Polycystic Ovary Syndrome (PCOS) : An Overview

Aram Rojanasakul MD.

Division of Gynaecologic Endocrinology, Department of Obstetrics and Gynaecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Abstract : *PCOS is a common gynecological disorder. While the etiology of this condition is still unknown, several abnormalities involving the pathophysiology of this syndrome have been demonstrated. Diagnosis of PCOS usually relies on clinical, biochemical and ultrasonic appearance of the ovary which is not difficult in most cases. Apart from suffering from menstrual disturbances, androgenic symptoms and infertility, if left untreated, this patient has high risk of developing endometrial hyperplasia and carcinoma, breast cancer, diabetes mellitus, hypertension and cardiovascular disease. Several therapeutic options are now available. For those who do not immediately desire pregnancy, treatment with combined oral contraceptives or progestogen is usually effective. For infertile women, ovulation induction, medically, is successful in most cases. Surgical treatment (cauterization of small peripheral cysts) is another alternative in selected case. (Thai J Obstet Gynaecol 1994;6:141-148.)*

Key words : polycystic ovary syndrome, pathophysiology, consequences, diagnosis, treatment.

The historical aspect of PCOS is dated back to 1935 when Stein and Leventhal reported patients with amenorrhea, hirsutism and enlarged polycystic ovaries. The so-called Stein-Leventhal syndrome[1] was subsequently shown to have wide range and spectrum of clinical, biochemical and pathological findings. The term "Stein-Leventhal syndrome" is rarely used at present and is replaced by polycystic ovary syndrome (PCOS).

PCOS is a common gynecological disorder. It is not a disease but a heterogenous clinical syndrome. The main characteristics of (PCOS) are chronic anovulation (abnormal gonadotropin secretion) and hyperandrogenemia. Chronic anovulation accompanying hyperandrogenemia however, are not always diagnostic for PCOS. These conditions can be found in several clinical situations such as Cushing's syndrome, late onset congenital adrenal hyperplasia, virilizing ovarian and adrenal tumor, hyperprolactinemia, thyroid dysfunc-

tion and obesity. These groups of patients are sometime called the syndrome of hyperandrogenism and chronic anovulation[2].

Etiology

The etiology of PCOS is still unknown. Several investigators have demonstrated the abnormalities involving the pathophysiology of this syndrome, including hypothalamic dysfunction, enzymatic abnormalities in the adrenal gland and ovary, and hyperinsulinemia. The relationship between various factors regulating ovarian function and development of PCOS have also been explored, such as gonadal peptides, several growth factors and renin angiotensin system. At present, several groups are interested in the role of insulin/insulin-like growth factors (IGFs) and insulin-like growth factor binding protein (IGF-BP) on PCOS[3]. However, the definite cause of PCOS remains unsettled. Since the clinical symptoms in most patients start around puberty, it has been suggested that the abnormality should begin at that period when the maturity of hypothalamic-pituitary-ovarian axis is not fully reached[4]. Peripubertal hormonal changes are also similar to the pattern found in patient with PCOS in many aspects[3].

Pathophysiology

While the etiology of PCOS remains unknown, the pathophysiology of this disorder has been illucidated, although not fully. Chronic anovulation leads to unopposed estrogen production which increases gonadotropin releasing hormone (GnRH) pulsatility. The event results in an increase of both amplitude and frequency of luteinizing hormone (LH). Follicle stimulating hormone (FSH), however, is usually normal or decreased, due to the negative feedback effect of estrogen. The sustained high LH level causes stimulation of theca cell function to secrete androgens (testosterone, androstenedione). The ovarian androgen production is also augmented by hyperinsulinemia and increased action of IGFs. Adrenal glands also play role in hyperandrogenemia in PCOS[4]. Decreased FSH and increased androgen levels inhibit follicular growth, therefore, ovulation doesn't occur. Without ovulation, the patient is in the vicious cycle of unopposed estrogen status. Total estrogen production in PCOS is the sum of estrogen from multiple tiny follicles and the peripheral conversion from androgen. This extraglandular source accounts for a significant portion in obese patients. In PCOS, level of sex hormone binding globulin (SHBG) and IGF-BP is lower than normal. Therefore, the level of free portion and the action of androgen as well as estrogen are increased.

Pathology

Polycystic ovary (PCO) is an anatomical term defining the ovary

with numerous small cysts. In typical cases, both ovaries are slightly enlarged with smooth thickened avascular white capsule. Cut section of the ovary reveals multiple subcapsular follicular cysts, diameter about 4-8 mm. Hyperplasia of theca-stromal cell is characteristic[5,6]. However, not all patients with PCOS has PCO. Some patients have normal sized ovaries or unilateral enlargement. In another aspect, PCO can also be found in other conditions apart from PCOS. This makes the diagnosis of PCOS sometime confusing.

