MINIREVIEW

Screening for and Treatment of Polycystic Ovary Syndrome in Teenagers

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Polycystic ovary syndrome (PCOS) usually arises during puberty and is marked by hyperinsulinemia and hyperandrogenism. Adolescents with PCOS are at an increased risk of developing health problems later on in life such as type 2 diabetes, cardiovascular disease, and infertility. Furthermore, the physical signs of PCOS can be detrimental to a teenage girl's self-image. Early diagnosis and treatment of PCOS in adolescents are essential in ensuring adulthood health and restoring self-esteem. Treatments for an adolescent with PCOS include diet and exercise, metformin, and oral contraceptive pills. Each of these options has been shown to be effective in improving certain aspects of PCOS, and probably the best treatment plan involves some combination of them. Exp Biol Med 229:369–377, 2004

Key words: polycystic ovary syndrome; adolescents; hyperinsulinemia; hyperandrogenism; oligomenorrhea; elevated testosterone

Although the first description of polycystic ovary syndrome (PCOS) is generally credited to Stein and Leventhal in 1935, it may have been observed as early as 1721, when Italian scientist Antonio Vallisneri observed "young married peasant women, moderately obese and infertile, with two larger than normal ovaries, bumpy and shiny, whitish, just like pigeon eggs" (1). This depiction sounds similar to the subfertility and obesity commonly found in PCOS. It was not until 1921 that Achard and Thiers noticed a relationship between hyperandrogenism and insulin resistance in their study of the "bearded diabetic woman" (2). This relationship is present in PCOS in what might be called the "hirsute hyperinsulinemic woman." In 1935, Stein and Leventhal made the connection between amenorrhea and polycystic ovaries. In addition, they noticed the occurrence of "masculinizing changes" in many patients with polycystic ovaries, including hirsutism and acne (3). Several, though not all, of their original case studies involved women who were overweight. In all seven of their case reports, attempts to treat ovulatory dysfunction with estrogenic hormone failed, and wedge resection was employed. Surgery for PCOS is uncommon now, but all of Stein and Leventhal's patients gained normal menstruation, and two become pregnant. Still, much has changed in the way we understand and treat PCOS.

Although the exact etiology of PCOS is still debated, studies conducted with family members of women with PCOS have suggested that there is a genetic role in its pathogenesis. In a study group of 15 prepubertal daughters of women with PCOS, all but one were found to have polycystic ovaries by ultrasound (4). In a twin study of PCOS, there was a concordance rate of 60% among the sampled dizygotic twin pairs and 74% among monozygotic twin pairs (5). Hyperandrogenemia, either with or without menstrual irregularity, is present in about one-half of sisters of women with PCOS (6). Additionally, the parents of women with PCOS have a high prevalence of impaired glucose tolerance and type 2 diabetes (T2DM), 30%–31% and 16%–27%, respectively (7).

There is evidence that PCOS may be a lifelong disorder where certain precursors are present well before the full onset of disease. In fact, polycystic appearing ovaries have been found in girls as young as 6 years, and some girls are probably born with polycystic ovaries (8). Experimental studies of hyperandrogenism in animals prior to birth further suggest that the hormonal aspect of PCOS is genetically predetermined (9). It seems as though patients with PCOS have at least some form of it throughout life. However, diagnosing the disorder before puberty is difficult because patients with PCOS are generally diagnosed only after seeking help for irregular menses or skin changes that do not take place until puberty.

Although several specific genes have been suggested as markers for PCOS susceptibility, there has been no clear

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evidence of any of them being strongly associated with PCOS inheritance. The fact that insulin resistance is such a prominent feature of PCOS has led to the hypothesis that PCOS is the result of so-called thrifty genes being expressed in an environment of plentiful food and minimal exercise (10). Many suspected genes, including the XbaI polymorphism of the glycogen synthetase gene, the T228A polymorphism of the SORBS1 gene, and the D85 and Y85 variants of the UGT2B15 gene, have been found to be no more common in women with PCOS than in the general population (11–13). The v-LH gene variant has been shown to play a minor role in PCOS, but more research is still necessary (14). The C/T single nucleotide polymorphism at the tyrosine kinase domain of the insulin receptor (INSR) gene has been implicated in PCOS susceptibility, but only among the population of lean women (15). The INS VNTR and CYP11alpha genes also show some association with PCOS (16). Calpain 10, IRS-1, IRS-2, and sex hormone binding globulin (SHBG) genes have been suggested to contribute to PCOS (17). Also, the study of PCOS theca cells has suggested even more genes, including aldehyde dehydrogenase 6 and retinal dehydrogenase 2, that may factor into the inheritance of PCOS (18).

Despite the fact that there is a strong familial component to PCOS, it clearly has a multifactorial pathogenesis. It is widely agreed that among women genetically predisposed to developing PCOS, an additional event triggers the development of the full-blown syndrome. For example, the increase in insulin levels and IGF-I activity that naturally occurs during puberty can activate the expression of PCOS (19). Other such events could be prolonged stress or weight gain (20).

Pathophysiology of PCOS

The underlying problem of PCOS is related to hyperinsulinemia (Fig. 1). Prolonged exposure to increased insulin concentrations may lead to acanthosis nigricans, increased body fat, and eventually the development of T2DM. Hyperinsulinemia also causes the pituitary to hypersecrete luteinizing hormone (LH), which in turn triggers anovulation. Additionally, high insulin concentrations contribute to the thickening of the ovarian theca, which in turn causes elevated production of androgens, specifically testosterone. Increased testosterone levels are responsible for the acne, hirsutism, and alopecia that often occur in PCOS.

