ANDROGEN EXCESS AND PCOS SOCIETY

Quarterly Review for Androgen Excess-PCOS Society
April 1st – June 30th, 2012

Contents

AEPCOS Publications in April – June, 2012

These selected highlights from the 8th Annual Meeting of the Androgen Excess and PCOS Society Annual Meeting in Munich, Germany (AEPCOS 2010) illustrate emerging concepts in PCOS. Studies into the pathogenesis of PCOS identified androgenic, glycemic, and inflammatory contributions implicating disordered TGF-beta signaling, while suggesting an analogous mechanism in affected male kin. Novel clinical approaches diversified the therapeutic options available to treat infertility in women with PCOS, and improved amelioration of PCOS symptoms, including metabolic dysfunction and hirsutism.

List of April – June, 2012 Quarterly Publications

Brief overviews of selected publications

Congenital Adrenal Hyperplasia and Disorders of Steroidogenesis

Witchel SF, Miller WL. Prenatal treatment of congenital adrenal hyperplasia-not standard of care. J Genet Couns. 2012 Oct;21(5):615-24. doi: 10.1007/s10897-012-9508-8. Epub 2012 May 26 ……..... 25

PCOS - Adolescence

Eleftheriadou M, Michala L, Stefanidis K, Iliadis I, Lykeridou A, Antsaklis A. Exercise and sedentary habits among adolescents with PCOS. J Pediatr Adolesc Gynecol. 2012 Jun;25(3):172-4. doi: 10.1016/j.jpag.2011.11.009. Epub 2012 Jan 20. ……..… 25

Raissouni N, Kolesnikov A, Purushothaman R, Sinha S, Bhandari S, Bhangoo A, Malik S, Mathew R, Baillargeon JP, Hernandez MI, Rosenbaum M, Ten S, Geller D. Altered glucose disposition and insulin sensitivity in peri-pubertal first-degree relatives of women with polycystic ovary syndrome. Int J Pediatr Endocrinol. 2012 May 29;2012(1):14. PubMed PMID: 22643321; PubMed Central PMCID: PMC3477027 ……..... 25

PCOS – Ovary

Tosi F, Negri C, Perrone F, Dorizzi R, Castello R, Bonora E, Moghetti P. Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2012 May;97(5):1712-9. PubMed PMID: 22419715.. 26

PCOS – Pregnancy Complications

Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Bloigu R, Puukka K, Ruokonen A, Tapanainen JS. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. J Clin Endocrinol Metab. 2012 May;97(5):1492-500. PubMed PMID: 22419702. …….. 26

List of April – June, 2012 Quarterly Publications

Congenital Adrenal Hyperplasia and Disorders of Steroidogenesis

Barbaro M, Soardi FC, de Mello MP, Wedell A, Lajic S. Functional studies of CYP21A2 mutants complement structural and clinical predictions of disease severity in CAH. Clin Endocrinol (Oxf). 2012 May;76(5):766-8. doi: 10.1111/j.1365-2265.2011.04275.

Brossaud J, Barat P, Fagour L, Corcuff JB. Cortisol assay in dried blood spots to reduce false positive rate in congenital adrenal hyperplasia screening. Clin Chim Acta. 2012 Aug 16;413(15-16):1306-7. doi: 10.1016/j.cca.2012.04.022. Epub 2012 Apr 25. PubMed PMID: 22561187.

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Cheng TQ, Speiser PW. Treatment outcomes in congenital adrenal hyperplasia. Adv Pediatr. 2012;59(1):269-81. doi: 10.1016/j.yapd.2012.04.009. Epub 2012 Jun 12. Review

Concolino P, Mello E, Patrosso MC, Penco S, Zuppi C, Capoluongo E. p.H282N and p.Y191H: 2 novel CYP21A2 mutations in Italian congenital adrenal hyperplasia patients. Metabolism. 2012 Apr;61(4):519-24. doi: 10.1016/j.metabol.2011.08.008

Falhammar H, Thorén M. Clinical outcomes in the management of congenital adrenal hyperplasia. Endocrine. 2012 Jun;41(3):355-73. doi: 10.1007/s12020-011-9591-x.

