PCOS & DIABETES:
NEW MANAGEMENT GUIDELINES

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting reproductive aged women[1] and is associated with a 4-times higher rate of T2D. The **Australian authors** of the new international PCOS guidelines[20] summarise what clinicians should look for, and what can be done about PCOS when it is found.

PCOS is a prevalent, complex condition with a heterogenous range of reproductive, metabolic and psychological symptoms. The condition is undiagnosed in up to 70% of affected women and key features such as a psychological burden and metabolic risks are under-recognised. Women with PCOS report dissatisfaction with diagnosis experiences, lack of quality information and inconsistent management practices. To achieve optimal health outcomes for women with PCOS a holistic, person-centered approach implemented within a biopsychosocial model of care is recommended.

EPIDEMIOLOGY

PCOS is an ancient, complex genetic disorder[2] with a genomic footprint going back 50,000 years.[3] It is postulated that the genetic regulation of fertility may have been advantageous in the feast or famine setting.[4] However, in the current obesogenic environment PCOS has detrimental short and long-term health impacts.

Intrauterine events may predispose to this condition, including hyperandrogenaemia in the uterus or excess maternal hormones (including anti-müllerian hormone) acting on the developing endocrine system.[5] Excess weight gain is significant in translating a predisposition to PCOS into clinical manifestation.[6]

PCOS is increasingly recognised as a condition-affecting women across the life span with hyperandrogenic symptoms (acne, hirsutism) most evident in adolescents and increased metabolic risks (diabetes, central obesity and CVD risk factors) more prominent later in life.

The prevalence of PCOS in reproductive aged women ranges from 8–13% depending on the criteria used to diagnose the condition.[7-9] Women at higher risk of manifesting PCOS include those who are overweight, Aboriginal and Torres Strait Islander women (21% in a Darwin study) and those with a family history of PCOS or T2D.

PATHOLOGY

The pathological determinants of PCOS include hyperandrogenism and insulin resistance. Reproductive and metabolic features of PCOS are underpinned by insulin resistance (IR) which stimulates ovarian androgen production and decreases hepatic sex hormone-binding globulin (SHBG production) thus increasing total and free androgens.[10] Androgen abnormalities are present with 60-80% of women with PCOS showing higher concentrations of circulating free testosterone and other androgens.[6]

CLINICAL FEATURES

Women with PCOS present with diverse features including psychological (anxiety, depression, body image),[11-13] reproductive (irregular menstrual cycles, hirsutism, infertility and pregnancy complications)[14] and metabolic features (IR, metabolic syndrome, prediabetes, T2D and cardiovascular risk factors).[15,16] Presentation varies across the lifespan and between ethnicities.

PCOS AND T1D

While PCOS is traditionally associated with T2D and insulin resistance, there is evidence to suggest that PCOS prevalence is also increased in women with T1D. The pooled prevalence of PCOS was 24% in adolescent and adult women with T1D in a meta-analysis,[17] which is significantly higher than in women without diabetes (8–13%). In a recent large community-based study, the self-reported PCOS prevalence in Australian women of reproductive age with T1D was 14.2%, compared to 5.1% of non-diabetic controls[18] (unpublished data).

While the mechanisms for PCOS in T1D are still unclear, it has been hypothesised that supraphysiological doses of subcutaneous insulin are needed to reach the portal circulation in T1D, leading to exogenous hyperinsulinism. Exposure to excessive concentrations of insulin is thought to be the driver for ovarian-mediated androgen production, culminating in PCOS and hyperandrogenic traits.[17,19]

