Polycystic Ovary Syndrome and Obesity

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Introduction

The importance of obesity rests in its clinico-pathological sequelae, which are far-reaching, and affect virtually every tissue of the body. It is these sequelae that contribute towards the ever-burgeoning obesity epidemic, through effects on morbidity, premature mortality, psycho-social functioning, work productivity and healthcare expenditure. Polycystic Ovary Syndrome (PCOS) is commonly associated with obesity in reproductive-age women [1–4].

PCOS is the commonest endocrine condition to affect reproductive-age women. Its prevalence varies between studies, but has been estimated at 6–10 % of pre-menopausal women [5–7], a figure that is likely to increase in the future as the global obesity epidemic ensues. The cardinal characteristics of PCOS, and those that form its diagnostic criteria include oligo-amenorrhoea (irregular and infrequent or absent menses) and hyperandrogenic features (hirsutism, acne, androgenic alopecia, or biochemical evidence of raised androgens such as testosterone) [4]. Although not a diagnostic feature, an important aspect of PCOS is its association with metabolic aberrations that include insulin resistance, dyslipidemia, non-alcoholic fatty liver disease [8] and a higher risk for developing Type 2 Diabetes Mellitus (T2DM) [9]. Obese women with PCOS generally manifest a metabolic 'double-whammy', resulting from effects of PCOS *per se* (that is associated with insulin resistance, independent of co-existent obesity) and obesity [4, 10]. Insulin resistance is implicated in the aetiology of PCOS, and this may explain why development of obesity (with associated insulin resistance) is usually required to unmask the clinical and biochemical features of PCOS [4, 11], and why PCOS often becomes manifest during adolescence [4]. It is also apparent that Obstructive Sleep Apnoea (OSA) (see also chapter 10 to be filled later), a condition that is associated with insulin resistance independent of fat mass, is common in women with PCOS, with risk of OSA being five- to tenfold higher in PCOS than in BMI-matched control women [12]. Furthermore, the increased risk of early-onset impaired glucose tolerance (30–40 %) and T2DM (10 %) in women with PCOS, may be further heightened through concurrence with OSA

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[12, 13]: PCOS, obesity and OSA representing a metabolic 'triple-whammy'.

In this chapter, the complex links between obesity and PCOS will be explored. This will include: analysis of evidence to support a link between obesity and PCOS; discussion of the role of fat in the manifestation of PCOS through effects on insulin resistance, steroid metabolism and adipokines; exploration of the heterogeneity of cardio-metabolic risk factors in PCOS; outline of fat distribution in PCOS, and review of the treatment strategies for obese women with PCOS.

Linking PCOS with Obesity Through Epidemiology and Genetics

There is clear evidence in the literature to support a link between PCOS and obesity. Epidemiological data reveal that the majority of women (between 38 and 88 %, depending on the study) with PCOS are either overweight or obese [4, 6, 7]. The link between PCOS and obesity is further strengthened from an aetiological perspective, with observations that even modest weight-loss of just 5 % in obese women with PCOS can result in improvements in the clinical and biochemical features of PCOS, including menstrual cyclicity, fertility, hirsutism and, of course insulin resistance and other cardio-metabolic risk factors [1, 2]. More recent evidence to corroborate the epidemiological and aetiological links between PCOS and obesity comes from genetic studies.

Following a genome-wide association study (GWAS) on obese subjects with T2DM versus controls, *FTO* (fat mass and obesity-associated gene) was the first gene demonstrated to have a robust effect on susceptibility for development of common polygenic obesity [14, 15]. Variants within *FTO* are known to influence fat mass, with a per-allele difference in BMI of approximately 0.36 kgm^{-2} [14]. Given that development of T2DM is influenced by fat mass, it was hypothesized that *FTO* variants contribute to susceptibility for development of T2DM (Odds Ratio [OR] 1.27) via effects on fat mass [14]. Given that PCOS development is also influenced by fat mass, our own group conducted a study on 463 UK PCOS cases compared with >1300 UK female controls, with genotyping of the rs9939609 single nucleotide polymorphism within *FTO* [11]. We demonstrated a significant association between this *FTO* variant and PCOS-status (OR per minor allele copy 1.30), attenuated by adjustment for BMI between cases and controls. In this study, we demonstrated the first genetic evidence to corroborate a mechanistic link between PCOS and obesity [11]. Association between variants in *FTO* and PCOS have since been confirmed in other studies from diverse populations [16–18]. As demonstrated in our study [11], it would appear that the association of *FTO* variants with PCOS is influenced by the disparity of BMI between cases and controls, further supporting mediation of effects of *FTO* through fat mass.

