The Original

Enhancing Women's Fertility: Insights and Strategies Based on Scientific Evidence

Noor Fouad Kadhim Al-Shammaa*

ALIraqia University, ORCID ID: https://orcid.org/0000-0002-4517-1538, Iraq.

Corresponding Author: Noor Fouad Kadhim Al-Shammaa
Email: noor.f.kadhim@aliraqia.edu.iq

Genet. Mol. Res. 24 (1): gmr24123
Received February 26, 2025
Accepted March 25, 2025
Published March 28, 2025
DOI http://dx.doi.org/10.4238/gmr24123

ABSTRACT. This study aims to offer practitioners evidence-based suggestions derived from a consensus of expert perspectives. The objective is to guide women on how they might increase their probability of developing a spontaneous conception without medical intervention, especially in cases where there is no confirmed infertility or any cause to question their reproductive capacity. Every interaction with non-pregnant women who are capable of reproduction provides a chance to offer guidance on promoting well-being and adopting healthy behaviors that can improve reproductive results.

The study examined several facets of female infertility, classifying the reasons into different categories. Furthermore, the crucial significance of genetic counseling in resolving infertility was emphasized. Female infertility can arise from a variety of conditions, including both hereditary and non-genetic causes.

Female fertility involves a wide range of psychological, social, and physical aspects of well-being. Observational studies indicate that women who are unable to conceive typically encounter psychological difficulties and indicate a variety of lifestyle choices that might affect their fertility to different extents.

Key words: Spontaneous conception; Fertility; Reproductive; Genetic factors; Genetic counseling; Healthy behaviors

INTRODUCTION

"Countries with low fertility rates have experienced a decrease in the average family size since the 1980s. (Frejka, 2006). have observed that this trend has coincided with an increase in the average age at which individuals begin parenthood. Concurrently, there has been a substantial increase in the number of births among individuals of advanced reproductive age, specifically those aged 35 and older (Prioux, 2005). It is crucial to acknowledge that late deliveries are not a recent phenomenon; they were relatively prevalent in the early 1950s, primarily as higher-order births. "The current trend in delayed fertility is significant because it is primarily characterized by first and second births, which can be attributed to the postponement of family formation (Beaujouan, 2020).

Although this trend is common throughout Europe, its rate and extent of advancement differ among other states. For example, the percentage of births to people aged 35 and beyond is significantly greater in Southern Europe. In contrast, the trend of having children at a later age is less common in Central and Eastern European nations (Sobotka, 2018).

"Age is often associated with societal expectations regarding acceptable conduct, and there is a collective agreement among individuals about the optimal timing for significant life events and the progression through different stages throughout one's life (Shanas, 1976). Studies suggest that age-related expectations have a substantial influence on various social behaviors, such as the timing of starting a family (Kim, 2021).

Spontaneous miscarriage is the spontaneous ending from a pregnancy at a phase where the embryo is incapable of remaining independently, generally defined in humans at prior to 20 weeks from gestation. Overall, reported spontaneous miscarriage rates in recognized pregnancies are 10% to 20%. Pregnant women are exposed to many infectious agents that are potentially harmful to the fetus and an increased risk of miscarriage (Qanbar et al., 2019).

Significantly, these social norms change over time and vary among different cultural contexts. Studying the differences in fertility behaviors throughout time and in different countries is crucial for understanding the large-scale changes that occur. This becomes more relevant during periods of substantial delay in fertility, prompting an investigation into how the perceived optimal ages for having children have changed. While current literature frequently examines individuals' views on the appropriate age for having children at a certain moment, more study is needed on how these views change over time. We base our approach on the study undertaken by (Billari et al., 2021).

THE AIMS OF THIS WORK

1.Facilitate women in enhancing their likelihood of conceiving naturally without the need for medical assistance.

2.Provide guidance on lifestyle modifications, healthy behaviors, fertility awareness, stress reduction, risk factors and overall well-being to enhance reproductive outcomes.

3.Eliminate hereditary causes of infertility and emphasize the importance of genetic counseling for couples experiencing fertility challenges

THE PRIMARY FACTORS CONTRIBUTING TO WOMEN'S FERTILITY ARE

Mental problems.

