



Metabolic Syndrome and Infertility in Women

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Abstract

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women and it affects approximately 5%-8% of premenopausal women. Metabolic syndrome has been reported in the reproductive literature to fall under a cluster of endocrine disturbances, including hypertension, obesity, dyslipidemia, and insulin resistance. Literature findings have demonstrated that conditions of negative energy balance and metabolic stress, such as diabetes mellitus type 1, acute inflammation, and chronic dietary restriction can affect fertility. These conditions cause hypogonadism by suppressing the expression of the hypothalamic KiSS or kisspeptin. Diabetes affects reproductive function in women. The objective of the current review is to explore the correlation between metabolic syndrome and infertility in women. To achieve this, a review of literature studies between 2007 and 2015 was undertaken to evaluate current evidence-based practice on the topic. Keywords, such as metabolic disorders, women fertility, and reproduction were used to search for data from PubMed, MEDLINE, CINAHL, ERIC, and EMBASE databases. The inclusion and exclusion criteria was based on the appropriateness of the research design in reference of research objectives, risks of bias, statistical issues, quality reporting, choice of measures of outcome, quality of intervention, and studies conducted between 2007 and 2015. The results from the highest evidence available confirm that metabolic disorders have adverse impacts on the reproductive health of women, and specifically their fertility. Metabolic disorders like hyperlipidemia, obesity, and diabetes can directly or indirectly affect the fertility of women through the interruption of either the ovarian functions or the pituitary-hypothalamic functions. Furthermore, metabolic disorders increase the risks of cervical and endometrial cancers in women that hamper the reproductive health and fertility of women.

Keywords: Obesity, Metabolic, Endocrinology

Introduction

Three major interrelated abnormalities characterize metabolic syndrome: elevated blood pressure, dyslipidemia, and elevated blood plasma (1). The three abnormalities directly contribute to pro-inflammatory and pro-thrombotic state, an outcome that predisposes an individual to the development of diabetes type 2 and atherosclerotic cardiovascular disease (2). Insulin resistance and hyperinsulinemia are the primary underlying metabolic abnormalities reported in metabolic syndrome and polycystic ovarian syndrome (3). Elevated circulating insulin levels and insulin resistance induces unfavorable changes in increased androgen production and lipid metabolism from theca cells (4). Having excess release of androgens can result in unfavorable metabolic problems resulting in central distribution of fat and dyslipidemia. Dyslipidemia and excess insulin in obese women may contribute to metabolic syndrome and polycystic ovarian syndrome (1). The android fat distribution pattern may be explained by hyperandrogenism, resulting in a vicious circle of central adiposity, hyperinsulinism, and metabolic abnormalities (1).

Metabolic Disorder

Metabolic disorders are caused by a malfunction in body metabolism. Examples of metabolic disorders include obesity, diabetes, and dyslipidemia, which together constitute

'metabolic syndrome' (see Figure 1). Metabolic syndrome, also called insulin resistance syndrome or syndrome X is a collection of metabolic abnormalities (5). It is condition typified by glucose intolerance, central obesity, dyslipidemia, and hypertension (6,7). Even though the term "metabolic syndrome" has been used to denote a collection of risk factors, there are debates concerning its existence, and various definitions have been used (8). The incidence of metabolic syndrome is on the rise globally (5). The terms metabolic disorder and metabolic syndrome will be used interchangeably in this discussion to refer to the same condition.

Prevalence

The global prevalence of metabolic syndrome ranges from less than 10% to as high as 46%. The prevalence is influenced by region, ethnicity, age, the interpretation of metabolic syndrome used and the environment (9,10), as well as the diagnostic criteria used (11). Metabolic syndrome is a major public health problem, particularly in the developed nations such as the United States and Europe. The prevalence in the United States is reported to be 23% among nondiabetic individuals (8). The prevalence of metabolic syndrome among the European American ethnic groups in Europe ranges from 20% to 30% (7). Cohort studies conducted in Iran have shown that the prevalence

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of metabolic syndrome is more than 30% and that it is significantly higher in women than in men (23.1% women vs. 18.4% male) (6,12).

