

Epidemiology of Female Infertility; A Review of Literature

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DOI: <http://dx.doi.org/10.13005/bbra/1165>

(Received: 10 November 2013; accepted: 06 December 2013)

The prevalence of infertility is varies worldwide ranging from 3% to 7%. The consequences of infertility are societal repercussions, personal suffering, psychological effects, clinical depression and sexual dysfunction. Therefore, the aim of the present study was a systematic review of the literature to determine the main risk factors of female infertility. MEDLINE, EMBASE and Cochrane Database were searched from 1980–2013. Information about study objectives, participants and type of study were searched systematically with extensive key words to optimize the sensitivity of data collection. Eighty-two published articles were included in the overall review. Ovarian factors, tubal and peritoneal factors, anomalies, advanced ages (over 35 years), hormonal disorders, habits, genetic factors, medical conditions and life style are the main causes of infertility in women. Changes of lifestyle, identifying and controlling chronic diseases, rapid and suitable treatments for sexually transmitted diseases can increase the chance of women fertility process.

Key words: Risk factors, Female infertility, Systematic review.

Infertility is an important condition in reproductive medicine¹ and defined as the inability of a couple to access of pregnancy after 12 months of regular, unprotected intercourse². The economic burden of infertility is also considerable as female infertility treatments impose a substantial financial burden³.

In developed countries, 80-90% of couples attempting to conceive are successful after 1 year and 95% after 2 years⁴. There are no reliable estimates for global prevalence of infertility⁵. The

incidence of female infertility is rising and varies from 10 to 20%⁶. Infertilities, either primary or secondary will occur for almost 15% of all women worldwide⁷. Female infertility occurs in about 37% of all infertile couples⁸. Infertility is divided in two groups of primary and secondary. Its rate has reported to be ranged from 0.6% to 3.4% for the primary infertility and 8.7% to 32.6% for the one infertility⁵.

There are several adverse effects associated with infertility issue. It has been suggested as a cause of instability in the lives of couples in which a case-control study has reported that the rate of remarriage is 3.5 times higher amongst infertile women⁹. The consequences of infertility are classified as societal repercussions, personal suffering, psychological disorders^{10, 11} and sexual dysfunctions¹². Marital discord is also common in infertile couples, particularly when they are under stressed for making medical decisions¹⁰. Clinical

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depression is also considerable in infertile women similar to women with heart disease or cancer¹³. Infertilities women experience higher rates of psychological distress compared with their fertile counterparts¹⁴. However, infertility is a clinical presentation and not a disease². Even couples undertaking In Vitro Fertility (IVF) have plenty of stress¹⁵.

A recent study has evaluated effects of infertility and its duration on female sexual functions. All primary infertile cases were categorized in three groups according to infertility duration: less than 2 years (Group I), 2-5 years (Group II), and 5 years or more (Group III). Sexual dysfunction was evaluated via Turkish version of female sexual function index. Comparison of fertile and infertile participants showed no significant difference between two groups in terms of scores of desire, arousal, lubrication, orgasm, sexual satisfaction, pain and total FSFI parameters. Although, all parameter and total FSFI scores were significantly different between three groups, but sexual satisfaction scores were almost identical¹⁶. In a case-control study, 119 infertile women were compared with 99 healthy females. Female Sexual Function Index scores, frequency of sexual intercourse and masturbation and sex-life satisfaction were investigated. One fourth of healthy females (25%) were at risk for sexual dysfunction. The corresponding rate for infertile women was 40%. Infertile women had lower scores in desire and arousal domains and lower frequency of intercourse and masturbation significantly, compared to the control group. Infertile patients reported a sex-life satisfaction score similar to that of the controls retrospectively before diagnosis, whereas their current sex-life satisfaction scores were significantly lower than control group³.

Factors associated with female infertility

The etiology of infertility is an important criterion for recognition and characterization of infertile women^{17,18}. A case-control study was carried out to determine clinical risk factors for female infertility. Cases were women who diagnosed as primary or secondary female infertility and controls were women without infertility. Advanced age, high body mass index, age of onset of sexual activity, prior pelvic surgeries and stress were the most significant risk factors associated with women's infertility⁶.

