MECHANISMS IN ENDOCRINOLOGY

Metabolic syndrome through the female life cycle

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Abstract

The normal function of the female reproductive system is closely linked to energy homeostasis with the ultimate scope of fertility and human race perpetuation through the centuries. During a woman's lifetime there are normal events such as puberty, pregnancy and menopause which are related to alterations in energy homeostasis and gonadal steroids levels followed by increase of body fat and insulin resistance, important components of metabolic syndrome (MetS). Pathological conditions such as premature adrenarche, polycystic ovary syndrome and gestational diabetes also present with shifts in gonadal steroid levels and reduced insulin sensitivity. The aim of this review is to discuss these conditions, both normal and pathological, analyzing the changes or abnormalities in ovarian function that coexist with metabolic abnormalities which resemble MetS in relationship with environmental, genetic and epigenetic factors.

Introduction

Metabolic syndrome (MetS) or insulin resistance syndrome or syndrome X was first described by G Reaven in 1988 (1). It refers to a clustering of cardiovascular disease risk factors whose underlying pathophysiology are thought to be related to insulin resistance and central obesity like glucose intolerance, dyslipidemia, hypertension, prothrombotic and proinflammatory factors (2). Since the first definition of MetS by the World Health Organisation (WHO) in 1998 at least four other definitions have been proposed with different diagnostic parameters and threshold values. The definition of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) in 2001 is more often used in epidemiological studies. Nowadays, many scientists doubt the existence of MetS and the usefulness of the

term, nevertheless the importance of the cardiovascular disease risk factors that it comprises cannot be doubted (3).

Adipose tissue functions as an endocrine gland with multiple actions in other organ-tissue targets including the brain (4). The synthesis and secretion of a great variety of proteins like leptin and adiponectin, cytokines like tumor necrosis factor-alpha (TNF-α) and interlukin-6 (IL-6) and metabolic substrates like free fatty acids allow adipose tissue to play an important role in energy balance and glucose homeostasis (5). Furthermore, adipose tissue participates actively in the regulation of coagulation/fibrinolysis and, through enzymatic conversion of sex steroids and corticosteroids can modify the function of the cardiovascular, immune and reproductive systems (6). Adipose tissue dysfunction leads apart from visceral

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obesity to ectopic accumulation of lipids in other tissues such as the skeletal muscles, liver, pancreas and heart, and contributes to insulin resistance and metabolic disease (7).

During a woman's lifetime, there are physiological events such as puberty, pregnancy and menopause, which are closely related to alterations in energy homeostasis and gonadal steroids levels followed by an increase of insulin resistance and body fat, important components of MetS (8). In addition, pathological conditions may exist such as premature adrenarche, polycystic ovary syndrome (PCOS) and gestational diabetes, which also present with alterations in gonadal steroid levels and increased insulin resistance (9).

The aim of this article is to discuss both physiological and pathological events during a woman's lifetime analyzing the changes or abnormalities in ovarian function that co-exist with metabolic abnormalities that resemble MetS.

Ovarian function and energy homeostasis

The relationship between reproductive function with energy homeostasis and fat stores is now well-established. Adipose tissue seems to be the connecting link between these two systems through a complicated network of endocrine, autocrine, intracrine and paracrine interactions (4, 10). The discoveries of leptin 20 years ago and of adiponectin and resistin more recently have contributed in understanding the interactions of energy metabolism in hypothalamus–pituitary and peripheral organs, such as gonads, skeletal muscles and adipose tissue (11). The onset of menarche and reproductive function prerequisites the existence of a critical adipose mass, which, through leptin, sends a message to hypothalamus that the woman's energy stores are sufficient to support a pregnancy. The age of menarche has been found to be correlated to risk factors for metabolic disease and this association worsened when obesity was present (12). On the other hand, obesity leads to menstrual abnormalities, chronic anovulation, subfertility and in the case of pregnancy to higher frequency of abortions, gestational diabetes and pre-eclampsia (13).

