Syndrome des ovaires polykystiques

Questionnaire validé servant au diagnostic

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RÉSUMÉ

OBJECTIF Produire et valider un questionnaire devant servir au diagnostic du syndrome des ovaires polykystiques (SOPK).

CONCEPTION Toutes les participantes répondaient à un questionnaire comportant des questions cliniques conçues pour aider au diagnostic du SOPK avant leur rendez-vous avec un endocrinologue. Une fois le questionnaire complété, l'endocrinologue (qui ne voyaient pas les réponses) posait ou excluait un diagnostic de SOPK à l'aide de critères cliniques et de données biochimiques, tel qu'indiqué. La puissance des questions pour prédire le SPOK était alors évaluée, permettant de produire un modèle comportant les éléments les plus fiables. L'exercice avait pour but d'établir un système permettant de prédire un diagnostic de SOPK.

CONTEXTE Une clinique d'endocrinologie et de reproduction à Calgary, en Alberta.

PARTICIPANTES Les patientes adultes référées à la clinique, notamment 50 patientes souffrant du SOPK et 50 qui n'en étaient pas atteintes.

PRINCIPALES MESURES DES RÉSULTATS Renseignements démographiques, bilan médical, diagnostics connexes, antécédents menstruels et de fertilité.

RÉSULTATS Des antécédents de menstruations non fréquentes, d'hirsutisme, d'obésité et d'acné étaient de solides facteurs de prédiction d'un diagnostic de SOPK. Des antécédents d'écoulement mammaire en dehors de la grossesse étaient un facteur puissant de prédiction d'absence de SOPK. Nous avons produit un questionnaire à 4 éléments devant servir au diagnostic du SOPK; le questionnaire avait une sensibilité de 85% et une spécificité de 85% dans la régression logistique multidimensionnelle et une sensibilité de 77% et une spécificité de 94% à l'aide de l'outil à 4 éléments. L'exactitude prédictive a été validée à l'aide d'un deuxième échantillon de 117 patientes, en plus de la validation interne au moyen d'une analyse auto-amorçage (bootstrap).

CONCLUSION Nous avons élaboré un outil clinique simple pour aider dans le diagnostic du SOPK. Ce questionnaire peut facilement être intégré dans l'emploi du temps chargé des médecins de famille.

POINTS DE REPÈRE DU RÉDACTEUR

- Ce questionnaire validé peut être utile pour dépister la présence du syndrome des ovaires polykystiques chez les femmes ayant des menstruations irrégulières, de l'hirsutisme ou d'autres constatations connexes. L'outil n'a cependant pas été validé dans un milieu de médecine familiale.
- Un score positif devrait déclencher une évaluation clinique rigoureuse pour détecter les complications métaboliques et néoplasiques du syndrome des ovaires polykystiques.

Cet article a fait l'object d'une révision par des pairs.
Le texte intégral est aussi accessible en anglais à **www.cfpc.ca/cfp.**
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Polycystic ovary syndrome

Validated questionnaire for use in diagnosis

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ABSTRACT

OBJECTIVE To construct and validate a questionnaire for use in diagnosis of polycystic ovary syndrome (PCOS).

DESIGN All participants completed a questionnaire, which asked clinical questions designed to assist in the diagnosis of PCOS, before their appointments with an endocrinologist. Following completion of the questionnaire, the endocrinologist (blinded to the answers) made or excluded a diagnosis of PCOS using clinical criteria and biochemical data as indicated. Questions were then evaluated for their power to predict PCOS, and a model was constructed using the most reliable items to establish a system to predict a diagnosis of PCOS.

SETTING An outpatient reproductive endocrinology clinic in Calgary, Alta.

PARTICIPANTS Adult women patients who had been referred to the clinic. Fifty patients with PCOS and 50 patients without PCOS were included in the study.

MAIN OUTCOME MEASURES Demographic information, medical history, related diagnoses, menstrual history, and fertility history.

