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Polycystic Ovary Syndrome in the Non-Gynaecological Practice – Can We Use a Common Medical Approach?

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1. Introduction

During a recent high-level endocrinology congress, the session on the polycystic ovary syndrome (PCOS) included a lecture on fertility problems. This was started with a remark that the gynaecologist and other medical professionals should bring their treatment efforts closer. I was glad to hear this but thereafter the lecturer talked exclusively about ovulation induction and in vitro fertilisation; and did not say anything about how these efforts affected other medical problems related to PCOS, or the future course of the disease, or what else could be done if the discussed fertility approaches fail (in a high proportion of cases). Why then did he call attention to bringing treatment protocols closer?

Somebody remarked that in their experience even a few months' pre-treatment with metformin improved the results but this was rebuffed by the lecturer that such efforts had not reached sound evidence. After the session, I asked him in private if his patients should have been treated for other existing problems beyond infertility like acne, hirsutism or obesity. The answer was short "They didn't complain about anything else" and he turned his back to me. Well, in all likelihood the patients must have had some hyperandrogenic symptoms as a prerequisite of the diagnosis. In addition, most published fertility studies in the PCOS literature include grossly obese patients. Since obesity alone is a well known contributor to infertility; would be wiser to wait until these women slim down... we have not come closer.

I was a bit angry for not having been taken seriously but it was not the first time I experienced a similar attitude. The patients with irregular periods usually visit the gynaecologist. The general advice that follows is the use of the contraceptive pill if the lady is not interested in becoming pregnant at the moment; or the pharmaceutical stimulation of the ovaries or the laparoscopic drilling to remove the cysts from them if the lady desires a baby.

I bring forth a story of a young girl. Eleni has no plans to get pregnant for years so upon the gynaecologist's advice she starts taking the pill. Her acne spots (all teenagers have pimples, haven't they) and some ugly hairs under her nose were not mentioned and were not commented on either during the visit. Since she doesn't remember or it had not been explained for how long the pills should be taken, she stops the pill after a year or so. She has

no boyfriend; the pill might have caused side effects. Despite her spots decreasing and having to remove hair from her face less frequently while on the pill, she gained more weight, interestingly, mainly around the waistline. Was it this why she has not attracted the boys? Off the pill, the annoying spots and hair growth return and the weight gain continues. Slowly she becomes more and more depressed and experiences sudden attacks urging her to take some chocolate or other sweets every now and again. She visits cosmeticians, dermatologists, and dieticians – everything in vain: the problems do not get solved; symptoms come back worsened.

Nobody mentions the suspicion of a chronic disorder that would require a different treatment approach. The irregularity of the periods persists but it is not a disturbing phenomenon; if she visits the gynaecologist, the answer is the same as before. Eventually Eleni gets married and despite making love unprotected for years she is still not pregnant. In desperation she visits fertility clinics where courses of medication are started in increasing doses. Sometimes she gets pregnant but the pregnancy is lost early; on other occasions the medication must be stopped due to dangerous side effects. After six months of ineffective stimulation more complicated and costly in vitro fertilization procedures follow. She is fortunate, with the aid of some further hormonal treatment, the pregnancy goes ahead. She gains more weight than she ought to, there is some fuzz about her elevating blood sugar, she hardly escapes insulin treatment. She can't deliver *per vias naturales* - Caesarean section is required for the oversized but otherwise healthy baby girl. Eleni is now more obese than ever, the menstrual cycles are just as irregular as before pregnancy, and she wonders what problems are inherited by this lovely creature from her.

Dozens of similar stories can be heard from overall the world. Nobody raises the suspicion that thousands of young women might have a very common endocrine-metabolic disorder that can be supposed from the very beginning by a proper look at them and by listening to their medical history?

Without meaning to exaggerate issues, this is a very grim picture. Every article on PCOS starts with the statement that this is the most common endocrine disorder. Despite the prevalence varying according to the diagnostic criteria, it is around 10% of the fertile female population (Azziz et al., 2004; March et al., 2010). PCOS is grossly under-recorded and insufficiently diagnosed in primary care – data from a well-developed country with widely respected health care (Mani et al., 2010).

When one thinks of PCOS, the diagnostic procedure looks complicated and the therapy advice is ambiguous. Usually the treatment options are listed according to the symptoms or explicitly state to start with the main complain of the patient. This is controversial as patients' considerations about their health problems may differ significantly from those regarded important in medical experience.

The most recent review of the American College of Physicians says "Drug therapy is aimed at treating the symptoms of PCOS ... If infertility is not the primary concern, then treatment is aimed at reducing the undesired effects of excess androgen and restoring regular menses to prevent endometrial hyperplasia" (Wilson, 2011). Does this mean that if infertility is the primary concern, nothing else matters? We don't treat tuberculosis only for cough or fever that could be the "primary concern" of the infected. Wherever possible, we use aetiopathogenetic treatment.

Something is missing from the general conception. The advice is definitely misunderstood by those who take it word by word and provide treatment to PCOS patients according to the patient's complain only. Shouldn't we give her the complete information about the nature of the problem with all possible late complications in order that *salus aegroti* will meet *voluntas aegroti* to avoid medico-legal confrontation?

Fortunately, the above cited review on PCOS (Wilson, 2011) says in the third paragraph at the beginning: "The information contained herein should never be used as a substitute for clinical judgment." I agree totally with this statement as it supports my concerns. However, my views will be detailed later in this chapter.

