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Camille Vatier, Sophie Christin-Maitre, Corinne Vigouroux

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Rôle de l'insulino-résistance sur la fertilité – focus sur le syndrome des ovaires polykystiques

Camille Vatier, Sophie Christin-Maitre, Corinne Vigouroux

Assistance Publique–Hôpitaux de Paris, Hôpital Saint–Antoine, Centre National de Référence des Pathologies Rares de l'Insulino–Sécrétion et de l'Insulino–Sensibilité (PRISIS) et Centre National de Référence des Maladies Endocriniennes Rares de la Croissance et du Développement (CRMERCD), Service d'Endocrinologie, Diabétologie et Endocrinologie de la Reproduction, Paris, France

Sorbonne Université, Inserm UMR_S 938, Centre de Recherche Saint–Antoine, Institut Hospitalo–Universitaire de Cardio–métabolisme et Nutrition (ICAN), Paris, France

Corresponding author : Corinne Vigouroux, Faculté de Médecine Sorbonne Université, 27 rue Chaligny, 75571 Paris. Email : corinne.vigouroux@inserm.fr

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Several lines of evidence show that gonadal functions and insulin sensitivity display multifaceted relationships, which extend far beyond the well-known association between polycystic ovary syndrome (PCOS), obesity, and metabolic syndrome.

In this brief review, we will summarize the main findings showing the pathophysiological role of insulin resistance in impairing reproductive functions. Extreme phenotypes of severe insulin resistance, due to primary defects in insulin receptor or to lipodystrophy syndromes, provide unique opportunities for the modeling of interactions between insulin signaling and ovarian endocrine functions. In addition, recent studies further suggest that common forms of dysfunctional adiposity, as well as altered production of adipokines, could represent important pathophysiological links between metabolic syndrome and infertility.

PCOS, insulin resistance and ovarian dysfunction

PCOS, which affects 5 to 15 % of reproductive aged women worldwide, is the most common disorder leading to female infertility [1,2]. Although the diagnosis of PCOS refers to different phenotypes of ovarian dysfunction, ovarian hyperandrogenism is the common denominator in most patients [2]. Insulin resistance, frequently associated with different clusters of comorbidities referred to as the metabolic syndrome, affects about one to two-thirds of women with PCOS. Obesity is an important risk factor for both metabolic syndrome and PCOS. However, insulin resistance is significantly more frequent in body-mass index (BMI)-matched women with PCOS than without PCOS, showing that obesity is not the primary driver of insulin resistance associated with the disease, and that intrinsic defects in insulin responsiveness could contribute to PCOS [3]. In addition, the severity of insulin resistance, adjusted for BMI, is correlated with that of menstrual cycle abnormalities in women with PCOS, further stressing the pathophysiological link between insulin resistance and ovarian dysfunction [4].

Insulin increases the production of androgens by the ovary, mainly in synergy with the luteinizing hormone (LH). Its effects are basically mediated through the insulin receptor, which is expressed in granulosa and theca cells [5]. In accordance, the theca cell-selective knockout of insulin receptor has been shown to prevent hyperandrogenic anovulation induced by high fat diet-related insulin resistance in mice [6]. Insulin-growth-factor 1 (IGF1) signaling, which also promotes ovarian steroidogenesis, can be stimulated by insulin,

although insulin binds the IGF1 receptor with far less affinity than its own receptor. Nevertheless, IGF1-R mediated effects are probably important, at least in the context of severe hyperinsulinemia, as discussed below.

It seems paradoxical to observe at the same time, on the one hand, exaggerated effects of insulin on the ovary, and, on the other hand, a state of systemic insulin resistance, characterized by impaired effects of insulin on glucose metabolism, as routinely assessed by absolute or relative hyperinsulinemia with regards to glycemia. The main hypotheses to reconcile those two concomitant situations were supported by *in vitro* studies showing that PCOS-associated insulin resistance could be tissue-specific, and could affect metabolic, but not mitogenic or steroidogenic post-receptor signaling pathways [6,7]. Selective insulin resistance, responsible for compensatory hyperinsulinemia, could thus contribute to excessive ovarian androgen production, as thecal cells are very sensitive to insulin. This has been demonstrated by *in vitro* culture of thecal cells from patients with polycystic ovarian syndrome [7]. Selective insulin resistance could also explain the preserved inhibitory effects of insulin on the production of IGF- and sex-hormone- binding proteins (IGFBP1 and SHBG) by the liver, which raises the levels of bioavailable fractions of IGF-1 and testosterone, respectively, further enhancing hyperandrogenism [7].

