

**CAUSES OF INFERTILITY IN WOMEN****Bushra Jawad Kadhim<sup>1\*</sup> and Rasha Hatem Abbas<sup>2</sup>**<sup>1</sup>Ministry of Health, Baghdad, Iraq.<sup>2</sup>Ministry of Health - Baghdad Medical Office - Al-Karkh Health Directorate, - Mohammed Baqer Al-Hakim Hospital, Baghdad, Iraq.Article Received on  
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**\*Corresponding Author.****Bushra Jawad Kadhim**Ministry of Health, Baghdad,  
Iraq.**ABSTRACT**

Infertility is defined as the failure to conceive, with no contraception, after one year of regular intercourse in women < 35 years and after 6 months in women > 35 years. A review on causes, management, and treatment of endocrine causes of female infertility was performed. Epidemiological data suggest that around 10% to 15% of couples are infertile. Anovulatory problem is responsible for 25% to 50% of the causes of female infertility. Advanced age, obesity, and drugs have a negative effect on fertility. Different hypothalamic, pituitary, thyroid, adrenal, and ovarian disorders may affect fertility as well. Infertility is

a growing phenomenon in developed societies. We here provide information about how to identify endocrine patients with ovulatory dysfunction. Women must be advised about limiting factors to be avoided, in order to protect their fertility.

**KEYWORDS:** Infertility, women.**INTRODUCTION**

Normal fertility or fecundity has not been properly defined. A couple is said to have decreased fertility if they have not achieved pregnancy within 12 unprotected cycles. However, this definition is arbitrary. Very fertile couples achieve pregnancy within the first few cycles, and others make it just within 12 cycles.<sup>[1]</sup>

There may, in fact, be important biological differences between couples who achieve pregnancy in one or two months and those who succeed only after 12 or more cycles. The care of the infertile couple must be based on an accurate assessment of fertility in both partners, so clinical examination and investigation of each partner must be designed with this

premise in mind. In taking a history, two elements are essential-the age of the woman and the duration of infertility. Fecundity in women decreases after the age of 30 years, and infertility accelerates after 35 years. These observations are supported by the demonstration that the pregnancy rate per single embryo transfer with natural cycle in-vitro fertilization (IVF) is 17% for women younger than 30, 13% for those aged 31-35, and 11% for those aged 36-40. Duration of infertility is another important variable in determining the chance of pregnancy. For example, analysis of the cumulative pregnancy rates in couples with male-factor problems, and a short duration of infertility indicates that substantial spontaneous pregnancy rates still occur.<sup>[2]</sup>

## BACKGROUND

Most studies from industrially developed countries indicate that about 15% of all couples will experience either primary or secondary infertility at some time during their reproductive lives, and about half these couples will never succeed in having as many children as they wish.<sup>[3]</sup>

Most epidemiological reports on fertility center on the USA and western Europe. Our knowledge of fecundity in the industrially less-developed countries is limited. Little is known about secular trends in the prevalence of infertility. Although some infectious causes such as tuberculosis and gonorrhoea are less common now, infertility due to chlamydia infections and environmental pollution may be increasing. Inconsistency in epidemiological studies makes it virtually impossible to offer firm conclusions about the trend in infertility rates. On the other hand, the numbers of patients attending fertility clinics are now so high that it may indeed reflect a growing problem. In 1990, women were 2-3 years older when they delivered their first child than in 1970; 3 significantly more women never had a child. 17% of Danish women employed in the financial sector had no children at the age of 35 / Whether this changing trend infertility is due to social or biological factors remains to be seen.<sup>[4]</sup>

### Causes of Female Infertility

The causes of infertility may vary from one geographic and social area to another. WHO task forces revealed the following causes of infertility in women: tubal factor 36%, ovulatory disorders 33%, endometriosis 6%, and no demonstrable cause 40%. A similar distribution was found in Asia, Latin America, and the Middle East, whereas in Africa most infertile women had tubal infertility. Unexplained infertility (both partners considered) has been found in 8 to 28% of couples. 6 Rather than reviewing all known causes, we shall focus on some

common causes of female infertility (table) and also emphasize new developments. Male infertility has been addressed in a companion article, in which sperm-oocyte fusion, unexplained infertility, and untreatable infertility have been discussed.<sup>[5]</sup>

