Although the aetiology of polycystic ovary syndrome (PCOS) is still not known and the search for causative genes is proving elusive, it is generally agreed that hyperandrogenism is at the heart of the syndrome. Here, it is proposed that excess androgens are the root cause of PCOS starting from their influence on the female fetus in programming gene expression, producing the characteristic signs and symptoms which are then exacerbated by a propagation of excess ovarian androgen production from multiple small follicles, anovulation and insulin resistance in the reproductive life-span, thus setting up a vicious perpetual circle of androgen excess. This opinion paper, rather than being a full-scale review, is intentionally biased in support of this hypothesis that androgen excess is the ‘root of all evil’ in PCOS; in the hope that its acceptance could lead to more direct treatment of the syndrome in all its facets rather than the symptomatic treatment of side effects of androgen excess that we are addressing today.

Key words: androgens / polycystic ovary syndrome / ovary / anovulation

Introduction

It is now more than 70 years since the polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal (1935) and we are still searching for the true pathogenesis of this enigmatic syndrome. Although the majority of cases are familial (Legro et al., 1998, 2002; Vink et al., 2006), genetic studies have failed so far to identify the specific genes involved. Many candidate genes have been proposed, investigated and, usually, later discarded when larger studies were completed. It is hoped that, in the future, microarray analysis will eventually identify the genes that are, probably, overexpressed. Whatever the genes involved, excess androgens seem to be the root cause of PCOS and, in this article, a model is constructed to demonstrate that excess androgens, from intrauterine development to the expression of clinical symptoms, form a vicious circle responsible for every stage in the pathophysiology of PCOS and the source of all symptoms and signs.

Perhaps one of the most encouraging signs of progress in recent years has been the emergence of the hypothesis of the developmental origins of PCOS (Abbott et al., 1997), initiated by the finding that the exposure of the female fetus to excess androgens in utero induces a PCOS in animal models. From intrauterine life and through adult life, the key role of excess androgens provides an explanation for every step in the pathophysiology, continuation and exacerbation of PCOS—a vicious, perpetual circle of androgen excess.

Here, I will discuss my opinion of the developmental hypothesis and the influence of excess androgens on polycystic ovary morphology, anovulation, symptomatology and late sequelae. Rather than being a full-scale review, data are presented to strengthen this hypothesis.

The developmental origins of PCOS

There is now little doubt that the intrauterine environment can have an influence on the programming of gene action in adult life (Gluckman et al., 2008). Specifically, regarding the influence of testosterone (T) on the female fetus, mounting evidence clearly links prenatal maternal T concentrations to gender role behaviour in pre-school girls, which is dose-related (Hines et al., 2002). Furthermore, girls exposed to high levels of T prenatally due to congenital adrenal hyperplasia (CAH) show distinct masculine type behavioural traits (Berenbaum and Hines, 1992). These developmental influences of T on brain and behaviour have also been shown to correlate with T concentrations in amniotic fluid (Grimshaw et al., 1995). It would then seem that, in the extreme, prenatal androgen levels may lead to virilization of the female fetus, whereas defeminization of sexual function provides evidence of the influence of androgen levels on brain function.

Clinical evidence of the property of fetal androgen excess to re-programme multiple organ systems is seen in the increased prevalence of PCOS in women with fetal androgen excess disorders such as classical CAH (21-hydroxylase deficiency) and congenital adrenal virilizing tumours (Barnes et al., 1994; Phocas et al., 1995; Merke and Cutler, 2001; Stikkelbroeck et al., 2003). Particularly illustrative is
the case of a female fetus with an androgen-secreting tumour removed shortly after birth, who developed PCOS in adulthood (Barnes et al., 1994).

