Impact of Polycystic Ovarian Syndrome, Metabolic Syndrome, and Obesity on Women's Health

12

Giulia Palla, Maria Magdalena Montt Guevara, Andrea Giannini, Marta Caretto, Paolo Mannella, and Tommaso Simoncini

12.1 Introduction

The definition of health given by the World Health Organization is that "Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." Being a man or a woman has a significant impact on health, as a result of both biological and gender-related differences.

Cardiovascular disease (CVD) represents the leading cause of death among women in the United States, and it is also the main cause of death in European women in all but two countries (European Cardiovascular Disease Statistics 2017, https://www.cdc.gov/heartdisease/women.htm).

Data have shown that the traditional atherosclerotic CVD risk factors, including diabetes mellitus type 2 (DMT2), smoking, obesity, hypertension, and physical inactivity, present in both women and men, may show a differential impact in women compared to men, as well as the emerging of nontraditional risk factors unique to, or more common in women, may help to recognize the mechanisms leading to gender-specific issues in development and diffusion of CVD between men and women.

For instance, DMT2 and hyperglycemia show a significantly greater risk of coronary death in women compared to men, even after adjusting for age and other CVD risk factors. The etiology of this discrepancy on the basis of gender is unclear; however, one option could be the high prevalence of the metabolic syndrome (MetS) in female diabetic populations. MetS is a well-known risk factor for CVD, and studies have shown that the risk is greater among women than among men, especially after menopause, underlining the strict relationship between steroid hormones, aging, and CVD risk factors.

G. Palla (✉) · M. M. M. Guevara · A. Giannini · M. Caretto · P. Mannella · T. Simoncini
Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

A. R. Genazzani et al. (eds.), *Impact of Polycystic Ovary, Metabolic Syndrome and Obesity on Women Health*, ISGE Series,
https://doi.org/10.1007/978-3-030-63650-0_12

In addition, newly identified CVD risk factors, such as gestational diabetes, hypertensive disorders of pregnancy, and polycystic ovarian syndrome (PCOS), may open new and fascinating horizons in understanding emerging, nontraditional CVD risk factors in women.

Furthermore, PCOS, MetS, and obesity determine other health's implications besides CVD risk, including fertility issues, oncology risk, depression, and an overall reduction of quality of life in females.

In this chapter, we aim to evaluate the impact of PCOS, metabolic syndrome, and obesity on women's health.

12.2 Polycystic Ovarian Syndrome (PCOS) and Women's Health

PCOS is one of the most common endocrine disorders in women of reproductive age, affecting up to 10% of adult women.

In women of reproductive age, there are three slightly different definitions of the syndrome. The US National Institutes of Health (NIH) proposed the presence of chronic anovulation and clinical or biochemical hyperandrogenism as diagnostic criteria for PCOS, after having excluded other metabolic or endocrine causes. In 2003, The Rotterdam criteria suggested the presence of polycystic ovarian morphology on ultrasound (12 or more follicles measuring 2–9 mm in diameter in each ovary and/or increased ovarian volume) as additional criteria, with two of three criteria required for the diagnosis. Furthermore, the Androgen Excess and Polycystic Ovary Syndrome Society (AEPCOS) stressed the presence of hyperandrogenism (biochemical or clinical) as main criterion, associated with either chronic oligomenorrhea or polycystic ovarian morphology [1, 2].

PCOS is the main cause of female infertility due to anovulation. This syndrome affects women's health from gestational life until senescence, leading to potential risks that negatively influence quality of life and possibly increase morbidity and mortality rates.

The pathophysiological mechanisms underlying the syndrome are still partially unknown, but probably due to the complex interaction between the functionality of the hypothalamic-pituitary-ovarian axis and metabolic disorders, such as obesity, insulin resistance, and compensatory hyperinsulinemia.

