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Infertility-Related Risk Factors: A Systematic Review

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Abstract

Objectives: Infertility is a universal barrier affecting people all over the world and its cause and importance may vary according to the geographical location and socio-economic condition. Infertility Awareness is the first step in maintaining pregnancy power in lifestyle modification.

Materials and Methods: Some studies were conducted on some databases such as PubMed, Scopus, Springer and Science Direct. Twenty-five English papers with similar subject as ours published from 2010 to 2015 were reviewed.

Results: Reproductive system disorders, the symptoms of sexually transmitted diseases and hormonal disorders are among the infertility causes in men and women. Lifestyle-related factors such as obesity, nutrition, smoking and alcohol consumption, mobile phone use, sexual violence and anxiety were evaluated as pregnancy changers.

Conclusion: Having a healthy lifestyle, running regular tests and checkups under medical supervision and maintaining normal body weight can prevent from fertility problems. Infertility in women will be treated by medicine, minor surgery, laparoscopic procedures, and hormone therapy and by avoiding early pregnancy failure. This article is useful and beneficial for all medical and scientific researchers who want to uproot infertility.

Keywords: Infertility-related risk factors, Infertility symptoms, Infertility causes

Introduction

Oxford English Dictionary defines the word "infertile" or barren as "inability to give birth or procreate." This definition refers to the "sterilization mode rather than visualization difficulty" and presents so many clinical perspectives (1). According to the reports of the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO), "infertility" is a couple's failure in pregnancy after 12 months of unprotected sexual intercourse and pregnancy attempts. Infertility is a global problem affecting people around the world whose cause and importance may vary according to the geographical location and socio-economic condition. According to the statistics, annually 60-80 million couples around the world suffer from infertility (2). The estimated fertility rate in Canada is 11.5% to 15.7%. One out of seven English couples suffers from fertility problems (3). The number of couples affected by infertility has increased from 42.0 million people (39.6 million people, 44.8 million people) in 1990 to 48.5 million people (45.0 million people, 52.6 million people) in 2010 (4). Ten to 12% of couples around the world are suffering from infertility in half of which, the man is infertile. The estimates show that in 35%-40% of cases, the man is infertile and in 35%-40% of cases, the woman is infertile and in 20%-30% of cases, it is related to the combination of other factors (5). Infertility occurs once pregnancies are ended up with abortion (ASR) or the delivery of a child with multiple hereditary diseases (6). Infertility diagnosis is different and may include the evaluation of sperm quality; Mormons, and analysis of imaging of uterus and fallopian tubes. According to the medical diagnosis, infertility may be treated by reproductive surgery, prescribing hormones or applying infertility technologies (2). Infertility awareness, like men and women's awareness of risk factors, is the first step in protecting pregnancy in lifestyle modification. Knowledge and awareness of fertility depends on education rather than personal fertility or motherhood and fatherhood experience. Health improving strategies started with educational interventions (3). Secondary infertility refers to a state in which pregnancy does not occur after one year (in some epidemiologic studies 2 years) of unprotected sexual intercourse despite at least one pregnancy in the past. Women with secondary infertility cannot give birth to alive child (7). Infertility may result from a wide range of abnormalities one or both of which exist. However, infertility is not much different in people and it can have a variety of causes (8). The primary and secondary causes of infertility are reviewed in this study. This study examines the following points: primary causes of infertility, such as genetic factors, hormonal disorders, genetic disorders, congenital defects or reproductive system diseases; secondary factors, including lifestyle related factors, such as obesity, diet, smoking, alcohol consumption and chemical environments, and secondary factors related to human infertility such as unsafe methods of childbirth and post-partum period as well as symptoms of sexually transmitted diseases.

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Materials and Methods

This study reviews the articles on infertility related risk factors. This research mainly aims to find risk factors that cause infertility. The infertility factors related to primary and secondary infertility are discussed in the main results of the published scientific papers. There were some studies conducted on database of PubMed, Scopus, Springer, Science Direct and thirty English articles with similar subject as ours were found in 2010-2015. Twenty-five articles were also evaluated.

Results

Some major factors of infertility include the impact of the reproductive system disorders, reproductive system diseases, hormonal disorders, age, alcohol consumption, and smoking, immune response, cell phone use, sexual violence, stress, obesity, nutrition, and any chronic disease reducing the chance of successful pregnancy and unknown factors.

Table 1 shows some articles with their study type, year of publication, authors, and their main findings on the infertility related risk factors.

