Chapter

Metabolic Syndrome in Reproductive Health: Urgent Call for Screening

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Abstract

Metabolic syndrome (MetSy) is a compilation of interrelated pathologic conditions characterized by central obesity, hypertension, insulin resistance and atherogenic dyslipidaemia. The prevalence of MetSy is rising globally. There is growing evidence which linked the individual components of MetSy to the increasing prevalence of poor reproductive health in both the male and female community. This text reviews the recent evidence associating MetSy to poor reproductive health as well as the underlying pathophysiology. The aims to study the relationship between MetSy and reproductive health. The effects of MetSy on fertility were examined and supporting evidence explaining the pathophysiology of dysfunction with each MetSy component extracted from the following medical databases, including CINAHL, MED- LINE, EMBASE, PubMed, and ERIC were described. Noncommunicable disease is rising at an alarming rate globally. Metabolic disorders like hyperlipidaemia, obesity, and insulin resistance can directly or indirectly affect the reproductive health and fertility in both men and women through the interruption of hypothalamic – pituitary – gonadal axis functions. Metabolic syndrome's adverse effects are likely transgenerational (Barker hypothesis), where children born to obese mothers are at increased risk for obesity, diabetes and cardiovascular disease later in life. Therefore MetSy deserves attention and screening should be upscaled at all contacts for all age group of patients to save the future generations.

Keywords: body mass index, diabetes, fertility, metabolic disorders, obesity, male and female reproductive health, screening

1. Introduction

Metabolic Syndrome (MetSy) is one of the fastest-growing non-communicable disorders globally [1, 2]. Metabolic syndrome (MetSy) is a precursor to Non-communicable Diseases (NCDs) and is responsible for the high prevalence of chronic diseases like diabetes, hypertension, heart conditions and cerebrovascular incidents. The burden of NCDs is rising globally and is becoming worse in developing countries, where more women than men are at risk. Women also bear the greatest morbidity and mortality in almost all countries [2]. By the year 2030, studies project that NCDs and related diseases will be the cause of more than 75% of deaths globally [3]. Cardiovascular diseases (CVDs) are predicted to be the future major cause of deaths in low-income countries, more than all the infectious diseases,

maternal and perinatal conditions, and nutritional disorders combined [2, 3]. The risk factors associated with NCDs include smoking, high blood pressure, unhealthy diet, inactivity, overweight and obesity, hypercholesterolemia, elevated blood sugar and alcohol consumption [4].

In 2016, the WHO recorded 39% of adults aged 18 years and over (39% of men and 40% of women) to be overweight and on the whole about 13% of the world's adult population (11% of men and 15% of women) were obese in 2016 [5]. Obesity and overweight). The worldwide prevalence of obesity nearly tripled between 1975 and 2016 [5]. Obesity in men in reproductive age is increasing worldwide, impacting negatively on reproductive potential, sperm function and assisted reproduction outcomes. Changes in modern eating behaviors are needed to invert the negative correlation between lifestyle and sperm quality [6]. Current studies predict that approximately 25% of children less than 16 years old will be obese by the year 2050. This is of serious concern as childhood obesity predisposes individuals to adult obesity and the associated obesity related medical sequelae. One such sequela is the impact on reproductive health in both the male and females population [7].

2. Defining the metabolic syndrome (MetSy)

Metabolic syndrome (MetSy) presents as a group of interrelated factors that increases the risk of acquiring cardiovascular disease (CVD) such as coronary heart disease (CHD), arterial atherosclerotic vascular disease and type-2 diabetes mellitus (T2DM), which was described as "Syndrome X" by Reaven in 1988. "Syndrome X" was characterized by impaired glucose tolerance (IGT), hyperinsulinemia, elevated triglycerides (TG), and reduced high-density lipoprotein cholesterol (HDLc) [8]. To date, several definitions of MetSy have been proposed by various international organizations and expert groups by incorporating its different components. These include definitions by the National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII), American Association of Clinical Endocrinology (AACE), International Diabetes Federation (IDF), American Heart Association (AHA) in collaboration with National Heart, Lung and Blood Institute (NHLBI), and World Health Organization (WHO) [9]. A summary of these definitions is presented in **Tables 1** and **2**.