12.2.1 PCOS and Fertility

Infertility, hirsutism, and menstrual disorders are the main clinical problems reported by PCOS women. Regarding infertility, although it is difficult to define the exact pathogenesis of anovulation, many possible mechanisms have been postulated [3]. Ovarian function in infertile PCOS women is mainly characterized by disordered folliculogenesis and anomalous steroidogenesis. Abnormalities in one cause disorder of the other, perpetuating a vicious cycle of anovulation. Ovaries of PCOS

women are characterized by multiple small follicles, which are arrested but capable of steroidogenesis. Abnormalities in gonadotrophin and insulin secretion and disordered paracrine function have been identified, including hypersecretion of LH (luteinizing hormone), hyperandrogenemia, and hyperinsulinemia [4]. All these factors seem to be interlinked and together might result in impaired ovarian function. Besides ovarian and central hormonal dysfunctions, with an overactivation of the hypothalamic-pituitary-gonadal axis, other possible anomalies contribute to reproductive failure, namely, obesity. The impact of obesity on reproductive function in PCOS women depends on multiple endocrine mechanisms [5]. Abdominal obesity reflects visceral adiposity, and it is linked to increased circulating insulin levels. Hyperinsulinemia determines reduced sex hormone–binding globulin (SHBG) synthesis with consequent increase of free functional androgen levels. In addition, peripheral adipose tissue is the source of chronic elevation of circulating estrogen caused by the production of estrogens from androgens trough the enzyme aromatase. Hyperleptinemia, which is significantly present in excessive weight, has a detrimental effect on ovarian follicular development and steroidogenesis and thus may contribute to reproduction difficulties in obese women.

Based on these concepts, in the last years, the idea of a PCOS "secondary" to obesity has been postulated [5], as will be further discussed in the following paragraphs.

12.2.2 PCOS and CVD Risk

The presence of insulin resistance and hyperinsulinemia is a common feature in PCOS adult women, with a prevalence of impaired glucose tolerance (IGT) and DMT2, respectively, of 20–37% and 7.5–15%, but the glucose metabolism disorders are probably more frequent when considering only a subset of obese PCOS women [6].

Women with PCOS are more likely to be obese and have an android fat distribution, with higher visceral fat amount, compared with weight-matched controls. Obesity can be found in approximately 50–70% of PCOS adult women. In addition, greater visceral and abdominal adiposity is associated with greater insulin resistance, which is a major predictor of DMT2 and MetS [7].

The cardiometabolic impairment in PCOS starts precociously. Several studies have suggested that adolescent PCOS girls were at substantially higher risk for MetS compared to controls. Besides obesity and insulin resistance, the presence of hyperandrogenemia is an important risk for MetS in young PCOS patients. The odds of having MetS increased approximately fourfold for every quartile increase in free testosterone, independently from BMI and IR [8]. Other data from Hughan et al. showed the presence of increased pulse wave velocity and vascular cell adhesion molecule-1 (VCAM-1) in obese girls with PCOS, which could be the earliest subclinical biomarkers of atherosclerosis [9]. Similarly, young women with PCOS also exhibit a greater risk of hypertension. Several studies indicated an association between hypertension and this endocrinopathy, revealing a twofold prevalence of

hypertension in the group with PCOS. The pathogenesis of high blood pressure in PCOS can be determined by the presence of insulin resistance and hyperinsulinemia. They are known to alter vascular smooth muscular cells determining hypertrophy of vascular smooth muscle and reduced compliance, and interfering with the endothelium-related vasodilatation, through the activation of the renin-angiotensin-aldosterone system.

Some studies report that women with PCOS have higher hsCRP (high sensitivity C-reactive protein) levels compared to control, suggesting the hypothesis that cardiometabolic impairment in PCOS patients may be linked to the presence of chronic inflammation [10]. However, it has also been suggested that serum hsCRP concentrations are related to obesity rather than to the presence of PCOS per se, stressing the idea that, at least in a subgroup of PCOS women, obesity is the main determinant of the increased CVD risk.

