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Advancements to treat various types of Male and Female Infertility

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ABSTRACT

Male infertility is a growing concern that affects approximately 15% of couples worldwide, with male factors contributing to nearly half of these cases. Recent studies have highlighted a significant relationship between obesity and male reproductive health, suggesting that excess body weight may negatively impact fertility through various biological mechanisms. Obesity is characterized by an increased accumulation of adipose tissue, which alters hormonal balance, particularly affecting testosterone levels and leading to metabolic dysfunction. Research indicates that obesity can lead to a state of chronic inflammation and oxidative stress, which can impair spermatogenesis and reduce sperm quality. Additionally, elevated body mass index (BMI) has been associated with lower sperm concentration, motility, and morphology. The mechanism behind these effects may include hormonal alternations, such as increased estrogen levels due to aromatization of testosterone in adipose tissue, as well as the detrimental impact of obesity –related comorbidities, including insulin resistance and diabetes. Endometriosis is a common estrogen-related disease in women of reproductive age, usually associated with chronic pelvic pain, infertility, and psychological distress, i.e., anxiety and depression. The condition is defined by the presence of endometrial glands and stroma implanted outside the uterine cavity, most typically found in the uterus, fallopian tubes, and ovaries. Pathophysiological processes include endocrine disturbances, immune derangement, and oxidative stress. Endometrial cells also secrete cytokines like MCP-1 and IL-6, which interfere with normal follicular development and luteal function. Sterility occurs in 30–50% of patients with endometriosis, creating management dilemmas and causing decreased quality of life. Diagnosis is largely dependent on non-invasive imaging studies, while therapy encompasses hormonal treatment, lifestyle changes, and ART like IVF. Surgical procedures have limited efficacy for established cases, and recurrence is frequent. New strategies such as high-intensity focused ultrasound (HIFU) and nanotechnology-based therapies hold great promise by treating lesions noninvasively and combating oxidative stress. Ethical dimensions of the treatment of endometriosis involve respecting patient autonomy, informed consent, and fair access to treatments. A multidisciplinary patient-centered model is necessary to maximize outcomes in endometriosis-associated infertility.

Keywords: *Endometriosis, infertility, estrogen-dependence, oxidative stress, IVF, HIFU, nanotechnology, MCP-1, IL-6, ART, ethical issues, reproductive health.*

1. INTRODUCTION

Reproductive outcomes are influenced by sperm quality (count, motility, morphology, and viability), which increases the likelihood of successful fertilization and the subsequent establishment of pregnancy (Agarwal et al., 2021). The correlation between sperm quality and fertility is complex, particularly in light of the potential for more precise assessments of sperm parameters from emerging modalities such as flow cytometry, computer-assisted sperm analysis [CASA], and others (Esteves et al., 2020). However, it has been challenging to estimate male fertility solely on sperm quality, and research has indicated that sperm characteristics alone do not necessarily indicate successful conception (Schneider et al., 2022). This demonstrates the necessity of more funding for studies and the creation of substitute evaluation techniques, including the molecular evaluation of sperm function (Björndahl et al., 2022). Furthermore, additional research indicates that when fertilization occurs with low-quality sperm, it may have negative consequences for the development of the embryo, epigenetic alteration, and the abnormalities of the offspring (Zhou et al., 2018; Jenkins et al., 2021). It is essential to characterize and improve sperm quality if we are going to improve fertility, in comparison to the welfare of future generations.

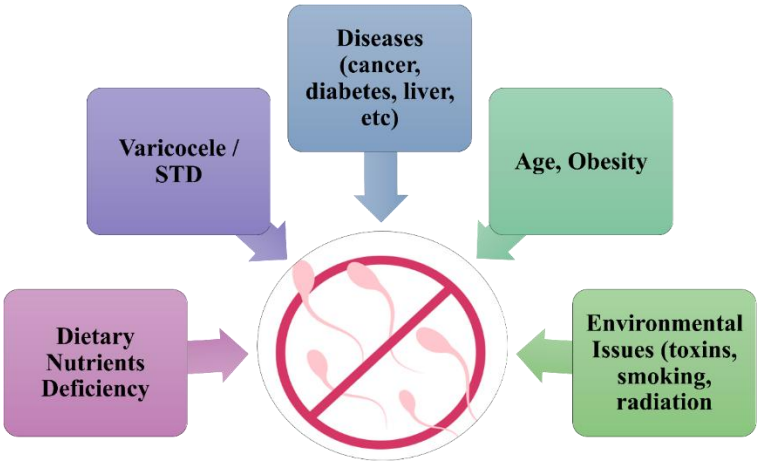


Fig. 1Causes of Male Infertility (Almujaydil, 2023)

Figure-represents male infertility factors. There are five sources of male infertility factors; nutritional deficits in diet, diseases (cancer, diabetes, liver disease), environmental factors (cigarettes, radiation, and poisonous exposures), aging and obesity alone and together, and reproductive health (varicocele, STDs). Multiple issues may affect male reproductive potential, which may also affect sperm quality, production, motility, and DNA quality. Not only must the five sources of male infertility factors be recognized and thoroughly understood, but it is also imperative to develop preventive and therapeutic strategies that will mitigate the state of reproductive health.

Biological and Environmental Factors Affecting Male Fertility

Male fertility is interrelated not only to biological factors, but also to environmental factors, and it affects not only sperm quantity, but also sperm quality and the reproductive consequences. Disorders of hormonal parameters, such as pituitary tumors, can inhibit hormone production or gonadotropins, and thus delay sperm production (Kumar et al., 2018). There are also testicular disorders, such as varicocele, torsion, and orchitis, that can injure the testes and change the way sperm is produced. Varicocele is often associated with low sperm counts and poor sperm motility in men (Shridharani et al., 2016). Klinefelter Syndrome is a genetic syndrome which can create barriers for male fertility through sperm production, and most commonly results in azoospermia or severe oligospermia (Kamischke et al., 2003). Infection and disease-based inflammation, including prostatitis and epididymitis, may simultaneously damage sperm or obstruct in way of the sperm duct, inducing infertility (Schuppe et al., 2017). Phthalates and bisphenol A (BPA), two environmental contaminants classified as EDCs (endocrine-disrupting chemicals), have been associated with adverse effects on sperm quality and endocrine function, along with several other environmental pollutants (Hauser et al., 2016). Low sperm counts and poor motility have also been linked to severe alcohol and tobacco use. Furthermore, smoking may decrease fertility or change the DNA of sperm (Kovac et al., 2013).

Obesity can result in changes in hormones, increased scrotal temperature, and reduced sperm quality (Eisenberg et al., 2018). Sperm quality has been adversely affected by diets high in processed foods and low in nutrients, including a known interference with fertility by a diet high in sugar and caffeine (Gaskins et al., 2018). The father's advanced age contributes to decreased sperm quality, subfertility, and increased age-related genetic changes (Kleinhaus et al, 2018).

Table 1. Biological and Environmental Factors Affecting Male Fertility

Factor	Description	Impact on Male Fertility	Citation
Temperature	Raised scrotal temperatures related to occupational heat stress, tight-fitting clothing, or varicocele.	Results in disrupted spermatogenesis and a lowered concentration and motility of sperm	(Durairajanayagam, 2018)
Seasonal Variation	Variation of duration of daylight and climate in the environment affects hormonal regulation.	Changes the testosterone, sperm production, and sperm quality seasonally.	(Jørgensen et al., 2018)

Oxidative Stress	An imbalance between free radicals and antioxidants in the reproductive system.	Causes decreased motility, DNA damage in sperm and abnormal morphology.	(Agarwal et al., 2020)
Endocrine Disruptors	Chemical exposure, including BPA, phthalates, and pesticides.	Changes in the hormonal regulation of sperm production and testosterone; capacity for sperm production, and reduction in testosterone.	(Sengupta et al., 2017)
Pollution	Exposure to industrial pollutants such as lead, cadmium, and mercury.	Induced DNA fragmentation, oxidative stress, and sperm dysfunction.	(Naha et al., 2021)
Personal behaviour	Chronic exposure to tobacco and alcohol consumption.	Decreases sperm concentration, motility, and increases in abnormal morphology.	(Kovac et al., 2015)
Metabolic Disorders	High BMI, diabetes, metabolic syndrome that throws off hormone levels.	Lowers testosterone levels, increased estrogen, and damages sperm function.	(Palmer et al., 2012)
Infections	Bacterial and viral infections such as chlamydia, and HPV.	Causes inflammation, sperm DNA fragmentation, and obstructive azoospermia.	(Salonia et al., 2019)
Radiation Exposure	Prolonged use of mobile phones, and laptops, and radiation exposure from work and home.	Increases DNA Damage, oxidative stress and reduces sperm motility	(Houston et al., 2016)

Sperm quality affects fertility in two significant ways: (1) It increases the risk of failure to fertilize and pregnancy. (2) Because it diminishes the male sperm quality, which not only affects fertility, but also the health and well-being of the offspring that arise from the fertilization. The success of reproduction depends heavily on the sperm quality factors: count, motility, morphology, and viability (Carrell & Hammoud, 2010). There is a demand for informative research and comprehensive assessment methods to understand the relationship between sperm quality and fertility. Although new measures of sperm quality are being established through computer assisted sperm analysis (CASA) and flow cytometry and generating quantitative measures of sperm, predicting male fertility is still difficult based on sperm quality alone (Krausz & Riera-Escamilla, 2018). Evidence suggests that production using poor quality sperm will have consequences for the offspring, including increased deformity and molecular profiling (Frans et al, 2008).

The genetic and epigenetic network is also important to male infertility. Genetic node signalling consists of genetic abnormalities. For example, removals of portions of Y-chromosomes (AZF regions) and genetic abnormalities of the CFTR gene, among others, may lead to the male infertility condition of oligospermia or azoospermia. Epigenomic node signalling consists of epigenomic alterations, such as the addition of a methyl group/units to a stretch of DNA, or modifying histones in a chromatin-like fashion, which can cause an impact on sperm quality and affect embryo development (Krausz & Riera-Escamilla, 2018). At the same time, there is a seminal microbiome that has an impact on aspects of male fertility and infection from Ureaplasma and/or Mycoplasma may affect sperm and cause inflammatory damage. The research sheds light on dietary supplements, including probiotics that can be administered with a regular diet and offer sperm quality improvements along with diminished oxidative stress (Mandar et al., 2015; Valcarce et al., 2017).

Seasonal Patterns in Semen Parameters

Male fertility is affected by multiple physiological and environmental factors, with seasonal factors among the significant factors impacting semen quality parameters. Seasonality impacts semen quality parameters, such as sperm production, motility, morphology, and overall reproductive health, in a number of ways; seasonal variations can take the form of temperature fluctuations, variations in photoperiod, or even lifestyle changes throughout the year (Jorgensen et al., 2001). Seasonalities were seen across different locations and climates where semen quality metrics were often significantly impacted; for instance, in Brazil and Denmark, semen quality parameters were positively impacted during cooler months, while during warmer months, semen quality significantly declined. (Levitas et al., 2013).

The environment around the human testicles is also susceptible to external physiological and physical stresses, such as heat stress, which affects spermatogenesis and sperm survival (Gaskins et al., 2009). Oxidative stress caused by heat stress may have an impact on sperm DNA fragmentation because of high temperatures, humidity, and environmental factors that may

eventually affect male fertility and, consequently, fertilization capacity (Vaamonde et al., 2012). Seasonal variations in semen characteristics can also impact reproductive results, as do seasonal variations in hormones like follicle-stimulating hormone (FSH) and testosterone (Ramos et al., 2015).This section explores seasonal variation in semen quality. To complete this, sperm concentration, motility, morphology, viability, and DNA characteristics will be examined. It is also possible to express global trends for seasonal variation in fertility by comparison of populations and climate. Knowing about global trends is important to enhance fertility treatment, the use of ART in clinics, and reproductive health measures to maximize the likelihood of pregnancy.

i) Role of Temperature, Photoperiod, and Hormonal Changes

Several previous studies have reported seasonal differences in sperm concentration and sperm count, and it has also confirmed environmental factors (such as temperature, photoperiod, and hormonal changes) can influence sperm production. These studies have documented suggestions that sperm concentration and sperm count do seasonally fluctuate, and sperm quality is better in the cooler months because sperm production is lessened in the summer months (Levitas et al., 2013). One article analyzed 6,455 samples of semen and also documented sperm concentration was lowest during the summer months, specifically August and September, and the highest levels during the winter or early spring (Levitas et al., 2013). An additional article published in 2011 which describes a study in Beijing China reported significantly higher sperm concentration and progressive motility in the spring with summer showing the most decline (Jørgensen et al., 2011).

