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Review Article

Mouse models to study polycystic ovary syndrome: A possible link between metabolism and ovarian function?

E. Leonie A.F. van Houten, Jenny A. Visser *

Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common cause of female infertility affecting 6–8% of women worldwide. PCOS is characterized by two of the following three criteria: clinical or biochemical hyperandrogenism, oligo- or amenorrhea, and polycystic ovaries (PCO). In addition, women with PCOS are often obese and insulin resistant, and are at risk for type 2 diabetes and cardiovascular disease. The etiology of PCOS remains unknown. Therefore, several animal models for PCOS have been generated to gain insight into the etiology and development of the PCOS-associated phenotypes. Androgens are considered the main culprit of PCOS, and therefore, androgenization of animals is the most frequently used approach to induce symptoms that resemble PCOS. Prenatal or prepubertal androgen treatment results in many characteristics of human PCOS, including anovulation, cyst-like follicles, elevated luteinizing hormone (LH) levels, increased adiposity, and insulin insensitivity. However, PCOS has a heterogeneous presentation, and therefore it is difficult to generate a model that exactly reproduces the reproductive and metabolic phenotypes observed in women with PCOS. In this review, we discuss several mouse models for PCOS, and compare the reproductive and/or metabolic phenotypes observed in several androgen-induced models as well as in several genetic models.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women in their reproductive years. It affects about 6–8% of women worldwide [1]. Based on the Rotterdam Criteria, PCOS is characterized by two of the three following criteria: clinical or biochemical hyperandrogenism, oligo- or amenorrhea, and polycystic ovaries (PCO) [2]. In addition, PCOS patients frequently have metabolic disturbances which closely resemble the metabolic syndrome. The metabolic syndrome is a cluster of risk factors for the development of cardiovascular diseases and comprises: diabetes and prediabetes, abdominal adiposity, high cholesterol and high blood

* *Corresponding author at*: Department of Internal Medicine, Room Ee532, Erasmus MC, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 7043577; fax: +31 10 7044862.
E-mail address: j.visser@erasmusmc.nl (J.A. Visser).

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pressure according to the National Cholesterol Education Adult Treatment Program [3]. Indeed, 38–88% (depending on the study) of the PCOS women are obese and 50–70% are insulin resistant [4–8]. As a consequence, PCOS is associated with long term health risks, such as a type 2 diabetes and cardiovascular disease [9].

PCOS may have its onset already before or during puberty [10,11]. Studies have suggested that girls with PCOS have an increased gonadotropin releasing hormone (GnRH) pulse frequency leading to excess luteinizing hormone (LH) secretion [12]. Combined with the premature acquisition of LH receptor expression by growing follicles at too early stages, this in turn causes increased ovarian androgen production [12]. However, also hyperinsulinemia may contribute to the elevated androgen production since insulin stimulates the steroidogenic response of the ovary in synergy with LH [13]. Premature androgen production may explain the arrested antral follicle development in PCOS [14]. In addition, also an intrinsic abnormal ovarian environment has been suggested to contribute to the follicular arrest [14], because PCOS patients seem to have a higher FSH threshold. For instance, anti-Müllerian hormone (AMH) has been proposed as a local inhibitor of FSH sensitivity, since serum and expression levels of AMH are elevated in PCOS [15]. However, is it is difficult to distinguish cause and effect in PCOS, since a block in folliculogenesis itself may lead to increased production of local inhibitors.

Besides the effects on folliculogenesis, androgens also have multiple effects on adipocyte function. In vitro experiments using adipocytes from healthy premenopausal women revealed impaired insulin-mediated glucose uptake when adipocytes were exposed to testosterone [16]. Furthermore, androgen exposure during prenatal and/or neonatal life is thought to have a programming effect on adipose tissue, causing increased adiposity and impaired glucose tolerance as seen in animal models [17–19]. In women with PCOS hyperandrogenism is associated with the android body fat distribution, characterized by accumulation of fat mainly in abdominal depots [20]. Interestingly, the presence of hyperinsulinemia is independent of obesity [21], and therefore may be an independent factor in PCOS. Whether hyperandrogenism causes hyperinsulinemia or vice versa hyperinsulinemia causes hyperandrogenism remains to be determined, and both may be possible [22]. In addition, it is unknown whether, besides androgens, other factors secreted by the increased follicle pool contribute to the metabolic phenotype.

So far the etiology of PCOS is still unknown and this is complicated by the fact that PCOS is a complex genetic disease and has a heterogeneous presentation as discussed above. Therefore, animal models of PCOS may help to better understand the development of PCOS-related pathologies. Furthermore, they may contribute to our knowledge about the long term health consequences of PCOS. An ideal animal model should replicate most common clinical features of PCOS, i.e. the reproductive and metabolic abnormalities. Naturally occurring animal models for PCOS are unknown. However, in the past decade several animal models of PCOS have been developed. Most of these models are based on hyperandrogenism induced pre- or postnatally or during adulthood, because it is generally agreed that elevated androgens are the main culprit of PCOS. Although hyperinsulinemia is known to be of importance in the etiology of PCOS, previous studies in rats showed that experimentally high insulin levels are not sufficient to induce PCOS [23]. Possibly, the application of insulin to induce PCOS in animal models has therefore not been further explored. Prenatally induced hyperandrogenism in non-human primates and sheep has resulted in the most suitable animal model, displaying many of the characteristics of PCOS, such as cystic ovaries, enhanced androgen production by theca cells, increased visceral fat mass, and insulin resistance [18,24–27]. Yet, these models have the disadvantage that they are quite expensive and have a relatively long reproductive lifespan and gestational cycle. Therefore, many researchers, including ourselves, use rodents as a model of PCOS, since rodents have the advantage of being affordable, having a shorter reproductive lifespan, easier handling, and having stable genetic backgrounds (reviewed in [28,29]). However, rodents are poly-ovulatory while women are mono-ovulatory, suggesting that, despite the similarities in the hypothalamus–pituitary–gonadal axis, the FSH-dependent follicle selection process in mice differs from that in women. Likewise, although the initial stages of follicular growth from primordial to preantral stage seem comparable between both species, differences in regulation by intra-ovarian growth factors cannot be ruled out. Finally, there are marked differences in the timing of onset of folliculogenesis in mice and women. While assembly of the primordial follicle pool and initiation of follicle growth already occur during the later stages of fetal development in human, these processes occur only during the early postnatal period in mice [30,31]. Thus, results obtained from mice may not be directly translated to women. Nevertheless, the use of mice provides the possibility of genetic manipulation and availability of various transgenic lines already generated. In this review several hormonally-induced and transgenic mouse models of PCOS will be discussed.

2. Induced hyperandrogenism in mouse models of PCOS

The excess of androgens is considered the main cause of PCOS. Therefore, not surprisingly, most PCOS animal models have been induced with androgens. Most commonly used androgens in mouse models of PCOS are testosterone, dehydroepiandrosterone (DHEA) and dihydrotestosterone (DHT). However, also estrogen treatment has been applied. The timing of androgen exposure varies widely, starting as early as prenatal exposure. But also neonatal, prepubertal and adult androgenization of mice has been applied. Since clinical symptoms of PCOS often start during puberty [11], treatment of mice before adulthood will likely more closely resemble PCOS in human.

2.1. *Dihydrotestosterone*

Treatment with DHT is the most frequently used approach to induce a PCOS-like phenotype in rodents. This can be explained by the fact that DHT is a non-aromatizable androgen