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Effect of a High Fat Diet on Ovary Morphology, Oocyte Quality, and In-Vitro Fertilization Rate

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Abstract: Obesity, largely driven by high-fat diet (HFD) consumption, is a significant global health concern that adversely impacts female reproductive health. This review explores the effect of HFD on ovarian morphology, oocyte quality and in vitro fertilisation (IVF) rates. Evidence shows that HFD exposure reduces primordial follicle reserves, increases follicular atresia, and induces lipotoxicity and mitochondrial dysfunction withing oocytes, leading to impaired maturation and fertilization potential. Additionally, HFD alters hypothalamic-pituitary-ovarian axis signalling, disrupts steroidogenesis, and promotes oxidative stress and chronic inflammation, collectively compromising fertility. IVF studies in both animal models and humans reveal that HFD-associated obesity lowers oocyte competence, fertilization rates and pregnancy success, despite sometimes unaffected embryo quality. Mechanistically, endocrine, endocrine and metabolic disturbances underlie these reproductive impairments. Understanding the pathways affected by HFD highlights the need for targeted nutritional and therapeutic interventions to mitigate fertility decline in obese female individuals.

Keywords: *Oocyte, Fertilization, Diet, Estrogen, Progesterone.*

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I. INTRODUCTION

Obesity is a chronic complex disease defined by excessive fat deposits that can impair health, i.e., it can lead to increased risk of type 2 diabetes, heart disease, certain cancers (endometrial, breast, or colon) (1) and can affect bone health and reproduction. The body mass index [BMI (kg/m^2)] is a surrogate marker of fatness. Obesity is a BMI ≥ 30 kg/m^2. In 2022, 2.5 billion adults aged 18 years and older were overweight [BMI ≥25 kg/m^2], including over 890 million adults who were living with obesity (2). Women are at a higher risk of obesity and this risk may increase with age. Though most obese women are not infertile, the negative impact of obesity on fecundity and fertility is well documented. Obese women have been shown to be three times more likely to suffer from infertility compared with women who have normal BMIs (3). Obesity reduces fertility, with a 2.7-fold increased risk of infertility in women with a BMI of >30 kg/m^2 and a 25-37% increased risk of miscarriage in pregnant women compared with normal-weight counterparts (4). Maternal BMI may also affect the risk of birth defects, such as spina bifida, and intellectual disabilities in offspring (5,6). It has been proposed that obesity impairs fertility through an effect upon the control of ovulation, oocyte development, embryo development, endometrial development, implantation and pregnancy loss(3). Jungheim et al demonstrated that apoptosis was specifically increased and oocytes were smaller in the preovulatory ovarian follicles of obese mice; reduction in oocyte maturity was also observed (7). In another study, Shah et al observed that obesity was associated with fewer normally fertilised oocytes, lower oestradiol levels, and lower pregnancy and live birth rates. Infertile women who require in vitro fertilisation (IVF) should be encouraged to maintain a healthy weight during treatment (8). Obesity has numerous causes and is multifactorial, yet many suffer from diet-induced obesity (DIO), in which a chronic positive energy balance leads to excess adiposity. Although overconsumption of any macronutrient can lead to excessive adiposity, diets high in fat are of interest. The definition of a high-fat diet (HFD) in humans varies from as low as 30% to as high as 75% of caloric intake (9,10).

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II. HIGH FAT DIET AND OVARY MORPHOLOGY

Several researches have examined the impact of HFD on ovarian morphology. In general, decrease in primordial follicle (11,12) and increase in follicular atresia (7,13,14) is observed when exposed to HFD. The effect on primary, secondary follicle, antral follicle and corpus luteum is not comprehensible as some studies observed an increase (11,12), some studies observed a decrease (15) and some studies observed no change (16) in number of various follicles. This variation may be caused due to- (a) species specific difference in follicle count; (b) wide range in fat content of the HFDs and control diets, (range- 45% to 60.9% & 4.8% to 18% fat); (c) different timespan of exposure (from 4 weeks to 24 weeks) etc. All the studies observed alteration after exposure to HFD in at least one follicular pool (7,11,12,14–16). HFD results in increased lipid deposition in the ovary and germinal vesicle oocytes, causing lipotoxic stress and apoptosis. Cumulus cells and oocytes from HFD-fed mice exhibit increased lipid content, decreased mitochondrial membrane potential, and elevated markers of endoplasmic reticulum stress (17). HFD leads to a decrease in oocyte maturation, with fewer oocytes reaching the metaphase II (MII) stage (12). These changes can potentially shorten the reproductive lifespan of female as depletion of primordial follicle reserve may lead to reduced reproductive capacity of females (18).

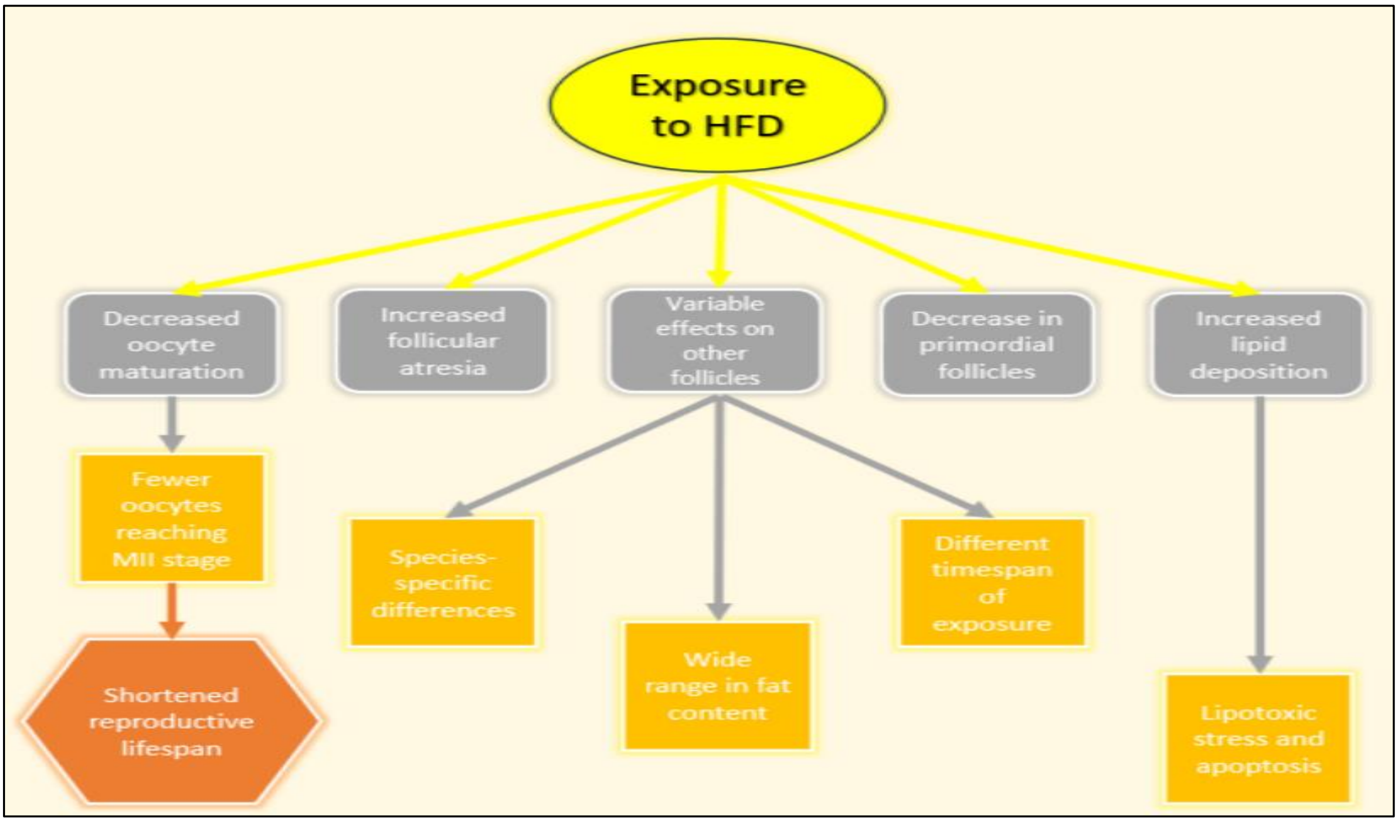

Fig 1 Effect of HFD on Ovarian Morphology: Consuming High Fat Diet Can Cause Increased Follicular Atresia, Increased Lipid Deposition, Decreased Oocyte Maturation, Decrease in Number of Primordial Follicles and These Effects Finally Leads to Shortened Reproductive Lifespan.