Ovarian steroids influence both fat disposal and tissue sensitivity to insulin action. Estrogens promote peripheral fat distribution and improve insulin sensitivity, whereas testosterone promotes central fat distribution and reduces insulin sensitivity (14). The role of adrenal androgens, DHEA and DHEAS remains to be elucidated. Recent data converge to an anti-atherogenic action of those hormones through an improvement both in insulin resistance and

lipids metabolism (15). Moreover, sex hormone-binding globulin (SHBG) alters the biologic effects of sex hormones (testosterone and estrogen) on peripheral tissues (i.e. liver, muscle, and fat). Higher levels of SHBG are associated with lower BMI, increased insulin sensitivity, lower likelihood of hypertension and more favourable lipid-profile and C-reactive protein (CRP) levels. Low SHBG levels are considered a biomarker of the MetS and may predict the development of type 2 diabetes and cardiovascular disease especially in women (16, 17, 18).

MetS and puberty

Puberty is a normal process through which an immature girl transforms to a mature and capable to reproduce woman. This transition period is characterized by rapid increase of length growth, appearance of secondary sex characteristics and alterations in psychology and behavior. Still, it is accompanied by alterations in body composition with increase in lean and especially fat mass. This is known as the 'critical weight hypothesis', which means that a minimum weight or body fat percentage is necessary for pubertal development and menstrual function. Furthermore, conditions of severe metabolic stress and energy unbalance are commonly linked to alterations in puberty onset (19, 20). Puberty can be described as an insulin-resistant condition. A 30% decrease in tissue insulin sensitivity is recorded during progression from Tanner stage 1 to Tanner stage 3, which is accompanied by high fasting glucose and insulin levels, and a decrease in glucose disposition index. This abnormality is fully restored by completion of puberty (19). The mechanism responsible for insulin resistance during puberty has not yet been clarified. In a cohort of 3530 Chinese children aged 6–18 years, leptin levels emerged as a stronger predictor of insulin resistance than traditional anthropometric characteristics (19). Recent data show that increased insulin resistance during puberty is related to parallel increase in growth hormone, insulin-like growth factor-1 (IGF-1), IGF binding protein-3 (IGFBP-3) and leptin levels and decrease in IGFBP-1 and SHBG levels whereas it seems to be independent of alterations in body fat and serum levels of androgens and estrogens (19, 20). In vitro studies have indicated that insulin has trophic actions on ovarian theca-stromal cells by elevating luteinizing hormone (LH)-induced androgen production. It is noted that high doses of insulin can stimulate theca cell androgen production even in the absence of LH (21). Additional studies showed a positive correlation between fasting insulin and free testosterone in groups of

pubertal girls (22, 23). Another study provided evidence that levels of insulin can also predict the levels of free testosterone (24).

Premature adrenarche is defined as the appearance of pubic hair before the age of 8 in girls due to premature increase in adrenal androgen secretion (DHEA and DHEAS) of unknown etiology. It has been shown that girls with premature adrenarche have higher levels of insulin and insulin resistance compared to normal girls with similar BMI and androgen levels, just before the beginning of puberty. Specifically, a cross-sectional study, which evaluated the association of MetS and premature adrenarche in 63 prepubertal girls with premature adrenarche and 80 healthy age-matched control girls demonstrated that childhood MetS was more common in those with premature adrenarche than control children by both the WHO and modified ATP definition criteria. Additionally, girls with premature adrenarche had higher BMI and insulin and DHEAS levels (25). Moreover, a higher prevalence of functional ovarian hyperadrogenemia, dyslipidemia, and obesity has been observed in these girls after puberty (26). The previous abnormalities are more frequent in low-birth weight girls (< −1.5 s.D.), a finding consistent with the theory of 'fetal programming' of reproductive function (27). Body weight reduction or metformin administration, either prepubertally or postpubertally in girls with premature adrenarche, resulted in a significant improvement in insulin sensitivity, lipid profile, adipokine levels and a decrease of androgen levels as well (28). Thus, premature adrenarche could be the precursor of MetS in adult life, particularly in low-birth weight girls.