Around 1993 Roy Homburg addressed a lecture on PCOS to the endocrinologists in Cyprus in which he interestingly stated that PCOS had an insulin resistance component in the background; and he advised to start co-cyprindiol (a contraceptive pill containing ethinyloestradiol and ciproterone acetate, a contraceptive combination with anti-androgenic effect which had already been in use on this side of the Atlantic for long) as soon as PCOS is diagnosed to regulate menstruation and to counteract hyperandrogenism; this way preventing progression of the disease. Despite the last part of this opinion being debatable, this lecture raised my curiosity. I started seeing patients with PCOS from this point of view. In the meanwhile the addition of the insulin sensitizer metformin to the treatment repertoire boosted my interest.

Now, nearly two decades on, several substantial aspects of PCOS have still remained unclear (Pasquali et al., 2011). In this chapter only the practical clinical approach to PCOS will be discussed comparing my experience with that of others known from the literature; arguing for a positive answer to the question raised in the chapter title.

2. Diagnostic problems: What is PCOS?

Until the exact pathomechanism is not fully explored PCOS will remain a syndrome: a rather diverse configuration of several endocrine-metabolic features of variable severity.

2.1 Contrasting diagnostic criteria

There have been three recently proposed sets of diagnostic criteria: those of the National Institutes of Health, the NIH criteria (NIH, 1991, as cited in The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004); the Rotterdam criteria (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004); and The Androgen Excess and PCOS Society, the AES criteria (Azziz et al., 2009). They differ in what positive findings are required for the diagnosis but agreed in one: other related (mainly endocrine) disorders must be excluded. I start with a short comment on this statement.

2.1.1 Exclusion of other related disorders

Even this common part of the diagnostic criteria may confuse the unwary. Most endocrine diseases present with symptoms found in PCOS (hyperandrogenic signs, infertility, polycystic ovaries, insulin resistance etc.) but PCOS has no discriminative diagnostic symptoms (none has been found yet) hence the differentiation from other endocrine

diseases must be an essential part of the diagnostic procedure. The problem is that PCOS is so frequent (whatever criteria are used) that merely on statistical grounds the same person may suffer from another endocrine disease synchronously.

How can this controversy between the diagnostic criteria and the probability of co-existence of PCOS with another endocrine disorder be solved? It must be obvious that the exclusion statement is meant to say this: any positively diagnosed endocrine disease should be controlled satisfactorily and if the criteria for PCOS still apply one can conclude that the same person suffers also from PCOS.

This coincides with the necessary medical steps emerging from the findings of the diagnostic procedure. Usually the "other" endocrine disorder is of more progressive or dangerous nature than PCOS and its treatment must have priority over PCOS. In consequence, the exclusion criterion would be more equivocal sounding like this: "PCOS exists (if the required diagnostic features apply) with the exclusion of other *uncontrolled* related disorders." Definitions must be robust but equivocal; ambiguity causes hesitation.

Most often hypothyroidism, hyperprolactinaemia or late-onset adrenocortical hyperplasia may coincide with PCOS. Less frequent but more dangerous conditions in the initial phase may also cause problems in the diagnostic procedure.

2.1.2 Positive findings required for the diagnosis

The real debate has been on what positive findings should be included in the diagnostic criteria. There are three main features in question: hyperandrogenism (HA), chronic oligo-anovulation (ANO), and the polycystic appearance of the ovaries on ultrasound (PCO).

The PCO sign was not included in the NIH criteria. The Rotterdam criteria include all three features of which at least two must be present. Later several participants of the Rotterdam consensus meeting realised that hyperandrogenism (androgen excess) is an essential part of PCOS; and their new proposal became known as the AES criteria. This joins ANO and/or PCO in one term, ovarian dysfunction (OD); and PCOS is a combination of HA and OD. In other terms, the combination of PCOS and ANO without HA (one possibility allowed by the Rotterdam criteria) should not be regarded as PCOS. Hyperandrogenism and ovarian dysfunction may not be independent contributors to the development of PCOS but the discussion of this is beyond the scope of this chapter.

2.2 Understanding the differences in the three sets of criteria

The differences of the different diagnostic criteria can be perceived easier using Venn diagrams. Circles represent the population suffering from features specified in the Rotterdam criteria (HA, ANO, and PCO). The overlapping areas (the intersections) of the circles mean the set of people with the common features.

For didactic reasons let us start with the Rotterdam criteria (Fig. 1). The trilobate gray area represents patients who meet at least two of the three possible features; the central pseudo-circle (the intersection of all three circles) includes those who have all three features.

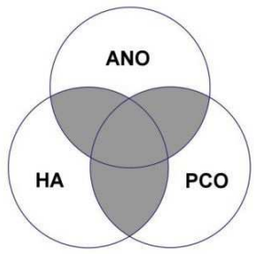


Fig. 1. Visual representation of the patient population diagnosed using the Rotterdam criteria

The gray coloured area in Fig. 2 shows the patients diagnosed by the AES criteria. Ovarian dysfunction is the union of ANO and PCO (and/or). Those who have no hyperandrogenism (the intersection of ANO and PCO less HA) are excluded from the diagnosis.