Research conducted by (Jönsson, 1991) found evidence of reduced reproductive rates in persons with severe mental illness based on a comparison of patients who were hospitalized in 1925. Irrespective of whether they were married or not, women who were diagnosed with mood disorders had considerably lower birth rates compared to women of the same age in the general population. More precisely, their fertility rate was 71.2% of the anticipated frequency. Consistent with the results of (Baron et al., 1982) study. Women with mood disorders had decreased fertility even before their initial mental hospitalization. The Harvard research of Moods and Cycles, a research that followed women nearing menopause, found that women with a previous diagnosis of serious depression had decreased conception rates (Harlow et al., 2003).

Women who now have a diagnosis or have had a history of serious depression were discovered to have a noticeably lower number of live births in comparison to those who do not have such a diagnosis. The study found that women who had a history of significant depression had greater rates of divorce, separation, and widowhood. However, it did not take into consideration important factors associated with fertility. These factors encompass the length of the marriage, the intention and actions taken to conceive, and any evaluations or interventions for infertility (Calzeroni et al., 1990).

Age-associated reduced female fertility

The correlation between pregnancy and ageing Fertility refers to the inherent ability to reproduce and give birth to children. The likelihood of becoming pregnant is often greatest in the early months of having unprotected sex and decreases as time goes on (Gnoth et al., 2003). Approximately 80% of couples are expected to achieve conception within the initial six months of attempting to conceive. The monthly fecundability rate, which refers to the probability of conceiving each month, is at its peak during the initial three months of attempting to conceive. According to research conducted by (Wesselink et al., 2017) a woman's fertility decreases by around 50% by the time she reaches the age of 40. This decline in fertility is significant compared to her most fertile years, which typically occur in her late 20s and early 30s.

Fertility differs among populations and decreases with advancing age in both sexes; nevertheless, aging has a greater influence on women's reproductive capacity (Menken et al., 1986). As maternal age increases, the likelihood of conception and live birth decreases significantly, which is linked to an increased risk of chromosomal disorders (premature birth) and abortion (Penzias et al., 2021). An important study of the Hutterite society, which traditionally encourages reproduction until menopause, discovered that pregnancies in their forties were uncommon, with the average age at last delivery just shy of 41 years. Additionally, indications of ovarian reserve decrease with age.

Ovarian reserve markers drop with age, but they are not good predictors of fecundity in women who are not infertile (Steiner et al., 2017). While men's sperm quality declines beyond the age of 35, major impacts on fertility are typically not seen until about the age of fifty (Dunson et al., 2004). Infertility *is* medically defined as the inability to conceive following at least 12 months of regular unprotected intercourse, based on the medical history and physical findings, early examination, and treatment may be necessary (The American Society for Reproductive Medicine, 2020).

Environmental hazards

Refer to the contact with artificial and naturally-occurring harmful substances present in many sources such as food, air, water, and everyday products. There is an increasing amount of research indicating that these exposures can adversely affect fertility in both genders.

Endocrine-disrupting chemicals are of particular concern; these exogenous molecules can disrupt the hormone and homeostatic systems found in organisms, leading to negative health outcome (Diamanti-Kandarakis et al., 2009).

The study suggests that there is little or no relationship between brief or occasional exposure to substances that disrupt the endocrine system and the time it takes to conceive. The period of time it takes for men and women to conceive does not seem to be impacted by exposure to chemicals that are frequently studied, such as triclosan, bisphenol A, and phthalates (Hipwell et al., 2019).

Concern over the possible negative consequences of air pollution on fertility is on the rise (Carré et al., 2017). Reduced fertility rates have been associated with higher air pollution levels in China (Xue, 2018), the United States (Xue, 2018), and Europe (Nieuwenhuijsen, 2014). Additionally, research indicates that couples who reside close to busy roads had higher rates of infertility (Mahalingaiah et al., 2016), and longer conception times, than couples who live farther away (Mendola et al., 2017).

Furthermore, research indicates that women who reside close to congested roads, where they are subjected to elevated levels of nitrogen dioxides and fine particulate matter both prior to conception and during the initial phases of pregnancy, are less likely to conceive and more likely to miscarry than women who live farther away (Nobles et al., 2018; Zhang et al., 2019).

Furthermore, a number of studies have demonstrated a direct link between worse semen quality and increased exposure to airborne contaminants. The sperm's genetic information is more fragmented, they have an aberrant number of chromosomes, their shape and mobility are diminished, and their hormone levels connected to reproduction are altered. researchers are currently investigating the direct effects of air pollution on sperm qualities and its impact on fertility in partners (Deng et al., 2016).