In an effort to provide more consistency in both clinical care and research of patients with MetSy, these various international organizations and expert groups published a consensus joint statement in 2009 on uniform diagnostic criteria, The Harmonized Definition of Metabolic Syndrome [10]. The Harmonized Definition of Metabolic Syndrome (MetSy) includes the presence of 3 of the 5 risk factors, these being enlarged waist circumference (WC) with population-specific and country-specific criteria (WC > 102 cm in men and WC > 88 cm in women), serum triglycerides ≥150 mg/dL or 1.69 mol/l, high density lipoprotein (HDL-c) < 40 mg/dL or 1.03 mmol/l in men and < 50 mg/dL or 1.29 mmol/l in women, systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg, as well as fasting glucose ≥100 mg/dL or 5.6 mmol/l. Also included are patients taking medication to manage hypertriglyceridemia, low high-density lipoproteins (HDL-c), hypertension and hyperglycaemia.

MetSy predicts that the development of type 2 diabetes mellitus (T2DM) leads, in addition, to increased cardiovascular morbidity [9]. Thus, the main components of MetSy are: dyslipidaemia, characterized by elevated triglycerides and low High-Density Lipoproteins (HDL cholesterol), elevated blood pressure (BP), hyperglycaemia, abdominal obesity and/or insulin resistance (IR). Metabolic syndrome is not a disease per se, but a combination of metabolic abnormalities which can present in different ways in accordance with the various components that constitute the syndrome.

National Cholesterol Education Program Adult Treatment Panel III (NCEP:ATPIII): Any three or more of the following: • Waist circumference > 102 cm in men and > 88 cm in women; • TG ≥ 150 mg/dl (1.69 mmol/l); • HDL-cholesterol <40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women; • BP ≥ 130/85 mmHg; • Fasting glucose ≥100 mg/dl (5.56 mmol/l).
American Association of Clinical Endocrinology (AACE): Impaired glucose tolerance plus two or more of the following: • BMI ≥ 25 kg/m2; • TG ≥ 150 mg/dl (1.69 mmol/l) and/or HDL-cholesterol <40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women; • BP ≥ 130/85 mmHg.
International Diabetes Federation (IDF): Central obesity (defined by waist circumference with ethnicity-specific values#, but can be assumed if BMI > 30 kg/m2), plus two of the following: • TG ≥ 150 mg/dl (1.69 mmol/l); • HDL-cholesterol <40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women; • BP ≥ 130/85 mmHg; • Fasting glucose ≥100 mg/dl (5.56 mmol/l).
American Heart Association in collaboration with National Heart, Lung and Blood Institute (AHA/NHLBI): Any three of the following: • Waist circumference ≥ 102 cm in men, and ≥ 88 cm or greater in women; • TG ≥ 150 mg/dl (1.69 mmol/l); • HDL-cholesterol <40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women; • BP ≥ 130/85 mmHg; • Fasting glucose ≥100 mg/dl (5.56 mmol/l). TG: Triglyceride; HDL: High density lipoprotein; BP: blood pressure: BMI: body mass index #See **Table 2**.1.
WHO clinical criteria for defining MetS: • Resistance to insulin by one of the following: Type 2 Diabetes • Impaired fasting glucose • Impaired Glucose Tolerance • Insulin resistance defined euglycemic hyperinsulinemic More any two of the following: • Antihypertensive and/or high blood pressure (systolic or diastolic ≥140 ≥ 90 mm/Hg) • Plasma triglycerides ≥150 mg/dl ˂HDL cholesterol 39 mg/dl (in women)˃BMI 30 kg/m^2 and/or the waist/hip ˃ 0.85 (in women) • Urinary albumin excretion rate ≥ 20 g/min or albumin creatinine ratio ≥ 30 mg/g

Table 1.
Metabolic syndrome definitions [9].

3. Pathophysiological development of metabolic syndrome

Many different factors such as genetics, lifestyle (diet and physical activity), obesity and insulin resistance have been hypothesized to play a role in the development of MetSy [8, 11, 12]. Visceral adiposity as a result of a high caloric intake has been demonstrated to be a primary trigger and a major causative factor for the pathogenesis in MetSy [13–15]. A metanalysis conducted by Ryckman et al. [16]