Abbott and colleagues, using prenatally androgenized female rhesus monkeys, in a remarkable series of experiments, have induced phenotypic mimics of PCOS signs and symptoms (Abbott et al., 1997, 1998, 2002; Dumesic et al., 2005). Mothers were injected with T starting at various gestational ages inducing circulating levels of T in the female fetus equivalent to those found in fetal males (Abbott et al., 2008). The timing of the start of androgenization is important as early prenatal injection would influence the early stages of differentiation of reproductive and metabolic organ systems, whereas late treatment–inducing androgen excess would be expected to influence functional maturation (Abbott et al., 2005). Both early and late androgenized mothers produced female offspring exhibiting distinct signs of PCOS. The phenotype of the PCOS differed according to the timing of the start of androgenization. Ovulatory dysfunction, manifested by oligo-amenorrhoea, was common to both phenotypes. Compared with controls, androgenized mothers produced female offspring with ovarian morphology distinctly resembling that of PCOS and an increased ovarian volume. In addition, leutinizing hormone (LH) hypersecretion was found exclusively in early treated monkeys indicating that the programming of hypothalamic action is compounded at this stage of pregnancy. This LH hypersecretion is thought to be due to an increase in pituitary responsiveness to GnRH, increased priming of the pituitary, maybe as a result of decreased ovarian hormone negative feedback regulation (Abbott et al., 2005; Sarma et al., 2005). Remarkably, early prenatally treated females had impaired insulin secretion, whereas late-treated females had insulin insensitivity and increasing adiposity (Eisner et al., 2000). This is further convincing evidence that ‘true’ PCOS can be generated by prenatal androgenization and provides a very strong basis for the belief that PCOS is ‘born’ in utero by the influence of androgen excess on gene expression in adolescent and adult life. Very similar results, a simulation of the reproductive phenotype of women with PCOS, have been produced in prenatal, testosterone-treated sheep (Padmanabhan et al., 2006).

The current hypothesis of a developmental origin of PCOS suggests an epigenetic phenomenon induced by fetal androgen excess. One possible pathway could be the enhancement of transforming growth factor (TGF)-β-regulated extracellular matrix protein production which would disrupt ovarian differentiation causing a polycystic phenotype (Abbott and Dumesic, 2009). This possibility is particularly attractive as androgen exposure increases the expression of these proteins (Jiang and Wang, 2003) and, additionally, other TGF-β family members, including anti-Mullerian hormone (AMH), regulate the expression of CYP17, the main androgen-producing enzyme (Lauring et al., 2002).

Many questions remain to be answered regarding the proposed developmental aetiology of PCOS. Although maternal testosterone would not normally be expected to cross the placenta, experimentally induced maternal hyperandrogenism induces fetal androgen excess. Pregnant women with PCOS have elevated serum levels of total and free testosterone (Sir-Petermann et al., 2002). Moreover, fetal testosterone concentrations correlate positively with maternal T concentrations (Gitau et al., 2005). Thus, pregnant women with PCOS may be delivering their androgen excess to the female fetus. This correlates with the well-known familial traits of PCOS (Vink et al., 2006). Experimentally induced fetal hyperandrogenism in turn induces increased fetal adrenal androgen output, possibly due to up-regulation of 17,20 lyase activity (Zhou et al., 2005). In addition, fetal plasma testosterone correlates positively with fetal cortisol concentrations (Gitau et al., 2005). These findings, implicating the role of the fetal adrenals in excess androgen production, may be important as the fetal ovaries have been thought to be almost completely inactive as far as hormone production is concerned. However, the fetal ovaries may not be as inactive as previously thought as the transient expression of the androgen biosynthetic enzyme CYP17 has been demonstrated in human fetal ovaries at mid-gestation (Cole et al., 2006). Recent data in a sheep model have suggested that the aberrant folliculogenesis in the polycystic ovary, rather than being caused by a direct effect of excess testosterone, may be due to its metabolism to estradiol (Stecker et al., 2007). Alternatively, fetal androgen excess may be entirely from a fetal source. The fetus may well have inherited the same hyperandrogenism-producing genes from the mother.

Whatever the source of the female fetal androgen excess, we now have a very plausible hypothesis that PCOS is programmed in utero. Extrapolation of this programing into adolescent and adult life may produce any or all of a number of consequences, all of which propagate further excess production of androgens (Fig. 1). First, the progression of primordial to primary and small antral follicles would be accelerated, and the rate of atresia of small antral follicles reduced (Hiller et al., 1997; Weil et al., 1999; Webber et al., 2003). Secondly, an upgrading of activity of androgen-producing enzymes in theca cells (P450-17α, lyase 17,20,17-hydroxylase) would be produced. Primary cultures of theca cells isolated from polycystic ovaries demonstrate greatly increased production of androgens (Gilling-Smith et al., 1994). Thirdly, increased secretion of LH, the physiological stimulus of androgen production, will exacerbate its effect. Fourthly, increased secretion of insulin will also encourage excess androgen production. One possible outcome of increased insulin output is an increase in utilization of the intracellular signalling pathway employing serine phosphorylation which, in turn, would increase the androgen-producing power of the enzyme lyase 17,20. Hyperinsulinaemia, whether due to insulin resistance or pancreatic β cell dysfunction, will also increase the concentrations of free (unbound, biologically active) testosterone by directly reducing the production of sex hormone-binding globulin (SHBG) in the liver.
In summary, the hypothetical consequences of exposure to excess androgens in utero would all encourage excess androgen production in later life.