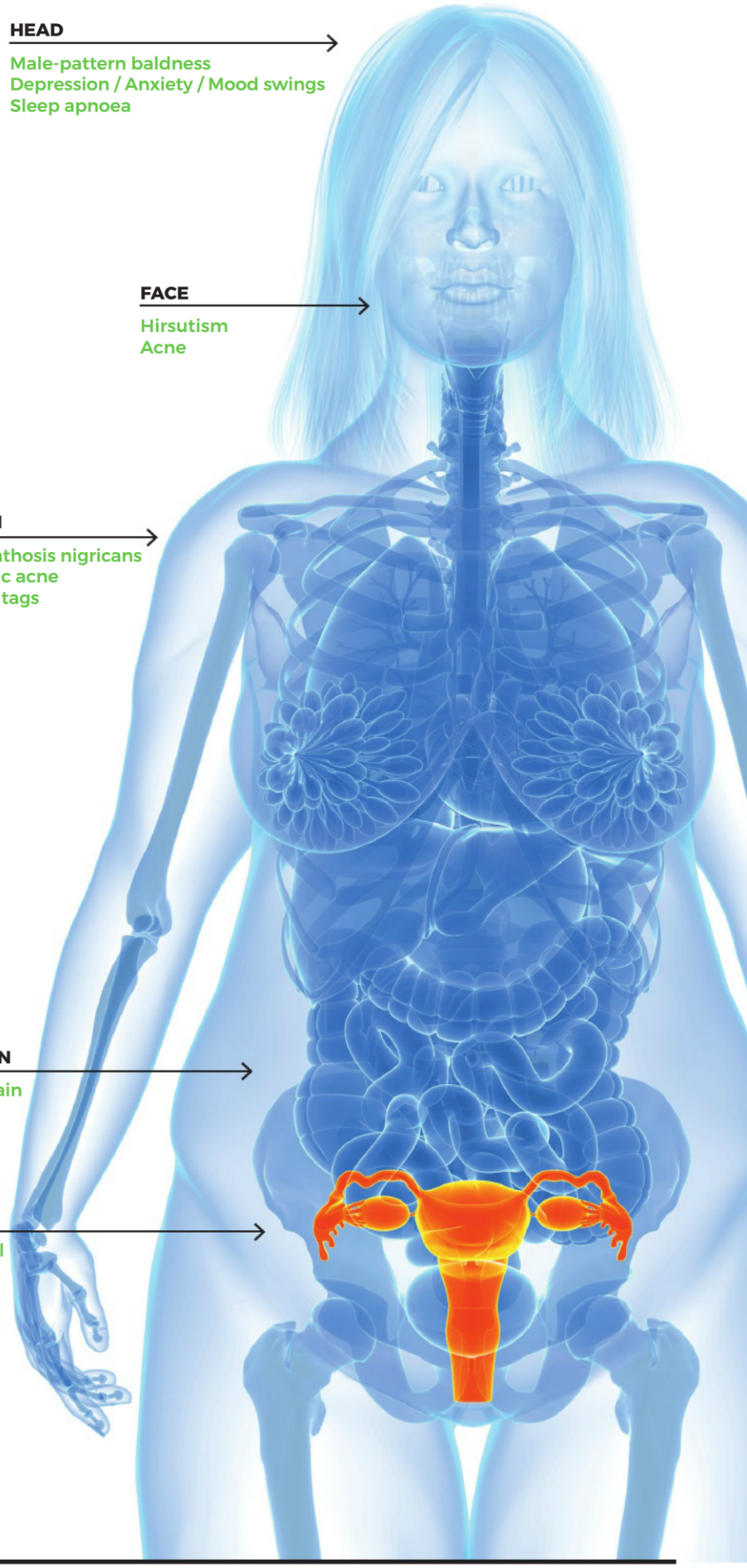
SCREENING FOR DYSGLYCAEMIA IN PCOS

The new PCOS guideline[20] recommends glycaemic assessment at baseline for all diagnosed with PCOS.

The assessment can be done using an oral glucose tolerance test (OGTT), fasting blood glucose or HbA1c. Of these, the guideline recommends an OGTT in presence of additional risk factors such as family history of diabetes, previous history of gestational diabetes, impaired fasting glucose or impaired glucose tolerance, high BMI (>25 kg/m^2, >23 kg/m^2 in Asians) and high risk

UNIQUE FEATURES OF
DIABETES MANAGEMENT
IN PCOS COMPARED TO THE
GENERAL POPULATION

- PCOS is underpinned by insulin resistance regardless of BMI. All women with PCOS, even if lean, are at increased risk of dysglycaemia.
- Women with PCOS have a 4 times higher risk of diabetes which manifests at a younger age compared with the general population.
- Lifestyle management is even more important, with higher rates of weight gain than in women without PCOS.
- Pre-conception counselling for weight and glycaemic management should be performed for all women with PCOS planning pregnancy.
- Women with PCOS should use appropriate contraception while taking a range of medications including GLP1 receptor agonists (for diabetes or weight loss) or spironolactone (for hirsutism).
- Use of metformin in pregnancy is still a question for further research. The authors do not recommend the use of metformin during pregnancy for PCOS management.