The testes typically function best at 2°C less than body temperature, which is an essential temperature for sperm production. Spermatogenesis is very temperature sensitive (Mandal et al., 2022). Hot summer environmental temperatures can disrupt spermatogenesis due to heat stress on Sertoli and Leydig cells, causing reduced sperm concentrations and motility, respectively (Carlsen et al., 2005). Variations in photoperiod may affect reproductive functions in addition to temperature. Though humans are not a seasonal reproducing species, some studies suggest that differences in the length of daylight may result in hormonal changes and modify the hormonal control of sperm production. Longer hours of daylight may modify the testosterone and significantly affect the spermatogenic efficiency (Mandal et al., 2022). Seasonal variation in the hormones, especially testosterone and gonadotrophic hormone (FSH) has been reported and relates to variances in sperm concentration and quality (Jørgensen et al., 2011).

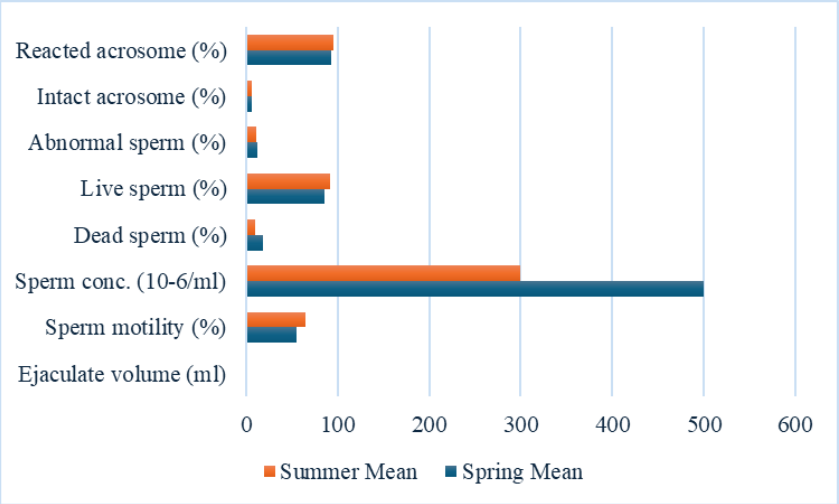


Fig. 2 Seasonal variations in New Zealand male rabbits during spring and summer seasons (Slovak, 2007).

Figure depicts seasonal differences for several sperm quality traits between spring and summer in New Zealand male rabbits and indicates the potential influence of factors such as ambient temperature and photoperiod on sperm quality and production. The ejaculate volume over several weeks varies in both spring and summer. In summer after week 4, volumetric values somewhat increase, indicating that while seasonal factor(s) may not greatly affect total ejaculate volume, they could affect aspects of sperm quality. The sperm motility is lower in summer than in spring, particularly in the first weeks, indicating that higher temperature negatively affects sperm motility, perhaps due to oxidative stress caused by heat or impaired sperm metabolism.In spring, the proportion of morphologically normal acrosome exceeds what occurs in the summer months, indicating that environmental factors such as heat impair the quality of sperm and, thus, its fertilization potential. Furthermore, the proportion of reacted acrosomes fluctuated through time and were marginally greater in summer suggesting that heat causes a premature acrosomal reaction, which may be detrimental to sperm functions. Collectively, sperm quality, including concentration, motility and viability were comparatively higher in spring, whereas increased summer heat

compromised spermatogenesis and sperm function; resulting in greater sperm norms and mortality respectively, while lending support to the importance of acknowledging seasonality in assessments of male fertility or studies of artificial insemination and human reproduction (Slovak, 2007). According to Levitas et al. (2013), Table 3 shows that sperm concentration, motility, and morphology are at their best in the winter and decrease in the summer.

Table 3: Seasonal Variations in human Sperm components (Levitas et al., 2013)

Season	Sperm Concentration	Fast Motility	Normal Morphology
Spring Season	65 million/mL	45 %	30 %
Summer Season	50 million/mL	35 %	25 %
Fall Season	55 million/mL	40 %	28 %
Winter Season	70 million/mL	50 %	35 %

ii) Impact of Heat Stress and Oxidative Stress on Spermatogenesis

Heat stress can cause damage to spermatogenesis in the testes through the exposure to a higher temperature exceeds normal levels. As heat stress significantly disrupts sertoli cells, and Leydig cell function, it can lead to a series of adverse effects to the testes, including germ cell apoptosis (increased levels of germ cell apoptosis as a result of heat stress have been demonstrated in humans by Rojas et al.), autophagy, necrosis, and arrest of the cell cycle, which all correspond to diminished sperm production and quality (Carlsen et al., 2005). The testes need a specified and optimal temperature for proper spermatogenesis, and even small temperature increases can interfere with physiological processes, such as hormonal signalling pathways, and the blood-testis barrier (Jørgensen et al., 2011). Studies have suggested that heat stress as a result of consistently 6 hours a day over 5 consecutive days of exposure to high temperature can lead to testicular atrophy, reduced sperm motility, and total sperm viability, respectively. heat stress greatly affects male fertility (Levitas et al., 2013).

Heat stress is strongly correlated to oxidative stress because it has been established that elevated temperature in the testicular environment increases the likelihood of reactive oxygen species (ROS) production, which causes further oxidative stress and oxidative damage to sperm cells (Aitken & Roman, 2008). Oxidative stress causes lipid peroxidation, DNA fragmentation, and protein modifications leading to impaired sperm functionality and infertility in male partners (Mandal et al., 2022), and it has also been implicated to disrupt epigenetic regulation in spermatogenesis - potentially inducing long-term negative, multigenerational effects on the quality and fertilisation potential of sperm cell (Aitken & Roman, 2008). As ROS levels exceed the antioxidant defences within sperm cells, oxidative stress exacerbates sperm dysfunction, inhibition of fertilization capacity, and heightens the risk for transmitting the DNA damage to the descendants (Carlsen et al., 2005).

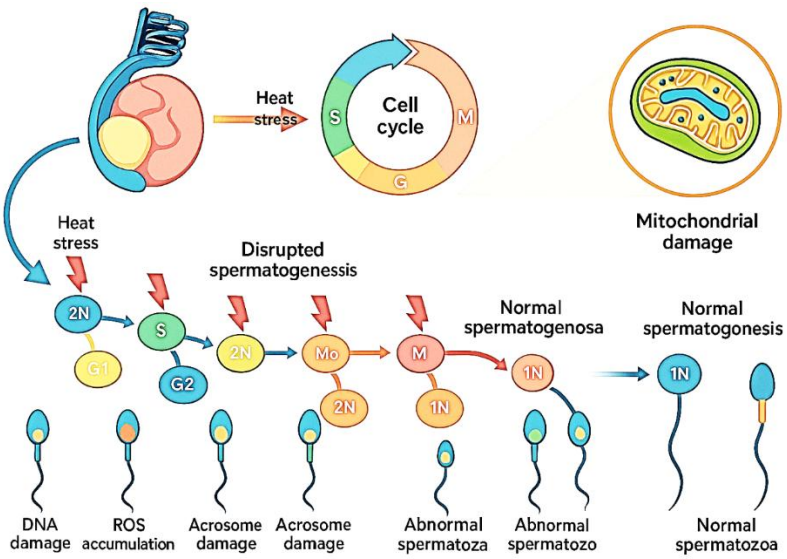


Fig. 3. Effect of heat stress on the course of spermatogenesis (Capela et al., 2022)

The fig. 4 illustrates the impact of heat stress on spermatogenesis, highlighting the various disruptions it causes in sperm development at different stages of the cell cycle. The process begins in the testis, where developing germ cells undergo

mitosis and meiosis to form mature spermatozoa. However, exposure to heat stress, indicated by red lightning symbols, disrupts this process at multiple points.

Heat stress interferes with the mitotic phase of spermatogenesis by inducing DNA damage, halting cell division, and impairing transcription, which prevents the normal progression of spermatogonia (2N) into spermatocytes (N). The disruption extends to meiosis, where meiotic cells fail to divide correctly, leading to incomplete or defective sperm formation. The figure also highlights how heat stress affects the cell cycle, particularly by stopping DNA replication, inhibiting transcription, and altering centrosomes and cytoskeletal structures, ultimately leading to mitotic catastrophe.Lifestyle, profession, and environmental exposures play a role in seasonal fluctuation in sperm quality. Those who work in situations where they are chronically exposed to environmental heat, such as factory working and agriculture, tend to present with less optimal sperm quality such as lower sperm mobility and worse DNA fragmentation. In addition, urban populations have higher exposure to stress, air pollution, and endocrine-disrupting chemicals. Urban populations could possibly have higher seasonal declines in sperm quality, whereas rural populations would have less decline, according to the decreased exposure to industrial pollutants, etc.Using global dataset meta-analyses provides an overall view of seasonal changes in sperm quality, confirming the significant roles that temperature, photoperiod, and environmental conditions play in reproductive health. They also highlight that the expected changes in seasonal variation are likely to be more substantial during colder times of year. The implications of global warming and environmental pollution could overwhelm the typical effects of seasonal variation in sperm quality, even in geographically stable climates. Knowing the expected variation in sperm quality is essential to assess fertility and to consider ways to address seasonal issues around reproduction. Semen quality is subject to seasonal fluctuations at different locations and climate conditions due to numerous variables such as temperature, photoperiod, and environmental exposures. Sperm parameters, such as concentration, motility, and morphology, all appear to have seasonal patterns, generally with less fluctuation in tropical climates as opposed to temperate climates.

Table 4: Impact of Seasonal Variations in various parameters of Semen among different Climatic conditions

Season	Climatic condition	Concentration of Sperm	Sperm Motility	Sperm Morphology
Winter season	Temperate region	Higher	Higher	Enhanced
Summer season	Temperate region	Lower	Lower	Declined
Wet season	Tropical region	Stable	Stable	Stable
Dry season	Tropical region	Stable	Stable	Stable

With emphasis on sperm concentration, motility, and morphology in both temperate and tropical climates, Table 4 illustrates how seasonal and climatic fluctuations affect sperm quality.Sperm quality tends to exhibit marked seasonal variation in temperate areas. Sperm concentration, motility, and sperm morphology are all higher in winter. A large contributing factor was likely to do with lower ambient temperatures greatly reducing testicular heat stress and oxidative damage, which positively affects spermatogenesis (Levitas et al., 2013). In summer, sperm concentrations and motility decreased, and sperm morphology was poorer. This was likely due to higher testicular temperatures, increased oxidative stress, dehydration leading to an impairment in spermatogenesis, and the development of morphological abnormalities in structural sperm (Vaamonde et al., 2012). Sperm in tropical environments tends to be more constant across wet and dry seasons as opposed to temperate zones, which fluctuate more dramatically with seasonal variability in temperature and duration of daylight. Sperm concentration, motility, and morphology tend to be relatively stable across time in tropical climates compared to temperate microbes. This suggests that the absolute number of environmental variables, such as the impact of a high temperature spike is grander in effect on its sperm quality in temperate regions than it is in tropical environments (Jorgensen et al., 2001). These phenomena reveal the significance of geographic location on male fertility and the more substantial temporal climatic changes associated with seasons. Furthermore, if the suitability of environmental context are taken into account while assessing fertility and reproductive planning then it could help optimize reproductive output others.

iv. Hormonal Regulation and Seasonal Variation

Reproductive hormones investigated seasonal differences, and variability may also interact with sperm production and fertility measures in males. Environmental cues (temperature, photoperiod or length of day) provide hormonal changes for spermatogenesis. Testosterone, follicle-stimulating hormones (FSH) and luteinizing hormones (LH) and melatonin are reproductive hormones that affect the seasonal aspect of male fertility. Testosterone, the steroid hormone, is produced in Leydig cells of the testis with stimulation of LH, is the primary androgen regulating spermatogenesis and sperm motility and secondary sex characteristics (Wehr et al, 2001)

Testosterone is also known to fluctuate seasonally (peak in winter and lowest to minimal movement in summer). The seasonal

pattern of testosterone levels, which correlates with mid and semi-motility sperm levels, indicates that reduced testosterone levels during summer months could contribute to reduced spermatogenic activity (y(Dabaja & Bryson, 2014). FSH is produced by the anterior pituitary, and it is important to stimulate Sertoli cells which support sperm cell development. Research indicates that FSH levels increase in colder seasons, supporting increased spermatogenesis, whereby FSH levels are lower in the warmer months, supporting decreased sperm production (Turek et al., 2021). Likewise, LH that stimulates testosterone production exhibits similar seasonal changes, with levels higher in the winter compared to the summer, supporting the role of seasonality on spermatogenesis. Multiple studies have shown to support seasonal testosterone fluctuations: Jorgensen et al. (2001) found that testosterone increases during winter and has winter peaks and summer declines to coincide with better sperm quality in winter. Dabaja & Bryson (2014) found that men living in temperate climates had reduced testosterone levels of 20-30% in summer compared to winter, as well as impaired sperm motility and morphology. Turek et al. (2021) determined positive relationships between high FSH/LH levels and sperm concentration in winter, showing that the seasonal fertility cycle is influenced by hormonal regulation. The pineal gland is the main source of melatonin, a naturally produced hormone in the body that is important to seasonal and circadian rhythms. Nearly all melatonin is released at night hours, with a negative relationship between exposure to sun light and released melatonin levels during the day. Melatonin production will last longer when winter nights are longer than summer days (Reiter et al., 2017). Melatonin has also been found to specifically affect the hypothalamic-pituitary-gonadal (HPG) axis by inhibiting the secretion of gonadotropin-releasing hormone (GnRH), thereby inhibiting the associated secretion of LH and FSH. High levels of melatonin, like winter days, have shown decreasing GnRH secretion by the hypothalamus leading to lower LH and FSH releases which would inhibit arousal stimulation and inhibit sperm production (Simonneaux & Bahougne, 2021). The complex process of sperm cell production is still being fully understood, which entails interactions between all hormones involved; melatonin, FSH, LH, testosterone, etc. Seasonal differences have important consequences for the motility, viability, and generation of sperm (Levitas et al., 2013).