**Polycystic ovary morphology**

The characteristic morphology of a polycystic ovary, as defined by The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004), consists of an ovary containing 12 or more follicles, 2–9 mm in diameter and/or an ovarian volume of 10 ml or more. These are the very features produced by exposing the female fetus of Rhesus monkeys to high concentrations of testosterone in utero (Abbott et al., 2005). The injection of androgens into young rodents has also produced typical polycystic changes in a hitherto normal ovary (Belosevsky et al., 2004). Painstaking work by Webber et al. (2003) has demonstrated a distinct difference in the proportion of pre-antral to primordial follicles of women with PCOS compared with those with no PCOS. Women with PCOS had six times the density of pre-antral follicles and a reciprocal decrease in the density of primordial follicles compared with the ovaries of normal women (Webber et al., 2003). This is explained by an acceleration of the normal progression of primordial to primary and early antral follicles and/or a reduced rate of atresia of early antral follicles. Excess androgens are the probable cause of both these phenomena (Fig. 2). In a series of elegant experiments, androgens have been shown capable of accelerating the progression of early (non-gonadotrophin dependent) follicle development (Hillier et al., 1997; Vendola et al., 1998; Weil et al., 1999). Furthermore, androgens have been demonstrated to increase sensitivity to FSH by increasing FSH receptor numbers in granulosa cells (Hillier and Tetsukara, 1997). In PCOS, small antral follicles arrest in development. A putative mechanism is that the production of AMH is greatly increased due to the large numbers of small antral follicles, the source of AMH (Laven et al., 2004; Pigny et al., 2006). The action of FSH in promoting follicular growth is counteracted by AMH (Pigny et al., 2003; Weenen et al., 2004). This reduction of the capability of FSH to promote further follicular growth may be compounded by the increased concentrations, found in women with PCOS, of epidermal growth factor, transformin growth factor alpha and follistatin (for review see Homburg, 1998). Reduced concentrations of growth differentiating factor-9 have also been implicated (Teixeira Filho et al., 2002).

Small antral follicles that do not grow would normally be expected to become atretic. This process does occur in PCOS but, apparently, at a much slower rate than in the normal ovary enabling these small antral follicles a longer lease of life. The characteristic response of the polycystic ovary to exogenous treatment with FSH makes it palpably obvious that these small antral follicles are viable and responsive. The abundance of anti-apoptotic factors (e.g. insulin and BCL-2) and relative lack of apoptotic factors (e.g. BCL-1, etc.) in women with PCOS may provide explanations and these have been detailed in a review (Amsterdam and Homburg, 1998).

In summary, the characteristic morphology of the polycystic ovary can be largely explained by the influence of excess androgens initiating and propagating the chain of events that may be described as being at the very heart of the syndrome.

**Anovulation**

Anovulation or oligo-ovulation is a very common presenting symptom of PCOS. Irregularity of menstruation, amenorrhoea or oligomenorrhoea, is first encountered in adolescence or present in the infertility clinic. The root cause of anovulation in PCOS is now thought to be associated with the multiple small follicles characteristic of the polycystic ovary (Jonard and Dewailly, 2004) (Fig. 3) and significant abnormalities in the very earliest stages of folliculogenesis (Franks et al., 2008). As described above, excess androgens encourage the development of pre-antral and small antral follicles from their primordial and primary stages. Although a relative lack of AMH may contribute to the acceleration of the primordial to small pre-antral stage of follicular development (Stubbs et al., 2005), the vastly increased number of small antral follicles in the polycystic ovary, compared with the normal ovary, produces AMH in significantly increased concentrations (Laven et al., 2004; Pigny et al., 2006). Although the function of AMH in the adult is not fully understood, its property in counteracting the actions of FSH has been well documented (Pigny et al., 2003; Weenen et al., 2004). The increased concentrations of AMH found in PCOS from the multiple small follicles may be a causal factor for anovulation.

