



# Acne - a potential skin marker of internal disease



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**Abstract** Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder in adult women. Hyperandrogenism is the crux of the pathogenesis of both acne and hirsutism, the most frequent clinical presentations of the syndrome. The chronic anovulation that may occur, often but not always associated with enlarged cystic ovaries, has long been recognized as an important feature of PCOS. In recent years major changes have occurred with regard to PCOS:

- (1) Sophisticated radiologic technology, together with increased awareness and clinical suspicion, have led to a massive increase in patients diagnosed with PCOS, and guidelines for diagnosis have been agreed upon, with any two of the following essential for a diagnosis: clinical or biochemical evidence of hyperandrogenism, chronic anovulation, or cystic changes in the ovaries.
- (2) Insulin resistance has been found to be a major component of PCOS; interaction can occur whereby hyperinsulinemia can promote hyperandrogenism and possibly also vice-versa. Insulin resistance is also thought to have a major role in the pathogenesis of metabolic syndrome, an ever-increasing worldwide cause of morbidity and mortality from ischemic heart disease and type 2 diabetes mellitus.
- (3) Patients with PCOS appear to have a fourfold increased risk of developing metabolic syndrome, although this is not equal in all PCOS patients.

Although management of the common cutaneous manifestations, mainly acne, hirsutism, alopecia, and acanthosis nigricans, remains strictly within the realm of daily dermatologic practice, the pendulum is shifting toward greater awareness of the longer-term systemic implications of PCOS, with emphasis on the unique opportunity and privileged position of the dermatologist to diagnose this potentially serious problem at an early stage, when effective long-term treatment can be instituted. Patients need to be advised that PCOS cannot be cured but can be controlled. Management should involve a multidisciplinary team with emphasis on lifestyle change, insulin sensitizing agents, androgen blockers, and attention to specific cutaneous manifestations.

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In 1935, two American gynecologists, Irving F. Stein, Sr. (1887-1976) and Michael L. Leventhal (1901-1971), at Michael Reese Hospital in Chicago<sup>1</sup> defined a syndrome consisting of obesity, amenorrhoea, hirsutism, and infertility

associated with enlarged polycystic ovaries. Polycystic ovary syndrome (PCOS) has evolved from a gynecologic curiosity to a multisystem endocrinopathy of apparently quasi-epidemic proportions, with the World Health Organisation (WHO) estimating 116 million cases in 2010. Dermatologists manage the cutaneous manifestations of PCOS and, therefore, play a key role in its diagnosis and management.

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Long before 1935, Hippocrates (460-370 BCE) had noted “*But those women whose menstruation is less than three days or is meagre, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant*”<sup>2</sup> and even earlier, Soranus of Ephesus (first century CE) remarked that “*sometimes it is also natural not to menstruate at all . . . It is natural too in persons whose bodies are of a masculine type . . . we observe that the majority of those not menstruating are rather robust, like mannish and sterile women.*”<sup>3</sup> Antonio Vallisneri (1661-1730) in 1721 described “*Young Italian peasant women moderately obese and infertile with two larger than normal shiny ovaries with a surface like pigeons eggs,*” and in 1844 Achille Chereau (1817-1885) noted “*Cyst-related changes to the ovaries.*”<sup>4</sup>

The prevalence of PCOS had been remarkably uniform in all ethnic races studied,<sup>5</sup> raising the possibility that gene variants that will eventually be found to be associated with PCOS will be similar across ethnic groups. The striking evolutionary paradox of this genetically based condition, which impairs fertility, is that not only should it have diminished in prevalence, but it should have done so rapidly—unless there has been some form of balancing selection, such as greater sturdiness and improved energy utilization, a rearing advantage for the children and kin of women with PCOS, and a reduction in the risk of perinatal mortality. The emerging discipline of evolutionary medicine can provide important insights into the causes and patterns of occurrence of common diseases such as PCOS.<sup>6</sup>

PCOS is a common endocrine disorder among women of reproductive age (5%-18%) with chronic anovulation and factors related to androgen excess. The hallmark features of hyperandrogenism and hyperinsulinemia have systemic long-term implications. The clinical definition of PCOS has changed in recent years and includes as one of its core criteria the dermatologic manifestations of hyperandrogenism, chiefly hirsutism, acne vulgaris, and androgenetic alopecia. Acanthosis nigricans, a cutaneous sign of hyperinsulinemia, may also be present. These dermatologic features may provide early clinical clues to recognition of PCOS.<sup>7</sup>