12.2.3 PCOS and Depression

International research has shown that PCOS has an adverse effect on the patient's quality of life. PCOS women also experience higher rates of depression and anxiety than women in the general population, and this appears to be independent of BMI. Although clinical features of high androgen levels deeply impact health-related quality of life, the association between hirsutism, acne, body image and perception, and depression remain unclear. Similarly, there is limited data on the association between variables such as biochemical hyperandrogenism or infertility and depression [11].

12.2.4 PCOS and Cancer Risk

PCOS is a well-known risk factor for endometrial cancer. The pathogenesis of the increased risk of endometrial cancer in PCOS include multiple determinants, such as obesity, DMT2, hypertension, nulliparity, and familiarity. A meta-analysis including more than 4000 women has evaluated the risk of endometrial cancer in PCOS women compared to the general population [12]. This study underlined that the odds of developing endometrial cancer is almost three times higher in women with PCOS compared to controls. These data translate into a 9% lifetime risk of developing endometrial cancer in PCOS compared to 3% in the general population. Accordingly, a case-control study of endometrial cancer and PCOS has further shown that young women with PCOS (age < 50 years) present a fourfold increased risk of endometrial cancer compared to peers without PCOS. Notably, this increased endometrial cancer risk is halved when adjusted for BMI, emphasizing obesity as a main confounding risk factor for developing endometrial cancer.

There are contradictory evidences regarding the risk of ovarian cancer in PCOS women. A long-term follow-up of UK women with PCOS showed the absence of correlation between PCOS and mortality due to ovarian cancer [13]. However, a

case control study reported an increased risk of epithelial ovarian tumor in women with self-reported PCOS compared to controls, even if the pathogenetic mechanism is still unclear.

No associations have been found between PCOS and breast cancer, though obesity and DMT2, which are high prevalent in PCOS, are also major risk factors for breast cancer. Therefore, clinicians should focus their attention on this subset of women to offer correct counselling and possibly apply preventive strategies.

12.3 Metabolic Syndrome (MetS) and Women's Health

MetS is defined in adult population as the presence of three of five of the following criteria: hyperglycemia (glycemia >100 mg/dl), hypertriglyceridemia (triglycerides >150), elevated blood pressure (> 130/85 mmHg), central adiposity (waist circumference >94 cm for white men, >80 cm for white women) [14]. MetS is one of the main health problems, and its worldwide incidence is continually increasing, even if with a large variability among countries.

Even if the prevalence is similar among women and men, the differences within ethnic groups are widely greater in females. There are fewer white women with MetS than white men, but MetS is significantly more frequent in both African American and Mexican American women compared to men. In addition, from the late 1980s to early 2000s, the age-adjusted prevalence of the MetS has increased by 23.5% among women and 2.2% among men, suggesting that the prevalence of MetS in women will quickly outnumber those in men in the near future [15]. Interestingly, increase in blood pressure, waist circumference, and triglyceride levels is the main responsible for the increased MetS prevalence among women.

12.3.1 MetS and Fertility

The effect of MetS on fertility is mainly linked to an altered pituitary-hypothalamic-ovarian function and the presence of overweight and obesity.

Evidences come from studies on diabetic women with secondary amenorrhea due to hypogonadotropic hypogonadism. In diabetic amenorrheic women decreased levels of gonadotropin seem to be related to disorders in gonadotropin-releasing hormone (GnRH) pulse generator, with a decrease in the number of LH pulses, wider pulses, and a decrease in pulse amplitude, compared to eumenorrheic controls [16]. Hyperglycemia is toxic on the neurons of the hypothalamus, and the toxic effect is proportional to the duration of diabetes and GnRH secretion abnormalities. In an immortalized GnRH cell line exposed to hyperglycemia apoptosis results to be increased [17]. In addition to the direct effect of hyperglycemia, other mediators of the central nervous system, including increased opioidergic activity and catecholamine levels, have been implicated in hypogonadism pathophysiology in diabetic patients.

Even in the absence of diabetes, hyperinsulinemia and hyperglycemia play a detrimental role on reproductive female system. Insulin acts on granulosa cells trough insulin receptors, promoting steroidogenesis and follicular development and increasing FSH-stimulated steroid secretion. Moreover, insulin plays a gonadotropic effect on folliculogenesis, driving follicle recruitment and follicular growth.