As outlined in the introduction, obesity is neither necessary for PCOS to develop (a minority of women with PCOS are lean), nor is PCOS an inevitable consequence of obesity (indeed, most obese women do not develop PCOS). Our current understanding, based on the known heritability of PCOS [19–21] and the epidemiological studies outlined above, is that two factors are usually required for manifestation of PCOS: (i) an underlying genetic susceptibility (likely oligogenic), and (ii) weight gain and obesity. This dual perspective would explain why not all obese women develop PCOS, this condition only manifesting in those women who are genetically predisposed to its development. In this sense, PCOS is analogous to the development of T2DM, which typically manifests following development of weight gain-related insulin resistance in those who are genetically predisposed.

Fat as a Contributor to Development of PCOS

Weight-gain and obesity are important prerequisites for manifestation of PCOS in most women who are genetically predisposed to its development. The mechanisms implicated warrant further discussion. In this section, we explore two important consequences of increasing

adiposity: enhanced insulin resistance and its effects on steroid metabolism and adipokines. For each, we discuss current evidence to support mediating roles in the development of PCOS.

Fat and Insulin Resistance in PCOS

PCOS is associated with insulin resistance [22] and between 50 and 90 % of women with PCOS are insulin resistant beyond that what would be expected in age- and BMI-matched control women without PCOS [23–25]. Insulin resistance results in compensatory hyperinsulinemia, which in turn has pleiotropic effects on peripheral tissues including ovary. Insulin has co-gonadotrophic effects within ovarian theca cells, interacting synergistically with luteinising hormone (LH) [26–28]. The synergy of insulin and LH (through activation of CYP17 [P450c17α], a key enzyme in ovarian androgen biosynthesis), results in enhanced generation and release of androgens [29]. Insulin also causes arrest of pre-antral follicle development [30, 31]. Through these mechanisms, insulin promotes hyperandrogenemia and menstrual disturbance respectively. Conversely, improvement in insulin sensitivity in PCOS (with a resulting fall in serum insulin levels) either through drug therapy or weight-loss results in improved metabolic profile, ovulatory function, menstrual cyclicity and fertility [2, 4, 32]. Thus, as with metabolic syndrome [33], insulin resistance (which is worsened by weight-gain) is believed to underlie aetiology of PCOS [4].

In addition to ovarian effects, insulin has been shown to enhance LH pulse amplitude in pituitary tissue in rodent models [24, 34]. There is also evidence in PCOS to implicate insulin in stimulation of adrenal P450c17α activity [29], and suppression of hepatic sex hormone binding globulin (SHBG) production [35, 36]. Such peripheral non-ovarian effects of insulin in PCOS would be expected to further exacerbate hyperandrogenemia through enhanced LH-stimulation of ovarian androgen production, enhanced adrenal androgen production, and an increase in free (biologically available) testosterone. Such ovarian and non-ovarian insulin-related mechanisms explain how hyperandrogenic features in PCOS become manifest with weight-gain and associated worsening of insulin resistance and serum insulin levels.

The adverse effects of raised serum insulin in PCOS, as outlined above, of course are dependent upon functioning insulin receptors and pathways. This raises an apparent paradox given that PCOS is an inherently insulin resistant condition. Understanding the molecular mechanisms involved provides resolution of this apparent paradox. Following stimulation of its receptor, insulin mediates its cellular functions via two key pathways, each having specific and disparate functions. These are the phosphatidylinositol 3-kinase (PI3-kinase) and mitogen-activated protein kinase (MAP kinase) pathways. The PI3-kinase pathway mediates metabolic effects of insulin within the cell (including glucose disposal into skeletal muscle). Conversely, the MAP kinase pathway mediates cell growth and steroidogenic effects [37]. In women with PCOS (analogous to T2DM), aberrant PI3-kinase pathway functioning pertains, whereas the MAP kinase pathway remains relatively intact [4]. Therefore, although resistance to the metabolic effects of insulin exist in PCOS, the compensatory hyperinsulinemia that ensues stimulates concurrently the intact steroidogenic post-insulin-receptor pathway [38]. A more accurate depiction of PCOS is that: this is a condition associated with concurrent but divergent responses to insulin, with resistance to its metabolic effects and sensitivity to its steroidogenic effects. What ensue are metabolic aberrations in the context of hyperandrogenemia and reproductive dysfunction: the quiddity of PCOS.