The Environmental hazards include:-

a- Nutrition and lifestyle: Research has shown that women who are underweight or obese have lower fertility rates. Nonetheless, there is no information about the effect of typical dietary changes on fertility in women with regular ovulation (Clark et al., 1998). Furthermore, there is a link between elevated levels of mercury in the blood, which is frequently produced by eating too much seafood, and infertility (Choy et al., 2002). To lessen the risk of neural tube defects, women intending to conceive should take at least 400 µg of folic acid daily (Lumley et al., 1996). Many research cohorts have investigated the link between food, macronutrients, and micronutrients and fertility. The Nurses Health Study II investigated the impact of a reproduction diet formulated by researchers. This dietary regimen advocates for the consumption of monounsaturated fats instead of trans fats, plant-based proteins rather than animal proteins, and carbohydrates with a low glycemic index. Many cohort studies have investigated the correlation between dietary patterns, including the consumption of high-fat dairy products, vitamin supplements, and iron derived from plant and food sources, and outcomes related to reproduction. The Nurses' Health Study II found that adopting to a 'fertility diet' decreases the likelihood of experiencing infertility caused by ovulatory problems., women who maintained to this diet had a reduced risk of infertility with a relative risk (RR) of 0.34. The 95% confidence interval (CI) for this risk extended from 0.23 to 0.48. Based on a study conducted by (Chavarro et al., 2007).

b-Tobacco consumption: Research has shown that smoking has a substantial negative effect on fertility. A comprehensive analysis of many studies has found that smokers are more likely to experience infertility compared to nonsmokers. The study reported an odds ratio of 1.60, with a 95% confidence interval ranging from 1.34 to 1.91. This indicates a higher risk of infertility among smokers. Furthermore, scientific evidence suggests that smoking might accelerate the occurrence of menopause by a duration of 1 to 4 years, as reported by (Mattison et al., 1989). Nevertheless, there is no histologic evidence to support this rapid loss of follicles (Peck et al., 2016).

Smoking has been related to a higher probability of miscarriages in both natural pregnancy and those produced through assisted reproductive techniques, (ART) (Winter et al., 2002). Although smoking has been found to decrease the density and movement of sperm, as well as induce abnormalities in sperm shape, the available research does not definitively prove that smoking affects male fertility (Povey et al., 2012). Smoking cigarettes is associated with noticeably higher levels of the oxidative stress-causing reactive oxygen species in the seminal fluid. Because of this, smoking may cause changes to the sperm plasma membrane and a significant amount of deoxyribonucleic acid fragmentation (Doaa et al., .(2023

The range of values is between 92 and 94. The detrimental impact of smoking on fertility in both males and females, as well as the underlying processes, are thoroughly examined in a specialized study by (Penzias et al., 2018).

c-Caffeine: Consuming a high amount of caffeine (500 mg, equivalent to more than 5 cups of coffee per day) is linked to a decrease in fertility (odds ratio, 1.45; 95% confidence interval, 1.03-2.04)—the study conducted by Jensen TK et al. in 1998. Regularly consuming 200 to 300 mg of caffeine per day during pregnancy, which is equivalent to 2-3 cups of coffee, may elevate the likelihood of experiencing a miscarriage. The studies conducted by (Signorello et al., 2004) have found no association between this factor and the likelihood of congenital abnormalities.

There is no evidence to suggest that consuming a moderate amount of caffeine (1-2 cups of coffee per day) has any detrimental effects on fertility or the outcomes of pregnancy. Furthermore, the use of caffeine has no impact on the characteristics of semen in males (Povey et al., 2012).

Genetic factor

a-Chromosomal Abnormalities: Chromosome abnormalities, such as polymorphisms, are quite frequent, occurring in 1.3-15.0% of infertile couples. Women have a 10.0% incidence of chromosomal abnormalities (Mierla et al., 2015). The likelihood of chromosomal abnormalities in ova rises with maternal age due to genetic alterations linked with aging. Environmental variables and lifestyle decisions both contribute to the development of chromosomal abnormalities (Otter et al., 2021).

Abnormalities in chromosomes are categorized as either numerical or structural, with numerical aberration being more prevalent. They are also categorized into two distinct groups: aneuploidy and polyploidy. Aneuploidy, including trisomy and monosomy, is the primary recognized factor behind spontaneous abortions and developmental disorders in humans. It commonly arises during oogenesis (Otter et al., 2021).