➢ *High Fat Diet and Oocyte Quality:*

In bisexual reproduction, female gametes provide the main energy and matter for zygote development, with follicular structures supporting their growth in mammals. During follicular development, germ cells undergo orderly arrest and restart of meiosis, completing nuclear and cytoplasmic maturation, while follicular cells proliferate, differentiate, and regulate germ cell development. A key feature of follicular initiation is oocyte growth, which determines embryo potential. Primordial follicles contain primary oocytes arrested in meiosis I. Upon reaching a certain size, oocytes gain the ability to resume meiosis, undergoing germinal vesicle breakdown (GVBD), chromosome separation, and first polar body extrusion. They then enter metaphase II until fertilization. However, oocytes from obese women and mice show poor quality, negatively affecting maturation (4).

- Mitochondria plays an important role in maturation, fertilization and embryonic development of oocytes (4). HFD-induced obesity impairs mitochondrial activity in oocytes, leading to reduced ATP production. It is important to note that mitochondria of mice oocytes had fewer cristae which were more disarrayed, decreased electron density of the matrix, increased swelling and a growing number of vacuoles and distribution of mitochondria from obese females was in an unorganized clumping pattern instead of being distributed evenly throughout the ooplasm in mitochondria from normal females (19). Various studies found that membrane

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potential of oocytes mitochondria from obese mice was lower than that of oocytes mitochondria from normal mice (4). HFD-induced obesity results in Increased mitochondrial ROS production which causes oxidative stress, leading to DNA damage and apoptosis (20). Apoptosis is specifically increased in the preovulatory ovarian follicle. Oocytes resulting from these follicles are smaller than controls and display decreased maturation (7). Oocytes from obese females producing more ROS had a higher mtDNA copy number than oocytes from lean mice (21).

- Lipid is deposited not only in adipose tissues, but also in non-adipose tissues, which leads to a high level of free fatty acids and triggering lipotoxicity characterized by ER stress, and ER stress links mitochondrial damage. Theres is evidence of ER stress in oocyte that cumulus-oocyte complexes (COCs) treated with ER stress inducer decreased cumulus cell expansion (a marker of oocyte quality) and led to poor pre-implantation development rates (4). HFD increases intracellular lipid droplets in oocytes, disrupting normal metabolic pathways and causing lipotoxic stress. Excess lipids interfere with fatty acid metabolism, leading to ER stress and apoptosis .Lipid-induced oxidative stress impairs the bidirectional communication between oocytes and cumulus cells, further compromising developmental competence (20). Overall, these findings suggest that ER stress plays a crucial role in cumulus-oocyte complex interactions as well as oocyte quality.

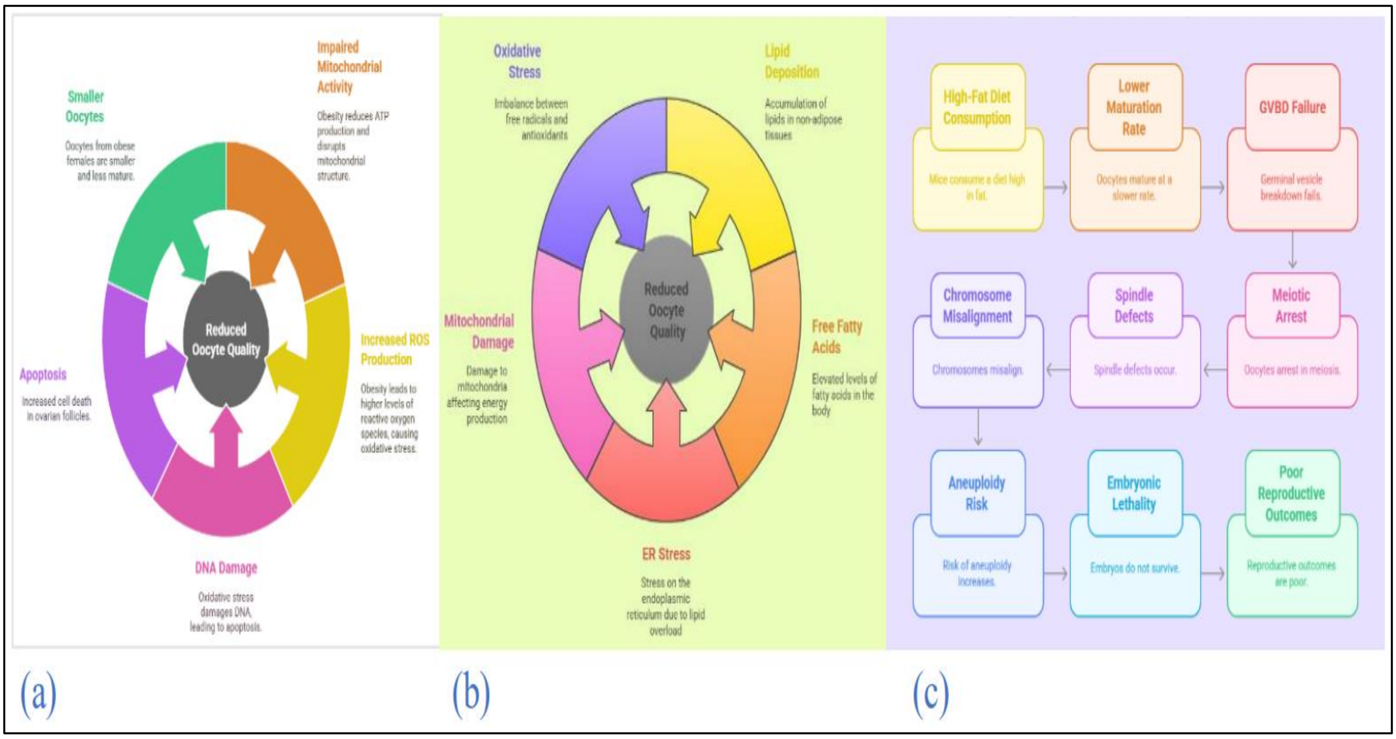

Fig 2 Consuming HFD Negatively Impacts Oocyte Quality Through Mitochondrial Dysfunction, Lipid Deposition and Interrupting Proper Formation Of COC: (A) HFD Results in Reduced ATP Production, Disarrayed Cristae Formation, Increased ROS Production in Mitochondria. (B) Increased Amount of Free Lipids Obtained from HFD Causes Lipotoxicity Which Triggers ER Stress Leading to Poor COC Expansion Resulting in Poor Oocyte Quality; (C) Maturation of GV Oocytes Also Gets Interrupted By HFD.

- The maturation rate of the GV oocytes from the HFD group was significantly lower than that of the control group. Oocytes from HFD-fed mice show increased rates of germinal vesicle breakdown (GVBD) failure, leading to meiotic arrest. Spindle defects and chromosome misalignment increase aneuploidy risk, which contributes to embryonic lethality and poor reproductive outcomes. Defective cytoplasmic and nuclear maturation results in lower fertilization rates and impaired embryonic development (20).

➢ *High Fat Diet and In-Vitro Fertilization Rate:*

- Maternal obesity is associated with poor outcomes across the reproductive spectrum including infertility, increased time to pregnancy, early pregnancy loss, foetal loss, congenital abnormalities and neonatal conditions (19).

- The study by Sohrabi et al. demonstrated that compared to the control group, the HFD group had a reduced number of MII oocytes collected from the fallopian tube. Reduction in number of fertilised oocytes that differentiated to the two-cell zygote stage was observed. There was also increased oocyte degeneration and an increased number of non-differentiated cells. These changes effects fertility (12).