Why It Is Important to Diagnose and Treat PCOS in Adolescence

PCOS is linked to a host of health problems, including T2DM, heart disease, hypertension, endometrial cancer, ovarian cancer, subfertility, and infertility. For example, women with PCOS have a higher incidence of gynecological cancer (21) and are about 2.5 times as likely as healthy women to develop ovarian cancer (22), and the persistent dysfunctional bleeding that affects some women with PCOS can lead to anemia. The early detection and treatment of PCOS during adolescence could delay the onset of, or even prevent, many of these maladies later on in adulthood. In addition, dermatological effects of PCOS, such as acne, hirsutism, acanthosis nigricans, and alopecia, have a deleterious effect on an adolescent's self-image.

When dealing with teenagers who have PCOS, one of the main concerns should be infertility as they mature. Although teenagers with PCOS do not complain about difficulty conceiving, they may later in life. Many adult patients are diagnosed with PCOS only after seeking treatment for infertility, but the emotional and financial strains that result could have been prevented if PCOS were diagnosed in the teenage years and closely followed by a physician. About one-third of pregnancies in women with PCOS end in spontaneous abortion (20). Obesity, which occurs frequently in about one-half of all women with PCOS, further complicates the situation as it increases the likelihood of gestational diabetes, preeclampsia, premature labor, neonatal macrosomia, and stillbirth (20). Therefore, effective treatment of an adolescent's PCOS and establishment of diet and exercise habits to prevent obesity will increase her likelihood of having a complication-free pregnancy and a healthy baby when the time comes.

Women with PCOS have a 5–10 times greater chance of being affected by T2DM than do women without PCOS (23). By the time they reach the age of 40, 40% of women with polycystic ovary syndrome have T2DM or impaired glucose tolerance (IGT; Ref. 24). It is not just obese women who are in danger. Nonobese women with PCOS have been shown to be at risk for IGT as well (25). The progression toward T2DM begins at an early age. Obese PCOS adolescents have one-half the peripheral tissue insulin sensitivity that obese non-PCOS adolescents have (26). Impaired β-cell function and abnormal production of hepatic glucose have also been found in obese adolescents with PCOS (27). The defects in insulin activity and secretion, β-cell dysfunction, and rise in hepatic glucose production are all precursors of T2DM. Since the average cost of health care for a person with diabetes is 2.4 times that of a nondiabetic person, this would not only improve the long-term health of PCOS patients but also reduce their health care expenses.

PCOS has been linked to unfavorable lipid profiles. As low high-density lipoprotein (HDL) levels are predictors of risk for coronary heart disease, it is significant to note that there is both a decline in the HDL levels of PCOS women when compared with healthy counterparts as well as a correlation between reductions in HDL and increases in obesity within the population of PCOS women (28). Rajkhowa *et al.* proposed that a modified activity of hepatic lipase or lipid transfer protein might be the culprit for the lipid abnormalities seen in PCOS (28). While obesity tends to play a large role in low-density lipoprotein (LDL), HDL, and cholesterol levels, it seems that hyperinsulinemia plays

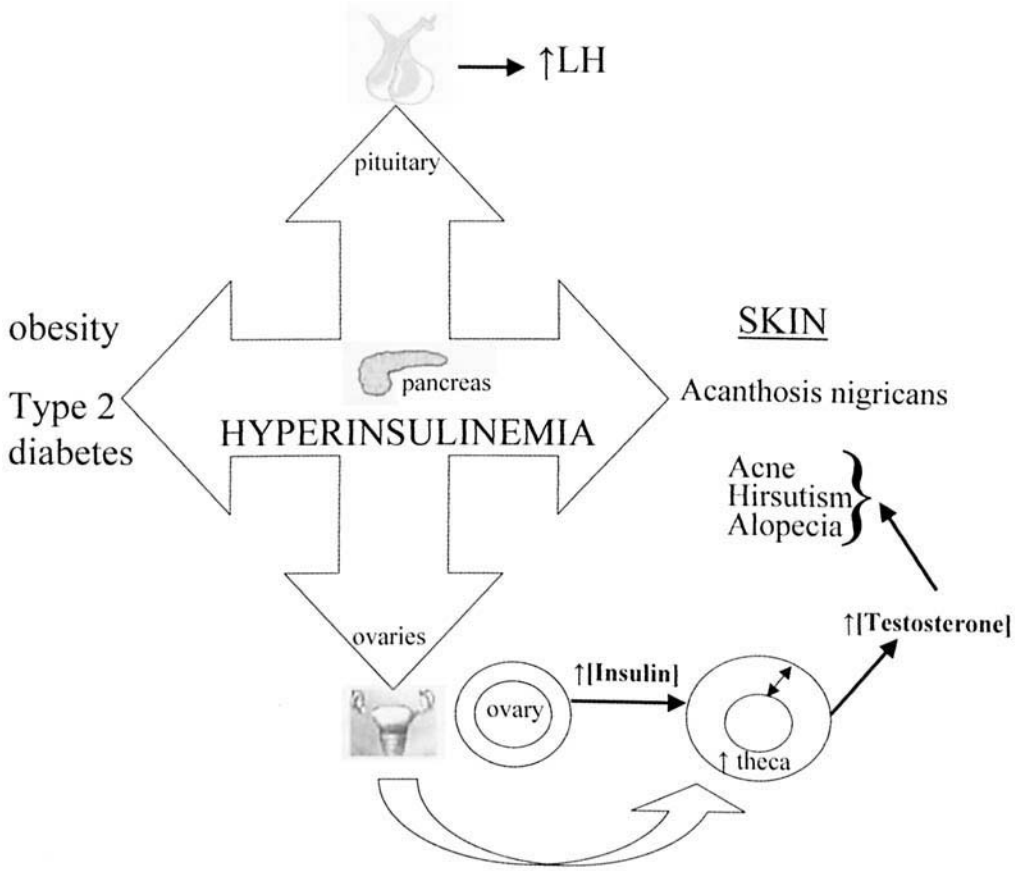

Figure 1. Increased insulin levels cause acanthosis nigricans, hypersecretion of luteinizing hormone (LH) by the pituitary, thickening of the ovarian theca (which causes hyperandrogenism), obesity, and type 2 diabetes.

the greatest role in triglyceride levels (20). It is apparent that among PCOS adolescents who are obese, early efforts at weight loss would be very beneficial to their lipid profiles and therefore their risk of cardiovascular disease.