In addition to the central pituitary effect, hyperglycemia may also determine a negative impact on female fertility due to peripheral effect. Elevated blood glucose is a known determinant of peripheral insulin resistance, which is strongly linked to the pathogenesis of PCOS, as discussed.

Hyperglycemia is also thought to directly affect ovarian function via the presence of advanced glycation products. These molecules link the receptors present in theca and granulosa cells and are probable determinants of impaired ovulatory function in diabetic women.

12.3.2 MetS and CVD Risk

MetS is a complex syndrome in which each component is an independent risk factor for CVD and the combination of these risk factors determines cardiac dysfunction, myocardial infarction, coronary atherosclerosis, endothelial dysfunction, and heart failure, thus increasing the rates and severity of cardiovascular morbidity and mortality. The CVD determinants in MetS include abdominal obesity, high triglycerides, reduced HDL cholesterol, impaired glucose tolerance, and/or hypertension. Besides these factors, other mechanisms have been postulated, including increased circulating levels of pro-inflammatory adipocytokines and the overactivation of the sympathetic nervous system and the renin-angiotensin system. Above all, adipokines have been suggested as key integrative elements linking the traditional CVD risk factors and the molecular mechanisms of increased CVD rates in MetS.

This seems particularly true in peri- and menopausal MetS women. Women in the menopausal transition with excessive body weight and MetS show increased resistin, adipsin, GIP, leptin, IL-6, and FGF21 and PAI-1 levels compared to normal weight ones [18]. Accordingly, several studies found that postmenopausal women with the MetS displayed significantly higher levels of leptin, resistin, adipsin, insulin, and HOMA-IR values in addition to lower adiponectin levels as compared to controls without the MetS [19]. In addition, postmenopausal women with the MetS also displayed higher IL-6 and lower uPA levels, markers of inflammation and endothelial dysfunction, respectively [20]. These detrimental changes may lead to the development and progression of clinically silent atherosclerosis (Fig.12.1).

12.3.3 MetS and Depression

The relationship between depression and MetS has been extensively studied. Several data suggested that a history of major depression is associated with an approximately twofold increased risk of the MetS in both women and men. A 7-year

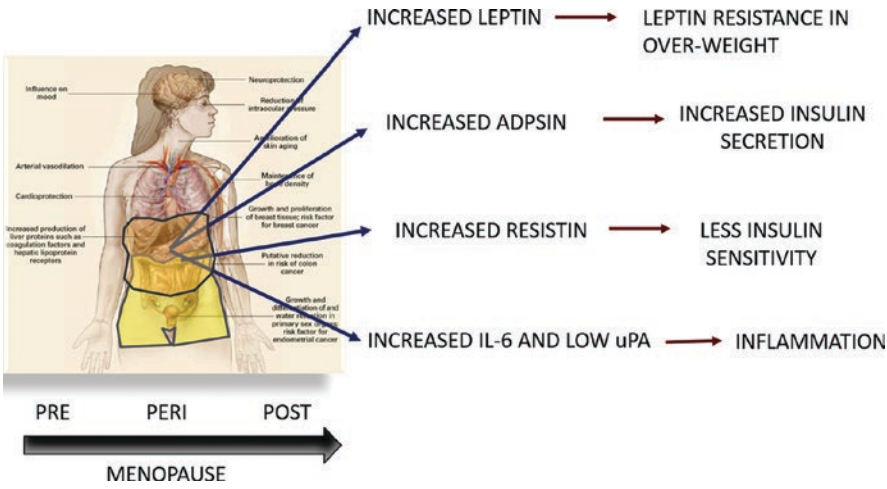

Fig. 12.1 Adipokines and cytokines' effect in insulin metabolism and adiposity during menopausal transition

follow-up study has indicated that women with depressive symptoms at baseline presented a 2.5-fold risk to have MetS at the end of the follow-up, significantly higher compared to men [21].