Ovarian dysfunctions in patients with extreme phenotypes of insulin resistance

Women with pathogenic variants in *INSR*, encoding the insulin receptor gene, auto-antibodies directed against the insulin receptor, or with genetic or acquired forms of lipodystrophy syndromes, are typically described with severe insulin resistance and ovarian hyperandrogenism, in the absence of obesity [8-19]. However, a few studies have reported the natural history of ovarian dysfunctions and consequences on fertility associated with these rare and severe insulin resistance syndromes. Vantyghem et al. have evaluated that PCOS and infertility could affect, respectively, 54% and 28% of women with *LMNA*-linked familial partial lipodystrophy [14], pointing to ovarian dysfunction as a major burden of the disease in women. A recent report involved a large cohort of patients with severe insulin resistance, either due to lipodystrophy (n=185) or insulin signaling defects (n=65), or considered as idiopathic (n=29) [19]. Serum total testosterone, which was significantly positively associated with fasting insulin, was above the normal range in 34% of the whole

cohort, but was highly variable, suggesting that ovarian response to hyperinsulinemia strongly vary among individuals. However, whatever the cause of insulin resistance, the ovarian phenotype, including ovarian histopathology in 9 patients, was close to that observed in PCOS [19]. Five patients, with different causes of extreme insulin resistance, developed ovarian tumors associated with virilization, which could be favored by long-term severe hyperinsulinemia. Importantly, testosterone was not elevated in pre-pubertal patients, showing that the pulsatile release of gonadotrophins plays a permissive role in insulin resistance-related hyperandrogenism [19], as previously reported [13]. The fact that the ovarian phenotype of patients with primary insulin receptor dysfunctions versus post-receptor insulin resistance states was highly similar, supports the hypothesis that hyperinsulinemia drives ovarian hyperandrogenism via its action on IGF1 receptors. Indeed, *INSR* loss-of-function mutations, which affect all tissues, and are predicted to disrupt all insulin signaling pathways, may not induce tissue-specific or selective insulin resistance. In accordance, serum concentrations of SHBG, IGFBP-1 and adiponectin are preserved, or even increased, in patients with insulin receptor defects, resulting from disruption of insulin-mediated effects on the liver and adipose tissue. In contrast, these markers are decreased in patients with post-receptor insulin resistance, characterized by the preservation of some, but not all, insulin signaling pathways [19,20].

Dysfunctional adiposity as a driver of insulin resistance and PCOS

Several studies have suggested that, rather than obesity or insulin receptor dysfunctions *per se*, adipose dysfunction could contribute to the pathophysiology of PCOS in the general population. Adipose tissue, in addition to its well-known effects on whole-body energy regulation, is an important endocrine organ whose altered distribution and/or dysfunction could lead to inflammation, oxidative stress, and/or lipotoxicity, all being associated with insulin resistance. Adipokines produced by adipose tissue also display important regulatory roles on the reproductive axis [21]. Defects in adipocyte differentiation and/or functions are the main determinants of lipodystrophy syndromes, associated with insulin resistance and PCOS features [10,11,14-17,19-24]. Leptin deficiency due to lipoatrophy contributes to insulin resistance, as shown by the metabolic benefit of substitutive therapy with the leptin analog metreleptin in generalized lipoatrophy [22]. Interestingly, metreleptin also improves ovarian function in women with lipodystrophy, by increasing insulin sensitivity and restoring