Hyperandrogenism, insulin resistance, hypertension, dyslipidemia, obesity, and ovulatory dysfunction regularly found in women with PCOS put them at much greater risk of developing heart disease, which is the most common cause of death among women (28). Women with PCOS have an incidence of coronary artery calcification (a predictor of cardiac disease) that is greater than three times that of matched controls (29). Compared with healthy women, women with polycystic ovary syndrome are 7.4 times more likely to develop ischemic heart disease and myocardial infarction (28). Additionally, the disparity in risk between PCOS women and normal women is greatest in young adults, particularly between the ages of 18 and 24 (30). Obese PCOS adolescents with impaired glucose tolerance lack a dip in their nocturnal blood pressure, which may signal an increased risk of cardiovascular disease (27). It has been suggested that obese adolescents with PCOS are a population in considerable danger of developing cardiovascular disease when they become adults (27, 29, 31), and therefore intervention at an early age should be implemented in order to improve their chances of avoiding heart disease or at least postponing it for as long as possible (29).

Finally, one of the most important yet overlooked reasons for adequate screening and treatment of PCOS in adolescents is the quality-of-life issue that weighs so heavily on patients. Because of the phenotype of this disorder, girls with PCOS experience a great emotional and psychological burden. Many of the symptoms common to PCOS, such as excess hair growth, acne, alopecia, and obesity, cause the patients to experience social trauma during a period when social acceptance is especially greatly valued, leading to higher rates of depression. Some PCOS adolescents become unhappy with their appearance at a point in their life where personality growth occurs most dramatically, which can have a severe negative impact on their self-esteem, confidence, and self-respect during their teens and beyond. Coupling this with the usual emotional difficulties of adolescence creates a decreased sense of quality of life (32), and about half of all women with PCOS suffer from some degree of depression (33). The hirsutism that affects many PCOS adolescents leads to increased social fears and anxiety compared to nonhirsute adolescents (34, 35). Women with PCOS feel that hirsutism, irregular menstruation, and infertility make them "less feminine" (36), and one unfortunate result of this is that some teenagers with

PCOS actively seek pregnancy as a way to prove their femininity to themselves. As mentioned earlier, fertility issues are of great concern among patients with PCOS. Not surprisingly, adolescents with PCOS are 3.4 more times as concerned with fertility as non-PCOS girls (37). Distressingly, about one-third of PCOS women have abnormal eating patterns, and 6% are bulimic, emphasizing a need to screen for such disturbances when dealing with PCOS patients (38).

How to Screen for PCOS in Adolescents

Because PCOS is a collection of conditions, it lacks a definitive identifying test, and so a proper diagnosis depends on consideration of many factors. Furthermore, since an exact definition of PCOS is not universally agreed on, the criteria for its diagnosis are somewhat amorphous. The most widely accepted diagnostic criteria are oligomenorrhea/amenorrhea, hyperandrogenism (clinical or biochemical), and absence of other causes of hyperandrogenism (virilizing tumor, hyperprolactinemia, congenital adrenal hyperplasia, Cushing's syndrome, and so on), set forth by a 1990 NIH/NICHHD conference (39). Insulin resistance, although not part of the NIH criteria, is a trademark feature of PCOS (40). Therefore, when a young female presents with irregular menses, hirsutism, acne, alopecia, central adiposity, acanthosis nigricans, and/or hyperinsulinemia, PCOS should be considered as a possible cause for her symptom(s), and an endocrine evaluation, including measurements of total and free testosterone and dehydroepiandrosterone sulfate (DHEAS), should be completed. Unfortunately, many adolescents with oligomenorrhea do not consult with a physician about their condition at all, and several who do seek help are prescribed oral contraceptives and not given endocrine evaluations. The basic screening formula provided in Figure 2 decreases the chance of such missed diagnoses. Table 1 shows our experience with a successful screening program in our teenagers in Santa Barbara County, California. Although hyperinsulinemia may be difficult to assess since a passing state naturally occurs during puberty, adolescents with hyperandrogenism have significantly higher insulin levels than otherwise normal pubertal adolescents (41). Oral glucose tolerance tests are useful in diagnosing PCOS, and they also determine IGT, which indicates an increased risk of T2DM. When diagnosing PCOS, it is important to rule out other possible causes of the patient's symptoms, such as runner's amenorrhea, hyperprolactinemia, hypothyroidism, ovarian or adrenal virilizing tumor, Cushing's syndrome, or idiopathic oligomenorrhea. Table 2 shows signs, symptoms, and laboratory values that are helpful with the differential diagnosis in our experience.

Furthermore, a proper medical history can help lead to a diagnosis of PCOS. Adolescents with a family history of PCOS or diabetes, male relatives with alopecia, or female relatives with infertility or menstrual problems should be assessed for PCOS because such familial associations put them at a much greater risk. Lifestyle parameters such as diet, exercise, and smoking should be evaluated, and appropriate recommendations should be given, as these factors have a significant effect on PCOS. Determining pubertal history is important since the first indication of PCOS is usually premature pubarche (42). Thus, hyperandrogenism should be checked for in such patients, as they are in danger of developing PCOS.

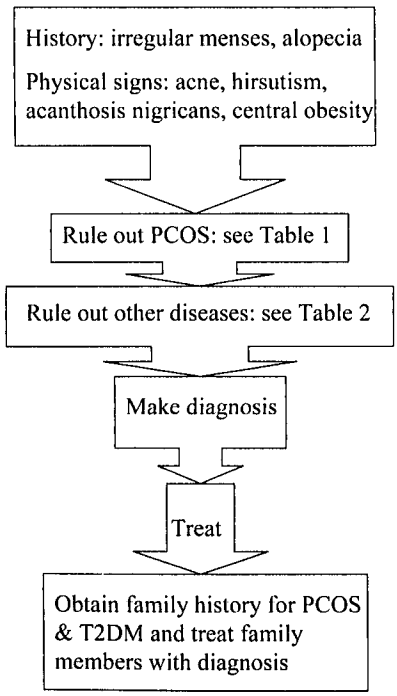

Figure 2. Polycystic ovary syndrome (PCOS) screening formula in Santa Barbara County.