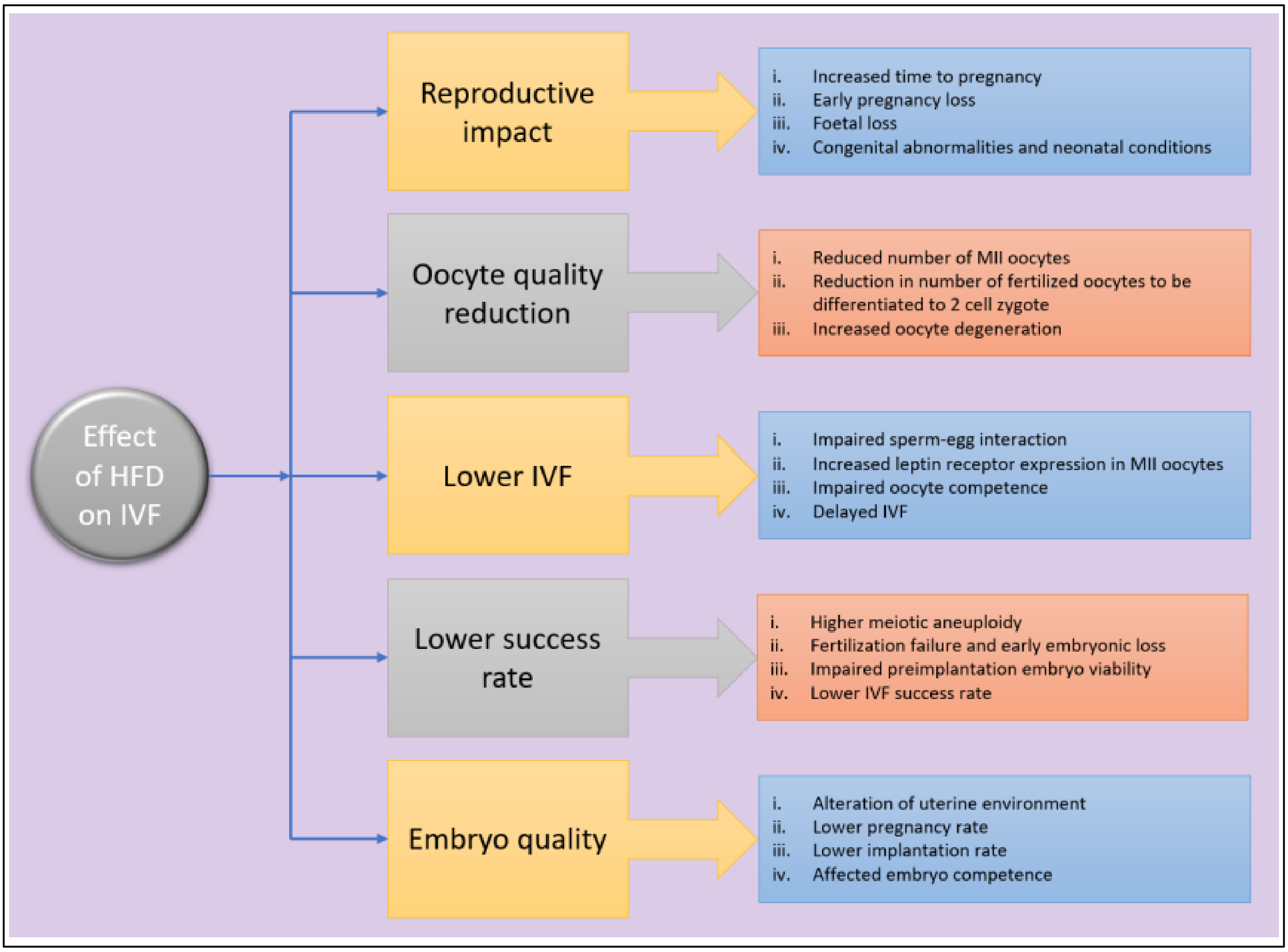

Fig 3 Effect of HFD on IVF Outcomes: Impaired Sperm-Egg Interaction, Increased Leptin Receptor Expression in Oocytes, Alteration of Uterine Environment, Increase in Time to Pregnancy, Congenital Abnormalities and Neonatal Conditions, Reduction in Number of Fertilized Oocytes Differentiated to Two Cell Zygote Stage Etc. And Eventually the Consumption of HFD Brings Down the Implantation Rate, Fertilization Rate and Overall, Success of the Procedure Performed.

- The same study observed a decrease in IVF rates among HFD-fed mice compared to controls, indicating that the diet-induced changes in oocyte quality negatively impact sperm-egg interaction and fertilization success. Increased leptin receptor expression in MII oocytes was noted, suggesting that leptin dysregulation due to obesity might impair oocyte competence (12). The maturation of obese mice in IVF was delayed (4).

- One study demonstrated that oocyte meiotic aneuploidy (abnormal chromosome number) was higher in HFD-fed mice, leading to fertilization failure and early embryonic loss (19). The study suggested that maternal metabolic disturbances impact preimplantation embryo viability, contributing to lower IVF success.

- Some IVF studies on obese women showed that embryo quality itself was not significantly affected, but implantation and pregnancy rates were lower, likely due to uterine environment alterations rather than intrinsic embryo defects (22). However, another study found that in younger women (<35 years), obesity was linked to poorer embryo utilization rates and lower mean embryo grades, suggesting that high BMI affects embryo competence as well (23).

III. MECHANISM OF ENDOCRINE DISRUPTION

Dietary habits play a crucial role in regulating female reproductive health, with excessive intake of saturated fats linked to endocrine dysfunction and infertility. The endocrine system controlling reproduction operates through complex feedback mechanism, primarily orchestrated by hypothalamic-pituitary-ovarian (HPO) axis. However, chronic exposure to a HFD disrupts this mechanism by altering gonadotropin secretion, impairing steroidogenesis and including metabolic dysregulation. The consequences of such disruptions include ovulatory disorders, reduced oocyte competence and impaired embryo implantation.

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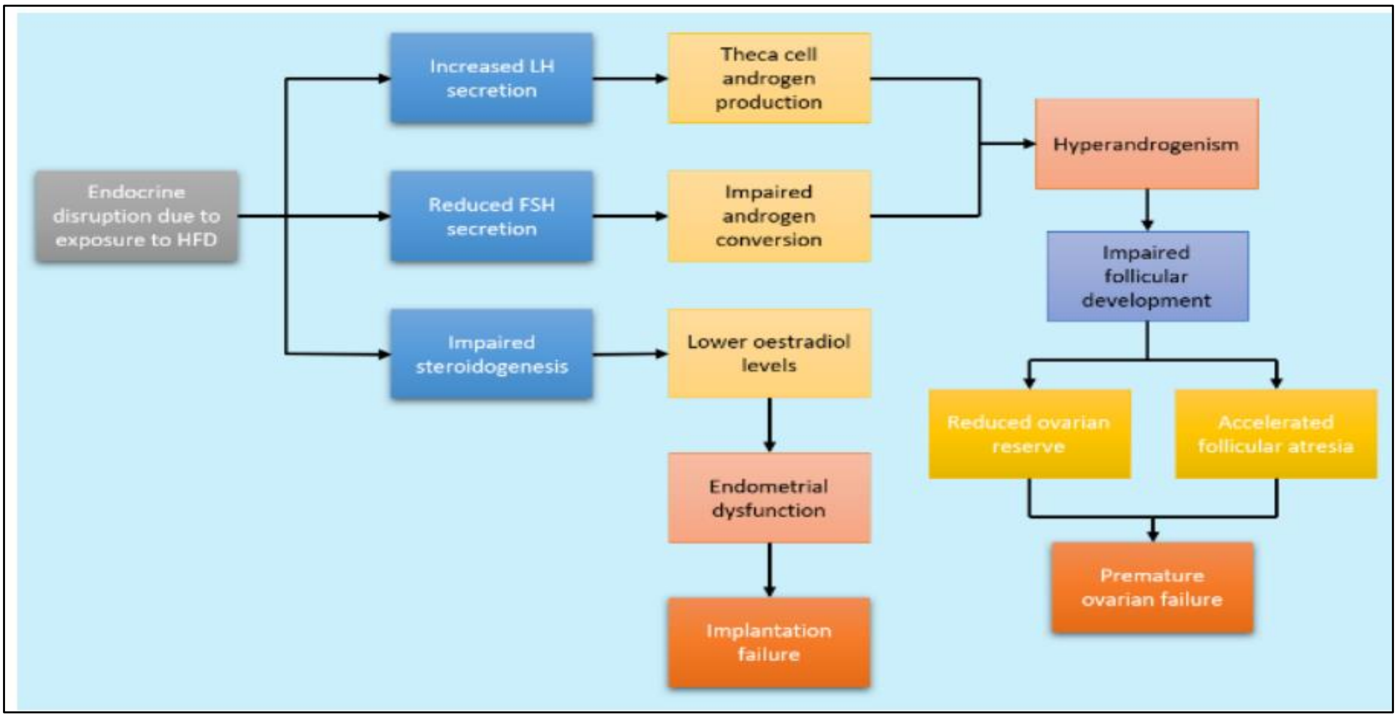

Fig 4 Schematic Diagram Shows How HFD Induces Ovarian Dysfunction and Steroidogenic Imbalance: HFD Causes Implantation Failure Through Endometrial Dysfunction and Premature Ovarian Failure Through Hyperandrogenism.

➢ *Disruption of the HPO Axis:*

The hypothalamus secretes GnRH, which regulates the release of FSH and LH from the anterior pituitary. These hormones drive ovarian follicle development and oestrogen production. However, a HDF alters GnRH pulsatility, primarily due to increased level of insulin, leptin and inflammatory cytokines, which overstimulate or desensitize GnRH neurons. This results in irregular menstrual and anovulation (20). Leptin, an adipokine secreted in excess under HFD conditions, initially enhance GnRH activity but later induces resistance, impairing gonadotropin release (1). Consequently, the pituitary gland exhibits an altered LH/FSH ratio, a condition commonly bserved in polycystic ovary syndrome (PCOS), which disrupts folliculogenesis and ovulatory cycles (17).

