Polycystic Ovary Syndrome

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"PCOS is a complex genetic disorder in women. "

Transcribed directly from MOGCAST Episode 16. Listen here:
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Hi, I'm Margreet Stegeman, I'm a Gynaecologist in Shepparton, Senior lecturer at Melbourne University and ERC Hub Educator. In this podcast I will talk about PCOS, which stands for Polycystic Ovarian Syndrome or disease.

PCOS is a complex genetic disorder in women. The prevalence is reported between 6 to 19%, depending on which diagnostic criteria are used. It is characterised by hyperandrogenism, chronic oligo or anovulation and insulin resistance, and it is associated with an increased risk for fertility issues, metabolic diseases such as Type II diabetes, dyslipidemia, and cardiovascular disease.

It is recognised as one of the most common endocrine metabolic disorders in women and was first described in 1935 by two gynaecologists, Stein and Leventhal. They described seven patients, of whom four were obese, and these patients had amenorrhoea, hirsutism, and enlarged polycystic ovaries. After performing a bilateral ovarian wedge resection, they all resumed regular periods and two became pregnant.

Now, I get asked very often what the cause for PCOS is, and there is actually no simple answer to this. It is not a specific endocrine disorder having a unique cause. It is more a complex disorder whereby numerous genetic and environmental factors play a role in the pathophysiology.

The genes that predispose to the increasing prevalence of complex metabolic disorders such as obesity, diabetes, and PCOS had probably a survival advantage in the past. In the hunter gatherer, having genes that organize the insulin action resistance according to availability of food resulted in better survival. Insulin resistance protects the organism from starvation and social stress. There's less loss of protein and more readily available glucose.

But in the setting of food abundance, it favors the development of metabolic disorders such as PCOS. With the obesity epidemic of recent decades, studies have suggested that excess weight may be increasing the prevalence of PCOS and maybe unmasking previously latent PCOS and increasing severity of the phenotypic presentation.

Overall in prehistoric times, or even a few decades ago when obesity was uncommon, women with PCOS genotypes might have been protected from severe infertility, a situation reversed in the setting of the modern obesity epidemic.

Natural selection can eliminate these deleterious genes, but the rapid changes in human lifestyle have not allowed enough time for a compensatory adaptation.

Other genetic factors related to hyperandrogenism and environmental or acquired factors, such as sedentary lifestyle and westernised dietary habits, together trigger the dysregulation of androgen synthesis, which is the main factor causing ovarian follicles not to grow and not form a dominant follicle, thus resulting in oligo or anovulation. This in turn leads to changes in the hypothalamic gene or H secretions, and different positive and negative feedback loops in women with PCOS.

PCOS women usually have increased LH concentrations, low normal FSH, and therefore increased LH:FSH

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ratios. The lack of progesterone peaks through the luteal phase of the menstrual cycle in anovulation leads to the increase in LH secretions. An increased LH secretion causes stimulation of androgen production in the ovaries. The adrenals also contribute to androgen excess in PCOS. In turn, the increased androgen synthesis is the main factor causing ovarian follicles not to grow, stabilizing the oligo or anovulation.

All the little follicles in polycystic ovaries produce androstenedione, which in fatty tissues gets aromatised to estrone, which in turn, due to negative feedback on the hypothalamus, lowers the production of FSH.

Inherited genetic factors and a westernised lifestyle can induce insulin resistance and/or obesity, both causing a hyper insulinemic environment, another stimulator of androgen synthesis. Insulin resistance and hyperinsulinemia are common features in obese and in a lesser extent in lean women with PCOS, and plays a role in the pathophysiology.

The higher levels of LH and insulin stimulate ovarian androgen production. The androgens and insulin, lower SHBG sex hormone binding globulin, which leads to more free androgen, which leads to increased insulin resistance leading to a feedback loop.

Consequently, PCOS develops under varying degrees of hyper androgenic and hyper insulinemic conditions that cause phenotypic variability, ranging from mild hirsutism to anovulation and infertility.

So this gives you an idea of how there are many factors that play a role in the pathogenesis of PCOS. Now, after all this talk about the heterogeneity of causes, how can we make a diagnosis?

There have been three tries to define the diagnostic criteria for PCOS, and they all include hyperandrogenism and menstrual dysfunction with exclusion of other known causes such as hyperprolactinemia, thyroid disease, premature ovarian failure, and non-classical congenital adrenal hyperplasia.