MetS and PCOS

PCOS is the most common endocrinopathy of women of reproductive age. Hyperandrogenism, insulin resistance, and chronic anovulation are the cardinal features of PCOS (29). The pathogenesis of PCOS is still unclear, though there is strong evidence that genetic factors are part of the syndrome's etiology, since high prevalence of the syndrome is recorded in members of the same family (30). Insulin resistance, high androgen levels (31) and dyslipidemia (32) have been found even in 'normal' members of patients' families. Research in determining the syndrome's background is focused to the two most prominent poles of its pathogenesis: steroidogenetic alterations and insulin resistance (33). Metabolic abnormalities met in PCOS are obesity, dyslipidemia, insulin resistance, hyperinsulinemia and glucose intolerance.

Obesity is reported in 25–70% of women with PCOS. This broad disparity is due to the different criteria used for the diagnosis of the syndrome and differences in geographical and environmental factors in relevant studies (34). Patients with PCOS usually show central obesity independently of BMI (35) and this characteristic affects the various phenotypes of the syndrome (36). It has been shown that PCOS women with central obesity have more often defects in insulin secretion and action, glucose intolerance, abnormalities in lipid metabolism, higher diastolic pressure and higher androgen levels compared to women of the same age and BMI (37). Obesity contributes to insulin resistance, which is an intrinsic feature of the syndrome and an aggravating factor of dyslipidemia (38). As insulin resistance is tightly related to adiponectin levels, women with PCOS have lower serum adiponectin levels than women without PCOS (39). With advanced age, the distribution of PCOS phenotypes seems to change with decline of hyperandrogenemia and worsening of insulin resistance (40). Moreover, age along with obesity appear to be better predictors of MetS in these women than the presence of the syndrome *per se* (41).

Dyslipidemia is probably the most frequent metabolic disorder in PCOS detected in 70% of patients according to the guidelines of NCEP and is due to its inherent characteristics (42). The most frequent abnormalities are low HDL-cholesterol, high LDL-cholesterol, low triglyceride and VLDL-cholesterol levels (43). A higher frequency of hypertension can be expected in women with PCOS, due to obesity and insulin resistance. However, hypertension is not a typical finding of the syndrome, at least during reproductive age (44).

Insulin resistance has been shown very early in a significant number of patients, independently of body weight (45), but tightly dependent on total fat mass and central fat mass (46). It is considered an important component of the syndrome and is thought to play a crucial role in PCOS pathogenesis. The assessment of insulin resistance in the various phenotypes of PCOS has shown that it is more pronounced in women with the severe phenotype and less in others with the ovulatory phenotype without any differences from control women (47). Insulin resistance is due to a defect in the intracellular transmission of insulin sign in muscles and adipose tissue, which appears to be related to excessive serine phosphorylation of the insulin receptor, in 50% of the patients. Insulin resistance in PCOS patients seems to be selective, as it only concerns metabolic and not mitogenic actions of insulin (48). There is a 35–40% reduction of insulin-depended glucose uptake by the

tissues similar to type 2 diabetes, which is independent of obesity, fat distribution and lean body mass (45). The noted insulin resistance leads to compensatory hyperinsulinemia with negative effects in various tissues. Hyperinsulinemia contributes to hyperandrogenemia that characterizes PCOS by increasing androgen secretion, due to direct stimulation of theca cells and by increasing androgen bioavailability due to decrease of SHBG secretion by the liver (49). Moreover, hyperinsulinemia is associated with endothelium dysfunction and alterations in lipid metabolism (50). In addition to insulin resistance there is a defect in early-phase insulin secretion in some patients (51), which along with positive family history of type 2 diabetes constitute predisposing factors for glucose intolerance and type 2 diabetes (52).

Recent data show that MetS in PCOS women may be present from puberty (53) and increases significantly by the third decade of life (54, 55). The increased prevalence of MetS in PCOS women has been reported in many ethnicities and different races (56). In the largest cohort study of Caucasian women with PCOS, the prevalence of MetS varied depending on PCOS criteria and MetS definition, but it was constantly and independently high when these women fulfilled the NIH criteria (57). Obesity and hyperandrogenemia seem to be aggravating factors (53, 56) while healthy lifestyle and Mediterranean diet acts beneficially (58).

Glucose intolerance or type 2 diabetes is reported in 20–40% of obese PCOS women by the fourth decade of their life, compared to 10% in the general population (59). Moreover, 15% of PCOS postmenopausal women present with type 2 diabetes, compared to 2.3% of normal women (60). It is noteworthy that glucose intolerance can be manifested even during puberty (59). In a recent meta-analysis PCOS was associated with a 2.5-fold higher risk for impaired glucose tolerance (IGT), a 4.5-fold for DM2 and 2.2-fold for MetS compared to BMI-matched control women (61).

