Metabolic features of the reproductive phenotypes of polycystic ovary syndrome

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TABLE OF CONTENTS

1. Overview
2. Methods
   - Diagnostic features of PCOS
   - Assessment of specific phenotypes for metabolic features
   - Non-NIH PCOS: hyperandrogenic ovulatory PCOS (phenotype C)
   - Non-NIH PCOS: non-hyperandrogenic anovulatory PCOS (phenotype D)
3. Discussion

BACKGROUND: Polycystic ovary syndrome (PCOS) is a common condition in women of reproductive age with well established metabolic abnormalities. There are numerous diagnostic criteria generating several reproductive diagnostic phenotypes [National Institute of Health (NIH) hyperandrogenic anovulatory PCOS and non-NIH PCOS including hyperandrogenic ovulatory or non-hyperandrogenic anovulatory PCOS]. There is ongoing debate regarding the optimal diagnostic criteria for PCOS and on the metabolic implications of newer non-NIH PCOS phenotypes.

METHODS: We reviewed the literature on the presence of risk factors for type 2 diabetes (DM2) and cardiovascular disease (CVD) across the reproductive diagnostic phenotypes of PCOS with the aims of comparing the metabolic features of the NIH and non-NIH groups and identifying potential high metabolic risk phenotypes of PCOS.

RESULTS: NIH PCOS patients present with greater obesity, abdominal obesity, insulin resistance (IR) and risk factors for DM2 and CVD compared with non-NIH ovulatory and non-hyperandrogenic PCOS patients. Where differences in metabolic features exist between the phenotypes, they are generally related to the degree of total and abdominal obesity. There is emerging evidence suggesting ovulatory and non-hyperandrogenic PCOS have greater metabolic abnormalities than controls primarily linked to abdominal adiposity. There is currently no evidence that non-hyperandrogenic PCOS is associated with a less adverse metabolic profile than ovulatory PCOS.

CONCLUSIONS: Current metabolic evidence appears to justify the inclusion of both non-NIH PCOS groups (ovulatory and non-hyperandrogenic) as PCOS subgroups. NIH PCOS is associated with a more adverse metabolic profile including greater total and abdominal obesity, IR and risk factors for CVD and DM2 than non-NIH phenotypes.

Key words: polycystic ovary syndrome / diagnostic criteria / insulin resistance / hyperandrogenism

Overview

Polycystic ovary syndrome (PCOS) is a common endocrine condition in women of reproductive age with prevalence estimated at 4–8% (Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000; Azziz et al., 2004). It is associated with a range of reproductive, obstetric, metabolic and psychological features. Reproductive and obstetric manifestations include hyperandrogenism, menstrual dysfunction, infertility and pregnancy complications. These include early pregnancy loss, gestational diabetes, pregnancy-induced hypertensive...
disorders and neonatal complications (Boomsma et al., 2006). Metabolic complications include an elevated risk of impaired glucose tolerance (IGT), type 2 diabetes (DM2) (Legro et al., 1999), the metabolic syndrome (Apridonidze et al., 2005), elevated cardiovascular risk factors (Meyer et al., 2005a, b) and potential increased risk for cardiovascular disease (CVD) (Shaw et al., 2008). Women with PCOS also have psychological features with increased depression, poor self-image and reduced quality of life (Himelein and Thatcher, 2006). PCOS thus constitutes a significant health and economic burden estimated at over $4 billion in the USA with ~30.1% of costs related to hormonal treatment of menstrual dysfunction, 12.2% infertility care, 14.2% treatment of hirsutism and 40.5% of DM2 (Aziz et al., 2005). An economic evaluation of PCOS recently advocated screening, diagnosis and intervention, justifiable by ameliorating or preventing serious sequelae. This is in keeping with the International Diabetes Federation recommendations to focus on early intervention and avoidance or delay or progression to DM2 (Alberti et al., 2007). However, before this is advocated greater understanding of appropriate screening, long-term risks and effective interventions to minimize metabolic morbidity is urgently needed in women with PCOS (Aziz et al., 2005).

Both the reproductive and metabolic features of PCOS are underpinned by insulin resistance (IR). This is a key factor in the aetiology of PCOS, with insulin stimulating ovarian androgen production and decreasing hepatic sex hormone-binding globulin (SHBG) production and increasing total and free androgens (Diamanti-Kandarakis and Papavassiliou, 2006). The majority of PCOS women have underlying IR, and there is ongoing debate as to whether this IR is intrinsic to PCOS, related to obesity alone or related to both factors. There is additionally potentially an increased prevalence of obesity and abdominal obesity in PCOS (Escobar-Morreale and San Millan, 2007), which worsens the IR-associated clinical features (Kiddy et al., 1990; Balen et al., 1995). It is hypothesized that lean women with PCOS therefore have PCOS-specific IR or intrinsic IR, which is augmented by the presence of obesity-specific IR (Teede et al., 2007).

There remains considerable controversy on the optimal diagnostic criteria for PCOS (Aziz, 2006; Franks, 2006). Although the National Institute of Health (NIH) criteria (hyperandrogenism and anovulation) were proposed in 1992 (Zawdaki and Dunaif, 1992), these have now been expanded to include the non-NIH diagnostic criteria. In 2003, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) diagnostic criteria were formulated as two of the three criteria of hyperandrogenism, polycystic ovaries on ultrasound (PCO) and irregular anovulatory periods. This introduced two new PCOS phenotypes of hyperandrogenic ovulatory women with PCO or non-hyperandrogenic anovulatory women with PCO (2004). An amendment to these criteria was proposed in 2006 by the Androgen Excess Society (AES) to exclude the phenotype of PCO and irregular cycles without hyperandrogenism (Aziz et al., 2006, 2009). The majority of literature to date has focused on the NIH diagnosis of PCOS, and research on the metabolic implications of non-NIH phenotypes is only just emerging. To date, there is limited understanding of the relative prevalence of risk factors for metabolic diseases (DM2 and CVD) across the reproductive diagnostic phenotypes of PCOS. Clarification of this will aid in determining whether to include non-NIH phenotypes as part of the complex condition of PCOS and in identifying if specific reproductive PCOS phenotypes have elevated metabolic risks.