Despite the condition's name, not all women with polycystic ovaries have PCOS, and not all women with PCOS have polycystic ovaries. Polycystic ovaries are found in up to one-fourth of all women, so their presence alone is not enough for diagnosis. However, ovarian morphology can still be useful in diagnosis of PCOS. For instance, ovarian volumes of greater than 10 cm^3 have a high sensitivity and specificity for PCOS (43, 44). Also, a ratio of ovarian stroma to total area of more than 0.34 is appreciably linked to PCOS (45).

Two other criteria that have been theorized to be indicators of PCOS are growth hormone and prolactin levels. However, prolactin secretion has not been found to be significantly greater in PCOS women, and amplified growth hormone secretion has been indicated only in nonobese adolescents with PCOS (46). Sometimes visual clues, like perceptible facial hair or skin changes, are good indications of PCOS. For example, acanthosis nigricans is an indicator of hyperinsulinemia (47), which has been suggested to lead to hyperandrogenism (48). Since both hyperinsulinemia and hyperandrogenism are identifying

Table 1. Laboratory Data That Are Helpful in Diagnosing PCOS in Adolescent Girls in Santa Barbara County, California[a]

Test	Value
Fasting insulin	>20 mIU/ml
Fasting glucose	>95 mg/dl
Testosterone	>40 ng/dl
LH:FSH ratio (in patients with BMI <27)	>3

[a] PCOS, polycystic ovary syndrome; LH, luteinizing hormone; FSH, follicle-stimulating hormone; BMI, body mass index.

features of PCOS, women with acanthosis nigricans should be examined for PCOS.

A particular subgroup of women with an increased risk of PCOS is patients with epilepsy. PCOS is overrepresented in this group, occurring in about 26% of women with epilepsy (49). Although there is debate over the relationship between epilepsy and PCOS, it is thought either that the hypothalamic control of reproductive function is disturbed by the disorder itself or that valproic acid, a drug used in the treatment of epilepsy, is somehow responsible (50). Since the prevalence of PCOS among women with epilepsy is three to five times greater than normal, screening for reproductive endocrine disorders in this population is warranted.

Screening for PCOS in the general public may be a feasible endeavor. A study done in northern Finland demonstrated that a simple questionnaire asking questions about oligomenorrhea and hirsutism could help identify women with PCOS-like endocrine abnormalities and insulin insensitivity (51). Since adolescent and adult PCOS diagnostic features are fairly similar (52, 53), such self-completed surveys are an easy and apparently effective way of detecting possible PCOS patients of any age.

Treatment

The course of treatment for women with PCOS largely depends on the severity of an individual's symptoms. For example, someone who is trying to become pregnant but cannot because of PCOS-related infertility will be most concerned with improving ovulation, whereas someone who is not trying to become pregnant but is hirsute will be most concerned with decreasing their androgen levels. Adolescents with PCOS tend to be troubled most by the cosmetic effects of PCOS, such as acne, hirsutism, and/or acanthosis nigricans. Therefore, treatment of the PCOS adolescent must address these issues as well as take into account the consequences of long-term hyperinsulinemia and ovulatory dysfunction. Surgical procedures, medications, and lifestyle changes all can improve symptoms of PCOS and prevent or delay the onset of complications associated with PCOS. Furthermore, since adolescents with PCOS suffer from lower quality of life, psychological factors must be taken into consideration as well.

Table 2. Laboratory Data That Can Help with the Differential Diagnosis of PCOS in Adolescent Girls[a]

Differential diagnosis	Sign/symptom/ laboratory value
Runner's amenorrhea	Extensive endurance exercise (running or jogging ≥30 miles/week)
	↓BMI
	↓FSH, LH
	↑Cortisol
	Normal testosterone
	↓Estrogen
	Normal to low insulin
Hyperprolactinemia	Galactorrhea, visual changes, headache
Microadenoma	24–100 ng/ml prolactin
Lactation	100–150 ng/ml prolactin
Macroadenoma	>200 ng/ml prolactin
	Rule out pituitary tumor: MRI, formal visual fields
Hypothyroidism	Weight gain
	Lethargy
	Depression
	Constipation
	Dry skin
	↑Cholesterol
	↑TSH
	↓FT4
Virilizing tumor	↑Testosterone, >200 ng/dl
	Look for ovarian or adrenal tumor
Cushing's syndrome	Weight gain
	Striae, purple in color
	Buffalo hump
	Bruising
	Moon facies
	24-hr urinary free cortisol >250–300 μg/24 hrs

[a] PCOS, polycystic ovary syndrome; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone; FT4, free thyroxine 4.

A primary anxiety of adolescents with PCOS is the effect that hyperandrogenism has on their skin. Spironolactone has been shown to diminish hyperandrogenism and even improved fertility in one out of three women with infertility in one study (54). Another antihirsutism agent, flutamide, also lowers androgen levels and improves ovulation (55). In addition, many treatment measures used for acne and hirsutism in non-PCOS populations are used successfully among adolescents with PCOS.