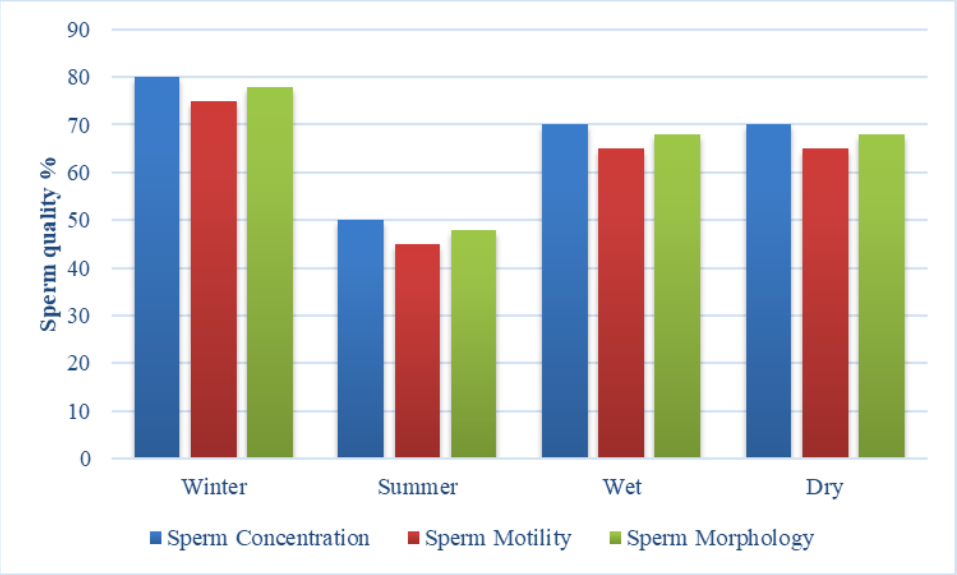


Figure 4: Seasonal variations in sperm quality across different climates

Figure 5 depicts the bar graph showing the seasonal variation of sperm quality parameters under different climatic. The bar graphs compare sperm concentration, motility, and morphology across winter, summer (in temperate climates), and wet/dry (in tropical climates) seasons. In temperate climates, sperm quality is higher in winter and lower in summer and is relatively stable in tropical climates.

v) Seasonal Timing of Conception

Epidemiological studies suggest natural conception rates follow seasonal patterns, with more natural conceptions occurring in autumn and winter in temperate climates (Wesselink et al., 2020). The seasonal changes in reproduction have been attributed to better sperm motility, DNA integrity and semen quality that occurs in cooler conditions. Seasonal variations in hormonal balance (particularly testosterone and melatonin) and exposure also help with improved reproductive performance in winter (Esteves et al., 2016). However, summer months will typically have lower fertility rates in males due to normal testicular function being impaired due to prolonged exposure to elevated heat, which negatively affects the testicle and subsequent sperm count and motility rates (Lamb and Agarwal, 2009). It has also been traditionally accepted that heat stress

results in oxidative damage to the DNA of sperm and could affect the embryo's ability to develop, and may influence pregnancy rates and success of implantation for naturally conceived pregnancies and ART (Capela et al., 2022). Lastly, fertility rates do not substantially vary for the year in tropical climates, although variations in humidity and photoperiod may contribute to the risk of reproductive success (Vaamonde et al., 2012).

Impact of Seasonal Variations on Sperm Count and Fertility Parameters

Sperm quality, hormonal homeostasis, and fertility potential in men have consistent impacts based on seasonal changes, specifically the summer, winter, and spring timelines. There are a multitude of publications describing the seasonal variations taking into consideration other seasonal environmental exposures like temperature, photoperiod and oxidative stress and their combined factors on sperm count, motility, morphology and viability (Jørgensen et al., 2001; Levitas et al, 2013). Various studies have shown that when summer arrives, the higher environmental temperatures create heat stress on the testis, which has negative effects on spermatogenesis. Not only has it been found that sperm concentration and motility are markedly lower during summer months, but levels of oxidative stress, scrotal temperature and hormonal deregulation were higher than what studies report during winter and spring (Capela et al., 2022).

Table 5 : Seasonal Variations in ART Success Rates (Levitas et al., 2013; Esteves et al., 2016; Rao et al., 2016)

Season	Climate Type	Sperm Quality	IVF Success Rate	ICSI Success Rate
Winter season	Temperate region	Highest	36.1%	40.3%
Summer season	Temperate region	Lower	27.1%	32.6%
Wet Season	Tropical region	Stable	34.5%	38.9%
Dry Season	Tropical region	Stable	35.2%	39.4%

Temperature influences the production of reactive oxygen species (ROS) that can damage the sperm DNA, compromising the viability of sperm cells and limiting full fertility potential (Agarwal et al., 2005). Increased heat stress even creates problems with testosterone and follicle-stimulating hormone (FSH) production, which are inextricably linked to sperm production (Vaamonde et al., 2012). Taken together, a reduction in quality of sperm during the summer months also adversely affects the overall success of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) rates, and reduced conception rates during the warm months of the year (Levitas et al, 2013).

Transitional Changes in Sperm Quality

Spring represents a transitional period, with sperm quality starting to recover from summer impacts but not back to winter or optimal levels of fertility (Levitas et al.,2013). Seasonal light exposure plays a role in controlling melatonin secretion, thereby influencing testosterone levels and sperm production. However, seasonal changes in spring are accompanied by increased daytime hours and Canada's testosterone levels have been steady during springtime, and sperm quality is improving (Wood et al., 2007). Above this, sperm collected in Spring showed moderate fertilizing potential, affecting mildly less IVF and ICSI success rates mildly less compared to summer and winter (Vaamonde et al., 2012).

Rational Studies on Seasonal Variation in Sperm Quality and Fertility: National and International Perspectives

Numerous studies have examined the seasonal fluctuation of sperm quality in various populations, taking into account the effects of temperature changes, environmental factors, and circadian rhythms on (male) fertility. Different climatic circumstances, lifestyles, and genetic adaptation may have an influence on sperm quality, according to studies conducted in national contexts (India and many Asian nations) and international contexts (Europe, North America, and tropical areas). All things considered, the sperm quality cycle of days, months, and years offers important genetic data to support effective ART usage and reproductive planning (family formation).

Male Fertility and Obesity.

Male obesity can particularly impact fertility through hormonal imbalances, metabolic issues, sperm quality, lifestyle patterns and psychological impact.

Impact of obesity on semen quality.

Worldwide variations in lifestyle factors and caloric imbalance habits in diet are majorly responsible for the developing obesity as global health crisis. As obesity is a medical condition which is defined as aggregation of excess body fat and white adipose tissue, with detrimental impact on health and lifespan. (Male obesity and semen quality: Any association?., 2018). Obesity has been related with harmful conditions including infertility. There is known relationship between obesity in women

and infertility. However, a corresponding association in men is still to be demonstrated. (Male obesity and semen quality: Any association?, 2018). Lately, male factor infertility has emerged as an independent cause of reproductive changes. It is a global issue, particularly in Nigeria, where many men often deny their contribution in the couple′s inability to conceive. 30% of infertility cases are attributed exclusively to male factors, with another 30% involving a combination of male and female factors. (Prevalence, Clinical Pattern and Major Causes of Male Infertility in Nnewi, South East Nigeria: A Five YearReview. , 2012) (Semen quality in male partners of infertile couples in Lagos Nigeria. , 2010).

A descriptive study took place from January – December 2008 at the research laboratory within the gynecology department of Lagos State University Teaching Hospital. Ethical clearance was requested and granted by the Hospital′s Research and Ethics Committee. This study reported 350 semen samples obtained from male partners in fertile couples. Around 260(75.7%) samples came from men with a history of achieving pregnancy, whereas 85(24.3%) samples from men who claimed they had never been able to do so. Numerous abnormalities were spotted in 242 samples (69.1%) where on the other side 108(30.9%) were observed to be largely normal. (Semen quality in male partners of infertile couples in Lagos Nigeria., 2010). Some recognized causes of male infertility include genital infections, testicular varicocele, testicular injury, scrotal surgeries, erectile dysfunction, chronic and severe systematic illnesses, hypogonadism, hypogonadotropic blockages in the reproductive tract and environmental toxins. Additionally, obesity has been reported as a contributing factor to male infertility, although there is no universal agreement on this. (Experience with a comprehensive university hospital-based infertility program in Nigeria. , 2008)

It has been suggested that obesity impacts male infertility through lowered semen quality and testosterone concentrations. (The effect of obesity on sperm disorders and male infertility., 2010). Studies have shown that adopting a healthier lifestyle with weight loss, when combine with healthier lifestyle habits, can improve erectile dysfunction. However, data confirming a causal effect or fertility improvements after weight loss intervention remain limited. (Estrogen regulation of testicular function., 2005). (Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. , 2004).

Obesity and oxidative stress.

Oxidative stress, defined as a disruption in the equilibrium between antioxidant and free radicals, is a fundamental process linking obesity with this related health issues. This oxidative environment may be a key factor initiating the other processes which contributes to tissue damage, excessive production of the extracellular matrix, activation of endoplasmic reticulum stress, and disruption of autophagic flux. (Oxidative stress in obesity. , 2022). In the context of obesity, this special issue points out the harmful effects of oxidative stress in different circumstances. Young patients with metabolic syndrome have been found to have the highest levels of oxidative stress in this regard. Furthermore, this study demonstrates that the two primary elements of the metabolic syndrome linked to oxidative stress are obesity and insulin resistance, indicating a close connection between oxidative stress and excessive fat accumulation. (Obesity and insulin resistance" is the component of the metabolic syndrome most strongly associated with oxidative stress., 2021). Lejawa M. et al.′s study examined the relationship between oxidative stress, obesity, and telomere length, demonstrating that young, metabolically unhealthy obese patients had shorter telomeres. Additionally, the study demonstrates a significant correlation between these patients telomere length, total oxidation status, and total antioxidant capacity. (Association of metabolically healthy and unhealthy obesity phenotypes with oxidative stress parameters and telomere length in healthy young adult men. Analysis of the magnetic study., 2021).

Endothelium – dependent vasodilation impairment or endothelial dysfunction is one of the first subclinical phases of the atherosclerotic process. (Endothelial dysfunction: role in obesity-related disorders and the early origins of CVD. , 2005). Cellular damage brought on by an imbalance between pro-oxidants like ROS and RNS reactive nitrogen species anti-oxidant is referred to as oxidative stress. ROS are oxidizing agents produced when oxygen is chemically reduced to produce unstable free radicals during cellular metabolism. (Reactive oxygen species and endothelial function–role of nitric oxide synthase uncoupling and Nox family nicotinamide adenine dinucleotide phosphate oxidases., 2012). However, antioxidants are required to keep the amount of ros in cells at a physiologically advantageous level. Through the inhibition of ROS formation and action or the repair of the cell damaged by ROS, antioxidants both -enzymatic or non- enzymatic molecules – significantly delay or prevent the oxidizing damage of ROS. (Free radicals, oxidative stress and importance of antioxidants in human health., 2011).

