Pathophysiology, diagnosis and treatment of polycystic ovary syndrome

Abstract
Polycystic ovary syndrome (PCOS) is an incurable disorder that is associated with ovarian dysfunction. It affects millions of women in the UK. The signs and symptoms of PCOS include ovarian cysts, acne and excess hair growth (hirsutism), and can have a negative effect on the self-esteem of women with the condition. PCOS is also a potential cause of reduced fertility. This article uses a case study approach to discuss the pathophysiology, signs and symptoms, and diagnosis of PCOS, as well as complications, treatment and psychosocial implications of the condition.

Keywords
acne, gynaecology, hirsutism, hyperandrogenism, infertility, ovarian dysfunction, PCOS, polycystic ovary syndrome, women’s health

POLYCYSTIC OVARY SYNDROME (PCOS) is a heterogeneous condition of ovarian dysfunction that presents in women of reproductive age (Kochlar 2011). It is associated with three main features: ovarian cysts; ovaries that do not release eggs regularly; and the presence of high levels of androgen (the hormone involved in the development and maintenance of male characteristics) in the blood (Tomlinson 2014). PCOS was previously known as Stein-Leventhal syndrome and was first described in 1935 (Laycock and Wise 1996). While the symptoms of PCOS can be treated, the condition cannot be cured (NHS Choices 2016a).

In the UK, the general prevalence of PCOS is approximately 6-7% (National Institute for Health and Care Excellence (NICE) 2013a), and the condition affects one in five women (NHS Choices 2016a). Although PCOS is not life-threatening, it can cause distress and embarrassment for women, and may affect their self-esteem (Raisbeck 2009). It is also a major cause of infertility (BMJ Best Practice 2016).

Using a case study approach, this article describes the aetiology, pathophysiology and signs and symptoms of PCOS. It discusses the diagnosis of the condition, and complications associated with it, as well as the available pharmacological and non-pharmacological treatments. It also outlines the psychosocial implications associated with PCOS.

Case study: Emma
Emma is a 21-year-old, final-year student studying law. She developed acne at the beginning of puberty, at 11 years old, which continued throughout her secondary school years. Her acne was on her face, mostly around her jaw and chin, décolleté (the lower neckline and upper chest area), shoulders and back. It mostly consisted of large, painful pus-filled spots (pustules), as well as some blackheads and whiteheads (comedones). For several years, Emma experimented with using a range of cosmetic face washes and creams to reduce her acne. When her acne did not subside by the time she turned 19 years old, she visited her GP. The GP prescribed...
a course of oral antibiotics and a topical treatment gel containing clindamycin and benzoyl peroxide. Following eight weeks of treatment, Emma began to see an improvement in the condition of her skin. After several months of continuing antibiotic therapy, her acne had cleared, although some scarring remained.

By the time Emma was 21 years old, her acne had returned to its previous state. She also became increasingly aware of excess hair growth (hirsutism) on her body, chin, areolas, abdomen and buttocks. The excess hair had first appeared during her school years. She also found that shaving the hair from her legs and underarms only lasted one day or so, before noticeable regrowth occurred.

Emma made an appointment with her GP, who examined her acne and areas of excess hair growth. Her height and weight were measured, and her body mass index calculated as 21.8, which is within the healthy range. The GP asked Emma if she had a regular menstrual cycle, to which Emma replied that her periods were often late and her menstrual flow was usually light. Emma informed her GP that her symptoms of acne and hirsutism had made her feel low in mood. She often felt anxious in social situations and self-conscious in relationships.

The GP took blood samples and referred Emma to the gynaecology and endocrine clinic at the local hospital. During her appointment at the clinic, the registrar gynaecologist assessed Emma’s medical history and lifestyle. Emma had no medical conditions, engaged in daily physical activity and was a non-smoker. Her father’s family had a history of type 2 diabetes. The registrar reviewed Emma’s blood results, and noted she had high levels of androgen in her blood. After conferring with the consultant it was confirmed that, although Emma’s androgen levels were high, they were not high enough to be indicative of an androgen-secreting tumour.

The registrar gynaecologist proceeded to perform a pelvic ultrasound on Emma. Cysts were evident on her ovaries. Emma was diagnosed with PCOS, and discharged from the clinic. She made an appointment with the practice nurse at her GP surgery, where they reviewed the available treatment options. Emma commenced the combined oral contraceptive pill. While her weight was within the healthy range, the practice nurse emphasised the importance of maintaining a healthy diet, with adequate physical activity. She was provided with a list of foods with a high glycaemic load that needed to be limited in her diet, to reduce androgen production. She was told to return to the surgery when she started to see an improvement in her symptoms or if she experienced any adverse effects as a result of her medication.