Triple X syndrome (47, XXX) is a frequent sex chromosomal aneuploidy in females, distinguished by an additional X chromosome. Triple X syndrome is not normally inherited but rather the result of chromosomal nondisjunction during maternal meiosis. In approximately 20% of instances, post-zygotic nondisjunction causes an extra X chromosome, resulting in 46, XX/47, XXX mosaicism in which only certain cells are affected. Individuals with mosaicism typically have milder symptoms, are fertile, and can have offspring with normal chromosomal counts (Otter et al., 2021).

Turner syndrome (TS), also known as monosomy X, is characterized by the partial or total loss of one of the X chromosomes in females. Clinical characteristics include growth problems, reproductive and cardiovascular abnormalities, and autoimmune illnesses (Cui et al., 2021*)*. Females with TS have a significantly increased risk of premature ovarian insufficiency (POI) and infertility. While 70-80% do not undergo spontaneous puberty, and 90% have primary amenorrhoea,

Some individuals may possess a restricted quantity of ovarian follicles from birth or during early development (Oktay et al., 2016).

Cytogenetic investigations in Turner syndrome (TS) patients indicate a variety of karyotype patterns. Approximately 40-50% of afflicted females have a 45, X karyotype; 15-25% show mosaicism (45, X/46, XX); 20% have isochromosomes, and a few have ring X chromosomes. Additionally, 10-12% have various quantities of Y chromosomal material (Yahaya et al., 2021).

Structural chromosomal disorders are categorized as either balance or imbalance categories. Balanced anomalies that do not include segment loss usually do not cause phenotypic alterations or illnesses in carriers. However, carriers can create unstable gametes with segmental losses or gains, which can result in progeny abnormalities (Yahaya et al., 2021).

Gene treatments can work in various ways, including adding, deleting, or modifying genetic information within a patient's cells. One way is to use vectors as carriers to convey genetic material to target cells. These vectors, which carry genetic material, can be delivered directly into the body or to grow cells outside the body (Noor, 2024).

Chromosomal deletion is the loss of a chromosomal section. The magnitude of the deletion influences the number of affected genes and the degree of the disease. Mutations in male and female chromosomes typically influence the progression of reproduction. Deletions in the X chromosome can produce defective chromosome junctions, meiotic detention, premature ovarian insufficiency (the POI), genital disorders, and sterility (Yahaya et al., 2021).

Chromosomal duplications cause replication of a chromosomal segment, resulting in higher gene dosage in the afflicted area. This can increase protein synthesis, which may have hazardous consequences owing to the imbalance. Extra gene copies can disturb embryogenesis, which is dependent on balanced protein levels,compromising gametogenesis and fetal development (Gekas et al., 2001).

b-Female Genital System Disorders: In mammals, the Mullerian ducts form the fallopian tubes, uterus, cervix, and upper vagina. Defects in Mullerian duct development can cause a variety of congenital abnormalities in the female genital tract. Malformation, blockage, and abnormal division of the fallopian tubes, the uterus, cervical area, or the vagina are all possible abnormalities. Several genes involved in Mullerian duct formation have been discovered (Yatsenko, 2019).

Hand-foot-genital disorder is a condition characterised by the merging of Mullerian structures and abnormalities in the uterus., as well as limb deformities, is known to be caused by heterozygous mutations, including loss and additions, in the polyadenosine terminal of the HOXA13 gene (Innis et al., 2022). In addition, aberrant production of HOXA11-AS1 an antisense RNA (a longer non-coding RNA) and uncommon variations within additional Homeobox A genes (HOXA10 and HOXA11) have been related to spontaneous uterine abnormalities and infertility in women with endometriosis(Yatsenko, 2019).