The impact of the reproductive system disorders

A review of articles shows that female infertility may be clue to solve ovulation problems, anatomical problems, such as fallopian tube damage or endometriosis (3). In womb, congenital disorders, muscle tissue gland, endometriosis, polyps and adhesions can also reduce fertility (8). The reasons for male infertility include unusual characteristics of semen, reproductive infection and disorder, erectile dysfunction or ejaculation disorder. After testing and treating each etiologic factor, couples may look for assisted reproductive technology (3).

Endometriosis

Endometriosis is a benign estrogen-dependent inflammatory disease which develops due to the ectopic endometrial implants. Endometriosis affects more than 10%-15% of women who are of childbearing age (3). The relationship between endometriosis and infertility has been mentioned in many resources. However, a cause and effect relationship is still controversial. The pelvic anatomy is deformed and fertility is decreased through mechanical adhesion, such as pelvic adhesion. These adhesions cause damage to ovule release or selection, decrease sperm motility, and causing disruption in myometrium contraction, such as fertilization disorder and embryo transfer. Infertile women are more likely to develop the disease. However, so much debate has been raised on the impact of diseases on fertility. Anti-genetic growth factors, inflammatory cytokines and normal genes are among the endometriosis-related etiologic factors of infertility (9).

The impact of Genital Infections and Diseases

Untreated sexually transmitted infections (STIs) are among the factors that cause damage to the reproductive system of men and women. Chlamydia and gonorrhea are most common STI which lead to infertility in men and women. Chlamydia is among the most common STI in England and 196 new cases affected with this infection were identified in 2011; youth (aged 15-24) were at risk of this disease more than others. This disease has no symptom. Thus, it cannot be diagnosed and treated. Chlamydia causes problems for men and women. If chlamydia is left untreated, the woman will be also at risk of pelvic inflammatory disease (PID). PID is a serious condition where the upper part of the female reproductive system and its supporting structures become inflamed (10). The studies show that pre-pregnancy diagnosis of *Chlamydia trachomatis* reduces the abortion caused by PID in 4 weeks. Valid evidence also shows that women with PID are at risk of ectopic pregnancy, fallopian tube infertility and chronic pelvic pain (11). Among the 14551 reasons or required treatment for IVF mentioned in 2010, most of them are related to fallopian tube. A relationship was observed between infertility and previous Chlamydia infection in women (12). There is so much evidence indicating the relationship between trachomatis infection and any changes in semen quality. Trachoma can affect the sperm function. In vitro experiments show that *C. trachomatis* Tyrosine phosphorylation affects sperm proteins, causes sperm premature death and develops an apoptosis-like reaction in sperms which increase sperm surface fragmentation levels (13).

The Impact of Age

Studies show that the risk of infertility increases with growing age (3). Young people's knowledge of infertility is hopeful and leads to the maintenance and improvement of pregnancy health (12). Evidence shows that age may play an important role in fertility. Pregnancy before 30 for women and before 35 for men has more chance of success. Men and women should know each other's ages that they could come to an agreement for a successful pregnancy (14).

The Impact of Hormonal Disorders

There are many hormonal disorders that cause infertility. Hypothyroidism, hyperprolactinemia (high male hormone levels) and luteal phase defect (low progesterone) are a few examples of these disorders. Hormonal disorders are a major cause of infertility in women. The inability of women at ovulation and regulation of hormone levels leads to too high or too low production of hormones. These hormonal disorders are characterized with symptoms such as irregular menstrual cycles, excessive bleeding, or very little bleeding, pelvic and abdominal cramps, absence of menstruation or long menstruation and excessive weight loss or weight gain. The following factors may cause hormonal disorders: gland problems such as thyroid gland, pituitary gland and hypothalamus gland problems. These preliminary glands are responsible for the production of sex hormones. Birth control pills, stress and some diseases such as hypothyroidism affect these glands. If any of these glands encounter any problem, a