Obesity and hormonal imbalances.

Adipocyte hypertrophy and hyperplasia, which are linked to obesity, alter men′s endocrine regulation, mainly through adipokine secretion. (Obesity and male infertility: Mechanisms and management. , 2021). The hypothalamic-pituitary – gonadal axis is the main way in which these physiological alternations negatively affect the male reproductive endocrine system. (Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling. , 2018). Obese men′s hypogonadism is a complex pathological condition marked by androgen deficiency and altered gonadal function. Over the past ten years, male hypogonadism prevakence rates have increased, although they are frequently under-diagonsed and under-estimated. Excess body weight and elevated leptin levels are important factors in obesity- related hypogonadism. This pathological condition affects bone mineralization, fat metabolism, body mass composition and sexual

and reproductive function. Major risk like hypo-estrogenism and hyper-leptinemia are part of the pathophysiology of male obesity-related secondary hypogonadism (MOSH). (MOSH syndrome (male obesity secondary hypogonadism): clinical assessment and possible therapeutic approaches. , 2018) (Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING)-a novel theory for the development of late onset hypogonadism in obese men., 2016).

Obesity causes physiological changes that negatively impact the reproductive endocrine system, which control reproductive processes. These changes to the HPG axis are illustrated. Increased conversion of testosterone to estradiol is the result of increased fat tissue accumulation. This is controlled by excess production and enhanced activity of the aromatase enzyme in the white adipose tissue. Indicators of male obesity, such as BMI, total body fat percentage and abdominalfat are indirectly related with low testosterone level and directly related to estrogen level in men. (Obesity and male infertility: Mechanisms and management., 2021)

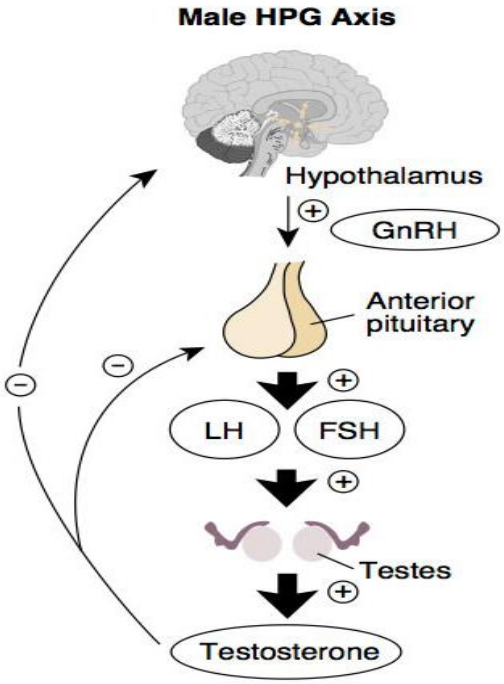


Figure 5. male HPG –axis.

Management of obesity.

The complex pathophysiology factors and coexisting metabolic disorders are the main causes of the multifaceted therapeutic approach to obesity- induced male infertility. Although lifestyle modification is still the main strategy of weight loss, nutraceuticals and herbal formulations may be used in addition.

Lifestyle modification.

Decreased seminal oxidative stress and enhanced sperm DNA integrity have been linked to central fat accumulation reduction, independent of BMI changes. (Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men., 2011). A modern western style diet that is characterized by consuming excessive amounts of refined carbohydrates, high calorie sugars, total fats and processed fatty acids and frequently lacking in fibers and omega -3 fatty acids from plant-based foods. Reduced sperm parameters and unfavorable fertility indicators, including men without underlying medical conditions, are associated with such diets. (Dietary patterns, foods and nutrients in male fertility parameters and fecundability: a systematic review of observational studies. , 2017). Mediterranean diets, rich in plant based foods, omega -3 fatty acids, whole grains, fiber, and antioxidant- enriched nutrients, have been linked to improved obesity related metabolic dysregulation of functions and male semen parameters. (Dietary patterns, foods and nutrients in male fertility parameters and fecundability: a systematic review of observational studies. , 2017). Research shows that consuming high amounts of anti-oxidants-rich foods, such as fruits, vegetables, nuts, seeds, and fish can improve sperm parameters. (Dietary patterns and semen quality in young men.Dietary patterns and semen quality in young men. , 2012). Anti-oxidants therapy reduces DNA damage, improves fertility, boosts ART success, and reduces pregnancy complications and miscarriages, according to research. (Nutrient supplementation: improving male fertility fourfold. , 2013). Physical activity

is crucial for combating obesity and diseases, but excessive intensity or duration can harm male reproductive function. (Smoke, alcohol and drug addiction and male fertility. , 2018). Exercise is recommended as the primary treatment for erectile dysfunction, as moderate physical activity enhances sexual performance and satisfaction in overweight men (Erectile dysfunction. , 2013).

Operative treatments

The effective care for individuals with obesity necessitates the assessment and management of all related heart, metabolic and hormonal issues. (Obesity and male infertility: Mechanisms and management., 2021). Bariatric surgery is a successful intervention for reproductive dysfunction in obese men, boosting testosterone levels and maintaining long-term results. However, restored erectile function may not be permanent and semen quality may not be consistent. (Male fertility, obesity, and bariatric surgery., 2012). Bariatric surgery is an effective weight loss strategy with sustained results, but understanding its benefits for male infertility associated with obesity remains in its early stages. (). Management of weight loss in obesity-associated male infertility: a spotlight on bariatric surgery. , 2017).

Clinical Implications and Fertility Treatment Considerations

Seasonal changes have a significant impact on ART (IVF and ICSI) success rates by affecting sperm parameters (concentration and motility), oocyte quality and/or implantation rates. variability among ART outcomes by season. Several studies have shown that ART outcomes are significantly variable by season and that ART success (pregnancy) rates are essentially optimized during the colder months (Levitas et al., 2013). This seasonal effect is likely a result of a pattern of less stress in cold weather, increased sperm motility and function due to higher testosterone levels and lower oxidative stress during winter (as opposed to summer) (Jung et al., 2005). Additionally, there is evidence that LH and FSH are considerably variable by season, which may mediate the patterns seen for ovarian response and/or embryo quality, which influence ART success (Rosenwaks et al., 2019).

Physiology of Ovulation and Induction Mechanisms

The primary stage of the menstrual cycle called ovulation occurs when the dominant ovarian follicle releases a mature oocyte. The process of ovulation requires hormonal feedback control plus the functioning of the hypothalamic-pituitary-ovarian (HPO) axis as explained by Holesh et al. in 2017. Through links between hypothalamus, pituitary gland and ovaries these structures keep hormones stable to guide normal follicle advancement toward an oocyte ready for release. Errors in the control system between hypothalamus and ovaries cause anovulation plus poor follicle development which need medical treatment through ovulation induction programs (Papadakis et al., 2020).

The ovulation process needs accurate hormone management plus pinpoint control over follicle growth leading to perfect timing of the luteinizing hormone to start ovulation. Hormone control selects a single dominant follicle during natural cycles to help develop medical solutions for ART treatments. Deeper knowledge of how hormones trigger ovulation and fertility treatment helps treat infertility effectively.

Hormonal Regulation of Ovulation: The Hypothalamic-Pituitary-Ovarian Axis

Ovulation control depends on a feedback mechanism which connects the hypothalamus to the pituitary gland with ovaries. Gonadotropin-releasing hormone (GnRH) emerges from the hypothalamus as the central main regulator through pulsatile hormonal secretion. The brain releases GnRH pulses that trigger FSH and LH secretion from the anterior pituitary. The dynamics of these pulses drive FSH and LH secretion through patterns that control ovarian regulation of follicular recruitment and growth with oocyte maturation (Herbison, 2018).

During the early follicular phase of the menstrual cycle FSH activates the growth mechanism of antral follicles. Upon FSH stimulation granulosa cells within these follicles initiate cellular multiplication while producing the estradiol hormone. In the time of menstrual cycle estradiol maintains follicle maturity through its dual function of regulating hormonal actions between hypothalamus and pituitary. When estradiol concentrations increase enough the positive feedback loop drives pituitary cells to release an LH surge which initiates ovulation following the follicular stage. The LH surge causes the dominant follicle to rupture so that the mature oocyte can travel through the fallopian tube (Holesh et al., 2017).

This hormone regulation process exhibits strong responsiveness to elements inside and outside the body. Irregular ovulation and anovulation may result when stress or weight changes and existing medical conditions perturb the HPO hormonal regulation mechanism. Effective ovulation induction protocols require thorough comprehension of disruptions during these stages for clinical practice. Flowchart of Hypothalamic-Pituitary-Ovarian (HPO) Axis is shown in figure 1.

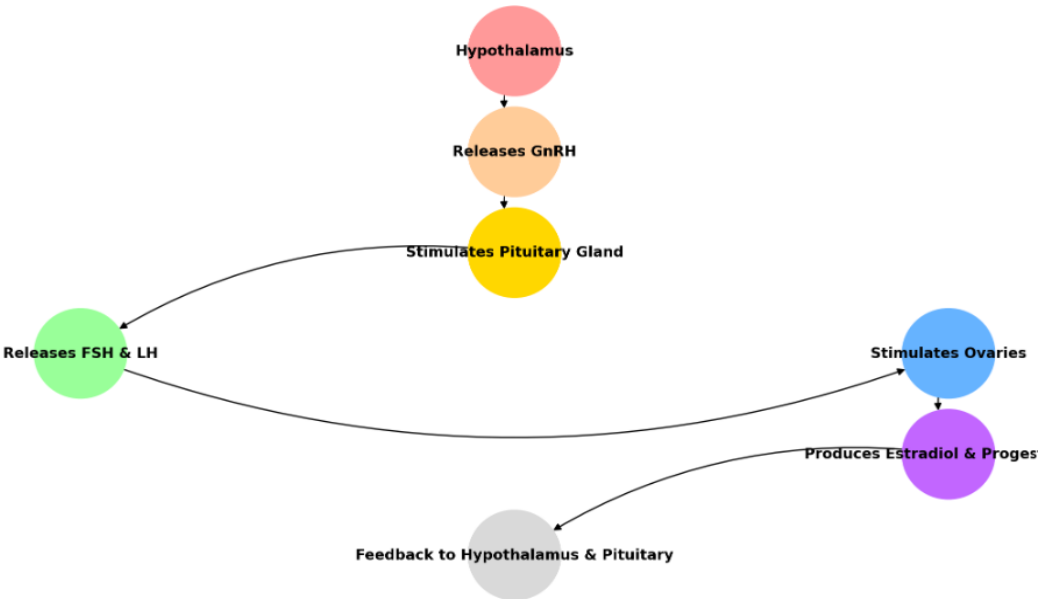


Figure 6: Hypothalamic-Pituitary-Ovarian (HPO) Axis Flowchart

Role of FSH, LH, and Estradiol in Ovulation

The three main hormones FSH, LH together with estradiol lead the process of follicular growth before ovulation occurs (Chappel and Howles, 1991). Through synergistic hormone activity they choose one dominant follicle to mature and simultaneously condition the endometrium for implantation. The physiological process of follicular development depends heavily on **Follicle-Stimulating Hormone (FSH).** By binding to granulosa cells FSH stimulates cell proliferation while simultaneously enhancing estradiol production. A natural rise in FSH concentrations during the follicular phase boosts the dominant follicle's ability to react to FSH stimulation. The incapable subordinate follicles exit the growth process therefore they die off through a process of atresia (Richards, 1980). The oocyte releases and completes its final stages of maturation because of **Luteinizing Hormone (LH).** LH secretion leads to follicular wall modifications triggered by elevated estradiol from the dominant follicle throughout the middle cycle. The follicular rupture through this process releases an oocyte ready for fertilization. Through LH hormone regulation the body establishes a corpus luteum that produces progesterone to reshape the endometrium for possible implantation. Under FSH-regulated production by granulosa cells **estradiol** serves a dual purpose. The HPO axis receives positive feedback regulation while undertaking negative feedback modulations from E2 throughout the follicular phase to drive endometrial tissue growth. High estradiol concentrations create positive feedback that leads to the LH surge which regulates ovulation. Estradiol performs both reproductive functions while also protecting bones and shaping cardiovascular health and systemic wellness throughout menstrual cycles (Prior, 2020).

Mechanisms of Action of Ovulation Induction Agents

Pharmacological agents used in ovulation induction work by replicating and amplifying natural functions of the HPO axis. Medicinal agents drive the development of follicles and activate ovulation besides helping certain fertility struggles through hormone regulatory mechanisms.