In this setting, the aim of this study was to review the literature on the metabolic implications (adiposity, abdominal adiposity and risk factors for DM2 and CVD) across the reproductive diagnostic phenotypes of PCOS. Specifically, we aimed to compare the metabolic features of the NIH and non-NIH groups and identify potential high metabolic risk phenotypes of PCOS to target future screening and prevention of metabolic diseases. We reviewed the metabolic features of PCOS with a particular focus on the differences between the reproductive diagnostic phenotypes: namely, NIH versus non-NIH PCOS; non-NIH PCOS versus non-PCOS controls and the different non-NIH subgroups compared with each other (hyperandrogenic ovulatory PCOS and non-hyperandrogenic anovulatory PCOS). We also examined whether differences in metabolic features between the reproductive phenotypes were due to different anthropometrics (total or abdominal adiposity) or differences in features such as IR and hyperandrogenism that vary across the diagnostic groups.

To address these aims, the key clinical questions with regard to the metabolic features of the PCOS reproductive phenotypes were shown in Fig. 1.

**Question 1:** Do hyperandrogenic ovulatory women with PCOS (non-NIH phenotype C) present with similar metabolic risk to NIH PCOS (phenotype A/B)?

**Question 2:** Do hyperandrogenic ovulatory women with PCOS (non-NIH phenotype C) present with elevated metabolic risk compared to controls?

**Question 3:** Do non-hyperandrogenic anovulatory women with PCOS (non-NIH phenotype D) present with similar metabolic risk to NIH PCOS (phenotype A/B)?

**Question 4:** Do non-hyperandrogenic anovulatory women with PCOS (non-NIH phenotype D) present with elevated metabolic risk compared to controls?

**Question 5:** Do hyperandrogenic ovulatory women with PCOS (non-NIH phenotype C) present with similar metabolic risk to non-hyperandrogenic anovulatory women with PCOS (non-NIH phenotype D)?

**Figure 1** Summary of relevant clinical questions with regard to the metabolic implications of the reproductive diagnostic phenotypes of PCOS.
Methods

A review was conducted of the medical literature to identify studies evaluating the implications of reproductive diagnostic criteria or reproductive phenotypes on the metabolic features of PCOS. Supplementary references were obtained from initial citations. We searched the database MEDLINE. Search terms as keywords in article text or as subject headings included polycystic ovaries, polycystic ovary syndrome, polycystic ovaries, PCOS or PCO, and diagnostic criteria, diagnosis, presentation or phenotype with searches limited to females and humans. This search resulted in 4512 papers. On screening for title or abstract, we selected 23 for our review that compared metabolic features of PCOS (impaired fasting glucose (IFG), IGT, DM2, metabolic syndrome, IR, glucose tolerance, lipid levels, blood pressure and adipokines and family history of coronary artery disease, CVD, DM2 or hypertension) between different diagnostic phenotypes (NIH and non-NIH) of PCOS. In addition, we hand-searched references of relevant reviews and systematic reviews and included studies to locate other potentially eligible studies. The results were presented as a comparison of (i) NIH PCOS with the non-NIH PCOS diagnostic phenotypes (hyperandrogenic ovulatory PCOS or non-hyperandrogenic anovulatory PCOS), (ii) non-NIH hyperandrogenic ovulatory PCOS or non-hyperandrogenic anovulatory PCOS with non-PCOS controls and (iii) non-NIH hyperandrogenic ovulatory PCOS with non-hyperandrogenic anovulatory PCOS (Fig. 1).

Diagnostic features of PCOS

PCOS is a heterogeneous condition, and diagnostic criteria are based on reproductive features: anovulation or menstrual disturbance, polycystic ovaries on ultrasound (PCO) and hyperandrogenism. Menstrual disturbances comprise anovulation, amenorrhoea (lack of menstruation for >3 months) and oligomenorrhoea (irregular menstruation). A recent review reported that 78.4% of PCOS patients present with oligomenorrhoea and 18.1% present with eumenorrhoea, amenorrhoea and anovulation (Goldzieher, 1981; Franks, 1989; Balen et al., 1995). PCO are defined as the presence of 12 or more follicles measuring 2–9 mm in each ovary and/or increased ovarian volume (>10 ml or cm³) (Balen et al., 2003) and are present in up to 22% of women in the general population (Farquhar et al., 1994) and 75% of women with PCOS (Azziz et al., 2006).

Assessment of clinical hyperandrogenism involves subjective clinical scoring of degrees of hirsutism (excessive growth of terminal hair in women in a male-like pattern) such as the Ferriman–Gallwey score, which is based on measurements of the summed areas of body sites with terminal hair (Ferriman and Gallwey, 1961). This scoring system is used to estimate the degree of androgen excess in women with PCOS (Azziz et al., 1998; Diamanti-Kandarakis et al., 2004). The majority of research has used NIH criteria for diagnosis of PCOS.

Non-NIH diagnostic criteria: ESHRE/ASRM and AES diagnostic criteria

In 2003, the ESHRE/ASRM (2004a, b) criteria were developed. These criteria diagnosed PCOS based on two of the three criteria of hyperandrogenism, irregular anovulatory periods and PCO, thus introducing two additional phenotypic subsets (PCO and anovulation/menstrual dysfunction or hyperandrogenism) (2004). There is currently no data on the prevalence of PCOS as defined by the ESHRE/ASRM criteria in the general population, although these would be expected to include more women than NIH criteria. There is some prevalence data in infertile or amenorrhoeic women with PCOS (Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000; Azziz et al., 2004). The majority of research has used NIH criteria for diagnosis of PCOS.

AES diagnostic criteria

In 2006, the AES published a position statement which suggested that androgen excess is the key component of PCOS related to clinical presentation and diagnostic criteria. The AES Position Statement (Azziz et al., 2006) expanded the population of women diagnosed with PCOS by over 20%.