Table 1. Summery and Details of the Articles

No.	Year	Authors	Main Results
1	2015	Jaiswal et al.	Apoptosis is an essential process including a wide range of physiological and pathological measures. In this study, functional polymorphism in the cell death pathway genes FASLG was genotype to review its role in male infertility.
2	2015	Jensen et al.	The men using saturated fat in their diet have a pathological life. These men have a lower BMI. BMI is not always related to fat mass, and the men using saturated fat may have a lower BMI due to their lower muscle mass. This lifestyle and demographic factors can affect semen quality.
3	2014	Seshadri and Sunkara	Meta-analysis studies have shown a difference of the number of peripheral NK cells in fertile and infertile women with RM in response to the fertility controls presented at higher levels of peripheral NK cells in fertile and infertile women with RM.
4	2014	Meneses and Holland	Young women who are still of childbearing age include 6% of breast cancer patients and their age-related requests for treatment and pregnancy protection are noteworthy. 5of bariatric surgery on the number and quality of eggs in patients who have experienced assisted reproductive technology
5	2014	Christofani et al	Fertility in women who underwent bariatric surgery increased compared with those who controlled obesity; especially those recognized by PCOS. Weight loss can reduce the symptoms of androgen and insulin resistance.
6	2014	Sheehan et al	The pathophysiological mechanisms relating varicocele to infertility must be fully understood. All men with varicoceles are not infertile. It means that molecular and genetic factors can contribute to finding the pathogenesis of varicocele infertility.
7	2014	Pastore et al	Nearly 10% of infertile/sub-fertile women are recognized with DOR….percent of whom will be automatically fertilized. Women with DOR, regardless of age, are less successful in assisted reproductive technology.
8	2014	Li et al	Fallopian tube damage caused by surgery, fallopian tube infections and diseases, or previous EP may lead to higher EP in women who underwent IVF treatment. The increased risk of EP in IVF women may be related to fallopian tube infertility or surgical procedure rather than IVF.
9	2013	Goundry et al	Youth have little information and knowledge about STI and infertility problem; they do not have full understanding in this regard. Sexual health education should start at an early age and focus on how untreated STI may cause infertility.
10	2013	Scarneciu et al	The impact of Smoking on the progress of many diseases has been proven, and experts have published it in special publications. In this study, smoking affected the analysis of the patient's sperm change, and the results were statistically significant.
11	2013	Sabarre et al	Since the undergraduate students of University of Ottawa regarded infertility as a biomedical health issue, reproductive inactivity. In this study, women and men regarded infertility as a biomedical problem and could identify several risk factors for male and female infertility.
12	2013	Cook and Adamson	Different endometriosis diagnosis tests, scoring systems, and medical data results have recently been published. EFI has presented a basis for predicting pregnancy rate in 3 years and provided a simple visual graph for training the doctor and the patient.
13	2013	Tsai et al	Women with PCOS have a higher BMI and a larger waist. Diet and energy and macronutrient distribution can contribute to high BMI of women with PCOS.
14	2012	Adisa et al	Schistosoma is one of the main causes of low fertility in endemic areas, and the primary diagnosis and treatment with praziquantel can treat infertility. In the large part of Africa, urogenital schistosomiasis is a major health problem caused by Schistosoma haematobium.
15	2012	Sami et al	Women who suffer from secondary infertility are more like housewives who used inappropriate approaches for delivery and post-natal and menstrual care. They used household vaginal washes which are a risk factor for secondary infertility. Secondary infertility risk factors include unsafe procedures during childbirth, post-partum and menstruation.
16	2012	Macer and Taylor	It is clear how rare diseases can cause infertility. These disorders cause damage to the ovule release and selection, decrease sperm motility, and causing disruption in myometrium contraction, such as removing fertilization and embryo transfer. The disease is likely to progress in infertile women.
17	2012	Palihawadana et al	Ovulation morbidity and impaired sex relationship are among the regular findings in the infertile. There were a few women with pelvic injury and Bilateral tubal obstruction.
18	2012	Nodine and Hastings-Tolsma	Obesity makes it difficult to do prenatal care, such as anatomic scans, estimation of fetal weight and hearing of fetus heartbeat. A fat body's physiology makes the pregnancy difficult for women, such as lower back pain. Metabolic disorder refers to central obesity focused syndrome and insulin resistance, and is a subclinical inflammation function.
19	2012	Cozaru et al	The decision to perform genetic test or consultation is influenced by pervious infertility experiences, medical symptoms, and acceptance of genetic synthesizer for their infertility in many infertile couples.
20	2011	Tang et al	Immunological mechanisms contribute to vaginal problems, including RM, infertility and implantation failure. Therefore, successful pregnancy depends on maternal compliance of immune response to the growing semi-allogeneic fetus. NK cells are a part of the innate immune system which is found in the peripheral blood and endometrium.
21	2011	Dhont et al	Prenatal and maternal care along with prevention and better management of HIV/STI will prevent from infertility. In addition, the reduction of dead child labor and neonatal mortality rate and Improvement of access to family planning plays an important role; especially for young mothers.
22	2011	Ashok et al	Mobile equipment and communication devices emit electromagnetic radio frequency waves which decrease sperm quality and normal functioning of the body. The testicles exposure to these waves can have a negative effect on Spermatozoon.
23	2011	Hickman and Gordon	The risk of SLE and its treatment are effective and important in infertility. In some patients, lupus symptoms progressed after one or more child labors, and in a significant proportion of patients, the disease was progressed prior to child birth.
24	2010	Akande et al	Typically, women realize the infection after several years being at risk of it. Therefore, the tests which only discover the existence of micro-organisms can be used to detect the pervious risk of C. trachomatis. In the case-control study of infertile women, serology determined the previous size of Chlamydia.
25	2010	Dhont et al	History of sexual violence, HIV and HSV-2 infection affect infertility of Rwanda women; especially infertility of fallopian tube factor. HIV and HSV-2 infection are the most important risk factor for infertility in men.

