Polycystic ovary syndrome

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Polycystic ovary syndrome is a heterogeneous endocrine disorder that affects about one in 15 women worldwide. The major endocrine disruption is excessive androgen secretion or activity, and a large proportion of women also have abnormal insulin activity. Many body systems are affected in polycystic ovary syndrome, resulting in several health complications, including menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome. Women with this disorder have an established increased risk of developing type 2 diabetes and a still debated increased risk of cardiovascular disease. The diagnostic traits of polycystic ovary syndrome are hyperandrogenism, chronic anovulation, and polycystic ovaries, after exclusion of other conditions that cause these same features. A conclusive definition of the disorder and the importance of the three diagnostic criteria relative to each other remain controversial. The cause of polycystic ovary syndrome is unknown, but studies suggest a strong genetic component that is affected by gestational environment, lifestyle factors, or both.

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Polycystic ovary syndrome is one of the most common endocrine disorders in women of reproductive age, and the most frequent cause of hyperandrogenism and oligo-anovulation,[1,2] both of which have substantial psychological, social, and economic consequences.[3] An increased awareness of this disorder in the general population and medical communities has taken place in recent years with the knowledge that women with polycystic ovary syndrome are susceptible to metabolic syndrome[4,5] and its associated comorbidities. Because of the heterogeneity in its presentation, the definition of polycystic ovary syndrome has been controversial in disciplines as diverse as internal medicine, gynaecology, and psychiatry. Therefore, polycystic ovary syndrome is a persisting challenge for clinical and basic research scientists who try to elucidate its origins and distinguish primary pathological changes from secondary environmental disruptions.

Classification and epidemiology

Three key diagnostic features of polycystic ovary syndrome have been proposed with various degrees of emphasis, dependent on the perspective of the investigator. These features are hyperandrogenism, chronic anovulation, and polycystic ovaries on ultrasonography.[6,7] Importantly, other conditions are known to cause or to mimic the features of polycystic ovary syndrome, and must be excluded prior to diagnosis. These include congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumours for hyperandrogenism and raised prolactin or insufficient luteinising hormone for anovulation. Although obesity, insulin resistance, and metabolic syndrome are frequently present in women with polycystic ovary syndrome, they are not regarded as intrinsic disturbances of the disorder.

At present, there are two main definitions for polycystic ovary syndrome, which are the topic of intense debate.[8,9] The 1990 National Institutes of Health (NIH) criteria require the presence of chronic anovulation plus clinical or biochemical signs of hyperandrogenism, whereas the 2003 Rotterdam criteria require the presence of two or more of: chronic anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries. By inclusion of polycystic ovaries as a diagnostic criterion, the Rotterdam definition recognises four phenotypes of polycystic ovary syndrome (table 1). This definition has raised controversial and unsolved issues that have implications for clinical diagnosis and study design. The Androgen Excess Society recently reported the results of an evidence-based review of phenotypes for polycystic ovary syndrome.[11] The results suggested that polycystic ovary syndrome should primarily be regarded as a disorder of excessive androgen biosynthesis, use, or metabolism. In terms of phenotypes of polycystic ovary syndrome, ovulatory women with hyperandrogenism and polycystic ovaries have a mild form of the disorder,[12] but women with polycystic ovaries in the absence of anovulation or hyperandrogenism do not. Disagreement continues as to whether chronic anovulation and polycystic ovaries without overt hyperandrogenism is a form of polycystic ovary syndrome. Although preliminary data suggest that women of this phenotypic group have subtle endocrine and metabolic abnormalities consistent with a mild form of the disorder,[12] the metabolic features of these women are regarded by some to be too mild or distinct to be associated with the increased risk of developing metabolic disease that is characteristic of women with polycystic ovary syndrome.[13,14]

The prevalence of polycystic ovary syndrome, as defined by the 1990 National Institutes of Health (NIH) criteria, in unselected populations of women of reproductive age is between 6·5 and 8%. Mexican American women might have a higher prevalence of polycystic ovary syndrome than white or black American women.[15] Immigrant

Search strategy and selection criteria

We searched the Cochrane library (up to 2005), Medline via PubMed (up to November, 2006) and EMBASE (up to July, 2006). We used the terms "PCOS"; "PCOD"; "PCO"; "Stein-Leventhal syndrome"; "hirsutism" not "PCOS". We selected articles in the past 5 years, but also used highly regarded older articles and several relevant review articles. The reference list was modified by each author and in response to comments from reviewers.

	Severe PCOS	Hyperandrogenism and chronic anovulation	Ovulatory PCOS	Mild PCOS
Periods	Irregular	Irregular	Normal	Irregular
Ovaries on ultrasonography	Polycystic	Normal	Polycystic	Polycystic
Androgen concentrations	High	High	High	Mildly raised
Insulin concentrations	Increased	Increased	Increased	Normal
Risks	Potential long-term	Potential long-term	Unknown	Unknown
Prevalence in affected women[10]	61%	7%	16%	16%

PCOS=polycystic ovary syndrome.

