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Gestational Diabetes and Infertility

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Abstract

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications which affect the mother and offspring. In addition to adverse perinatal outcomes, it may lead to permanent health problems for the mother, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), while increasing the risk of future obesity, CVD, T2DM and GDM in the child. Approximately 15% of women seek fertility treatment. Over the last decade, it has come to attention that patients with an infertility history are more prone to having GDM during their pregnancies, and this review examines the relationship between GDM and infertility. The elevated estrogen, progesterone, leptin, placental lactogen and growth hormone are the main reasons for increased insulin resistance during pregnancy. Despite some confounding factors in the mechanism of GDM in patients with an infertility history, infertility treatment increases the risk, according to numerous studies. The obesity epidemic and associated disorders have become a significant public health concern worldwide. Lifestyle modification for weight loss before pregnancy is encouraged, but there is no strong evidence for improvement in perinatal results. GDM, infertility and infertility treatment have a potential risk of alteration in the embryo's environment and cause epigenetic reprogramming, which may be inherited to the next generation. The fertility treatment impacts the patient's and offspring's health. Patients should be informed about the risks so that they consent and get involved in the decision. Infertility treatment may be accepted as a reason for high-risk pregnancy, and patients can be screened for GDM in early pregnancy.

Keywords

Gestational Diabetes Mellitus, Infertility, Polycystic Ovary Syndrome (PCOS), *In Vitro* Fertilization (IVF), Assisted Reproduction Treatment (ART)

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common pregnancy

complications which affect the mother and offspring. Although it resolves after delivery, it may bring permanent health problems to the mother, such as type 2 diabetes (T2DM) and cardiovascular disease (CVD), while increasing the risk of future obesity, CVD, T2DM and GDM in the child [1] [2]. It is advised to screen the patients at 24 - 28 weeks of pregnancy. The high-risk patients are screened in the first trimester to avoid secondary results for gestational diabetes, such as preeclampsia and maternal-fetal adverse effects.

Over the last decade, it has come to attention that patients with an infertility history are more prone to having gestational diabetes during their pregnancies [3] [4] [5]. These studies suggest underlying issues in infertile patients might cause gestational diabetes. It is also suspected that the treatment may also cause insulin resistance. Interestingly, gestational diabetes or *in vitro* fertilization (IVF) treatment may be causing infertility in the next generation [6]. There is no study that specifically examines the relationship between gestational diabetes and infertility extensively. Therefore, this review will discuss various aspects and facets of GDM and infertility.

2. Gestational Diabetes Mellitus

Gestational diabetes mellitus is the presence of hyperglycemia in women who were not diagnosed with diabetes before. Approximately 16.5% of pregnancies are complicated by GDM, which has been rising continuously along with the obesity epidemic [7].

The pregnancy causes significant hormonal changes in the body to supply the rapidly growing fetus in utero with nutrients. Increased insulin resistance associated with increased insulin secretion is critical for providing the necessary supply during pregnancy. The elevated estrogen levels, progesterone, leptin, placental lactogen and growth hormone are the main reasons for increased insulin resistance during pregnancy. Insulin resistance causes a slight glucose elevation to enhance glucose transport, leading to hypertrophy and pancreatic beta-cell hyperplasia. GDM appears when the body cannot compensate for the hyperinsulinemic state due to the beta cell dysfunction. Even though GDM typically resolves after childbirth, as many as 70% of individuals who have had GDM may develop T2DM later in their lives.

Although there are different approaches to detecting GDM; the recommended approach for screening GDM is to administer a two-step oral glucose tolerance test to all pregnant women between 24 and 28 weeks of gestation. Early screening in the first trimester is crucial for the ones at risk, such as obesity, advanced maternal age, polycystic ovary syndrome (PCOS) and family and personal history of GDM and, due to severe effects on the fetus and the future life of the offspring if not managed well.