Fat, Steroids and Adipokines in PCOS

Enhanced steroidogenesis is a key component of pathogenesis of PCOS. Steroidogenic pathways in PCOS appear to be influenced by adiposity. In the largest study to date on urinary steroid profiles in women with PCOS (n = 178) compared with 100 BMI-matched control women, our own group demonstrated a clear association of PCOS with enhanced

5-alpha reductase activity [39]. We also demonstrated, in both the PCOS and control group, that 5-alpha reductase activity associates with increasing adiposity [39]. Enhanced 5-alpha reductase activity (expressed predominantly within the skin and the liver) has two main effects: (i) conversion of testosterone into a more androgenic product (5-dihydroxytestosterone), thereby contributing towards the association between weight gain and androgenicity in PCOS, and (ii) conversion of cortisol into its breakdown products. This second effect results in diminished negative feedback at the level of the pituitary, and enhanced hypothalamo-pituitary adrenal (HPA) activity. This over-drive of the HPA axis results in enhanced adrenal steroid (including androgenic steroid) production, thereby further contributing towards association between adiposity and androgenicity in PCOS [39].

A further mechanism whereby adiposity contributes towards development of PCOS is through effects on adipokine release [40]. One of the most studied adipokines in PCOS is adiponectin, with >30 (mostly observational) studies published to date. In a meta-analysis on >3400 subjects, serum adiponectin levels were shown to be lower in PCOS than in control women, following adjustment for BMI [41]. As adiponectin is known to inhibit androgen production from ovarian theca cells [42], suppressed adiponectin levels in PCOS may allow enhanced ovarian androgen production [40]. Consistent with this hypothesis, linking adiponectin with the androgenicity of PCOS, are data from a study on 56 pubertal girls with Type 1 Diabetes Mellitus, in which reduced levels of adiponectin correlated with increased levels of testosterone and ovarian volume [43]. In addition to effects on androgenicity, reduced levels of adiponectin may also contribute towards insulin resistance in this condition [41]. It should be noted, however that there is controversy regarding the role of total adiponectin versus high molecular weight (HMW) adiponectin in influencing insulin sensitivity, and that HMW adiponectin (a component of total adiponectin) may be more closely associated with insulin sensitivity in humans [44, 45]. In a study on 50 women with PCOS versus 28 control women, our own group showed equivalent levels of HMW adiponectin between the two groups, following adjustment for fat mass and age [46]. The androgenic and metabolic effects of lowered adiponectin levels in PCOS, the mechanisms implicated and how these relate to the components of adiponectin (specifically HMW-adiponectin) should be areas for further better-focused studies.

Visfatin is another adipokine that may be implicated in development of PCOS [40]. Visfatin is a multifunctional protein implicated in metabolism, inflammation and development of insulin resistance [40, 47]. In a study on lean PCOS versus controls, higher levels of visfatin were demonstrated in the women with PCOS [47]. Other studies have confirmed higher levels of visfatin in PCOS than in control women matched for age and BMI [48, 49] and in studies on an Asian population [50]. There is therefore ample evidence from clinical studies for an association between PCOS and elevated visfatin levels. There is also evidence for association between PCOS and elevated levels of resistin [51]. Evidence for a potential role of resistin in promotion of hyperandrogenemia in PCOS comes from demonstration of enhanced activity of 17 α-hydroxylase (an enzyme implicated in ovarian steroidogenesis) activity in cultured human theca cells from women with PCOS, in the presence of resistin and forskolin or a combination of resistin, forskolin and insulin [51].

Weight gain, adiposity and development of PCOS are inextricably linked. The epidemiology of this association and evidence for involvement of genetic factors has been outlined earlier. In this section, some of the mechanisms that mediate effects of weight gain and obesity on development of the cardinal metabolic, hyperandrogenic and reproductive components of PCOS have been explored. These mechanisms implicate insulin resistance, steroidogenesis and adipokines.

Cardio-Metabolic Risk Factors Across Phenotypic Subgroups of PCOS

Compared with BMI-comparable control women, metabolic syndrome is commoner in women with PCOS, and has been estimated at 34–46 %

of US-based white women with PCOS using National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria [9]. The risk of developing T2DM is also greater in PCOS [10]. Although PCOS is clearly associated with cardio-metabolic risk, it is unclear whether this actually translates into future increased risk of cardiovascular events (which would require a long-term prospective study) [4]. It would seem reasonable though, given the translation of cardio-metabolic risk into future cardiovascular events in the general population that the same correlation would pertain in PCOS [4]. Given this reasonable assumption, it is important to ascertain any heterogeneity of cardio-metabolic risk across the Rotterdam-defined [52] phenotypic subgroups of PCOS, so that appropriate screening and management of such risk is apportioned appropriately, and based on best evidence.