Table 1: **Phenotypes for polycystic ovary syndrome based on 2003 Rotterdam criteria**

populations from the Indian subcontinent to the UK, and Australian women of Aboriginal heritage also have a high prevalence of polycystic ovary syndrome.[16,17] Adoption of the 2003 Rotterdam criteria for the diagnosis of this disorder will presumably increase the prevalence of polycystic ovary syndrome because the scope for inclusion is broader than it is with the 1990 NIH criteria.[8] Indeed, in a study of women with normogonadotropic anovulatory (WHO type 2) infertility, the prevalence of polycystic ovary syndrome was 1·5-fold higher when defined by the 2003 Rotterdam criteria than when defined by the 1990 NIH criteria.[13]

Clinical features and diagnosis

Polycystic ovary syndrome has many signs and features; three main characteristics must be assessed to establish whether a woman conforms to one of the recognised phenotypes of the syndrome that are summarised in table 1.

Hyperandrogenism

Hyperandrogenism is the most constant and prominent diagnostic component of polycystic ovary syndrome, but reliable detection of this feature is not straightforward, and indices vary substantially dependent on ethnic origin, bodyweight, and age. Hyperandrogenism is assessed by clinical features, biochemical indices, or both. Clinically, hyperandrogenism is diagnosed by the mostly subjective assessment of cutaneous manifestations of excessive androgen activity, such as hirsutism, acne (especially in young women), and female-pattern alopecia (more apparent in old women). Hirsutism is the most common of these symptoms, being present in about 60% of women with polycystic ovary syndrome,[18–20] although it is rarely present in Asian women.[21] Degrees of hirsutism vary greatly in different ethnic populations, and the threshold of abnormality should be measured on a population basis.[22] Debate exists as to whether the frequency of acne and alopecia in women with polycystic ovary syndrome is higher than in the general population, and present recommendations regard them as unreliable clinical signs of hyperandrogenism, particularly if they are the only diagnostic feature.[23]

Biochemically, hyperandrogenaemia is most commonly assessed by measurement of serum total testosterone (T) and sex hormone binding protein (SHBG), followed by calculation of the free or bioavailable (free and weakly bound to albumin) fraction by the free androgen index (T/SHBG×100) or the mass action equation, respectively.[24–26] The mass action equation is regarded as the method of choice to calculate free serum testosterone, if reliable assays are used and normative data specific to each assay are developed.[25,26] Radioimmunoassays that claim to measure free testosterone directly are available and widespread, but are highly unreliable and should not be used.[25,26] The concentrations of other serum androgens such as androstenedione or the adrenal androgen prasterone sulfate (known as DHEAS) are often high in women with polycystic ovary syndrome, but their measurement is of little value in the average clinical setting. However, some workers have suggested that ethnic groups, even distinct populations of caucasian ethnic origin, might differ greatly with respect to the concentrations of specific androgens in the serum of women with polycystic ovary syndrome.[27]

Unfortunately, serum analysis fails to measure the biochemical hyperandrogenism of polycystic ovary syndrome in about 20–40% of patients,[20] and even semiquantitative measurements such as the modified Ferriman-Gallwey score for hirsutism[28] might underestimate clinical hyperandrogenism.[22] Most commercial assays for total serum testosterone are not designed or validated for detection within the range for women,[26] raising concern about their real diagnostic value. Moreover, the range that is regarded as healthy for women by commercial laboratories is very broad, and has been shown to include many hyperandrogenic women, even those with severe hirsutism.[29] Until more accurate methods of measurement are developed, many investigators think that failure to detect biochemical or clinical hyperandrogenism should not exclude diagnosis of polycystic ovary syndrome in the presence of other clinical signs.

Chronic anovulation

Diagnosis of chronic anovulation is easier than diagnosis of hyperandrogenism, because the major clinical signs—namely, oligomenorrhoea or amenorrhoea—vary in duration but are generally unambiguous. Oligomenorrhoea is defined as less than eight periods per year, or cycles that are longer than 35 days, and amenorrhoea is absence of menstruation for more than 3 months without pregnancy. However, a high rate of false negatives is possible if menstrual history alone is investigated. Regular cycles do not exclude chronic anovulation without evidence of a progesterone concentration in serum during the luteal phase of the menstrual cycle that is consistent with a recent ovulation. When chronic anovulation is present, serum prolactin and luteinising hormone (LH) assays should be done to

exclude hypothalamic and pituitary diseases, which would cause hyperprolactinaemia (prolactin >20–30 μg/L), gonadotropin deficiency (LH <2 IU/L), or both. Additionally, chronic anovulation due to polycystic ovary syndrome should not be confounded with some forms of functional hypothalamic amenorrhoea that are caused by extreme caloric restriction, exercise, or both, in which amenorrhoea is associated with low plasma oestrogen, is not responsive to progestagen withdrawal to induce menstruation, and is characterised by normal or low gonadotropin.[30]

Polycystic ovaries on ultrasonography

The definition of the diagnostic features for polycystic ovaries by ultrasonography has been controversial because technical advancements, including high-frequency vaginal probes and image-enhancing software, have improved resolution and measurement capabilities. Previous definitions, which were based on transabdominal ultrasonography,[31] have now been revised on the basis of transvaginal techniques,[32] and state that in the follicular phase ovary (lacking follicles larger than 10mm in diameter), the presence of 12 or more follicles measuring 2–9 mm in diameter, or increased ovarian volume (>10 mL) suffice to make a diagnosis of polycystic ovaries (figure). Although there are other characteristic features, priority has been given to follicle number and ovarian volume because both have the advantage of being measured in real time and are regarded as key and consistent features of polycystic ovaries. The assessment of polycystic ovaries in adolescent girls should be done by transabdominal ultrasonography with measurement of ovarian volume only, because the criterion based on follicles is much less reliable by the abdominal route, especially in obese individuals.[32] The adult upper healthy threshold volume of 10 mL seems to be also appropriate for post-menarchal adolescents.[33] Measurement of serum anti-Mullerian hormone (AMH), which is secreted by granulosa cells of developing follicles, is emerging as a potential surrogate for ultrasonography, because values correlate closely with antral follicle count in pilot investigations.[34] This assay might facilitate the diagnosis of polycystic ovary syndrome in circumstances in which ultrasonography is inappropriate or unavailable, although the assay is not valid for women older than 35 years.