It is important to diagnose and manage GDM appropriately as it has many consequences for mother and child. The maternal risks include an increased incidence of caesarean delivery, preeclampsia, and polyhydramnios. The long-term

risks are related to recurrent GDM pregnancies and the substantial risk of developing T2DM and cardiovascular diseases.

The potential risks to the infant from GDM are stillbirth, macrosomia, shoulder dystocia, premature delivery, neonatal hypoglycemia, hyperbilirubinemia, and neonatal intensive care unit (NICU) admission. They also have a higher likelihood of developing obesity and diabetes mellitus during both childhood and adulthood.

Initially, most of the patients can be managed with adequate physical activity and lifestyle modifications. Self-monitoring of blood glucose, dietary modification and monitoring nutrition are parts of management for both GDM and maternal weight. Pharmacotherapy is required in 15% - 30% of the patients. Insulin is the safest profile during pregnancy; it is a large molecule and does not cross the placenta. Most of the oral hypoglycemic agents have not been adequately studied for possible long-term effects on offspring. However, some of them including metformin and glyburide might be an alternative for patients who refuse or cannot get insulin [8].

3. Infertility and Treatment

Women who cannot conceive after one year of unprotected sexual intercourse are defined as infertile. Approximately 12.7% of reproductive-age women seek infertility treatment each year. The workup for infertility is encouraged after six months if the patient is over 35. Even earlier, if there is a reason, such as older 40 years old, women with oligomenorrhea, amenorrhea, known or suspected tubal, peritoneal disease or male factor infertility. Infertility can be attributed to various causes, including ovulatory dysfunction, male infertility, and tubal disease, with approximately 15% of cases remaining unexplained. Women account for one-third of cases, while men account for another third, the remaining third involves a combination of factors. Ovulatory dysfunction is responsible for 25% of cases of infertility, with a majority of cases (about 70%) being associated with PCOS [9].

The medical treatment aims to stimulate ovaries and increase the chance of pregnancy. First-line treatment involves oral medications including clomiphene citrate which is a selective estrogen receptor modifier, and letrozole which is an aromatase inhibitor. Initially timed intercourse, then intrauterine insemination (IUI) may be used to achieve fertilization during ovulation. Administering HCG to induce ovulation can assist the timing of ovulation and enhance the chances of conception.

Injectable gonadotropin with IUI is the next level for which oral agents are unsuccessful. However, ovulation induction brings the risk of multiple pregnancies. Finally, assisted reproduction techniques (ART) is the choice for ovulatory problems if pregnancy is not yet achieved [9].

IVF is considered the first line treatment for couples with tubal problems, severe male factors, or needing a third party (donation cycles). IVF allows the

couples to complete their family by the help of a third person donating their gamete. The couples who need a third-party gamete due to azoospermia or ovarian insufficiency may choose to use donor gamete. It is also possible to use a surrogate mother if the female is not able to carry the pregnancy. IUI or ART cycles with donated sperm are among options for single women and same sex partners.

With an increased usage of ART in infertility management, there has been a concern regarding whether ART is linked to a higher likelihood of GDM [10]. Additional studies suggested that ART increases the likelihood of pregnancy-related maternal complications, including GDM, pregnancy-induced hypertension, abruption and caesarean delivery. Thus, all patients undergoing ART procedures should receive pre-conceptional counselling regarding the associated obstetric risks and consider ART pregnancy as a high-risk pregnancy [11] [12].

4. The Association between Diabetes and Infertility

Does infertility treatment cause GDM? Providing a simple answer to this question is difficult. We need to discuss confounding factors, effects of medications on metabolism, the different ART techniques used in infertility treatment, and other possible endocrinologic disorders underlying for infertile patients.

Glucose metabolism abnormalities and infertility may be more likely to occur in individuals who have advanced age, history of multiple pregnancies, high body mass index (BMI), a family history of diabetes, and who smoke [7] [9] [13] [14] [15]. Socioeconomic status affects the prevalence of fertility treatments but not the perinatal outcomes [16].