Table I The different diagnostic criteria for PCOS

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<td>Oligo-ovulation and clinical and/or biochemical signs of hyperandrogenism and exclusion of other aetiologies*</td>
<td>Two out of three oligo- and/or anovulation or clinical and/or biochemical signs of hyperandrogenism or polycystic ovaries and exclusion of other aetiologies*</td>
<td>Hyperandrogenism (hirsutism and/or hyperandrogenemia) and ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) and exclusion of other androgen excess related disorders*</td>
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*Congenital adrenal hyperplasia, androgen-secreting tumours, Cushing’s syndrome, 21-hydroxylase-deficient non-classic adrenal hyperplasia, androgenic/anabolic drug use or abuse, syndromes of severe IR, thyroid dysfunction, hyperprolactinaemia.
long-term morbidity. The AES suggested that the diagnostic criteria be modified to include only those with hyperandrogenism (biochemical or clinical) and PCO and/or ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) (with the exclusion of other related disorders) (Azziz et al., 2006). This definition excluded the phenotypic subset of PCO and ovarian dysfunction but no hyperandrogenism (Table II).

Concerns with the current diagnostic criteria include the fact that the ultrasound criteria are non-specific enough to be observed in other common conditions, including functional hypothalamic anovulation secondary to situations such as stress, weight loss or exercise. As noted by Dewally et al. (2006), this may lead to artificial PCOS phenotypes being created with medical and psychological implications. However, this classification (World Health Organisation Class I anovulation or hypogonadotrophic hypogonadal ovulation) is not normogonadotrophic and therefore not World Health Organisation Class II and should not be considered as PCOS. Where there is potentially uncertainty, it is important to exclude World Health Organisation I or hypothalamic anovulation. This can be excluded either with vaginal ultrasound for endometrial thickness or progestin-induced withdrawal bleed to test for estrogen status. Women with relatively mild endocrinological disturbances may also, potentially, be inappropriately diagnosed with PCOS. For example, a case of acne and PCO in the context of normal biochemical hyperandrogenism and ovulation may still be theoretically defined as PCOS. However, this is controversial and many would consider this group to not have PCOS (Norman et al., 2007).

Hyperandrogenism itself, in the absence of ovulatory disturbances, may also contribute to an adverse metabolic profile and IR. Emerging evidence suggests that hyperandrogenism increases abdominal obesity, which in turn increases IR (Escobar-Morreale and San Millan, 2007). Pre-adipocytes are known to have androgen receptors, and adipose cell function is regulated by androgens at a mechanistic level. Increased androgens have also been shown to induce selective IR in cultured adipocytes (Corbould, 2007). This is further supported by the effects of anti-androgens like spironolactone, which appear to reduce IR in some (Ganie et al., 2004) but not all studies (Sahin et al., 2004; Vrbikova et al., 2004; Gambineri et al., 2006). Furthermore, the metabolic syndrome in women without PCOS has been linked to increasing androgen status at menopause in the setting of increased abdominal obesity (Janssen et al., 2008).

For simplification, PCOS can be subdivided into four reproductive phenotypes: NIH-diagnosed PCOS either with (phenotype A) or without PCO (phenotype B); biochemical/clinical hyperandrogenism with PCO but no oligo/anovulation (phenotype C), or no biochemical/clinical hyperandrogenism with PCO and oligo/anovulation (phenotype D) (Fig. 1, Table II). Although it has been suggested that these newer non-NIH phenotypes (C and D) generally demonstrate a milder reproductive presentation than NIH-diagnosed PCOS (A and B) (Belosi et al., 2006), there is conflicting data on the metabolic implications of the different phenotypes.

Reproductive severity reflected by the number of clinical features of PCOS (menstrual irregularity, acne, hirsutism, elevated testosterone and elevated luteinising hormone) is associated with metabolic severity with increased body fat, waist-to-hip ratio (WHR) and IR (fasting insulin and HOMA-IR) (Michelmore et al., 2001). Hence, with the introduction of the newer diagnostic phenotypes with milder reproductive features of PCOS, there is the potential for the inclusion of women with milder metabolic presentations and lower long-term reproductive and metabolic risks. Furthermore, PCOS is associated with impaired psychosocial health (Himelein and Thatcher, 2006), and the relative contribution of the different features of PCOS to this (metabolic, hirsutism, impaired reproductive function, obesity) across the phenotypes is not clear. Thus, potentially the overall severity of reproductive features may track with metabolic and psychological features, rendering the phenotypes A and B more severe than C and D.

The relative prevalence of the PCOS subgroups are also difficult to determine from the current literature (Supplementary Appendix I) with bias introduced by the variable recruitment strategies from endocrinology or fertility clinics rather than the general population. Depending on the population recruited from, up to 18% of women with PCOS by ESHRE/ASRM criteria can have non-hyperandrogenic PCOS (D) and up to 25% of women can have ovulatory PCOS (C). This indicates an increasing number of women with PCOS who may experience different reproductive and metabolic risks, when compared with those who have NIH PCOS with potential implications for research, screening and clinical practice.

### Assessment of specific phenotypes for metabolic features

Within these four main phenotypes of PCOS (Fig. 1), it is clinically relevant to understand how the metabolic features track with the reproductive phenotypes in order to provide insights into how to target metabolic screening and prevention strategies. There are currently few studies that specifically compare the different reproductive diagnostic phenotypes or presentations of PCOS and their metabolic implications.

### NIH PCOS: phenotypes A and B

IR is a key pathophysiological feature of PCOS and a significant contributor to both reproductive and metabolic complications. The link between IR, IGT, DM2 and CVD in the general population is well established (Haffner et al., 1990; Lundgren et al., 1990; Lillioja et al., 1993; Folsom et al., 1997; Ruige et al., 1998; Lehto et al., 2000; Rutter et al., 2005), suggesting women with PCOS and IR have an elevated risk of these metabolic conditions. Consistent with the increased IR, women with PCOS display an increased prevalence of IGT and DM2. A recent study reported a 5-fold risk of developing DM2 over a period of 8 years in women with PCOS, compared

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### Table II Comparison of the different reproductive diagnostic criteria for PCOS resulting in potentially different phenotypes

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<td>Hyperandrogenism (biochemical or clinical)</td>
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<td>Oligo- or anovulation</td>
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<td>Polycystic ovaries</td>
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<td>NIH criteria</td>
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<td>ESHRE/ASRM criteria</td>
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Implications of different diagnostic criteria

The development of the new ESHRE/ASRM and AES criteria has introduced greater heterogeneity into PCOS from a reproductive and possibly from a metabolic perspective.
with the risk calculated using age- and weight-matched controls (Boudreaux et al., 2006). There is also emerging evidence that women with PCOS have a greater chance of developing gestational diabetes, with a recent meta-analysis reporting an OR of 2.94 (Boomsma et al., 2006).