Women with PCOS are a unique biological model to examine the combined effects of androgen excess, insulin resistance and dyslipidemia on the cardiovascular system. Metabolic abnormalities in PCOS may appear early in adolescence. Consequently these young patients are in high risk for early development of cardiovascular disease (62). There is controversy between the results of the studies assessing the potential association between PCOS and cardiovascular comorbidities. Particularly, the study by Wild *et al.* (63) showed that women with PCOS did not differ from age-matched controls in coronary artery mortality and morbidity despite having significantly

higher prevalence of both diabetes and family history of cardiovascular disease (63). On the other hand, PCOS patients have been estimated to have seven times greater risk of myocardial infarction (64). Similarly a fourfold risk in cardiac events among women with PCOS was reported in a cohort from the Czech Republic (65). Studies in a small numbers of patients showed high serum markers of early atherogenesis in women with PCOS like CRP, IL-18 and homocysteine (66) and endothelium dysfunction (67, 68, 69). The cardiometabolic risk has been reported to be worse in women with PCOS with hyperandrogenism compared to women without hyperandrogenism (70). Accordingly, higher androgen levels were reported in women with PCOS and MetS compared to women without PCOS and MetS (71). The assessment of preclinical or asymptomatic vascular disease with non-invasive procedures showed increased predisposition for atherosclerosis in young and middle-aged women with PCOS while a greater carotid intima-media thickness has been recorded (72, 73) compared to healthy women.

Two studies in younger (25–34 years old) (74) and older (35–62 years old) (75) women with PCOS demonstrated an elevated accumulation of coronary artery calcium measured by electron beam tomography independently of age and BMI. Data from small cross-sectional studies support an increased predisposition for atherosclerosis in premenopausal women with PCOS, but this has not been confirmed in retrospective studies (64, 76). Moreover, there are no clear answers if this premature atherosclerosis translates into increased cardiovascular morbidity or mortality after menopause (77, 78).

MetS and pregnancy

Pregnancy is a normal but stressful condition, characterized by various hormonal, biochemical and anatomical changes, as a gradual adjustment of the mother's body for a normal development of the fetus (79). These changes comprise increased insulin resistance, immunologic tolerance with a dominant Th2 response, thrombophilia and hyperdynamic circulation. Pregnancy is very important for the possible development of MetS both for the mother and the fetus. Regarding the mother, the adaptive changes can lead to the onset of gestational diabetes and/or preeclampsia, in a genetically predisposed person. Regarding the fetus, the nutritional, hormonal and metabolic environment afforded by the mother may program differentiating target tissues of the offspring towards the development of MetS and/or PCOS phenotype, which shares many components of MetS, in adult life.

Mother

The most important metabolic change that is noted in pregnancy is the gradual decrease in insulin sensitivity after the middle term of pregnancy that reaches the levels of type 2 diabetes (45–70%) in the third trimester. Insulin resistance increases in parallel to the growth of the embryo-placental unit and decreases immediately *postpartum*. These changes seem to be the result of mother's body weight increase and insulin-desensitization action due to increased circulating galactogen and progesterone levels, secreted by the placenta, prolactin and cortisol levels. As the pancreas responds to insulin resistance with a parallel increase of insulin production, there is a two- to threefold increase in fasting and postprandial insulin levels in normal pregnant women, which is attributed both to pancreas β-cells hyperplasia and increased sensitivity to secretive stimulations (79). BMI before pregnancy and antenatal fasting plasma glucose has been found to be the most predictive factors of MetS after delivery (80).