Due to the known maternofetal risks of multiple pregnancies, the main goal in infertility treatment is obtaining a single and healthy pregnancy. However, ovulation inductions and ART techniques may cause multiple pregnancies, which leads to an increase in the risk of morbidity and mortality [17]. High BMI is a common problem in infertile patients; they already have the risk for GDM when they get pregnant. Moreover, a study by Dayan *et al.* pointed to the supra-additive effects of high BMI and IVF on the risk of preeclampsia and gestational diabetes compared to spontaneous pregnancies [18].

In physiologic pregnancy, the increase in hormone levels is one of the reasons for having GDM. IVF treatment needs multiple injections of gonadotropins leading to multiple follicular growths resulting in significantly high estrogen levels. Additionally, high-dose progesterone is given to the body to support the luteal phase, help with embryo implantation and prevent miscarriage. Progesterone is also used to prevent preterm delivery as it has an anti-inflammatory effect. IVF treatment creates higher hormone levels for estrogen and progesterone, leading to a higher risk for GDM [19] [20].

Additionally, women with underlying endocrinologic disorders associated with glucose metabolism abnormalities are more prone to the risk of infertility and GDM, especially when combined with IVF treatment [7].

One of the most prevalent endocrine disorders among women who desire to conceive is PCOS. Irregular menses, hyperandrogenism that could cause hirsut-

ism, and polycystic ovaries characterize it. According to the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria, 15% - 20% of women are diagnosed with PCOS. The most common clinical presentation is oligomenorrhea, amenorrhea, hirsutism, and infertility. 50% - 70% of women with PCOS are affected by insulin resistance, leading to comorbidities including metabolic syndrome, hypertension, dyslipidemia, glucose intolerance, and diabetes. Lifestyle modifications and weight loss improve menstrual irregularities, symptoms of androgen excess, and infertility. The management of the patients depends on fertility desire. Menstrual irregularities and hirsutism can be managed with oral contraceptives. Spironolactone and finasteride are used to treat symptoms of androgen excess. For infertility, clomiphene and letrozole are first-line treatments. Gonadotropins, IUI and ART are the next steps. Metformin is advised to control insulin resistance and induce ovulation. Diagnosing and managing women with PCOS is essential to treat infertility appropriately and prevent future metabolic, endocrine, psychiatric, and cardiovascular complications [21] [22].

PCOS is a wide-spectrum disease which brings difficulty in both diagnosis and management. Patients with Insulin resistance, hyperandrogenism and obesity are commonly associated with difficulty getting pregnant, high-risk pregnancies and postpartum problems [23] [24]. The expected maternal complications are preeclampsia, polyhydramnios, preterm delivery, cesarean section, and operative deliveries, while fetal complications are macrosomia, shoulder dystocia, NICU admission, hypoglycemia, as well as obesity, diabetes, CVD in childhood and adult life.

A small proportion of PCOS patients may respond to gonadotropin treatment exaggeratedly, leading to ovarian hyperstimulation syndrome (OHSS). Haas *et al.* suggested that OHSS did not increase the risk for GDM [25]. However, Hu *et al.* showed increased thrombosis, GDM and neonatal NICU admission compared with matched IVF counterparts later [26]. OHSS is a potentially fatal complication of ovarian stimulation, causing very high estrogen levels and increased vascular permeability. To prevent any potential cumulative effects of HCG if the patient becomes pregnant, it is recommended to freeze all embryos and delay the embryo transfer.

The embryo is thawed and transferred to the uterine cavity along with the endometrium preparation, either in a natural cycle or an artificial cycle suppressed with estrogen and then supported with progesterone to mimic the natural cycle and create the appropriate hormonal environment for implantation. The hormonal treatment is maintained for up to 12 weeks to support the fetus until the placenta can grow and produce progesterone to continue the pregnancy. However, progesterone increases the risk of GDM if it is in the injectable form [20].