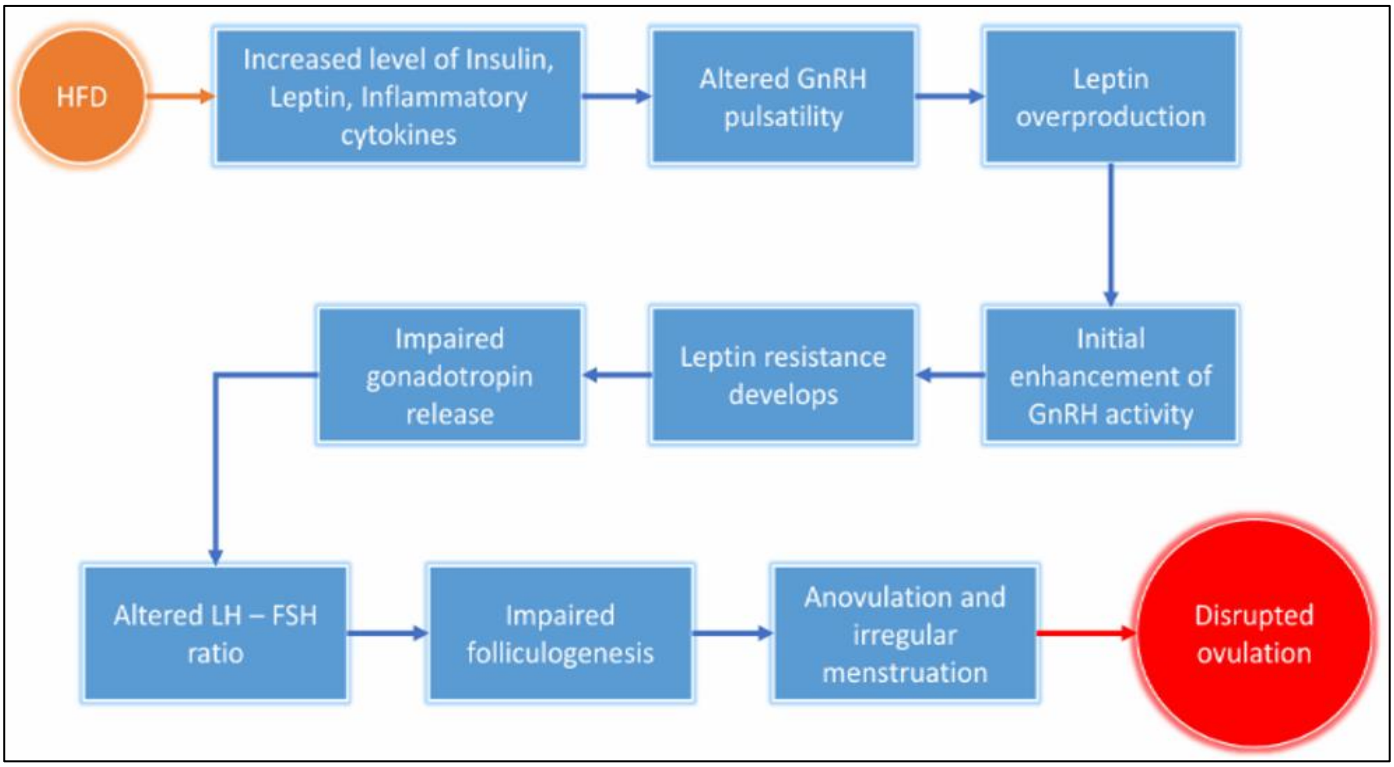

Fig 5 Effect of HFD on HPO Axis: Schematic Diagram Shows How Intake of HFD Eventually Leads to Disrupted Ovulation.

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➢ *Ovarian Dysfunction and Steroidogenic Imbalance:*

The ovarian response to gonadotropins is severely affected by HFD-induced endocrine disruption. Increased LH secretion stimulates theca cells to produce androgens, but a concurrent reduction in FSH prevents their conversion into oestrogen, leading to hyperandrogenism (22). This hormonal imbalance impairs follicular development, reducing ovarian reserve and accelerating follicular atresia (19). Studies in murine models show that HFD exposure leads to a decline in the number of primordial and antral follicles, culminating in premature ovarian failure (21). Furthermore, impaired steroidogenesis results in lower oestradiol levels, contributing to endometrial dysfunction and implantation failure (12).

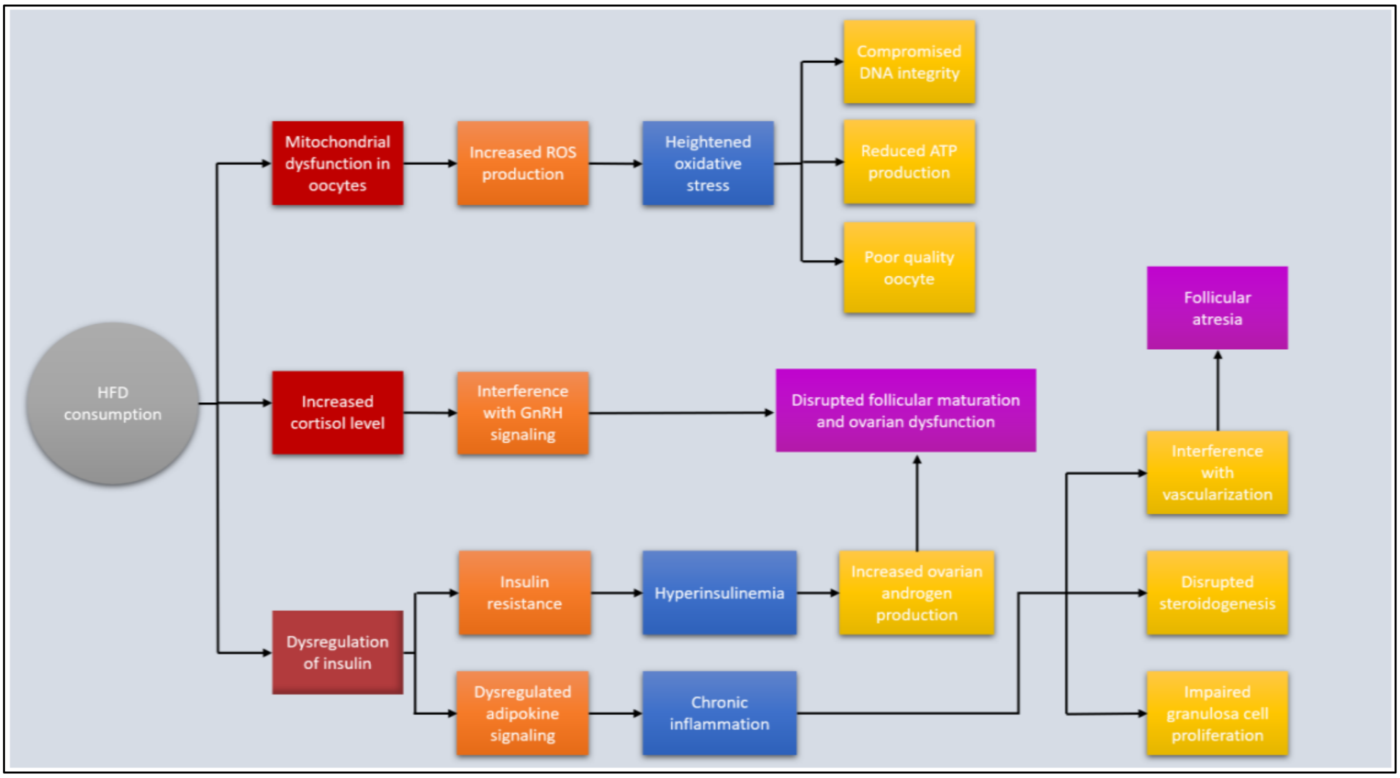

Fig 6 Schematic Diagram Showing How HFD Affects Reproductive Health Through Various Endocrine Pathways: HFD Induces Mitochondrial Dysfunction, Increased Cortisol Level and Dysregulation of Insulin. These Alterations Interfere with Gnrh Secretion, ROS Production, Steroidogenesis Etc. Increased ROS Production Leads to Heightened Oxidative Stress Which Causes Breakdown of DNA Of Germ Cells and Various Other Disturbances; Dysregulation of Insulin Causes Insulin Resistance and Hyperinsulinemia Followed by Increased Ovarian Androgen Production; Insulin Dysregulation Also Aids in Dysregulation of Adipokines Which Leads to Chronic Inflammation in Some Cases and Then Disruption in Steroidogenesis and Vascularization Occurs. All These Factors Finally Lead to Disrupted Follicular Maturation, Follicular Atresia and Ovarian Dysfunction.

➢ *Metabolic Dysregulation and Steroidogenic Imbalance:*

HFD-induced obesity is associated with insulin resistance, hyperinsulinemia and dysregulated adipokine signalling, all of which negatively impact ovarian function. Insulin resistance increasing the risk of ovulatory dysfunction (19). Additionally, HFD increases circulating cortisol levels, which interfere with GnRH secretion, compounding reproductive dysfunction (20). The metabolic stress imposed by excessive fat intake extends beyond the ovary, affecting mitochondrial function in oocytes. Mitochondrial dysfunction in oocyte leads to increased reactive oxygen species (ROS) production, which compromises DNA integrity, ATP production, and overall oocyte quality (21).