Ovarian factors

Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome causes infertility in young women and provides 70% of unovulation infertility¹⁹, and 15.6% of primary infertilities. Although polycystic ovaries were present in all cases of secondary infertility²⁰. This proportion was estimated to be 39.2 % in another study⁷.

Premature Ovarian Failure (POF)

Premature ovarian failure is defined as the loss of function of the ovaries before age of 40; with a prevalence rate estimation of 1% of the population. Approximately 5-10% of POF women, can become pregnant spontaneously²¹.

High levels of the hormone Prolactin

Prolactin is a pituitary-derived hormone and the role of hyperprolactinemia as an endocrine cause of infertility in women has been well recognized²². The hyper-prolactinemia, affects normal gonadal function⁸.

Body weight

Almost one-fifth of all infertilities are happened in either underweight or overweight women²³. Obesity is strongly associated with female infertility⁷. Although, the mechanism underlying this relationship is largely unknown, but it is clear that fat cells produce estrogen²³. A retrospective epidemiologic study was conducted on 1,140 women aged 20-45 years. Infertile women were significantly more likely to have higher body mass index, compared to fertile women²⁴. It has also been found that obesity was associated with insulin resistance in metabolic tissues²⁵. In a case-control study, 440 patients were classified in two groups of cases (220 women with primary or secondary female infertility) and controls (220 women without infertility). Increased Body Mass Index, was a significant factor associated with infertility ($p < 0.001$),⁶. Therefore, weight loss should be considered as a first option for overweight infertile women²⁶. Despite of several reports confirming strongly association between obesity and female infertility, the mechanisms underlying this relationship has remained largely unknown²⁴. A review study in 2010 concluded that overweight and obesity had powerful impact on fertility and sub fertile women had a reduced chance of successful fertility treatment and their pregnancies are associated with more complications and costs²⁷.

Slightly body fat causes inadequate production of estrogen and upset of the menstrual cycle. Both under and overweight women have irregular cycles in which ovulation does not occur or it is inadequate. Proper nutrition in early life is also a major factor for later fertility²⁸.

Emotional stress

The correlation between emotional stress and infertility has been investigated for many years. The biological interaction between stress and infertility is the result of the action of stress hormones at the brain level, especially on the hypothalamus-pituitary as well as on female reproductive organs²⁹. There is evidence that emotional stress affects fertility directly by altering the hypothalamic-pituitary pathways, tubal spasm, and indirectly via vaginismus, dyspareunia and frigidity³⁰. Stress hormones such as Catecholamines and the hypothalamic-pituitary-adrenal axis interact with hormones which are responsible for normal ovulatory cycles, gonadotropin releasing hormone (GnRH), Prolactin, LH and FSH. Endogenous opiates and melatonin secretion are altered by stress and interfere with ovulation normal ovulatory cycles. However, there are controversial conclusions implying that stress is the consequence and not the cause of infertility which will be aggravated as time passes and the couple remains infertile²⁹.

Tubal and peritoneal factors

Inflammatory diseases

Pelvic inflammatory occurs in 3.1% and 16.7% of primary and secondary infertility cases respectively³¹. A case-control study has concluded reproductive tract infections as the main cause of the fallopian tubes adhesions increasing secondary infertility³². Genital infections represent one of the most important causes of infertility, affecting: fallopian tubes, endometrial mucosa and sperm parameters^{33, 34}.

Previous studies suggest that hydrosalpinx may be a trustworthy marker of impending infertility, and that rCPAF is a promising candidate to prevent infertility resulting from repeated genital chlamydial infections³⁵.

Women with either primary or secondary infertility were recruited to assess the role of *C. trachomatis* which was detected in 28.1% of infertile women. The corresponding rate for healthy fertile controls was 3.3%. Meanwhile, Chlamydial positivity was observed in 27% of women with

primary infertility and 30.6% women who had secondary infertility³³.