### **Age-Related Infertility**

A woman's fertility declines as she ages because both the quality and the number of her eggs gradually decline. Unlike a man, who continues to produce sperm throughout his life, a woman is born with all the egg-containing follicles in her ovaries that she will ever have. Only about 300 will be ovulated during her reproductive years, which naturally come to an end about five years before menopause. The gradual decrease in the number of follicles remaining is called "loss of ovarian reserve." The more eggs a woman has left, the better her chance of getting pregnant. Low ovarian reserve can make it difficult to get pregnant – even with treatment. Egg quality decreases as the number of remaining eggs decreases. Also, as a woman gets older, more of her eggs may have genetic abnormalities such as too many chromosomes.<sup>[6]</sup>

If one of these eggs is fertilized, the embryo also will have an extra chromosome. Down Syndrome is an example of a condition that results when the embryo has an extra chromosome. Most embryos with this kind of abnormality do not result in pregnancy at all or result in miscarriage. This is one of the reasons for the lower chance of pregnancy and a higher chance of miscarriage in older women. Tubal Factor Infertility – The fallopian tubes are very important to the reproductive process. If eggs or sperm are blocked from the fallopian tube, then fertilization can't occur. The most common cause of blockage or damage is scar tissue. Abnormal Ovulation – Ovulation is the monthly release of an egg by the ovary. Some women do not ovulate at all, or ovulate infrequently, resulting in irregular periods and infertility.<sup>[7]</sup>

### **Chromosome Abnormalities**

Chromosome abnormalities may cause infertility in both men and women, although they are most common among men. Sex chromosome abnormalities in the phenotypic female include variants of gonadal dysgenesis (including Turner's syndrome) and androgen insensitivity, but these patients rarely attend fertility clinics. In contrast to patients with androgen insensitivity syndrome, women with gonadal dysgenesis usually have a preserved uterus. Thus, they may achieve pregnancy by egg donation and IVF.<sup>[8]</sup>

### **Ovulatory disorders**

Hypothalamic and hyperprolactinaemic anovulation is caused by an abnormal pulsatile release of gonadotropin-releasing hormone (GnRH)-probably due to altered endorphinergic or dopaminergic tone. Hypothalamic anovulation is often reversible when mediated by exogenous factors such as the stress of weight loss. Premature ovarian failure may be genetically determined or associated with autoimmune disease. In the resistant ovarian syndrome, primordial follicles are present but fail to mature owing to lack of sensitivity to follicle-stimulating hormone (FSH). Luteinizing hormone (LH) receptor antibodies, not linked to the presence of an autoimmune disease, may also be a cause of ovarian failure. The polycystic ovarian disease is thought to be the commonest cause of anovulatory infertility. Besides anovulatory disturbances, the condition is associated with hirsutism, obesity, and endometrial carcinoma. The early miscarriage rate after induction of ovulation is also increased.<sup>[9]</sup>

Weight loss is often followed by the return of ovulatory cycles. Research based on serial hormone measurements and ultrasonography has given us new knowledge on the normal and abnormal menstrual cycle. A conception cycle is characterized by a preovulatory follicle with a diameter of at least 18 mm, follicle reduction to less than 50% of its size at ovulation, and serum progesterone above 25 nmol/L in the luteal phase. Many abnormal cycles previously classified as being due to a luteal insufficiency may be a result of anovulation due to the failure of the follicle to rupture. Such events can be classified as a "cyst" cycle. Other cycle aberrations include luteinized unruptured follicle, the empty follicle, and ovum retention (or entrapment). The clinical significance of such abnormal cycles as causes of infertility remains to be elucidated.<sup>[10]</sup>

### **The oocyte factors**

Deterioration of oocyte quality causing a lower pregnancy rate and an increased abortion rate may be responsible for the considerable age-related decrease in female fecundity. Thus, there is a 50% decrease in female fecundity from age 25 to 35.8 It is of interest that the decrease in fecundity does not seem to be due to recognizable ovulatory disturbances in older women, and egg donation to women above 40 years of age is associated with a normal conception rate.<sup>[11]</sup>

Kola and colleagues<sup>11</sup> have emphasized that this decrease in female fecundity is often due to chromosomal abnormalities in human eggs. Aneuploidy occurs in about 26% of human oocytes but in only 10% of human spermatozoa. This high rate of abnormality is apparently due to the precocious division of chromosome univalents at anaphase I of meiosis; this causes trisomy and becomes more frequent with increasing maternal age.