There is currently no good data to establish whether clinical cardiovascular events are increased in PCOS and there are limited long-term studies appropriately addressing this question (Pierpoint et al., 1998; Wild et al., 2000; Shaw et al., 2008). However, women with PCOS have an increased prevalence of traditional (hyperlipidaemia) and novel (increased homocysteine, inflammation, oxidative stress and leukocyte counts and impaired fibroinolysis and metabolic syndrome) risk factors for CVD mostly compared with weight-matched controls. They also display increased clinical and subclinical markers of premature atherosclerosis (endothelial dysfunction, impaired pulse wave velocity (PWV)); increased carotid intima-media wall thickness (IMT); presence of carotid plaque and increased coronary artery calcification, as demonstrated by our group and others (Apridonidze et al., 2005; Meyer et al., 2005a, b; Bhattacharya, 2008; Cussons et al., 2008). PCOS is thus defined as a population with a high risk of developing IGT and DM2 and a potentially high risk for CVD. These elevated risks occur independent of obesity and are worsened by the presence of obesity (Legro et al., 1999, 2001; Boudreaux et al., 2006; Ehrmann et al., 2006). However, the majority of the aforementioned literature on the metabolic implications of PCOS was conducted prior to the introduction of the newer non-NIH diagnostic phenotypes. As such, it is not yet known whether these recognized metabolic implications of PCOS are applicable to all the reproductive diagnostic phenotypes of PCOS.

NIH PCOS with or without PCO: phenotypes A and B

The majority of women with NIH PCOS also have PCO (phenotype A). Of those that do not, the few studies specifically comparing NIH PCOS with or without PCO (phenotype A versus B) have generally shown similar glucose tolerance, IR [fasting or oral glucose tolerance test (OGTT) insulin or insulin sensitivity index] or lipid profiles (Loucks et al., 2000; Legro et al., 2005; Dewailly et al., 2006; Hahn et al., 2006; Welt et al., 2006b; Diamanti-Kandarakis and Panidis, 2007; Hsu et al., 2007; Shroff et al., 2007). Conversely, in one study increased IR [assessed by insulin tolerance test (ITT)] was reported for PCOS with PCO (phenotype A) compared with PCOS without PCO (phenotype B) (Najmabadi et al., 1997). In addition, higher low-density lipoprotein cholesterol (LDL-C), total cholesterol, family history of DM2 (Shi et al., 2008) and triglycerides (Chae et al., 2008) were reported for women with NIH PCOS without PCO, when compared with NIH PCOS with PCO despite similar weight, BMI, waist or hip circumference. Overall, the evidence suggests a similar risk of metabolic disease for the two phenotypes of NIH PCOS.

Non-NIH PCOS: phenotypes C and D

The metabolic literature examining the newer phenotypes of PCOS introduced by the ESHRE/ASRM is contradictory. There is emerging evidence that these phenotypes have a less adverse metabolic profile than NIH PCOS. A number of studies have demonstrated elevated BMI, WHR, waist circumference (Belosi et al., 2006; Hsu et al., 2007; Pehlivanov and Orbetzova, 2007), fasting insulin, homeostasis assessment of IR (HOMA-IR), metabolic syndrome prevalence (Pehlivanov and Orbetzova, 2007) and IR on euglycaemic hyperinsulinaemic clamp (Belosi et al., 2006) for NIH PCOS when compared with ovulatory PCOS or non-hyperandrogenic PCOS. Where NIH and non-NIH PCOS women were of similar BMI (Cenk Sayin et al., 2003; Diamanti-Kandarakis and Panidis, 2007) and WHR (Diamanti-Kandarakis and Panidis, 2007), similar metabolic features such as surrogate markers of IR were generally reported (Cenk Sayin et al., 2003; Diamanti-Kandarakis and Panidis, 2007), although one study reported a less adverse lipid profile for non-NIH PCOS (Cenk Sayin et al., 2003). Differences in total and abdominal adiposity between NIH PCOS and non-NIH PCOS may therefore account for differences in IR and metabolic risk. However, these studies did not assess metabolic and anthropometric comparisons within the non-NIH diagnostic phenotypes to determine the relative degree of metabolic impairment for phenotypes C and D (Fig. 1).

Non-NIH PCOS: hyperandrogenic ovulatory PCOS (phenotype C)

Non-NIH PCOS (hyperandrogenic ovulatory PCOS) compared with NIH PCOS

A number of studies have compared NIH PCOS with non-NIH hyperandrogenic ovulatory PCOS (Fig. 1). The majority of studies report less adverse metabolic profiles for ovulatory PCOS. Elevated BMI (Carmina et al., 2005, 2006a, b; Welt et al., 2006b; Barber et al., 2007) and waist or hip circumference (Welt et al., 2006b; Barber et al., 2007) were observed for NIH PCOS compared with hyperandrogenic ovulatory PCOS in association with significantly increased IR [fasting insulin, HOMA-IR or quantitative insulin sensitivity check index (QUICKI)] (Carmina et al., 2005; Welt et al., 2006b; Barber et al., 2007) and metabolic syndrome prevalence (Welt et al., 2006b; Barber et al., 2007) and worsened cardiovascular risk factors (elevated triglycerides, hsCRP and homocysteine and lower HDL-C) (Carmina et al., 2005).

Not all metabolic parameters differed between phenotypes and no differences in DM2, IFG, glycosylated haemoglobin A1c (HBA1c) and fasting glucose were observed between ovulatory and NIH PCOS (Welt et al., 2006b). Furthermore, on adjustment for age and BMI, no differences in lipids, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Welt et al., 2006b) or HDL-C and triglycerides (Barber et al., 2007) were observed between subjects. This indicates a contribution of elevated adiposity to the worsened metabolic risk factors present in classic NIH PCOS. Age differences also existed across the PCOS subsets. This could account for differences in metabolic parameters between groups, although specific statistical details were not provided (Barber et al., 2007).