The probable role of *Chlamydia trachomatis* (CT) antigen, *Ureaplasma urealyticum* (UU), *Mycoplasma hominis* (MH) and *Neisseria gonorrhoeae* (NG) in the endocervical secretions and *Chlamydia trachomatis* antibodies IgA, IgG, IgM in the serum has recently been investigated. Despite of low association between genital MH/UU and infertility, even though, the correlation of the CT infection and infertility was obviously observed³⁴.

Consequences of *Chlamydia trachomatis* (*C. trachomatis*) infection are more destructive for reproductive health of women than men. In New South Wales (NSW), Australia, between 2001 and 2008, the rate of Chlamydia notifications and hospitalizations for female infertility or ectopic pregnancy in women aged 15-44 years was evaluated. The annual rate of chlamydia has been increased from 157 to 477 per 100,000 population from 2001 to 2008 ($p<0.001$). The hospitalization rate for women who have infertility of female origin ranged from 479 to 554 per 10000 women who were looking for pregnancy³⁶.

Genital tuberculosis has also been suggested as one of the infertility causes. One hundred fifty women with infertility and forty five women with general gynaecological problems were compared. Genital tuberculosis was diagnosed in 7.2% of infertilities women and 2.8% of general gynecological problems women. As well as used of Anti-tuberculosis cure resulted in declaration of symptoms other than infertility in over 90% of cases³⁷.

A recent Chinese case-control study has evaluated risk factors of female infertility among 383 child-bearing aged women in Nanchang area found the pelvic inflammatory diseases as a significant risk factor ($OR=7.078$, 95% CI: 3.462-14.467) for women infertility³⁸.

A prospective study investigating the role of cytomegalovirus (CMV) infection in sub fertile couples, found that the semen quality was not significantly influenced by the existence of CMV in semen. The presence of CMV in endocervical mucus was not associated with a reduced quality of any female infertility factors. There was no link between the presence of CMV in the semen and endocervical material of the female partners³⁹.

Endometriosis

Endometriosis can lead to anatomical distortions and adhesions. It has been suggested that endometriotic lesions release certain agents which are harmful for gametes or embryos⁴⁰. Endometriosis has been involved with 12.5% and 11.1% of primary and secondary infertilities respectively. Ovarian cyst was only detected in 6.3% of cases with primary but not secondary infertility. The most common causes responsible for infertility were tubal occlusion, endometriosis, per tubal and per ovarian adhesions³¹. Peritoneal adhesions and endometriosis have already been identified as significant risk factors associated with infertility. However, its patho-physiology has not been clearly understood yet⁴¹.

Fallopian tube obstruction

The fallopian tube obstruction has been reported as a major cause of almost one fifth of female infertilities⁴². These women are unable to let the ovum and the sperm converge, thus making fertilization impossible.

Anomalies

Uterine anomalies

The uterine malformation is defined as female genital abnormality caused by an abnormal development of the Müllerian duct during embryogenesis. The prevalence of uterine malformation is estimated to be 6.7% in general population, 7.3% in infertile women, and 16% in women with a history of recurrent miscarriages⁴³. Adenomyosis is of anomalies that proposed as a cause of infertility. Its mechanism is not understood well, as it is only detected by hysterectomy specimens, despite of using new imaging techniques⁴⁴.

The Asherman's syndrome is characterized by adhesions and/or fibrosis within the uterine cavity due to polyps. It has been occurred in 25% of dilatations and curettages (D&Cs) performed within 1–4 weeks post-partum^{45, 46}, up to 30.9% of D&Cs performed for missed miscarriages⁴⁷, and 6.4% of D&Cs performed for incomplete miscarriages⁴⁸.

Tubule anomalies

The tubal blockage has been reported in 21.9% and 33.3% of primary and secondary infertility cases respectively³¹. In a cross-sectional study, the unilateral tubal occlusion was observed in 9.1 % of cases, while it was bilateral in only 1%

of cases⁴⁹. A recent study found that Trachomatis was associated with pelvic inflammatory disease leading to tubal infertility⁵⁰.