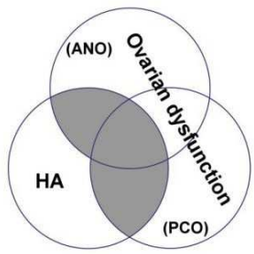


Fig. 2. Visual representation of the patient population diagnosed using the AES criteria

Patients diagnosed by the NIH criteria are those who have both HA and ANO (the intersection of HA and ANO); see in Fig. 3. The PCO sign plays no role in the diagnosis; its inclusion in the diagram is solely for comparative purposes. The number of patients found with PCOS using these NIH criteria is the smallest among the three sets.

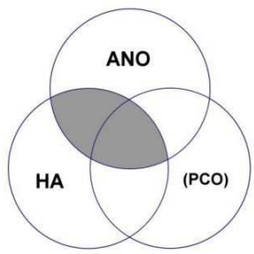


Fig. 3. Visual representation of the patient population diagnosed using the NIH criteria

The size of the circles in Fig. 1, 2, and 3 is arbitrary. The prevalence of HA and ANO in the fertile female population is not known. Around 30% have polycystic ovaries but only a fraction suffers from PCOS (depending on the criteria used for the diagnosis).

The prevalence of PCOS in a community sample of 728 women was found as follows: NIH criteria, 8.7%; AES criteria, 12%, Rotterdam criteria, 17.8% (March et al., 2010). The study used interviews of women who were born in a certain area. The article also emphasizes that at least two third of the cases were previously undiagnosed.

3. PCOS patients in a medical outpatient practice

I work as a private medical practitioner in the Republic of Cyprus on an island in the Eastern Mediterranean; a member state of the EU; with almost exclusively Europid (white, "Caucasian") population. Beyond doing general medicine I am a specialist for endocrinology, diabetes, and metabolic diseases. Private practitioners in Cyprus work independently from the governmental health services, free of territorial or insurance company obligations.

Such practice experience may not be representative for the whole Cypriot population but there have been no published PCOS related data in Cyprus. What we do know is that the prevalence of both Type 2 diabetes and the metabolic syndrome is of the highest in Europe therefore one can suspect a relatively high number of patients living in Cyprus suffering from of all kinds of disorders related to insulin resistance including PCOS (Loizou & al., 2006).

3.1 Patient selection and diagnosis

I raise the possibility of PCOS each time when a female patient turns up presenting any symptom which is compatible with the syndrome; independently of her primary complaint. On detection of other symptoms compatible with PCOS during history taking and physical examination, the suspicion is discussed thoroughly with the patient. Upon informed consent, we continue with the formal diagnostic procedure.

Related disorder	Number	%
Subclinical hypothyroidism	45	61.6
Thyrotoxicosis	3	4.1
Multinodular euthyroidic goitre	10	7.3
De Quervain thyroiditis	1	1.4
Late-onset adrenocortical hyperplasia	3	4.1
Microprolactinoma	3	4.1
Impaired fasting glucose	3	4.1
Impaired glucose tolerance	1	1.4
Type 2 diabetes mellitus	1	1.4
Type 1 diabetes mellitus	1	1.4
Metabolic syndrome	1	1.4
HAIRAN syndrome	1	1.4
Total	73	100

Table 1. The distribution of related disorders co-existing with PCOS in 73 patients

Since 2003, 323 women who had not been using hormonal contraceptives for at least six months have undergone the full diagnostic procedure. The necessary hormonal tests and pelvic ultrasound were performed as recommended by the Rotterdam criteria; occasionally further tests became necessary for differentiation from related disorders. A formal 75 g oral glucose tolerance test was performed in all women diagnosed positively for PCOS except those with known diabetes.

Late-onset adrenocortical hyperplasia was found in one patient and the HAIR-AN syndrome (Hyperandrogenism – Insulin Resistance – Acanthosis Nigricans) in another one without PCOS.

321 women were diagnosed positively for PCOS using the Rotterdam criteria; aging 14 – 46 years (mean 25 years). Only 2 women had no hyperandrogenic signs therefore 319 women (>99%) met also the AES criteria; and only 180 (56%) could have been diagnosed by the NIH criteria.

In 73 patients (22.7%) PCOS was a secondary diagnosis where after the satisfactory control of any related disorder the Rotterdam criteria still applied. The distribution of co-existing disorders of these 73 patients is shown in Table 1.

3.2 Initial symptoms

The following definitions, grading of symptom severity, and abbreviations will be used in this and consecutive sections:

- Acne score: The Global Acne Grading System (Doshi et al., 1997) for its simplicity; requiring only visual assessment of signs in six body areas.
- Hirsutism: Score higher than 8 in the classical Ferriman-Gallwey scale (Ferriman, 1962, as cited in Rosenfield, 1990); by visual assessment of hairiness in nine body areas.
- Weight surplus: body mass index (BMI) ≥25 kg/m^2
  - Overweight: BMI between 25 and 29.9 kg/m^2
  - Obese: BMI between 30 and 34.9 kg/m^2
  - Grossly obese: BMI over 35 kg/m^2
- Abdominal obesity: Waist-to-hip circumference ratio (W/H) ≥0.80
- Irregular menses: menstrual periods <9/year; or periods shorter than 21 or longer than 35 days
- Infertility: no spontaneous pregnancy despite active, non-protected sexual life for at least two years
- Early pregnancy loss (EPL): spontaneous abortion during the first trimester.