Prevalence

The prevalence of PCOS is difficult to establish. It is the most common cause of estrogenic anovulation and hirsutism. It has been estimated to affect as much as 5 percent of the female population[7]. By using ultrasonic criteria, PCO was found in 32 percent of women with secondary amenorrhea, 87 percent of oligomenorrhea, and 87 percent of hirsute women who had history of normal menstruation[6]. In Ramathibodi's study, the prevalence of PCOS in women presenting with acne was about 37 percent[8].

Diagnosis

The diagnosis of PCOS at present relies on clinical, biochemical and ultrasonic features[4,6,7,9]. The wide clinical spectrum of PCOS is the results of chronic anovulation (menstrual disturbances and infertility) and hyperandrogenemia. Several forms of menstrual disorders are observed in these patients i.e. amenorrhea, oligomenorrhea, dysfunctional uterine bleeding, menorrhagia and metrorrhagia. The symptoms begin at peripubertal period in most cases. Infertility is also a common presenting symptom in married women. However some patients experience sporadic ovulation and subsequent spontaneous pregnancy does occur. In PCOS, only mild to moderate degree of hyperandrogenism are presented which lead to cosmetic problems such as acne and hirsutism. Severe degree of androgenic symptom, such as clitormegaly, is rare. In Thai patients, the prominent androgenic symptoms are acne and seborrhea. Hirsutism, in contrast to the patients in western countries, is less common. Degree of hirsutism does not depend only on the androgen level but also on the sensitivity of the pilosebaceous unit to androgen. Asian women are generally less hirsute than the Caucasian. Obesity is also common. In the severe cases, hyperpigmentation in the neck region, axilla and breast fold (acanthosis nigricans) may also be presented. Pelvic examination may reveal bilateral ovarian enlargement in some cases.

The common hormonal changes in PCOS are elevated level of LH and low or normal FSH. The LH to FSH ratio is raised more than twice. However, in some cases elevated LH/FSH could not be demonstrated mainly due to the pulsatile nature of

LH secretion. Due to the inconsistent finding, some groups have abandoned the LH to FSH ratio as a diagnostic criterion for PCOS[10]. While serum LH may not be increased in some patients, the bioactive LH was found to be elevated in almost all cases[11]. The bioactive LH assay at present, however, is not available for routine test. Serum androgens are elevated. Total testosterone is increased but usually not more than 1.8 ng/ml. Serum dehydroepiandrosterone sulfate (DHEAS), adrenal androgen, is also mildly elevated (<700 ug/dl). Mild to moderate rise of prolactin level may be observed in about 1/3 of the cases[12].

During the last decade, the development of high resolution ultrasonography enables gynecologists to use it in a non-invasive study of the ovarian morphology. The typical ultrasonic findings of PCO are slightly enlarged ovaries with multiple sonolucent cystic structures along the periphery and dense echogenic stroma (Fig. 1). Vaginal ultrasound is preferable to the abdominal route in this aspect[6,13].

Late consequences

PCOS is a syndrome which should receive great concern from both the patients and physicians. Apart