Miscarriage is more frequent in PCOS patients, and a study showed that patients with a history of early pregnancy loss show a higher risk of GDM [27]. A recent study found a statistically significant association between the fetal female

sex and the development of gestational diabetes mellitus in gravidae with polycystic ovarian syndrome [28].

Stern *et al.* published a paper on adverse pregnancy and birth outcomes with an underlying diagnosis with and without ART treatment in 2015. They analyzed the data of more than 300,000 women and found that GDM was increased for women with ovulation disorders. However, a high proportion of the population was diagnosed with PCOS, and this disorder, with multiple metabolic abnormalities, is likely a contributor to many of these adverse outcomes, including hypertension and diabetes mellitus [29].

Hu *et al.* in 2020 found no significant differences in perinatal outcomes, including GDM, between young patients with diminished ovarian reserve undergoing ART and those without diminished ovarian reserve [30].

4.1. Other Endocrinologic Disorders and Infertility Treatment

The human body is a highly intricate metabolic system, characterized by multiple inter-system communication pathways or cross-talks. Hence, ovaries are in continuous interaction with the other endocrine organs, while the central dysregulation of the hypothalamic-pituitary-gonadal axis, specifically at the GnRH neuron function level, is the final brain output for regulating reproduction [31] [32].

Moreover, reproduction results from a healthy organism, which means it is ready to invest in the next generation. If any functional or organic problem occurs at any part of the body, it directly or indirectly affects the reproductive system. Hyperprolactinemia, thyroid disorders, metabolic syndrome, obesity, diabetes, and congenital adrenal hyperplasia are some of them. Furthermore, gestational diabetes and infertility are closely related to other endocrinologic disorders.

Leptin is a satiety hormone secreted primarily by adipocytes in response to adequate fuel stores, acting on hypothalamus to decrease appetite and increase energy expenditure. Individuals who are obese often have elevated levels of leptin due to leptin resistance. Therefore, high leptin levels are associated with obesity. Leptin mediates the crosstalk between adipose tissue and reproduction. Placenta also secretes leptin during pregnancy to facilitate nutrient transport contributing to macrosomia in GDM [7] [33].

Obesity has become a significant public health concern all over the world. Abnormal leptin metabolism contributes to hyperinsulinemia, hyperlipidemia, hyperleptinemia, and chronic inflammation. Obese people are more likely to have cardiovascular disease, diabetes and reproductive disorders. Moreover, infertility treatment adds to the inflammatory state of individuals with metabolic syndrome (MetS) [19]. Having MetS in the presence of obesity was associated with GDM, lower rate of live birth and macrosomia in women with PCOS receiving ovulation induction in a study by Arya *et al.* [34].

A recent study illustrated the independent association between thyroid autoimmunity and adverse pregnancy outcomes, including pregnancy induced

hypertension (PIH) and GDM [35]. Thyroid autoimmunity (TAI) and thyroid dysfunction are prevalent in women of reproductive age and have independently been associated with adverse fertility and pregnancy outcomes, in the case of spontaneous conception or after ART. It is recommended that women who are trying to conceive and experiencing infertility undergo screening for TSH and TPO-abs [36].

A significant portion of the population experiences vitamin D deficiency, making it a prevalent condition. It has become increasingly concerning over the last two decades with many unknowns. Numerous studies show a close relationship between fertility and pregnancy outcomes. Lack of vitamin D is associated with infertility and adverse pregnancy outcomes, including GDM and PIH [37]. Thalassemia, among other disorders, is a recessively inherited hemoglobin disorder characterized by repetitive transfusions and iron accumulation, which involves multiple endocrine systems leading to infertility and diabetes. Preexisting diabetes and ART are associated with an increased risk for maternal and neonatal complications [38]. Congenital Adrenal Hyperplasia (CAH) patients, and SLE patients also commonly need fertility treatments, and they are more susceptible to gestational diabetes mellitus as they undergo ART treatment [39] [40].