It is imperative to discuss the possibility of the risk of unwanted pregnancies in sexually active patients treated for PCOS. Oral contraceptive pills (OCPs) should be used in conjunction with metformin. The use of OCPs is very helpful in alleviating acne and hirsutism. OCPs are also beneficial to the PCOS adolescent for many other reasons. They increase bone density, lessen follicular activity, reduce the risk of ovarian and endometrial cancers, return

Table 3. Studies of Metformin Use in Adolescents with PCOS[a]

Study	Metformin dose	Outcome
Arslanian *et al.* 2002 (69)	850 mg BID for 3 months (850 mg/d for first 1–2 weeks)	BMI decreased, glucose and insulin AUCs improved, total and free testosterone levels decreased, 40% had better menstrual cyclicity
Glueck *et al.* 2001 (70)	1500–2550 mg QD for 10.5 ± 6.4 months	Of 11 girls, 10 resumed normal menses, 9 lost weight, 11 regained normal fasting glucose
Ibáñez *et al.* 2000 (71)	1275 mg QD for 6 months	Insulin parameters, lipid profile, free androgen index, and hirsutism were all improved
Ibáñez *et al.* 2003 (72)	1275 mg QD (with flutamide 62.5 mg QD) for 3 months	Fasting insulin/glucose ratio, T, SHBG, lipid profile, oligomenorrhea, and body fat measures all improved
Freemark *et al.* 2001(73)[b]	500 mg BID for 6 months	Fasting blood glucose dropped from 84.9 to 75.1 mg/dl, and fasting insulin dropped from 31.3 to 19.3 μU/ml

[a] PCOS, polycystic ovary syndrome; BID, twice a day; BMI, body mass index; AUC, area under curve; QD, once a day; T, testosterone, SHBG, sex hormone–binding globulin.
[b] Study subjects were obese adolescents with fasting hyperinsulinemia and family history of type 2 diabetes, not adolescents with PCOS.

menstrual regularity, and ward off anemia (56). Although OCPs have been implicated in raising triglyceride levels and total cholesterol in adolescents with PCOS, LDL/HDL ratios remain constant (57–59). OCPs increase neither body weight nor body fat in teenage women with PCOS (58).

The most preferred and most effective method of treatment for PCOS is lifestyle modification. Exercise, such as regular walking, has been shown to reduce waist-to-hip ratio, an indicator of diabetes and other morbidities, and homocysteine levels, an indicator of cardiovascular risk, in overweight PCOS women (60). Weight loss improves practically every parameter of PCOS. In obese, anovulatory PCOS women, weight loss restores ovulation and pregnancy rates, decreases insulin levels, diminishes acanthosis nigricans, lowers testosterone levels while raising SHBG levels, and improves psychological considerations (61, 62). Modifying dietary intake by increasing the protein-to-carbohydrate ratio appears to be endocrinologically beneficial to overweight PCOS women (63). A large study in Finland demonstrated that an adolescent's weight at 14 years and how it changes over the next 17 years has the strongest predictive power on future hormonal and metabolic perturbations (51). Thus, weight control is possibly the best method to prevent PCOS complications.

Metformin is emerging as an important component of PCOS treatment. In addition to the expected improvements in insulin sensitivity and glucose metabolism, metformin therapy also ameliorates hyperandrogenism and menstrual irregularity (64–66). Although most studies of metformin have involved obese PCOS women, nonobese PCOS populations profit from treatment as well (67), and metformin is able to restore ovulation in about three-fourths of women who are resistant to clomiphene citrate (68). As beneficial as metformin can be for adults with PCOS, it appears even more effective in adolescents with PCOS. A summary of metformin treatments and outcomes in adolescents is given in Table 3. Hyperinsulinemia and hyperandrogenism improve just as much as in adults, but an even higher success rate at normalizing menses and decreasing hirsutism occurs in the younger group (69, 70, 71, 74). Also, metformin has reduced the total cholesterol, LDL cholesterol, and triglycerides of PCOS adolescents while increasing HDL cholesterol (71). In addition, metformin has been shown to decrease C-reactive protein levels, which are predictive of cardiovascular disease (75). Metformin's various beneficial effects, combined with its safety record in people with T2DM, make it an appealing choice of medication for PCOS. However, it should be noted that metformin use in the treatment of PCOS might be lifelong. Ibáñez *et al.* showed that in adolescents with PCOS, all the improvements in menstruation, hirsutism, hyperinsulinemia, dyslipidemia, and hyperandrogenism were lost 3 months after cessation of metformin treatment (71). Also, since metformin can improve ovulation, the risk of pregnancy can increase, and if pregnancy occurs, use must be discontinued immediately, as metformin crosses the placenta.

Another group of insulin-sensitizing agents, thiazolidinediones (TZDs), may be effective in treating PCOS. However, it should be noted that the use of TZDs is not indicated in teenagers, and the recent findings of hepatotoxicity of troglitazone will probably necessitate further study of the safety of other TZDs. Nevertheless, rosiglitazone has been shown to improve insulin sensitivity, decrease androgen levels, lessen hirsutism, and improve ovulation (76). Also, pioglitazone has been shown to improve androgen and lipid profiles in obese PCOS women as well as improve insulin secretion, sensitivity, and clearance (77). In a study of PCOS women who had difficulty responding to metformin, the addition of pioglitazone to their treatment regimen improved glucose/insulin parameters, lowered DHEAS levels, raised SHBG and HDL levels, and enhanced cycle regularity (78). D-chiro-inositol has also been implicated as an insulin sensitizer with possible

benefits for PCOS patients (79), but very little research has been done in this area.

Drug therapy is not the only treatment option for PCOS. A study of the Chinese herb tiangui fang demonstrated its ability to ease hyperinsulinism, lower serum testosterone, and restore normal menses as well as metformin (80). The recent evidence for supplemental chromium as a potential aide in the treatment of T2DM has raised the possibility that it may be of benefit to PCOS patients. Chromium not only has been known to lower fasting blood glucose but also has been shown to improve glucose tolerance and potentiate insulin action (81, 82). Although it is believed that chromium supplementation may benefit only those with a deficiency, its excellent safety record and effect on glucose/insulin parameters commonly found in PCOS make further research worthwhile.

