no less or it indicate hyper or hypospermia respectively) (iv) Color, the normal color of seminal fluid should be pearl white or yellowish (v) pH should be >7.1 while decreased values indicate efferent vessels digenesis that lead to decreased sperm concentration (vi) concentration, should be >15 million spermatozoa for each 1 milliliter of ejaculation (vii) Motility should be >32% (viii) Vitality should be >58% of live spermatozoa (ix) leukocyte should be < 1million per 1 milliliter (x) morphology should be >4% have normal morphology (xi) anti-sperm antibody (attachment of >50% of the sperm to other cells or particles indicated of immune disorders [7, 29].

2.2.2. Reactive oxygen species (ROS)

Most of male with idiopathic infertility (30-80%) shows increased concentration of ROS [30]. The Oxidative stress (OS) increased when there was increased in ROS with decreased anti-oxidant neutralizing capacity, in male reproductive system; the ROS produced from sperm, but the leukocyte produce 1000 time more than sperm, so there were 10-20% of infertile men have leukocyte in ejaculation [29]. Despite of free oxygen radicle control maturation of sperm, activation and capacitation in addition to sperm-oocyte fusion, it can also started protein damage, lipid peroxidation and apoptosis

[31]. So both low and high value of ROS can affect sperm maturation, motility and morphology in addition to fertilization capacity [32].

There were other male infertility markers like sperm DNA fragmentation (SDF), genomic markers, transcriptomic and epigenomic markers, and proteomic and metabolomics markers used for best diagnosis and accurate treatment [7].

3. Female infertility

3.1. Multifactorial etiology of female infertility

Female infertility may be happened due to underlying medical condition like fallopian tubes damage that interfere with ovulation, pelvic inflammatory disease, polycystic ovaries, endometriosis, and premature ovarian failure and may be due to environmental conditions, aging process, weight changes, and life styles.

3.1.1. Environmental factors

The environmental causes like toxins, Volatile organic solvents and silicones, chemical and physical agents in addition to pesticides and chlorinated hydrocarbons are discovered to have harmful environmental effect that lead to miscarriage also direct exposure to chemical increased chance of primary and secondary female infertility [33].

3.1.2. Weight changes

Ovarian failure may occur in weight loss or excessive weight with BMI of more than 27 kg\m^2 [34]. High weight can affect the assisted reproductive technique efficacy and its outcome, estrogen produced by primary sex organs and fat cells so obese patient or high body fat produce excessive estrogen that interfere with pregnancy [35]. Also emaciated women or too low body fat produced insufficient estrogen that causes menstrual disturbance and unovulatory cycle [36].

3.1.3. Aging

Female's peak fertility period; between 18-24 years [37]. While it begins to drop after age of 27 years and it drops at greater extent at age of 35 years [38]. The ovarian reserve of female at age of 30 years about 12% and at 40 years she had only 3% and about 81% of ovarian reservation variation due to age alone [39]. So the aging process considered as more important factor in female infertility [38].

3.1.4. Life style

Life style can affects female infertility such as tobacco smocking affects folliculogenesis because it interfere with estrogen production, also the smocking can affect; embryo transfer and endometrial receptivity in addition to uterine blood supply and myometrium [40]. 60% of infertile women more likely to be smokers, smocking reduce the chance of IVF by 34% to give live baby and increased the chance of IVF miscarriage by 30% [41]. While alcohol consumption increased estrogen production which leads to decrease in FSH production, that in turn reduce folliculogenesis and in anovulatory cycle [42].

3.1.5. Hormonal change

The gonadotropin releasing hormone that released from hypothalamus control pituitary gland hormones that in turn control releasing most of body hormones in direct or indirect ways, so any abnormality in chemical signaling of this axis lead to anovulatory cycle and female infertility [43]. The hormonal imbalance that affects the ovary are; hyperthyroidism, hypothyroidism, polycystic ovarian syndrome, hyperprolactinemia and abnormalities in hypothalamus-pituitary-adrenal axis that may happened due to the stress, all these changes leads to decrease in number of mature follicles and anovulatory cycle [44].

3.1.6. Hyperprolactinemia

Prolactin hormone produced from anterior pituitary gland in response to breast growth and development during pregnancy and lactation, hyperprolactinemia represent abnormally high quantity of prolactin level in blood larger than 580 mIU\L in women [45]. Hyperprolactinemia may occur physiologically as in breast feeding, sleep, mental stress, hypothyroidism and pregnancy, or it occur pathologically secondary to disease affecting hypothalamus or pituitary gland also happened in disease affecting liver, kidney and thyroid, in addition to drugs, heavy metal that affects normal regulations of prolactin hormones level in blood, infertility by hyperprolactinemia caused by increase release of

dopamine from hypothalamus that in turn prevent release of gonadotropin releasing hormone and then gonadal steroidogenesis and infertility [38].

3.1.7. Ovarian function problem

There are many types of ovarian function problems like complete absence of egg, ovarian blockage, ovarian dystrophy (physical damage to ovary or ovary with multiple cysts), luteinized unruptured follicles syndrome (matured follicles that fail to burst or the follicle burst occur without releasing egg leading to anovulatory cycle [46]. Polycystic ovary syndrome (POCS) in which the ovaries produce too much androgen usually testosterone hormones also high level of LH and low level of FSH leading to many sign like oligomenorrhea and amenorrhea yielding anovulatory cycle, also produce obesity, facial hair and acne, PCOS usually hereditary disease and account for 90% of female infertility [47].

3.1.8. Others

There are others factors affecting female fertility state like

- Tubal factors (tubal occlusion, tubal adhesion, tubal dysfunction, pelvic inflammatory disease and endometriosis) that prevent transferring egg through the fallopian tube and infertility [48].
- Uterine factors (uterine malformation, septal uterine, asherman syndrome, polyps, leiomyoma, and benign fibroid) large fibroid may cause female infertility by impairing lining and tubal blockage in addition to distortion the shape of the uterus [49].
- Thyroid disease (hyperthyroidism and hypothyroidism) hypothyroidism cause to decrease in thyroid stimulating hormone that lead to decrease in negative feedback mechanism yielding increasing in TRH from hypothalamus and stimulating both thyrotophs and lactotrophs as a result there is ovulatory failure due to hyperprolactinemia [50].
- Sexual transmitted disease (STD), pelvic inflammatory disease (PID), structural obstruction, and chemotherapy [38].

4. Assisted reproductive technique (ASTs)

These techniques consist of ovarian stimulation, sperm retrieval, in vitro-gamete assessment, intrauterine insemination (IUI), embryo-cryopreservation, IVF and intra-cytoplasmic sperm injection (ICSI) [7].

IUI is the first choice if the female partner is fertile, and in presence of active spermatozoa of $>10^6$ motile sperm, when >3 cycle of IUI fail; the partners should be prepared for IVF (in vitro-fertilization) by ICSI is usually recommended [51]. However there were some complications accompanied the ARTs like multiple pregnancies, low birth weight, hyper stimulation syndrome [52].

5. Conclusion

This review yield the importance of infertility as serious medical problem, affecting the partners life and focus on the important etiological factors affecting the fertile male or female as life style and smocking state in addition to aging, hormonal state, infections and systemic disease, also this review focus on the importance of assisted reproductive technique and its complication.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest in connection with the publication of this manuscript.

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