Application of the 'Rotterdam' diagnostic criteria for PCOS [52] leads to emergence of four distinct phenotypic subgroups: 'HO', 'PHO', 'PH' and 'PO' H = hyperandrogenism; P = polycystic ovarian [PCO] morphology; O = oligoamenorrhoea. It is important to explore and compare cardio-metabolic risk between these subgroups, particularly with regard to the controversial 'PO' subgroup, given that by definition this subgroup displays normal androgens. We reported data on 309 UK-based Europid women with Rotterdam-defined PCOS [52, 53]. Subgroups included 'PHO' (n=191), 'PH' (n=76) and 'PO' (n=42) and data were compared with those from control women (n=76) [53]. We demonstrated clearly that insulin resistance is confined to women in the 'PHO' subgroup, even following adjustments for BMI and age [53]. Conversely, women in the 'PH' and 'PO' subgroups were metabolically-equivalent to women in the control group, with comparable insulin sensitivity [53]. There was also a preponderance of metabolic syndrome in women from the 'PHO' subgroup [53]. Many other reported studies on women with PCOS from diverse populations have demonstrated consistent results, both in terms of metabolic normality (including insulin sensitivity) of the 'PO' subgroup [54–57] and insulin resistance of the 'PHO' subgroup [58, 59]. A large study in a Chinese population of PCOS cases (n=719) and control women (n=85) also showed consistent patterns of metabolic profile across the phenotypic subgroups [60]. It would seem reasonable to conclude on the basis of current evidence that insulin resistance and metabolic dysfunction in PCOS is heterogeneous and predictable based on Rotterdam-defined phenotypic subgroup [52]. Insulin resistance and metabolic aberrations in PCOS are more prevalent in the majority subgroup of women who manifest the cardinal dual clinico-biochemical reproductive and hyperandrogenic features with PCO morphology ('PHO'). Conversely, those women who display either reproductive or hyperandrogenic features (without the other) are more likely to be metabolically normal and insulin-sensitive.

A limitation of the studies outlined above is their retrospective and 'snap-shot' approaches. Although the literature is clear regarding the heterogeneity of cardio-metabolic risk factors amongst women with PCOS within specific phenotypic subgroups at any one time, what is unclear is the translation of such heterogeneity into differences in cardiovascular outcomes over the longer-term. This will require longitudinal studies, where women with PCOS in each phenotypic subgroup are followed-up prospectively over many years. Such a study would also enable tracking of women over time, to explore migration between phenotypic subgroups, in which predictors and metabolic implications of such migrations would emerge.

To summarise this section, we have learnt that insulin resistance and other metabolic aberrations are heterogeneous across the phenotypic subgroups of PCOS. We have also learnt that insulin resistance is an inherent feature of 'PHO'-PCOS compared with BMI-adjusted control women.

Fat Distribution in PCOS

Visceral adipose tissue is known to be associated with metabolic aberrations including insulin resistance, through hepatic and peripheral effects of adipokines and fatty acid release [61–63]. It is important to explore the possibility that differences in visceral fat quantity and fat

distribution between PCOS and control women contribute towards disparity in insulin resistance between these groups [40]. Such a hypothesis, promoted by some researchers [64], is based on studies using imaging techniques such as lipometer [65], ultrasound [66], and dual-energy X-ray absorptiometry (DEXA) [67, 68]. Limitations of these studies though include operator-dependence (especially ultrasound), lack of ability to discern between abdominal fat depots, and problems with image resolution [40]. Some of the studies also failed to include PCOS and controls with similar BMI [40].

To explore further the fat distribution in PCOS, our own group employed Magnetic Resonance (MR), with the advantage of highly-resolved images and clear delineation of fat depots [69]. In this study, we compared 22 obese BMI- and fat mass-matched pairs of PCOS and their controls. Measurements were taken from cross-sectional areas of fat depots based on axial MR images at anatomically pre-defined sites [69]. Fat depot areas (including visceral and abdominal and gluteal subcutaneous depots) were equivalent between women with PCOS and control women [69], despite the PCOS group being significantly more insulin resistant than controls. Data from our study [69] were corroborated by data from a subsequent MR-based study on abdominal fat depots in 31 age- and BMI-matched pairs of PCOS cases and controls (BMI range: 19–41 kgm^{-2}). Volumes and distributions of abdominal fat depots were equivalent between groups [70]. In a further smaller MR-based study on ten lean BMI-matched pairs of PCOS and control women, there was a tendency for women with PCOS to have less visceral fat than control women [71].