Clinical medicine frequently employs Clomiphene Citrate (CC) as one of its primary ovulation induction agents. Clomiphene Citrate works as a selective estrogen receptor modulator because it ties up estrogen receptor sites along the hypothalamus. Endogenous estrogen acts through negative feedback mechanisms that GnRH blocks which enables GnRH increases followed by FSH and LH elevation. The hormonal fluctuations within the body both activate ovarian follicle maturation and trigger the process of ovulation. The primary uses of CC therapy occur in women who have irregular menstrual cycles or exhibit polycystic ovary syndrome (PCOS) (Sovino et al., 2002).The hormone Letrozole functions as an aromatase inhibitor that healthcare providers use as a possible substitution for Clomiphene Citrate (CC). The enzyme aromatase inhibitor letrozole suppresses testosterone from forming estrogen allowing estrogen levels to decrease temporarily. This reduction alleviates the negative feedback on the hypothalamus and pituitary, increasing FSH secretion. The low multiple pregnancy potential of Letrozole combined with its capacity to promote single follicle development makes it an attractive drug selection for specific situations (Legro et al., 2014). The treatment of ovaries requires Gonadotropins which consist of recombinant FSH and LH. These substances direct follicle development by skipping both hypothalamus and pituitary control for improved gonadal stimulation. The agents find their optimal use in women with hypothalamic dysfunction along with patients who undergo assisted reproductive technologies such as in vitro fertilization (IVF). Doctors must monitor gonadotropins closely in order to prevent potential cases of ovarian hyperstimulation syndrome (OHSS) (Howles, 2002). Healthcare providers give Human Chorionic Gonadotropin (hCG) as the trigger to start ovulation. hCG functions similarly to LH because its structure

matches. Medical professionals administer hCG to complete oocyte development and trigger follicular rupture when stimulation cycles reach specified follicle size (Pandey, 2021).

The hormone treatment used for ovarian stimulation triggers control is comprised of GnRH Agonists and Antagonists to avoid untimely LH surges. The pituitary receptors of GnRH agonists experience two phases; first there is a gonadotropin release boost (flare effect) followed by complete receptor downregulation. GnRH antagonists work differently because their design blocks GnRH receptors directly at their site for rapid suppression and optimal results. Medical experts use these agents to time ovulation precisely and they are common in ART treatments. Medical professionals heavily rely on Metformin to induce ovulation among women affected by PCOS (Sharpe et al., 1996). Metformin offers two benefits; it enhances insulin sensitivity and decreases hyperinsulinemia which restores typical ovarian function. Doctors commonly prescribe CC or gonadotropins alongside this medication to achieve superior treatment results.Scientists are investigating kisspeptin analogues to treat the early regulation of GnRH secretion (Miller and Newton, 2013). The upcoming agents present a promising method of ovulation stimulation that competes with physiological mechanisms while minimizing adverse impacts.

The influence of male-derived factors on embryo development:

The Effect of Sperm Health on Embryo Growth

Sperm concentration and motility are key factors in successful fertilization. A low sperm count and poor motility can lead to decreased fertilization rates and difficulties in achieving normal embryo development (49).

(1) Sperm Concentration on Embryo Development:

According to the World Health Organization, sperm concentration—an essential parameter in semen analysis—plays a crucial role in male fertility and the development of embryos (50).

(2) Sperm Motility on Embryo Development:

Sperm motility describes the capacity of sperm to swim properly and with purpose, and is an important factor in determining a man's fertility and has a big impact on the growth of the infant. The World Health Organization (2021) claims that (50).

(3) Sperm Morphology

Irregular sperm shape is a key sign of reduced sperm quality and has been connected to compromised embryo development. Sperm with abnormal shapes may have difficulty penetrating the oocyte, which can result in fertilization failure or the creation of embryos with chromosomal abnormalities. Research indicates that sperm morphology, evaluated according to the Kruger strict guidelines, correlates with embryo quality and implantation success (51).

(4) DNA Fragmentation

Damage to sperm DNA plays a significant role in male fertility, with elevated DNA fragmentation associated with reduced fertilization success, compromised embryo quality, and a higher chance of miscarriage. This damaged DNA can hinder early embryo development, potentially causing embryos to stop developing at the cleavage stage or fail to form viable blastocysts (52).

(5) Genetic Factor

Improper packaging of sperm chromatin has been associated with chromosomal abnormalities, such as aneuploidy, in developing embryos (53)(54). Chromosomal aneuploidy describes an alteration in the typical number of chromosomes, either in somatic cells, where the diploid count is affected, or in gametes, impacting the haploid count. Such abnormalities are commonly found in early-stage human embryos (55).

(6) Oxidative Stress

Oxidative stress arises from an imbalance between reactive oxygen species (ROS) and antioxidants, leading to damage at the cellular level. Sperm are especially susceptible to this stress, and elevated ROS levels in semen can damage sperm DNA and affect the early stages of embryo development. This oxidative stress may hinder fertilization and disrupt the cleavage of embryos, which can lead to developmental delays and a higher risk of implantation failure (56).

(7) Lifestyle and Environmental Factors

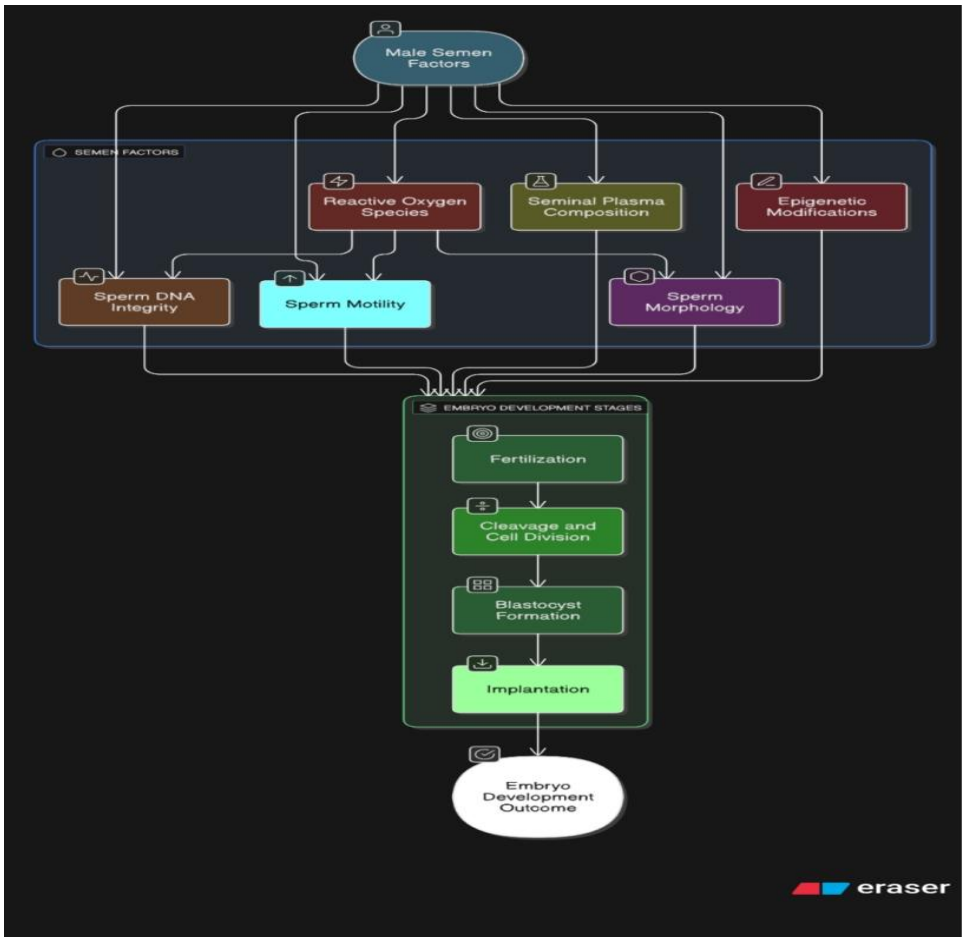
(a) Obesity: Obesity may lead to hormonal disruptions, such as lower testosterone levels, which can negatively impact sperm performance (57).

(b) Smoking and Alcohol: It has long been recognized that smoking and alcohol use adversely affect sperm quality. Smoking leads to oxidative damage and breaks in sperm DNA, whereas alcohol consumption can alter sperm morphology and motility. These lifestyle. Factors are associated with developmental abnormalities in embryos and an increased chance of pregnancy loss during assisted reproductive technologies (58).

(8) Environmental Factors

Lifestyle Factors: Smoking, heavy drinking, and unhealthy eating habits have been associated with decreased sperm quality and negative effects on embryo development. Research has demonstrated that these lifestyle choices adversely affect sperm movement, shape, and the integrity of their DNA (59).

Figure .Overview of different factors affecting Embryo Development



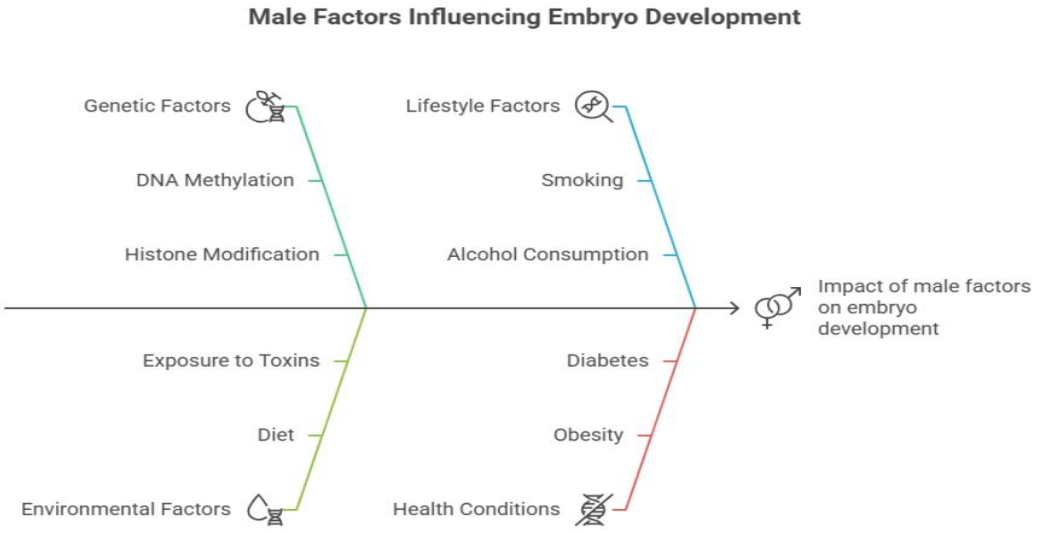


Fig. 7. Impact of male factor on embryo development

Various studies highlight how sperm quality influences embryo development:

