

# Polycystic Ovarian Syndrome Conference

November 16-18, 2015 Seattle, USA

## GAB1 in PCOS, new insights

**Ricardo Francalacci Savaris**

Universidade Federal do Rio Grande do Sul, Brazil

In a previous microarray analysis, GRB2-associated binding protein 1 (GAB1), a docking protein closely related to the insulin receptor substrate was down-regulated in endometrium of women with polycystic ovary syndrome (PCOS). The objective of the study was to characterize the cyclic expression of endometrial GAB1 in vivo in normal women and those with PCOS as well as investigate the possible mechanisms of endometrial regulation of GAB1 expression and action in vitro. This was an experimental and case-control study. The study was conducted at a tertiary university hospital. Normal proven fertile women (controls; n=31) and women with PCOS (cases; n=26) participated in the study. Interventions included timed endometrial biopsies at different phases of the menstrual cycle. Ishikawa cells were cultured with  $\beta$ -estradiol (E2), medroxyprogesterone acetate and E2+medroxyprogesterone acetate. Transfection of small interfering RNA for GAB1 in Ishikawa cells incubated with or without insulin. GAB1 mRNA expression in Ishikawa cells and in endometrium of cases and controls was measured. Protein expression of phosphorylated MAPK by Western blot was also measured. Immunohistochemical localization and expression of phosphorylated GAB1 in endometrium was also measured, using a digital histological score. In endometrial tissue, GAB1 mRNA was reduced in the proliferative phase of PCOS women compared with controls ( $P=0.003$ ; ANOVA). When all the phases of the menstrual cycle were grouped, GAB1 protein expression was reduced in endometrium of PCOS women ( $P<0.0001$ ; Student T-test). E2 increases GAB1 mRNA expression in Ishikawa cells ( $P=0.001$ ; ANOVA). Phosphorylated MAPK is reduced in cells transfected with small interfering RNA for GAB1 ( $P=0.008$ ; ANOVA) and incubated with insulin. GAB1 mRNA expression is positively modulated by E2. Endometrial GAB1 protein and mRNA expression are reduced in women with PCOS, suggesting that the endometrium of PCOS women have a defect in insulin signaling due to GAB1 down-regulation.

[rsavaris@hcpa.edu.br](mailto:rsavaris@hcpa.edu.br)

## Polycystic ovary syndrome

**Shailaja Nair**

Drexel University College of Medicine, USA

PCOS is the most common cause of anovulatory infertility in females. It is a syndrome complex comprising of ovarian hyper-androgenism and hyper-insulinemia. Most patients have biochemical and clinical signs and symptoms of hyper-androgenemia with acne, hirsutism and alopecia. Patients also have anovulatory and irregular cycles and some have polycystic ovaries. Hyper-insulinemia may manifest as obesity, difficulty losing weight, pre-diabetes or Type-2 diabetes mellitus. The pathophysiology is multi factorial but is related to insulin resistance in many cases. Hyper-insulinemia causes disordered release of gonadotropins from the pituitary glands with high levels of Luteinizing Hormone. There is also increased secretion of estrogen from the ovaries, which is converted to testosterone causing the hyper-androgenic symptoms. The complication of PCOS encompasses a wide range of metabolic disorders including pre-diabetes, metabolic syndrome and Type-2 diabetes mellitus, in addition to infertility and irregular cycles. Patients with PCOS are also at higher risk of developing endometrial hyperplasia and possibly endometrial cancer due to the unopposed action of estrogen on the endometrium. Studies have also shown a link between PCOS and Obstructive Sleep Apnea, NASH and cardiovascular disease. In the past, patients were treated with oral contraceptives to suppress the hypothalamic-pituitary-ovarian axis. This usually helps with the temporary relief of hyper-androgenemic symptoms, but does not treat the underlying insulin resistance. We use insulin sensitizers to treat our PCOS patients. The first line is still metformin for our insulin resistant patients, as this is safe to use in pregnancy and is known to help prevent early trimester pregnancy loss. We have had success in using newer insulin sensitizers as well, especially Glucagon-Like Peptide-1 receptor agonists like exenatide, liraglutide and dulaglutide.

[Shailaja.Nair@DrexelMed.edu](mailto:Shailaja.Nair@DrexelMed.edu)