Abbreviations: BMI, body mass index; PCOS, polycystic ovary syndrome; NK, natural killer; RM, recurrent miscarriage; EFI, Endometriosis Fertility Index; STI, sexually transmitted infection; EP, ectopic pregnancy; IVF, in vitro fertilization; DOR, diminished ovarian reserve.

disorder can prevent from the full process of ovulation, and thereby, pregnancy will become difficult. In addition, some treatments can cause hormonal disorders. Targeted cancer therapies can cause anatomical and hormonal changes which negatively affect the breast cancer patient's sexual potential. There are large differences in the evidence-based interdisciplinary treatment and management of breast cancer young patients who are treated and are fertile now and there are concerns about pregnancy after cancer treatment (15).

The Impact of Smoking and Alcohol Consumption

Meta-analyzes have shown that 40% of infertile men are smokers (3). Chemicals (such as nicotine, cyanide and carbon monoxide) in cigarettes cause a rapid destruction of ovules. Unfortunately, ovules cannot be replaced if destroyed. It means that female smokers experience menopause one to four years sooner. The number and quality of sperm decrease in male smokers; sperm mobility is reduced and the number of sperms with abnormal appearance increases. Smoking may make the sperm unable to fertilize eggs (16). Female smokers do not get pregnant like non-smoking women. Infertility rate in male and female smokers is almost double the infertility rate in non-smoking women. The reproductive risk increases with the daily number of cigarettes. Even fertility treatments such as in vitro fertilization (IVF) may not be able to completely eliminate the effects of smoking on fertility. During IVF, female smokers need more drugs to stimulate ovulation and have fewer ovules. Female smokers have 30% lower chance of pregnancy through IVF method compared to non-smoking women (15). Alcohol consumption in men reduces sperm count; and motility and number of normal morphology sperm in them (3).

The Impact of Immune Responses

Immunological mechanism plays an important role in sexual problems, such as recurrent miscarriage (RM) (three or more RSA), infertility and implantation failure. This shows that successful pregnancy depends on the maternal immune response to the growing semi-allogeneic fetus (17). Embryo implantation is affected by local and systemic immune responses including immunoglobulins, cytokines, and hormonal and endometrial factors. Contribution of these factors to the success of implantation and pregnancy is critical. Natural killer cells play an important role in female sexual function. This cells are correlated with inductive failures, NK cell cytotoxicity induced abortion or infertility and gene expression (18).

The Impact of Mobile Phone Use

Mobile device emits radio frequency electromagnetic waves that can reduce sperm quality and disrupt the normal function of the body. There are many real mechanisms emphasizing the impact of mobile phones on sexual ability of men. All these mechanisms rely on the impact of mobile phones on biological system, such as thermal and non-thermal effects. Since testicles are a shallow organ, it may absorb the radiant energy more than other organs. Oxidative stress (OS) developed in testicles because cell phones cause free radicals in sperm. OS is a major cause of infertility in men (19).

The Impact of Sexual Violence

The literature shows that the history of sexual violence is associated with infertility. The psychological trauma caused by sexual violence leads to ovulation infertility or sexual dysfunction. Infertile women had experienced sexual violence three times in their lives compared to fertile women. Although the relationship between sexual violence and fallopian tube infertility could be easily explained, this relationship with any infertility other than fallopian tube infertility is vague and confusing. This may be due to the fact that fallopian tube pathology was diagnosed using human chorionic gonadotropin (HSG) against laparoscopy as a gold standard method. HSG is an unreliable test for tube openness with an intensity of 62% and sensitivity of 83%. Therefore, non-tubal infertility group includes an unknown number of undetectable tubal infertility (20).

The Impact of Anxiety

Although the impact of anxiety on male infertility has not been clearly proved, the incidence of such problems in the lives of men may cause anxiety. Once faced with their infertility, men may have excessive stress, including the anxiety related to power, masculinity, and sexual adequacy. The anxiety may decrease the intimacy between partners and avoid the sexual behavior (21).