A simpler explanation for the apparent failure of FSH to enable the development of a dominant follicle is the increased production of estradiol, by the large number of small antral follicles, invoking the
negative feedback mechanism at the hypothalamic/pituitary level and reducing FSH concentrations to below threshold levels of follicle sensitivity.

Further indirect evidence of the role of the increased number of small antral follicles as a prime factor in the aetiology of anovulatory PCOS stems from the fact that following the reduction of numbers of follicles by wedge resection, laparoscopic drilling or, indeed, reaching the age of 40 or older (Elting et al., 2003), regular menstruation and ovulation are often restored. All these events are followed by a reduction in androgen concentrations. The ability of the anti-androgen medication flutamide to restore ovulation in anovulatory PCOS women has been clearly demonstrated (DeLeo et al., 1998), along with a restoration of sensitivity of the GnRH pulse generator to inhibition by estradiol and progesterone (Eagleson et al., 2000). In addition to the continuing disadvantageous action of excess androgens on ovarian function, it will be remembered that androgens are the probable initiators of the multifollicular development in the first place.

Hyperinsulinemia is strongly associated with irregularity of ovulation and, in turn, with both high androgen concentrations and multiple small follicle development. However, this association may be due to the propensity of insulin to increase ovarian androgen production and exacerbate already established pathological features, rather than a direct factor. Insulin sensitizing agents, in particular, metformin, have proved capable of restoring regular ovulation in women with PCOS. Although it is the common view that metformin achieves this by reducing insulin resistance and thereby insulin levels, metformin has also been shown to directly inhibit ovarian androgen production (Atitia et al., 2001; Mansfield et al., 2003; Misugi et al., 2006) and has improved ovulation rates in women with PCOS but no demonstrable insulin resistance/hyperinsulinemia (Liu et al., 2006) nor changes in fasting glucose concentrations, fasting insulin or insulin responses to a glucose challenge after 14 weeks of therapy (Fleming et al., 2002). In addition, evidence that androgens can induce hyperinsulinemia (Beloosesky et al., 2004; Abbott et al., 2005; Manneras et al., 2007; Perello et al., 2007) as well as the well-documented influence of hyperinsulinemia in exaggerating androgen excess lends credence to the hypothesis that hyperinsulinemia, from intrauterine hyperglycæmia or adult adiposity-dependent insulin resistance, is a ‘second-hit’ following the ‘first-hit’ of androgen excess disrupting hypothalamic sensitivity to ovarian steroid negative feedback (Abbott and Dumesic, 2009).

Whatever the order in this ‘hit-parade’, there is clear evidence of a self-perpetuating ‘vicious circle’ of androgens–insulin–androgens which can be broken by either anti-androgen or insulin-lowering means.

An additional consideration is that the lack of progesterone in the circulation in PCOS is likely to induce increased secretion of LH which, in turn, will encourage further production of androgens, perpetuating the vicious circle of androgen action in this syndrome.

**Clinical expressions of hyperandrogenism**

Hirsutism, persistent acne and seborrhoea and, in the extreme, alopecia are all undisputed clinical expressions of hyperandrogenaemia. High androgen concentrations have a deleterious effect on the development, growth and activity of the sebaceous glands and hair follicles. Testosterone is a strong androgen that binds to intracellular androgen receptors in the skin and is converted by 5α reductase to dihydrotestosterone (DHT), which has an even more potent androgen effects on the hair follicle and sebaceous gland (Fig. 4). Although acne and hirsutism are both androgen-driven conditions, both involving the single morphological entity of the pilosebaceous unit and quite often presenting simultaneously, especially in PCOS, they do not always appear concomitantly. It was hypothesized, therefore, that there may be some dichotomy in the final pathway of endocrine pathogenesis and, indeed, it was found that DHT is further reduced to 3α-androstanediol and its glucuronideride only in hirsute patients but not in acne patients (Toscano et al., 1993). It was concluded that DHT may undergo different metabolic pathways at the skin level, supporting the hypothesis that the two clinical entities may be expressions of the different metabolic fate of DHT itself.

Reduction of androgen concentrations enables amelioration and even disappearance of these symptoms whether accomplished by weight loss, specific anti-androgen medications (e.g. flutamide, finasteride, cyproterone acetate or spironolactone) or even by combined oral contraceptives or metformin (Homburg, 2005).