Pathogenesis

The pathogenesis of metabolic syndrome is not completely clear; nonetheless, there are some factors that have been implicated, including dietary habits and sedentary lifestyles, increasing age and body mass index (7). For instance, factors like the history of maternal gestational diabetes, decreased parity, and postmenopausal status have been shown to increase the risk of metabolic syndrome in women (13). Recent studies have demonstrated that there are sex differences concerning risk predictors of metabolic syndrome, implying that levels of sex hormones and estrogen/androgen balance potentially play a vital role in determining metabolic syndrome (14,15).

A section of earlier studies has postulated that men are likely to have a higher prevalence than age-matched premenopausal women are (13). Nonetheless, the relationship seems not to hold after menopause (16), with prevalence being significantly higher among women compared to men, particularly after the age of 60 (16). Kim et al (17) demonstrated postmenopausal status was linked to a higher metabolic syndrome risk independent of normal aging in Korean women. Cho et al (18) reported similar findings in Chinese subjects.

Methodology

The literature review for the metabolic disorder and fertility in women covered a period of eight years; that is from 2007 to 2015. The study articles were extracted from five medical databases, including CINAHL, MEDLINE, EMBASE, PubMed, and ERIC. The articles were researched using keywords like diabetes, reproductive health, metabolic disorders, body mass index, female fertility and metabolic diseases. Initial approach reviewed the journal abstracts for their research objectives and relevance. The inclusion criteria took into account the appropriateness of the research methodologies of the articles, the research objectives, statistical issues, risks of bias, the measures of outcomes, quality reporting, studies undertaken between 2007 and 2015, and the quality of intervention.

Results

Metabolic Disorder and Women's Fertility

Energy stores and metabolism in the body determine the onset of puberty and fertility, albeit the mechanism by which these occur, remains unclear (19-21). The current body of literature shows that conditions of negative energy balance and metabolic stress, such as diabetes mellitus type 1 in primates and rodents (20,22) acute inflammation in rats, and chronic dietary restriction can affect fertility (23,24). These conditions cause hypogonadism by suppressing the expression of the hypothalamic KiSS/kisspeptin, implying that Kiss1 neurons are sensitive to alterations in metabolic status (25,26).

According to Roa et al (26), acute administration of kisspeptin is sufficient to normalize the secretion of gonadotrophin in diabetic rats, and testosterone levels in diabetic males). Chronic treatment with kisspeptin-10 has also been shown to ameliorate significantly many long-term reproductive deficits in diabetics (27). The findings demonstrate that defective Kiss1 tone in the hypothalamus significantly contributes to the hypogonadotropic hypogonadism (28,29), mostly seen in individuals with poorly controlled diabetes mellitus type 1 (30).

Besides, women who are obese and diabetic have been shown to have an elevated risk of complications associated with pregnancy (31). In particular, glycemic control has been associated with undesirable effects on the reproductive of women with both type 1 and type 2 diabetes mellitus. Uncontrolled diabetes has been associated with sexual dysfunction in women. It has also been associated with increased risk of morbidity and mortality in the offspring (32).

Pathophysiology of the Reproductive Axis in Patients With Metabolic Disorder

Pituitary-Hypothalamic Function

Earlier studies carried out in females have demonstrated that individuals with insufficient metabolic control and primary and secondary amenorrhea exhibit low levels of estradiol (30). The women also present insufficient Luteinizing hormone (LH) and follicle stimulating hormone (FSH), which have mostly been associated with a lack of residual insulin secretion (33). The poor metabolic control observed in a majority of these patients explain the perturbations (34). The hypogonadotropic hypogonadism seen in amenorrheic diabetic females has been shown to be similar to that linked to other metabolic stress forms, including strenuous exercise and anorexia nervosa (35). However, other reports have shown that diabetic patients with secondary amenorrhea due to hypogonadotropic hypogonadism failed to recover following their improvement in metabolic control (36), implying that a certain group of diabetic patients is prone to hypogonadism (34). The hypothalamic origin of the decreased levels of gonadotropin in amenorrheic and diabetic patients has been explained (25,26). Abnormalities of gonadotropin-releasing hormone (GnRH) pulse generator are hypothesized on LH pulses studies, indicating the secretory activity of the GnRH neurons (37). Such studies have demonstrated a decrease in the number of LH pulses, wider pulses, and a decrease in pulse amplitude in patients with diabetes and amenorrhea relative to those with normal menstrual cycles (34,37).