It would appear therefore that women with PCOS appear to manifest global adiposity, with similar distribution to BMI-matched control women. Data from our own study [40, 69], corroborated by a large DEXA-based study on women with PCOS (n = 110) and weight-matched control women (n = 112) [72], demonstrate a similar relationship between increased fat mass and abdominal fat in women regardless of whether or not they have PCOS. Although differences in eutopic fat distribution between PCOS and control women do not appear to explain why PCOS is an inherently insulin resistant condition, it remains possible that differences in ectopic fat pertain in PCOS, and this should be a focus for further MR-based studies.

Treatment Strategies for Obese Women with PCOS

Unfortunately, many of our current therapies for PCOS provide little more than a 'medical sticking plaster'. Menstrual cyclicity can be improved through use of combined oral contraceptive pill (cOCP), and there are various therapies for hyperandrogenism [4]. However, there are serious concerns regarding use of cOCP in obese women with PCOS that include heightened risk of thromboembolism [73]. Furthermore, anti-androgenic drugs (such as spironolactone and finasteride) generally confer risk of teratogenicity [74]. As a result of our incomplete understanding of pathogenesis of PCOS, and our lack of armamentarium in this clinical arena, we do seem limited in our treatment options for PCOS, with current therapies informed and directed generally by patient-specific priorities (including fertility, menstrual cyclicity and hyperandrogenic features).

There is a clear need for development of novel therapies for PCOS that can target underlying pathogenic mechanisms, and accordingly would address the triple problems of hyperandrogenism, reproductive, and metabolic features that characterize this condition. In this chapter, the evidence linking weight-gain and obesity with development of PCOS has been explored. However, there is also good evidence that weight loss (even as little as 5 %) can translate into significant improvements in menstrual cyclicity, fertility, insulin resistance and hyperandrogenic features in those women who already manifest established PCOS [4]. This scenario is similar to the clinical improvements with weight-loss of other obesity-related conditions, including T2DM and OSA [75]. Given the close association between weight gain and obesity with development of PCOS, it should not be a surprise that the reverse is also

true. It should also not be a surprise that weight-loss remains the most important and key therapeutic strategy for obese women with PCOS. Losing weight is, however, not easy. Weight-loss through lifestyle implementation is largely focused on dietary modification [76, 77]. Unfortunately, to maintain any weight loss, activity levels necessarily need to increase and this can be difficult to implement on a regular basis [78]. Women with PCOS often suffer from low self-esteem and other mental health problems such as depression that conspire to cause loss of interest in exercise and other forms of outdoor activities [79]. Although therapies such as metformin can be considered for management of metabolic dysfunction in PCOS [80], there are very few therapies currently licensed for weight-loss, with little evidence for use in context of PCOS [81]. Although currently unlicensed for use in obese women with PCOS (at the time this chapter was written), there is some evidence to support effective weight-loss with Glucagon Like Peptide-1 (GLP-1) agents in this group [82]. Future therapeutic innovations for women with PCOS should focus on novel strategies for establishment, and maintenance of weight-loss.

An interesting future target for weight-loss therapeutics in PCOS and one that holds great potential is human brown adipose tissue (BAT). Physiologically, BAT functions in an antithetical way to white adipose tissue (WAT). Instead of storing energy as fat, BAT burns energy through uncoupling oxidative phosphorylation, thereby releasing heat in the process [83]. The discovery of active BAT in human adults a few years ago resulted in a re-awakening of interest in this field [84]. From a metabolic perspective, BAT activation confers favorable effects on glycaemia, lipid profile and fat mass through burning off calories. It has been estimated that a sugar-cube volume of BAT, if activated for a year would burn its way through between 3 and 4 kg of WAT [85]. Therapeutic strategies implicating BAT might include augmentation of BAT mass through stem cells or trans-differentiation from WAT into 'beige' cells (with functionality similar to BAT), or alternatively activation of existing BAT depots. The study of human BAT is in its infancy, and there are many important questions that need to be addressed as a priority. One such question relates to how many of us have any BAT. Our own group is tackling this through use of a type of MR to image human BAT: we recently published the first proof of concept paper using MR to image BAT in a living human adult using histological and immunohistochemical verification [86]. We hope to develop this technique as a radio-quantifier for BAT content in humans.