Gestational diabetes mellitus (GDM) appears as a result of the pancreas secretive failure to respond to the metabolic stress of pregnancy. In the majority of women, this occurs in the second half of pregnancy as mild glucose intolerance and is actually the evolution of MetS, which usually preexists (81). In a Greek cohort maternal MetS according to NHLBI/AHA criteria was found to predispose to gestational diabetes (relative risk=3.17) (82). The prevalence of GDM has been increased in developed countries during the last 20 years from 2.9% to 8.8% and even more in susceptible immigrant populations, partly as a result of the increased prevalence of obesity. Kim *et al.* 2002 estimated that 50–60% of the women which developed GDM are more prone to develop type 2 diabetes after 10 years (83). A prospective population-based study, which estimated the prevalence and the risk for diabetes and hypertension 20 years after delivery, the Northern Finland Birth Cohort, confirmed that women who were both overweight and developed GDM had significantly higher risk for diabetes and hypertension. Overweight women with normal oral glucose tolerance test prior to pregnancy showed increased risk for subsequent diabetes and hypertension (84). Two other prospective studies in Caucasian women showed that the prevalence of MetS in women with a history of GDM treated by diet alone was threefold higher compared to controls after 10 years of follow-up. In this group of women, the prevalence was even higher (5.6- to sevenfold) if they were overweight (85, 86).

Preeclampsia is a multi-systemic abnormality of unknown etiology affecting 3–5% of pregnancies. This disorder warrants high morbidity for the mother and serious implications for the embryo (perinatal death, premature labour, endometrial growth delay). It is characterized by inappropriate vascular response to placentogenesis, which is related to endothelium dysfunction and increased peripheral vascular resistance, coagulation system activation and platelet agglutination. It is clinically manifested by hypertension and proteinuria with or without other multi-systemic anomalies. The embryo usually presents with delay in endometrial growth, decrease in amniotic fluid and oxygen insufficiency (87). Moreover, several epidemiological studies revealed that preeclampsia is associated with an increased cardiovascular risk and a predisposition for chronic renal disease (88).

Obesity, insulin resistance and preexisting diabetes are risk factors for the development of preeclampsia (89, 90). Many epidemiological studies showed higher prevalence of insulin resistance in women with preeclampsia compared to controls, both prior and during pregnancy (91). Many researchers share the opinion that insulin sensitivity reduction, as expressed by the decrease in SHBG or adiponectin levels, predisposes to preeclampsia. Specifically, it was shown that women with decreased levels of SHBG during the first trimester of pregnancy presented an increased risk for preeclampsia (92). In accordance, decreased levels of serum high-molecular weight adiponectin were correlated with mild preeclampsia (93).

Fetus

Evidence suggests that the environment afforded by the mother may permanently program differentiating target tissues of the offspring toward the development of MetS and/or PCOS phenotype in adult life (94). In general, we could say that the association of birth weight and MetS seems to be U-shaped, with a higher prevalence of MetS occurring in subjects with both low and high birth weights.

At first, epidemiological observations provided a link between intrauterine undernutrition and increased risk for later obesity. Individuals who were *in utero* during the Dutch famine at the end of World War II had low birth weight and impaired glucose tolerance at the age of 50 years. This association was stronger regarding the last trimester of pregnancy (95, 96). After this very interesting study, other epidemiological studies followed showing that low birth weight is associated with increased BMI, higher prevalence of impaired glucose tolerance and/or high risk of coronary heart disease (97, 98).

A number of clinical studies have shown that association between low birth weight and MetS in adult life (99, 100, 101), with some supporting that higher prevalence of diabetes occurs in subjects with both low and high birth weights (99). The second association can be largely explained by the presence of maternal diabetes during pregnancy. High birth-weight children from mothers with GDM or MetS during pregnancy are at high risk for the development of obesity and MetS, during early childhood. A 15-year follow-up Chinese study confirmed that adolescent offspring of mothers with GDM, independently of birth weight, showed a 17-fold increase in MetS and a tenfold increase in overweight at adolescence (102). Obese mothers tend to have obese children (103) but clinical interventions targeting maternal weight loss can have a positive effect on reducing risk of obesity in offspring (104).

Of great interest, other studies have shown that the highest risk for development of MetS and diabetes occur in adults who are born small and become overweight in early childhood. This is also associated with early pubertal development in girls followed by functional hyperandrogenism in adolescence and the development of PCOS in adult life (105, 106). This phenomenon can be explained by the very early development of insulin resistance that affects body composition and leads to PCOS through an hyperinsulinemic pathway (105, 106). However, a direct link between birth weight and PCOS has not yet been documented (107).