➢ *Oxidative Stress and Inflammation in the Ovarian Microenvironment:*

A major consequence of HFD consumption is heightened oxidative stress, which exacerbates reproductive impairment. Increased ROS production damages ovarian cells, leading to poor oocyte quality and early embryo loss (12). Chronic inflammation, characterized by elevated levels of tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), further impairs ovarian function by disrupting steroidogenesis and granulosa cell proliferation (20). Additionally, inflammatory mediators interfere with vascularization, reducing blood supply to grow follicles and leading to follicular atresia (1).

➢ *Impaired Pregnancy Outcomes and Assisted Reproductive Technologies:*

The reproductive consequences of HFD extend to pregnancy outcomes. Women with obesity exhibit lower implantation rates, higher miscarriage rates, and an increased incidence of gestational diabetes. Even in assisted reproductive technologies (ART), HFD-induced metabolic dysregulation negatively affects in vitro fertilization (IVF) rates, despite normal embryo quality (22). The altered uterine environment, rather than intrinsic embryo defects, is suggested to be the primary cause of poor pregnancy outcomes in obese women undergoing ART (12).

IV. SIGNALLING PATHWAYS INVOLVED IN THE DISRUPTION MECHANISM:

The intricate regulation of female reproductive function relies on a delicate balance of hormonal, metabolic, and cellular signalling pathways. Under conditions of metabolic stress, such as those induced by a high-fat diet (HFD), this balance is profoundly disturbed, leading to impaired ovarian physiology and subfertility. The molecular underpinnings of these disruptions involve a complex network of signalling cascades that respond to nutrient overload, oxidative stress, inflammation, and hormonal imbalances.

Key pathways implicated in mediating the deleterious effects of HFD on female reproduction include the PI3K/AKT/mTOR, which governs cellular metabolism and follicular development; the PERK-eIF2α–CHOP arm of the unfolded protein response (UPR), which responds to endoplasmic reticulum stress; the NF-κB pathway, a central mediator of inflammation; mTORC1 signalling, which integrates nutrient and energy signals; and the MAPK/JNK pathway, known for its role in cellular stress and apoptosis. Additionally, the JAK2/STAT3 pathway, particularly in the context of leptin resistance, critically links energy status with reproductive hormone regulation.

Together, these pathways orchestrate a multifaceted response to HFD-induced metabolic challenges, driving ovarian dysfunction through mechanisms such as inflammation, oxidative stress, apoptosis, and hormonal dysregulation. Understanding the roles and interactions of these signalling cascades is essential for unravelling the molecular basis of obesity-related reproductive impairment and for identifying potential therapeutic targets.

The following sections provide an in-depth review of each of these signalling pathways and their contributions to the disruption of female reproductive health in the context of a high-fat diet-

➢ *JAK2/STAT3 Signalling and Leptin Resistance:*

The JAK2/STAT3 signalling axis plays a fundamental role in the regulation of leptin-mediated communication between energy balance and reproductive function. Leptin, secreted by adipose tissue in proportion to fat mass, exerts its effects via binding to the long-form leptin receptor (Ob-Rb), initiating the phosphorylation of Janus kinase 2 (JAK2). This activation subsequently leads to the phosphorylation and nuclear translocation of signal transducer and activator of transcription 3 (STAT3), promoting transcription of downstream genes involved in metabolic and reproductive processes (24).

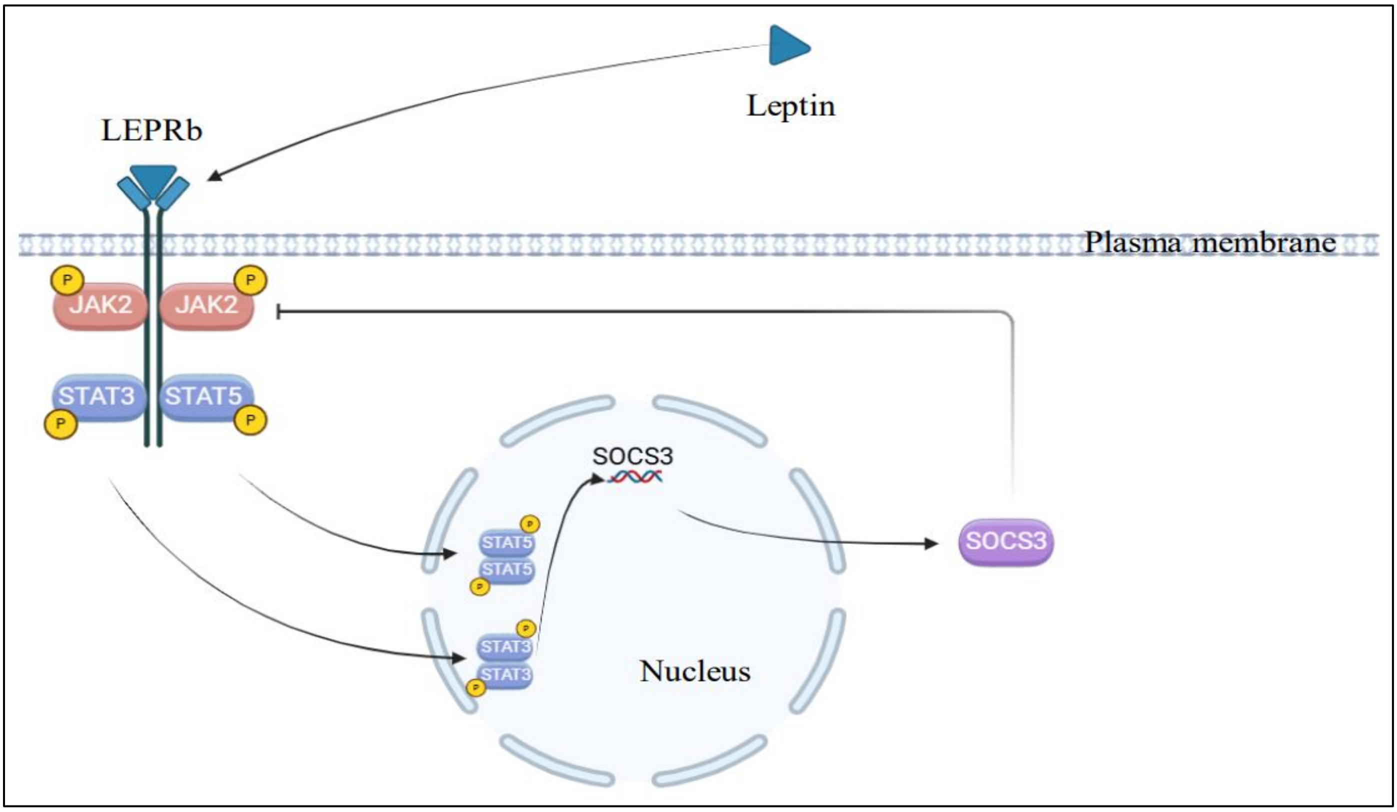

Fig 7 JAK2/STAT3 Pathway of Leptin Mediated Signalling Which Activates the Regulation of Other Downstream Signalling Cascades Involved in Metabolic and Reproductive Processes.

Under physiological conditions, leptin's signalling through JAK2/STAT3 is essential for maintaining normal reproductive function, including the regulation of gonadotropin-releasing hormone (GnRH) secretion and ovarian folliculogenesis. However, in the context of obesity or high-fat diet (HFD) consumption, the sustained

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hyperleptinemia leads to a state of leptin resistance, where leptin signalling is blunted despite elevated levels of the hormone. This resistance has been documented in both the central nervous system and peripheral tissues, such as the ovary (25).

Centrally, leptin resistance in the hypothalamus disrupts GnRH pulsatility and downregulates kisspeptin neurons, resulting in impaired luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release—both of which are critical for ovulation and corpus luteum formation. In parallel, leptin resistance in the ovary reduces granulosa and theca cell responsiveness to hormonal cues, suppresses steroidogenesis, and impairs oocyte maturation (25,26)

Notably, research in ovarian cell models and mouse models of diet-induced obesity demonstrates that defective leptin receptor signalling via the JAK2/STAT3 pathway compromises oocyte developmental competence. For instance, Kumar et al. showed that the disruption of leptin signalling via JAK2/STAT3 altered ovarian cell phenotype and gene expression, affecting not just metabolism but also inflammatory pathways. This cross-talk amplifies the inflammatory milieu already exacerbated by adiposity (24)

Moreover, high-fat diet feeding has been shown to reduce STAT3 phosphorylation in the ovary, indicating impaired leptin receptor signalling. This phenomenon was observed by Hohos et al. (2021), who reported ovulatory defects and dysregulated expression of endothelin-2—a gene downstream of leptin action. The resulting anovulation, follicular arrest, and poor oocyte quality are now recognized as hallmarks of obesity-related reproductive dysfunction.

Collectively, these findings underscore that leptin resistance, through inhibition of JAK2/STAT3 signalling, represents a key mechanistic link between excessive energy intake and infertility. It affects not only the hypothalamic regulation of gonadotropins but also direct ovarian function, leading to subfertility or infertility in obese females. Understanding this disrupted signalling cascade may offer therapeutic targets—such as leptin sensitizers or anti-inflammatory agents—to restore normal reproductive capacity in obese women.