RESULTS A history of infrequent menses, hirsutism, obesity, and acne were strongly predictive of a diagnosis of PCOS, whereas a history of failed pregnancy attempts was not useful. A history of nipple discharge outside of pregnancy strongly predicted no diagnosis of PCOS. We constructed a 4-item questionnaire for use in diagnosis of PCOS; the questionnaire yielded a sensitivity of 85% and a specificity of 85% on multivariate logistic regression and a sensitivity of 77% and a specificity of 94% using the 4-item questionnaire. Predictive accuracy was validated using a second sample of 117 patients, in addition to internal validation using bootstrap analysis.

CONCLUSION We have constructed a simple clinical tool to help diagnose PCOS. This questionnaire can be easily incorporated into family physicians' busy practices.

EDITOR'S KEY POINTS

- This validated questionnaire can be useful for screening women with menstrual irregularities, hirsutism or other related findings for the presence of polycystic ovary syndrome. The questionnaire, however, has not been validated in a family medicine setting.
- A positive score should prompt careful clinical assessment for the metabolic and neoplastic complications of polycystic ovary syndrome.

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Polycystic ovary syndrome (PCOS) is a metabolic disorder characterized by hyperandrogenism and insulin resistance. It is the most common endocrinopathy affecting premenopausal women, with a prevalence of approximately 4.6%.[1]

Previously there were no widely accepted diagnostic criteria for PCOS. However, a consensus from a conference sponsored by the National Institutes of Health in 1990 determined that the criterion standard diagnosis of PCOS is clinical, defined by the following factors:

- the presence of ovulatory dysfunction (irregular menstrual cycles and subfertility);
- the presence of hyperandrogenism (hirsutism or acne); and
- the exclusion of other related disorders.[2]

These criteria were recently expanded to include polycystic ovaries apparent on ultrasonography and biochemical hyperandrogenemia, but these criteria are not necessary for diagnosis.[3]

Polycystic ovary syndrome presents a diagnostic challenge[4] to family physicians because of the controversy that has surrounded the diagnostic criteria and because the presenting complaints in PCOS are variable. Most often, patients present with menstrual dysfunction, oligomenorrhea, or infertility[5]; they can also present with a pregnancy-related complication, such as gestational diabetes[6,7] or spontaneous abortion.[8,9] Hirsutism or acne could be the patient's primary concern, which can result in profound psychological distress.[8]

Polycystic ovary syndrome is associated with several comorbid conditions, including type 2 diabetes,[10] dyslipidemia,[11] hypertension,[12] hepatic steatosis, obstructive sleep apnea,[13] endometrial carcinoma, and potentially breast and ovarian cancer.[14] It is important to diagnose PCOS as early as possible in the course of disease so that screening, education, and appropriate preventive action and treatment of these patients can be initiated.

To our knowledge, there are no validated tools available in the literature to assist in making the clinical diagnosis of PCOS. We constructed and validated a simple questionnaire for use in screening women for the possible presence of PCOS.

METHODS

Study population

We recruited unselected white patients 18 years or older from an endocrinology reproductive clinic in Calgary, Alta, between January and June 2003. There were no exclusion criteria for participants. The main reasons for referral to this clinic are menstrual irregularity, fertility concerns, and hirsutism. All participants provided written informed consent, and the Conjoint Health Research Ethics Board of the University of Calgary approved the protocol.

Study protocol

Patients were asked to complete the 2-part questionnaire before their appointments with the endocrinologist. The first component requested general demographic information and a medical history, including specific questions regarding known diagnoses of diabetes, hypertension, and dyslipidemia.

The second component of the questionnaire requested a menstrual and fertility history. Patients were instructed to answer these questions excluding time spent pregnant or using pharmaceutical contraception. Questions concerned frequency of menses; history of failed attempts at pregnancy; and history, sites, and treatment of coarse midline hair growth and acne. Patients were asked about a history of breast discharge, a history of obesity, and variability of symptoms with changes in weight.

Once patients completed the questionnaire, the endocrinologist completed the assessment for the criterion standard diagnosis of PCOS (according to the National Institutes of Health criteria). This endocrinologist was blinded to patients' answers on the questionnaire.