A new hypothesis is that hypersecretion of LH during the mid and late follicular phase of the cycle is responsible for the impairment of fertilization of the oocytes and increased early pregnancy loss. Experience from IVF treatments indicates that high LH concentrations during the late follicular phase are associated with lower rates of fertilization, cleavage, and pregnancy. Furthermore, oocytes are more fragmented and show asymmetry of blastomere size, indicating that the oocyte might be in the early stage of atresia when fertilized. These findings were supported by an observation of a significantly higher conception rate after 2 years of follow-up among 147 women who had normal mid follicular serum LH than did a group of 46 women with high LH concentrations (88% vs 67%) and lower frequency of miscarriage (12% vs 65%).<sup>[12]</sup>

The precise effect of raised LH is not known; oocytes seem to lack LH receptors. Some investigators find that patient age and low serum oestradiol are better than serum LH for predicting miscarriage in women with the polycystic ovarian disease. It has been speculated that high LH concentrations cause premature cumulus expansion followed by disruption of intercellular coupling and untimely initiation of meiosis. The final result of this ill-timed but otherwise normal sequence of events would be ovulation of physiologically "aged" oocytes. Animal and human data suggest that delayed fertilization is associated with poor fertilization and increased early pregnancy loss.<sup>[13]</sup>

### **Tubal infertility**

A history of salpingitis is associated with the highest relative risk of infertility. Pelvic inflammatory disease (PID) due to sexually transmitted microorganisms, such as gonococci, chlamydia, or other pathogens, is the main cause of tubal infertility. In addition, PID is associated with a 2 to 8-fold risk of subsequent ectopic pregnancy. Follow-up studies on fertility of women with laparoscopically documented PID have shown that for each episode of infection there is at least a 10% risk of subsequent tubal infertility, irrespective of the type of microorganism causing infection. The effect seems to be additive, with the risk of tubal infertility doubling after the second episode of PID. Chlamydia is the most common cause of

tubal infertility; 3 out of 4 women with tubal infertility will be seropositive for chlamydia compared with 1 out of 4 fertile women.<sup>[14]</sup>

Work on laboratory animals has thrown some light on the mechanisms behind PID-induced tubal damage. After a single inoculation of chlamydia in the ovarian tubes of monkeys, there is negligible or no damage. Serial inoculations, however, cause alterations in the tubal mucosa, intratubular adhesions, and distal obstruction; this may represent immune-mediated destruction or exacerbation of chronic infection. Tubal infertility may also follow septic abortion, puerperal infection, supportive appendicitis, peritonitis of other causes, or abdominal surgery. Infertility caused by some of these conditions is partly preventable; uncomplicated appendectomy does not increase the risk of the subsequent tubal blockade, whereas a ruptured appendix causes a 5-fold increase in such risk.<sup>[15]</sup>

### **Endometriosis**

The cause of endometriosis is unknown. The diagnosis is frequently made because of the technical ease of modern video laparoscopy. The glib explanation is that endometriosis follows retrograde menstruation, but many laboratories and clinical evidence suggests that endometriosis is more complex than this. We have recently suggested that endometriosis is a disease of angiogenesis's since in endometriosis, the endometrium, as well as endometriosis plaques, seems to have greater angiogenic activity than does the endometrium of normal women. Severe endometriosis can compromise fertility by causing pelvic adhesions, distorted anatomy, and ovarian or tubal damage. In addition, the ovulatory process and ovum capture may be disturbed.<sup>[16]</sup>

The relation between minimal endometriosis and infertility is based on indirect evidence, such as the higher fecundity of infertile women requiring donor insemination without visible endometriosis than women with endometriosis. This association is less clear than earlier believed. Firstly, the apparently high frequency (20-40%) in infertile women compared with fertile controls (< 10%) may be due to the observer and reporting bias.<sup>6</sup> Secondly, neither medical nor surgical treatment of the endometriotic foci increases the pregnancy rate.<sup>[17]</sup>