Analyte	Range	Classification
Total Cholesterol[1] (mmol/L)	< 5.2	Desirable
	5.2–6.1	Borderline high
	> 6.1	High
HDL[1,2] (mmol/L)	> 1.53	Less than average risk
	1.03–1.53	Average risk (male)
	1.29–1.53	Average risk (female)
	< 1.03	Increased risk (male)
	< 1.29	Increased risk (female)
LDL[1] (mmol/L)	< 2.6	Optimal
	2.6–3.3	Near optimal
	3.4–4.1	Borderline high
	4.2–4.9	High
	> 4.9	Very high
CHOL/HDL[3,4] (mmol/L)	< 3.5	Optimal (male)
	< 3.4	Optimal (female)
	> 5.0	Above average risk (male)
	> 4.4	Above average risk (female)
VLDL5[5]	0.1-1.7	Normal / near optimal
	> 0.77	High
Non-HDL[1,2] (mmol/L)	< 3.4	Optimal
	3.4–4.1	Near optimal
	4.2–4.9	Borderline high
	5.0–5.7	High
	> 5.7	Very high
Triglycerides[1] (mmol/L)	< 1.69	Desirable
	1.69–2.25	Borderline high
	2.26–5.63	High
	> 5.63	Very high
Glucose[6,7,8] (mmol/L)	< 5.6	Normal (fasting)
	< 7.8	Normal (non-fasting)
	4.1–6.6	Reference interval (fasting)
	< 2, > 30	Critical

[1]*National Cholesterol Education Program ATP III.*
[2]*Lab Tests Online - Lipid Panel.*
[3]*Harvard Medical Health Guide.*
[4]*American Heart Association.*
[5]*Lab Tests Online – VLDL.*
[6]*Abaxis – Piccolo® Lipid Panel Plus Reagent Disc.*
[7]*American Diabetes Association.*
[8]*Mayo Clinic.*

Table 2.
Reference ranges for clinical and biochemical measurements.

found that the presence of a single element of metabolic syndrome could contribute to the development of metabolic syndrome, and that diabetes alone will later contribute to the development of hypertension. Obesity appears more common in

females and this is attributed to the fact that most women gain weight outside the recommended levels during pregnancy [17].

4. Global epidemiology of metabolic syndrome

Due to the aging population, global increase in obesity and sedentary lifestyles, the prevalence of MetSy is increasing throughout the world and it has become an epidemic of the 21st century [18]. Prevalence rates vary widely due to the criteria used, age of the population, gender, ethnic group, prevalence of obesity in the background population, and environment. The incidence of MetSY often parallels the incidence of obesity and incidence of T2DM. The global prevalence of MetSy has be estimated to be about one quarter of the World population [19]. The prevalence of MetSy is 0–50% or more in African populations, commoner in females and increases with age and urban housing (Okafor, 2012) [20].

5. Screening for MetSy in the general public

Screening can include individuals with pre-symptomatic or unrecognized symptomatic disease [21]. Several studies have shown the importance of screening [22–24].

Health-screening programmes have been effectively used to pinpoint public-health challenges [25–40], and many countries have implemented nationwide health screening and intervention programmes that specifically target MetSy [41]. The first Framingham Risk Score is a gender-specific score that identifies patients at risk of developing cardiovascular complications within a 10-year period. It factors in age, sex, LDL cholesterol, HDL cholesterol, smoking, blood pressure and also whether the patient is on treatment or not for hypertension, lipidaemia and diabetes, and smoking [42]. Artigao-Rodenas et al. [42] applied the Framingham Risk Score in a prospective cohort study of four years in Spain and found that the model had a good predictive value, with negative predictive values in both sexes, a specificity of 85.6% in women and sensitivity of 79.1% in men in a population with high risk of cardiovascular disease. The model had a significant cumulative probability of individual survival by tertiles in both sexes with a p value <0.001.

6. Obesity screening anthropometric indices: body mass index (BMI) and mid-upper arm circumference(MUA)

BMI is currently the metric measure used to determine categories of bodyweight in adults (**Table 3**). Other methods and techniques of estimating body fat and body-fat distribution includes measurements of the waist circumference (WC), waist-hip ratio, underwater weighing, bioelectrical impedance analysis, skin-fold thickness and imaging techniques such as ultrasound, computed tomography, and magnetic resonance imaging with the later giving the most accurate estimates of body composition [44]. The problem of using MUAC is that there is no consensus on its cut-offs internationally [45]. Waist circumference has likewise been shown to estimate body fat, but is a fairly better guide to cardiometabolic disease risks as it identifies people with relatively low BMI but with increased intra-abdominal fat accumulation [46].