Experimental animal studies investigating the link between early programming and adult metabolic disease have mainly concentrated on the effects of prenatal nutritional environment and especially on the effects of calorie or protein restriction and showed that the effects of intrauterine deprivation are either due to inadequate maternal diet or poor placental function. Both functions are thought to be mediated by glucocorticoids. Furthermore, it has been proposed that overexposure of the fetus to excess glucocorticoids may be implicated in the association between fetal growth restriction and the programming of adult metabolic disease (108, 109).

Intrauterine deprivation may program adipocyte metabolism and fat mass to give rise to later obesity or may affect the pancreatic islet neogenesis impairing the capacity of β-cell regeneration (108). Besides prenatal undernutrition models, metabolic intrauterine environment may also be modified in case of prenatal over-nutrition and this has been shown by experimental models as well, which gave evidence that increased dietary fat intake during pregnancy and lactation predisposes the offspring to developing an MetS-like phenotype in adult life (110). A number of animal studies, most of them using the prenatally androgenized female rhesus monkey, have also shown that experimentally induced androgen excess during fetal life may lead not only to reproductive but also metabolic abnormalities in later life that resemble those found in women with PCOS (111).

The mechanisms of fetal programming are not well understood. At first, the altered tissue differentiation may be the result of the phenomenon of developmental plasticity which represents homeostatic adaptations due to alterations in fetal nutrition (17). For example, the fetus can decrease basal metabolic rate and nutrient delivery to tissues by reducing the capillary network (112). It can also reduce the size of the most metabolically active tissues such as nephrons or alter the balance between energy-consuming and energy-storing tissues (113). Furthermore, tissues under the influence of androgen excess which may act as potent gene transcription factors may be directed toward a more masculine phenotype in fact toward to MetS and/or PCOS adult phenotype (114). Of great interest, androgens are potent inhibitors of adipogenic differentiation of pre-adipocytes into adipocytes. Thus, when androgens are in excess the capacity of subcutaneous adipose tissue expansion in a metabolically safe way is diminished. This may lead to a more visceral fat distribution phenotype in adult life (115).

The role of epigenetics cannot be overlooked. The term refers to heritable changes, which affect gene function without modifying the DNA sequence. Epigenetic marks are tissue specific and include DNA methylation and histone modifications. Methylation is usually obtained through the addition of a methyl group (CH_3—) to a cytosine positioned next to a guanine nucleotide. Methylation in a promoter region results in the repression (silencing) of gene expression. Potential epigenetic mechanisms have been suggested for MetS and refer mostly to: the *FTO* locus, which is a DNA-demethylase enzyme (116), the *MC4R* gene which has reduced methylation following long-term exposure to a high fat diet (117), the *PPAR*γ protein, which interacts with histone acetyltransferases during adipogenesis and on the effect of diet on methylation of *POMC* (118) and *Leptin* (119). Interestingly, epigenetic changes can be inherited, explaining at least in part the familial clustering of MetS.

MetS and menopause

Menopause is a normal biological phenomenon due to the final exhaustion of ovarian pool of follicles and is defined

clinically by the absence of menstrual bleeding for at least 12 months. It is accompanied by hormonal alterations and signals a high-risk period for the manifestation of metabolic abnormalities and cardiovascular disease.

During menopause, a significant fall in estrogen levels is observed (80%), though ovarian androgen production is reduced only by 30% due to the maintenance of a small steroidogenic ability, which comes from epithelial and mesenchymatic cells of the stroma and mainly concerns the production of androgens (120). This 'relative' adequacy of androgens seems to be independent of menopause and is related to the normal procedure of ageing. Adipose tissue contributes to partial restoration of this alteration of steroid hormones through aromatization of weak adrenal androgens (DHEA and DHEAS), into more active androgens or/and estrogens (121).