However, in these studies due to the lack of weight matching, it is not possible to determine whether the worsened cardiometabolic profile in NIH compared with non-NIH ovulatory PCOS is due to differences in adiposity or other factors. It is possible that weight may be the modulating factor that primarily worsens IR and reproductive and metabolic function in PCOS (Carmina et al., 2005). In support of this, a small number of studies comparing weight-matched NIH PCOS and non-NIH hyperandrogenic ovulatory PCOS reported similarities in the groups including: similar fasting glucose (Diamanti-Kandarakis and Panidis, 2007), IR [fasting insulin (Carmina and
Lobo, 1999; Diamanti-Kandarakis and Panidis, 2007; Shroff et al., 2007; Kauffmann et al., 2008), OGTT insulin and minimal model insulin (Kauffmann et al., 2008), QUICKI, glucose-to-insulin ratio (G/I) and HOMA-IR (Shroff et al., 2007), lipid profile (Shroff et al., 2007; Kauffmann et al., 2008) IGF, DM2, metabolic syndrome, family history of coronary artery disease and DM2 (Shroff et al., 2007).

In contrast to this, NIH PCOS (phenotypes A/B) had significantly higher IR [ITT (Robinson et al., 1993), fasting insulin (Sharp et al., 1991; Carmina et al., 2003) and QUICKI (Carmina et al., 2003)] than ovulatory PCOS (phenotype C) despite similar age and weight (Sharp et al., 1991; Robinson et al., 1993; Carmina et al., 2003). Abdominal obesity was not measured in these studies which could account for the worsened metabolic risk reported in NIH PCOS. This is supported by the finding that waist circumference is one of the most sensitive markers of the metabolic syndrome in women with NIH PCOS (Ehmann et al., 2006). In support of this, similar waist circumferences for NIH compared with age- and BMI-matched ovulatory PCOS were observed in association with similar fasting insulin (Dewailly et al., 2006). Furthermore, when comparing BMI-matched anovulatory and ovulatory PCOS, ovulatory PCOS had lower abdominal fat [by dual X-ray absorptiometry (DEXA)] with lower IR (QUICKI, fasting insulin), hsCRP and higher adiponectin (Carmina et al., 2008). Thus, even when total adiposity is constant, differences in metabolic features between PCOS phenotypes may be due to differences in abdominal or visceral fat.

Conversely, Norman et al. (1995a) reported higher post-OGTT and fasting insulin and OGTT glucose for NIH compared with ovulatory PCOS despite weight and WHR matching, although no differences in total cholesterol, triglycerides and HDL-C between the subsets were observed and the relative age of the different subsets was not stated. Hence, some research suggests reduced IR in ovulatory PCOS is largely a function of reduced adiposity. Others report higher IR in the NIH phenotypes to be either an inherent feature or related to increased abdominal fat. The lack of measurement or use of a more imprecise measure of adiposity distribution [waist circumference or WHR (Norman et al., 1995a; Dewailly et al., 2006) versus DEXA (Carmina et al., 2008)] in the majority of studies limits conclusions in this area.

Summary of findings for Question 1

Do hyperandrogenic ovulatory women with PCOS (phenotype C) present with similar metabolic risk to NIH PCO (phenotype A/B)?

Non-NIH (hyperandrogenic ovulatory) PCOS (phenotype C) generally have lower body weight and BMI and better metabolic profiles compared with NIH PCOS (phenotypes A/B). Non-NIH (hyperandrogenic ovulatory) PCOS and weight-matched NIH PCOS appear to present with similar metabolic risk profiles, particularly where abdominal fat is similar between subjects.

Non-NIH PCOS (hyperandrogenic ovulatory PCOS) phenotype C compared with non-PCOS controls

Further assessment of the metabolic risk associated with ovulatory PCOS can be demonstrated by a comparison of risk factors for DM2 and CVD with controls (Fig. 1). Where BMI is higher in ovulatory PCOS, there is an increased prevalence of metabolic syndrome but no differences in IFG, DM2, fasting glucose, lipid profile or family history of coronary artery disease or DM2 (Shroff et al., 2007). Similarly, where abdominal adiposity (waist circumference or WHR) was elevated for ovulatory PCOS compared with age- and weight-matched controls, greater IR (fasting insulin, G/I or QUICKI) (Carmina and Lobo, 2001; Carmina et al., 2003, 2005; Dewailly et al., 2006) and lipid profile (increased hsCRP, total cholesterol and LDL-C or decreased HDL-C) were observed (Carmina and Lobo, 2001; Carmina et al., 2005).

Where controls and hyperandrogenic ovulatory women with PCOS were closely age- and weight-matched, no differences in lipids, fasting or post-OGTT insulin and glucose or minimal model glucose testing were observed (Kauffmann et al., 2008). In another study, higher OGTT glucose and fasting insulin (Robinson et al., 1993) but equivalent fasting insulin and glucose (Robinson et al., 1993; Diamanti-Kandarakis and Panidis, 2007) and surrogate markers of IR (OGTT insulin and ITT) (Robinson et al., 1993) were observed for ovulatory PCOS compared with weight-matched controls. The controls were older, potentially confounding the results (Robinson et al., 1993; Diamanti-Kandarakis and Panidis, 2007). Furthermore, as abdominal obesity was not measured, it is not possible to rule out different visceral obesity between PCOS and controls. Where abdominal adiposity (WHR or waist circumference) was similar between BMI-matched hyperandrogenic ovulatory PCOS and controls, similar IR (fasting insulin or HOMA-IR) (Norman et al., 1995a; Welt et al., 2006b; Carmina et al., 2008), OGTT insulin (Norman et al., 1995a), QUICKI (Carmina et al., 2008), OGTT glucose (Norman et al., 1995a), adiponectin (Carmina et al., 2008), SBP, DBP, lipid profile and prevalence of the metabolic syndrome, IFG and DM2 (Welt et al., 2006a) are also seen, although in one study controls demonstrated a lower BMI and higher HDL-C and apolipoprotein A1 (Norman et al., 1995a). The literature generally supports similar metabolic profiles for hyperandrogenic ovulatory PCOS and controls where adiposity or abdominal adiposity are matched.