In most studies which have measured estimated total body fat by a reference method, BMI was found not to be a strong predictor of body fat [47] and therefore other methods should be developed to better classify individuals at risk of

	BMI (kg/m2)	Obesity Class	Disease Risk* (Relative to Normal Weight and Waist Circumference)	
			Men ≤40 in (≤.102 cm) Women ≤.35 in (≤.88 cm)	> 40 in (> 102 cm) > 35 in (> 88 cm)
Underweight	< 18.5		—	—
Normal†	18.5–24.9		—	—
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9 35.0–39.9	I II	High Very High	Very High Very High
Extreme Obesity	≥.40	III	Extremely High	Extremely High

**Disease risk for type 2 diabetes, hypertension, and CVD.*
†Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Table 3.
Body mass index and obesity [43].

developing MetSy [48]. This is important because there are established ethnic differences in the relationship between abdominal adiposity and metabolic disease risk [49, 50]. Baloyi and Mokwena [51] conducted a prospective cross-sectional study among the pregnant women attending antenatal care at Regional Hospital in Bloemfontein, South Africa in which they excluded BMI and WC in defining MetSy but considered the presence of 3 of the 5 risk factors based on the Harmonized Definition of Metabolic Syndrome. The prevalence of MetSy in this sample was 15.46% and the screening tool enables the screening of pregnant women for metabolic syndrome in all trimesters.

Adapted from "Preventing and Managing the Global Epidemic of Obesity. Report of the World Health Organization Consultation of Obesity." WHO, Geneva, June 1997.

7. Gender as risk factors for metabolic syndrome

Studies have demonstrated that there are sex differences concerning risk factor predictors of MetSy, suggesting that levels of sex steroids hormones, estrogen/androgen, balance potentially play a vital role in determining MetSy [52–56]. In women, raised BMI, low HDL cholesterol, increased WC and hyperglycaemia were significantly greater contributors to the MetSy, whereas in men hypertension and elevated triglycerides were the main factors [55]. Case and Menendez [57] found two factors in SA that contributed to the gender prevalence disparity, nutritionally deprived during childhood and a higher socio-economic status than males. They identified women to have been nutritionally deprived during childhood; and having a higher socio-economic status. The contributing risk factors prevalent in women are abdominal obesity and insulin resistance, as well as physical inactivity, aging and polycystic ovarian syndrome in some [58]. Other factors contributing to the higher prevalence of MetSy in women is that women live longer than men, and it is reported that women develop cardiovascular disease (CVD) at an older age compared to men [59, 60]. There is a wide disparity in economic status among the black population compared to the other ethnic groups, and this correlates with the wide gap in the prevalence of obesity and disease between these ethnic groups that may be partly attributed to or mediated by these social inequalities [61].

8. Lifestyle habits as risk factors for metabolic syndrome in women

There is an inverse relationship between socio-economic status and obesity in high-income countries but consistent positive association between obesity and socio-economic status in low- resource countries [62]. The transition towards Western lifestyle and urbanization which is accompanied by access to clean water and electricity, reduced housing density, more money available to spend on food, higher energy intake, commuting by taxi/vehicle and reduced physical activity or increased sedentary behavior have positively associated with obesity [56, 63]. The risk of developing specific components of MetSy such as obesity, hyperlipidaemia, hypertension, and elevated fasting blood sugar, has been largely attributed to environmental stressors including poor nutrition with consumption of high-calorie diets which are cheaper and fill the stomach at a cheaper price than healthy food, lack of exercise, and smoking [4]. There is a growing trends among the youths and young adult engaging in alcohol binge drinking, this conduct was found to be significantly associated with lower levels of high-density lipoprotein cholesterol (HDL-C). The low HDL-C increases the risk of developing cardiovascular diseases among these participants [64].

9. Consequences of the metabolic syndrome

Available data support the theory of "developmental origins of adult disease" hypothesis, the "Barker Hypothesis", which posits that a significant portion of the risk for adult metabolic conditions is determined by exposure occurring in the perinatal period [65]. The "Barker Hypothesis" proposes that a poor in-utero environment produced by maternal dietary or placental insufficiency may "program" susceptibility in the foetus to later development of cardiovascular and metabolic disease. The "Barker Hypothesis" further proposes that maternal MetSy has an epigenetic effect, making the next generation unwell and leading to an increase in T2DM and cardiovascular disease in juvenile age and in later life from obesity [65, 66]. The MetSy is further associated with polycystic ovary syndrome in girls, obstructive sleep apnoea, hypogonadism and some form of gynecological cancers especially endometrial cancer [67].

10. Metabolic syndrome and reproductive health

10.1 The physiology of the hypothalamic – pituitary – gonadal axis

Under normal conditions in both males and females, gonadotropin-releasing hormone is produced and released from the hypothalamus, which stimulates the production and release of the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. FSH and LH act on the respective gonads, testicles in men and ovaries in women, to stimulate spermatogenesis and steroidogenesis, and folliculogenesis and steroidogenesis respectively [68].