A toxic effect of hyperglycemia on the neurons of the hypothalamus has been proposed by observations of reduced LH response to GnRH stimuli (34). The toxic effects have also been reported with increasing duration of diabetes and by GnRH secretion abnormalities and increased apoptosis in an immortalized GnRH cell line exposed to hyperglycemia (37). These findings are suggestive that chronic hyperglycemia is likely to trigger glucotoxicity

in GnRH neurons; nonetheless, mediators of the central nervous system such as increased opioidergic activity, catecholamine levels, and dopaminergic tone have also been implicated in hypogonadism pathophysiology in diabetic patients (38).

Ovarian Function

The invention of modern intensive treatment for diabetes has been associated with reduced hypogonadism prevalence as demonstrated by the reduction in amenorrhea prevalence (30). Sadly, an increase in the incidence of reproductive abnormalities caused by insulin excess, particularly during polycystic ovary syndrome, excessive weight gain, and hyperandrogenism has been reported (34). Under normal physiological circumstances, the pancreas secretes insulin into the portal circulation, and the liver eliminates a significant fraction of the secreted insulin (39).

In patients with diabetes type 1, insulin is usually administered into the subcutaneous tissue from where it is absorbed into the systemic circulation, omitting the hepatic first-pass step and consequently exposing the peripheral tissues to supra-physiologic levels of insulin (33). The significance of insulin action on human reproductive function is underscored by insulin receptor expression in several tissues, including ovaries, uterus, hypothalamus, and pituitary (40). Insulin promotes ovarian steroidogenesis and follicular development through insulin receptors in granulosa cells. Insulin has also been shown to augment FSH-stimulated steroid secretion (41). Additionally, its gonadotropic effects on folliculogenesis promote recruitment and pre-ovary follicular growth. These numerous actions of insulin form the basis for the potential impact of disturbed insulin secretion on the development and functions of the ovaries (34,41).

Hyperglycemia also affects reproductive function in women. Elevated blood glucose triggers peripheral insulin resistance. Existing insulin resistance and hyperinsulinemia have been shown to cause polycystic ovary syndrome (PCOS) (42). Hyperglycemia is also thought to affect ovarian function via the presence of advanced glycation products and receptors. These receptors have been reported to exist in theca and granulosa cells of healthy women (43). Few studies have investigated ovulatory function in diabetic women. Some have reported delays in ovulation in women trying to become pregnant, implying that such women have a longer follicular phase (44-46).

Codner and colleagues conducted a prospective study on ovulation in non-hyperandrogenic adolescents with type 1 diabetes ($n = 31$) and compared them with a control group ($n = 52$). They found out that the diabetic girls did not experience a decrease in ovulation. They found similarity in the fraction of ovulatory cycles in both the treatment and control groups (34.5% and 36.3% respectively). Metabolic control was found to have a slight effect on the rate of ovulation. An increased rate of ovulation every 100 days and a higher percentage of ovulatory cycles were reported in diabetic girls to optimal metabolic control that diabetic

girls with insufficient control (25).

Even though these data are suggestive of preserved ovulation, most studies have reported fewer pregnancies and live births in women with diabetes mellitus type 1 (47). Fecundability has been reported to be lower in diabetic women, and this has been associated with sexual dysfunction in such women. Reports show that diabetic women experience sexual dysfunction, particularly dyspareunia, decreased desire, as well as changes in the arousal phase, which have been associated with depressive symptoms and marital problems (48). Studies evaluating fertility treatments on diabetic women agree that the main factor in ensuring successful pregnancy is achieving optimal metabolic control before using more invasive techniques (30). In vitro fertilization treatments in women with type 1 diabetes have been shown to have similar results to those in non-diabetic women when optimal metabolic control is achieved (2,34,49).