4.2. Assisted Reproductive Technology and Gestational Diabetes

Assisted reproductive technology has been increasingly used over the last decades. Many studies show an increase in GDM in patients undergoing ART treatment. However, every patient is different. It is individualized according to the patient's needs and the availability of the techniques. Intracytoplasmic injections, freezing and vitrifying oocyte, sperm and embryos, selection techniques of sperms, and donation cycles increase the success rate of IVF [9]. Many studies are looking into different types of treatments to reveal the possible effects on perinatal outcomes of ART treatments.

The IVF treatment started with conventional fertilization in the beginning. Over time, intracytoplasmic sperm injection (ICSI) gained prominence in IVF treatments due to its higher fertilization rates, particularly in cases related to male factor infertility, surpassing conventional fertilization as the preferred method. The studies are controversial. A study in 2014 found a significant increase in PIH in the IVF-ICSI group but no difference in GDM [41]. Another study by Liu *et al.* in 2020 on obstetric and perinatal outcomes of intracytoplasmic sperm injection versus conventional *in vitro* fertilization in couples with nonsevere male infertility found no difference between groups [42], while a more recent one by Hu *et al.* showed an increased risk for GDM but no difference in patients with male infertility [43].

High-quality sperm selection is essential to increase the success rate, especially in male factor infertility cases. Magnetic-activated cell sorting (MACS) technology allows the user to choose the best sperm to inject in the egg. A randomized controlled trial comparing the effects of MACS and conventional swim up me-

thods on obstetric and perinatal outcomes showed no difference between groups [44].

In vitro maturation was implemented after the conventional method. As it does not involve controlled ovarian stimulation, it is mainly indicated in patients with a high risk of ovarian hyperstimulation syndrome, particularly in patients with PCOS. However, there are concerns over the developmental potential of the *in-vitro*-culture of immature oocytes and its impact on children's health. A systematic review and meta-analysis on maternal and neonatal outcomes and children's development after medically assisted reproduction with *in-vitro* matured oocytes showed no difference in GDM frequency between *in vitro* maturation (IVM) and controlled ovarian stimulation (COS). However, hypertensive disorders in singleton pregnancies of women with PCOS were significantly more frequent after IVM compared to COS [45].

Although double embryo transfer (DET) increases the chance of pregnancy, single embryo transfer is preferred to avoid the severe complications of twin pregnancy. While some twin pregnancies are reduced spontaneously, selective fetal reduction (SEFR) is also an option to decrease the risks. Compared to single embryo transfer (SET), the pregnancies with SEFR and spontaneous fetal reduction (SPFR) had a higher rate of GDM, and other pregnancy related adverse outcomes. It is recommended that DET with subsequent fetal reduction should only be considered a rescue method for multiple pregnancy patients with potential complications, and SET is more advisable [46]. Another study by Márton *et al.* showed vanishing twin pregnancies after IVF had a worse perinatal outcome and higher rate of GDM as compared with those of their spontaneously conceived counterparts [47].

Frozen embryo transfer (FET) is commonly preferred in ART cycles. Studies support that FET is more successful than fresh embryo transfer in general. Freezing all embryos is a good strategy to avoid the risk of OHSS in PCOS patients. Moreover, freezing the remaining embryos after transferring the selected one, helps to keep others for the next attempt whenever needed. The studies, including a meta-analysis comparing frozen and fresh embryo transfer, found no difference in GDM [48] [49] [50]. FET can be along with the natural cycle or hormone replacement treatment (HRT) cycle supporting the pregnancy with estrogen and progesterone in oral, vaginal, rectal, or injectable forms. According to a study by Lin *et al.* HRT is not a significant risk factor for GDM, gestational hypertension, preeclampsia, preterm delivery, small for gestational age (SGA) and large for gestational age (LGA) [51]. However, the injectable progesterone used in FET was a risk for increased rate of GDM [20].