The incidence of cardiovascular disease, which is the leading single cause of death among women, increases substantially after menopause. The prevalence of cardiovascular disease differs significantly between men and premenopausal women of similar age possibly due to the action of estrogens as no difference has been observed between men and postmenopausal women at the age of seventy (122). Estrogens exert a cardio-protective role in several ways: direct actions on vascular wall (increased vascular dilation, inhibition of the response to vessels injury), improvement in lipid profile and insulin sensitivity and enhanced peripheral deposition of fat. The role of androgens in cardiovascular disease pathogenesis in women has not yet been clarified and results from epidemiologic studies are contrasting. Whether or not menopause has a causative contribution to the deteriorating metabolic profile that is independent of chronological aging is still being debated (121). Pro-atherogenic changes in lipid and apolipoprotein profiles seem to be specifically related to ovarian aging; unfavorable changes in other cardiovascular risk factors may be influenced more by chronologic aging (122). The onset of MetS after menopause is mostly due to estrogen deficiency that encourages an unfavourable change of body composition, mainly increase in central obesity (123).

Changes recorded after menopause that are stably related to MetS are: i) redistribution of body fat, ii) decrease in tissues' insulin sensitivity and glucose intolerance that are directly related to the degree of central obesity, iii) alterations in lipid profile with a decrease in HDL_2-cholesterol and increase in triglycerides, LDL-cholesterol and Lp(a), iv) increase in plasminogen activator inhibitor-1 (PAI-1) and activator of tissue plasminogen (t-PA) and v) increase in pro-inflammatory

markers, like IL-6 and CRP 9 (120, 121, 122, 123, 124). Very recent studies showed an association between MetS and serum leptin levels in postmenopausal women (125) and a possible inverse association of higher serum 25(OH)D concentrations with adiposity, triglycerides, triglyceride:HDL ratio and MetS (126). Also, low levels of SHBG are independently related to the degree of central obesity, insulin resistance and pro-inflammatory states in older women and are considered a biomarker of the MetS in menopause (18, 19).

Conclusions

Women with premature adrenarche, PCOS, GDM in combination with obesity, low or high birth-weight and positive family history for type 2 diabetes and cardiovascular disease should be evaluated for metabolic abnormalities. Menopause, although a normal event in a woman's life, is associated with weight gain, increased central fat mass, abnormal lipid metabolism, insulin resistance and susceptibility to MetS (Fig. 1).

The increasing prevalence of obesity, MetS and comorbidities necessitate prompt identification and early management of subjects at high risk. Recognition and
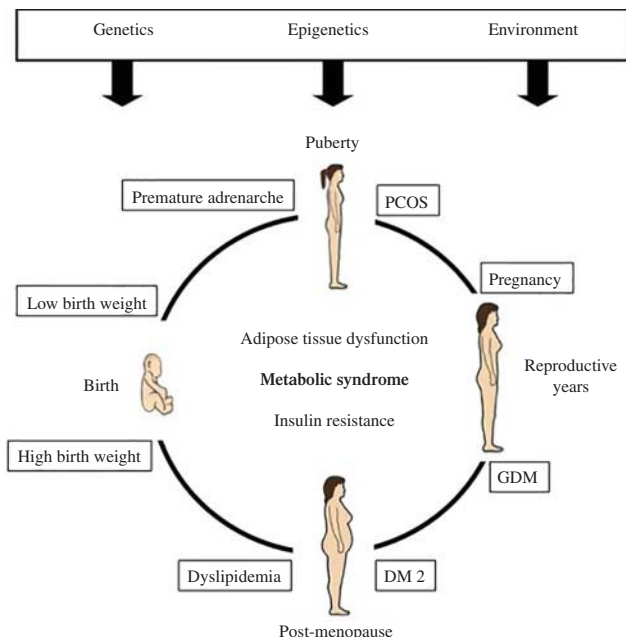

Figure 1

Normal and pathological events related to metabolic syndrome through the female life cycle. A full colour version of this figure is available at http://dx.doi.org/10.1530/EJE-15-0275.

treatment of MetS from childhood should be the main target for clinicians. Modification in lifestyle, such as balanced diet and frequent physical activity, are interventions of great importance in order to improve the metabolic abnormalities and achieve a decrease of subsequent cardiovascular risk. In the case of women, all these gain double importance, not only for themselves but also for their, continuing the perpetual cycle of life.

Author contribution statement

A Vryonidou contributed in the conception, design, drafting and revision of the paper critically for important intellectual content. S A Paschou contributed in the conception, design and drafting the paper. G Muscogiuri, F Orio and D G Goulis contributed in revising the paper critically for important intellectual content.

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