Although the use of insulin-sensitizing agents has diminished surgery's usefulness, it is sometimes added to the treatment regimen of the adult with PCOS who wishes to become pregnant. In Stein and Leventhal's time, surgery was the most effective treatment for PCOS-related infertility, while today it is usually the last resort after clomiphene citrate, insulin sensitizers, and gonadotropin therapy fail. Though ovarian drilling by diathermy or laser is probably the preferred method, improvements in wedge resection techniques have resulted in impressive pregnancy rates and fewer adhesions than ever before (83, 84). Still, surgery is not indicated in teenagers, as it does little to improve PCOS symptoms beyond infertility, and pregnancy induction is not desirable in this group.

Conclusion

Despite the prevalence of PCOS, its etiology has yet to be clearly elucidated. Evidence suggests there are familial and genetic roles in becoming predisposed to PCOS from birth, while an additional event such as puberty brings about the fully developed syndrome. Therefore, until more sophisticated methods of detecting PCOS before puberty are formulated, screening for PCOS in adolescents is the best chance at early diagnosis and treatment. PCOS should be considered in any adolescent female with irregular menses, acne, hirsutism, alopecia, insulin resistance, and/or acanthosis nigricans, and diagnosis should rule out other causes of hyperandrogenism. Adolescents with PCOS not only suffer from the psychological effects of acne and hirsutism but also have an increased risk of negative health consequences, such as subfertility, cardiovascular disease, T2DM, dyslipidemia, and gynecological cancers. Even though several treatment options exist, including the highly effective metformin, healthy diet and regular exercise are the most beneficial in treating PCOS symptoms and preventing further health dilemmas.

1. Kovacs G, Smith J. A Guide to the Polycystic Ovary: Its effects on health and fertility. Castle Hill Barns, UK: TFM Publishing, 2002.
2. Achard C, Thiers J. Le virilisme pilaire et son association à l'insuffisance glycolytique (diabète des femme à barbe). Bull Acad Natl Med 86:51–83, 1921.
3. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol 29:181–191, 1935.
4. Battaglia C, Regnani G, Mancini F, Iughetti L, Flamigni C, Venturoli S. Polycystic ovaries in childhood: a common finding in daughters of PCOS patients. A pilot study. Hum Reprod 17:771–776, 2002.
5. Jahanfar S, Eden JA, Warren P, Seppala M, Nguyen TV. A twin study of polycystic ovary syndrome. Fertil Steril 63:478–486, 1995.
6. Legro RS, Driscoll D, Strauss JF III, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci U S A 95:14956–14960, 1998.
7. Yildiz BO, Yarali H, Oguz H, Bayraktar M. Glucose intolerance, insulin resistance, and hyperandrogenism in first degree relatives of women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:2031–2036, 2003.
8. Bridges NA, Cooke A, Healy MJ, Hindmarsh PC, Brook CG. Standards for ovarian volume in childhood and puberty. Fertil Steril 60:456–460, 1993.
9. Abbott DH, Dumesic DA, Franks S. Developmental origin of polycystic ovary syndrome—a hypothesis. J Endocrinol 174:1–5, 2002.
10. Holte J. Polycystic ovary syndrome and insulin resistance: thrifty genes struggling with over-feeding and sedentary life style? J Endocrinol Invest 21:589–601, 1998.
11. Rajkhowa M, Talbot JA, Jones PW, Clayton RN. Polymorphism of glycogen synthetase gene in polycystic ovary syndrome. Clin Endocrinol 44:85–90, 1996.
12. Witchel SF, Trivedi RN, Kammerer C. Frequency of the T228A polymorphism in the SORBS1 gene in children with premature pubarche and in adolescent girls with hyperandrogenism. Fertil Steril 80:128–132, 2003.
13. Tomboc M, Witchel SF. Frequencies of the D85 and Y85 variants of UGT2B15 in children and adolescent girls with hyperandrogenism. J Pediatr Endocrinol Metab 16:719–726, 2003.
14. Tapanainen JS, Koivunen R, Fauser BC, Taylor AE, Clayton RN, Rajkowa M, White D, Franks S, Antilla L, Pettersson KS, Huhtaniemi IT. A new contributing factor to polycystic ovary syndrome: the genetic variant of luteinizing hormone. J Clin Endocrinol Metab 84:1711–1715, 1999.
15. Siegel S, Futterweit W, Davies TF, Concepcion ES, Greenberg DA, Villanueva R, Tomer Y. A C/T single nucleotide polymorphism at the tyrosine kinase domain of the insulin receptor gene is associated with polycystic ovary syndrome. Fertil Steril 78:1240–1243, 2002.
16. Xita N, Georgiou I, Tsatsoulis A. The genetic basis of polycystic ovary syndrome. Eur J Endocrinol 147:717–725, 2002.
17. Legro RS, Strauss JF. Molecular progress in infertility: polycystic ovary syndrome. Fertil Steril 78:569–576, 2002.
18. Wood JR, Nelson VL, Ho C, Jansen E, Wang CY, Urbanek M, McAllister JM, Mosselman S, Strauss JF III. The molecular phenotype of polycystic ovary syndrome (PCOS) theca cells and new candidate PCOS genes defined by microarray analysis. J Biol Chem 278:26380–26390, 2003.
19. Nobels F, Dewailly D. Puberty and polycystic ovarian syndrome: the insulin/insulin-like growth factor I hypothesis. Fertil Steril 58:655–666, 1992.
20. Carmina E, Lobo RA. Polycystic ovary syndrome (PCOS): arguably the most common endocrinopathy is associated with significant morbidity in women. J Clin Endocrinol Metab 84:1897–1899, 1999.
21. Meirow D, Schenker JG. The link between female infertility and cancer: epidemiology and possible aetiologies. Hum Reprod Update 2:63–75, 1996.
22. Schildkraut JM, Schwingl PJ, Bastos E, Evanoff A, Hughes C. Epithelial ovarian cancer risk among women with polycystic ovary syndrome. Obstet Gynecol 88(4, Pt 1):554–559, 1996.