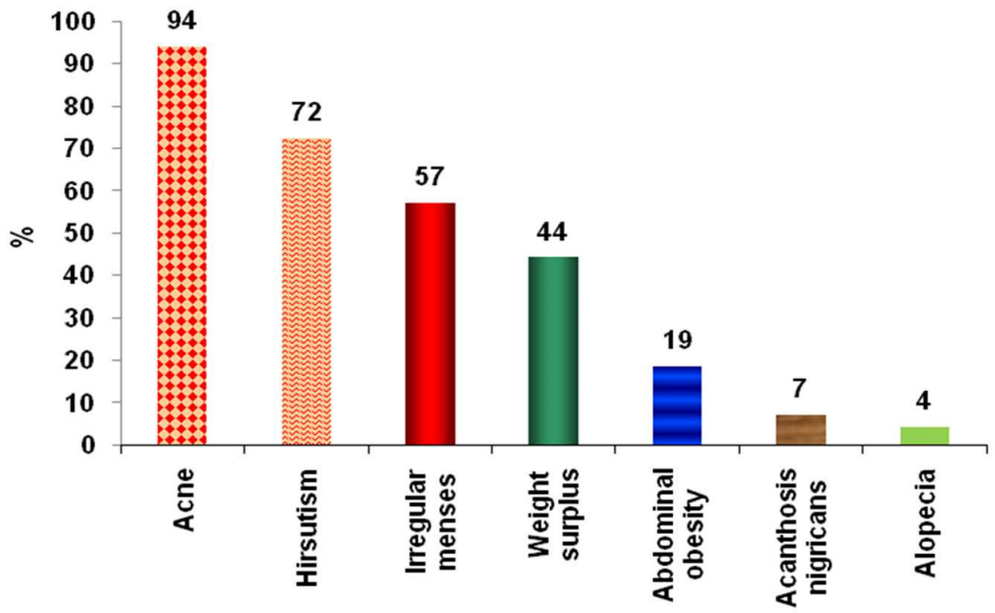


Fig. 4. The distribution of symptoms in 321 women with PCOS at time of diagnosis

The distribution of the initial symptoms of the 321 women found with PCOS according to the Rotterdam criteria (including those with co-existing disorders after full control) is shown in Fig. 4.

The overall majority had easily detectable acne and/or hirsutism with or without laboratory hyperandrogenism; only three patients (0.93%) had laboratory hyperandrogenism without acne or hirsutism. 57% had irregular menstrual periods. 44.3% had weight surplus in the following proportions: overweight, 21.5%; obese, 10.6%; and grossly obese, 12.1%. Acanthosis nigricans occurred only in obese or grossly obese patients.

The fertility rate cannot be verified for the whole group because the majority had not planned pregnancy. Infertility was revealed by history taking in 23 of 108 married women (21.3%); 5 had early pregnancy losses (4.6%). 11 early pregnancy losses occurred in 11 of 85 women (12.9%) having had live births from earlier pregnancies.

4. Testing the efficacy of treatment forms

The following symbols will be used for statistical analysis in this section:

- ***: P<0.001
- ** : P<0.01
- * : P<0.05
- n.s.: not significant

The other symbols and abbreviations are as described in Section 3.2.

4.1 Choice between taking the contraceptive pill or metformin

Before 2002 the standard treatment advice for my patients was the anti-androgenic combined contraceptive pill as mentioned in the introduction. The pill was stopped when the woman wanted to become pregnant; usually the previous symptoms recurred while waiting for (in many cases, only hoping for) conception.

Between 2002 and 2006 I offered the insulin sensitizer metformin treatment to all freshly diagnosed PCOS patients who had contraindications or negative experience with the pill, or simply did not want to take hormonally active medication, or wanted to become pregnant. The efficacy of the two treatment forms (the pill or metformin) was compared in those who completed twelve moths' treatment. The two groups were comparable in size and age distribution. Table 2 shows the results.

	Pill	**Metformin**
Number of patients	17	19
Age (year)	24 (20-31)	23 (15-36)
Acne score	16.9 ± 7.1 – 2.7±2.9 ***	19.7 ± 11.2 – 6.6 ± 6.9 ***
F-G score	15.2 ± 2.7 – 6.6 ± 3.5 ***	16.4 ± 7.2 – 10.9 ± 6.0 ***
BMI	24.0 ± 6.4 - 23.7 ± 5.8 n.s.	26.7 ± 7.8 - 25.4 ± 7.8 n.s.
W/H ratio	0.73 ± 0.1 - 0.71±0.1 n.s.	0.75 ± 0.1 – 0.74 ± 0.1 n.s.

Table 2. Changes during a twelve-month treatment period on the pill or metformin

Both the acne and hirsutism scores decreased significantly during the twelve-month treatment period; BMI and W/H did not change significantly in either group. Further statistical analysis was not made since the two groups differed in the indication of treatment; and the metformin group had more severe symptoms in average. However, this study convinced me that metformin was a simple, safe; and effective first choice of medical treatment in PCOS. In many patients metformin restored the regularity of the menstrual cycles. Spontaneous pregnancies with live births also occurred (Petrányi, 2005; Petrányi & Zaoura, 2007).

4.2 Metformin treatment with or without lifestyle changes

Since 2006 lifestyle changes (Tang & al., 2006) have been advised parallel to the pharmacological treatment for all new patients: the increase of daily physical activity and low glycaemic index diet; including calorie restriction to the overweight. The two treatment forms (metformin with or without lifestyle changes) were compared in the following way (Petrányi & Zaoura, 2011).