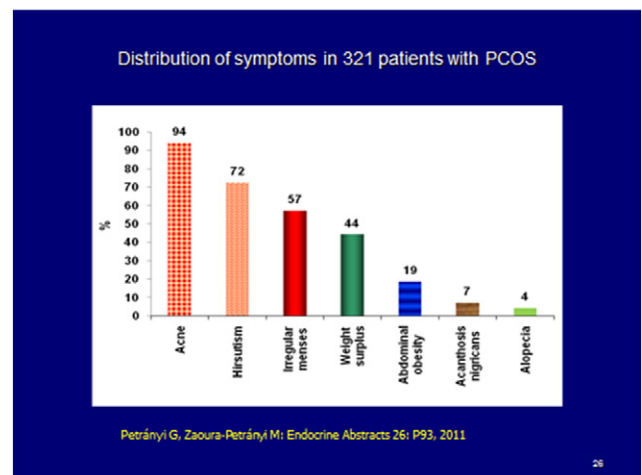
In 1990, “hyperadrenalism” was reported to occur in 10% of patients with late-onset acne,<sup>8</sup> but it is likely that the vast majority of women with severe acne have PCOS. This is partly due to a real increase in PCOS and partly due to a broadening of the criteria for its diagnosis. In particular, modern imaging techniques have revealed the presence of polycystic ovaries in normal women and mildly polycystic ovaries in hirsute women with normal menses. Many women, labelled as having idiopathic hirsutism, have PCOS.<sup>9-11</sup> The increase in PCOS has been linked to childhood obesity (American Association of Clinical Endocrinologists Position Statement on Childhood Obesity Linked to Early Development and PCOS in Young Girls-September 13, 2005) eating disorders, and increasingly stressful lifestyles.

The dermatologic manifestations of hyperandrogenism include hirsutism, persistent acne, male pattern alopecia, and

occasionally acanthosis nigricans. Clinical findings vary within a patient population as a result of the complex relationships between genetics, end-organ susceptibility, and hormonal variations<sup>12</sup>. Acne may frequently be the presenting problem and has occurred in over 90% of PCOS patients diagnosed at an endocrinology clinic (Figure 1). In this series, obesity occurred in less than 50% of patients, whereas hirsutism and alopecia were found in 70% and 10%, respectively. In a recent report<sup>13</sup>, acne was the most commonly observed dermatologic manifestation (95.0%), followed by hirsutism (60.0%), seborrhea (47.5%), acanthosis nigricans (AN) (20.0%), and androgenetic alopecia (12.5%). Earlier studies reported a prevalence range, 9.8%-50%.<sup>14,15</sup>

PCOS is prevalent in women with late-onset acne, persistent acne, and acne resistant to conventional therapies,<sup>16</sup> but only a minority of women presenting with acne are known to have prior PCOS: Approximately 80% of women with severe acne, 50% with moderate acne, and 30% with mild acne have some elevation of plasma androgen.<sup>17</sup> In a recent study, the prevalence of acne, hirsutism, seborrhea, androgenetic alopecia, and AN was 53%, 73.9%, 34.8%, 34.8%, and 5.2%, respectively. Acne was not associated with hormonal, metabolic, and anthropometric variables. Hirsutism had positive associations with total testosterone, fasting glucose, and total cholesterol and a negative association with age. Seborrhea was found to be related with free testosterone, fasting glucose, and insulin.<sup>18</sup>

Numerous factors contribute to the development of acne, foremost being androgens and androgenic stimulation of the sebaceous glands. A number of women with acne may have at least one abnormal hormone level. Both circulating serum androgens and locally produced androgens play a role. Some studies have reported a positive correlation between acne severity and circulating serum androgen levels. Women with acne have been reported occasionally to have elevated serum levels of total testosterone, free testosterone, dehydroepiandrosterone



**Fig. 1** Presenting symptoms of polycystic ovary syndrome (PCOS) patients in an endocrinology clinic. (From Petranyi G, Zaoura-Petranyi M. *Endocr Abstr.* 2011;26:93.)

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