**Aetiology and pathophysiology**

The ovaries are female gonads that are responsible for the production of sex hormones and ova (eggs), and are between 2.5cm and 3.5cm in length, 2cm thick and 1cm wide (Waugh and Grant 2014). Women have two ovaries, which are oval in shape (Snell 2012). Ovaries have endocrine functions, in that they release the hormones necessary for physiological changes observed in the reproductive cycle. These hormones are oestrogen, progesterone and inhibin, which are contained in the ovarian follicles (Waugh and Grant 2014). The ovaries lie adjacent to the lateral pelvic wall just below the pelvic inlet (Drake et al 2014), and receive their blood supply from the mesovarium (Waugh and Grant 2014).

Oogenesis (egg production) occurs at the site of the ovaries, with mature eggs ovulating into the peritoneal cavity and moving into the adjacent openings of the uterine tubes (Drake et al 2014). The hypothalamus and anterior pituitary gland control maturation of the ovaries, and release follicle-stimulating hormone (FSH) and luteinising hormone (LH), which are collectively called gonadotropins, and act on the ovaries, triggering and leading to ovulation (Waugh and Grant 2014).

The World Health Organization classifies PCOS as a group II ovulation disorder, which are dysfunctions of the hypothalamic-pituitary-ovarian axis (ESHRE Capri Workshop Group 2012). The underlying pathophysiology of PCOS is not fully understood, but it is considered to be multifactorial (Allahbadia and Agrawal 2007, Perry 2013).
understood, but it is considered to be multifactorial (Allahbadia and Agrawal 2007, Perry 2013). It is thought that the interaction between environmental factors, particularly obesity and diet, and genetic factors cause the menstrual and metabolic disturbances that characterise PCOS (Kovacs and Norman 2011). PCOS also appears to be more prevalent among women of certain ethnicities; for example, a higher prevalence has been noted among South Asian women, compared to Caucasian women (Royal College of Obstetricians and Gynaecologists (RCOG) 2014).

Symptoms of PCOS are thought to run in families (National Institutes of Health 2013). Follicular cysts of the ovary are common, both in normal ovaries and in PCOS (Snell 2012). It is thought that insulin resistance has a role in PCOS, because it can lead to an elevation of LH levels, which may cause overstimulation of ovarian theca cells, resulting in excess androgen production (hyperandrogenism) by the ovaries (Johansson and Stener-Victorin 2013, Kochlar 2015).

Signs and symptoms
There is a range of signs and symptoms associated with PCOS, which can vary over time in individual women. Women might experience many or some of the signs and symptoms; the condition will affect each woman differently. Some signs and symptoms can be considered cosmetic issues, such as acne and hirsutism, while others are considered gynaecological issues, such as irregular periods and reduced fertility (Tomlinson et al 2013). Nurses encountering patients who present with the symptoms of PCOS should consider the potential for this condition to be diagnosed and offer appropriate support to the individual (Raisbeck 2009). The signs and symptoms Emma experienced were gynaecological and cosmetic in nature.

Polycystic ovaries
Polycystic ovaries are characterised by the presence of small cysts on the ovaries; twice the number of follicles compared with those on normal ovaries. The size of the ovary is also slightly larger than the usual size of an ovary (RCOG 2015) (Figure 1).

Acne
The features of acne include comedones and pustules, which usually form during puberty but can continue into adulthood. They vary in severity and location (British Skin Foundation 2017). If the sebaceous glands are sensitive to the effects of androgens, they produce excess oil, which can result in the build up of dead skin cells lining the pores of the skin. When these cells are not adequately shed, they clog the pores and can produce comedones. The oil accumulation produced by the sebaceous glands may also allow for the Propionibacterium acnes bacterium to multiply, causing spots or pustules (British Association of Dermatologists 2017).

Hirsutism
Hirsutism is defined as male-pattern hair distribution occurring in women (Onselen 2011). This symptom is often distressing and results from hyperandrogenism. Desire for the removal of facial hair is one of the main reasons that women with PCOS present in clinical settings (Elghblawi 2007).