Patients from the metformin monotherapy era served as historical control group consisting of 29 women (age 18 to 39 y, mean, 26) to whom the recent metformin + lifestyle changes group was compared consisting of 34 patients with comparable age distribution. The following parameters were recorded every three months during the 6-month observation period: acne and hirsutism scores, body mass index (BMI), waist-to-hip ratio (WH), and the regularity of the menstrual periods. Patients with carbohydrate metabolic disorders (impaired fasting glucose, impaired glucose tolerance, diabetes mellitus) or those who became pregnant during the six-month period were not included in the evaluation.

Table 3 shows the changes of the four easily measurable symptoms during the six-month observation period by the mean ± SD, and the difference (Δ) both in the metformin and the metformin + lifestyle treatment groups; and the difference between the two treatment forms. Not all patients suffered from acne or hirsutism; their number within the groups is also included in the table.

	Metformin (n=29)	**Metformin +lifestyle (n=34)**	**Difference**
Acne	(n=27)	(n=32)	
	20.3±9.9 – 12.4±8.9	25.2±8.2 – 15.9±7.7	
	Δ=7.9 ***	Δ=9.3 ***	1.4 n.s.
Hirsutism	(n=22)	(n=21)	
	15.1±6.0 – 12.8±6.2	11.7±2.1 - 9.2±2.7	
	Δ=2.3 ***	Δ=2.5 ***	0.2 n.s.
BMI	26.6±6.9 - 26.4±6.7	27.5±7 - 26.7±6.3	
	Δ=0.26 n.s.	Δ=0.88 ***	0.62 *
W/H	0.74±0.07 - 0.74±0.07	0.76±0.08 - 0.74±0.07	
	Δ=0.001 n.s.	Δ=0.019 **	0.017 *

Table 3. Comparison of the efficacy of metformin versus metformin + lifestyle treatment

Acne and hirsutism score improved significantly and similarly in both treatment forms.

BMI did not show significant change during the metformin monotherapy but it improved significantly in the combined therapy group. The combined therapy diminished BMI in the

overweight women by 1.1 kg/m² *** and 0.64 kg/m² * in those of normal weight; without causing problem to them.

W/H did not change during metformin monotherapy but decreased significantly with metformin + lifestyle changes.

Table 4 shows the changes in the regularity of menstrual cycles during the six-month treatment period. The proportion of patients who changed from irregular to regular was not significantly different between treatment forms (Fisher's exact test, P=0.29).

	Metformin (n = 29)	**Metformin + lifestyle (n = 34)**
Irregular menses at start	12	22
Remained irregular	4	8
Became regular	8	14
Regular menses at start	17	12
Remained regular	17	12
Became irregular	0	0

Table 4. Number of patients changed regularity of the menstrual cycle during six months

The individual changes in the acne and the hirsutism scores during the combined therapy are shown in the following two figures. The acne score improved in all patients by three months with further improvement by six months (Fig. 5). The hirsutism score did not improve in few patients by three months but everybody improved by six months (Fig. 6).

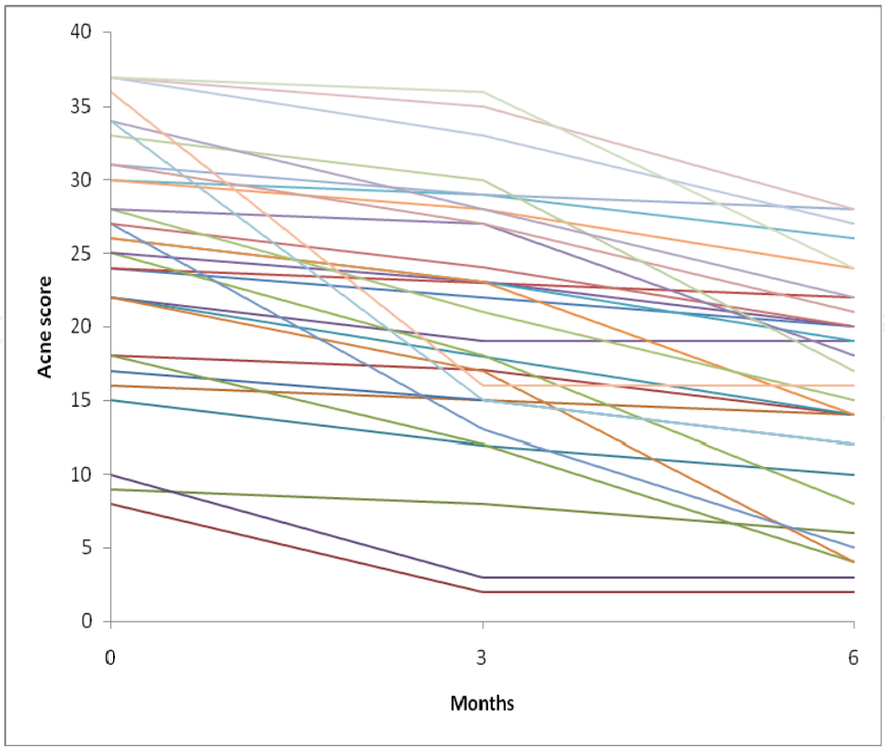


Fig. 5. Individual changes of the acne score under metformin + lifestyle treatment