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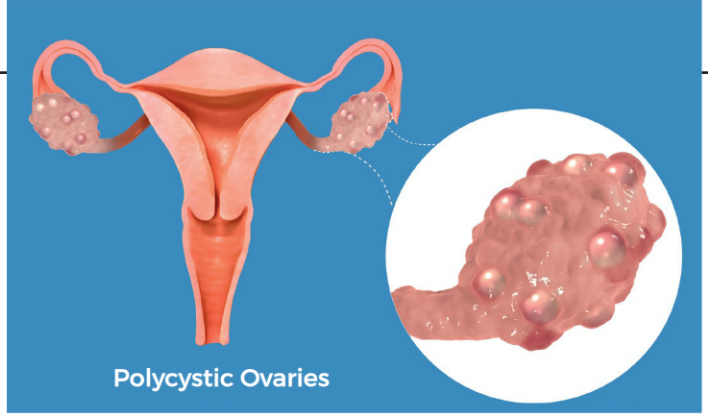

ethnicities. Follow up assessment can be done 1-3 yearly depending on risk factors. This risk of diabetes is independent of but exacerbated by obesity.[21]

An OGTT should also be recommended to all women with PCOS who are planning a pregnancy, or before 20 weeks' gestation if not performed pre-conception.[20] Pregnant women with normal glucose tolerance initially, should be offered a repeat OGTT at 24-28 weeks of gestation.

MANAGEMENT OF DYSGLYCAEMIA IN PCOS

Lifestyle modifications: The rate of obesity and weight gain is more in women with PCOS compared to those without PCOS.[22] Weight loss of just 5-10% is shown to significantly improve hormonal and metabolic features of PCOS including insulin resistance and glycaemic control.[21,23]

High BMI is often a major concern to women with PCOS,[24] and evidence suggests a lower quality of life (measured socially and psychologically) in those with obesity compared to those without.[24] Weight management, while important, is a sensitive subject that needs to be discussed, explaining the purpose and goals and asking permission beforehand.

The new guidelines recommend educating all women with PCOS regarding general principles of healthy eating and the importance of regular exercise. Monitoring weight is beneficial, aiming to prevent weight gain at first stage, particularly from adolescent age. A goal of 5-10% weight loss over 6 months is often achievable and leads to significant clinical improvement. No one diet has been shown to be advantageous over others in PCOS.

Regarding exercise, the guidelines recommend a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both in adults. There is a lack of evidence regarding the effect of exercise in lean women with PCOS.[25] However, some evidence in other populations suggest that insulin resistance would improve with regular exercise even without weight loss.[26,27]

Metformin: Metformin, an insulin sensitiser, is known to prevent or delay progression to diabetes in individuals with impaired glucose tolerance.[28] The new international guidelines recommend metformin for women with PCOS and impaired glucose tolerance or diabetes and those from high risk ethnicities. Although it is not a weight loss medication, metformin should also be offered to women with PCOS with BMI>25 kg/m^2, regardless of diabetes status to manage weight and metabolic outcomes,[29] where lifestyle modification does not address metabolic features.

Use of metformin in PCOS (without diabetes) is off-label on a private prescription, and the health professional should discuss the evidence, side effects (gastrointestinal and vitamin B12 deficiency) and elicit any concerns.[20] Gastrointestinal side effects are often dose dependent and can be self limiting.[30] We recommend a starting dose of 500mg daily with 500 mg increments every 1-2 weeks, to a tolerated dose of 1500mg daily. Extended release form of metformin may cause fewer side effects.

Bariatric surgery: Indications for bariatric surgery in the general population could be applied to women with PCOS who have a BMI ≥ 40 kg/m^2 or those with a BMI≥ 35 kg/m^2 and one or more obesity-related complication if non-surgical interventions fail and if pregnancy is not desired.

Bariatric surgery is shown to be beneficial for weight loss and diabetes management in the general population and in women with PCOS.[31,32] However, there is limited evidence regarding the effect on fertility and pregnancy outcomes and there are concerns regarding perinatal adverse effects including small for gestation babies and shorter gestation.[33] Pregnancy should be avoided for at least 12 months after bariatric surgery, using appropriate contraception.[20]

PCOS is a complex condition underpinned by insulin resistance. The PCOS guideline (2018) provides clear guidance on screening, prevention and management of diabetes risk in women with PCOS.

An extensive research translation program has been delieved to assist practitioners implement the PCOS guideline recommendations. To access the extensive range of practice tools and consumer resources, including the first evidence-based PCOS app, go to www.monash.edu/medicine/sphpm/mchri/pcos or search for "Monash PCOS".

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