However, the pathogenesis of the increased risk of MetS in population diagnosed with depression is still unclear. In a recent large population of middle-aged adults, a history of depression was associated with an augmented risk of arterial stiffness assessed peripherally, and this association was partly mediated through MetS. Specifically, approximately one third of the association of depression with arterial stiffness index seemed to be mediated through MetS. In addition, when evaluated the individual components of MetS, abnormal waist circumference was the main contributor of the association between depression and arterial stiffness among women, but not in men [22].

12.4 Obesity: The Key Common Denominator in Women's Health

The rising prevalence of obesity is one of the main concerns in modern society. The World Health Organization estimates that more than 1 billion people are overweight and 300 million are obese. Up to 30% of nonpregnant women ages 20–39 are obese, and 8% of women in reproductive age are extremely obese, putting them at greater risk not only for severe cardiovascular and metabolic disorders but also for pregnancy complications.

Obesity negatively affects women's health in many ways. Being overweight or obese increases the risk of DMT2 and coronary artery disease in women. Furthermore, obesity negatively affects both contraception and fertility. Maternal

obesity is linked with higher rates of pregnancy complications, including gestational hypertension and preeclampsia, gestational diabetes, and cesarean delivery. Fetuses from excessive weight women are at higher risk for malformation, prematurity, stillbirth, macrosomia, and labor injury. Finally, children from obese women are at increased risk for long-term complications, as adulthood obesity and DMT2 [23].

12.4.1 Obesity and Fertility

Obesity affects fertility throughout a woman's life. Soon at young age, obesity determines alterations on reproductive system. Obese girls frequently experience the onset of puberty at a younger age than their normal-weight peers. This is probably one of the main determinants, in the last 40 years, of the decrease in the median age of menarche in developed countries.

Obesity negatively affects contraception as well. Previous studies have reported that hormonal contraception methods are less effective in obese women [24]. A retrospective cohort study suggested that women in the highest quartile of body weight had a higher risk of failure than women of lower weight and the risk of failure was greater in women using very low-dose or low-dose oral contraceptives [25]. In contrast, a recent large European cohort study did not demonstrate that BMI alters significantly contraceptive efficacy of oral contraceptive pills [26]. Interesting evidence come from studies evaluating non-oral contraceptive methods in obese women compared to lean controls. A study of more than 1000 women using the levonorgestrel vaginal ring demonstrated increased rates of failure after 1 year of use in the group of heavier patients, weighing 80 kg or more, compared to lean controls. The intrauterine device may be proposed as one of the most reliable contraception options since BMI seems not to influence the efficacy [27].

The association between obesity and menstrual disturbances is strong. Cross-sectional studies report that up to half of overweight and obese women have irregular menses, mostly oligomenorrhea and amenorrhea [28]. In this scenario, the link between obesity and PCOS-related disorders is solid. The potential role of obesity in favoring the development of PCOS has been determined the development of the concept of "PCOS secondary to obesity" [5]. Obesity may impact on the development of PCOS in several ways. The presence of obesity during childhood and adolescence probably plays a key role. It has been extensively suggested that female children and young girls presenting obesity have a significantly higher risk of PCOS compared to lean controls. Moreover, adolescent obese girls with irregular menses present alterations in menses and anovulation which persists for many years, even after weight loss. This can be explained since excess body weight negatively affects hypothalamic-pituitary-gonadal axis during puberty, leading to high LH levels and androgen excess. Adiposity in both girls and boys can determine an early activation of the axis and precocious central activation of puberty. In addition, obesity per se may determine an increased androgen production in both young girls and adults, particularly those with android fat distribution, which is often found in PCOS

women. Peripubertal obesity is associated with hyperandrogenemia, evaluated by high total testosterone and/or free androgen index, abnormal LH secretion, and hyperinsulinemia, and BMI is the best indicator for androgen excess [29]. Interestingly, in obese girls, both ovarian and adrenal androgens appear elevated, suggesting that in presence of overweight during puberty, a mixed adrenal and ovarian oversecretion of androgens may favor the development of PCOS.