- *PI3K/AKT/mTOR Pathway and Insulin Resistance:*

The PI3K/AKT/mTOR signalling pathway is a fundamental regulator of cellular growth, proliferation, and metabolism, and plays an essential role in ovarian follicle development, oocyte maturation, and steroid hormone production. Under physiological conditions, this pathway modulates the activation of primordial follicles and supports granulosa cell proliferation, ensuring proper folliculogenesis and fertility (27,28).

Obesity and metabolic stress induced by HFD lead to systemic insulin resistance and chronic low-grade inflammation, which impact ovarian tissue signalling. Insulin resistance disrupts normal PI3K/AKT pathway activation, causing compensatory hyperactivation in granulosa cells and oocytes. Such hyperactivation results in aberrant follicular development, including premature activation of primordial follicles and accelerated depletion of the ovarian reserve, a phenomenon associated with early reproductive aging (29).

Furthermore, excessive activation of mTOR, a downstream effector of AKT, promotes granulosa cell apoptosis via increased oxidative stress and mitochondrial dysfunction. These changes impair oocyte quality, reducing fertilization potential and embryo developmental competence. Experimental models demonstrate that mice fed an HFD exhibit elevated phosphorylation of AKT and mTOR in ovarian tissues, correlating with decreased ovulation rates and poor embryo quality. In vitro studies also confirm that inhibiting mTOR partially rescues oocyte maturation defects caused by lipid overload (30,31).

Furthermore, excessive activation of mTOR, a downstream effector of AKT, promotes granulosa cell apoptosis via increased oxidative stress and mitochondrial dysfunction. These changes impair oocyte quality, reducing fertilization potential and embryo developmental competence. Experimental models demonstrate that mice fed an HFD exhibit elevated phosphorylation of AKT and mTOR in ovarian tissues, correlating with decreased ovulation rates and poor embryo quality (Zhang et al., 2021). In vitro studies also confirm that inhibiting mTOR partially rescues oocyte maturation defects caused by lipid overload (32).

The PI3K/AKT/mTOR pathway also interacts with inflammatory signalling cascades such as NF-κB and stress response pathways, amplifying the deleterious ovarian microenvironment. This crosstalk exacerbates follicular atresia and disrupts steroidogenesis, further impairing reproductive function (Robker et al., 2011). Clinically, women with metabolic syndrome and obesity often exhibit altered PI3K/AKT/mTOR signalling, contributing to conditions like polycystic ovary syndrome (PCOS), characterized by anovulation and subfertility (33).

In summary, HFD-induced dysregulation of the PI3K/AKT/mTOR pathway leads to oxidative stress, apoptosis, and premature follicle depletion, critically impairing female fertility. Therapeutic strategies targeting this pathway may offer potential to mitigate reproductive damage in obese women.

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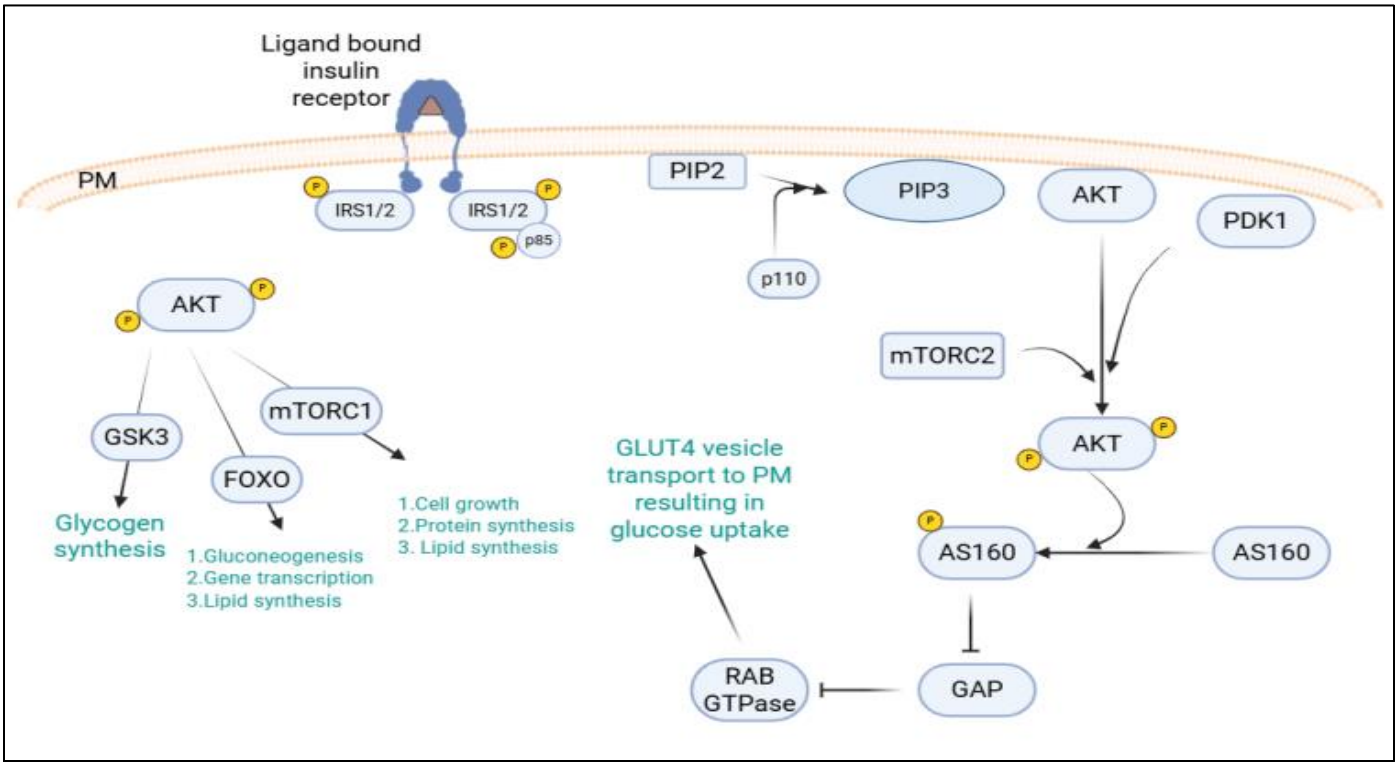

Fig 8 Insulin Mediated PI3K-AKT-Mtor Signalling Cascade Which Eventually Ensures Proper Folliculogenesis and Fertility Through the Activation of Primordial Follicle, Granulosa Cells Proliferation Etc.

➢ *PERK-eIF2α–CHOP / Unfolded Protein Response (UPR) Pathway:*

The PERK-eIF2α–CHOP signalling axis represents a crucial arm of the unfolded protein response (UPR), a cellular adaptive mechanism triggered by endoplasmic reticulum (ER) stress. ER stress arises when protein folding demand exceeds the ER capacity, leading to accumulation of misfolded or unfolded proteins, a situation exacerbated by metabolic insults such as a high-fat diet (HFD). In female reproductive tissues, prolonged ER stress activates apoptotic pathways via PERK-mediated phosphorylation of eIF2α and induction of the pro-apoptotic transcription factor CHOP, contributing to ovarian dysfunction (34).

The ovary is particularly vulnerable to ER stress due to the high protein synthesis load required for hormone production and oocyte maturation. Under HFD conditions, lipid accumulation and oxidative stress impair ER function in granulosa cells and oocytes. This triggers activation of the UPR sensors—PERK, IRE1, and ATF6—with PERK-eIF2α-CHOP playing a pivotal role in determining cell fate (35).

Upon ER stress, PERK autophosphorylates and phosphorylates eIF2α, leading to a global reduction in protein translation to alleviate the folding load. However, phosphorylation of eIF2α selectively promotes translation of ATF4, which induces CHOP expression. CHOP then promotes apoptosis by repressing anti-apoptotic Bcl-2 family proteins and enhancing oxidative stress, thereby tipping the balance toward cell death when ER stress is unresolved (36).

Studies on HFD-fed mouse models reveal significant upregulation of PERK phosphorylation, eIF2α phosphorylation, and CHOP expression in ovarian granulosa cells and oocytes, which correlates with increased apoptosis, follicular atresia, and decreased ovarian reserve. In vitro exposure of granulosa cells to saturated fatty acids such as palmitate recapitulates this ER stress response, highlighting the direct lipotoxic effect of HFD on ovarian cells. This ER stress-induced apoptotic signalling impairs oocyte quality and disrupts foliculogenesis, leading to compromised fertility outcomes including reduced fertilization rates and poor embryo development. Furthermore, persistent ER stress interacts with oxidative stress and inflammatory pathways, exacerbating ovarian damage in obese females (25,37).