Oligomenorrhea and amenorrhea
Oligomenorrhea is characterised by infrequent ovulation (Cooper 2007), with menses occurring more than 35 days apart (Bielack 2017). The absence of menstruation for three or more months is known as amenorrhea, and results from failure of the hypothalamic-pituitary-gonadal axis (Rebar 2017). The failure of accumulating, under-developed follicles to mature causes menses to be erratic or absent, and lack of cyclical control in relation to normal mechanisms of feedback between the ovary and pituitary gland can lead to reduced fertility (Raisbeck 2009). Women experiencing oligomenorrhea or amenorrhea as a result of PCOS are at increased risk of developing endometrial hyperplasia and endometrial cancer, although there is no increased risk of breast or ovarian cancer (NICE 2013a, RCOG 2014).
Other common symptoms of polycystic ovary syndrome

Other common symptoms associated with PCOS include:

» Alopecia. This is male-pattern hair loss and is associated with hyperandrogenism (Setji and Brown 2014).

» Ovulatory disorders. These account for approximately 25% of infertility cases in the UK (NICE 2013b). The ovaries are inactive before puberty, but the stroma – the layer of connective tissue making up the cortex of the ovary – contains primordial follicles that are present in females from birth. In women of childbearing age, one or more of the Graafian (ovarian) follicles matures, ruptures and releases its ovum into the peritoneal cavity (ovulation) (Waugh and Grant 2014). PCOS is present in around 70% of women who have issues with ovulation, leading to infertility (Royal Berkshire NHS Foundation Trust 2017). Anovulation is when ovulation does not occur at all (Cooper 2007). However, while a major cause of anovulation, PCOS does not cause infertility in all women (ESHRE Capri Workshop Group 2012).

» Obstructive sleep apnoea. This is a major cause of chronic sleep obstruction, characterised by episodes of complete or partial obstruction of the upper airway, leading to intermittent hypoxia (Nitsche and Ehrmann 2010). The decrease in respiratory flow causes snoring, apnoea and arousals, leading to sleep fragmentation (Sweeting 2011). Obstructive sleep apnoea appears to be present in a disproportionate number of women with PCOS and may be associated with distinct endocrine and metabolic alterations (Nitsche and Ehrmann 2010).

**Diagnosis**

No single test is used to diagnose PCOS (Teede et al 2010). The presence of polycystic ovaries alone does not establish a diagnosis of PCOS. It should be noted that an individual can be diagnosed with PCOS in the absence of polycystic ovaries (NICE 2013a). Diagnosis rates will vary depending on the criteria used (Kochlar 2015). NICE (2013a) guidelines advise that a diagnosis of PCOS should be made when other causes of menstrual disturbance and hyperandrogenism have been ruled out, and if two or more of the criteria listed in Box 1 have been met.

Emma met all three criteria for the diagnosis of PCOS (Box 1) – oligomenorrhoea and hyperandrogenism, which presented clinically in the form of acne and hirsutism and biochemically from the results of the blood tests that showed elevated androgen levels in her blood, and the presence of polycystic ovaries as confirmed by an ultrasound scan. At the time of initial diagnosis, assessment of the patient's cardiovascular disease risk factors should be undertaken, including (RCOG 2014):

» Cigarette smoking.

» Dyslipidaemia (a disorder of lipoprotein metabolism).

» Family history of type 2 diabetes.
Hypertension.
Impaired glucose tolerance.
Lack of physical activity.
Obesity.
Type 2 diabetes.

While Emma demonstrated a healthy and active lifestyle, assessment by the registrar gynaecologist revealed a family history of type 2 diabetes on her father’s side.

**Treatment**

PCOS tends to be diagnosed by a gynaecologist. It is important that the long-term implications of the diagnosis are understood to ensure a holistic approach to treatment of the disorder (RCOG 2014). Treatment often focuses on individual symptoms rather than treatment of the syndrome itself, because the underlying pathophysiology of PCOS is not fully understood (Sirmans and Pate 2014).

In addition to pharmacological therapy, RCOG (2014) guidelines recommend changes to lifestyle factors, such as diet, exercise and weight loss, which are initiated as the first-line treatment for women with PCOS to improve potential long-term outcomes of the condition.

**Pharmacological treatment**

PCOS is incurable, but its symptoms can be treated (NHS Choices 2016a). However, there is no medication available that completely reverses the underlying hormonal imbalance and treats all of the associated clinical symptoms of PCOS (Teede et al 2010).

**Combined oral contraceptive pills**

NICE (2013a) recommends offering a standard combined oral contraceptive pill or co-cyprindiol. Co-cyprindiol is a licensed drug in the UK and is indicated for the treatment of acne and hirsutism, if there are no contraindications, such as uncontrolled hypertension and breast cancer. In addition, hormonal treatment should be stopped if a woman becomes pregnant. Co-cyprindiol has contraceptive properties that regulate menstruation. It also contains cyproterone, which blocks the effect that male hormones have on the skin (NICE 2013c). The combined oral contraceptive pill reduces free testosterone by increasing sex hormone binding globulin levels. LH and FSH are suppressed and ethinylestradiol is combined with drospirenone.