10.1.1 Luteinizing hormone

In both sexes, LH stimulates secretion of sex steroids from the gonads. In the testes, LH binds to receptors on Leydig cells, stimulating synthesis and secretion

of testosterone. Theca cells in the ovary respond to LH stimulation by secretion of testosterone, which is converted into estrogen by adjacent granulosa cells. In females, the LH surge leads to ovulation of mature follicles on the ovary and later to form corpus luteum, which secrete the steroid hormones progesterone and oestradiol. In the event of pregnancy progesterone is necessary for the maintenance of that pregnancy.

10.1.2 Follicle-stimulating hormone

The FSH is responsible for the maturation of ovarian follicles. Administration of FSH to humans and animals induces "superovulation", an increased number of mature gametes. FSH is also critical for spermatogenesis and sperm cell maturation at the Sertoli cells.

10.1.3 Control of gonadotropin secretion

LH and FSH secretion is under the influence of gonadotropin-releasing hormone (GnRH, also known as LH-releasing hormone). GnRH is a ten amino acid peptide that is synthesized and secreted from hypothalamic neurons and binds to receptors on gonadotrophs.

As depicted in **Figure 1** below, GnRH stimulates secretion of LH, which in turn stimulates gonadal secretion of the sex steroids testosterone, estrogen and progesterone. In a classical negative feedback loop sex steroids(oestrogens, progesterone, testosterone) inhibit secretion of GnRH and also appear to have direct negative effects on gonadotrophs.

This regulatory loop leads to pulsatile secretion of LH and, to a much lesser extent, FSH. The number of pulses of GnRH and LH varies from a few per day to one or more per hour. In females, pulse frequency is clearly related to stage of the cycle.

Several hormonal substances such as inhibin and activin from the gonads, which selectively inhibit and activate FSH secretion from the pituitary, influence GnRH secretion, and positive and negative control over GnRH [69]. Thus gonadotropin secretion is actually considerably more complex than depicted in **Figure 1** below.

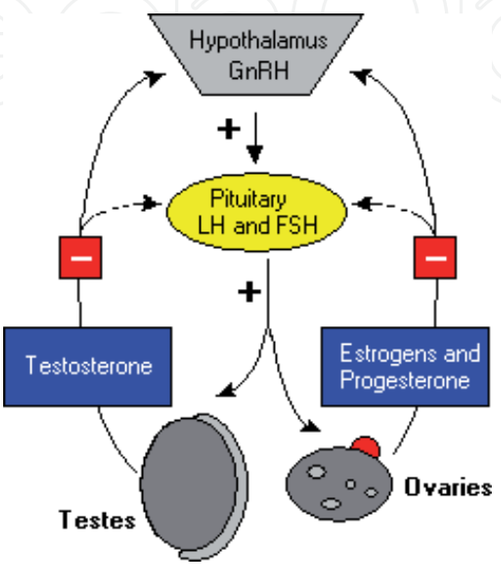

Figure 1.
(vivo.colostate.edu).

10.2 Metabolic syndrome and impact on reproductive health

Obesity is a cardinal feature of MetSy and has been increasing in [70]. The effect of obesity on reproduction and as a cause of female infertility has been more extensively studied in females [70]. Obesity has been recently associated with an increased incidence of male factor infertility. A study from Norway looked at planned pregnancies and the time to achieving pregnancy, after adjusting for female BMI and smoking habits, the results showed that overweight and obese men had an odds ratio of infertility of 1.19 and 1.36, respectively [71]. Ramlau-hansen et al. [72] conducted a similar study comprising nearly 48,000 couples for six years assessing the effects of both male and female obesity on infertility and found that overweight and obese men coupled with normal- weight females had an odds ratio for reduced fertility of 1.18 and 1.53, respectively. A further observation was that couples where both parents were overweight or obese, the odds ratios for reduced fertility were 1.41 and 2.74, respectively [73]. Obese people have decreased gonadotropin levels, and increased circulating estrogen levels [74]. The increase in estrogen is likely secondary to peripheral aromatization of androgens from cholesterol in the adipose tissue. A hypogonadotropic hypogonadism state is created due to estrogen negative feedback onto the hypothalamus [74].