The success of implantation relies on the condition of the sperm and egg, along with the particular assisted reproduction method used, which all play a role. As a result, male-related factors that affect embryo development may greatly contribute to the unsuccessful outcomes of these reproductive techniques. Ongoing Studies have shown that they can more clearly comprehend the clinical implications and potential risks of passing on genetic or epigenetic abnormalities, to guarantee the reliability and safety of fertility treatment methods (60). Most researchers attribute the reduced pregnancy rate in cases of male infertility primarily to decreased fertilization rates (61-65). Only one recent study has examined the impact of sperm parameters on embryonic quality (66). where high concentrations of spermatozoa with morphological defects or antisera auto-antibodies were linked to delayed fertilization. The male infertility group in the current investigation was distinguished by a noticeably smaller caliber of shape of embryos compared to tubal illness. As female traits (age, baseline hormone levels, and follicular growth parameters) While many factors were similar between the two groups, variations in embryo quality could be attributed to differences in semen quality, suggesting a male influence rather than a female one (67).According to the current study, low semen parameters are linked to lower rates of fertilization and cleavage, which may indicate that Paternal contributions to embryo development start at a very early stage. Since the human embryo relies on maternal mRNA for regulation before the activation of its genome, which occurs after the 4-cell stage, this finding is particularly compelling (68). As a result, paternal effects on embryonic development are unlikely to be evident before the embryo reaches the 8-cell stage or the morula phase. However, it appears from our data that at these early stages, paternal factors may influence embryo development by reducing the transcriptional activity of the male pronucleus, a process essential for the proper formation of the nucleolus (69). The ability of sperm to reach the target is highly correlated with their motility. Oocyte in a normal conceive; hence, Methods for selecting sperm are being employed, which compel the sperm to undergo a motility test, such as the swim-up technique, or be passed through a density gradient to mimic the natural selection process that occurs inside the body (70).Our primary goal was to evaluate the rate of blastocyst development, which is an important measure of embryo quality and its likelihood of successful implantation. Embryos transferred at the blastocyst developmental stages have been linked to an increased chance of successful implantation (71-75) Blastocyst formation is influenced by numerous factors. To determine if the relationship between semen quality and blastocyst development was independent of oocyte characteristics or other female-related factors, we developed a multiple logistic regression model that accounted for maternal age, the number of mature (MII) oocytes retrieved, and the number of embryos that underwent cleavage. The results showed that, compared to patients with normal semen parameters, those with mild or severe semen abnormalities were strongly associated with a decreased chance of blastocyst development, by 50% and 35%, respectively—even after accounting for female-related factors (76). Semen quality is strongly associated with the incidence of sperm aneuploidy (77). Studies show that in men with typical semen characteristics, the proportion of aneuploid sperm is typically below 10%. However, this percentage rises significantly in cases of abnormal semen quality (78). Aneuploid sperm can lead to the formation of aneuploid embryos following fertilization. Studies have found that the occurrence of aneuploid embryos is notably higher in couples with male partners exhibiting irregular semen characteristics (79). When evaluating male fecundity, the duration required to achieve conception is commonly used as a key indicator (80). Studies have indicated that men's fecundity significantly decreases as paternal age increases, even when adjusting for maternal age and other possible confounders. Compared to the reference group of Compared to men younger than 25, the likelihood of achieving pregnancy within a year declined with age; men aged 30–34 had an odds ratio of 0.62, those aged 35–39 had 0.50, and men over 40 had an odds ratio of 0.51 (80). There is broad agreement that the age of the father is linked to decreased fertility, particularly among couples in which the man is over 40 and the woman is 35 or older (81,82). Studies have indicated that assisted pregnancy rates decline as paternal age increases (83,84).Evidence indicates that paternal age of 35 years or older is linked to a decreased likelihood of achieving clinical pregnancy (83). It was reported that the rate of artificial conception significantly declined, A decrease in pregnancy rates per cycle has been noted, dipping from 12.3% for males under 30 to 9.3% for men over 45.

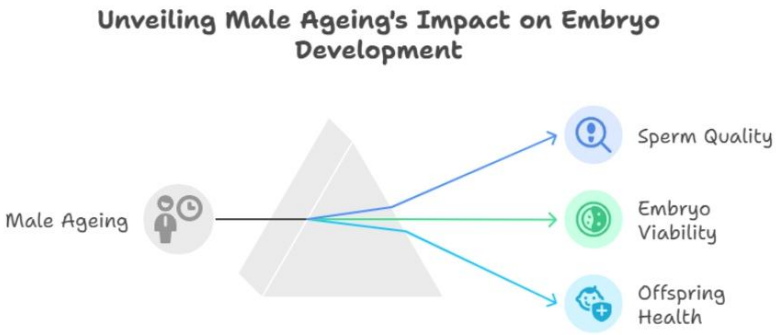


Figure 8: Impact of male ageing on Embryo Development

Endometriosis

When endometrial glands and stroma grow and are present in organs and locations outside of the uterine cavity, it is diagnostic of endometriosis, a persistent gynecologic condition. Impairment in fertility and persistent pelvic pain are the primary symptoms of the condition. Endometriosis lesions can appear anywhere in the body, although uterus, broad ligaments, cul-de-sacs, ovaries, and posterior cul-de-sacs are the most common sites of involvement [1]. Intestinal and urinary tract organs (such as the ureter, bladder, and urethra) are also impacted by endometriotic nodules. Endometriosis, however, can cause harm to the structure outside of the pelvis as well, such as the pleura, pericardium, or central nervous system [2]. Infertility, the inability to conceive following at least one year of unprotected sex at least once per menstrual period is usually defined as the problem of reproductive system of a person (give examples). Infertility may result due to male, female or un-explained variables. There are causes of infertility which can be prevented. Assisted reproductive technology such as in vitro fertilization (IVF) is one of the most usual treatments of infertility. Infertility may be caused by varied problems of the man or woman reproductive organs. Obesity, smoking, and heavy alcohol consumption are among lifestyle variables that might impact fertility. Furthermore, gametes (eggs and sperm) can be directly poisoned by environmental contaminants and poisons, leading to a decrease in both quantity and quality [3].

For a long time, people argued about whether endometriosis caused infertility or not. The fertility decreases with age and it is between 0.15 and 0.20 per month in a healthy couple. Endometriosis is associated with a decrease in monthly fecundity of approximately 0.02-0.1% in women. A reduced live birth rate is also linked to endometriosis. Endometriosis affects infertile women at a rate six to eight times higher than fertile women. There has been a lot of speculation on the relationship between endometriosis and infertility, but no clear consensus has emerged from the study. Disproportions in the pelvis, problems with the ovaries and hormones, changes in the way the peritoneum works, and changes in how the endometrium handles hormones and cell-mediated processes are all examples of these mechanisms [4]. Endometriosis has important clinical and therapeutic consequences, thus understanding its pathophysiology is critical. No theory has been able to account for the disease's many clinical manifestations and its natural history to this point. Figure 1 shows the probable microenvironment that may drive the beginning, maintenance, and progression of the disease. All theories point to a complex dysregulated hormonal signaling [5].

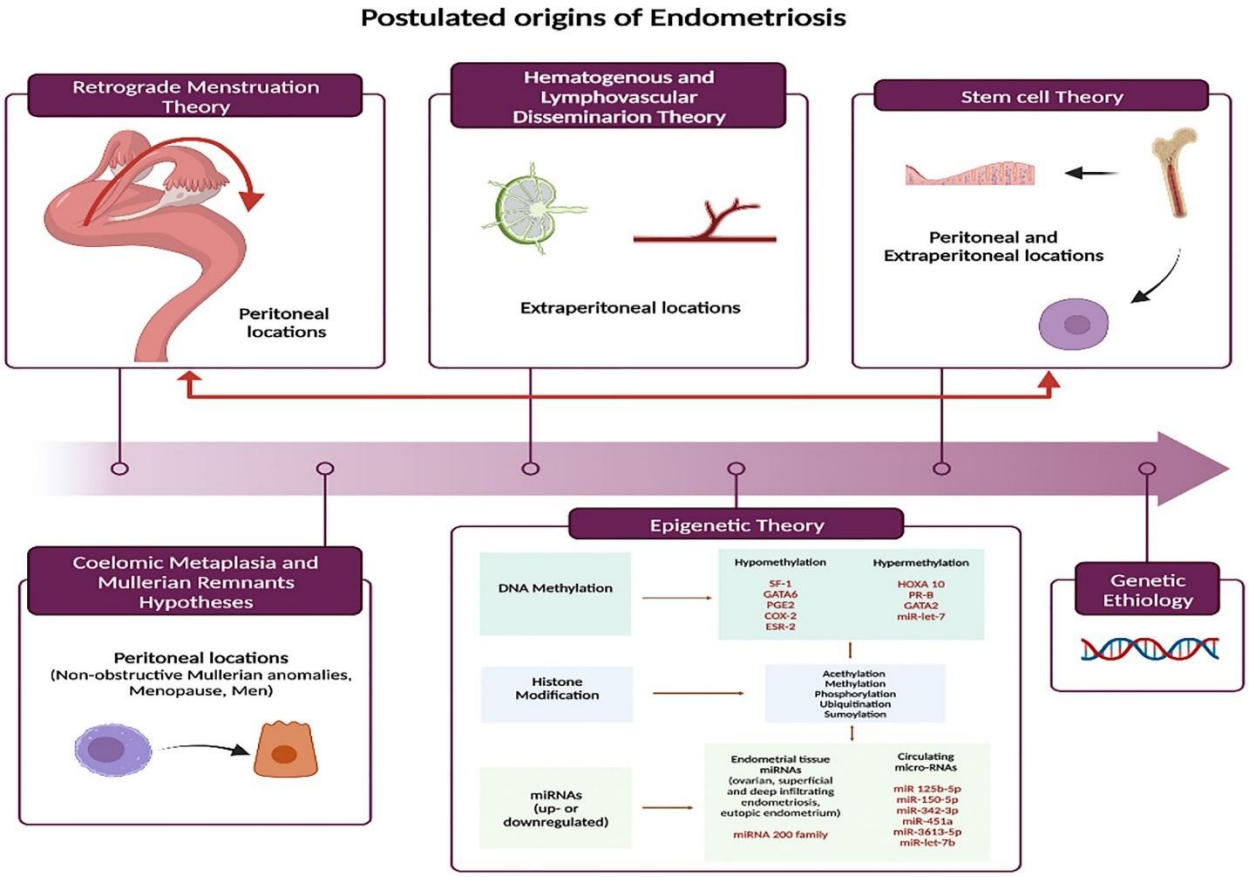


Fig.9. Postulated origins of Endometriosis

When comparing the subset of endometriosis patients having IVF in the US to the aggregate of patients with all diagnoses, there are no significant changes in implantation or pregnancy rates, according to Assisted Reproductive Technology [6].

Although endometriosis is typically identified through clinical examination, surgical investigation is necessary for confirmation. The final pathology of an endometrioma can only be detected after surgery, but imaging may reveal it as a cyst. Because it can diagnose and treat endometriosis, laparoscopy is essential, particularly in cases when an endometrioma is present. Hormonal therapy is the mainstay of medical treatment for endometriosis; however, patients experiencing resistant symptoms or those with a large endometrioma are best treated surgically. How severe the illness is and whether future fertility is a priority dictate the surgical method. Conservative methods, sometimes performed laparoscopically, include destroying the lesion with a laser or cautery, draining the endometrioma, and removing the cystic capsule [7]. Fig. 2 shows the new approaches to endometriosis treatment, which include drug delivery platforms, gene therapy, immunotherapy, stem cell treatment, and hormone therapy transfusions [8].

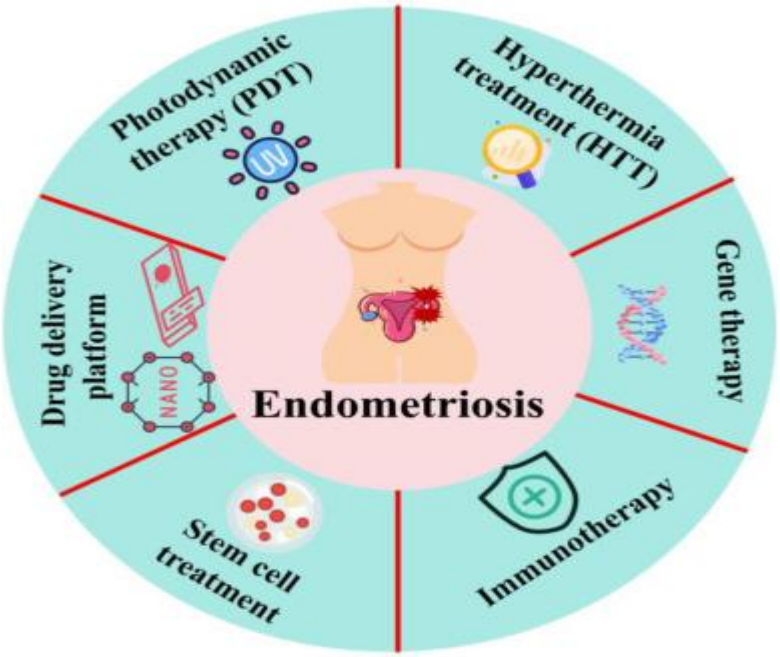


Fig.10. Emerging strategies for endometriosis

- **Photodynamic therapy (PDT):** Medical professionals often employ photodynamic treatment (PDT), also known as photochemotherapy, to eliminate cancer cells and other harmful cells. [9].
- **Hyperthermia treatment (HTT):** When it comes to adjuvant cancer therapy, hyperthermic treatments show a lot of promise since they boost oxygen and blood supply to tumors without damaging healthy tissues around them [10].
- **Gene Therapy:** The goal of gene therapy is to treat diseases by changing the biological characteristics of living cells by modifying or manipulating the expression of genes [11].
- **Immunotherapy:** The elevated level of immune cells, ectopic lesions and peritoneal fluid, cytotoxic and activation of immune cells are the symptoms of endometriosis, which has been linked to inflammation of the peritoneum in recent years. Changes in the immune system's innate and adaptive mechanisms are thought to be the root cause of endometriosis [12].
- **Stem Cell treatment:** Stem cells can go through a process of differentiation into many distinct types of cells since they can self-renew. There appears to be substantial promise in the field of regenerative medicine, according to the remark made earlier. [13].