Thirdly, there are conflicting data about the monthly fecundity of women with minimal or mild endometriosis. Controlled studies have not shown any treatment-dependent improvement in fertility with medical suppression of endometriosis or surgical excision and ablation.<sup>16</sup> This includes the newer endoscopic operative laparoscopy approaches. Therefore,

the laparoscopic diagnosis of minimal or mild endometriosis does not necessarily mean that the cause of infertility has been found. Implantation failure Little is known about the role of implantation failure as a cause of infertility.<sup>[18]</sup>

The traditional concept is that in some women insufficient secretion of progesterone will cause an endometrium that is non-receptive. The uterine receptivity for nidation of the blastocyst is thus impaired, resulting either in lack of nidation or in early pregnancy loss. This notion has been seriously questioned. Firstly, the endometrial histology may not reveal a valid "bioassay" of progesterone secretion.<sup>[19]</sup> Secondly, "luteal insufficiency" may occur as often infertile as in infertile women, and there is no association between this condition and the fecundity of the couple. Thirdly, deficient progesterone secretion may primarily reflect ovulatory disturbances. Endometrial receptivity, nidation, and early blastocyst development are crucial. As much as 10% of early implantations occur without clinical evidence of pregnancy; this can be due either to defective implantation or to blastocyst defects. The endometrial structure, as assessed by transvaginal ultrasonography, is of some value in predicting the chance of pregnancy and of early pregnancy loss. A thick, triple-layered endometrium with normal echogenicity predicts a favorable outcome. Recent work has shown that the secretion of an oligosaccharide epitope produced by the endometrial glands during the peri-implantation phase and glycoproteins serving as adhesion molecules may be markers of disturbed endometrial receptivity. Thus, new developments in the assessment of endometrial receptivity are promising and may lead to a diagnosis of specific endometrial defects causing infertility.<sup>[20]</sup>

### **Recurrent miscarriage**

One-third of women with repeated pregnancy wastage also have subfertility, defined as delays in the conception of more than 12 months.<sup>[21]</sup> Recurrent abortion is associated with parental chromosome abnormalities, antiphospholipid antibodies, and uterine cavity abnormalities. Perhaps the single most important cause was polycystic ovaries, which was found in 46% of 500 cases. 600, of women with polycystic ovaries, had evidence of abnormal LH secretion. Thus, although two-thirds of women with recurrent abortions have no difficulty in achieving pregnancy there is little doubt that there is a link between repeated abortion and infertility.

### Lifestyle factors

As in men, several lifestyle factors may have consequences for reproduction, including habits of diet, clothing, exercise, and the use of alcohol, tobacco, and recreational drugs. Little is known about these lifestyle factors apart from tobacco smoking in women. There is evidence of an increased risk of infertility and delayed conception rate among women who smoke. Furthermore, the eggs of smokers have decreased IVF capacity.<sup>[22]</sup>

### Psychological and occupational factors

Being infertile may generate psychological disturbances. However, do psychological factors actually have a causal or contributory role in some cases of infertility? One myth about infertility is that adoption increases the couple's fertility. This is not so. Several studies have used psychological testing of large populations of infertile women compared with controls.<sup>[23]</sup>

However, no consistent differences in psychological variables, such as anxiety, depression, and social adjustment, were found. There might be an association between stress and infertility among women with ovulatory disorders or unexplained infertility, but the precise role of stress is uncertain. This does not mean that stress cannot cause infertility. Hypothalamic amenorrhoea, for instance, can be induced by stressful life events, and anorexia nervosa is clearly a psychogenic condition.<sup>[24]</sup>

**Table 1** Infertility cause and occurrence in couples

Cause of infertility	Occurrence
Sperm defects or dysfunction	30%
Ovulation failure (e.g. PCOS)	25%
Unexplained infertility	25%
Tubal infective damage (due to chlamydia infection)	20%
Endometriosis (causing damage)	5%
Failure or infrequency of sexual intercourse	5%
Cervical mucus defects or dysfunction	3%
Uterine abnormalities	Less than 1%

**Table 2** Factors impacting on fertility

Convincing evidence of impact	Probable evidence of impact
Age	Psychological stress
Smoking	Caffeine
Drug use	Alcohol
Weight	Environmental pollutants
Diet	
Physical activity	