10.3 Metabolic syndrome and female reproductive health

Metabolic disorders, including diabetes, obesity, and hyperlipidaemia plays a significant role in the development of female-specific reproductive health issues, which have a significant impact on public health. MetSy also increases the risk of reproductive cancers such as, breast, endometrial, bladder and cervical cancers [73]. Obesity particularly impacts women of reproductive age, as it is associated with an increased risk of infertility and adverse obstetric outcome such as miscarriage, stillbirth, birth defects and cesarean section [70, 75, 76]. MetSy can affect women's reproductive health and fertility directly or indirectly by interfering with the hypothalamic – pituitary – gonadal (HPG) axis function. MetSy creates conditions of negative energy balance and metabolic stress which cause hypogonadism by suppressing the expression of the hypothalamic KiSS/kisspeptin [77, 78].

In addition to the effect of peripheral aromatization which create the hypogonadotropic hypogonadism state in obese women, a lack of residual insulin secretion in diabetes is also associated with the status quo [79]. The hypothalamic origin of the decreased levels of gonadotropin in amenorrhoeic and diabetic patients are related to a toxic effect of hyperglycaemia on the neurons of the hypothalamus leading to reduced LH response to GnRH stimuli [80].

10.3.1 Premature adrenarche in girls

Adrenarche is the puberty of the adrenal gland. Pubarche is denoted by the appearance of pubic hair and or axillary hair. Premature adrenarche in girls is when pubarche occurs before age 8 years in girls and 9 years in boys. The chief hormonal products of adrenarche are DHEA and DHEAS produced from zona reticularis. Premature adrenarche represents an early clinical feature of MetSy (obesity, hypertension, dyslipidaemia, insulin resistance) for some girls. Conceivably the early recognition of these children will permit allow early intervention, such as lifestyle modifications, including dietary, activity level intervention with possibility of using insulin-sensitizing agents in some individuals. Premature pubarche due to premature adrenarche and hyperinsulinemia may precede the development of ovarian hyperandrogenism [81].

Interference with the hypothalamic – pituitary – gonadal axis function may affect follicular recruitment and impact subsequent oocyte quality and affecting overall subfertility in obese women. Studies of women undergoing assisted reproductive technologies (ART) have demonstrated that obesity also has direct effects on the quality oocytes and embryos and on the status of the endometrium. Audit data from retrospective studies demonstrated obesity to be associated with increased risk for miscarriage in spontaneous conceptions [82] as well in pregnancy achieved through donor oocytes after IVF [83]. The pathophysiology underlying this association is complex and likely multifactorial, involving the oocyte, embryonic development, and the endometrium. Apart from fertility and pregnancy problems, female adiposity may influence the timing of onset of puberty, associated with irregular menses, ovulatory dysfunction and ovarian aging [77].

10.3.2 PCOS and obesity

Polycystic ovary syndrome (PCOS) is a hormonal disorder common, among women of reproductive age affecting 5 to 10 percent, often complicated by chronic anovulatory infertility and hyperandrogenism with the clinical manifestations of oligomenorrhoea, hirsutism and acne [84, 85]. The link between PCOS and obesity is complicated. Signs and symptoms of polycystic ovarian syndrome begin for some females soon after menarche. Women with PCOS have insulin resistance (IR) [86]. This insulin resistance is one reason why women with PCOS tend to gain weight or experiences challenges in losing weight. In some females, PCOS develops later on, following substantial weight gain. Women affected by obesity are also more likely to face reproductive problems like polycystic ovarian syndrome (PCOS) and women with PCOS have a greater risk for obesity. Obesity and PCOS share some common features, anovulation and hyperandrogenism although simple or non-syndromic obesity is much more prevalent than PCOS and seems to have a different pathophysiology with respect to the obesity-related reproductive impairment [87]. The difference in the two is that PCOS is characterized by increased serum LH whereas obese women typically have in general lower serum LH. Obesity may modify some aspects hypothalamic – pituitary – gonadal axis function [88]. Although obesity can affect many facet of PCOS, it is a cause of this syndrome and without doubt have an effect on reproduction regardless of PCOS symptomatology [87]. In this review, we will focus on how obesity in the absence of PCOS affects the HPO axis.

10.4 Metabolic syndrome and male reproductive health

Obesity, as a cardinal feature of MetS, has been associated with an increased incidence of male factor infertility. Although the effect of excess body fat on reproduction has been more extensively studied in females, there has been a recent increase in literature assessing the relationship between obesity and semen characteristics, male endocrine changes, male sexual function and male factor infertility. Over the past decade, numerous studies have found an inverse correlation between increased obesity and semen quality that negatively affects male fertility, with an increased chance of subfertility among couples in which the male partner is obese. Various mechanisms for this relationship have been proposed and can be broadly divided into direct negative effects on spermatogenesis and sperm function (lower sperm counts, poorer sperm quality), hormonal factors and, and increased rates of erectile dysfunction [89, 90]. In males, a state of primary hypogonadism is also well defined as an underlying feature associated with MetS [89].