Pathogenesis

Androgen abnormalities

60–80% of women with polycystic ovary syndrome have high concentrations of circulating testosterone,[19,20,35] and about 25% have high concentrations of prasterone sulfate (DHEAS),[36] leading some investigators to surmise that uncontrolled steroidogenesis might be the primary abnormality in this disorder.[37] Polycystic ovaries have a thickened thecal layer, and thecal cells derived from these ovaries secrete excessive androgens in vitro under basal conditions or in response to LH stimulation.[38] The excessive secretion persists in cultured cells over many passages,[39] suggesting a genetic association, but up to now none of the genes implicated in steroid biosynthesis has been linked to polycystic ovary syndrome through relevant polymorphisms or mutations.[40] However, the expression and activity of many steroidogenic enzymes is increased in thecal cells from patients with the disorder, and this hyperactivity might be caused by a disturbance of intracellular signalling pathways that have not previously been implicated in the pathogenesis of this disorder.[41]

Abnormalities of folliculogenesis

Polycystic ovaries have two to six times more primary, secondary, and small antral follicles than do healthy ovaries.[42–44] These early developing follicles seem to be functionally normal in most respects. The mechanism that determines excess numbers of follicles is unknown, but several lines of evidence implicate abnormal androgen signalling. As defined by strict consensus criteria, 90–100% of women with polycystic ovary syndrome have polycystic ovaries,[12,14] and several studies have reported a positive correlation between follicle number and serum testosterone and androstenedione concentrations in these women.[14,45,46] Administration of dihydrotestosterone to female rhesus monkeys induces a polycystic-ovary-like morphology, including increased ovarian volume and increased follicle numbers, suggesting a direct action of androgens on ovarian cells.[47] Although a similar result has been reported in female-to-male trans-sexuals after long-term testosterone treatment,[48] such women seemed to have a high frequency of polycystic ovaries before hormone administration.[49,50] However, the notion of androgen-induced polycystic ovaries is supported by the findings of one study in which monotherapy with the non-steroidal anti-androgen flutamide reduced ovarian volume and improved the abnormal follicle profile in adolescent girls with polycystic ovary syndrome.[51] Additionally, a polymorphism in the androgen receptor that affects the potency of its activity has been implicated in the disorder.[52,53] Although the increase in follicle numbers in polycystic ovaries might

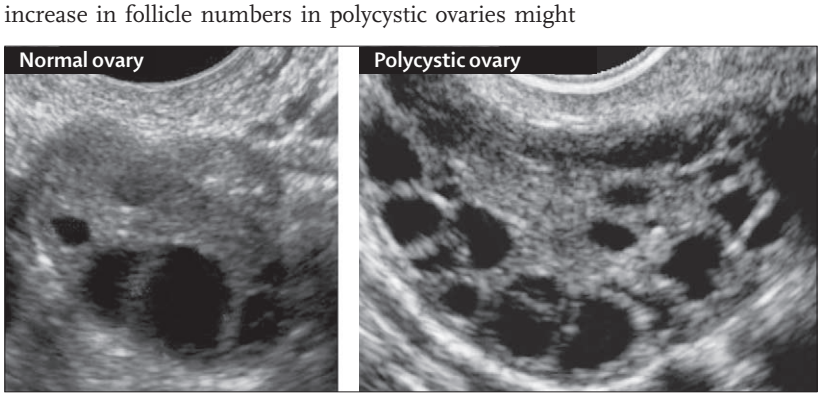

Figure: **Normal and polycystic ovary shown by transvaginal ultrasonography during the follicular phase of a menstrual cycle**
The fluid-filled antrum of a developing follicle appears as a dark circle. When compared with a normal ovary, the polycystic ovary is typically enlarged and contains an abnormally increased number of developing follicles.

be due to a trophic effect of androgens on primate follicular cells,[47,54] it might also be that the follicles of a polycystic ovary grow very slowly, creating a stockpiling effect. This slow growth might be mediated by deficient growth signals from the oocyte[44] or by the inhibitory effect of excess AMH.[55]

In anovulatory women with polycystic ovary syndrome, antral follicle growth stops when the follicle is less than 10 mm in diameter, which is the stage just before emergence of a dominant follicle. Follicular arrest is associated with excessive stimulation of follicular cells by insulin, LH, or both, in addition to a hyperandrogenic environment.[56] Insulin enhances the responsiveness of granulosa cells to LH, and in the ovaries of hyperinsulinaemic women with polycystic ovary syndrome, arrested follicles show signs of premature luteinisation.[57] Granulosa cells from women with polycystic ovary syndrome also seem to be selectively insulin resistant, whereby insulin-stimulated glucose metabolism is impaired but insulin-stimulated steroidogenesis is normal,[58,59] suggesting that deficient energy mobilisation within the follicle contributes to anovulation. The association between hyperinsulinaemia, insulin resistance, and anovulation in women with the syndrome inspired the use of insulin sensitisers such as metformin as a therapeutic approach to induce ovulation.