Another contributing factor for PCOS development in obesity is hyperinsulinemia. Insulin excess is able to directly stimulate adrenal steroidogenesis and increase insulin growth factor-1. In addition, it has been suggested that, in susceptible girls, obesity-related hyperinsulinemia during puberty may cause hyperandrogenemia, by interfering with the normal negative feedback in the hypothalamus and thus enhancing GnRH pulsatility and increasing LH secretion. On the other hand, hyperandrogenemia seems to be able to reduce insulin sensitivity in both fat tissue and muscles. In both subcutaneous tissue and muscles, androgens may interfere with insulin signaling, inhibiting glycogen synthesis and increasing insulin resistance [30].

12.4.2 Obesity and Pregnancy

Obesity has become the major contributor to the global burden of disease worldwide, and its prevalence is growing in pregnant women, even with a large variability among countries and continents. In Australia up to one third of the pregnant women are overweight or obese; accordingly, in the USA it has been recorded a 69% increase in obesity among pregnant women from 1993 to 2003. The obesity rate in pregnant women in Mediterranean countries is far less [31, 32].

Obesity is associated with reduced fecundity mostly but not exclusively related to anovulation. Prolonged time to pregnancy (>12 months) is present also in obese women with regular cycles. Obesity is also linked to poor oocyte and embryos quality in obese women undergoing assisted-reproductive techniques, with a lower live birth rate in obese compared with normal-weight women [33]. Therefore, in overweight and obese women seeking pregnancy, weight-loss interventions, including diet, exercise, and eventually medication treatment, should be addressed as the initial management of infertility women.

Obesity during pregnancy may determine severe complications in both mother, fetus, and newborns, with an overall health-care expenditure, measured by length of hospital stay and use of services to handle long-term complications.

Obese pregnant women have higher risk of fetal anomalies, including neural tube defects and spina bifida, cardiovascular malformations, and cleft lip and palate. Moreover, prepregnancy obesity and excessive gestational weight gain are the main contributor of the development of pregnancy-induced hypertension, late preeclampsia, and gestational diabetes. Obese women are also at higher risk of receiving a cesarean section, and performing obstetrics surgery is more difficult in obese women, besides a higher postoperative thrombotic and infective risk [23].

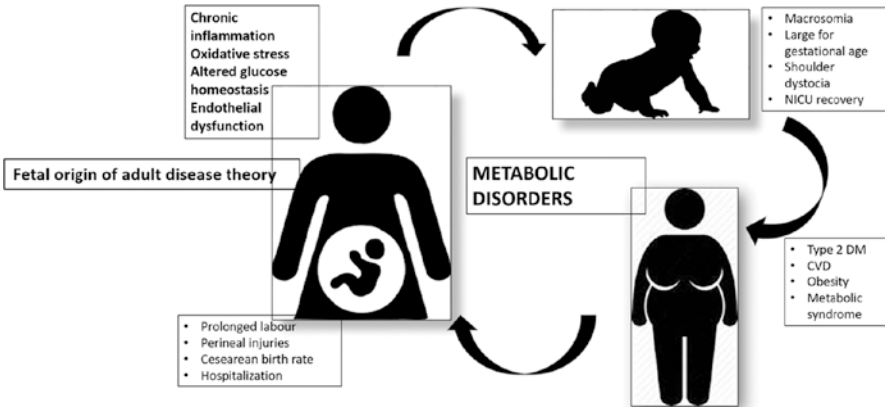

Fig. 12.2 Complex relationship between metabolic disorders in pregnancy and short- and long-term consequences for mother, fetus, and newborn

Bariatric surgery can be the preferred option in obese women seeking pregnancy. Several studies have pointed that after bariatric surgery the possibility of achieving pregnancy is higher and faster. In a large proportion of PCOS women, bariatric surgery determines the normalization of sex hormone levels and the correction of menstrual cycle disorders. Women who had delivered children after surgery showed decreased rates of gestational hypertension, preeclampsia, gestational diabetes, and fetal macrosomia, compared with women who delivered before surgery [34].