Endometriosis related to Infertility

Infertility is a common condition among women who are able to have children. In addition to the discomfort it causes, endometriosis may also have an adverse effect on fertility. Female infertility may be due to endometriosis-related endocrine diseases, immunological issues, or structural abnormalities brought on by adhesions and fibrosis. Similarly to other forms of infertility, in vitro fertilization (IVF) may be an effective treatment option when the problem is in its early stages. Success rates with in vitro fertilization are lower for women whose endometriosis has progressed to a more severe stage [14]. Infertility affects 30% to 50% of women who have endometriosis, and the prevalence of the condition rises sharply in this population, reaching 25% to 50%. Women suffering from untreated endometriosis have a fecundity rate of 2% to 10%, in contrast to the 15% to 20% seen in healthy reproductive-age couples who do not have infertility [15]. Over a three-year

period, the likelihood of conception was much lower for ladies suffering with moderate endometriosis in contrast to others whose fertility remains a mystery. In vitro fertilization studies have shown that women suffering from severe endometriosis had low-quality embryos and oocytes, as well as poor implantation [16].

Pathophysiology and mechanism of Infertility n Endometriosis

Ten percent of reproductive-age women suffer from endometriosis, endometriosis as a disorder that is estrogen-dependent and characterized by endometrial gland implantation of the stroma outside the uterus [17]. Anxieties and despair affect both the patient and their partner in the case of infertility, which affects 30–50% of endometriosis patients [18]. Infertility in women can be caused by mechanical damage in advanced endometriosis, and which may be occasioned by the pelvic adhesions and ectopic ovarian cysts. This can cause constriction in release of oocytes, cause blockage of fallopian tube and destruction of the uterine environment that embryos should implant into. The characteristic feature of endometriosis, which is an estrogen-sensitive disorder affecting "10 percent of women in reproductive ages" is implantation of endometrial glands and extrauterine stroma, Both the patient and their spouse may feel frightened and depressed when 30 to 50% of endometriosis patients become infertile. Major endometriosis may cause foetal sterility in women because of mechanical elements of the pelvis adhesion, and ectopic ovarian cysts, which can block the fallopian tubes, delay oocyte release, and disrupt the uterine environment for embryo implantation [19]. Infertility is caused by a complex interplay of factors, including the immune system, oxidative stress, and the endocrine. Some of these factors are oxidative stress, sex hormones, the neuro-endocrine axis, and their interplay of the immune system with endometrial cells [20].

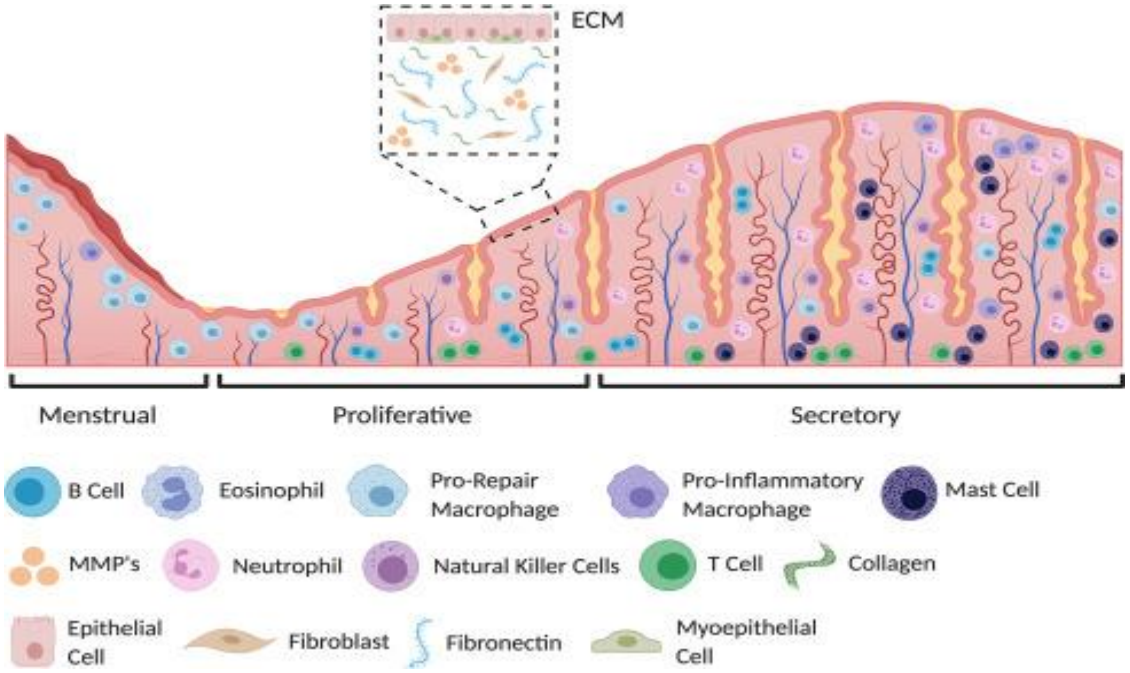


Fig 10. Overview of Endometrium [21].

The Endocrine System

- **"The hypothalamic-pituitary-ovarian (HPO) axis and related hormones:** In endometriosis, alterations were noted in the HPO axis that regulates the ovulation of the dominant follicle, the cyclic secretion of gonadotropins and steroid hormones and the fertilization and implantation sequence that ensues it.
- **Follicle-stimulating hormone (FSH) and luteinizing hormone (LH):** The release of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) is observed in the reproduction process as part of the functions of the pituitary gland travels towards the ovaries via blood. At that site, they collaborate to activate folliculogenesis, oocyte maturation, ovulation, granulosa cell increase, and aromatase manufacture [23].
- **Estrogen and estrogen receptors (ERs):** There is an estrogen-dependent pathology in endometriosis condition; the buildup of estrogens impacts the development of endometriotic lesions through the binding and activation of estrogens receptors, such as ERα and Erβ [24]. A high rate of implantation failure in patients with infertile ovarian endometriosis is caused by elevated estrogens levels and the upregulated expression of 17β-hydroxysteroid dehydrogenase 1, an enzyme essential for E2 synthesis, in the in-situ endometrium**"** [25]. Endometriotic tissue survival and inflammation are caused by the ERβ signaling system, which is driven by an overproduction of E2.
- **Progesterone and the progesterone receptor:** Endometrial stromal cells undergo decidualization at regular intervals,

and progesterone, which is secreted by the ovaries, controls this process and helps create an endometrial milieu that is favorable for blastocyst receptivity and embryo implantation. Infertility caused by endometriosis is believed to be caused by aberrant signaling that lowers oocyte quality, which includes an overproduction of progesterone during the follicular phase [26].

Stress hormones and the hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis has a role in stress regulation, depression, and anxiety, and dysfunction has been found in endometriosis patients [27]. Patients with endometriosis-related infertility had higher serum cortisol and prolactin levels, which was associated with a substantial link with infertility and difficulty with sexual intercourse [28].

Interaction between endometrial cells and the immune system

The distinct causal links between immune cells and endometriosis were established using using a two-sample Mendelian randomization approach; they detected some specific immune cell types that are involved in the development of various types of endometrioses [29]

- **Endometrial cells**
  a) **Epithelial cells and EMT:** Endometriosis pathogenesis are associated with EMT, a change in cell type from polarized epithelial cells to highly motile mesenchymal cells [30]. Exposure to persistent pollutants, such as plasticizers, has been associated with an uptick in endometriosis-related EMT formation, which in turn has contributed to the start and progression of the illness [31]. The world's plastic usage has also been on the rise. When mesothelial cells become abnormal and start acting like fibroblasts, a process known as MMT happens. This is a type II EMT. Several complications, including fibrosis of the peritoneum, It is possible to develop angiogenesis, implantation of an ectopic endometrium, due to the MMT and the development of cell adhesions as a result of peritoneal mesothelial cells, [32].
  b) **Dedecidualized stromal cells are prominent in endometriosis**, as are pro-inflammatory factors [33]. An upsurge in peritoneal macrophages can be explained by endometrial cells secreting IL-6 and monocyte chemoattractant protein (MCP)-1 [34]. At least in the early stages of endometriosis-associated infertility, MCP-1 plays an important role in regulating follicular development, “ovulation, luteal development and induction of an inflammatory state” intrafollicular [35].

Immunocytes Ectopic endometrial implants have the potential to perpetuate the disordered condition and hinder the ability to procreate [36] through causing chronic inflammation and inadequate immune surveillance. Infertility due to endometriosis is caused by cytokine activation, which is carried out by immune cells [37].

a) **Oxidative stress** chronic inflammation, even at a modest level, can cause oxidative stress. In female reproduction, reactive oxygen species (ROS) which are formed by immunocytes and cytokine in the milieu of follicular fluid are useful in two ways. Endometriosis patients had altered oxidative stress [38]. Ovarian reserve, oocyte, and embryo development can be negatively impacted by oxidative stress, which is caused by long-term and intense exposure to pro-oxide chemicals and antioxidant defenses. Significant fibrinogen oxidation and structural changes can occur in response to elevated systemic oxidative stress; these changes are linked to decreased fibrin polymerization and the resistance to plasmin induced lysis [39].
b) **Oxidative stress and mitochondrial function:** Infertility caused by endometriosis has oxidative stress as one of its pathophysiological components. Follicle fluid from endometriosis patients contains high concentrations of oxidative stress sensitive indicators such as myeloperoxidase and advanced oxidation protein products. The above markers slow down mitochondrial metabolism and spindle formation during meiosis in oocytes accelerating the process of follicular depletion, reducing oocyte quality and reducing the fertilization rate [40].
c) **Oxidative stress and dysregulated lipid metabolism:** The study identified 55 metabolites that were elevated and 67 metabolites that were downregulated. The process results in a decrease in the quantity of mature oocytes through cellular reactive oxidative stress, inhibition of cell multiplication, cell aging and death and regulation of MAPK-ERK1/2 pathway [41]. The senescence-related secretory phenotype factors (IL-1 0, MMP-9 and keratinocyte growth factor) are helpful indicators for assessing the quantity of mature oocytes and retrieved oocytes, and their upregulated expression can worsen endoplasmic reticulum stress.

Oxidative stress and iron toxicity: Endometriosis patients have abnormally high iron levels in their ovarian follicles, ectopic cyst fluid and peritoneal fluid due to the large number of lysed erythrocytes in the collected and refluxed menstrual blood [42]. Follicle, oocyte, sperm, and embryo cells are directly damaged when iron toxicity occurs in the context of transferrin deficiency and excess iron. This oxidative stress is induced by the most biologically potent ROS reaction is Fenton reaction which gives rise to superoxide anions and hydroxyl radicals [43]. The iron overload technique might involve several pathways of signaling that result in oocyte damage and embryotoxicity such as ferroptosis mediated by the nuclear receptor coactivator 4- dependent ferritinophagy [44], glutathione peroxidase 4-dependent downregulation [45], and heme oxygenase 1 overexpression [46]. **Diagnostic approaches and management of endometriosis related infertility**

Diagnostic approaches. The existing guidelines advocate a non-surgical diagnosis that depends on symptoms and the findings of physical examination and imaging as opposed to laparoscopic view of endometriosis lesions and histological confirmation, which was formerly the gold standard for diagnosis [47]. The realization that surgery is not a cure-all and comes with hazards has prompted this shift, as does the fact that relying on a surgical diagnosis might cause an unacceptable wait (up to 11 years) between the beginning of symptoms and the beginning of effective treatment [48]. Symptom variability, inadequate health practitioner and patient understanding of the illness, social normalization of women's discomfort, stigma associated with discussing gynecologic complaints, and other variables all contribute to a delay in diagnosis [49]. Medical professionals can help alleviate some of these issues by regularly enquiring about menstruation, endometriosis symptoms, and their effect on patients' quality of life. It is important to get the patient's permission before beginning and to take it slow so they may gauge their own tolerance at each stage. Regular check-ins are also necessary. Endometriomas and profound endometriosis can be nonsurgical diagnosed with imaging. Patients suspected of having endometriosis should have transvaginal ultrasonography as a first-line inquiry because it is a cheap and easily accessible diagnostic [50].

Management of endometriosis related approaches: The treatment of infertility caused by endometriosis is still controversial and fraught with difficulty. Endometriosis can cause infertility in several ways, but one of the most straightforward ways is by reducing ovarian reserve, among other things. Ovarian reserve is reduced for two reasons: endometriosis and surgery of endometriosis. ART is the best treatment in cases of infertility; medical/hormonal treatment must not be used except in an exceptional case in conjunction with it. Due to its ease of administration, intrauterine ultrasound (IUI) is the preferred first-line approach following surgical treatment for minimal to mild endometriosis. Patients who have severe endometriosis have the possibility of (IVF) [51].