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, also known as Mullerian agenesis, is a leading cause of primary amenorrhea. It presents as Uterine aplasia is a condition where the uterine cavity, cervical area, and upper vaginal are not present from birth in otherwise healthy individuals with a genetic makeup of 46 XX. The prevalence of MRKH disorder is around 1 in 4,500-5,000 newborn females. There are two sorts of classification for this condition: MRKH sort 1, which specifically impacts the areas of the upper vagina, the cervix and the uterus, and MRKH sort 2, which furthermore involves other abnormalities. MRKH type 2 frequently accompanies Mullerian Nephro Cervical Somite (MURCS), a medical disorder marked by anomalies in the cervix and thoracic region, as well as renal and skeletal abnormalities. The simultaneous presence of problems in Mullerian duct formation and deficiencies in other organs indicates the need for alterations in the embryonic developmental pathways of structures that originate from the intermediate layer of mesoderm (Fontana et al., 2017).

c-Hypogonadotropic Hypogonadism: A decrease in the secretion or function of gonadotropin-releasing hormone, commonly referred to as GnRH, is the definition of hypogonadotropic hypogonadism . It is frequently linked to the development of infertility and delayed puberty. The ANOS1 (KAL1), SOX10, IL17RD, FGFR1, CHD7, PROKR2, GHRHR, FGF8, and WDR11 genes are frequently implicated in this illness, which has substantial variability, as evidenced by the discovery of over 25 genes that affect both spontaneous and hereditary disorders (Qin et al., 2015).

One particular group of individuals with hypogonadotropic hypogonadism, typified by anosmia, or a primary loss of smell, is known as having Kallmann syndrome. When anosmia is present, physicians should look at Congenital Hypogonadism of the Hypogonadotropic Type (CHH) and employ genetic testing to identify patients with this condition (Qin et al., 2015).

d- Premature ovarian insufficiency: Menstruation ends before the normal age of menopause, which is defined as happening before the age of 40, in primary ovarian insufficiency (POI), sometimes referred to as premature ovarian failure or premature menopause. FSH levels raised above normal validate the diagnosis. Premature ovarian insufficiency (POI) occurs at about 1% of women under 40 and 0.1% of women under 30 years old, according to a study by (Tang et al., 2019). The higher incidence of Turner syndrome (TS), triple X syndrome, and fragile X premutation makes genetic testing for these disorders recommended for those with primary ovarian insufficiency (POI) (Goswami et al., 2003).

One protein that is encoded by the FMR1 gene interacts with RNA to control translation process. Females with a CGG premutation in the FMR1 gene's 5'untranslated region express more mRNA. FMR1 protein is overproduced as a consequence in granulosa cells and neurons alike. Unfertility and premature ovarian insufficiency (POI) are associated with overexpression of this gene. Around 1 in 150–300 people have the FMR1 premutation (Qin et al., 2015). According to a research, bearers of the premutation range from 2% to 15% of women with isolated premature ovarian insufficiency (POI) and 14% to 20% of women with family POI. The reference comes from a research by (Goswami et al., 2003).

e- Polycystic Ovary Syndrome: The endocrine disorder known as polycystic ovarian syndrome (PCOS) is identified by increased androgen release from the ovaries, infertility, and non-ovulation(Breehl &Caban**,** 2019). Over 10% of women in their reproductive years suffer with polycystic ovarian syndrome (PCOS), the primary cause of infertility in women. PCOS is associated with increased rates of pregnancy loss even in cases of low-level conception (McAllister et al., 2015).

Familial clustering and twin exams demonstrate the substantial genetic component of PCOS. Daughters of mothers with PCOS have a five times greater risk of having the disorder compared to the general population (Costa-Barbosa et al., 2013). The incidence of the condition in the offspring of women with PCOS is approximately 60-70% (Culha et al., 2012). The identification of potential genes related with PCOS has been achieved by genome- wide association research. These genes include DENND1A, LHCGR, FSHR, ZNF217, YAP1, INSR, RAB5B, and C9orf3. Furthermore, the expression of miRNAs in plasma may be a significant factor in the pathogenesis and progression of PCOS, as evidenced by the disparities in miRNA expression between women with PCOS and healthy individuals (Breehl**,** 2019).

f- Gonad dysfunction: Gonad disorders is a hereditary condition that occurs during he early embryonic phases or fertilization, resulting in partial or absent gonadal development (Breehl**,** 2019). Swyer syndrome, also known as 46, XY total gonad disorders, is a sexually distinct condition characterised by a feminine phenotype. The gonads are replaced by fibrous stroma, and female genital organs such as the vagina, the uterus, and the fallopian tubes, become undeveloped of afflicted people. Furthermore, there is usually no breast development. The foetal testes regulate the degree of testicles tissue differentiation and the synthesis of testosterone and anti-Müllerian hormone (AMH). 46, XY total gonad disorders, is a sexually distinct condition characterised by a feminine phenotype. The gonads are replaced by fibrous stroma, and female genital organs such as the vagina, the uterus, and the fallopian tubes, become undeveloped of afflicted people. Furthermore, there is usually no breast development. The foetal testes regulate the degree of testicles tissue differentiation and the synthesis of testosterone and anti-Müllerian hormone (AMH) regulate the phenotypic distinctions between complete and incomplete gonadal dysgenesis (Culha et al., 2012).