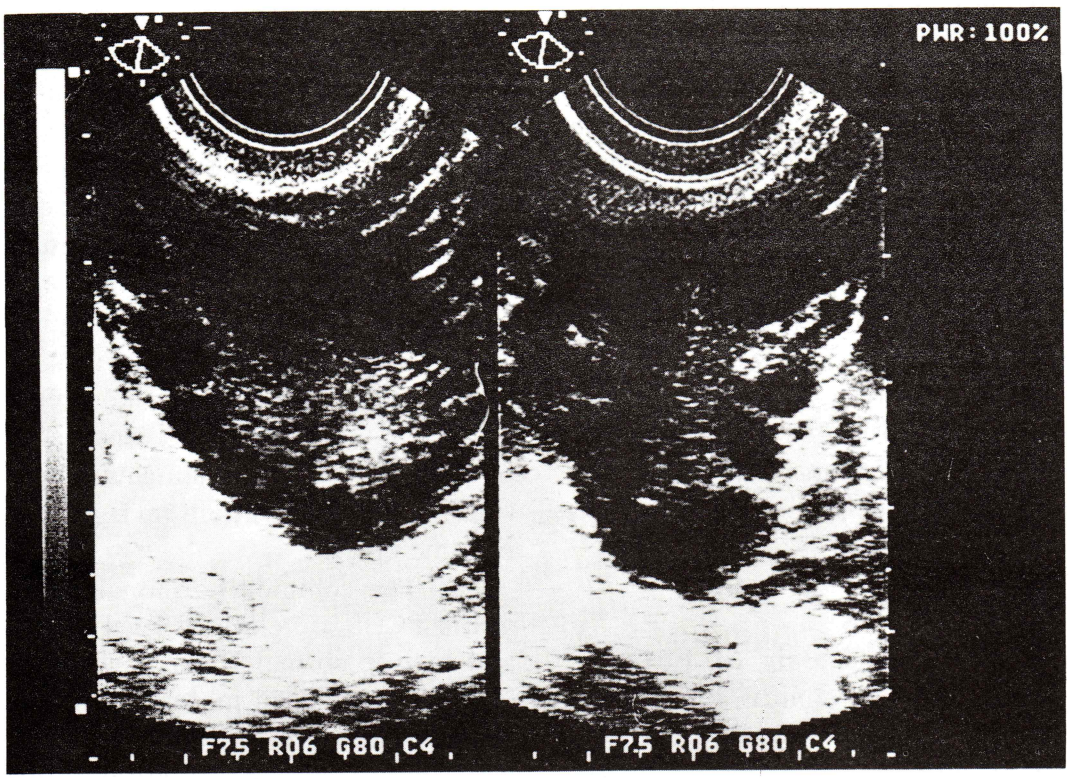

Fig. 1 Transvaginal ultrasonic appearance of the polycystic ovary in PCOS patient.

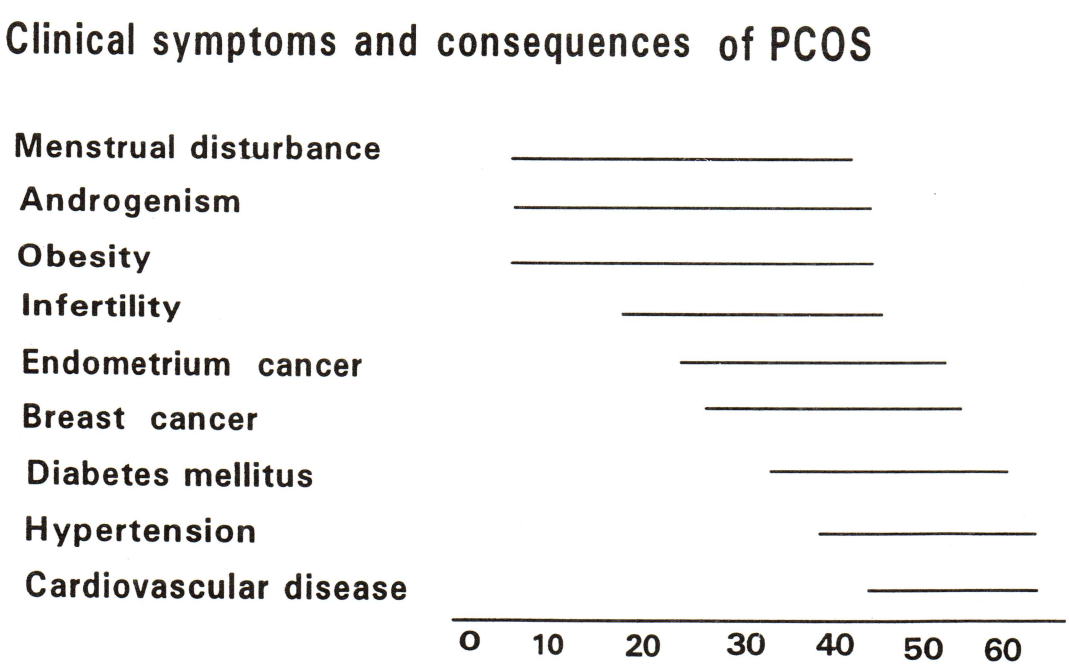

Fig. 2 Purposed consequences of PCOS in relationship to the age of patient (year).

from the clinical problems above, if left untreated, the patients have high risk of developing endometrial hyperplasia and carcinoma, breast cancer, diabetes mellitus, hypertension and cardiovascular disease[14-17]. The purposed development of these consequences is shown in Fig 2. The predisposing factors of these late consequences in PCOS patient include obesity, abnormal lipid profile and increased insulin resistance. These potential sequelaes should alert the physician for early diagnosis and treatment of this disorder.