Gonadotropin abnormalities

Women with polycystic ovary syndrome display abnormal patterns of gonadotropin pulsatility, which is characterised by excessive secretion of LH but normal secretion of follicle-stimulating hormone (FSH).[60] This pattern of secretion gives rise to an abnormal circulating LH to FSH ratio in some patients, mostly those of normal weight.[61] The pattern is exacerbated by gonadotropin-releasing hormone challenge tests, which further increase circulating LH and 17-hydroxyprogesterone concentrations in women with the disorder.[62] Overall, these data suggest the presence of a defect of the hypothalamic–pituitary axis in polycystic ovary syndrome, which is further supported by evidence of increased pituitary sensitivity to stimulation with corticotropin-releasing factor, resulting in an excessive adrenocorticotropic hormone and cortisol response in women with this disorder.[63] However, high concentrations of androgens desensitise the hypothalamus to negative feedback by progesterone,[64] suggesting that the abnormalities of gonadotropin release in polycystic ovary syndrome are secondary to abnormal steroid release by the ovaries or adrenal glands.

Insulin action abnormalities

Women with polycystic ovary syndrome seem to have a level of peripheral insulin resistance that is much like that of women with type 2 diabetes, which is characterised by a 35–40% decrease in insulin-mediated glucose uptake.[65] Normoglycaemic women with the syndrome display both fasting and glucose-challenged hyperinsulinaemia,[66] and a β-cell compensation that is inadequate for their degree of peripheral insulin resistance,[67,68] suggesting that they are at high risk of type 2 diabetes.[69] Indeed, about 40% of obese women with polycystic ovary syndrome have impaired glucose tolerance after a standard challenge with 75 g oral glucose,[70–72] although the frequency is lower in thinner women with the syndrome.[73]

Insulin resistance might contribute to hyperandrogenism and gonadotropin abnormalities through several mechanisms. High concentrations of insulin reduce circulating SHBG values, thereby increasing the bioavailability of testosterone,[74,75] and might also serve as a co-factor to stimulate adrenal and ovarian androgen biosynthesis, thereby contributing to abnormal gonadotropin concentrations.[76–79] Insulin might also act directly in the hypothalamus, pituitary gland, or both, to regulate gonadotropin release,[80] but the contribution of insulin resistance to manifestation of gonadotropin abnormalities in polycystic ovary syndrome remains uncertain.[81] Insulin resistance in the disorder is characterised by selective-tissue insulin sensitivity, in which some tissues seem highly resistant (ie, skeletal muscle) and others sensitive (ie, adrenal and ovary). In affected tissues, metabolic pathways are generally resistant to stimulation by insulin, but mitogenic or steroidogenic pathways are not.[82]

The reconfiguration of polycystic ovary syndrome as a metabolic syndrome with reproductive implications has led to detailed studies of women affected by this disorder for signs of insulin resistance. Women with polycystic ovary syndrome have also proved to have dyslipidaemia,[83–85] high levels of inflammatory markers,[86,87] endothelial dysfunction,[88,89] and an increased frequency of sleep apnoea.[90–92]

Causes and risk factors

The cause of polycystic ovary syndrome remains unknown, although, like most complex heterogeneous diseases, both environmental and genetic factors are implicated. With time and technological advances, focus has shifted from the ovary[93] to the hypothalamic–pituitary axis,[60] to some primary defects of insulin activity[94,95] as the primary pathological cause of the syndrome. Compelling evidence exists to implicate all three sources, and because they form an interacting system of factors that regulate ovarian function, it is possible that there are many different primary disturbances that result in the same pathological outcome. A priority for the future is to understand the relation between the phenotypes of polycystic ovary syndrome and their underlying pathophysiology.

Familial aggregation of polycystic ovary syndrome has been recognised for many years.[96–98] In a twin study, the genetic component of the syndrome as a single variable characterised by self-reported oligomenorrhoea in the

presence of either hirsutism or acne was estimated to be 79%.[99] Polycystic ovary syndrome does not show clear Mendelian inheritance, is regarded as a complex disorder, and poses unique challenges to geneticists.[100] Genetic analysis is hampered by low fecundity, absence of a male phenotype, absence of an animal model, age-related changes in the reproductive phenotype, and variation in the diagnostic criteria. Epigenetic variation has also been implicated as a confounding factor.[101] Various genetic associations of uncertain meaning have been reported, most of which have not been replicated. Linkage disequilibrium has consistently been reported between polycystic ovary syndrome and a microsatellite marker (D19S884) on chromosome 19p13.2, located in non-conserved intronic sequences between exons 55 and 56 of the fibrillin 3 (FBN3) gene,[100,102,103] which encodes an extracellular matrix protein implicated in the regulation of the activity of specific growth factors. The association has been shown by some investigators,[104] but not by others,[105] although none of them tested for genetic linkage. The meaning of D19S884 is still under investigation. Overall, several genetic associations have been shown in polycystic ovary syndrome, but at present there is no clinical indication for genetic testing in women with this disorder.