23. Ovalle F, Azziz R. Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. Fertil Steril 77:1095–1105, 2002.
24. Kidson W. Polycystic ovary syndrome: a new direction in treatment. Med J Aust 169:537–540, 1998.
25. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 84:165–169, 1999.
26. Lewy VD, Danadian K, Witchel SF, Arslanian S. Early metabolic abnormalities in adolescent girls with polycystic ovarian syndrome. J Pediatr 138:38–44, 2001.
27. Arslanian SA, Lewy SD, Danadian K. Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and beta-cell dysfunction and risk of cardiovascular disease. J Clin Endocrinol Metab 86:66–71, 2001.
28. Rajkhowa M, Neary RH, Kumpatla P, Game FL, Jones PW, Obhrai MS, Clayton RN. Altered composition of high density lipoproteins in women with the polycystic ovary syndrome. J Clin Endocrinol Metab 82:3389–3394, 1997.
29. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:2562–2568, 2003.
30. Talbott E, Guzick D, Clerici A, Berga S, Detre K, Weimer K, Kuller L. Coronary heart disease risk factors in women with polycystic ovary syndrome. Arterioscler Thromb Vasc Biol 15:821–826, 1995.
31. Macut D, Micic D, Cvijovic G, Sumarac M, Kendereski A, Zoric S, Pejkovic D. Cardiovascular risk in adolescent and young adult obese females with polycystic ovary syndrome (PCOS). J Pediatr Endocrinol Metab 14(Suppl 5):1353–1359 (discussion, 1365), 2001.
32. Trent ME, Rich M, Austin SB, Gordon CM. Quality of life in adolescent girls with polycystic ovary syndrome. Arch Pediatr Adolesc Med 156:556–560, 2002.
33. Rasgon NL, Rao RC, Hwang S, Altshuler LL, Elman S, Zuckerbrow-Miller J, Korenman SG. Depression in women with polycystic ovary syndrome: clinical and biochemical correlates. J Affect Disord 74:299–304, 2003.
34. Barth JH, Catalan J, Cherry CA, Day A. Psychological morbidity in women referred for treatment of hirsutism. J Psychosom Res 37:615–619, 1993.
35. Sonino N, Fava GA, Mani E, Belluardo P, Boscaro M. Quality of life of hirsute women. Postgrad Med J 69(809):186–189, 1993.
36. Kitzinger C, Willmott J. "The thief of womanhood": women's experience of polycystic ovarian syndrome. Soc Sci Med 54:349–361, 2002.
37. Trent ME, Rich M, Austin SB, Gordon CM. Fertility concerns and sexual behavior in adolescent girls with polycystic ovary syndrome: implications for quality of life. J Pediatr Adolesc Gynecol 16:33–37, 2003.
38. McCluskey S, Evans C, Lacey JH, Pearce JM, Jacobs H. Polycystic ovary syndrome and bulimia. Fertil Steril 55:287–291, 1991.
39. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, Merriam GR, Eds. Polycystic Ovary Syndrome. Boston: Blackwell, pp377–384, 1992.
40. Lewis V. Polycystic ovary syndrome: a diagnostic challenge. Obstet Gynecol Clin North Am 28:1–20, 2001.
41. Apter D, Bützow T, Laughlin GA, Yen SSC. Metabolic features of polycystic ovary syndrome are found in adolescent girls with hyperandrogenism. J Clin Endocrinol Metab 80:2966–2973, 1995.
42. Kent SC, Legro RS. Polycystic ovary syndrome in adolescents. Adolesc Med 13:73–88, 2002.
43. Herter LD, Magalhaes JA, Spritzer PM. Relevance of the determination of ovarian volume in adolescent girls with menstrual disorders. L Clin Ultrasound 24:243–248, 1996.
44. Dramusic V, Goh VH, Rajan U, Wong YC, Ratnam SS. Clinical, endocrinologic, and ultrasonographic features of polycystic ovary syndrome in Singaporean adolescents. J Pediatr Adolesc Gynecol 10:124–132, 1997.
45. Fulghesu AM, Ciampelli M, Belosi C, Apa R, Pavone V, Lanzone A. A new ultrasound criterion for the diagnosis of polycystic ovary syndrome: the ovarian stroma/total area ratio. Fertil Steril 76:326–331, 2001.
46. Garcia-Rudaz MC, Ropelato MG, Escobar ME, Veldhuis JD, Barontini M. Amplified and orderly growth hormone secretion characterizes lean adolescents with polycystic ovary syndrome. Eur J Endocrinol 147:207–216, 2002.
47. Richards GE, Cavallo A, Meyer WJ III, Prince MJ, Peters EJ, Stuart CA, Smith ER. Obesity, acanthosis nigricans, insulin resistance, and hyperandrogenemia: pediatric perspective and natural history. J Pediatr 107:893–897, 1985.
48. DeClue TJ, Shah SC, Marchese M, Malone JI. Insulin resistance and hyperinsulinemia induce hyperandrogenism in a young type B insulin-resistant female. J Clin Endocrinol Metab 72:1308–1311, 1991.
49. Bilo L, Meo R, Valentino R, Di Carlo C, Striano S, Nappi C. Characterization of reproductive endocrine disorders in women with epilepsy. J Clin Endocrinol Metab 86:2950–2956, 2001.
50. Meo R, Bilo L. Polycystic ovary syndrome and epilepsy: a review of the evidence. Drugs 63:1185–1227, 2003.
51. Taponen S, Martikainen H, Jarvelin MR, Laitinen J, Pouta A, Hartikainen AL, Sovio U, McCarthy MI, Franks S, Ruokonen A. Hormonal profile of women with self-reported symptoms of oligomenorrhea and/or hirsutism: Northern Finland birth cohort 1966 study. J Clin Endocrinol Metab 88:141–147, 2003.
52. Bili H, Laven J, Imani B, Eijkemans MJ, Fauser BC. Age-related differences in features associated with polycystic ovary syndrome in normogonadotrophic oligo-amenorrhoeic infertile women of reproductive years. Eur J Endocrinol 145:749–755, 2001.
53. Gulekli B, Turhan NO, Senoz S, Kukner S, Oral H, Gokmen O. Endocrinological, ultrasonographic and clinical findings in adolescent and adult polycystic ovary patients: a comparative study. Gynecol Endocrinol 7:273–277, 1993.
54. Vetr M, Sobek A. Low dose spironolactone in the treatment of female hyperandrogenism and hirsutism. Acta Univ Palacki Olomuc Fac Med 135:55–57, 1993.
55. De Leo V, Lanzetta D, D'Antona D, la Marca A, Morgante G. Hormonal effects of flutamide in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 83:99–102, 1998.
56. Jensen JT, Speroff L. Health benefits of oral contraceptives. Obstet Gynecol Clin North Am 27:705–721, 2000.
57. Creatsas G, Koliopoulos C, Mastorakos G. Combined oral contraceptive treatment of adolescent girls with polycystic ovary syndrome. Lipid profile. Ann N Y Acad Sci 900:245–252, 2000.
58. Lloyd T, Lin HM, Matthews AE, Bentley CM, Legro RS. Oral contraceptive use by teenage women does not affect body composition. Obstet Gynecol 100:235–239, 2002.
59. Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. Fertil Steril 77:919–927, 2002.
60. Randeva HS, Lewandowski KC, Drzewoski J, Brooke-Wavell K, O'Callaghan C, Czupryniak L, Hillhouse EW, Prelevic GM. Exercise decreases plasma total homocysteinc in overweight young women with polycystic ovary syndrome. J Clin Endocrinol Metab 87:4496–4501, 2002.
61. Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, Norman RJ. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod 10:2705–2712, 1995.
62. Apter D. How possible is the prevention of polycystic ovary syndrome