CONCLUSION

Women in their reproductive years are susceptible to infertility. To determine the cause, a thorough assessment of both spouses is necessary. A comprehensive investigation involving intensive questioning, complete physical examination, ovulation detection testing, and hormone profile is necessary to evaluate the ovulatory component thoroughly.

It is advisable to avoid smoking and recreational drug usage in women who are attempting to conceive.

It is suggestion to restrict caffeine intake to low or moderate amounts when trying to conceive. Adopting a wholesome lifestyle and adhering to a nutritious diet are advised due to their beneficial impact on overall well-being. Women who are trying to conceive should consume a daily folic acid supplement of 400 µg (micrograms).

It is recommended that persons of reproductive age should be informed to reduce their exposure to hormone damaging compounds found in water, air, food, products for personal care, and pollution in the environment. An assessment is needed to examine the connection between mental health status, lifestyle variables, and female infertility.

Efficient genetic counseling is essential for determining the appropriate genetic testing and implementing preventive medicine by identifying vulnerable siblings in addition to patients.

The genetic foundation of infertility is complex, impacted by several variables that impact the formation of gametes, reproductive organs, their functioning, and the differentiation of embryos. Infertility can be caused by genetic diseases, which can be chromosomal, caused by mutations in a single gene, or multifactorial. Therefore, it is necessary to utilize sophisticated diagnostic methods in order to detect both well-known and new genes associated with infertility.

AUTHOR CONTRIBUTIONS

The research concept and the manuscript was mainly written by dr. Noor AL -Shammaa.

REFERENCES

Adnan D, Mohammed AA, Abbood MS. (2023). Study the Influence of Smoking in Male on Sperm Chromatin Immaturity and ICSI Outcomes. *Iraqi Journal of Embryos and Infertility Researches.* 13: 21-33.

Al-Shammaa NF. (2024). Advancing Medicine: The Potential of Gene Therapy to Treat Genetic Disorders. *Genetics and Molecular Research.* 23: 1-9.

Baron M, Risch N, Mendlewicz J. (1982). Differential fertility in bipolar affective illness. *Journal of Affective Disorders.* 4: 103-12.

Beaujouan E. (2020). Latest-late fertility? Decline and resurgence of late parenthood across the low-fertility countries. *Population and development review.* 46: 219-47.

Billari FC, Badolato L, Hagestad GO, Liefbroer AC, et al. (2021). The timing of life: topline results from round 9 of the European Social Survey. *European Social Survey Topline Results Series.* 11: 2-177.

Breehl L, Caban O. (2019). Genetics, gonadal dysgenesis. In: StatPearls. Treasure Island (FL).

Costa-Barbosa FA, Balasubramanian R, Keefe KW, Shaw ND, et al. (2013). Prioritizing genetic testing in patients with Kallmann syndrome using clinical phenotypes. *The Journal of Clinical Endocrinology & Metabolism.* 98: E943-53.

Calzeroni A, Conte G, Pennati A, Vita A, et al. (1990). Celibacy and fertility rates in patients with major affective disorders: the relevance of delusional symptoms and suicidal behaviour. *Acta psychiatrica scandinavica*. 82: 309-10.

Carré J, Gatimel N, Moreau J, Parinaud J, et al. (2017). Does air pollution play a role in infertility?: a systematic review. *Environmental Health.* 16: 1-6.

Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. (2007). Diet and lifestyle in the prevention of ovulatory disorder infertility. *Obstetrics & Gynecology.* 110: 1050-8.

Choy CM, Lam CW, Cheung LT, Briton-Jones CM, et al. (2002). Infertility, blood mercury concentrations and dietary seafood consumption: a case–control study. *BJOG: an international journal of obstetrics and gynaecology*. 109: 1121-5.

Clark AM, Thornley B, Tomlinson L, Galletley C, et al. (1998). Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Human Reproduction (Oxford, England).* 13: 1502-5.

Cui X, Cui Y, Shi L, Luan J, et al. (2018). A basic understanding of Turner syndrome: Incidence, complications, diagnosis, and treatment. *Intractable & rare diseases research.* 7: 223-8.