Treatment

Since the pathogenesis of PCOS remains unclear, the preventive measure has not been established. However, there are considerably effective therapeutic strategies for these patients. The management generally depends on patients' problems and their desire of pregnancy. In those who want to become pregnant, ovulation induction should be considered[7,18]. Clomiphene citrate remains the first line ovulation inducing agents. The addition of dexamethasone to suppress adrenal androgen may be advantageous in some cases. Patients with elevated prolactin level may benefit from dopamine agonist. Ovulation could be acheived in almost 80 percent of the patient. Pregnancy, however, occurs in about half. Human menopausal gonadotropin and pure FSH are more effective in induction of ovulation and pregnancy but more costly. During the treatment

course, the patients should be closely monitored to avoid the serious complications, including ovarian hyperstimulation syndrome and high ordered multiple pregnancy. Using the threshold principle, low dose FSH (step up) therapy could effectively induce monofollicular development, avoiding such complication. Another problem frequently occurred during gonadotropin treatment in PCOS is premature luteinization, which can be found in 20-30 percent of cycles. The introduction of gonadotropin releasing hormone agonist (GnRHa) which suppress endogenous LH leads to dramatic decrease of this problem. At present, the combination of GnRHa and gonadotropin appears to be the most effective method of ovulation induction in PCOS patients.

For PCOS patients who do not wish to become pregnant immediately, the treatment should aim to interrupt the vicious cycle of this disorder. Progestogens alone induce regular endometrial shedding and decrease androgenic symptoms. More effective therapy could be accomplished by the use of combined oral contraceptive, (OCs) containing estrogen and progestogen[4,14,19]. There are several therapeutic advantages of using combined OCs in women with PCOS. Cyclic shedding of endometrium results in regular cycle, thus prevents endometrial hyperplasia and cancer. Improvement of androgenic symptoms is usually observed during OCs treatment. Progestogens suppress LH secretion effectively, thus lessen theca cell activity. Estrogen increases sex hormone binding globulin (SHBG) level, thus decreases free testosterone fraction. The amount of estrogen in low dose OCs is enough to cause this effect. OCs also decrease DHEAS, an adrenal androgen, but the exact mechanism is not known, Recent studies have also shown that OCs have decreasing effect on IGF-I and increasing IGFBP-I which result in reduction of ovarian androgen production. Other than the above properties, OCs also inhibit binding of dihydrotestosterone (DHT) to androgen receptor. In PCOS patient recieving OCs, the improvement of acne and oily skin are usually achieved within the first few cycles, but the clinical effect on hirsutism takes about 6 to 12 months.

While the usefulness of OCs in PCOS patients is well established, the pill should be carefully selected. The appropriate OCs for women with PCOS should contain progestogen which is devoid of androgenic activity or has anti-androgenic properties, i.e., the new generation combined OCs or the pill containing cyproterone acetate (CPA)[20,21]. The patient should be on OCs for long term until the pregnancy is desired, since the discontinuation of treatment results in the recurrence of symptoms in most cases[18].

Surgical treatment of PCOS by wedge resection of the ovaries which was commonly performed in the past is almost outdate at present. Surgical treatment did not eliminate the cause of PCOS. After surgery, the syndrome

reappears in most of the cases. Pelvic adhesion, a sequelae of surgical procedure, is also the great concern in the infertile cases. During recent years, less invasive surgical treatment has been introduced. The small peripheral cysts were cauterized by using electric or laser through laparoscopy[22,23]. The effectiveness of this method remains to be seen in long term follow up.

Since most patients with PCOS are obese, weight reduction by dietary restriction and exercise should be strongly advocated. This measure will lessen hyperinsulinemia and hyperandrogenemia. Some patients have spontaneous ovulation and pregnancy after weight reduction[24].

Conclusion

PCOS is a common disorder of women in reproductive years. The pubertal onset of menstrual disturbances, clinical manifestations of hyperandrogenemia and obesity should alert the physician to look for this disorder. Diagnosis of PCOS usually relies on clinical, biochemical and ultrasonic appearance of the ovary. Once diagnosis has been made, proper management should be given to prevent the late consequences of this disorder. Knowledge about PCOS grows rapidly during the past decade, but many questions remain unanswered. This topic will remain one of the most interesting issue in gynecological endocrinology in the next decade.