Obesity has a substantial effect on the manifestation of polycystic ovary syndrome.[106] Excess weight exacerbates metabolic and reproductive abnormalities in women with the syndrome, and family studies suggest that weight gain might promote the phenotype of polycystic ovary syndrome in a susceptible population.[107] Obesity in women with polycystic ovary syndrome is prevalent in North America.[69,108,109] In an unselected population from Alabama, 24% of women with the syndrome were overweight (body mass index [BMI] 25·0–29·9) and 42% were obese (BMI >30).[110] Women with the syndrome from other countries tend to be thinner: in a study from the Netherlands, the mean BMI was 28–29, and prevalence studies have shown BMIs in the range of 25–28 in the UK, Greece, and Finland.[19,111–113] The reasons for the prevalence of excessive weight in women with polycystic ovary syndrome in the USA might be due to insufficient physical exercise or diet,[114] and the high prevalence of obesity in the general population.

Evidence that the syndrome is caused by factors in the environment which mimic hormones, and are able to disrupt endocrine activity, is scarce. However, research is in progress, and compelling evidence exists that exposure of pregnant non-human primates and sheep to excess androgens predisposes female offspring to develop a syndrome similar to polycystic ovary syndrome.[115] A similar effect in human beings is difficult to ascertain, although female offspring of women with congenital adrenal virilising disorders have a masculinisation of neuroendocrine function that shares some similarities with the abnormalities in women with polycystic ovary syndrome.[116] Theoretically, the gestational environment and lifestyle factors in early childhood mediate the effect of predisposing genetic factors, and thereby programme individuals for development of reproductive disorders such as polycystic ovary syndrome later in life.[117] The effects of fetal programming, lifestyle factors, or both, in the cause of polycystic ovary syndrome might arise through epigenetic modifications of DNA.[101]

Health implications

The potential health consequences of polycystic ovary syndrome are a lifelong issue (table 2). There is little doubt that the prevalence of impaired glucose tolerance and diabetes mellitus is increased substantially in women with polycystic ovary syndrome,[70,71] although the magnitude of the increase depends on the prevalence of obesity in the population,[118] and racial influences are evident. Conversion rates of glucose tolerance from normal to abnormal are accelerated in polycystic ovary syndrome,[71,119,120] and up to 10% of women with this disorder develop diabetes during the third or fourth decade.[70,71] The evidence for increased risk of cardiovascular disease in women with polycystic ovary syndrome is less clear, although cardiovascular risk factors are substantially increased, including hyperlipidaemia, hyperandrogenaemia, hypertension, markers of a prothrombotic state, and markers of inflammation.[121] Altered vascular and endothelial function in young women with polycystic ovary syndrome is well documented, and increased death rates from cardiovascular disease have been shown in women with menstrual irregularity (possibly with polycystic ovary syndrome) in the Nurses' Health Study.[122]

There have been several definitions of metabolic syndrome[123] and several reports of an increased prevalence of metabolic syndrome in women with polycystic ovary syndrome.[5,124] However, whether this increase is caused by a feature specific to polycystic ovary syndrome or is merely a consequence of adiposity is still unclear. An increase in central fat, hyperinsulinaemia, glucose intolerance, increased blood pressure, and other isolated features of metabolic syndrome are more common in women with polycystic ovary syndrome than they are in the general

	Prenatal or childhood	Adolescence, reproductive years	Postmenopausal
Reproductive	Premature adrenarche Early menarche	Menstrual irregularity Hirsutism Acne Infertility Endometrial cancer Miscarriage Pregnancy complications	Delayed menopause?
Metabolic	Abnormal fetal growth	Obesity Impaired glucose tolerance Insulin resistance Dyslipidaemia Type 2 diabetes	Obesity Impaired glucose tolerance Insulin resistance Dyslipidaemia Type 2 diabetes
Other	..	Sleep apnoea Fatty liver Depression	Cardiovascular disease?

Table 2: **Lifelong health complications**

population. Although there is insufficient evidence to suggest that the increased prevalence can be explained by polycystic ovary syndrome alone, excess androgen in women has been shown to be a risk factor for metabolic syndrome independent of obesity and insulin resistance.[125]

Management

Lifestyle changes

The association between excessive weight, hyperandrogenaemia, impaired glucose tolerance, menstrual abnormalities, and infertility emphasises the need to address lifestyle issues in women with polycystic ovary syndrome, particularly nutrition and exercise. Realistic and achievable weight loss can be set to improve an individual's reproductive and metabolic fitness because only a small (2–5%) reduction of bodyweight can greatly improve these indices.[126] A small reduction of bodyweight was sufficient to restore ovulation and increase insulin sensitivity by 71% in obese anovulatory women.[127] Loss of abdominal fat, which is associated with insulin resistance, seems to be crucial to restore ovulation in these women. Weight loss also increases SHBG concentration, reduces testosterone concentration and androgenic stimulation of the skin, improves menstrual function and conception rates, and reduces miscarriage rates.[128–131] Although drugs to increase insulin sensitivity in diabetics are used to treat women with polycystic ovary syndrome, weight reduction is more effective and should be the initial treatment for obese women with this disorder.[132] Little is known about the best exercise patterns, but evidence-based dietary approaches exist in short-term studies. Caloric restriction seems more important than macronutrient composition, and there is little evidence that a high-protein diet is better than a high-carbohydrate diet.[133,134] Although acute weight loss can be achieved with severe caloric restriction, long-term weight maintenance is rare, and acute weight loss potentially has dangerous effects for reproduction.[135]