Culha C, Ozkaya M, Serter R, Sahin I, et al. (2012). Swyer's Syndrome: In a fifty-year-old female. *The Journal of Obstetrics and Gynecology of India.* 62: 571-4.

Deng Z, Chen F, Zhang M, Lan L, et al. (2016). Association between air pollution and sperm quality: a systematic review and meta-analysis. *Environmental pollution.* 208: 663-9.

Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, et al. (2009). Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocrine reviews*. 30: 293-342.

Dunson DB, Baird DD, Colombo B. (2004). Increased infertility with age in men and women. *Obstetrics & Gynecology.* 103: 51-6.

Fontana L, Gentilin B, Fedele L, Gervasini C, et al. (2017). Genetics of mayer–rokitansky–küster–hauser (MRKH) syndrome. *Clinical genetics.* 91: 233-46.

Frejka T, Sardon JP. (2006). First birth trends in developed countries: Persisting parenthood postponement. *Demographic research.* 15: 147-80.

Gekas J, Thepot F, Turleau C, Siffroi JP, et al. (2001). Chromosomal factors of infertility in candidate couples for ICSI: an equal risk of constitutional aberrations in women and men. *Human Reproduction.* 16: 82-90.

Gnoth C, Godehardt D, Godehardt E, Frank-Herrmann P, et al. (2003). Time to pregnancy: results of the German prospective study and impact on the management of infertility. *Human reproduction.* 18: 1959-66.

Goswami R, Goswami D, Kabra M, Gupta N, et al. (2003). Prevalence of the triple X syndrome in phenotypically normal women with premature ovarian failure and its association with autoimmune thyroid disorders. *Fertility and sterility.* 80: 1052-4.

Harlow BL, Wise LA, Otto MW, Soares CN, et al. (2003). Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. *Archives of general psychiatry.* 60: 29-36.

Hipwell AE, Kahn LG, Factor-Litvak P, Porucznik CA, et al. (2019). Program collaborators for Environmental influences on Child Health Outcomes Exposure to non-persistent chemicals in consumer products and fecundability: A systematic review. *Hum. Reprod.* 25: 51-71.

Innis JW, Adam MP, Ardinger HH, Pagon RA, et al. (2022). Gripp KW.Hand-foot-genital syndrome GeneReviews® Seattle (WA).

Jönsson SA. (1991). Marriage rate and fertility in cycloid psychosis: comparison with affective disorder, schizophrenia and the general population. *European archives of psychiatry and clinical neuroscience.* 241: 119-25.

Kim EJ, Cho MJ. (2021). The association between assisted reproduction technology (ART) and social perception of childbearing deadline ages: a cross-country examination of selected EU countries. *Int J Environ Res Public Health.* 18: 2111.

Lumley J, Watson L, Watson M, Bower C. (1996). Cochrane Pregnancy and Childbirth Group. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. *Cochrane Database Syst Rev.* 3: CD001056.

Mattison DR, Plowchalk DR, Meadows MJ, Miller MM, et al. (1989). The effect of smoking on oogenesis, fertilization, and implantation. *InSeminars in reproductive endocrinology.* 7: 291-304.

Mahalingaiah S, Winter MR, Aschengrau A. (2016). Association of prenatal and early life exposure to tetrachloroethylene (PCE) with polycystic ovary syndrome and other reproductive disorders in the cape cod health study: A retrospective cohort study. *Reproductive Toxicology.* 65: 87-94.

McAllister JM, Legro RS, Modi BP, Strauss JF. (2015). Functional genomics of PCOS: from GWAS to molecular mechanisms. *Trends in Endocrinology & Metabolism.* 26: 118-24.

Mendola P, Sundaram R, Louis GM, Sun L, et al. (2017). Proximity to major roadways and prospectively-measured time-to-pregnancy and infertility. *Science of the Total Environment.* 576: 172-7.

Menken J, Trussell J, Larsen U. (1986). Age and infertility. *Science.* 233: 1389-94.

Mierla D, Malageanu M, Tulin R, Albu D. (2015). Prevalence of chromosomal abnormalities in infertile couples in Romania. *Balkan Journal of Medical Genetics.* 18: 23-30.

Nieuwenhuijsen MJ, Basagaña X, Dadvand P, Martinez D, et al. (2014). Air pollution and human fertility rates. *Environment international.* 70: 9-14.