Therapeutic interventions aimed at alleviating ER stress, such as chemical chaperones (e.g., 4-phenylbutyric acid) or antioxidants, have shown promise in improving granulosa cell survival and restoring ovarian function in HFD models. This suggests that modulation of the PERK-eIF2α–CHOP pathway might be a potential strategy to mitigate reproductive dysfunction associated with obesity and metabolic syndrome.

In conclusion, HFD-induced chronic ER stress activates the PERK-eIF2α–CHOP axis, triggering granulosa cell apoptosis and follicular degeneration. This pathway's disruption underlies impaired folliculogenesis and oocyte competence, contributing significantly to subfertility in obese females.

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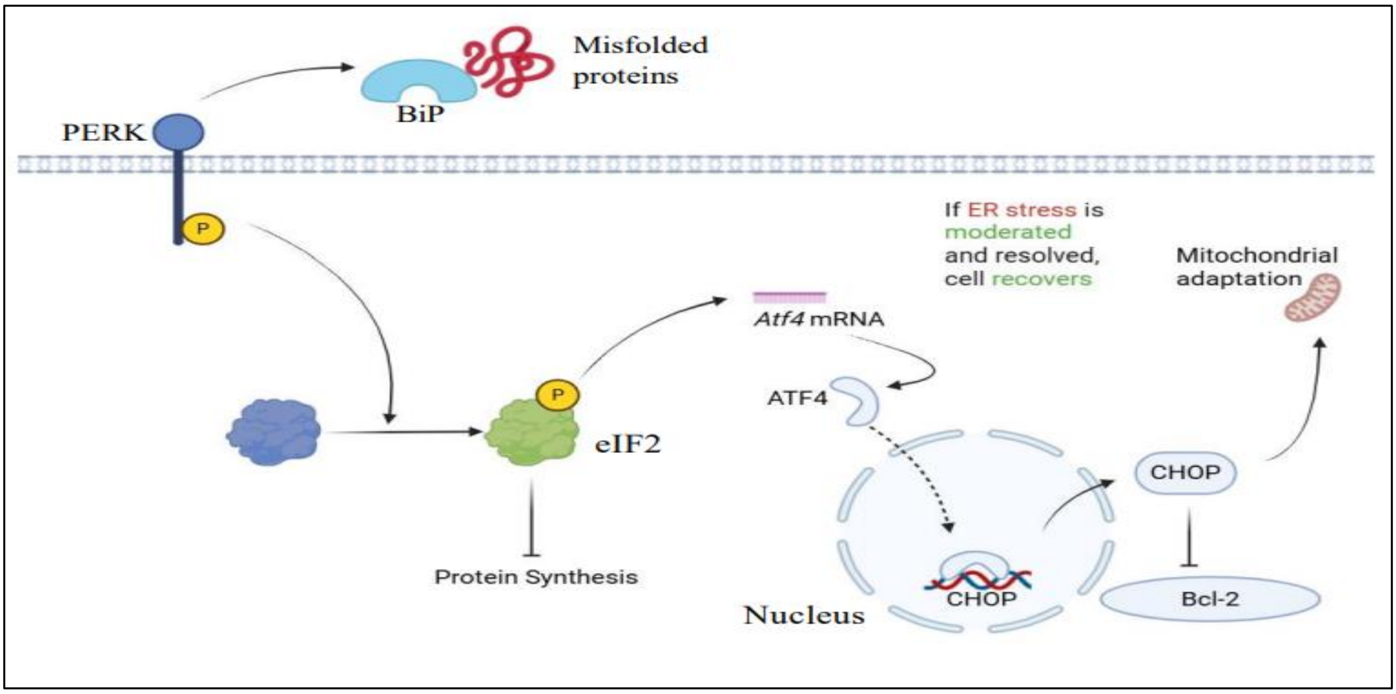

Fig 9 PERK-Eif2α–CHOP/ UPR Pathway Associated with Adaptations of Cell When Exposed to ER Stress. It Ensures Mitochondrial Adaptation and Helps Cell Recover from the Damages.

➢ *NF-κB Signalling Pathway:*

The nuclear factor kappa B (NF-κB) pathway is a master regulator of inflammation and immune responses, critically involved in maintaining tissue homeostasis. However, its aberrant activation is strongly implicated in metabolic disorders and associated complications, including female reproductive dysfunction under conditions of high-fat diet (HFD)–induced obesity. Chronic consumption of a HFD promotes systemic low-grade inflammation characterized by increased circulating pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). These inflammatory mediators activate the NF-κB pathway in ovarian tissues, particularly in granulosa cells and theca cells, as well as in hypothalamic regions that regulate reproductive hormones. Activation of NF-κB involves the phosphorylation and degradation of inhibitor IκB proteins, allowing NF-κB transcription factors to translocate into the nucleus and promote expression of pro-inflammatory genes, perpetuating inflammation and oxidative stress (38).

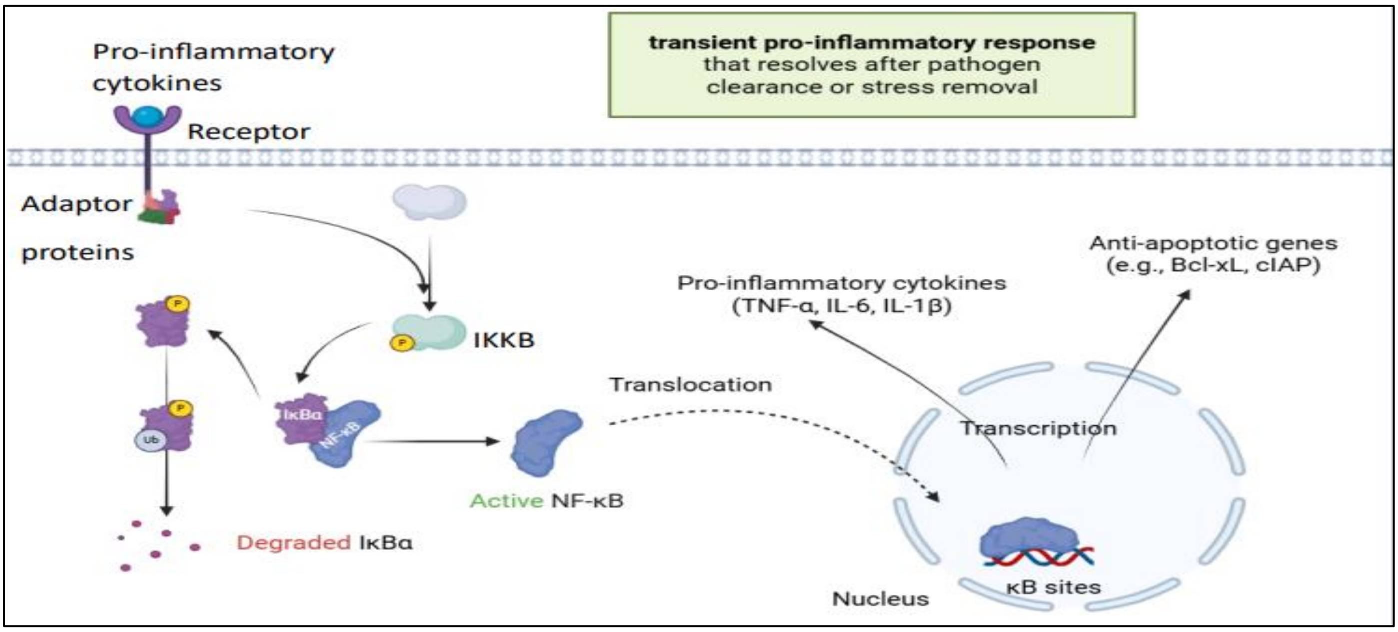

Fig 10 NF-Kb Signalling Pathway Activated Due To Increased Inflammatory Responses and the Downstream Signalling Enhances Anti-Apoptotic Gene Transcription and Induces Pro-Inflammatory Responses. The Responses Get Neutralized After Pathogen Clearance or Stress Removal.

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In the ovary, NF-κB-driven inflammation interferes with key processes such as folliculogenesis, steroidogenesis, and ovulation. Elevated ovarian inflammation leads to increased granulosa cell apoptosis, follicular atresia, and impaired steroid hormone biosynthesis, culminating in irregular estrous cycles and subfertility. Experimental models using mice fed with HFD demonstrate enhanced NF-κB activation in ovarian tissue concomitant with increased local levels of TNF-α and IL-6, linking inflammation to disrupted ovarian function (38,39).

Moreover, NF-κB activation exacerbates ovarian insulin resistance by downregulating insulin receptor substrate signalling, further impairing glucose uptake and metabolic function in ovarian cells (40). This metabolic disruption synergizes with inflammatory stress to compromise oocyte quality and developmental competence. Clinical studies corroborate these findings, showing that obese women with elevated inflammatory markers often experience anovulation and poor reproductive outcomes, suggesting a critical role for NF-κB-mediated inflammation in obesity-related infertility. Importantly, the NF-κB pathway also interfaces with other stress pathways activated by HFD, such as the unfolded protein response and oxidative stress pathways, forming a vicious cycle that amplifies ovarian dysfunction. Targeting NF-κB and associated inflammatory signalling has thus emerged as a potential therapeutic strategy. Pharmacological inhibitors of NF-κB or anti-inflammatory agents have demonstrated partial restoration of ovarian function and improved fertility parameters in HFD animal models (40,41).