In 2003, in Rotterdam in the Netherlands, combined efforts from American and European societies led to the development of the Rotterdam criteria. To diagnose PCOS you need to have two out of the three following criteria - one oligo or anovulation, second, clinical or biochemical hyperandrogenism, and a third, the vaginal ultrasound showing polycystic ovaries. The vaginal ultrasound is not absolutely necessary if the first two criteria are present, you have made the diagnosis.

Especially in adolescence there is an inordinate amount of times that we will find polycystic ovaries on the ultrasound without it necessarily being part of PCOS. And when do we call periods irregular? Because irregularity is normal in the first year after starting the periods. Otherwise there are different criteria, but anything shorter than 21 and longer than 45 days would definitely be called irregular.

So if there are irregular cycles and clinical hyperandrogenism, then you have the diagnosis of PCOS. If there is no clinical hyperandrogenism, you do blood testing, and the tests that are done at least is free testosterone and free androgen index. If there's only either irregular cycles or hyperandrogenism, then you do the ultrasound to assess the ovaries. And if there is polycystic ovary, you have the diagnosis as well.

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"The endometrial cancer risk in women with PCOS is 2 to 6 times increased. "

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The ultrasound criteria for diagnosing polycystic ovaries vary, but most used is more than 20 follicles in at least one ovary and/or an increase in the volume of an ovary over 10ml.

Before we go on to the risks associated with PCOS, I would like to clarify one aspect. It is often postulated that obesity is an essential part of PCOS, but this is not so. About 60% of women with PCOS are obese, but the overall prevalence of PCOS among different BMI groups is actually quite similar in that there is 8% in underweight women, 9.9% in overweight, 9% in obese women, and 11.5% in morbidly obese women. So obesity is a common but not essential feature of PCOS.

It is also postulated that PCOS itself may predispose to weight gain and obesity. Now, there are risks associated with PCOS and the most important ones are cardiovascular, impaired glucose tolerance and endometrial cancer, so screening will need to happen. The risk is especially high if there is more intra abdominal fat, because visceral fat is more active metabolically than subcutaneous fat.

On average, though, you have to realize that lean women with PCOS also have an increased percentage of body fat and more visceral fat. The hyperinsulinemia is associated with chronic low grade inflammation and hypertension. The high androgens increase LDL cholesterol and triglycerides, and very often there is central obesity, part of the diagnosis towards metabolic syndrome.

All these factors predict a high risk for cardiovascular disease. Other cardiovascular disease risk factors should be taken into consideration and in overweight or obese women with PCOS a fasting lipid profile should be done and how often to repeat this will depend on the results and the global cardiovascular disease risk. Overall, there should be regular monitoring for weight changes and excess weight, waist circumference and blood pressure.

Regarding the diabetes risk, insulin resistance leads to hyperinsulinemia, leading to a decline in pancreatic beta cell reserve, leading to glucose intolerance and ultimately diabetes. Obesity aggravates the degree of insulin resistance and hyperinsulinemia, so 35% of women with PCOS have impaired glucose tolerance and up to 10% are Type II diabetics. Women with PCOS have a 3 to 7 fold increased risk to develop diabetes compared to women the same age without PCOS.
So all women diagnosed with PCOS should therefore have a GTT, and this should be repeated every two years. If a woman with PCOS is pregnant and a GTT has not been done, then it should be done before 20 weeks gestation.

The endometrial cancer risk in women with PCOS is 2 to 6 times increased and can present before menopause, but the absolute risk remains relatively low. In women with PCOS if on trans vaginal ultrasound, the endometrium is persistently thickened a biopsy needs to be done, especially if there is also prolonged amenorrhoea and abnormal vaginal bleeding or excess weight. On the other hand, routine screening for endometrial thickness in women with PCOS is not recommended.

To prevent endometrial cancer it is good to either keep the endometrium less stimulated or regular shedded so continuous OCP, the pill, the oral contraceptive pill or progesterone therapy in women with a cycle longer than 90 days is recommended.

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Other aspects to be aware of is an increased prevalence of sleep apnoea, moderate to severe anxiety and depression in women with PCOS, so screening for this should happen if it is suspected. There is also an increase in psychosexual dysfunction, negative body image and eating disorders.

Now we get to the treatment of PCOS and the aim is to treat the immediate, but also the long term consequences such as menstrual irregularities, the risk of developing endometrial hyperplasia and cancer, hyperandrogenism, fertility issues and reduce the risk for developing diabetes and cardiovascular disease. The treatments should, though, address the immediate needs. It is no good to put someone on the pill if they want to fall pregnant, for instance.