Nobles CJ, Schisterman EF, Ha S, Buck Louis GM, et al. (2018). Time-varying cycle average and daily variation in ambient air pollution and fecundability. *Human Reproduction.* 33: 166-76.

Oktay K, Bedoschi G, Berkowitz K, Bronson R, et al. (2016). Fertility preservation in women with Turner syndrome: a comprehensive review and practical guidelines. *Journal of pediatric and adolescent gynecology.* 29: 409-16.

Otter M, Crins PM, Campforts BC, Stumpel CT, et al. (2021). Social functioning and emotion recognition in adults with triple X syndrome. *BJPsych Open.* 7: e51.

Peck JD, Quaas AM, Craig LB, Soules MR, et al. (2016). Lifestyle factors associated with histologically derived human ovarian non-growing follicle count in reproductive age women. *Human Reproduction.* 31: 150-7.

Penzias A, Azziz R, Bendikson K, Cedars M, et al. (2021). Fertility evaluation of infertile women: a committee opinion. Fertility and sterility. 116: 1255-65.

Penzias A, Bendikson K, Butts S, Coutifaris C, et al. (2018). Smoking and infertility: a committee opinion. *Fertility and sterility.* 110: 611-8.

Povey AC, Clyma JA, McNamee R, Moore HD, et al. (2012). Participating Centres of Chaps-UK. Modifiable and non-modifiable risk factors for poor semen quality: a case-referent study. *Human reproduction.* 27: 2799-806.

Practice Committee of the American Society for Reproductive Medicine. (2020). Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertility and sterility.* 113: 533-5.

Prioux F. (2005). Late fertility in Europe: some comparative and historical data. *Revue d'épidémiologie et de santé publique.* 53: 3-11.

Qanbar FJ, Ali SF, Al-Bassam AN. (2019). Infections Among Women Suffered from Spontaneous Miscarriage Compared with Normal Delivery Women. *Iraqi Journal of Embryos and Infertility Researches*. 9: 55-64.

Qin Y, Jiao X, Simpson JL, Chen ZJ. (2015). Genetics of primary ovarian insufficiency: new developments and opportunities. *Human reproduction update.* 21: 787-808.

Shanas E, Binstock RH. (1976). Handbook of aging and the social sciences. Van Nostrand Reinhold. pp. 33-55.

Signorello LB, McLaughlin JK. (2004). Maternal caffeine consumption and spontaneous abortion: a review of the epidemiologic evidence. *Epidemiology.* 15: 229-39.

Sobotka T, Beaujouan É. (2018). Late motherhood in low-fertility countries: Reproductive intentions, trends and consequences. *Preventing age related fertility loss.* Pp. 11-29.

Steiner AZ, Pritchard D, Stanczyk FZ, Kesner JS, et al. (2017). Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. *Jama.* 318: 1367-76.

Tang R, Lin L, Guo Z, Hou H, et al. (2019). Ovarian reserve evaluation in a woman with 45, X/47, XXX mosaicism: A case report and a review of literature. *Molecular Genetics & Genomic Medicine.* 7: e00732.

Wesselink AK, Rothman KJ, Hatch EE, Mikkelsen EM, et al. (2017). Wise LA. Age and fecundability in a North American preconception cohort study. *American journal of obstetrics and gynecology.* 217: 667-e1.

Winter E, Wang J, Davies MJ, Norman R. (2002). Early pregnancy loss following assisted reproductive technology treatment. *Human Reproduction.* 17: 3220-3.

Xue T, Zhu T. (2018). Increment of ambient exposure to fine particles and the reduced human fertility rate in China, 2000–2010. *Science of the total environment.* 642: 497-504.

Xue T, Zhu T. (2018). Association between fertility rate reduction and pre-gestational exposure to ambient fine particles in the United States, 2003–2011. *Environment international.* 121: 955-62.

Yahaya TO, Oladele EO, Anyebe D, Obi C, et al. (2021). Chromosomal abnormalities predisposing to infertility, testing, and management: a narrative review. *Bulletin of the National Research Centre.* 45: 1-5.

Yatsenko SA, Rajkovic A. (2019). Genetics of human female infertility. *Biology of reproduction.* 101: 549-66.

Zhang L, Liu W, Hou K, Lin J, et al. (2019). Air pollution-induced missed abortion risk for pregnancies. *Nature sustainability.* 2: 1011-7.