Cosmetic issues

Skin and hair disorders can be substantial in women with polycystic ovary syndrome, and are physically and psychologically very damaging. Although standard commercial cosmetic approaches are used initially, ovarian suppression through oral contraceptives is widely prescribed for hirsutism and acne, especially in the adolescent population. This treatment option has the advantage of regulating the menstrual cycle and providing contraception. Cyproterone in combination with oestrogen is one of the most effective treatments of hirsutism, although side-effects such as tiredness, reduced libido, and changes in liver function are common. Laser electrolysis alone or in combination with topical application of eflornithine cream to retard hair growth is also very effective to reduce hirsutism.[136] Acne often responds well to oral contraceptives with low doses of cyproterone or drospirenone.[137] Evidence exists that insulin-sensitising agents such as thiazolidinediones[108] and metformin[138] might be useful in the treatment of hirsutism and acne because insulin resistance affects both disorders, but the recommendation of these drugs for cosmetic purposes is premature. For androgenic alopecia in women, 2–5% topical minoxidil is regarded as the most effective treatment.[139,140]

Menstrual irregularity

The abnormal hormonal concentrations characteristic of polycystic ovary syndrome might predispose women with this disorder to development of endometrial cancer, although the data that support this finding are not very convincing.[141] The number of menstrual cycles is less important than the avoidance of endometrial hyperplasia, and intermittent induction of menstruation by any means, most commonly by progestagens or administration of oral contraceptives, either cyclically or continuously, prevents abnormal uterine proliferation.

Use of combined oral contraceptives is the most common treatment for symptoms of polycystic ovary syndrome because they interfere with androgen activity via several mechanisms, including reduced androgen production, increased hepatic SHBG synthesis, and competitive binding to androgen receptors by some progestagens. However, the potential long-term metabolic side-effects of combined oral contraceptives in women with polycystic ovary syndrome is being debated, especially since women with this disorder have a propensity for development of obesity and metabolic abnormalities. Combined oral contraceptives have been shown to decrease insulin sensitivity, impair glucose tolerance, and alter lipid profiles in healthy populations of women, but seemingly not to a degree that affects the risk of diabetes mellitus or cardiovascular disease.[142] Published work on the metabolic consequences of combined oral contraceptives in women with polycystic ovary syndrome is equivocal, and studies generally do not satisfy the criteria for evidence-based medicine.[142] Therefore, the assumption that the use of combined oral contraceptives in women with the syndrome is safe is premature, especially because women with this disorder often start taking oral contraceptives early in adolescence, continue taking them for long periods, and are already susceptible to metabolic perturbations. Treatments that couple combined oral contraceptives with insulin sensitisers, antiandrogens, or both, are emerging with potential beneficial effects on metabolic abnormalities, especially in young women with the syndrome.[142,143]

Infertility

Women with polycystic ovary syndrome form the largest group of women with WHO class 2 ovulatory dysfunction, which is characterised by chronic anovulation in the presence of normal FSH and oestradiol concentrations. Induction of ovulation is the first-line treatment for this class of anovulation, and is aimed at the introduction of

an endocrine milieu that promotes growth and ovulation of a single dominant follicle with consequent singleton pregnancy.

Clomifene is a selective oestrogen-receptor modulator that antagonises the negative feedback of endogenous oestrogen on the hypothalamic–pituitary axis. Treatment with clomifene should return LH to normal and increase FSH secretion, and thereby stimulate follicle growth and ovulation. Clomifene has been the gold standard treatment for induction of ovulation in women with polycystic ovary syndrome for many decades,[144,145] and a meta-analysis has shown that the use of clomifene is six times more likely to result in pregnancy than is placebo in such women (numbers needed to treat=5·9, 95% CI 3·6–16·7).[145] A prospective follow-up of thin women with ovulatory dysfunction has shown high conception rates in ovulatory responders treated with clomifene, approaching 50% after three cycles of treatment, and 75% within nine cycles.[146] The examination of follicle development by ultrasonography and measurement of serum concentrations of oestradiol might help to avoid multifollicular development. One of the side-effects of clomifene is increased risk of multiple pregnancy,[147] which is possibly reduced by tailoring the treatment regimen to account for patients' characteristics that predict specific outcomes.[146] Despite a high degree of efficacy, some women with polycystic ovary syndrome are resistant to clomifene and do not ovulate, or fail to achieve pregnancy despite ovulation. Failure to achieve pregnancy might be due to adverse effects of clomifene on the endometrium.[148] Factors that affect resistance to clomifene or failure to achieve pregnancy are, in order of importance, hyperandrogenaemia, obesity, ovarian volume, and menstrual dysfunction. A prediction model has been developed to assess the chance of a woman treated with clomifene being able to ovulate and become pregnant, taking these variables into account.[149]

Like clomifene, aromatase inhibitors reduce oestrogen stimulation of the hypothalamic–pituitary axis, but do so by reducing oestrogen biosynthesis. Patients who are resistant to clomifene are allegedly more sensitive to induction of ovulation with aromatase inhibitors such as letrozole that have less side-effects on endometrial thickness than has clomifene, and possibly a lower risk of multiple pregnancy.[150] A randomised controlled trial has shown that there is less ovarian stimulation with letrozole than with clomifene,[151] which might contribute to a lower risk of multiple pregnancy. However, concern about the possibility of fetal abnormalities as a result of aromatase inhibition has led to avoidance of these drugs in some countries.