Obesity and Women's Fertility

Lifestyle factors can have negative or positive effects on women's fertility. Obesity, which is a component of metabolic syndrome, has been shown to have a significant impact on female fertility. Reports show that there is a high prevalence of obese women in the infertile population. Similarly, obesity has been linked to infertility (50). Obese women mostly have decreased insulin sensitivity putting them at an increased risk of several adverse outcomes in pregnancy. Metabolic syndrome is associated with increased risk of inflammation, metabolic disturbances of nutrient metabolism, and hypertensive disorders during pregnancy.

Even though these conditions can be resolved clinically, the woman remains at risk of metabolic syndrome in later life (51,52). Obese women have been shown to have a 10%-15% increased risk of preeclampsia, which has been associated with poor pregnancy outcomes (53). Obese women have also been shown to have lower sex hormone-binding globulin concentrations than lean women (51). Furthermore, obese women have reduced fertility about women with normal body weight in both conceptions achieved by assisted reproduction techniques and natural conception. The subfertility in obese women is partly ascribed to the complete absence or reduced frequency of ovulation (53). Obesity has been reported to have a negative impact on assisted reproduction techniques because it adversely affects the duration of stimulation of the ovaries, fertilization rate, quality, and some oocytes and embryos, the rate of embryo transfer, and pregnancy rates (54). Consequently, obese women have been shown to require higher doses of gonadotropins and longer durations of ovarian stimulation. Higher incidence of follicular synchrony and higher cancellation rates has also been reported (55).

The lower number of oocytes retrieved in obese women about normal weight women could be attributed technical difficulties or lower number of follicles (56). Furthermore, obesity can hinder accurate transabdominal ultrasonographic imaging during embryo transfer. These mecha-

nisms explain the decrease in implantation and rates of pregnancy in obese women undergoing assisted reproduction techniques. Overweight and obesity have also been associated with menstrual irregularities and reduced rate of conception. Also, it increases the risk of miscarriage and contributes to perinatal and maternal complications (57).

Diabetes and Women's Fertility

Hyperglycemia and insulin resistance have been shown to induce oxidative stress resulting in an imbalance between free oxygen radical activity and antioxidant defense mechanisms at the cellular level (58). Oxidative stress is also postulated to deteriorate fetal development (59). Studies conducted on a female and male animals have demonstrated that uncontrolled diabetes is likely to result in a profound hypogonadotropic state, typified by low basal levels of sex steroids and gonadotropins, defective gonadotropin responses to gonadectomy, and reduced LH pulsatility, resulting in disturbed negative-feedback responses (60).

Positive-feedback disruption in females has been shown to cause delayed or absent preovulatory LH surges and anovulation in females. Reports have suggested that some of the reproductive deficits associated with diabetes in women could result from ovarian alterations (61,62). Follicular growth and survival abnormalities, including increased granulosa and follicular apoptosis, as well as impaired oocyte-granulosa communication, oocyte maturation, and development of ovarian follicles have been observed in diabetic animal models. Ovarian steroidogenesis perturbation and ovulation have also been observed in female diabetic mice (63).

Furthermore, insulin deficiency has been linked to defective ovulation, and this can be reversed through treatment with insulin in diabetic rodents. Ovarian protein glycation has been described in non-diabetic mice and hamsters (65) and has the likelihood of affecting ovarian aging in mice (65). These observations are suggestive of the direct harmful effects of hyperglycemia and low insulin levels on ovarian functions, which in turn have a direct impact on women's fertility (66,67).

Metabolic Disorders and Reproductive Cancers in Women

Reports show that there is a direct correlation between metabolic disarrangements seen in metabolic syndrome and carcinogenesis (68). Cancers affecting the reproductive organs such as the uterus have a negative impact on a woman's fertility because the uterus plays a key role in accommodation of the fetus. Carcinogenesis is associated with lifestyle factors, with excess weight gain being acknowledged as a major risk factor accounting for almost half of endometrial cancer cases in industrialized countries (69). Metabolic disorders such as obesity and diabetes are thought to increase the risk of developing reproductive health cancers such as endometrial or breast cancer (70). Kurdoglu et al (63) reported that oxidative stress characterized by decreased antioxidant and increased oxidant