In summary, HFD-induced activation of the NF-κB pathway promotes chronic ovarian inflammation and insulin resistance, which disrupt follicular development, steroidogenesis, and oocyte quality. This chronic inflammatory milieu is a central mediator of female reproductive impairment in obesity and metabolic syndrome (38).

- *MAPK/JNK Signalling Pathway:*

The Mitogen-Activated Protein Kinase (MAPK) pathway, particularly the c-Jun N-terminal kinase (JNK) branch, is a critical mediator of cellular stress responses, apoptosis, and inflammation. In ovarian physiology, MAPK/JNK signalling regulates granulosa cell function, oocyte maturation, and follicle development. However, under pathological conditions such as high-fat diet (HFD)-induced obesity, aberrant activation of MAPK/JNK contributes to ovarian dysfunction and subfertility. HFD promotes excessive accumulation of saturated fatty acids, which induces oxidative stress and lipotoxicity in ovarian cells. These metabolic insults activate stress-responsive kinases including JNK. Activation of JNK leads to phosphorylation of transcription factors such as c-Jun, which triggers expression of pro-apoptotic genes and inflammatory cytokines, resulting in granulosa cell apoptosis and follicular atresia (42).

Experimental studies using HFD-fed mouse models demonstrate increased phosphorylation of JNK in granulosa cells and oocytes, correlating with elevated levels of reactive oxygen species (ROS), mitochondrial dysfunction, and impaired oocyte competence. JNK activation disrupts granulosa cell proliferation and steroidogenesis by interfering with FSH signalling, which is vital for follicle growth and estrogen production. Moreover, the MAPK/JNK pathway interacts with other signalling cascades activated by HFD, including NF-κB and PERK-eIF2α UPR pathways, amplifying inflammatory and apoptotic responses within the ovary. This crosstalk creates a detrimental ovarian microenvironment, leading to reduced ovulation rates, poor oocyte quality, and compromised embryo development (43,44).

Pharmacological inhibition of JNK in HFD animal models has been shown to reduce granulosa cell apoptosis and oxidative damage, restoring some ovarian function and improving fertility parameters. These findings suggest that targeting MAPK/JNK signalling could be a promising approach to mitigate HFD-induced reproductive impairment. Clinically, women with obesity and metabolic syndrome exhibit elevated markers of JNK pathway activation in ovarian tissues, which correlates with conditions such as polycystic ovary syndrome (PCOS) and infertility. Thus, the MAPK/JNK pathway is a critical mediator linking metabolic stress to ovarian dysfunction in the context of a high-fat diet.

In conclusion, HFD-induced activation of the MAPK/JNK pathway promotes oxidative stress, apoptosis, and inflammation in ovarian cells, disrupting folliculogenesis and oocyte quality. This pathway's dysregulation plays a central role in obesity-associated female reproductive disorders (27).

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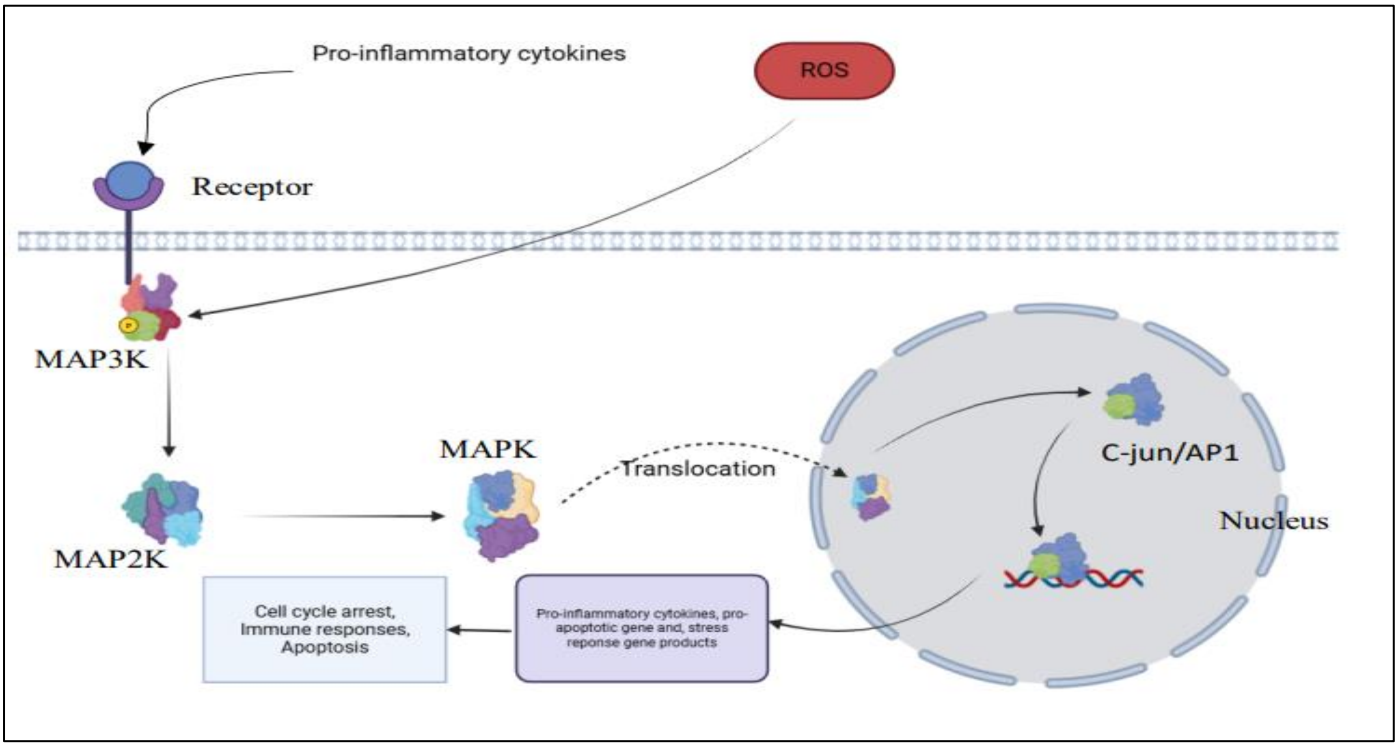

Fig 11 Activated by Growth Factors and Gonadotropins, The MAPK/JNK Signalling Pathway Regulates Granulosa Cell Proliferation, Oocyte Maturation, and Folliculogenesis, Thereby Maintaining Hormonal Balance, Supporting Ovulation, and Ensuring Optimal Female Reproductive Function and Fertility.

V. FUTURE DIRECTION OF RESEARCH

One promising research area is nutritional interventions to counteract HFD-induced oxidative stress and inflammation. While some studies suggest antioxidants improve ovarian function, the precise mechanism remain unclear (17). Investigating dietary modifications, such as optimizing fat composition, could help determine the best nutritional strategies to mitigate reproductive risks.

Another important avenue involves molecular mechanism of HFD-induced reproductive dysfunction. Epigenetic modifications in oocytes are suspected contributors to transgenerational infertility, but their exact pathways remain poorly understood (19). Research into mitochondrial dysfunction in oocytes and its reversibility is another crucial area (21).

The gut microbiota’s role in reproductive health is emerging as an important but understudied field. The gut microbiome regulates systemic inflammation and metabolic function, yet its connection to ovarian function remains to be fully explored. Preliminary evidences suggests that probiotic supplementation could improve metabolic and reproductive outcomes, but long-term human studies are lacking (17).

Lastly, more studies are needed to evaluate pharmacological interventions targeting metabolic pathways. Treatments that modulate insulin sensitivity, leptin signalling or inflammation could mitigate reproductive dysfunction in HFD-exposed individuals (1). However, their long-term safety, particularly in reproductive-age women, remains unclear (22).

VI. CONCLUSION

A high fat diet exerts profound detrimental effects on female reproductive health by disrupting ovarian morphology, compromising oocyte quality, and reducing fertilization and implantation success. Mechanistically, HFD induces lipotoxicity, mitochondrial dysfunction, oxidative stress, inflammation and endocrine dysregulation, ultimately impairing the hypothalamic-pituitary-ovarian axis and oocyte developmental competence. These alterations shorten the reproductive lifespan, lower IVF success rates, and increases the risk of pregnancy complications. While growing evidence supports these associations, future researches must focus on delineating the molecular mechanism involved, investigating the reversibility of HFD-induced damage, and developing targeted interventions, such as nutritional modulations, antioxidant therapies, and metabolic regulators. Addressing HFD-related reproductive dysfunction id critical for improving fertility outcomes in the context of the rising global obesity epidemic.

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