

Resistin – Adipocyte Hormone as a Regulator of Female Reproduction

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Obesity is a rapidly growing new worldwide epidemic. According to The World Health Organization, 1.6 billion people on the worldwide are overweight (body mass index (BMI) between 25 and 30 kg/m²) and 400 million are obese (BMI >30 kg/m²) [1]. In the USA and UK more than half of all women are either overweight or obese [2], and many are of reproductive age [3]. Childhood obesity is associated with a number of medical complications, among the most worrisome being metabolic risk factors for future atherosclerotic vascular disease e.g., insulin resistance, hyperglycaemia, hypertension, and dyslipidaemia. Obesity during the pubertal transition may also promote the development of Adolescent Polycystic Ovary Syndrome (PCOS), leads to menstrual disorders, rare menstruation anovulatory cycles and infertility in adult life [4]. Effect of body weight on woman's fertility is visible at every stage of reproduction, from deregulation of menstrual cycle through complications of pregnancy, childbirth and postpartum. In obese women, there are numerous diagnostic and clinical problems. Doctors have difficulty in conducting an ultrasound, for example, to detect defect in the fetus. In obese pregnant threefold increased risk of hypertension and fourfold increased risk of gestational diabetes and venous thrombosis [5].

During the last decade, studies provided evidence that adipose tissue is not only as a reservoir of energy-rich molecules but also as height specialized, active endocrine organ directly involved in the control of metabolism and reproductive function through a large number of secreted cytokines and hormones (name adipokines or adipocytokines), including leptin, adiponectin and resistin. Adipokines, which are secretory proteins that act through endocrine, paracrine or autocrine mechanisms, participate in a wide variety of physiological processes, including food intake, insulin sensitivity, vascular sclerotic processes, immunity and inflammation [6,7].

Resistin, relatively recent discovered, 12.5 kDa adipokine, belongs to a family of cysteine-rich C-terminal domain proteins called resistin-like molecules (RELMs) [8]. In human studies, resistin gene expression is detected in adipocytes, and its levels are increased in morbidly obese humans compared with lean control subjects [9,10]. Whether resistin is involved in energy homeostasis is still uncertain; however, it does have similar patterns of expression as leptin [11,12]. Fasting reduces leptin and resistin, and both increase after feeding [11,13]. Some studies found a significant association between resistin and the development of obesity and insulin resistance [14]. In recent years, compelling evidence found a close link between resistin and reproduction function. Resistin dose dependently increased both basal and human chorionic gonadotropin (hCG)-stimulated *in vitro* testosterone secretion from rat testicular tissue [15]. Additionally, they suggest that resistin gene expression was regulated by the pulses of pituitary hormones LH and FSH. There are some studies concerning effect of resistin on female reproduction. Resistin gene expression in adipose tissue increases during puberty in 45-day old female rats [16], indicating that resistin could be an important factor in time of puberty. Pituitary expression of resistin was regulated in a nutritional, age and gender-specific manner. Additionally, resistin gene expression increases to a peak level in the pituitary of prepubertal mice [17]. In the pig ovaries collected from prepubertal animals resistin expression was increased during follicular development [18]. Concentration of resistin increased during follicular growth, with the highest level in large follicles, and it was correlated with estradiol levels in follicular fluid. Puberty is characterized by

increasing concentrations of estradiol, driven by increasing levels of pituitary gonadotropins which are, in turn, regulated by gonadotropin-releasing hormone that is released by hypothalamic neurons. Estradiol stimulated resistin gene expression in a dose- and time-dependent manner. Effect of resistin on female reproduction function was dependent of animal species. Most recently, Maillard et al. [19] demonstrated that resistin is expressed in whole bovine and rat ovaries and can modulate ovarian cells steroidogenesis and proliferation. Using RT-PCR, immunoblotting and immunohistochemistry methods they showed the presence of resistin in rat and bovine whole ovary. In the cow, resistin was widely expressed in small and large follicles, Corpus Luteum (CL), oocyte and cumulus, theca and Granulosa Cells (GC). In addition that resistin gene expression was present in rat CL but very weakly in fresh GC (undetectable in cultured GC), and that resistin protein was localized in rat oocyte, theca cells, CL and weakly present in GC. The next interesting results in this paper showed that after 48 hrs of GC incubation, resistin at physiological dose (10 ng/ml), decreased progesterone (P4) and estradiol (E2) secretions by primary bovine ovarian cells, while in rat resistin induced the P4 secretion without effect on E2 release [19]. Whereas resistin treatment did not affect the rat GC proliferation, in the cow it increased the basal proliferation and decreased the IGF1-induced GC proliferation associated with a decrease in cyclin D2 protein level. Finally, in both species, recombinant resistin stimulated AKT and p38-MAPK kinase phosphorylation and had the opposite effect on the AMPK pathway, while ERK1/2-MAPK was only affected in rat [19]. The recent publication by Spicer et al. [20] showed that resistin preferentially inhibited steroidogenesis of undifferentiated GC of small follicle and inhibited proliferation of differentiated GC in large follicle indicated that in cattle ovarian response to resistin was altered during follicular development. Results presented above showed variability of resistin expression and influence on ovarian cells physiology in particular animal species. Other ovarian cells have also been described to response to a resistin stimulation. Munir et al. [21] had demonstrated in primary human theca cells that recombinant resistin increased 17 α -hydroxylase activity, which is a marker of ovarian hyperandrogenism in women with PCOS syndrome. This result suggests that resistin might play a local role in stimulating androgen production by theca cells. Furthermore, resistin gene expression in the adipocytes from PCOS women is 2-fold higher than that in controls [22]. However, levels of serum resistin remain unchanged in normally cycling women, suggesting that physiological changes of sex steroid levels have no effect on resistin secretion from adipocytes [23]. Next, studies which confirm effect of resistin on female reproduction was observed by Jones et al. [24] who demonstrated that

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in rat ovaries resistin gene expression was normally expressed at a basal level throughout the estrous cycle and it was elevated in animals with induced ovarian cysts.

In summary, resistin is new adipokine which was expressed in ovary and control female reproduction. However, effect of resistin on ovarian function was dependent of animal species, used doses of resistin, and source of ovarian cells. Potential involvement of resistin in the regulation of ovarian function merits further study. Future studies should involve location of resistin expression in the ovary and its participation in the hormone secretion. However, the mechanism of resistin action in the ovary will not be able to fully understand until its receptor will not be identified.

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