In the context of obese women with PCOS (and obesity *per se*), a therapy that facilitates enhanced energy expenditure through BAT augmentation and activation would represent a novel weight-loss, anti-glycemic and anti-lipidemic therapy to complement other lifestyle measures such as dietary modification. Such a therapy, through enhancement of energy expenditure, could provide a 'metabolic panacea' in obese women with PCOS and would also facilitate maintenance of weight-loss. A BAT-enhancing therapy would act independently from reproductive and steroidogenic pathways thereby facilitating complementarity with other therapies, and would represent a significant breakthrough in the effective management of PCOS and other weight-related conditions. Until such a therapy is developed, we will have to persist with traditional weight-loss strategies that include lifestyle (including dietary) measures and of course the option of bariatric surgery.

Concluding Remarks

Obesity and PCOS are inextricably linked. A major challenge for the future is to disentangle the complex mechanisms that weave together these two clinical entities of obesity and PCOS. Our current understanding of PCOS is that its clinico-biochemical manifestation usually depends upon a diverse aetiology. It is clear that genetics plays an important role [87]. The first pathogenic pre-requisite scenario is therefore a genetic (likely oligogenic) predisposition towards future development of PCOS. The second pre-requisite scenario for development of PCOS is subsequent weight-gain (often resulting in

obesity) occurring against this genetic backdrop of predisposition to PCOS [4]. Of course, this view is necessarily over-simplified in that exceptions exist: not all women with PCOS are obese. Therefore, in a lean subgroup of PCOS the presumption is that genetic predisposition is such that PCOS will become manifest regardless of future weight gain. This hypothesis is further complicated by recent emergence of potential role of epigenetics in the pathogenesis of PCOS [88]. It is apparent however, given the strong links between obesity and PCOS outlined in this chapter, that weight-gain is necessary for the manifestation of PCOS in the majority of women with this condition. We will perhaps never know how many genetically-predisposed women 'escape' development of PCOS through avoidance of weight gain during their reproductive years. It is clear, however that weight gain *per se* in women is not sufficient for features of PCOS to become manifest in that not all obese women develop PCOS: some women are presumably genetically protected from developing PCOS regardless of how much weight they gain (much in the same way that a subgroup of people seem protected from development of T2DM following weight gain). The situation becomes even more complex when one considers that BMI itself is also heritable. Given that PCOS is associated with obesity, and weight gain is on a pathogenic pathway for PCOS, it is possible that at least some of the genetic predisposition for PCOS is mediated via genetic association with a gain in fat mass. The study outlined above on *FTO* variants in PCOS supports this view [11]. Similarly, genetic variants that influence insulin resistance may also be implicated in development of PCOS. Future genome-wide association studies will shed novel insights into pathogenesis of PCOS and also provide direction for future therapeutic targets.

Unfortunately, the name 'Polycystic Ovary Syndrome' belies its strong association with obesity and cardio-metabolic risk. Shakespeare said 'What's in a name?' That which we call PCOS by any other name would maintain intrigue and inner beauty. To the uninitiated though, and even to some healthcare professionals, the term 'PCOS' does what it says on the tin, and may imply to them little more than a few ovarian cysts. It has been suggested that the name 'PCOS' be changed to 'female metabolic syndrome' or 'syndrome XX', to reflect its cardio-metabolic aberrant associations [89]. Whether its name is eventually changed or not, what is important is that all those involved in the management of PCOS, appreciate its importance as a condition with often profound implications and consequences for the patient, their partner, friends and family: a condition comprising multidimensional reproductive, hyperandrogenic and metabolic aberrations, with broader implications for mental health and psycho-social functioning [90]. In a sense, the name 'PCOS' is the door that Alice entered, leading into a world of edificial proportions. Like Alice, we are only just beginning to understand this complex world beyond the door. Given that our genetic constitution is unlikely to change radically over coming years, the ever-burgeoning obesity epidemic will ensure that numbers of women developing PCOS will continue to rise globally. Whilst it is not too late to act, there is a danger of doing too little too late, and that, like Rabbit, we will collectively peer at our waistcoat watches with lateness anxiety in future. Let us avoid this grim scenario by acting NOW, to give PCOS and obesity the respect they deserve, to develop novel and effective therapies that include weight-loss strategies, and to mitigate the potentially devastating impact of an impending tsunami of obesity-associated and PCOS-related sequelae.

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