The preimplantation genetic test is indicated in recurrent failure in IVF treatment and in couples with a genetic disease. Blastocyst-stage embryo biopsy has been a well-established and relatively safe method for this purpose for a considerable period of time. The studies on embryo biopsy for the results for adverse maternal-fetal outcomes have found no significant difference in sex ratio or the

risks of hypertensive disorders in pregnancy, diabetes in pregnancy, placenta previa, preterm premature rupture of membranes, low birth weight, very low birth weight, macrosomia, SGA, LGA or congenital defects [52] [53] [54].

Oocyte donation might be a choice for poor responders with poor oocyte quality and ovarian insufficiency. While a study with twin pregnancies with donated oocytes showed no difference in perinatal outcomes [55], other studies supported the increased risk for GDM in oocyte donation pregnancies [56] [57].

Surrogate pregnancies are also a risk factor for adverse perinatal outcomes, including maternal gestational diabetes and hypertension, compared with those conceived spontaneously and carried by the same woman. Data suggest that assisted reproductive procedures may affect embryo quality [58].

Endometriosis is a common peritoneal factor in infertility that frequently needs ART treatment. Endometriosis patients and those undergoing ART treatment did not show a significant difference in diabetes or gestational diabetes mellitus (GDM) risk [59] [60].

There is limited data for poor oocyte quality. A study with a small sample size by Akamine *et al.* found no difference for GDM [61]. Unexplained infertility has no specific adverse pregnancy outcome in singleton pregnancies after ART [62].

5. Management of GDM and Infertility

5.1. Prevention

Given that high body mass index (BMI) is a significant risk factor for GDM in patients undergoing infertility treatment. Some studies have been designed to illustrate the effect of lifestyle changes prior to pregnancy for infertile women. While acknowledging that a decrease in BMI in obese infertile women during the periconceptional period may potentially reduce the rate of adverse perinatal outcomes, the available evidence may not be sufficient to establish the clear benefits of weight loss. Although lifestyle modifications are recommended, the available evidence supporting their effectiveness is of low quality, highlighting the need for additional research [63] [64] [65].

A clinical study of PCOS patients treated for infertility showed that PCOS patients with hyperandrogenic phenotypes are more prone to GDM [24]. Supporting this result, Li *et al.* showed that patients with PCOS are more likely to develop GDM, PIH, and premature delivery. And pretreatment with ethinylestradiol/cyproterone acetate EE/CPA was associated with a lower risk of GDM, PIH, and premature delivery in this retrospective study [66].

A randomized, double-blinded, controlled study suggested that myo-inositol can be used as a supplement to prevent GDM in overweight women [67].

Vitamin D metabolism is closely related to fertility and gestational diabetes and commonly deficient in women. Supplying vitamin D improves fasting blood glucose. However, insufficient scientific evidence exists for vitamin D supplementation/treatment during pregnancy. So well-designed, prospective clinical intervention trials with sufficient patient numbers are necessary [68].

According to guidelines, routine screening between 24 and 28 weeks of gestation is recommended for GDM, while early screening is needed if there are risk factors [8]. Women who undergo fertility treatments should be considered high-risk for developing gestational diabetes [69], and early screening should be recommended if they have high fasting blood sugar levels (≥84.5 mg/dl) in the first trimester of pregnancy and a pre-pregnancy BMI of ≥25.4 kg/m^2. The combination of BMI and fasting blood sugar levels can provide a better prediction of gestational diabetes, and high-quality prenatal care should be provided to these patients [70].

5.2. Treatment

Pharmacotherapy, including the use of insulin and oral medications, is recommended for managing hyperglycemia in patients with gestational diabetes mellitus (GDM) who are unable to achieve adequate blood glucose control through dietary modification and physical activity. Insulin is the safest first-line therapy as it does not cross the placenta. Metformin and glyburide may be the choice for patients who cannot use or refuse to use insulin. As glyburide is shown to be associated with neonatal hypoglycemia and higher birth weight, metformin is preferred when compared with glyburide.