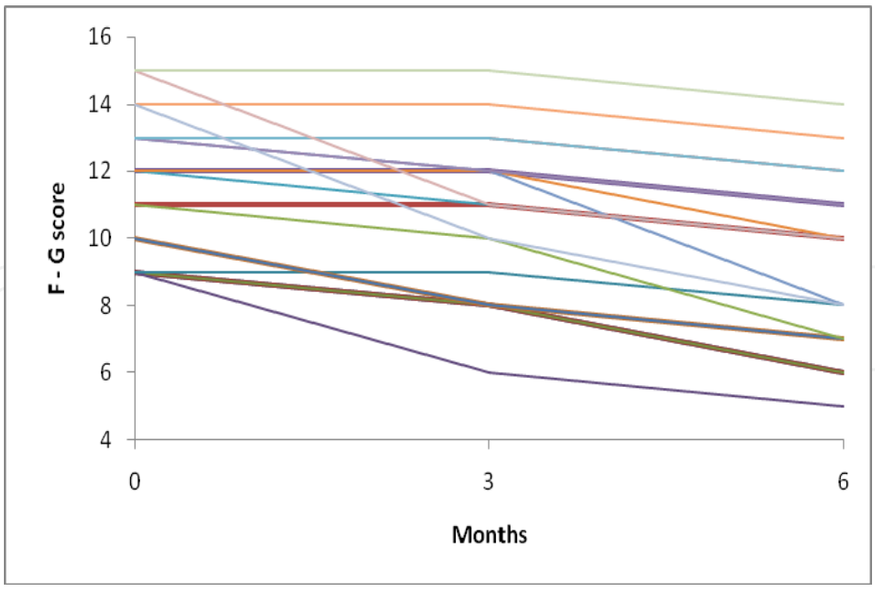


Fig. 6. Individual changes of the hirsutism score under metformin + lifestyle treatment

The favourable change in the body size indexes (BMI and W/H) has been the significant difference between the two treatment forms. In conclusion, the combined treatment can be regarded as superior to metformin monotherapy and therefore I have been offering this combined treatment (under the name of triple basal treatment) for all newly diagnosed patients and for long term use.

4.3 Additional treatment experience with metformin in PCOS

4.3.1 Recurrence of symptoms when treatment is stopped

Whatever treatment option is used its efficacy is limited; stopping treatment results in the renewal of the symptoms. It is most obvious for treatment approaches which have nothing to do with the pathophysiology of PCOS like hair removal, dermatological treatment for acne (local agents, antibiotics, and isotretinoin). After stopping the contraceptive pill, symptoms usually come back within a few months. This applies also to lifestyle changes and/or metformin.

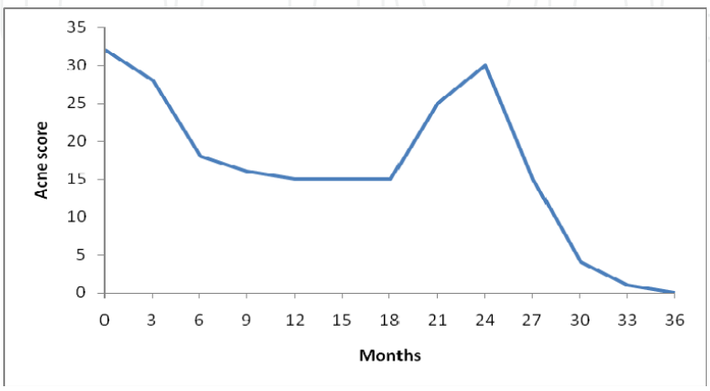


Fig. 7. Relapse of acne on stopping metformin; improvement on treatment restart

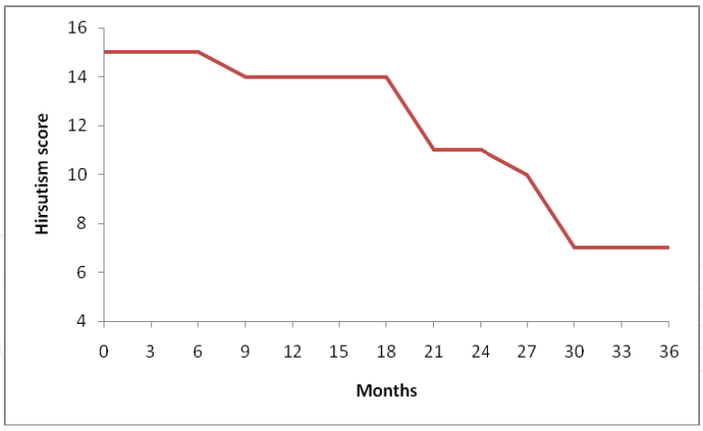


Fig. 8. Stagnation of hirsutism on stopping metformin; improvement on treatment restart

Fig. 7 and Fig. 8 show this happen in a patient who initially was responding favourably to long-term metformin treatment. After a while the improvement became unsatisfactory and by 21 months acne relapsed; by 24 months hirsutism stagnated. Then she acknowledged that she had stopped metformin taking months before. On restart of metformin both symptoms improved and one year later she was free from acne and hirsutism.

This case demonstrates that acne responds to metformin treatment within three months and worsens within three months after stopping treatment. The effect on hirsutism takes more months to show; and the beneficial effect still lasts for more months after stopping treatment.