Female age is the most important determinant of spontaneous conception and treatment-related conception.<sup>[25]</sup> Fertility begins to decline in females from the age of 30, although the reduction in fertility is greatest in women in their late 30s and early 40s.<sup>[26]</sup> The number of competent oocytes in the ovaries declines with increasing age. For women up to 25 years old the cumulative conception rate is 60% at six months and 85% at one year, but conception rates for women aged over 35 are less than half of this.<sup>[27]</sup> Current recommendations state that women aged over 35 should be classed as having advanced reproductive age and referred more promptly for early investigations and active treatment.<sup>[28]</sup> There is a significant association between smoking and reduced fertility among female smokers.

It has been estimated that smokers are 3.4 times more likely to take more than a year to conceive than non-smokers, and in each cycle, smokers have two thirds the chance of conceiving compared with non-smokers. A large UK longitudinal study (ALSCPAC) found that both active and passive smoking by women is associated with delayed conception.<sup>[29]</sup>

Smoking has been found to have an adverse effect on fertility and conception as well as most phases of the development of the child in the womb and on post-natal survival.<sup>[30]</sup>

Some of the negative reproductive consequences associated with smoking include quicker depletion of ovarian follicles, conception delay, increased risk of spontaneous miscarriage in both natural and assisted conception cycles, and increased risk of birth defects.<sup>[31]</sup>

There are a number of prescribed, over-the-counter and recreational drugs that are known to impact on fertility. Non-steroidal anti-inflammatory drugs, commonly used to treat pain or inflammation are known to inhibit ovulation. Cytotoxic chemotherapy drugs are also known to cause ovarian failure in some women. Recreational drugs such as marijuana can have an adverse effect on ovulation and cocaine appears to adversely affect tubal function. The time to conceive is longer in women who are over- or underweight (BMI of over 25 or less than 19). Obesity and overweight are associated with decreased pregnancy rates, increased requirements for gonadotrophins<sup>6</sup> and a higher miscarriage rate. These differences are evident at a BMI of over 25.<sup>[32]</sup>

A high BMI is also associated with adverse pregnancy outcomes such as gestational diabetes and hypertension. Evidence on the effect of diet composition on infertility is scarce. Several studies investigating the effect of various dietary factors on fertility have been conducted

using data gathered from 17,544 women enrolled in the Nurses' Health Study II. These studies found a reduced risk of infertility due to ovulatory disorder among women whose diet favored foods with a low glycaemic index<sup>7</sup> and a limited intake of nutrients that may increase insulin resistance, such as trans fatty acids. This supports the hypothesis that glucose homeostasis<sup>8</sup> and insulin sensitivity are important determinants of ovulatory function and fertility in otherwise healthy women.<sup>[33]</sup>

## CONCLUSION

Infertility can cause considerable social, emotional and psychological stress. It is estimated that one in six Iraqi couples are considered to be infertile according to the WHO definition of infertility.

The prevalence of infertility is increasing across the developed world. The main reasons for this are the trend for putting off pregnancy until later in life, an increase in obesity, and the higher rate of sexually transmitted infections. Doctors predict that these health and social changes could lead to a rapid increase in demand for fertility treatment in the coming years.

The main reasons women postpone starting a family include: extended time spent in education; extended time spend developing career; professional stability; use of contraception; late meeting of partner; falsely reassuring information on the progress in ART; second child desire after late first pregnancy; second marriage and child desire in the redefined couple. The average age of women in Ireland had their first child is 30.6, which is higher than in the UK (28.7) and the EU average (29.6). Postponement of pregnancy has led to an increase in the incidence of 'unexplained infertility' due to age-related decline in the quality of eggs and the decline in the reserves of eggs in the ovaries.

The level of obesity in young women has been increasing, which leads to increased rates of anovulation and polycystic ovary syndrome (PCOS), as well as poorer response to fertility treatment. The incidence of notified cases of chlamydia infection has increased every year from 245 cases in 1995 to 3,353 cases in 2005, although there was a slight decrease to 3,144 in 2006. It is estimated that around 3% of women with chlamydial infection in the lower genital tract will become infertile.

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