The Association Between Clinical and Biochemical Hyperandrogenism in Women With Female Pattern Hair Loss

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Background: The exact association between clinical and biochemical hyperandrogenism (HA) is heterogeneous and cannot be ascertained, especially in normoandrogenic women. **Aim:** Evaluate any association between clinical HA phenotypes and biochemical parameters in premenopausal women with female pattern hair loss (FPHL). **Methods:** A cross-sectional observational study on 362 women with different degrees of FPHL, who were assessed for general characteristics, the degree of FPHL by Sinclair's score, hirsutism by modified Ferriman-Gallwey (mFG) score. Evaluation for biochemical HA included total testosterone (TT), sex-hormone-binding globulin (SHBG), calculated free testosterone (FT), calculated bioavailable testosterone (BT), and dehydroepiandrosterone sulfate (DHEA-S). The variables of clinical HA which were used in this study are FPHL, hirsutism, and acne. We used the Free and Bioavailable Testosterone Calculator to calculate the FT and BT. **Results:** The enrolled young premenopausal women's age range was (14-47 years). Around 78% of them were overweight or obese. Eighty-percent of women had a mild FPHL, with a median duration of three years where 2/3 of women had a duration < 3 years, and had no significant relationship to FPHL degree. About 73% of women had either a mild to moderate hirsutism, and around 16% had acne. The biochemical HA was confirmed in around 52% of women (n=188), who show high levels of calculated FT. The calculated BT is high in 78.5% of the enrolled women (n=284). The means of biochemical indicators for HA were in their reference ranges or slightly above, with no specific change pattern with the corresponding FPHL severity. None of these parameters had a significant relationship to the severity of FPHL. The duration of FPHL was not affected by any presumed variable of clinical or biochemical HA. **Conclusions:** FPHL severity is associated with other clinical HA signs like hirsutism and acne, but not to HA's biochemical parameter. Other parameters, like SHBG, HOMA-IR, and BMI, had no significant relation to the severity of FPHL. **Clinical implications:** FPHL severity does not correlate with the magnitude of hyperandrogenism. The assessment of women with FPHL is primarily clinical. The biochemical picture assists the diagnostic process.

Reproductive Endocrinology

HYPERANDROGENIC DISORDERS THROUGHOUT THE LIFESPAN AND INTO THE NEXT GENERATION

The Major Impact of Obesity on the Development of Type 2 Diabetes (T2D) in Women With PCOS: A Systematic Review and Meta-Analysis of Observational Studies.

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Background/Aims: Polycystic ovary syndrome (PCOS) is associated with disordered carbohydrate metabolism and an increased risk for T2D. However, there are limited data on the magnitude of this risk. Furthermore, 50-80% of women with PCOS are obese and obesity is known to have a synergistic deleterious effect on glucose tolerance in affected women. We systematically reviewed the literature regarding the association between PCOS, obesity and T2D risk. **Methods:** A comprehensive search was conducted in PubMed, CENTRAL and Scopus databases. Data are expressed as relative risk (RR) with 95% confidence intervals (CI). The I^2 index was employed for heterogeneity. The available data, did not allow us to analyze the impact of weight status as normal, overweight and obese and as a consequence the studied subjects were stratified as obese (BMI>30 kg/m^2) and non-obese (BMI<30kg/m^2). **Results:** Twelve studies fulfilled eligibility criteria, yielding a total of 224,284 participants (45,361 PCOS and 5,717 T2DM cases). Women with PCOS had a higher risk of T2D compared with to unaffected women (RR 3.13, 95% CI, 2.83-3.47, p<0.001; I^2 40.1%). When women with PCOS were stratified according to the presence or absence of obesity, the RR for developing T2D in obese compared with non-obese women with PCOS was 4.20 (95% CI 1.97-9.10; p<0.001). Moreover, compared to control women, the RR for developing T2D was significantly increased only in obese PCOS, RR 4.06 (95% CI 2.75-5.98; p<0.001). There was a trend toward significantly increased risk in non-obese PCOS women [RR 2.68 (95% CI 0.97-7.49; p=0.06). **Conclusion:** Women with PCOS have a >3-fold increased risk of T2D compared to women without PCOS, but this risk is substantially increased by the presence of obesity. Accordingly, weight reduction should be pursued in these women. **References:** 1. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989;38(9):1165-1174.2. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab. 1999;84(1):165-169.3. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance

and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999;22(1):141-146.4. Rubin KH, Glintborg D, Nybo M, Abrahamsen B, Andersen M. Development and risk factors of type 2 diabetes in a nationwide population of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2017;102(10):3848-3857.