Effects of endometriosis on ovarian function

Ovulation that occurs naturally may be disrupted if endometriosis is present [52]. Possible causes of decreased ovarian reserve include endometriosis and other anatomical modifications in the ovarian cortex [53]. Mechanical injury to the ovarian tissue, including the follicle, can occur when an increasing ovarian cyst is present. On the other hand, the cyst can compress the adjacent ovarian cortex, which disrupts vascularization and reduces blood circulation [54].

"Medical treatment options in infertile patients with endometriosis"

Treatment of endometriosis this may be accomplished by means of surgery or medicine. Pharmacological choices include GnRH agonists, aromatase inhibitors, oral contraceptives, and progestins. Inhibitors of ovarian function are the basis of these medicinal treatments. Medication used for this reason often causes problems with fertility or contraception, so it's not a good choice for treating endometriosis-related infertility and getting pregnant or having a baby [55].

Robotic surgery, laparoscopy, and laparotomy are three methods for executing surgical procedures. The laparoscopic technique is now the gold standard for diagnosing and removing endometriotic lesions because of its many benefits, such as a reduced risk of complications and a quick recovery time [56].

Effect of ovarian surgery on ovarian reserves- The risk of ovarian harm is present during endometriosis surgical procedures [57]. It is possible to injure healthy ovarian tissue during endometrioma removal using the stripping approach [58]. Follicle loss may occur because of removing too much ovarian tissue or the walls of ovarian cysts [59]. Vascular structures can be affected by further ovarian tissue injury, which can compromise circulation [60]. Ovarian function decreases one week after surgery due to inflammation, edema, vascular damage, and ischemia [61].

Effect of ovarian surgery on fertility- The rate of spontaneous conception was higher with operational laparoscopy compared to basic diagnostic laparoscopy when assessing the effect of fulguration of endometriotic implants in patients with mild endometriosis [62]. Laparoscopic surgery, which involves removing or ablating endometriotic lesions, may increase the rate of spontaneous pregnancies and live births in patients with minimal and mild endometriosis (ASRM I and II), as compared to expectant care [63].

Impact of Ovarian Endometriosis

Endometriosis is associated with poor pregnancy outcomes for several reasons. Issues with implantation owing to decreased endometrial receptivity, a decline in ovarian reserve, a small number of retrieved oocytes, and embryos of inferior quality are among them. Complications during pregnancy, such as stillbirth, early delivery, hypertension, and intrauterine growth restriction, are more common in women with endometriosis.

Mechanisms of Ovarian infertility in endometriosis- Hormonal alterations, Chronic Inflammation, TuboPeritoneal distortion during implantation, reduced ovarian reserve are the four parts that make up the links between endometriosis and infertility.

Chronic inflammation- Chronic inflammation is a hallmark of endometriosis [64]. The immune system normally removes refluxed endometrial tissue from the peritoneum; however, a tendency to endometrial cell proliferation and implantation may result from deregulation of this clearance process [65]. These cytokines include inflammatory IL-1, IL-6, MCP-1, and TNF-α, as well as angiogenic IL-8 and VEFG, which are made by macrophages [66].

Tuboperitoneal distortion- Adhesions throughout the fallopian tubes, ovary, as well as Douglas pouch are caused by endometriosis. Endometrioma-affected ovaries often have a strong adhesion to the fossa ovarica, which can hinder oocyte retrieval. Tubal motility can be reduced by adhesions on the tuboovarian junction. Distal tubal illness can be caused by these adhesions that are located on the tubal end. Hysterosalpingography is a simple and accurate way to diagnose distal tubal diseases, the most common of which are fimosis. Hydrosalpinx, a complete loss of function, can occur because of distal tubal disease progression.

Hormonal changes on implantation- The main pathophysiology underlying poor ovulation is the impaired synthesis of LH [67]. An elevated number of activated macrophages and the secretory products of these cells indicate a sterile low-grade inflammatory reaction in the peritoneal cavity, which is linked to endometriosis and the luteinized unruptured follicle syndrome [68]. Lower levels of LH are associated with endometriosis because of GnSAF, which is mainly produced by tiny follicles.

Decrease in ovarian reserve- - A decrease in ovarian reserve, specifically in cases of bilateral involvement, is a symptom of ovarian endometriosis [69]. With less reserve, oocyte and embryo quality would suffer, which might reduce the success rate of both natural conception and in vitro fertilization and intracytoplasmic sperm injection. Fewer preovulatory follicles, slower follicular growth, larger dominant follicles, and higher follicular estradiol concentrations are all symptoms of endometriosis [70]. Follicle fluid from these patients shows an imbalance of hormones, with less estrogens, testosterone, and progesterone and more activin [71].

Emerging Technology of Endometriosis Related Infertility

High intensities focused ultrasound (HIFU); Nanotechnology is the promising technology in treating endometriosis infertility. In addition, Assisted Reproductive Technology (ART) like IVF, ovarian cryopreservation remains an option for females suffering from endometriosis infertility.

HIFU: By concentrating the ultrasonic beam on a specific area, this treatment can generate a lesion in the tissue with a controlled burst of energy [72]. Necrosis of the target volume results from the spatial juxtaposition of many lesions produced by the HIFU beam. When dealing with localized prostate malignancies, high-intensity focused ultrasound (HIFU) is a typical treatment option [73].

Nanotechnology: Endometriosis has been greatly affected by the nanomaterial treatment strategy. Methods like controlled medication delivery, magnetic hyperthermia, NP-mediated photothermal therapy, and others fall under the umbrella term "nano therapies" used in the diagnosis and treatment of endometriosis [74].

Diagnosis: The intrinsic properties of certain NPs, especially those made of materials like gold or iron oxide, allow them to improve the contrast agents employed in optical or magnetic imaging [75].

Assisted Reproductive Technology (ART)

The recurrence rate was higher in the control group and the ART group among patients with advanced disease stages. In addition, recurrence occurred more quickly in patients who had pelvic pain during their initial endometriosis surgery [76]. For infertile women suffering with endometriosis, the best course of action was a combination of surgical removal and assisted reproductive technology (ART) [77]. The severity of the illness and the age of the patients determine the timing [78]. Since controlled ovarian stimulation for IVF/ICSI does not raise cumulative endometriosis recurrence rates, ART following surgery may be offered to infertile women with endometriosis [79].

Outcomes of ART in infertile patients

IUI- Couples with mild to moderate endometriosis and normal semen quality have been successfully implanted by intrauterine insemination (IUI), a less complex method than in vitro fertilization (IVF) [80]. As an alternative to IUI alone, IVF, or additional surgical therapy, controlled ovarian stimulation (with clomiphene citrate or gonadotropins) with IUI may be a reasonable treatment option for patients with surgically diagnosed and treated ASRM I or II endometriosis [81].

In- vitro fertilization- The results of in vitro fertilization (IVF) are negatively impacted by moderate to severe endometriosis. The ovarian response in in vitro fertilization cycles was not negatively affected by surgical removal of endometrioma, according to certain writers [82]. Finally, women experiencing infertility due to modest to mild endometriosis might seek surgical therapy followed by intrauterine insemination (IUI) with ovarian stimulation.

Other issues when treating infertile women

Risk of Ovarian cancer: Among reproductive-age women who had previously undergone ART treatment, there was no increased 5-year risk of cancer, according to a big population-based study conducted recently. Ovarian endometrioma and ovarian cancer with clear cell or endometrioid histology have been linked in numerous prospective and retrospective investigations [83]. Hence, the physician should treat patients with full awareness that endometrioma could be cancer or develop into cancer, regardless of how remote the chance of this being the case is.

Risk of Complications during Pregnancy: Complications during pregnancy or disruptions in the normal physiological development of the pregnancy might result from endometriosis. Intrauterine growth limitation, pre-eclampsia, and obstetric hemorrhages are all possible outcomes of placental insufficiency or placenta previa, both of which can be caused by delayed implantation. [84]. Endometriosis may be associated with an increased risk of miscarriage, placenta previa, premature delivery, and kids that are tiny for their gestational age, although epidemiological studies have shown conflicting results.

Disease Progression Risk during IVF Cycle: Endometriosis is an estrogen-based sickness: Consequently, during an IVF process, it is inclined toward the development of the sickness**.** dependent condition, some may wonder if regulated ovarian stimulation for assisted reproductive technology influences endometriosis recurrence or disease development. The cumulative recurrence rate of ART-treated patients was comparable to the control groups, and the natural course of endometriotic lesions was unaffected by gonadotropin treatment [85].

Risk of Contamination during IVF Cycle: Many substances found in endometriomas are believed to be harmful to oocytes, such as metalloproteinases, cytokines, free iron, and reactive oxygen species (ROS) [86]. It is important to prevent accidentally puncturing the endometrioma and to wash the oocyte immediately if contamination is detected because small-scale studies suggest that such contamination may affect the fertilization or pregnancy rates [87].

Psychological effects of endometriosis related infertility

Infertility associated with endometriosis can have severe psychological consequences for affected women, affecting their emotional stability, self-esteem, and social relationships. Endometriosis is usually characterized by chronic pain and uncertainty, which in turn create increased levels of anxiety and depression. Studies show that the emotional toll of infertility is similar to that of life-threatening diseases since the lack of ability to conceive can test a woman's identity and future. Frustration, helplessness, and social isolation are frequent feelings, particularly when confronted with serial treatment failures or intrusive medical interventions. Societal pressure to be a mother can add to these feelings, and guilt and self-blame can ensue. Women frequently complain of tense relationships with partners as a result of the emotional burden of infertility and the physical requirements of treatments. Moreover, the variability of endometriosis symptoms can interfere with daily life, impacting work, social functioning, and overall well-being.

The psychological effect does not stop the patient, affecting family life as well as social engagements. Infertile women suffering from endometriosis end up avoiding social meetings or those involving children or pregnancy news, perpetuating social isolation. Marital tension is also of notable concern, as couples go through the emotional and economic pressures of medical interventions. Partner, family, and doctor support largely helps to alleviate these effects. Psychological counseling and support groups have been found to enhance coping strategies, offering a secure environment to exchange experiences and alleviate emotional distress. Incorporating mental health care into fertility treatment is critical to address the psychological issues of endometriosis-related infertility, enabling women and their families to cope with the emotional nuances of the condition better

2. DISCUSSION

Infertility associated with endometriosis is caused by an intricate pathophysiologic interaction among immune dysregulation, oxidative stress, and hormonal disturbance. Peritoneal lesions produce cytokines like IL-6 and MCP-1, generating a pro-inflammatory environment that inhibits follicular growth and decreases luteal function—mechanisms pivotal to decreased fertility [88]. In parallel, increased reactive oxygen species (ROS) and decreased antioxidant defenses, such as glutathione and vitamins A, C, and E, have been shown in peritoneal and follicular fluids of patients with endometrial receptivity problems, resulting in mitochondrial impairment, DNA damage to oocytes, and reduced embryo quality [89]. There is also increasing evidence of estrogen-mediated macrophage activation in the peritoneal cavity that adds to oxidative damage and cytokine release through NF-κB signaling pathways. These results highlight the extent to which the synergistic interaction of hormonal, immunological, and oxidative stress pathways severely compromises reproductive potential in endometriosis in women with poor oocyte competence and adverse fertility prospects [90].

3. CONCLUSION

Endometriosis is a multifaceted, estrogen-dependent disease with far-reaching consequences for fertility and global quality of life in reproductive-age women. Conventional treatments, such as surgery and hormonal therapy, are ineffective in severe cases, prompting the application of assisted reproductive technologies such as IVF. Advances in imaging, ultrasound therapy, and nanomedicine are revolutionizing the therapeutic scene by providing non-invasive, targeted, and more potent forms of therapy. Endometriosis management is best achieved through a multidisciplinary strategy that harmonizes medical, surgical, and fertility-oriented treatment with care to emotional and ethical issues.

4. FUTURE ASPECTS

In the future, endometriosis treatment will be based on precision medicine with the convergence of molecular diagnostics and tailored treatment approaches. Nanotechnology and bioengineering will probably have increasing roles to play, with

improved drug delivery systems and innovative drug therapies able to target specific disease pathways with less toxicity. More studies are necessary to define the long-term safety and effectiveness of new therapies such as HIFU and nanoparticle-based treatments. In addition, increasing access to advanced fertility care and promoting ethical care among diverse populations will be key to ensuring equitable, patient-focused care. Multi-disciplinary partnerships among clinicians, researchers, and policy makers will be necessary to enhance early diagnosis, prevent recurrence, and optimize reproductive outcomes in women with endometriosis.

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