Metformin has been more popular recently to regulate glucose metabolism, decrease insulin resistance, and control hyperandrogenemia in PCOS patients, which helps regulate periods and achieve ovulation spontaneously. Metformin is commonly prescribed to patients with PCOS who are undergoing ART to improve success rates and reduce the risk of miscarriage during early pregnancy. While metformin has been shown to reduce the risk of OHSS in patients undergoing ART, it remains unclear whether metformin has any significant impact on the live birth rate in these patients [71].

However, there might be some adverse effects on the fetus. Nayak *et al.* shed that metformin affects the developmental competence of cleavage-stage embryos [72]. Another study by Faure *et al.* suggests intrauterine exposure to metformin reduces the fertility of male offspring in adulthood [73].

Myo-inositol is a natural compound involved in many biological pathways. It is well-tolerated and effective in treating PCOS and GDM. It regulates insulin and androgens [74]. It can also prevent the onset of neural tube defects. Due to safety and efficiency, myo-inositol is a treatment that may substitute several pharmaceuticals, which are contraindicated in pregnancy [75]. SGLT2 treatment has been investigated as an alternative to PCOS. However, it has not yet been shown to be safe in pregnancy [76].

Bariatric surgery is also an alternative for morbid obese PCOS patients who do not benefit from other treatments. Pregnancy and fertility rates in very obese women with PCOS increase after bariatric surgery. While bariatric surgery reduces the risk of preeclampsia and gestational diabetes, there is an increased risk of small for gestational age and a possible increased risk of stillborn or neonatal death [77] [78].

Furthermore, we expect to see targeted therapies using nanoparticles in a reproductive setting which allows safe and directed therapy reducing the risk for the fetus in future. Pre-clinical research in the development of therapeutic nanoparticle delivery is being undertaken in many fields of reproductive medicine [79].

6. Fetal Programming

In IVF treatment, injectable gonadotropins cause high estradiol levels and elevated vascular endothelial growth factor levels. The significant alterations in the environment of gametes and embryos during oocyte retrieval and embryo culture may promote epigenetic changes such as DNA methylation and histone modification of chromatin that lead to changes in gene expression and phenotypic characteristics, adverse perinatal outcomes and long-term health [80].

Abnormal hormonal traits, associated with hyperandrogenism and LH excess, may be observed as early as two months of age in daughters of women with PCOS, suggesting the potential for lifestyle or therapeutic interventions before and during pregnancy [81].

Gestational Diabetes also alters the intrauterine environment and causes epigenetic reprogramming in the fetal ovary, predisposing the offspring to ovarian dysfunction and subfertility in adult life [82]. Mao *et al.* showed intrauterine and postnatal exposure to high fat, high sucrose diet suppressed testis apoptosis and reduced sperm count in animals [83]. Another study showed that GDM changes the metabolomes of human colostrum [84], which may be a continuation of the effect on the offspring. Due to the strong association between GDM and offspring obesity, reproductive dysfunction is a concern for men and women whose mothers experienced maternal hyperglycemia. There is a need for human cohort studies to establish a link between maternal health and the long-term reproductive health of offspring, specifically regarding those born from pregnancies complicated by GDM, with a focus on potential sex-specific differences [85].

7. Conclusions

An association between GDM and infertility has been identified, with several studies indicating that infertility treatment can elevate the risk of GDM. However, it is important to note that there may be other factors that can influence these findings. GDM is a serious complication of pregnancy that can lead to increased morbidity and mortality for both the mother and the child, both during the pregnancy and later in life. Additionally, all of these factors—GDM, infertility, and infertility treatment—have the potential to modify the environment of the developing fetus and result in epigenetic changes that could be inherited by subsequent generations.

In particular, the fertility treatment has an impact on the patient's and offspring's health. Patients should be informed about the risks so that they consent and get involved in the decision. Additionally, infertility treatment may be accepted as a

reason for high-risk pregnancy, and patients can be screened for GDM in early pregnancy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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