This was not the only case of non-compliance with long-term treatment recommendations. More difficult to maintain is the adherence to lifestyle changes; especially the achievement of slimming in the overweight; like in other metabolic disturbances.

4.3.2 Improvement of fertility

Ten previously infertile women expressed the desire for having a baby before the initiation of metformin treatment. Metformin taking during pregnancy and breast feeding were discussed and encouraged; all consented.

Eleven conceptions happened among nine women while taking metformin; notably varying between the first and 29th month of treatment; the majority (seven conceptions) occurred after the 6th month of treatment. No gestational diabetes or other complications occurred during pregnancy. Two pregnancies ended with early loss. Nine healthy and normal weight babies were born in term and were breast fed for at least three months. All children showed normal development.

4.3.3 No recurrence of preeclampsia during the next pregnancy when taking metformin

One woman had five previous pregnancies with preeclampsia; one pregnancy was terminated because of the serious condition and one pregnancy was lost early. She presented with thyrotoxicosis caused by toxic multinodular goitre but PCOS could be

diagnosed after thyroidectomy and stabilisation with levothyroxine. She conceived during the first month of taking metformin and she continued metformin throughout this pregnancy upon my advice. Preeclampsia did not recur during this pregnancy and a healthy baby was born in term (Petrányi, 2005).

5. Discussion

I have seen many, mostly young women suffering from PCOS. Despite growing interest by the medical public and remarkable progress in research during the past two decades, the medical literature has not provided equivocal help how to treat PCOS. It is true that there is no evidence based universal treatment option but the advice found in textbooks, consensus statements and "experts' opinions" does not give clear guidance what to do in general with these patients. The treatment advice is usually grouped around the symptoms of PCOS but not against PCOS as a pathophysiological entity, which is a chronic, progressive disorder leading to irreversible damage through late complications.

Most publications deal with the fertility aspects of PCOS regardless of the other endocrine and metabolic aspects of the disease. Infertility is an just once important issue but does not affect all women with PCOS and even so only for a limited period while the other problems exist and cause harm throughout their life. Usually fertility studies are limited to six months – the time length beyond clomiphene stimulation (the advocated treatment of choice for PCOS related infertility) cannot be recommended (BNF 2010). Such studies are unsuitable to demonstrate whether other but longer treatment forms could not result in similar or better outcome and safety records (avoiding overstimulation, ensuring singleton pregnancies, prevention of macrosomia, gestational diabetes, preeclampsia etc). Longer treatment would of course require more patience from the patient but could give more chance to improve other pathological processes in favour of the general health of the woman. Fertility results are especially disappointing in obese women; they have only a 1:4 chance to give live birth using clomiphene stimulation (Legro et al., 2007). Assisted reproduction methods are complicated, very costly; and increase the risk of malformations (El-Chaar et al., 2009).

The majority of my patients have been suffering from disturbing symptoms of hyperandrogenism (almost all from acne and/or hirsutism, rarely from alopecia); and the metabolic consequences of insulin resistance (obesity, abdominal obesity). Irregular menses is also frequent among them but it is rarely the main complaint. Few in my clientele wanted to be pregnant urgently. According to my medical judgement these women need a long-term, uniform treatment (knowing that short-term attempts are unsuitable) which is simple, cheap, safe, effective for almost all features of PCOS, and can be combined with other treatment forms if the improvement is not satisfactory in certain symptoms.

Whatever is the main complaint of the patient, we will certainly find a long list of symptoms during the diagnostic procedure. Some of these are pre-requisites of the diagnosis like hyperandrogenism (that rarely exists without somatic signs); anovulation related symptoms (oligo-amenorrhoea, sub- or infertility); and the well-known metabolic consequences of PCOS cannot be left out: weight surplus that can be extreme, carbohydrate metabolic problems, lipid disorders – all these deserve treatment and/or preventive measures not to

develop into late cardiovascular problems. We should also think of the increased dangers during pregnancy of PCOS patients: pregnancy loss, gestational diabetes, macrosomia. These all should be discussed with the patient before offering any treatment.

My observations with metformin in PCOS proved to meet these requirements, and the combination with lifestyle changes helped also the weight problems, too. I cannot use placebo control; the patients come for effective treatment not for experimenting.

It is not only my opinion that PCOS should be dealt with like any other chronic metabolic disorders (diabetes, obesity or the metabolic syndrome), which all have insulin resistance in the background and end up with similar late complications. We have to think about the future of the patient, not only the actual complaints.

Insulin resistance is hypothesised in the background of PCOS even if there is no simple and precise method to prove it individually. Fortunately, the measurement of insulin during the oral glucose tolerance test is not included in the recommendations of the diagnostic procedure; this imprecise method may be used only for statistical comparisons of different populations or treatment forms. Treatments which increase insulin sensitivity have been proved useful in PCOS for all aspects of the disease. Reduction of obesity, increased physical activity (lifestyle changes), and insulin sensitizers – primarily, metformin has been found effective in treating PCOS. Other insulin sensitizers have also been tested but because of their controversy in diabetes and unknown safety in pregnancy they cannot be recommended in PCOS for the time being.

Metformin is not a miracle drug but it is cheap and safe, it can be administered without time limitation; and has very few contraindications in the relatively young and (in this respect) healthy female population suffering from PCOS. Its long-term and lasting metabolic benefits are well known from more than fifty years' clinical experience in diabetes and beyond; and can be used from the age of ten onwards (Bailey et al., 2007).