In addition, obesity and maternal hyperglycemia during pregnancy may induce intrauterine overnutrition and fetal hyperinsulinemia, resulting in excessive fetal growth. Fetal macrosomia is associated with an increased risk of perinatal morbidity and mortality. Large babies have increased risk of intrapartum complications such as prolonged labor and shoulder dystocia [35]. Moreover, the environmental and metabolic characteristics of intrauterine life deeply influence the individual in the long-term as a child and through adulthood, with possible adverse metabolic consequences, including predisposition to insulin resistance and obesity. Children born to hyperglycemic/hyperinsulinemic intrauterine environment could serve as a unique model of a high-risk population to study fetal programming or early origins of obesity [36] (Fig. 12.2).

12.4.3 Obesity and Cancer Risk

Obesity has been related to a large number of cancers in both women and men. In females, the greater risk is for colon, breast, and endometrium cancer. The physiological mechanisms to explain the effects of adiposity on cancer risk include an increased endogenous production of reactive oxygen species and consequent greater oxidative DNA damage, alterations in carcinogen-metabolizing enzymes, and impairment in endogenous hormone metabolism [37, 38].

In breast and endometrium cancer, abdominal fat may determine alterations in the metabolism of sex steroids, mostly androgens, estrogens, and progesterone. Sex steroids participate in the balance between cellular differentiation, proliferation, and apoptosis, and may also determine the selective growth of preneoplastic and neoplastic cells.

In addition, obesity, and specifically the accumulation of visceral fat, determines an increased secretion of insulin from pancreas. Consequently, chronically increased insulin levels lead to reduced synthesis of IGF-binding protein-1 and 2 (IGFBP1 and 2), with an increased IGF1 activity. Insulin and IGF1 also strongly stimulate cell proliferation, inhibit apoptosis, and can enhance angiogenesis [39]. Finally, insulin and IGF1 both inhibit the synthesis of SHBG, the major carrier glycoprotein for circulating sex hormones, thus increasing the amount of unbound sex-steroid available for bioactivity, which again can participate in tumorigenesis.

References

1. Broekmans FJ, et al. PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG. 2006;113(10):1210–7.
2. Azziz R, et al. The androgen excess and PCOS society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91(2):456–88.
3. van der Spuy ZM, Dyer SJ. The pathogenesis of infertility and early pregnancy loss in polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol. 2004;18(5):755–71.
4. Bellver J, et al. Polycystic ovary syndrome throughout a woman's life. J Assist Reprod Genet. 2018;35(1):25–39.
5. Pasquali R, Gambineri A. New perspectives on the definition and management of polycystic ovary syndrome. J Endocrinol Investig. 2018;41(10):1123–35.
6. Ehrmann DA, et al. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999;22(1):141–6.
7. Legro RS. Obesity and PCOS: implications for diagnosis and treatment. Semin Reprod Med. 2012;30(6):496–506.
8. Coviello AD, Legro RS, Dunaif A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. J Clin Endocrinol Metab. 2006;91(2):492–7.
9. Hughan KS, et al. Early biomarkers of subclinical atherosclerosis in obese adolescent girls with polycystic ovary syndrome. J Pediatr. 2016;168:104–11. e1
10. Oh JY, et al. Serum C-reactive protein levels in normal-weight polycystic ovary syndrome. Korean J Intern Med. 2009;24(4):350–5.
11. Dokras A. Mood and anxiety disorders in women with PCOS. Steroids. 2012;77(4):338–41.
12. Chittenden BG, et al. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed Online. 2009;19(3):398–405.
13. Pierpoint T, et al. Mortality of women with polycystic ovary syndrome at long-term follow-up. J Clin Epidemiol. 1998;51(7):581–6.
14. Expert Panel on Detection, E. and A. Treatment of high blood cholesterol in, executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA, 2001. 285(19): p. 2486–2497.
15. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and nutrition examination survey. JAMA. 2002;287(3):356–9.