Induction of ovulation with gonadotropins has been shown to be very effective as a low-dose regimen with gradual increase in dose as needed after close examination of hormone and ultrasound response,[152] and some investigators suggest that this regimen is preferable to clomifene for first-line treatment in women with polycystic ovary syndrome.[153] Alternative methods of gonadotropin induction, such as treatment onset with a high dose followed by a gradual reduction (step-down protocol), demand more skills and are not more effective than the low-dose regimen.[154] Overall, ovulation induction with gonadotropins has a reasonable success rate both in terms of ovulation and cumulative pregnancy rates.[147,155] As with clomifene, multiple pregnancies remain a major drawback of gonadotropins,[156–158] but this complication can be substantially reduced with adequate examination and a low threshold for readiness to cancel the stimulation. In addition, polycystic ovaries are very sensitive to gonadotropic stimulation and ovarian hyperstimulation syndrome is a serious, potentially life-threatening, outcome of induction of ovulation with gonadotropins in patients with polycystic ovaries.[159]

Ovarian drilling with laser or diathermy has also been shown to be very effective in the induction of ovulation in women with polycystic ovary syndrome,[160] but has risks related to the operation and development of intrapelvic adhesions. Benefits might be longlasting, and the risks of multiple pregnancies are not increased.

Insulin sensitisers, including thiazolidinediones[108] and D-chiro-inositol,[161] have also been shown to increase ovulation and reduce hyperandrogenism in women with polycystic ovary syndrome, but metformin remains the most commonly used agent. Metformin is not approved by the US Food and Drug Administration (FDA) to induce ovulation, and the best possible dose is unknown. However, metformin does not seem to be associated with any known fetal toxic effect or teratogenicity. In a meta-analysis, metformin was shown to have a substantial benefit in the induction of ovulation in women with polycystic ovary syndrome.[162] Ovulation was achieved in 46% of women who received metformin, compared with 24% in the placebo group (numbers needed to treat=4·4), which is similar to the benefit conferred by clomifene.[162] However, a 6-month multicentre trial that directly compared the effects of clomifene and metformin as single-agents found clomifene was better than metformin overall for treatment of infertility.[164] This trial showed that the livebirth rate in women given clomifene (22·5%, 47 of 209) was higher than in those given metformin (7·2%, 15 of 208; p<0·001).[164] The first adequately powered multicentre trial to examine the combined effect of clomifene and metform showed no benefit for ovulation or pregnancy rates compared with clomifene alone (cumulative pregnancy rate 40% vs 46%; risk difference –6%; 95% CI –20 to 7).[163] This finding was recently supported in a study that also showed no additional beneficial effect of combination treatment on livebirth rate compared with clomifene alone.[164] Although multiple pregnancies occurred only in women treated with clomifene and not with metformin, the overall rate (about 5%) was low.[164] These studies have shown the

need for increased scrutiny of the role of metformin in the treatment of infertility in women with polycystic ovary syndrome.

Induction of ovulation with clomifene or gonadotropins might be associated with a higher rate of early pregnancy loss in women with polycystic ovary syndrome than in women who ovulate and conceive normally, but this effect is difficult to prove definitively. Similarly, whether women with the syndrome have a higher rate of early pregnancy loss because of endocrine disruptions that are inherent to the disorder or whether early pregnancy loss is higher in women with polycystic ovary syndrome because of treatment for induction of ovulation per se is debatable, although mounting evidence favours the first hypothesis.[165] Hyperinsulinaemia, insulin resistance, or both, might have a key role in the pathological cause of early pregnancy loss, prompting studies to examine the potential benefit of metformin treatment to reduce its occurrence. However, at present there are no adequately designed studies to address the role of metformin in the reduction of the putative increased frequency of early pregnancy loss in women with polycystic ovary syndrome,[166] although some randomised trials have shown decreased early pregnancy loss in groups treated with metformin.[167,168] By contrast, a large multicentre trial showed a non-significant but concerning increased rate of first-trimester pregnancy loss in the group treated with metformin (10 of 25 individuals) compared with that of clomifene-containing groups (14 of 62 individuals in the group treated only with clomifene, and 20 of 80 individuals in the group treated with both clomifene and metformin).[164] In this study, metformin treatment was stopped with confirmation of pregnancy.

In vitro fertilisation is the last option that should be considered in the treatment of infertility in anovulatory women with polycystic ovary syndrome, but is often needed when infertility is related to men or to unrelated additional female factors. By contrast with protocols to induce ovulation that aim to produce a single dominant follicle in anovulatory women, hyperstimulation with gonadotropins before in-vitro fertilisation (IVF) aims to inhibit dominant follicle selection and promote multifollicular growth for subsequent surgical aspiration of mature oocytes, whether a woman is anovulatory or not. Similar to induction of ovulation with gonadotropins, ovarian hyperstimulation syndrome is a common complication of ovarian hyperstimulation in women with polycystic ovaries.[159] Lower doses of FSH, early cancellation, and coasting (ie, avoidance of FSH for several days) might be needed to avoid ovarian hyperstimulation syndrome.[169] Retrieval of immature oocytes followed by in-vitro maturation without gonadotropin stimulation is an emerging alternative option for infertile women with polycystic ovary syndrome who are prone to ovarian hyperstimulation syndrome.[170]