10.4.1 Pathophysiology of obese male factor infertility

Obesity in men contribute to the poor reproductive function through numerous postulated mechanisms. First, hormonal perturbations that involves peripheral conversion of testosterone to estrogen in excess peripheral adipose tissue may lead to secondary hypogonadism through HPG axis inhibition. Second, elevated levels of inflammatory mediators and reactive oxygen species (ROS), generating oxidative stress at the level of the testicular micro environment may result in decreased spermatogenesis and sperm DNA fragmentation. Lastly, the accumulation of supra pubic and inner thigh fat may result in increased testicular heat, which cumulatively can have substantial, detrimental effects on spermatogenesis [74, 90–92].

Men with obesity, the metabolic syndrome and type 2 diabetes have low total and free testosterone and low sex hormone-binding globulin SHBG. On the other hand, the presence of low testosterone and/or SHBG predicts the future development of metabolic syndrome and T2DM [93]. Thus, the observed decrease in testosterone levels in obese males is likely due to several factors, including decreased synthesis of testosterone, inhibition of SHBG synthesis, and decreased gonadotropin secretion [93]. In summary, total testosterone, free testosterone and SHBG are all commonly decreased in obese males. Obesity is also characterized by higher insulin levels and insulin resistance this is suggested to impair steroidogenesis at the Leydig cells which may negatively impact the male reproductive function in the case of obesity [94, 95]. Derby et al. [96] conducted a longitudinal trial of 942 men ages 40–70 years enrolled in the Massachusetts Male Aging Study, demonstrated that BMI was negatively associated with total testosterone, free testosterone, and SHBG, as well as that these levels decline more rapidly with age in obese men.

Adipose tissue behaves like an endocrine gland, it produces hormonally active proteins involved in satiety and metabolism as well as HPG axis regulation [97]. The white adipose tissue produces leptin [74, 97] which has been found to stimulate gonadotropin-releasing hormone secretion in the hypothalamus and FSH and LH secretion in the anterior pituitary in the rat animal studies [98, 99]. Leptin is also believed to have a direct effect on regulation of testosterone production in the testicle taking into account the presence of leptin receptors in Leydig cells [100]. Obesity generates a leptin resistant state, given that high circulating leptin levels are linked with increased adiposity and lower testosterone levels [101].

Obesity creates a proinflammatory state with production of adipokines and cytokines by adiopocytes that result in an increase in systemic inflammation [102] Any form of Inflammation of the reproductive tract has been shown to be associated with infertility in male patients. The cytokines tumor necrosis factor (TNF-a) and interleukin-1(IL-1) have been implicated as the main mediators of the inflammatory process [103]. Inflammation increases levels of reactive oxygen species generating oxidative stress at the level of the testicular that can negatively impact normal reproductive pathways [104]. Elevated oxidative stress leads to increased DNA damage of spermatozoa and is negatively correlated with normal sperm morphology [105–107]. Tunc et al. [108] compared reactive oxygen levels in semen samples from both overweight/obese men and men of normal BMI and found that there was a weak but statistically significant positive correlation between increasing BMI and reactive oxygen species levels.

Spermatogenesis is also adversely effected by elevated testicular temperature. Increased adiposity in the legs and pannus overlying the scrotum may lead to increased testicular temperatures. Shafik and Olfat [109] performed lipectomy to remove the excess scrotal lipoma from a series of infertile men and later observed improvements in their semen parameters in 64.7% of study participants and

pregnancies in 19.6% [109]. Prolonged inactivity in obese men has also been associated with increased scrotal temperatures [110].

11. Intervention approaches to reduce the burden of MetSy

11.1 Health promotion (Ottawa charter)

Health promotion is 'the process of enabling people to increase control over and to improve their health' Introduced into public health in Ottawa in 1986 [111]. Health promotion strategies can be achieved by developing and changing lifestyles, to impact on the social, economic and environmental conditions that determine health.