**Long-term sequelae of PCOS**

It is now well established that women with PCOS are at increased risk for developing diabetes mellitus, glucose intolerance, hypertension, hyperlipidaemia, the metabolic syndrome and cardiovascular disease. Although the high prevalence of insulin resistance in women with PCOS, especially the obese, has been largely held accountable for these long-term sequelae, there is now emerging evidence for a role of androgen excess in these processes which is more than merely permissive (Diamanti-Kandarakis et al., 2007). There is a strong association between hyperandrogenaemia, an increased free androgen index, and the metabolic syndrome in premenopausal women with or without full-blown PCOS (Korhonen et al., 2003; Apridonize et al., 2005; Cussons et al., 2008). Moreover, among obese hyperandrogenic adolescents, hyperandrogenaemia was found to be a significant predictor of the metabolic syndrome, independent of obesity and insulin resistance (Coviello et al., 2006). A recent study to analyse the risk of cardiovascular events in 390 post-menopausal women, involving angiographic evaluation for suspected ischaemia...
Androgen excess

↓

Visceral fat

Lipolysis

Insulin sensitivity

↓

HDL

LDL

?Direct vascular action

?Renal hypertension

↓

Atherosclerosis – CV morbidity

Figure 5 The putative role of androgen excess in the increased cardiovascular morbidity associated with PCOS.

(Shaw et al., 2008), identified 104 women with PCOS as defined by a premenopausal history of irregular menses and current biochemical evidence of hyperandrogenaemia. As in previous reports, this study also demonstrated that women with clinical features of PCOS were more often diabetic, obese, had more angiographic coronary artery disease and a lower cumulative 5-year event-free survival compared with their non-PCOS counterparts. However, a fascinating finding was that the decrement of cardiovascular event-free survival correlated with increasing free testosterone levels in post-menopausal women and that this relationship was independent of insulin resistance indices, waist circumference and the presence of diabetes. This provides convincing evidence that long-term premenopausal androgen excess may be an independent cardiovascular risk factor with clinical consequences (Shaw et al., 2008).

The adverse effects of androgen excess may be manifested in several systems (Fig. 5). Androgen receptors are present in adipocytes, and testosterone has an anti-lipolytic effect on abdominal subcutaneous preadipocytes (Andersson et al., 2002) apparently through selective inhibition of catecholamine-induced lipolysis (Faulds et al., 2003). Androgen excess would therefore be expected to produce fat accumulation and the abdominal obesity commonly found in PCOS, according to the above two studies of lean women with PCOS. However, in obese PCOS women, the androgen action in adipocytes may differ from that observed in lean women with PCOS, as a decrease in androgens induced by a GnRH agonist in obese PCOS was shown to produce increases in visceral fat (Dumesic et al., 1998). Further, bioactive testosterone levels in obese PCOS correlate negatively with lipoprotein lipase activity and positively with catecholamine-stimulated lipolysis in subcutaneous abdominal adipocytes (Rebuffe-Scrive et al., 1989).

Androgen excess is known to lower circulating high-density lipoprotein and increase low-density lipoprotein cholesterol (Diamanti-Kandarakis et al., 2007). Conversely, flutamide, an androgen receptor blocker, is capable of ameliorating this dyslipidaemia (Diamanti-Kandarakis et al., 1998). This adverse effect of androgen excess is obviously pro-atherogenic.

Insulin resistance, exacerbated by obesity, undoubtedly plays the major role in the metabolic abnormalities associated with PCOS. There is also little doubt that hyperinsulinaemia increases ovarian androgen production and circulating concentrations of free, biologically available testosterone by decreasing hepatic production of SHBG. However, the relationship between androgens and insulin may well be reciprocal. The androgenization of pre- and post-pubertal rats produces an impairment of insulin sensitivity accompanied by increased adipocyte size, increased subcutaneous and visceral fat depots and a disturbed serum lipid profile (Manneras et al., 2007; Perello et al., 2007) and hyperinsulinaemia (Beloosesky et al., 2004). Even more ‘incriminating’ evidence that androgens can induce hyperinsulinaemia (and not just vice versa) comes from the prenatally androgenized female rhesus monkey studies (Abbott et al., 2005). Females who had been exposed to androgen excess during gestation demonstrated insulin resistance, abdominal obesity and impaired insulin response to glucose and hyperlipidaemia. This ‘chicken or oocyte’ situation is further complicated by the fact that androgen excess can directly perpetuate insulin resistance (Diamanti-Kandarakis et al., 2007) by acting directly on the insulin signalling cascade inhibiting muscle glycogen synthase activity and by increasing the number of less insulin-sensitive type IIb skeletal muscle fibres (Holmang et al., 1992; Rincon et al., 1996; Corbould, 2007). Finally, reduction in androgen concentrations in women with PCOS by a GnRH agonist was shown to be accompanied by an improved insulin sensitivity (Dahlgren et al., 1998).