Statistical analysis

Statistical analyses were carried out using Stata, version 8.2. Baseline characteristics of study patients were summarized in terms of frequencies for categorical variables and ranges (mean ±SD) for continuous variables. Bivariate analysis was conducted to assess the association of the predictor variables with the outcome variable of PCOS diagnosis.The Fisher exact test was used for categorical variables, and unpaired *t* tests were used for continuous variables.

The sample size calculation was powered at 80% to detect a relative risk of 2.5 for a positive response to an item among patients with PCOS relative to patients without PCOS, at an α of .05. This sample size also ensured that the precision of 95% confidence intervals around the sensitivity and specificity of our measure would be no wider than ±10%, provided that our observed values for sensitivity and specificity were 85% or greater.

Logistic regression modeling was used to examine the relationship between patient predictor variables and the outcome of PCOS versus the outcome of no PCOS. All significant ($P<.05$) baseline predictor variables and interaction terms were used to obtain the backward stepwise selection for the multivariable model. Correlations among the predictors included were checked to avoid colinearity. The final model was assessed by the area

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under the receiver operating characteristic curve. The goal was to maximize the sensitivity and specificity of the final tool.

Bootstrap analysis was employed to estimate the bias in the predictive accuracy of the model.[15] For each bootstrap sample, patients were drawn randomly, with replacement, from the original data set. For each of the 1000 bootstrap samples, the model was then refitted on each bootstrapped data set, with the results inspected for consistency using the bias-corrected confidence intervals for sensitivity and specificity.

Following construction of the model and simplified questionnaire, the questionnaire was issued to a second sample of patients in the same clinic for validation. Sensitivity and specificity were calculated on this validation sample.

RESULTS

Demographic characteristics

A total of 100 subjects participated in the initial phase of the study. Fifty subjects had PCOS and 50 did not have PCOS by the criterion standard. The following diagnoses were established for patients without PCOS: 19 had hypothalamic amenorrhea, 18 had hyperprolactinemia, 5 had premature ovarian failure, 3 had hypopituitarism, 1 had adult-onset congenital adrenal hyperplasia, 1 had idiopathic hirsutism, 1 had menstrual irregularity not yet diagnosed, and 2 were not seen because of menstrual or fertility concerns. Patients with PCOS had a higher average body mass index and a higher prevalence of hypertension than women without PCOS had (**Table 1**), but the groups did not differ with respect to other demographic characteristics (**Table 2**).

Menstrual and fertility history

Significantly more PCOS patients reported a history of long or variable menstrual cycles than patients without PCOS did (36/48 vs 14/49, $P=.001$) (**Table 3**). More women with PCOS reported a history of obesity than women without PCOS did (37/48 vs 11/49, $P<.001$). Patients with PCOS were more likely to report a history of increasing menstrual irregularity with weight gain than those without PCOS were (14/46 vs 3/48, $P=.003$).

There was no difference in proportion of each group who had previously been pregnant (**Table 3**). There was no difference between groups with respect to a reported history of 1 year of failed conception attempts. Significantly more patients without PCOS reported a history of nipple discharge outside of pregnancy than women with PCOS did (22/49 vs 3/50, $P<.001$).

Significantly more women with PCOS reported coarse hair growth than women without PCOS did. Women with PCOS reported hair growth at more of 8 possible sites than women without PCOS did (3.7 ± 2.5 vs 0.8 ± 1.7, $P<.001$). Women with PCOS who reported hair growth were more likely to report feeling troubled by their hair growth and to have sought treatment for the hair growth than women without PCOS did. More women with PCOS reported that hair growth increased with weight gain than women without PCOS did.

A history of acne was more common among women with PCOS than among women without PCOS (27/50 vs 15/50, $P=.03$). However, there was no difference in the proportions of each group who had taken prescription treatment for acne.

Predictive model development

Several of the highly predictive variables were considered for inclusion in the model. All factors with a P value <.05 were included in the multivariate analysis. No interaction terms were found to be significant. Four

Table 1. Patient characteristics

DEMOGRAPHIC CHARACTERISTICS	PCOS (N = 50) N ± SD	NO PCOS (N = 50) N ± SD	*P* VALUE
Age (y)	30.4 ± 7.14	33.5 ± 10.6	.094
Weight (kg)	85.6 ± 20.6	66.1 ± 14.7	<.001
Body mass index (kg/m^2)	31.4 ± 8.2	24.0 ± 5.9	<.001
Average number of months of oral contraceptive use	64.0 ± 53.7	54.4 ± 57.7	.397

PCOS—polycystic ovary syndrome.