Summary of findings for Question 2

Do hyperandrogenic ovulatory women with PCOS (phenotype C) present with elevated metabolic risk compared with controls?

There is some evidence that ovulatory PCOS are more adversely metabolically affected than controls, but this is not universally observed and appears to be strongly related to the presence of adiposity and specifically abdominal adiposity.

Non-NIH PCOS: non-hyperandrogenic anovulatory PCOS (phenotype D)

The most controversial newer non-NIH PCOS subgroup has been non-hyperandrogenic anovulatory PCOS (phenotype D), which was included in the ESHRE/ASRM diagnostic criteria and excluded from the AES diagnostic criteria in the AES position statement (Azziz et al., 2006).

Non-NIH PCOS (non-hyperandrogenic anovulatory PCOS) phenotype D compared with NIH PCOS

There are limited studies examining non-hyperandrogenic women with PCOS (Fig. 1). The majority of these show reduced weight, BMI or
prevalence of obesity (Broekmans et al., 2006; Welt et al., 2006b; Barber et al., 2007; Shroff et al., 2007) and reduced WHR and waist circumference (Welt et al., 2006b; Barber et al., 2007) for non-hyperandrogenic compared with NIH PCOS (Broekmans et al., 2006; Welt et al., 2006b; Barber et al., 2007; Shroff et al., 2007). Of these studies, two reported lower blood glucose (Broekmans et al., 2006) and less IR (G/I < 0.25 mmol/mU) (Barber et al., 2007) for non-hyperandrogenic compared to NIH PCOS. This again suggests that where metabolic differences occur between phenotypic subsets, they may be accounted for by adiposity. When obese subsets were compared, the prevalence of IR remained lower in phenotype D PCOS (Broekmans et al., 2006) and differences in IR between the PCOS subsets remained on adjustment for age and BMI (Barber et al., 2007) suggesting less metabolic impairment for non-hyperandrogenic PCOS independent of adiposity. Conversely, an increase in the prevalence of the metabolic syndrome but no differences in IR (Welt et al., 2006b; Shroff et al., 2007), IFG, DM2, fasting glucose, total cholesterol, LDL-C, family history of coronary artery disease or DM2 (Shroff et al., 2007) was reported for non-hyperandrogenic PCOS compared with NIH PCOS. However, only fasting measures of IR were assessed (fasting insulin, HOMA-IR, QUICKI or G/I), which are less optimal in PCOS than post-OGTT measures (Ciampelli et al., 2005). The literature, although limited, suggests that non-hyperandrogenic anovulatory women with PCOS have a more favourable metabolic profile compared with NIH PCOS, an observation again potentially related to greater adiposity and abdominal adiposity in NIH PCOS.

Reduced adiposity and abdominal adiposity contributes to a more favourable metabolic profile in non-hyperandrogenic anovulatory PCOS. This is confirmed by reports that BMI- or WHR-matched non-hyperandrogenic anovulatory PCOS and NIH PCOS (Norman et al., 1995a; Diamanti-Kandarakis and Panidis, 2007; Kauffman et al., 2008) generally have similar lipid profiles (Kauffman et al., 2008), fasting and OGTT glucose (Norman et al., 1995a; Kauffman et al., 2008) and IR (fasting insulin, OGTT insulin or QUICKI) (Norman et al., 1995a; Diamanti-Kandarakis and Panidis, 2007; Kauffman et al., 2008), although in one study elevated triglycerides were reported for the non-hyperandrogenic PCOS and it was not always possible to determine if the groups were age-matched (Norman et al., 1995a). However, conclusions from this literature are limited as sample size for the non-hyperandrogenic PCOS phenotype was often very small (Norman et al., 1995a). Kauffman et al. (2008) also excluded women with DM2 and very obese women, potentially removing a subgroup with greater metabolic abnormalities that may have differed between the PCOS phenotypic subsets. Furthermore, when non-hyperandrogenic PCOS present with lower waist circumference or WHR, despite being weight-matched with NIH PCOS, they also display reduced fasting (Dewailly et al., 2006; Chae et al., 2008) or OGTT insulin (Chae et al., 2008). Overall, this supports the strong role of abdominal adiposity in the pathogenesis of IR in PCOS.

**Summary of findings for Question 3**

**Do non-hyperandrogenic anovulatory women with PCOS (phenotype D) present with similar metabolic risk to NIH PCOS (phenotype A/B)?**

Non-hyperandrogenic PCOS (phenotype D) generally present with lower BMI and less adverse metabolic profiles compared with NIH PCOS (phenotype A/B). Non-hyperandrogenic PCOS and NIH PCOS matched for total and abdominal obesity generally present with similar metabolic profiles.

**Non-NIH PCOS (non-hyperandrogenic anovulatory PCOS) compared with non-PCOS controls**

Some evidence exists to suggest that non-hyperandrogenic anovulatory PCOS have an adverse metabolic profile compared with controls (Fig. 1). Where non-hyperandrogenic anovulatory PCOS displayed elevated BMI compared with controls, increased triglycerides, fasting and OGTT insulin, OGTT glucose, lower HDL-C and apolipoprotein A1 are reported (Norman et al., 1995a). Other research has also shown elevated WHR for non-hyperandrogenic women with PCOS compared with BMI-matched controls (Dewailly et al., 2006), suggesting increased abdominal fat independent of total adiposity, although this was not associated with elevated fasting insulin and no other measures of IR or metabolic parameters were made. Moreover, when non-hyperandrogenic PCOS displayed similar age, weight, BMI, waist circumference, metabolic syndrome, IFG and DM2, fasting glucose, SPB, DBP and lipids to controls, they still demonstrated elevated insulin and HOMA-IR (Welt et al., 2006b), suggesting some metabolic impairment independent of total or abdominal fat.