References:

1. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol 1935;38: 465-478.
2. Lobo RA. Hirsutism in polycystic ovary syndrome. Clin Obstet Gynecol 1991; 34:817-826.
3. Nobels F, Dewailly D. Puberty and polycystic ovarian syndrome : the insulin/ insulin-like growth factor I hypothesis. Fertil Steril 1992;58:655-666.
4. Yen SSC. Chronic anovulation caused by peripheral endocrine disorders. In : Yen SSC, Jaffe R, eds. Reproductive Endocrinology. Philadelphia : WB Saunders Company 1991;576-630.
5. Hughesdon PE. Morphology and morphogenesis of the Stein-Leventhal ovary and the so-called "hyperthecosis". Obstet Gynaecol Surv 1982;37:59-77.
6. Franks S. Morphology of the polycystic ovary. In : Dunaif A, Givens JR, Haseltime FP, Merriam GR, eds. Polycystic ovary syndrome. Boston : Blackwell Scientific Publications 1992:19-28.
7. Falcone T, Bourque J, Granger L, Hemmings R, Miron P. Polycystic ovary syndrome. Curr Probl Obstet Gynaecol Fertil 1993;16:65-95.
8. Timpatanapong P, Rojanasakul A. Hormonal profiles and prevalence of polycystic ovarian syndrome in Thai women with acne (Submitted for publication).
9. Rojanasakul A, Sirimongkolkasem R, Tongyai T, Piromsawasdi S, Sumavong V, Chailurkit L. Clinical presentation, hormonal profiles and ultrasonic ovarian morphology in women with suspected polycystic ovarian disease. Asia-Ocenaia J Obstet Gynaecol 1989;15:59-65.
10. Clayton RN, Rodin DA, Robinson S, Hodgkinson J, Worswick L. Epidemiology, clinical and hormonal diagnosis of polycystic ovaries and polycystic ovarian syndrome. In : Shaw RW eds. Polycystic ovaries : a disorder or symptom? Lancs :

The Parthenon Publishing Group 1991: 1-16.

11. Lobo RA, Kletzky OA, Campeau JD, dizerega GS. Elevated bioactive luteinizing hormone in women with polycystic ovary syndrome. Fertil Steril 1983;39:674-678.
12. Rojanasakul A, Nillius SJ. Use of bromocriptine in normoprolactinaemic gynaecological disorders. Gynae-Endocrine 1984;2:11-22.
13. Pache TD, de Jong FH, Hop WC, Fauser BCJM. Association between ovarian changes assessed by transvaginal sonography and clinical and endocrine signs of the polycystic ovary syndrome. Fertil Steril 1993;59:544-549.
14. Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility. Baltimore : Williams & Wilkins, 1989:213-263.
15. Wild R. Consequences and treatment of polycystic ovary syndrome. In : Dunaif A, Givens JR, Haseltime FP, Merriam GR, eds. Polycystic ovary syndrome. Boston : Blackwell Scientific Publications 1992:311-317.
16. Dahlgren E, Johansson S, Lindstedt G, et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long term follow-up focusing on natural history and circulating hormones. Fertil Steril 1992;57:505-513.
17. Dunaif A. Diabetes mellitus and polycystic ovary syndrome. In : Dunaif A, Givens JR, Haseltime FP, Merriam GP, eds. Polycystic ovary syndrome. Boston : Blackwell Scientific Publications 1992:347-358.
18. Kelly AC, Jewelewicz R, Alternate regimens for ovulation induction in polycystic ovarian disease. Fertil Steril 1990;54:195-202.
19. Rojanasakul A, Sirimongkolkasem R, Phiromsawat S, Sumawong V, Chailurkit L, Chaturachinda K. Effects of combined ethinylestradiol and desogestrel on hormone profiles and sex hormone binding globulin in women with polycystic ovarian disease. Contraception 1987;36:633-640.
20. Eden JA. The polycystic ovary syndrome presenting as resistance acne successfully treated with cyproterone acetate. The Medical Journal of Australia 1991;155: 677-680.
21. Falsetti L, Casarotti GA, Gastaldi A. Endocrinological and clinical findings on the therapy with Diane-35 in polycystic ovary syndrome. In : Schindler AE ed. Antiandrogen-Estrogen therapy for signs of androgenization. Berlin : Walter de Gruyter 1987:83-92.
22. Gjonnaess H. Polycystic ovarian syndrome treated by ovarian electrocautery through the laparoscope. Fertil Steril 1984;41:20-255.
23. Dabirashrafi H, Mohamad K, Behjatnia Y, Moghadami-Tabrizi N. Adhesion formation after ovarian electrocauterization on patients with polycystic ovarian syndrome. Fertil Steril 1991;55:1200-1201.
24. Bates GW, Whitworth NS. Effect of body weight reduction on plasma androgens in obese, infertile women. Fertil Steril 1982;38:406-409.