Now, an important part to start off with will be lifestyle interventions. Healthy eating and regular physical activity should be recommended in all women with PCOS. Weight reduction of 2 to 5% results in significant improvement in metabolic and reproductive function. Losing the abdominal fat is the most important part.

Weight loss also increases the levels of SHBG, binding the free androgen and reducing hirsutism. It improves ovulatory function, thus increasing pregnancy rates and possibly reducing miscarriage rates. There is no specific diet that should be advised, but more important is to reduce the caloric intake. Metformin can suppress appetite, but this is not consistent in every body and should therefore not be used primarily for weight reduction.

Education, counselling, and ongoing monitoring is important. These lifestyle interventions could or should also include behavioural strategies. Moderate intensity of physical activity appears effective and more likely to be sustainable.

If there is no immediate pregnancy wish, the oral combined pill is the first line of treatment to regulate the period and prevent endometrial hyperplasia. The pill also increases hepatic SHBG production and has therefore an effect on hyperandrogenism. If there are contraindications to the pill, then cyclical progesterone will induce regular withdrawal bleeds as well, but is not effective for treating hyperandrogenism.
If there is suspicion for endometrial hyperplasia an endometrial biopsy should be taken, and this can be done in the clinic with a tiny suction tubing.

About 70% of anovulatory women have hirsutism, and this is depending on the androgen levels, but also on genetically how sensitive the hair follicles are to the androgens. Treatment of hirsutism is either cosmetic, such as a laser hair removal, plucking, waxing or electrolysis, or pharmacological, such as the pill, or androgens such as spironolactone or cyproterone acetate also found in some pills such as Diane or Brenda. If more than six months on the pill is ineffective, then consider adding an anti androgen. In this case, you have to be aware of virilization of the female fetus so good contraception is needed.

With regards to fertility the anovulation is the most important factor. But endometrial implantation problems or oocyte quality can play a role as well. First line treatment again is lifestyle interventions. Second line is ovulation induction with letrozole, clomiphene or clomiphene with metformin. Cumulative pregnancy rates after three cycles is 50%. After 6 to 9 cycles, it is around 75%. There is a 5 to 8% multiple pregnancy rate. Third line are gonadotrophins with more risk for multiple gestation or laparoscopic ovarian drilling, whereby a

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couple of holes are made in the ovaries, which changes the hormonal balance or environment with resulting ovulations. In this case, the laparoscopic drilling, there is a risk for adhesion formation and some loss of ovarian reserve. Fourth line would be IVF.

Monitoring during pregnancy is important as there is an increased risk of adverse maternal and fetal outcomes. At the moment, continuing metformin in the pregnancy is not advised as the pros and cons don't weigh up yet.

Bariatric surgery is considered experimental in regards to having a healthy baby. The risk benefit ratio is currently uncertain to advocate this as a fertility therapy. Things to consider if bariatric surgery is prescribed is the cost, the need for weight management program, perinatal risks such as small for gestational age, premature delivery, possible increased infant mortality, and potential benefits such as reduced incidence of large for gestational age fetus, and gestational diabetes.

Because of rapid weight loss in the first 12 months after bariatric surgery, it is advised not to fall pregnant within this time frame. If they do fall pregnant, there can be nutritional deficiencies, so specialist interdisciplinary care is advised and fetal growth should be monitored.

In women with increased diabetes risks, such as women with an impaired glucose tolerance or high risk ethnic groups a second line treatment is adding metformin. Metformin is also postulated generally as a risk reducer for cardiovascular and diabetic risks. It increases insulin sensitivity by 20%, decreases weight and BMI by 3 to 5%, decreases blood pressure and LDL cholesterol, decreases the CRP, a marker for inflammation and therefore reflecting a lower level of chronic inflammation. It may improve endothelial function and coronary flow rate. Now, the pill can aggravate the underlying chronic inflammatory state. So combination therapy is possibly the way to go, as in the pill with metformin or an anti-androgen. But more research is needed here.

For the cardiovascular risks, there are studies on statins with or without the pill in women with PCOS. They are teratogenic, so contraindicated in pregnancy. Even though promising more research is needed here also.

Anti-obesity medication can be considered, but that is the same as in the general population guidelines.

Inositol makes insulin work more effective, is currently considered experimental, but there is emerging evidence of efficacy.

So in short, treatment for women with PCOS should not only be treating their immediate symptoms, but also possible consequences in the future.

This leads to the end of my talk and thank you very much for listening. If you would like more information, Speroff 's Clinical Gynecologic Endocrinology and Infertility is a very good reference book. Thank you again.