Table 2. Patients' education levels and history of illnesses: *Apparent discrepancies in percentage values are due to a few patients failing to answer some questions.*

EDUCATION AND HISTORY	PCOS (N=50) N (%)	NO PCOS (N=50) N (%)	*P* VALUE
Education			
• Partial high school	2 (4)	1 (2.0)	
• Completed high school	10 (20)	2 (4.1)	
• Partial postsecondary	10 (20)	10 (20.4)	
• Completed postsecondary	28 (56)	36 (73.5)	
Patient history			
• Diabetes mellitus	2 (4)	0 (0)	.495
• Hypertension	9 (18)	0 (0)	.003
• Dyslipidemia	5 (10)	3 (6)	.715
• Anorexia or bulimia	2 (4.4)	4 (8.3)	.678
• Hypothyroidism	2 (4.4)	6 (13)	.267
• Use of oral contraceptives	46 (92)	41 (82)	.234

PCOS—polycystic ovary syndrome.

Table 3. Menstrual and reproductive history

PATIENT HISTORY	PCOS	NO PCOS	*P* VALUE
Oligomenorrhea			
• Variable or long menstrual cycles	36/48	14/49	<.001
• <9 menses annually	38/48	15/48	<.001
• Irregular menses with weight gain	14/46	3/48	.003
Obese between ages 16 and 40	37/48	11/49	<.001
Pregnancy			
• Previously pregnant	13/48	20/49	.20
• Previously attempted	22/50	28/50	.32
• Previously attempted without success for ≥1 year	15/22	14/27	.38
Nipple discharge exclusive of pregnancy or breastfeeding	3/50	22/49	<.001
Coarse hair growth*			
• At 1 or more sites	44/50	15/50	<.001
• At 2 or more sites	40/50	10/50	<.001
• At 3 or more sites	31/50	6/50	<.001
• Troubled by hair growth	42/44	10/15	.009
• Treatment for hair growth	36/44	8/15	.04
• Increased growth with weight gain	26/48	4/48	<.001
Had acne as an adult	27/50	15/50	.03
• Medical treatment for acne	10/27	8/15	.35

PCOS—polycystic ovary syndrome.
*Average number of sites (P<.001) was 3.7 ± 2.5 for patients with PCOS and 0.8 ± 1.7 for patients without PCOS.

variables (history of obesity, history of long or variable menses, coarse hair growth reported at 3 or more sites, and history of nipple discharge) were included in the final model. The predictive strength of the fit was 0.94 (determined by area under the receiver operating characteristic curve). When a cutoff probability of .45 is used to indicate PCOS, the model has a sensitivity and specificity of 85.4%. Results from the bootstrap analysis showed minimal bias, as indicated by a bias of 2.9% for the sensitivity (bias-corrected 95% CI 63.6%-94.1%), and a bias of 0.8% for the specificity (bias-corrected 95% CI 64.0%-96.3%).

Because the clinical application of a logistic regression model requires calculating probabilities, a cutoff value was selected and significant variables were simplified to develop a scoring system for use in clinical practice. As the coefficients for each item are essentially equal, an equal weighting was assigned to each item (**Table 4**). The scoring system is a simple sum of each of the 4 items (**Table 5**). The fourth item regarding a history of nipple discharge generates a negative score, as this item supports a diagnosis other than PCOS. A score of 2 or higher is required for a positive result for PCOS; a score of 1, 0, or -1 represents a negative result. When reapplied to the sample, the sensitivity of the scoring system is 77.1% (95% CI 62.7%-88.0%) and the specificity is 93.8% (95% CI 82.8%-98.7%).