levels that are independent of insulin resistance may play a role in the pathogenesis of polycystic ovarian syndrome in young non-obese women. Hyperinsulinemia, which is caused by hyperglycemia has been shown to facilitate carcinogenesis by increasing circulating free insulin-like growth factors-1 (IGF-1). People with elevated IGF-1 concentrations have been shown to have a higher risk of developing cancer (71). The pathways for insulin receptor activating signaling can trigger proliferation of cancer cells, protecting from apoptotic stimuli, metastasis, and invasion. It can also stimulate the proliferation of normal cells such as the smooth muscle cell and migration, which are required for cancer cell growth (72). Hyperglycemia and impaired regulation of glucose have also been shown to promote the growth of cancer cells (73). Cancer cell glucose transporting proteins have been shown to increase in an attempt to respond to the increased glucose demands (74).

Epidemiological studies have also shown that there is an association between diabetes and endometrial cancer (75). Similarly, hypertension has also been positively associated with an increased risk of endometrial cancer (76). On the other hand, data on the association between endometrial cancer and dyslipidemia is scarce (77). Friedenreich and colleagues (70) carried out a case-control study to examine the role of metabolic dysfunction in endometrial carcinogenesis in women with endometrial cancer (n=515) in Alberta, Canada. Their study revealed that there was a clear association between metabolic syndrome and increased risk of endometrial cancer.

The association between metabolic syndrome and risk of cervical cancer has also been investigated. Hypertriglyceridemia has been shown to increase the risk of cervical cancer and thus can have an impact on women's fertility. Elevated triglycerides have been shown to promote the proliferation of cancer cells and their anti-apoptotic activity by causing oxidative stress and generating reactive oxygen species, which induce DNA damage (78,79). Penranda and colleagues (65) conducted a case-control study to investigate the association between metabolic syndrome in women (n=585924) aged 21 years and above in the United States. Their study demonstrated that there was increased odds of a history of cervical cancer among those subjects with metabolic syndrome (80). Also, cancers and their associated treatments, including chemotherapy, radiotherapy, surgery, biologic, and endocrine therapy have been shown to affect profoundly gonadal function and subsequently, women's fertility (81).

Conclusion

Reproduction is an important process in human lives. Metabolic disorders can have adverse effects on women's reproduction by affecting their fertility. Metabolic disorders, including diabetes, obesity, and hyperlipidemia can affect women's fertility directly or indirectly by interfering with the pituitary-hypothalamic function or ovarian function. Also, they increase the risk of reproductive cancers such as endometrial and cervical cancer in women. These

factors affect women's reproductive health and interfere with women's fertility in particular.

Metabolic disorders cause hypogonadism through the suppression of the suppression of the hypothalamic KiSS/kisspeptin expression. In diabetic patients, elevated blood glucose triggers peripheral insulin resistance. The existing insulin resistance and hyperinsulinemia can potentially trigger the development of PCOS. Hyperglycemia is also thought to affect ovarian function via advanced glycation products and receptors. Their receptors have been reported to exist in theca and granulosa cells of healthy women. The findings also indicate that obesity, which is a component of metabolic syndrome, has a significant impact on female fertility as evident from reports that show a high prevalence of obese women in the infertile population. Obese women mostly have decreased insulin sensitivity, putting them at an increased risk of several adverse outcomes in pregnancy.

Furthermore, the review has shown that metabolic disorders are thought to increase the risk of developing reproductive health cancers such as endometrial or breast cancer. Hyperinsulinemia, which is caused by hyperglycemia, has been shown to facilitate carcinogenesis by increasing circulating free insulin-like growth factors-1 (IGF-1). Hypertriglyceridemia has been shown to increase the risk of cervical cancer and thus can have an impact on women's fertility. Elevated triglycerides have been shown to promote the proliferation of cancer cells and their anti-apoptotic activity by causing oxidative stress and generating reactive oxygen species, which induce DNA damage.

Ethical Issues

Not applicable.

Conflict of Interests

The author has no conflicts of interest to disclose.

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