Ethinylestradiol with drospirenone is a combined oral contraceptive pill that contains a progestogen, which acts as an antiandrogen (Kochlar 2015). The combined oral contraceptive pill may also be used as treatment to prevent endometrial hyperplasia and to induce withdrawal bleeding at least once every three months. Alternatively, the levonorgestrel intrauterine system may be offered (NICE 2013a).

**Insulin-sensitising agents**

High levels of circulating insulin are thought to contribute to anovulation and excess androgen production (RCOG 2008). The potential for the long-term use of insulin-sensitising drugs in women with PCOS is of interest because hyperinsulinaemia is important in the development of hyperandrogenaemia and disrupted folliculogenesis – drugs such as metformin decrease insulin secretion and may improve normal endocrinological function (NICE 2013a). Insulin-sensitising agents are only licensed in the UK for use in patients with diabetes. While evidence suggests the drugs are safe, there is no evidence at present to suggest that the long-term use of insulin-sensitising agents confers any long-term benefit in PCOS. However, the use of weight-reduction drugs in overweight woman might be useful in

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**BOX I. National Institute for Health and Care Excellence diagnostic criteria for polycystic ovary syndrome**

- Infrequent ovulation or absent ovulation. This often presents as oligomenorrhoea or amenorrhoea.
- Hyperandrogenism. This may present clinically, for example hirsutism, acne or male-pattern alopecia, or biochemically, for example increased levels of total or free testosterone. The patient should be asked if they are experiencing any excess hair growth. Hirsutism might not be clinically evident during assessment, but it is important to remember that many women will remove excess hair (Kamangar and Shinkai 2012). Consideration should also be given to whether hair growth is rapid as a result of neoplastic causes of androgen production (Kochlar 2015).
- The presence of polycystic ovaries on ultrasonography, in which there are 12 or more follicles in at least one ovary, measuring 2-9mm in diameter, or where ovarian volume is greater than 10mL.

(National Institute for Health and Care Excellence 2013a)
reducing hyperandrogenaemia in women with PCOS (RCOG 2014).

The RCOG (2014) emphasises that, because insulin-sensitising drugs such as metformin and thiazolidinediones are not licensed medications for PCOS, women should be counselled before their use to enable them to make an informed decision about the treatment they may receive. For example, metformin may result in gastrointestinal disturbances. Only specialists, such as gynaecologists, should prescribe these drugs for PCOS.

It is recommended that screening for impaired glucose tolerance, type 2 diabetes and cardiovascular risk should be offered to women with PCOS because of the increased risk of developing related conditions (NICE 2013a). Women who are pregnant and have PCOS should be screened for gestational diabetes and impaired glucose tolerance, with an oral glucose tolerance test before 20 weeks’ gestation. It is important to note that there is an increased risk of pregnancy-induced hypertension, pre-eclampsia and pre-term birth in women with PCOS (NICE 2013a).

Anti-oestrogens
Clomifene citrate is an antioestrogen used for female infertility caused by oligomenorrhoea or secondary amenorrhoea, such as in the case of PCOS (British National Formulary 2017). Its mode of action involves blocking oestrogen receptors in the hypothalamus and encouraging normal secretion of LH and FSH, thus stimulating ovulation, as well as improving acne and causing the excess hair to become finer in texture and lighter in colour (Raisbeck 2009). Clomifene citrate has long been the first-line treatment for irregular or absent ovulation. A course lasting between three and six ovulatory cycles is usually sufficient to ascertain if pregnancy will be achieved when using the drug (Homburg 2003). Clomifene citrate does not guarantee fertility but can increase the fertility of women taking the drug to that of the average women in the general population (Raisbeck 2009). Women who wish to use clomifene citrate should be advised that there is a risk of multiple births, although this is rarely more than twins (British National Formulary 2017).

Non-pharmacological treatment
A healthy lifestyle should be encouraged to reduce the long-term risks associated with PCOS. It should be emphasised that being overweight can cause worsening of the woman’s symptoms, such as reduced fertility and higher androgen levels (NICE 2013a). Non-pharmacological treatment is required to limit adiposity in women with PCOS (Goss et al 2014). Reducing dietary carbohydrate may be one such approach in reducing abdominal and total adiposity in women with PCOS (Goss et al 2013). Women who are obese and infertile and have PCOS should be advised that weight loss is the most effective treatment and can improve ovulation and their chances of becoming pregnant (NICE 2013a).