The Ottawa Charter for Health Promotion set out five strategies that are essential for the success for any health promotion strategy: Build healthy policy; Create supportive environments; Strengthen community actions; Develop personal skills; and Reorient health services. Health promotion actions should target the population at risk, early in life to stop the metabolic storm, by increasing their knowledge and warning them about the dangers of MetSy, enforcing bans on alcohol and tobacco advertising, promotion and sponsorship, raising taxes on alcohol and tobacco and reducing the price of healthy diet food. It is of vital importance to note that the ideal time for intervention is pre-conception. Health-care workers who attend to women of reproductive age and diagnose obesity, have a duty to counsel and refer these patients to high-risk obstetric specialists for consultation to discuss the many risks associated with obesity in pregnancy [112].

These obese patients should be encouraged strongly to undertake nonsurgical interventions to achieve weight reduction to achieve ideal body weight (BMI, 18.5–24.9 kg/m2) before conception. These include, among others, behavioral modification, dietary changes, exercise, and pharmacotherapy [113]. Dietician consultation is recommended for diet advice that is high in fiber, fresh fruit, vegetables, lean protein, and complex carbohydrates, while avoiding foods that contain large amounts of sugar, saturated fats, and cholesterol. Regular fitness exercises based on available facilities such as brisk walking, stair climbing, jogging, or swimming that use the larger skeletal muscles should be incorporated into weight reduction programs. Once the diagnosis of MetSy in Pregnancy or elements of it is made, it's possible to provide intervention to prevent progression of the condition and complications in pregnancy and the associated adverse perinatal outcomes [114].

Insulin resistance and central obesity are regarded as the main underlying causes of metabolic syndrome. Therefore, reduction in body weight will lead to fatty acid mobilization and should be the key focus in management of the MetSy [115]. Stinson et al. [116] showed that overconsumption of poor diet is an important component of the MetSy, and thus needs to be targeted for its reduction and treatment. A literature review on randomized control trials has shown improvement in MetSy following intervention focusing on diet and lifestyle modification, either in certain components or taken as a whole syndrome within a period of 2 weeks–1 year [117]. Informing and educating the public should include nutrition, promotion of regular physical activity, reduction of substance abuse as well as prevention or management of central adiposity, diabetes, atheromatosis and hypertension, and setting a national agenda to motivate all population groups to change stereotype perceptions and behaviors aimed at health and quality-of-life promotion.

Literature provides evidence of efficacy in adhering to the Mediterranean diet (MeD) in reducing body weight [118]. The Mediterranean Dietary pattern is comprised of fruit, cooked vegetables and legumes, grains (whole, not refined) and, in

moderation, wine, nuts, fish and dairy products, particularly yogurt and cheese. It is a food pattern that has the potential of improving health and quality of life in people who adhere to it appropriately, characterizing a way of life and culture [119]. These interventions to alter diet and lifestyle have the potential to succeed only if they are executed early, and thus, offer enough evidence to develop appropriate public policies.

11.2 Bariatric surgery and pregnancy

Obese women with overtly high BMI of more than 40 kg/m^2 or BMI of 35 kg/m^2 with the presence of comorbid NCD conditions (such as diabetes mellitus, coronary artery disease, or severe sleep apnea), should be referred to a specialist surgeon for possible bariatric surgery [120]. Great success has been reported with women who have undergone Bariatric surgery followed by healthy lifestyle modifications [121], by generally demonstrating overall recovery in quality-of-life measures and resolution of their medical comorbidities [122, 123].

Patients who have undergone bariatric surgery should be counseled to avoid pregnancy for a period of 12–18 months after the procedure. Falling pregnant during this interval has been associated with higher risk of surgical complications and exposure of the foetus to rapid weight change [124].

12. Summary

MetSy is not only as a predictor of cardiovascular disease but also as a potential contributing factor to poor reproductive health and interfere with fertility in both male and female affected across her lifespan. Perhaps the most concerning information presented in this chapter is the Barker hypothesis, that the metabolic syndrome's adverse effects are likely transgenerational where children born to obese mothers are at increased risk for obesity, diabetes and cardiovascular disease later in life. There is also increasing and worrying evidence that lifestyle factors such as alcohol binge consumption increases the incidence of metabolic syndrome. Obesity exerts it detrimental effect in the human body by generating a physiological resistant state in the such as a leptin resistant state, insulin resistant.

Noncommunicable disease is rising globally at an alarming rate, future studies focus should be on the strategies needed to improve public health programs and policies aimed at reducing the prevalence of metabolic syndrome through screening at all contacts for all types of patients to save the future generations. Instituting early and targeted lifestyle interventions such as balanced diet and frequent physical activity for metabolic syndrome is a medical exigency.

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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