development in adolescent patients with early onset of hyperandrogenism. J Endocrinol Invest 21:613–617, 1998.
63. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:812–819, 2003.
64. Chou KH, von Eye Corleta H, Capp E, Spritzer PM. Clinical, metabolic and endocrine parameters in response to metformin in obese women with polycystic ovary syndrome: a randomized, double-blind and placebo-controlled trial. Horm Metab Res 35:86–91, 2003.
65. Kazerooni T, Dehghan-Kooshkghazi M. Effects of metformin therapy on hyperandrogenism in women with polycystic ovary syndrome. Gynecol Endocrinol 17:51–56, 2003.
66. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, Zanolin E, Muggeo M. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. J Clin Endocrinol Metab 85:139–146, 2000.
67. Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, Tapanainen JS. Merformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 88:148–156, 2003.
68. Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, Nestler JE. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. Fertil Steril 75:310–315, 2001.
69. Arslanian SA, Lewy V, Danadian K, Saad R. Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab 87:1555–1559, 2002.
70. Glueck CJ, Wang P, Fontaine R, Tracy T, Sieve-Smith L. Merformin to restore normal menses in oligo-amenorrheic teenage girls with polycystic ovary syndrome (PCOS). J Adolesc Health 29:160–169, 2001.
71. Ibáñez L, Valls C, Potau N, Marcos MV, de Zegher F. Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. J Clin Endocrinol Metab 85:3526–3530, 2000.
72. Ibáñez L, de Zegher F. Flutamide-metformin therapy to reduce fat mass in hyperinsulinemic ovarian hyperandrogenism: effects in adolescents and in women on third-generation oral contraception. J Clin Endocrinol Metab 88:4720–4724, 2003.
73. Freemark M, Bursey D. The effects of metformin on body mass index and glucose tolerance in obese adolescents with fasting hyperinsulinemia and a family history of type 2 diabetes. Pediatrics 107(4):E55, 2001.
74. Loverro G, Lorusso F, De Pergola G, Nicolardi V, Mei L, Selvaggi L. Clinical and endocrinological effects of 6 months of metformin treatment in young hyperinsulinemic patients affected by polycystic ovary syndrome. Gynecol Endocrinol 16:217–224, 2002.
75. Morin-Papunen L, Rautio K, Ruokonen A, Hedberg P, Puukka M, Tapanainen JS. Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:4649–4654, 2003.
76. Ghazeeri G, Kutteh WH, Bryer-Ash M, Haas D, Ke RW. Effect of rosiglitazone on spontaneous and clomiphene citrate-induced ovulation in women with polycystic ovary syndrome. Fertil Steril 79:562–566, 2003.
77. Romualdi D, Guido M, Ciampelli M, Giuliani M, Leoni F, Perri C, Lanzone A. Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome. Hum Reprod 18:1210–1218, 2003.
78. Glueck CJ, Moreira A, Goldenberg N, Sieve L, Wang P. Pioglitazone and metformin in obese women with polycystic ovary syndrome not optimally responsive to metformin. Hum Reprod 18:1618–1625, 2003.
79. Nestler JE, Jakubowicz DJ, Iuorno MJ. Role of inositolphosphoglycan mediators of insulin action in the polycystic ovary syndrome. J Pediatr Endocrinol Metab 13(Suppl 5):1295–1298, 2000.
80. Hou J, Yu J, Wei M. Study on treatment of hyperandrogenism and hyperinsulinism in polycystic ovary syndrome with Chinese herbal formula "tiangui fang." Zhongguo Zhong Xi Yi Jie He Za Zhi 20:589–592, 2000.
81. Anderson RA. Chromium, glucose tolerance, and diabetes. Biol Trace Elem Res 32:19–24, 1992.
82. Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, Feng J. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. Diabetes 46:1786–1791, 1997.
83. Duleba AJ, Banaszewska B, Spaczynski RZ, Pawelczyk L. Success of laparoscopic ovarian wedge resection is related to obesity, lipid profile, and insulin levels. Fertil Steril 79:1008–1014, 2003.
84. Yildirim M, Noyan V, Bulent Tiras M, Yildiz A, Guner H. Ovarian wedge resection by minilaparatomy in infertile patients with polycystic ovarian syndrome: a new technique. Eur J Obstet Gynecol Reprod Biol 107:85–87, 2003.