Metformin has not been licensed for PCOS in any country in the world. This prevents or restricts its prescription for PCOS in some countries. The patients' acceptance of metformin is overwhelming (Hillary et al., 2009); researchers complain that patients do not want to cease treatment, even for few months because they considered the treatment as effective (Muth at al., 2004).

Some patients experience gastrointestinal disturbance (bloating, abdominal pain, watery diarrhoea) or sometimes nausea, metallic taste while taking metformin. This can be avoided in the majority of cases by gradual dose increase. Only few patients cannot tolerate even one 500 mg tablet daily. I have no personal experience with the extended release formulation or the powdered form, which have been developed to overcome these unpleasant symptoms.

One side effect deserves real consideration: metformin may cause or exaggerate vitamin B_{12} deficiency; therefore annual test for B_{12} level is advisable for long-term metformin users to select who needs vitamin B_{12} supplementation.

Treatment experience with metformin in PCOS comes from relatively short studies but longer ones has also been published (Cheang et al., 2009, Oppelt et al., 2010). Detailed

discussion in favour of the use, including long-term use of metformin in PCOS for all possible aspects, indications, contraindications, and safety issues has also been published in growing numbers (Diamanti-Kandarakis et al., 2010; Nestler, 2008; Palomba et al., 2009) including metformin taking during pregnancy and lactation.

Vitamin D is probably the next candidate substance to be used widely in PCOS especially in the obese patients (Kosta et al., 2009). The high prevalence of depression in patients with PCOS (Dokras et al., 2011) also requires true consideration but these topics are not discussed in this chapter.

6. Conclusions

The patients want (and deserve) effective treatment. There is no evidence based general treatment option for all patients suffering from PCOS but the advice to treat the patients according to their main complaint (or symptomatically) is also not evidence based.

We'd better do our best using common sense; based on available evidence combined with our experience to provide benefit (Stuebe, 2011).

For the time being the combination of lifestyle changes and metformin treatment appears to be beneficial for the majority of patients suffering from PCOS by controlling their symptoms with potentials for preventing progression and most complications.

Until a sound and better solution is found, my medical advice to all newly diagnosed patients with PCOS from the time of diagnosis (even from puberty) is this:

- The patient diagnosed with PCOS should be fully informed about her medical condition; which of her symptoms are connected to this disorder, and what other ill conditions may develop by time.
- The patient should know that at present there is no final cure for the problem but a long-term, cheap and safe treatment combination may revert or attenuate most of the symptoms.
- The initial treatment (triple basal treatment) consists of long-term lifestyle changes: the increase of the daily physical activity and a low glycaemic index diet (with calorie restriction for the overweight to normalize body weight) and taking metformin tablets.
- Metformin should be started stepwise. The starting dose is one 500 mg tablet after dinner; increased to twice daily (after breakfast – after dinner) after one week and to three times daily (after breakfast, after lunch and after dinner) from the third week onwards. Eventual side-effects must be consulted with the doctor; any dose increase should be postponed until the dissolution of the disturbing phenomena.
- If certain symptoms do not improve satisfactorily in suitable time (depending on the nature of the symptom; for example, acne in six months, and hirsutism in one year; stagnation of weight surplus; oligo-amenorrhoea continues, infertility) the following options should be considered:
  - Revision of diagnosis
  - Compliance with treatment recommendations
  - Further calorie restriction in the overweight with or without increased dose of metformin (up to daily 2000-2500 mg)
  - Addition of other medication depending on the nature of the problem:

- Anti-androgenic contraceptives, spironolactone, flutamide
- Dermatological treatment for acne (antibiotics, isotretinoin)
- Ovarian stimulation and/or other fertility interventions upon consultation with the fertility specialist.

- The triple basal treatment may help the patient conceive. Effective contraceptive methods should be discussed with all those who do not want become pregnant or take teratogenic medication (anti-androgens, isotretinoin) before commencing treatment.
- The patient should be reviewed for symptoms and adherence to the therapeutic advice every three months for at least one year and thereafter at least twice yearly if the condition improves satisfactorily.
- Annual monitoring of kidney and liver function, lipid profile, glycosylated haemoglobin, vitamin B_{12} levels is mandatory.

This proposal remains a working hypothesis until properly planned, long-term clinical studies find a better alternative.

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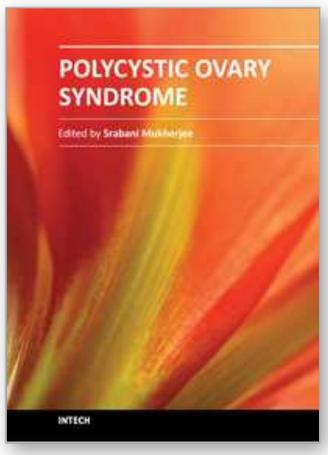
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Brought into the limelight many decades ago, Polycystic Ovary Syndrome (PCOS) is still, to date, surrounded by controversy and mystery. Much attention has been attracted to various topics associated with PCOS research and there has been a healthy advance towards bettering the understanding of the many implications of this complex syndrome. A variety of topics have been dealt with by a panel of authors and compiled in this book. They span methods of diagnosis, reproductive anomalies, metabolic consequences, psychological mindset and ameliorative effects of various lifestyle and medical management options. These books are designed to update all associated professionals on the recent developments in this fast-growing field and to encourage further research into this thought-provoking subject.

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