A meta-analysis of early pregnancy in women with polycystic ovary syndrome after IVF showed that pregnancy rates, miscarriage rates, and birthweight were equivalent to those in controls.[171] However, the pregnancies of women with the syndrome are more likely to be complicated by gestational diabetes, pre-eclampsia, pregnancy hypertension, and preterm labour, and neonates are more likely to be admitted to intensive care with a higher perinatal mortality rate, unrelated to multiple pregnancy[166] (panel). These data were supported by a large prospective trial[164] of women with polycystic ovary syndrome treated with metformin, clomifene, or their combination to induce ovulation, who were followed up from conception to delivery. The study showed that the most common pregnancy complications (in descending order) were: pre-eclampsia, gestational diabetes, and preterm labour.[164] Overall, the rate of pregnancy complications after fetal heart motion approached 40%. The status of polycystic ovary syndrome of women undergoing fertility treatment should therefore be established before starting treatment protocols.

Issues for peripuberty

Overweight children are more likely to have premature puberty than normal-weight children, and those with a low birthweight, premature pubarche, or both, are particularly prone to an early menarche and development of polycystic ovary syndrome in adolescence.[172] Ibanez and de Zegher[143] prevented insulin resistance and features of polycystic ovary syndrome in young girls with premature pubarche by administration of metformin with very low doses of an androgen antagonist, flutamide, alone or in combination with an oral contraceptive containing drospirenone as the progestagen. These findings need verification through adequately powered randomised controlled trials. Whether this effect can be generalised to adult women and to women of diverse ethnicities remains to be

Panel: **Complications of infertility treatment, pregnancy, and the perinatal period that are significantly increased in women with polycystic ovary syndrome**

Infertility treatment
- Multiple pregnancy after ovulation induction
- Ovarian hyperstimulation syndrome
- IVF cycle cancellation

Pregnancy
- Early pregnancy loss
- Gestational diabetes
- Pregnancy-induced hypertension
- Pre-eclampsia
- Delivery by caesarean section

Perinatal period
- Admission to a neonatal intensive care unit
- Perinatal mortality
- Premature delivery

ascertained. Caution should be applied before administration of these drugs to children and adolescents because of potential teratogenicity in an unplanned pregnancy.

Health issues for family members

Although the genetics of polycystic ovary syndrome remain unclear, a strong familial component exists, as shown by family studies and twin records. The discovery that insulin resistance and hyperandrogenaemia are more common in the sisters of women with polycystic ovary syndrome[173] than in other women led to additional studies which show that first-degree relatives of women with polycystic ovary syndrome have similar metabolic disorders, possibly predisposing to metabolic and cardiovascular disease.[174–177] In a large family study of 336 women with polycystic ovary syndrome and 307 probands, indicators of hyperinsulinaemia were more common in the sisters of women with the syndrome than in control women, and hyperandrogenaemia was the major predictor of insulin resistance.[107] In 162 non-Hispanic white mothers of women with polycystic ovary syndrome, the total cholesterol and LDL cholesterol concentrations were higher than in 62 control women, whereas triglyceride and HDL cholesterol concentrations did not change.[177] Therefore, the diagnosis of polycystic ovary syndrome should initiate a thorough review of family members in addition to investigation of the patient.

Additional clinical investigations

Because of its genetic and metabolic implications, clinical investigation of polycystic ovary syndrome should include examination of family history of diabetes mellitus, cardiovascular disease, and hyperlipidaemia, possibly with assessment of relevant risk factors in siblings and older family members. Lifestyle issues, including history of diet and exercise, should be investigated. Clinical measurements might include calculation of BMI, relative waist circumference (waist to hip ratio), serum lipids (cholesterol, triglycerides, and HDL cholesterol), and glucose metabolism. Assessment of insulin either as a fasting hormone or as a surrogate of insulin resistance (eg, homoeostasis model assessment) is of little clinical value, although widely used for research studies. Repeated measurements of glucose and lipid status should take place more regularly in women with polycystic ovary syndrome than in women without the syndrome, because conversion from healthy to pathological status happens more frequently in the disorder.[71,119,120]

Health-related quality of life is generally worse in women with polycystic ovary syndrome than in women without the disorder, and appropriate counselling might be needed for some individuals.[178] A questionnaire of health-related quality of life specific for women with polycystic ovary syndrome has been developed and validated for this purpose.[179,180] Psychological studies have shown higher frequency of depression and psychological and psychosexual morbidity in women with polycystic ovary syndrome than in women without the disorder, women with other non-reproductive diseases, or both.[181] Obesity and hirsutism have a major effect on health-related quality of life in women with polycystic ovary syndrome, and improvement of these physical symptoms might greatly improve the psychosocial and psychosexual situation for these women.[182]

Future prospects

Polycystic ovary syndrome is a diverse and complex female endocrine disorder, which is presently recognised as a major economic health burden that is likely to expand together with obesity.[3] Future priorities in relation to polycystic ovary syndrome include the development of evidence-based criteria for diagnosis and treatment, and determination of the natural history, cause, long-term consequences, and prevention of the disorder.[183]

Conflict of interest statement

RSL has served as a consultant to Glaxo Smith Kline and Ferring, and has received lecture fees from Serono, meeting support from Abbott, and grant support from Pfizer. Other authors declare that they have no conflict of interest.

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