Other natural ways for women to enhance their fertility include: supplementing their diet with folic acid, and aloe vera, which assists in the restoration of female hormones (Elghblawi 2007). Women with fertility difficulties should also be considered for referral to secondary care services for fertility treatment (NICE 2013a). If make-up is used to disguise acne, non-comedogenic and non-acnegenic products are recommended, because they are oil-free. Cleansers used to remove make-up should also be oil-free (British Association of Dermatologists 2017). Some literature has reported on the use of acupuncture for the treatment of PCOS (Lim et al 2011); however, there is no reliable evidence relating to its use for the treatment of the condition (NICE 2013a).

Case study: Emma’s treatment
Emma commenced the combined oral contraceptive pill and was encouraged by the practice nurse to continue maintaining her healthy and active lifestyle. However, Emma expressed some concerns, because she had heard that ‘the pill’ can cause blood clots. The combined oral contraceptive pill contains oestrogen, which causes blood to clot more easily.
The signs and symptoms of PCOS, such as infertility, acne and hirsutism, may challenge a woman’s feminine identity and can affect her quality of life. This can lead to depression and anxiety (Zangeneh et al 2012). Mood implications are clinically relevant, because treating PCOS requires the patient to implement lifestyle changes and the self-motivation to do so (Deeks et al 2010).

**Psychosocial implications**

The signs and symptoms of PCOS, such as infertility, acne and hirsutism, may challenge a woman’s feminine identity and can affect her quality of life. This can lead to depression and anxiety (Zangeneh et al 2012). Mood implications are clinically relevant, because treating PCOS requires the patient to implement lifestyle changes and the self-motivation to do so (Deeks et al 2010). Emma explained to her GP that her symptoms affected her mood and resulted in increased anxiety. She became uneasy in social situations and felt unable to wear clothing that exposed her décolleté, shoulders or back, and often applied make-up to conceal her acne. Emma’s quick hair regrowth under her arms and on her legs also made her feel self-conscious. She often wore clothes that covered those areas, which became problematic and uncomfortable in warm environments and during the summer months.

While Emma enjoyed using her university’s gym a few times each week, she often felt uneasy in the changing rooms because of the hair growth on her body. In addition, her quick facial hair regrowth made her feel anxious when she engaged in intimate relationships. Hahn et al (2005) found that the changes to women’s physical appearance can affect their quality of life and lead to decreased sexual satisfaction, as well as feelings of being sexually unattractive. Emma experienced such feelings. Regardless of the severity of signs and symptoms, or a woman’s response to treatment, clinicians should consider the psychosocial implications of PCOS on an individual basis (Hahn et al 2005). Nurses managing the care of women with PCOS should have a comprehensive understanding of the condition and associated treatments to provide effective support to women undergoing treatment (Banning 2006).

During her appointment with the practice nurse, Emma expressed her concerns and distress at realising she had a lifelong condition, which she had often heard was associated with infertility. The practice nurse explained that PCOS, although lifelong, is not life-threatening, and adherence to treatment can assist in the management of the condition. The practice nurse also emphasised to Emma that being diagnosed with PCOS does not always cause infertility and that many women who previously attended the practice when diagnosed with PCOS have gone on to have children.

After several months of taking the combined oral contraceptive pill and maintaining her active and healthy lifestyle, Emma’s symptoms improved. Her acne began to improve, as did the excess hair on her body, with some areas of excess hair clearing up completely. The improvement in these symptoms improved Emma’s confidence and she no longer felt anxious in social situations.

**Conclusion**

Emma’s case describes the situation of a patient of reproductive age presenting to her GP with the signs and symptoms of PCOS. PCOS is an incurable disorder of ovarian dysfunction. It is thought to be linked to an interaction between environmental and genetic factors and insulin resistance. During diagnosis, it is important to consider other conditions, such as potential neoplastic causes of androgen production, which may result in symptoms associated with PCOS. Emma’s symptoms of oligomenorrhea, hyperandrogenism and the presence of polycystic ovaries confirmed by ultrasound scan, meant that she met the criteria for a diagnosis of PCOS.

Pharmacological treatment available to
patients with PCOS includes the combined oral contraceptive pill, which was prescribed for Emma by the practice nurse. Non-pharmacological treatment can also reduce the long-term risks of PCOS. PCOS can be distressing for women and may affect their quality of life. It is important for nurses to provide individualised support to women undergoing treatment for the condition.

References