Table 4. Generation of prediction model and coefficients of variables: *Parameter estimates of the logistic regression model.*

SYMPTOM VARIABLES	COEFFICIENT	STANDARD ERROR	95% CONFIDENCE INTERVAL
Variable or long (≥35 d) menstrual cycles	2.44	0.74	0.98-3.90
Coarse hair at 3 or more sites	2.91	0.81	1.32-4.51
History of obesity	2.59	0.72	1.18-4.00
Lactation unrelated to pregnancy	-2.45	0.93	-4.2 to -0.63
Constant	-2.98	0.78	-4.51 to -1.46

Questionnaire validation

The questionnaire was validated by issuing the modified 4-item questionnaire to a second sample of 117 patients at the reproductive endocrinology clinic, 41 of whom had been diagnosed with PCOS by criterion standard. In this sample, sensitivity for the diagnosis of PCOS was 85.4% (95% CI 71.6%-93.1%) and specificity was 93.4% (95% CI 85.5%-97.2%).

DISCUSSION

We have constructed and validated a simple casefinding tool that can help physicians diagnose PCOS and can guide them in treating menstrual irregularity, infertility, and cosmetic concerns. This tool can also alert clinicians to screen for associated and potentially devastating comorbid conditions.

This tool has been developed among women whose primary complaint is infertility. Many clinical symptoms among these patients have substantial overlap. For example, women with hyperprolactinemia often present with secondary amenorrhea,[16] as do women with PCOS. This selection bias in the referral patient population is likely also reflected in similarity of fertility rates

Table 5. Clinical tool for diagnosis of polycystic ovary syndrome

QUESTION	CRITERIA TO ATTAIN SCORE VALUE	SCORE VALUE
Please answer this question, NOT INCLUDING any time spent pregnant, receiving birth control pills or injections, after menopause, or after having both ovaries or the uterus surgically removed: Between the ages of 16 and 40, about how long was your average menstrual cycle (time from first day of one period to the first day of the next period)? (select ONE only) • <25 d • 25-34 d • 35-60 d • More than 60 d • Totally variable	Patient indicates any one of • 35-60 d • more than 60 d • totally variable	1
During your menstruating years (not including during pregnancy), did you have a tendency to grow dark, coarse hair on your (circle ALL that apply) • upper lip? • chin? • breasts? • chest between the breasts? • back? • belly? • upper arms? • upper thighs?	Patient indicates 3 or more sites	1
Were you ever obese or overweight between the ages of 16 and 40? (circle ONE) • Yes • No	Patient indicates Yes	1
Between the ages of 16 and 40, have you ever noticed a milky discharge from your nipples (not including during pregnancy or recent childbirth)? (circle ONE) • Yes • No	 Patient indicates Yes Patient indicates No	1 -1 0
TOTAL		If ≥ 2, consistent with diagnosis of PCOS If <2, not consistent with diagnosis of PCOS

PCOS—polycystic ovary syndrome.

between women with PCOS and women without PCOS. Despite similarities in clinical presentation among women, however, this questionnaire was still able to discriminate between various disease processes with high sensitivity and specificity. Although this tool has not been formally validated in a family medicine clinic, it could discriminate between PCOS and no PCOS even better among women in this population, where primary complaints are often more heterogeneous than in a reproductive endocrinology clinic.

This model includes a history of obesity as a predictor of PCOS, as a history of obesity was strongly predictive of PCOS in our patient population. Although obesity is prevalent among women with PCOS and exacerbates the clinical manifestations of PCOS,[13] it must be emphasized that obesity is not essential for the diagnosis of PCOS. Polycystic ovary syndrome is a disorder of excessive androgen production, which is often aggravated by associated insulin resistance.[17] Although insulin resistance is closely associated with obesity, it can also manifest clinically in lean patients. The prevalence of obesity among PCOS women ranges from 30% to 75%.[13,18] In our population, 52% of women with PCOS were obese.

We included a history of nipple discharge in our clinical prediction tool, as a history of nipple discharge was strongly predictive of a diagnosis other than PCOS. This could reflect selection bias in our population; that is, patients with elevated prolactin levels and amenorrhea are frequently referred to reproductive endocrinology clinics for further assessment. Yet previous research shows that, when pregnancy and PCOS are excluded, one third of patients presenting to family physicians with amenorrhea will have pituitary disease or dysfunction.[19] Consequently, it is prudent to include nipple discharge as an important negative predictor of PCOS among women with menstrual irregularity.