Although insulin resistance is the most obvious mechanism of vascular dysfunction in PCOS, young women with PCOS without other identifiable cardiovascular risk factors have been found to have functional and structural vascular dysfunction (Orio et al., 2004). Furthermore, in young women with PCOS, androgen excess was shown to be the major independent determinant of increased carotid intima media thickness (Luque-Ramirez et al., 2007).

Although obesity is a major factor in causing hypertension in PCOS women, after adjusting for this and other possible factors, bioavailable testosterone levels have been directly associated with elevated blood pressure (Chen et al., 2007). Stimulation of the renal renin–angiotensin–aldosterone system seems to be the mechanism of this androgen action.

Sympathetic nerve activity to the muscle vascular bed is increased in PCOS and this also may contribute to the increased cardiovascular risk of this syndrome (Sverrisdottir et al., 2008). Of particular interest was the fact that serum testosterone concentration was found to be the strongest independent predictor of high sympathetic nerve activity in PCOS.

There is well-documented evidence for a strong association between obstructive sleep apnoea and cardiovascular disease. Women with PCOS were found to be 30 times more likely to suffer from sleep disordered breathing and reported significantly more daytime sleepiness than controls (Vgontzas et al., 2001). In this study, insulin resistance was found to play the principal role but a further study (Fogel et al., 2001) on obese PCOS women also found a correlation between sleep apnoea and total and unbound testosterone concentrations.

When discussing these latter studies and considering the relative contributions of insulin and androgens, the absence of statistical association with insulin is not necessarily the proof of lack of biological association or less association than with androgens. It should be remembered that circulating levels of insulin have not only day-to-day but also minute-to-minute variations, that insulin is secreted in bursts...
every 11 min and has a half-life of 4–5 min (Mao et al., 2004), whereas androgens and SHBG are relatively stable throughout the day. Thus, biological, rather than statistical, associations are difficult to establish and limit interpretation of epidemiological data on the relative contribution of androgens and insulin.

Closing the androgen circle

If the story of exposure to androgen excess starts during intrauterine life of the female fetus and is perpetuated and maintained by a series of chain reactions as illustrated here (and in Fig. 6), then since PCOS is clearly, in the main, a familial syndrome, the pregnant woman with PCOS closes the androgen circle by either passing on her ‘PCOS genes’ or exposing her female fetus to androgen excess, so starting another cycle. Acceptance of this concept could lead to more direct treatment of PCOS in all its facets, rather than the piecemeal, symptomatic treatment, mostly of ‘side effects’ of androgen excess that we are addressing today.

References


Attia GR, Rainey WE, Carr BR. Metformin directly inhibits androgen production in human thecal cells. Fertil Steril 2001;76:517–524.


Chen MJ, Yang WS, Yang JH, Ho CN, Ho HY, Yang YS. Relationship between androgen levels and blood pressure in young women with polycystic ovary syndrome. Hypertension 2001;41:1442–1447.

Cole B, Henslenger K, Maciel GA, Chang RJ, Erickson GF. Human fetal ovary development involves the spatiotemporal expression of PCOS with androgen excess playing a central role.


Coviello AD, Legro RS, Dunai A. Adolescent girls with polycystic ovary syndrome have an increased risk of the metabolic syndrome associated with increasing androgen levels independent of obesity and insulin resistance. J Clin Endocrinol Metab 2006;91:3654–3661.


Elting MW, Kwee J, Korsen Tj, Rekers-Momborg LT, Schoemaker J. Aging women with polycystic ovary syndrome who achieve regular menstrual cycles have a smaller follicle cohort than those who continue to have irregular cycles. Fertil Steril 2003;79:1114–1160.