Ovarian anomalies

A cross-sectional study has shown that ovulatory dysfunction was attributed in more than half (53%) of all women infertility cases. Irregular menstrual cycles, acanthosis nigricans, hirsutism, polycystic ovary syndrome, a LH:FSH ratio of >1, and increased TSH or testosterone levels were the clinical findings associated with ovulatory dysfunction⁴⁹.

A study that has investigated 127 histopathological slides of adnexitomies or ovarian cystectomies to determine the relationship between infertility and ovarian dysplasia found that the drugs used to induce ovulation may play a role in the ovarian epithelial dysplasia among infertilities women⁵¹.

Cervical anomalies

Cervical stenosis might affect natural fertility by impeding the passage of semen into the uterus. Cervical stenosis is making troubles for infertilities women by complicating the intrauterine insemination (IUI) or in vitro fertilization (IVF) procedures⁵². The frequency of abnormal cervical cytology in 490 infertile women who had Pap tests during treatment period with 7,150 fertile women who had routine Pap tests in the same period has been compared. The abnormalities of cervical squamous epithelial was significantly higher in infertile women (9.8%) compared to 3% in controls. The rate of high-grade lesions epithelial abnormalities was more in women with secondary infertility compared with women with primary infertility. In the same situation, the frequency of squamous intraepithelial lesions was significantly higher in infertile women than fertile women⁵³.

Advanced ages (over 35 years)

Age is a main effective factor of woman's fertility. The woman's fertility peaks in the early and mid twenties, after which it starts to decline⁵⁴. As majority of women in developed communities in particular, choose to delay childbearing, they will be faced to age-related fertility problems. Therefore, several studies investigated the effect of ageing on women infertility^{6, 55, 56}.

In a study carried out in Aberdeen Fertility Centre from 1993-2006, factors effecting couples infertility including age of male and female partner,

year of first visit, diagnosis, duration and type of infertility were investigated. Of all participants, 26.9% were over the age of 35 years and 51.4% had primary infertility. The mean female age was 31.2 (5.2 SD) years. There was an association between female age and the cause of female infertility. More women over 35 had unexplained infertility (26.6 versus 21.0%, $p < 0.001$). Compared with women under 30 years, the adjusted odds ratio (95% confidence intervals, CI) of the following diagnoses in women over 35 were: unexplained infertility; 1.8 (1.4-2.2), ovulatory dysfunction; 0.3 (0.3-0.4) and tubal factor; 2.2 (1.7-2.7),⁵⁷.

Hormonal disorders

Hypothalamus

A hypothalamic casualty role for female infertility needs an appropriate clinical context, with tests pointing to a hypogonadotropic hypogonadism. This role can have functional, physiological or organic sources. Acromegaly and Cushing's diseases may also impair women's fertility at different levels. However, its mechanisms have not been defined well yet⁵⁸.

Pituitary gland

A cross-sectional study has evaluated the proportion of clinical and investigatory findings associated with a LH:FSH ratio of >1 and found an increased TSH or testosterone levels⁴⁹. Growth hormone (GH) is produced by pituitary gland and ovary apart from it being produced from pituitary. Growth hormone is used in management of female infertility by playing in ovarian stimulation and increased pregnancy rates in poor responders infertility women⁵⁹.

Habits

Smoking increased the risk of infertility among women⁶⁰ by its side effects on the ovaries. Several European studies have already revealed the adverse effects of pregnancy smoking on child bearing process⁶¹⁻⁶⁹. The extent of injury is based on the amount and length of time a woman smokes or is exposed to a smoke-filled environment. There are several mechanisms have been suggested for how nicotine and other harmful chemicals in cigarettes affects women infertility. Cigarette smoking interferes with folliculogenesis, embryo transport, endometrial receptivity, endometrial angiogenesis, uterine blood flow and the uterine myometrium⁷⁰. In some cases, the damage is unclear, but in others, smoking cessation prevents

further damage. Smokers are 60% more likely to be infertile than non-smokers. Smoking reduces the chances of IVF producing a live birth by 34% and increases the risk of an IVF pregnancy miscarrying by 30%. Also, smoking women have an earlier onset of menopause by approximately 1–4 years⁷¹. In the United States, approximately 30% of women and 35% of men of reproductive age, smoke cigarettes. Substantial harmful effects of cigarette smoke on fecundity and reproduction have already become apparent but are not generally appreciated⁷².