Conversely, a comparison of non-hyperandrogenic women with PCOS and controls with similar BMI (Shroff et al., 2007; Kauffman et al., 2008) and waist circumference (Barber et al., 2007) showed no differences in IR (fasting insulin, QUICKI, G/I or HOMA-IR) (Barber et al., 2007; Kauffman et al., 2008), lipid profile (Barber et al., 2007; Shroff et al., 2007; Kauffman et al., 2008), prevalence of IFG, DM2 (Shroff et al., 2007) or the metabolic syndrome (Barber et al., 2007; Shroff et al., 2007) and family history of coronary artery disease and DM2 (Shroff et al., 2007). However, in two of these studies, controls were older, which could worsen their metabolic profile independent of their non-PCOS status (Barber et al., 2007; Shroff et al., 2007) and abdominal fat distribution was not measured in one study (Shroff et al., 2007). Chae et al. (2008) reported that despite lower waist circumference for non-hyperandrogenic PCOS versus BMI-matched controls, PCOS women displayed elevated SBP, DBP, triglycerides, HOMA-IR, fasting insulin but similar total cholesterol and HDL-C. However, this study comprises a different ethnic subgroup (Korean) and there is emerging evidence that ethnicity profoundly affects metabolic parameters in PCOS (Norman et al., 1995b; Kauffman et al., 2002; Wijeyaratne et al., 2002, 2004; Al-Fozan et al., 2005; Carmina et al., 2006a, b; Ehrmann et al., 2006; Kauffman et al., 2006; Essah et al., 2008).

The evidence for worsened risk factors for DM2 and CVD in non-hyperandrogenic PCOS compared with controls is therefore limited. Limited data report that IR, independent of adiposity or abdominal adiposity, may exist in the absence of hyperandrogenism in PCOS with this IR potentially contributing to the reproductive features of PCOS. Additionally, despite this subgroup of PCOS being less hyperandrogenic than the other diagnostic phenotypes, they can still present with either similar (Norman et al., 1995a; Barber et al., 2007; Chae et al., 2008; Kauffman et al., 2008) or higher androgens (Dewailly et al., 2006; Welt et al., 2006b; Hsu et al., 2007) than controls that could independently impact on IR, reproductive and metabolic parameters. One possibility is that the severity of hyperandrogenism varies in women with PCOS, and while hyperandrogenism drives PCOS in the majority of phenotypes (A, B and C), in women with a mild abnormality in androgens (phenotype D or non-hyperandrogenic
PCOS), a greater contribution of inherent or environmentally induced abdominal-obesity-related IR may be required to induce reproductive and ovarian dysfunction (Escobar-Morreale and San Millan, 2007).

Summary of findings for Question 4

Do non-hyperandrogenic anovulatory women with PCOS (phenotype D) present with elevated metabolic risk compared with controls?

There is currently little evidence to indicate non-hyperandrogenic women with PCOS matched for abdominal obesity have a more adverse metabolic profile than controls.

Hyperandrogenic ovulatory PCOS phenotype C compared with non-NIH PCOS (non-hyperandrogenic anovulatory PCOS) phenotype D

There are even fewer studies comparing the non-NIH phenotypes of hyperandrogenic ovulatory PCOS (phenotype C) and non-hyperandrogenic anovulatory PCOS (phenotype D) and the literature is very conflicting (Fig. 1). No differences in family histories of coronary artery disease, DM2, prevalence of IFG and DM2 (Shroff et al., 2007), IR [G/I, QUICKI, HOMA-IR (Shroff et al., 2007), fasting insulin (Shroff et al., 2007; Kauffman et al., 2008) or OGTT insulin (Kauffman et al., 2008)] or lipid profile (Kauffman et al., 2008) were reported for heavier (Shroff et al., 2007) or weight-matched (Kauffman et al., 2008) groups. The lack of measurement of abdominal adiposity in these studies limits the conclusions that can be drawn. However, in another study, the strong effect of abdominal obesity on IR and metabolic profiles in the PCOS phenotypes was confirmed by lower waist circumferences and fasting insulin levels for non-hyperandrogenic women with PCOS compared with age- and BMI-matched ovulatory PCOS (Dewailly et al., 2006). When adiposity and abdominal adiposity (WHR or waist circumference) were matched, one study reported similar SBP, DBP, HBA1c, metabolic syndrome, IFG, DM2, fasting insulin, HOMA-IR and lipid profile (Welt et al., 2006b). An earlier study with a very small number of non-hyperandrogenic PCOS (n = 6) reported elevated triglycerides, fasting insulin and OGTT glucose and insulin (Norman et al., 1995a) for non-hyperandrogenic PCOS compared with ovulatory PCOS. This indicates higher rather than lower metabolic risk factors in non-hyperandrogenic ovulatory PCOS. From this limited literature, non-hyperandrogenic anovulatory PCOS do not display improved metabolic risk factors compared with hyperandrogenic ovulatory PCOS. There is thus currently limited evidence to support the exclusion of non-hyperandrogenic PCOS as a phenotype of PCOS based on metabolic presentation.

Summary of findings for Question 5

Do hyperandrogenic ovulatory women with PCOS (non-NIH phenotype C) present with similar metabolic risk to non-hyperandrogenic anovulatory women with PCOS (non-NIH phenotype D)?

There is currently little evidence to indicate non-hyperandrogenic women with PCOS have a less adverse metabolic profile than ovulatory PCOS.