Reproductive Endocrinology

IMPLANTATION AND PREGNANCY: IMPACT ON MATERNAL AND FETAL HEALTH

ANGPTL3 Levels in Healthy and Mild Preeclamptic Pregnant Women

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Introduction: Throughout normal pregnancy, different metabolic and hormonal adaptations are presented, among others, significant modifications in the profile of lipids and lipoprotein metabolism. On the other hands, Angiopoietin-like protein 3 (ANGPTL3) are involved in the regulation of triglyceride metabolism in the fed state by inhibiting the enzyme lipoprotein lipase in oxidative tissues. **Objective:** Thus, the objective of this study was to determine the profile of serum ANGPTL3 levels during three periods of gestation and three months after delivery. **Design, setting and Participants:** Serum ANGPTL3 levels were analyzed by ELISA, throughout pregnancy in a case-control study nested within a longitudinal prospective cohort of healthy pregnant (n = 52) and mild preeclamptic women (n = 20), women in the third month postpartum (n = 20) and healthy non-pregnant women (n = 20). The results obtained were correlated with biochemical, hormonal, and anthropometric variables. **Results:** A significant reduction in ANGPTL3 levels was observed from the first to the third trimesters of pregnancy in healthy and preeclamptic pregnant women when compared with healthy non-pregnant and postpartum women ($p<0.01$). There were no significant differences in serum ANGPTL3 levels between normal and preeclamptic women. Serum ANGPTL3 levels were positively correlated with triglyceride, very-low-density lipoprotein cholesterol, and total cholesterol levels in healthy non-pregnant ($p<0.05$); whereas there were no significant correlations between ANGPTL3 with the same variables in healthy and preeclamptic pregnant women. Besides, there were no significant correlations between serum ANGPTL3 with body mass index, high-density lipoprotein cholesterol, glucose, insulin, leptin or HOMA-IR in the study groups described above. **Conclusions:** The results of the present study show for the first time that ANGPTL3 could be playing a fundamental role in the homeostasis of lipid metabolism throughout gestation. Thus, low levels of ANGPTL3 during pregnancy might favor the accumulation of lipid in oxidative tissues as a deposit of maternal energy source, while preserving glucose and amino acids for the fetus.

Reproductive Endocrinology

IMPLANTATION AND PREGNANCY: IMPACT ON MATERNAL AND FETAL HEALTH

BMP6 Mediates BMP2-Increased Human Trophoblast Invasion

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TGF-β superfamily proteins play divergent roles in regulating human extravillous trophoblast (EVT) invasion and their coordinated effects are essential for adequate placentation during pregnancy [1]. Bone morphogenetic protein 2 (BMP2), which belongs to the BMP subfamily of TGF-β superfamily, has been shown to promote human EVT invasion and the acquisition of endothelial-like phenotype [2,3]. It has been reported that BMP2 promotes EVT invasion by up-regulating Activin A, a growth factor which also belongs to TGF-β superfamily. However, whether BMP6 mediates the pro-invasive effect of BMP2 has yet to be determined. Herein, we firstly treated immortalized trophoblast cells (HTR8/SVneo) with recombinant BMP2 protein for 6 and 24 hrs, and our bulk-RNA sequencing results demonstrated significantly increased BMP6 mRNA levels after BMP2 treatment. Furthermore, we confirmed the up-regulatory effects of BMP2 on BMP6 mRNA and protein levels in both HTR8/SVneo and primary EVTs isolated from first-trimester villi. Notably, siRNA-mediated down-regulation of BMP6 significantly attenuated both basal and BMP2-induced cell invasion in HTR8/SVneo cells as measured by Matrigel-coated transwell invasion assay. In summary, our results firstly demonstrated the up-regulatory effect of BMP2 on BMP6 expression in human trophoblasts and identified the mediation role of BMP6 in BMP2-promoted EVT invasion, suggesting the interplay between BMP subfamily members during EVT invasion regulation. Our ongoing research focusing the underlying molecular mechanisms and signaling pathways could further benefit the advancement of diagnostic and therapeutic strategies for EVT invasion dysregulation-related pregnancy disorders, e.g., pre-eclampsia. **Reference:** (1) Li Yan et al., Trends Endocrinol Metab 2021 18: S1043-2760(20)30266-6. (2) Hong-Jin Zhao et al., FASEB J 2020;34(2):3151-3164. (3) Hong-Jin Zhao et al., Cell Death Dis 2018;9(2):174.

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Bone Morphogenetic Protein 2 Increases Human Trophoblast Invasion by Up-Regulating Integrin Beta3

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