Genetic factors

There are many genes mutations that causes female infertility, as shown in Table 1. Also, there are additional conditions involving female infertility which are believed to be genetic but where no single gene assigned to be responsible including the Mayer-Rokitansky-Küstner-Hauser Syndrome (MRKH),⁷³. Furthermore, an unknown number of gene-environmental mutations cause infertility and pregnancy disorders⁷⁴.

Medical conditions

Diabetes

The association between medical complications and female infertility has already been reported⁶. Despite of type of treatment, diabetic women are at increased risk of infertility, delayed puberty and menarche, menstrual irregularities and possibly earlier menopause⁷⁵. A Chinese study on 1895 women in reproductive age found that the occurrence of infertility was correlated with body mass index and some concurrent diseases⁷⁶.

Thyroid

Thyroid disorders, both hyperthyroidism and hypothyroidism, can interact with the ovaries, through direct effects on ovarian function, but autoimmunity may be involved, as well as alterations of the sex hormone binding protein levels⁵⁸. Infertile women have higher prevalence of thyroid autoimmunity (TAI) compared to the parous age-matched women. This is especially the case in women with endometriosis and the polycystic ovarian syndrome⁷⁷.

In a recent study, the Anti-thyroglobulin and anti-thyroperoxidase levels were measured in both follicular fluid and serum on the day of oocyte retrieval in women with thyroid autoimmunity. It was observed that the presence of anti-thyroid antibodies in ovarian follicles can play a significant

role in female infertility⁷⁸.

Cancers

Patients with cancer are at risk of loss of gonadal function due to the cancer treatment. Chemo- and radiation therapy are known to induce gonadal failure in both men and women and especially treatment with alkylating agents and/or abdominal or testicular radiation therapy poses a high risk. Methods exist to preserve fertility and these should be discussed with and offered to the patient if necessary and possible. For men, cryopreservation of semen is simple, non-invasive and low-cost. For women, cryopreservation of oocytes, embryos or ovarian tissue is an option in order to preserve fertility⁷⁹.

Life style

Exercise

Regular exercise is always beneficial regardless of age, sex or body power. However, there are evidences confirming that excessive exercise may lead to adverse effects on the reproductive system and fertility⁸⁰. In a survey evaluating the association between physical activity, fertility and parity, women who were often active were 3.2 times more likely to have fertility problems than inactive women⁸¹. The rate of luteal phase defects was reported to be 48% in women who were physically active. Since the short luteal phases caused poor endometrial maturation as a result of inadequate progesterone production, therefore it is associated with infertility and habitual spontaneous abortions⁸².

Occupation

A cross-sectional study investigates the risks of negative reproductive outcome among female hairdressers. Study was conducted on 16,907 women and shown that infertility and spontaneous abortion were higher among female hairdressers than among women in other occupations (adjusted relative risks; 1.30; 95% confidence intervals; 1.08 to 1.55 and 1.31; 1.07 to 1.60, respectively)⁶⁰.

CONCLUSIONS

Approximately 5-10% of women in the reproductive ages are affected by infertility which is associated with depression, anxiety, disturbed eating behavior, sexual dysfunction and interpersonal relationship. Many of these risk factors are preventable. Improvement of lifestyle, avoiding

excessive exercise and smoking are of helpful activities. Identifying and controlling chronic diseases such as diabetes and hypothyroidism, may increase fertility prospects. In addition, rapid and suitable treatments for sexually transmitted diseases increase the chance of women fertility process. Mothers in advanced ages are less likely to be fertile. Women with familial history of biological disorders might also be at special risk for premature menopause leading to infertility.

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