Limitations of the existing literature

The studies discussed above include a wide range of ethnic groups (Caucasian of American, Australian, European or the UK origin, Mexican American, African American, Asian, Non-Mexican American Hispanic, Asian, Arab/Mediterranean, Afro-Caribbean of UK origin, Chinese, the Netherlands and Icelandic [Supplementary Appendix I]). Overall the literature suggests that different ethnicities of PCOS present with differences in metabolic features, adiposity, abdominal adiposity, hyperandrogenism, hirsutism, adrenal hormones, lipid profile, homocysteine or IR (Norman et al., 1995b; Kauffman et al., 2002, 2006; Wijeyaratne et al., 2002, 2004; Al-Fozan et al., 2005; Carmina et al., 2006a, b; Ehrmann et al., 2006; Essah et al., 2008), although this is not universally observed (Welt et al., 2006a). Further variability in metabolic risk factors in PCOS may relate to the number of clinical features and the majority of studies do not categorize PCOS populations based on number or severity of features. For example, those with biochemical and clinical hyperandrogenism and oligo-ovulation were the most severely metabolically affected and subjects with clinical hyperandrogenism only had lower prevalence of IR (Yildiz and Gedik, 2001; Chang et al., 2005; Diamanti-Kandarakis and Panidis, 2007), although this is not reported by all investigators (Hassa et al., 2006). Control subjects in these studies were also variably defined. A number were precisely defined as regular ovulatory menses with no clinical or biochemical hyperandrogenism; some only specified non-hirsute and did not assess biochemical hyperandrogenism and not all assessed the presence of PCO in control subjects. Although not uniformly observed (Michelmore et al., 2001; Legro et al., 2005), women with PCO only may have adverse reproductive and metabolic parameters reported in association with increased obesity (Clayton et al., 1992), androgens (Kousta et al., 1999; Adams et al., 2004), risk factors for CVD including reduced arterial compliance (Lakhani et al., 2002) and surrogate markers of IR (Adams et al., 2004), potentially influencing the metabolic status of the control subjects. Furthermore, despite the recognition of IR as a contributor to the metabolic presentation of PCOS, there is a lack of consensus on the agreed defined biochemical cut off, the appropriate method to use its measurement and longitudinal studies to validate surrogate measures (Ciampelli et al., 2005). The measurement of IR remains a useful research tool in women with PCOS but is not currently recommended for routine clinical practice (Samaras et al., 2006). The impact of ethnicity, more precisely defined PCOS and control populations as well as the use of more accurate methodologies to examine androgen status, IR and abdominal fat distribution are needed to clarify the metabolic implications of PCOS.

Discussion

There is an increasing body of literature devoted to examining the metabolic implications of the reproductive diagnostic phenotypes of PCOS. The evidence currently suggests that those with NIH PCOS, who are hyperandrogenic and generally IR, have the most severe metabolic features. The adverse metabolic profile is related to obesity and abdominal obesity, which appears to be more marked in NIH PCOS than in other non-NIH phenotypes. Hyperandrogenism
and IR have both been implicated in adverse metabolic profiles and are both likely to underpin the metabolic phenotypes of women with PCOS, either directly or through an increased predilection for abdominal obesity. The newer reproductive phenotypes (ovulatory PCOS and non-hyperandrogenic PCOS) have milder metabolic phenotypes than NIH PCOS and again these are strongly related to abdominal obesity. While the ovulatory subgroup is more hyperandrogenic, evidence suggests the non-hyperandrogenic group has similar IR than ovulatory PCOS. In the setting of either hyperandrogenism or IR, metabolic abnormalities are observed. This review provides insights into the pathophysiology of metabolic abnormalities in PCOS. It is possible that intrinsic PCOS-related abnormalities in insulin signalling and/or a predisposition to visceral weight gain may be greater in the NIH phenotypes contributing to their more severe reproductive and metabolic presentation. Accumulation of obesity and abdominal or visceral obesity then further exacerbates the metabolic abnormalities seen in PCOS.

There is ongoing controversy over the diagnostic criteria for PCOS. The inclusion of ovulatory PCOS, and even more so of non-hyperandrogenic PCOS, has received criticism (Azziz et al., 2006). From a metabolic perspective, although the literature is limited, it appears that both of the newer PCOS phenotypes (ovulatory and non hyperandrogenic) demonstrate a less adverse reproductive and metabolic profile, compared with NIH PCOS. However, when weight-matched the metabolic profile of the newer phenotypes is similar to the profile seen in NIH phenotypes. The newer phenotypes also appear to have a more adverse metabolic profile than controls, but this is not universally observed and is strongly related to adiposity and abdominal adiposity. Finally, non-hyperandrogenic women appear to have a similar metabolic profile to ovulatory PCOS with limited evidence even suggesting they present with more severe IR and dyslipidaemia. Therefore, we propose that the metabolic literature in PCOS supports the inclusion of both the newer phenotypes of PCOS based on the ESHRE/ASRM Rotterdam diagnostic criteria and suggests these phenotypes are a more mild form of PCOS.

The limitations of the literature on metabolic features of PCOS are not insignificant. Ethnic diversity, recruitment sources of participants, consistency in the use of end-points and inconsistently defined controls are but a few of the concerns. Current research has also primarily focused on metabolic syndrome features or on surrogate markers of DM2 and CVD. No studies have adequately examined the natural history of metabolic disease in PCOS across the different diagnostic phenotypes of women, especially in the newer phenotypes. The majority of research has additionally studied risk factors for metabolic disease and only a few papers examined clinical disease outcomes (e.g. DM2, coronary artery disease, subclinical or clinical atherosclerosis) (Welt et al., 2006b; Barber et al., 2007; Pehlivanov and Orbetzova, 2007; Shroff et al., 2007; Chae et al., 2008). Robust, well designed studies with well-defined controls and longitudinal follow-up to capture clinical outcomes are needed to resolve many of the outstanding questions on the metabolic phenotype of PCOS. Furthermore, the majority of the literature reports elevated risk factors for DM2 and CVD in family members of women with PCOS (Yilmaz et al., 2005; Sam et al., 2006; Baillargeon and Carpentier, 2007; Crisosto et al., 2007; Unluhizarci et al., 2007), but this is poorly examined across the diagnostic phenotypes of PCOS (Shi et al., 2008; Shroff et al., 2007; Chae et al., 2008).

In conclusion, abdominal obesity appears to be the primary determinant of metabolic abnormalities in PCOS. IR and hyperandrogenism may also, either directly or indirectly, influence metabolic abnormalities and potentially contribute to abdominal obesity. However, more research is needed to provide a greater understanding of the interaction between hyperandrogenism, IR and abdominal adiposity in PCOS. The optimal screening and treatment for each PCOS phenotype and their relatives also needs to be better understood. Overall, there remain considerable gaps in the literature which require further research. Ultimately, classification of the metabolic complications for each phenotype will provide an evidence base for screening of metabolic risk upon diagnosis of PCOS and may guide optimal treatment to prevent metabolic complications of PCOS. Insights in these areas across the phenotypes will also assist in understanding the underlying pathophysiology of metabolic features of this condition.

**Supplementary data**

Supplementary data are available at http://humupd.oxfordjournals.org/.

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