Use of this tool does not obviate clinical assessment of these patients. The criterion standard for diagnosing PCOS remains clinical assessment by an expert

in the field. This diagnostic tool has been developed using the criterion standard for comparison, however, and thus serves as a reliable casefinding tool. A positive result must prompt a careful clinical assessment for metabolic and neoplastic complications of PCOS. A negative result does not rule out PCOS with certainty; in situations of doubt, referral to a reproductive endocrinologist is prudent.

Construction of this questionnaire is subject to some limitations. The sample size of 100 on which the tool was based and the limited number of categories our simplified tool uses to predict outcome restrict our ability to estimate the sensitivity for this measure. We believe that the simplicity of this clinical tool outweighs these limitations, and we hope that future research with this tool will provide a more accurate assessment of its validity.

CONCLUSION

We have constructed and validated a simple clinical tool that is highly sensitive and specific for a diagnosis of PCOS. This questionnaire can be easily used in family physicians' busy practices.

Contributors

Drs Pedersen, Faris, *and* **Corenblum** *contributed to study concept and design, analysis and interpretation of data, and preparing the article for submission.* **Ms Brar** *contributed to analysis and interpretation of data and preparing the article for submission.*

Competing interests

None declared

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References

1. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998;83(9):3078-82.
2. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, Merriam GR, editors. *Polycystic ovary syndrome*. Boston, Mass: Blackwell; 1992. p. 377-84.
3. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19:41-7.
4. Lewis V. Polycystic ovary syndrome. A diagnostic challenge. *Obstet Gynecol Clin North Am* 2001;28(1):1-20.
5. Hunter MH, Sterrett JJ. Polycystic ovary syndrome: it's not just infertility. *Am Fam Physician* 2000;62(5):1079-88,1090.
6. Gjonnaess H. The course and outcome of pregnancy after ovarian electrocautery in women with polycystic ovarian syndrome: the influence of body weight. *Br J Obstet Gynaecol* 1989;96(6):714-9.
7. Bjercke S, Dale PO, Tanbo T, Storeng R, Ertzeid G, Abyholm T. Impact of insulin resistance on pregnancy complications and outcome in women with polycystic ovary syndrome. *Gynecol Obstet Invest* 2002;54(2):94-8.
8. Sonino N, Fava GA, Mani E, Belluardo P, Boscaro M. Quality of life of hirsute women. *Postgrad Med J* 1993;69(809):186-9.
9. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002;17:2858-64.
10. Ehrmann DA, Cavaghan MK, Barnes RB, Imperial J, Rosenfield RL. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 1999;22(1):141-6.
11. Mather KJ, Kwan F, Corenblum B. Hyperinsulinemia in polycystic ovary syndrome correlates with increased cardiovascular risk independent of obesity. *Fertil Steril* 2000;73(1):150-6.
12. Holte J, Gennarelli G, Berne C, Bergh T, Lithell H. Elevated ambulatory daytime blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? *Hum Reprod* 1996;11:23-8.
13. Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005;352(12):1223-36.
14. Balen A. Polycystic ovary syndrome and cancer. *Hum Reprod Update* 2001;7(6):522-5.
15. Efron B, Tibshirani RJ. *An introduction to the bootstrap.* London, Engl: Chapman and Hall; 1994.
16. Serri O, Chik CL, Ur E, Ezzat S. Diagnosis and management of hyperprolactinemia. *CMAJ* 2003;169(6):575-81.
17. Azziz R. Androgen excess is the key element in polycystic ovary syndrome. *Fertil Steril* 2003;80(2):252-4.
18. Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Hanley R, Fereshetian AG, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2001;86(4):1626-32. Comment in: *J Clin Endocrinol Metab* 2001;86(10):5090-1.
19. Reindollar RH, Novak M, Tho SP, McDonough PG. Adult-onset amenorrhea: a study of 262 patients. *Am J Obstet Gynecol* 1986;155(3):531-43.