The Impact of Obesity

According to the researchers, obese women, especially women with abdominal fat hardly become pregnant and have low chance of infertility treatment. In women with a body mass index (BMI) >25, compared with BMI <25, the pregnancy rate is lower (respectively, 10.5% vs. 253%). The correlation between obesity and polycystic ovary syndrome (PCOS) contributes to the infertility in obese women (22). PCOS is an androgen excess mode with insulin resistance which makes pregnancy difficult. The role of obesity in pregnancy focuses on the physiology of fat body and metabolic disorders (16). Articles show that nearly 10% of sub-fertile or infertile women have been diagnosed with diminished reduced ovarian (DOR) (23). Polycystic ovary is one of the common reasons of ovulation disorder in women of childbearing age (24). Some studies have shown that usually 30%-70% of women with PCOS are obese. Overweight and obesity in women with PCOS exacerbates the severity of androgen and disorders metabolic profile (25).

The impact of Diseases That Can Cause Infertility

Systemic lupus erythematosus (SLE) is a multiple automatic system that affects fertility in women and men. Genital tract in women and men may be affected by cytotoxic treatment due to the disease activity. Fertility disorder

may be due to the problems which prevent from successful fertilization and thus lead to infertility, avoid the effective implantation in the uterine wall and cause problems in maintaining pregnancy after implantation and complications during childbirth (26). Varicocele is a pathological enlargement of the pampiniform venous plexus in the scrotum that affects testicular function and can lead to infertility. However, the pathophysiological mechanism that leads to varicocele infertility is not fully understood. The following five mechanisms seem to contribute to the impact of varicocele on testicular function, reduced blood flow leading to hypoxia, thermal stress, oxidative stress, hormonal imbalance and detoxification (27).

The Impact of Nutrition

Although no definitive relationship was discovered, selection of supplements or food groups is crucial before and during pregnancy attempt to improve fertility in women and men (28). A high saturated fat diet is associated with reduced sperm quality. Changes in diet over the last decades may partly explain the high frequency of abnormal sperm count. Decrease in saturated fat intake in general and reproductive health benefit (29). Lower sperm concentration and total sperm count are correlated in men with saturated fat diet (3).

Unknown Factors

There are numerous factors affecting infertility and nature has multiple roles in this fact. The special impact of some of these factors on fertility is still uncertain and unclear. The relationship of these factors with fertility in humans remains unclear and further research is required in this regard (14).

Discussion

As reported by the WHO, reproductive health is influenced by several environmental factors which intervene and interfere in the organism and its function or psychological nature (30). Due to the multiple roles of the nature of these factors, such as a variety of factors affecting fertility, these factors and their relationships will be measured and controlled; it is difficult to reduce fertility. The transparent relationship between this factor and parameters makes it difficult to evaluate fertility. That is why the specific impact of these factors on fertility is still unclear. That is because the special impact of these factors on fertility is still unclear and their relationship with human fertility is still unclear and further research is required in this regard (14).

Lifestyle factors, such as early start age in the family, nutrition, weight management, exercise, mental stress, smoking, use of prescribed drugs and self-medications without prescription, use of alcohol and caffeine, occupational and environmental risks, preventive care, and other behaviors are modifiable and may affect fertility (31). Overweight or very low weight men and women are in danger of negative side effects including changes in hormone levels which affect their fertility. Recent studies suggest that weight has a significant role in fertility. That is, weight control and maintenance is an ideal way for couples to increase fertility. Exercise is also very important. However, excessive exercise is harmful. Lean and low weight men and women who do so much exercise may be at risk of sub-fertility. So, weight balance is the best chance of achieving pregnancy (29).

This article tries to explain the different perspectives that lead to infertility. Thus, we have reviewed many articles. In general, each article discusses a relevant factor and this study has gathered all the significant factors. Through these articles, researchers obtain a wide insight about infertility factors.

Conclusion

Female infertility may occur in the form of lack of ovulation, blocked fallopian tubes, endometriosis or uterine abnormalities. Male infertility factor is morphologically determined by reducing the production of motile and normal sperm. Genetic abnormalities, hormonal imbalances, and congenital genital abnormalities and infections are among the common reasons for infertility in women and men. Lifestyle factors such as obesity, diet, smoking and alcohol consumption along with exposure to environmental chemicals have been studied as infertility modifiers. In general, women should be properly trained and have enough knowledge of safe exercise during pregnancy and childbirth. Endurance in health lifestyle, regular checkups and normal weight should avoid infertility problems. Female infertility can be definitely treated by medicine, minor surgery, laparoscopy meters, hormone therapy and prevention from early pregnancy failure. Such reviews are conducted by all medical and scientific researchers trying to end infertility.

Ethical Issues

Not applicable.

Conflict of Interests

The authors declare no conflict of interests.

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