16. Codner E, Merino PM, Tena-Sempere M. Female reproduction and type 1 diabetes: from mechanisms to clinical findings. Hum Reprod Update. 2012;18(5):568–85.
17. Pal L, et al. In vitro evidence of glucose-induced toxicity in GnRH secreting neurons: high glucose concentrations influence GnRH secretion, impair cell viability, and induce apoptosis in the GT1-1 neuronal cell line. Fertil Steril. 2007;88(4 Suppl):1143–9.
18. Palla G, et al. Perimenopause, body fat, metabolism and menopausal symptoms in relation to serum markers of adiposity, inflammation and digestive metabolism. J Endocrinol Investig. 2020;
19. Chedraui P, et al. Circulating leptin, resistin, adiponectin, visfatin, adipsin and ghrelin levels and insulin resistance in postmenopausal women with and without the metabolic syndrome. Maturitas. 2014;79(1):86–90.
20. Chedraui P, et al. Angiogenesis, inflammation and endothelial function in postmenopausal women screened for the metabolic syndrome. Maturitas. 2014;77(4):370–4.
21. Vanhala M, et al. Depressive symptoms predispose females to metabolic syndrome: a 7-year follow-up study. Acta Psychiatr Scand. 2009;119(2):137–42.
22. Dregan, A., et al., Associations between depression, arterial stiffness, and metabolic syndrome among adults in the UK biobank population study: a mediation analysis. JAMA Psychiatry, 2020.
23. ACOG. Practice bulletin no 156: obesity in pregnancy. Obstet Gynecol. 2015;126(6):e112–26.
24. Group, E.C.W. Nutrition and reproduction in women. Hum Reprod Update. 2006;12(3):193–207.
25. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. Obstet Gynecol. 2002;99(5 Pt 1):820–7.
26. Dinger JC, et al. Oral contraceptive effectiveness according to body mass index, weight, age, and other factors. Am J Obstet Gynecol. 2009;201(3):263.
27. Lash MM, Armstrong A. Impact of obesity on women's health. Fertil Steril. 2009;91(5):1712–6.
28. Practice Committee of American Society for Reproductive, M., Obesity and reproduction: an educational bulletin. Fertil Steril, 2008. 90(5 Suppl): p. S21–9.
29. McCartney CR, et al. Obesity and sex steroid changes across puberty: evidence for marked hyperandrogenemia in pre- and early pubertal obese girls. J Clin Endocrinol Metab. 2007;92(2):430–6.
30. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33(6):981–1030.
31. Callaway LK, et al. The prevalence and impact of overweight and obesity in an Australian obstetric population. Med J Aust. 2006;184(2):56–9.
32. Kim SY, et al. Trends in pre-pregnancy obesity in nine states, 1993-2003. Obesity (Silver Spring), 2007 15(4): 986–93.
33. Fedorcsak P, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod. 2004;19(11):2523–8.
34. American College of, O. and Gynecologists, ACOG practice bulletin no. 105: bariatric surgery and pregnancy. Obstet Gynecol, 2009. 113(6): p. 1405–1413.
35. Committee on Practice, B.-O., Macrosomia: ACOG Practice Bulletin, Number 216. Obstet Gynecol, 2020. 135(1): p. e18-e35.
36. Parlee SD, MacDougald OA. Maternal nutrition and risk of obesity in offspring: the Trojan horse of developmental plasticity. Biochim Biophys Acta. 2014;1842(3):495–506.
37. Manjgaladze M, et al. Effects of caloric restriction on rodent drug and carcinogen metabolizing enzymes: implications for mutagenesis and cancer. Mutat Res. 1993;295(4–6):201–22.
38. Muskhelishvili L, et al. Age-related changes in the intrinsic rate of apoptosis in livers of diet-restricted and ad libitum-fed B6C3F1 mice. Am J Pathol. 1995;147(1):20–4.
39. Khandwala HM, et al. The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev. 2000;21(3):215–44.