LH pulsatility [23]. Importantly, leptin deficiency by itself is not sufficient to inhibit pubertal development in patients with congenital lipodystrophy, and metreleptin therapy does not modify the onset of puberty in these patients. Therefore, the insulin-sensitizing effect of metreleptin is probably the major driver of the decrease in testosterone concentrations and the restoration of normal menses in women with lipodystrophy [23]. Besides, Dumesic et al. have recently reported that preadipocytes originating from subcutaneous adipose tissue of women with common forms of PCOS display an abnormal adipogenic behavior as compared to controls [25]. Expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which convert inactive cortisone to active cortisol, is increased in subcutaneous adipose tissue of women with PCOS as compared to age- and BMI-matched women [26], as well as in granulosa cells [27]. Furthermore, in rats, 11β-HSD1 ovarian overexpression induces PCOS, while 11β-HSD1 knockdown or pharmacological inhibition reverses PCOS, increases fertility and improves insulin sensitivity [27]. Adipose tissue from women with PCOS also differentially expresses several genes involved in inflammation and lipid metabolism, as well as in adipocytokines production and responsiveness [28-30]. However, studies fail to draw a integrated picture of the pathophysiological mechanisms linking metabolic and secretory functions of adipose tissue with development of PCOS.

Genetic and epigenetic contributors could lead to both insulin resistance and PCOS

As observed in severe insulin resistance syndromes, with or without lipodystrophy, and as confirmed by mendelian randomization studies, insulin resistance is probably an important determinant of PCOS [31]. In accordance, all life-style interventions and treatments increasing insulin sensitivity globally decrease hyperandrogenism and improve ovulation in women with PCOS [1,2]. However, congenital virilization leads to PCOS metabolic and reproductive features [2] and a bidirectional relationship between insulin resistance and hyperandrogenism is not ruled out in common PCOS [1,2,31]. A unifying hypothesis could be that genetic and epigenetic factors could lead to both adipose tissue dysfunction, insulin resistance, and PCOS. Familial studies strongly support that PCOS is inherited as a polygenic disease in which multiple risk loci with small effects contribute to disease, a pattern similar to the genetics of type 2 diabetes [2]. In line, a polygenic model of type 2 diabetes in rats was recently shown to spontaneously recapitulate not only the metabolic features, but also the reproductive characteristics of PCOS, which are developmentally programmed [32].

Several susceptibility loci which could modulate metabolism and reproductive functions have been identified from genome wide association studies (GWAS) in humans. However, although two-third of the susceptibility to PCOS could be due to genetic factors, only a minority of the genetic loci involved has been identified [1]. GWAS performed in PCOS patients from China, the United States and in United Kingdom have identified a susceptibility locus near the insulin receptor *INSR* gene [33]. However, the menstruation number per year, ovarian follicular number, ovarian volume, and insulin sensitivity index were not associated with any single nucleotide polymorphisms in 1,810 women with PCOS [34].

Recent studies have highlighted the major role of epigenetic modifications, including in utero epigenetic programming of postnatal development, in the pathophysiology of PCOS [35,36]. Upon Anti-Mullerian Hormone prenatal exposure (AMH), mice develop reproductive and metabolic PCOS features later in life, which are transmitted in unexposed offspring through several generations, along with hypomethylation of several genes involved in ovulation defects, hyperandrogenism and metabolic syndrome. Furthermore, pharmacological treatment with methyl donors rescued the PCOS phenotype in mice, and similar epigenetic alterations were observed in women with PCOS [36]. Last, PCOS could be considered as an evolutionary adaptation to both genetic factors that conferred a survival advantage for ancestral population, and epigenetic modulators resulting from our current environmental conditions [37].

The relationships between insulin resistance and PCOS are tight and complex. From a clinical point of view, it is important to keep in mind that improvement of insulin sensitivity and prevention of diabetes and cardiovascular diseases should be integrated into the medical care of patients with PCOS. Conversely, since hirsutism and oligomenorrhea can reveal severe insulin resistance syndromes [12,16], a careful clinical examination should allow to detect lipodystrophy and/or signs of primary insulin receptor defects, and to set up appropriate diagnosis and care protocols [10-20]. Indeed, severe insulin resistance syndromes, and in particular lipodystrophy, are probably not as rare as previously evaluated [38].

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