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Insulin resistance

See citations in the section “PCOS - Metabolic Dysfunction/Cardiovascular Disease/Inflammation”.

Polycystic ovary syndrome (PCOS)

PCOS – Adolescence

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PCOS – Dermatology and Body Hair Complications

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None.

PCOS – Etiology and Animal Models

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None.

PCOS – After the Menopause

None.

PCOS – Metabolic Dysfunction/Cardiovascular Disease/Inflammation

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PCOS – Phenotypic Variation

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PCOS – Protocol Reviews

None.

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PCOS – Thyroid Complications

None.

PCOS – Uterus

Diamond MP, Kruger M, Santoro N, Zhang H, Casson P, Schlaff W, Coutifaris C, Brzyski R, Christman G, Carr BR, McGovern PG, Cataldo NA, Steinkampf MP, Gosman GG, Nestler JE, Carson S, Myers EE, Eisenberg E, Legro RS; Eunice Kennedy Shriver National Institute of Child Health and Human Development Cooperative Reproductive Medicine Network. Endometrial shedding effect on conception and live birth in women with polycystic ovary syndrome. Obstet Gynecol. 2012 May;119(5):902-8. PubMed PMID: 22525900.

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Premature Adrenarche

Bird IM. In the zone: understanding zona reticularis function and its transformation by adrenarche. J Endocrinol. 2012 Aug;214(2):109-11. doi: 10.1530/JOE-12-0246

Murphy R, Ibáñez L, Hattersley A, Tost J. IGF2/H19 hypomethylation in a patient with very low birthweight, preocious pubarche and insulin resistance. BMC Med Genet. 2012 May 30;13:42

Brief summaries of selected publications

Congenital Adrenal Hyperplasia and Disorders of Steroidogenesis

Witchel SF, Miller WL. Prenatal treatment of congenital adrenal hyperplasia-not standard of care. J Genet Couns. 2012 Oct;21(5):615-24. doi: 10.1007/s10897-012-9508-8. Epub 2012 May 26.

Starting in the 1980's, supraphysiologic glucocorticoid treatment was used to decrease the virilization of the external genitalia of affected female fetuses. More recent clinical observations, results of animal studies and greater knowledge regarding the details of human fetal adrenal physiology raise concerns about the safety of this prenatal treatment. The pathophysiology of CAH and the safety and ethical considerations of prenatal dexamethasone treatment are reviewed in this article.

PCOS - Adolescence

Eleftheriadou M, Michala L, Stefanidis K, Iliadis I, Lykeridou A, Antsaklis A. Exercise and sedentary habits among adolescents with PCOS. J Pediatr Adolesc Gynecol. 2012 Jun;25(3):172-4. doi: 10.1016/j.jpag.2011.11.009. Epub 2012 Jan 20.

The authors performed structured interviews to assess lifestyle habits of girls with PCOS. Specifically, they obtained information regarding the level of physical activity and sedentary habits of girls with PCOS (n=35) and compared them to controls (n=46). The authors report that girls with PCOS engaged in physical activities less than controls. Indeed, frequency and intensity of exercise was decreased among the girls with PCOS. The girls in the control groups were more often involved in sporting activities. The authors concluded that the athletic and sedentary habits of adolescents with PCOS may interact with other factors leading to obesity.

Raissouni N, Kolesnikov A, Purushothaman R, Sinha S, Bhandari S, Bhangoo A, Malik S, Mathew R, Baillargeon JP, Hernandez MI, Rosenbaum M, Ten S, Geller D. Altered glucose disposition and insulin sensitivity in peri-pubertal first-degree relatives of women with polycystic ovary syndrome. Int J Pediatr Endocrinol. 2012 May 29;2012(1):14. PubMed PMID: 22643321; PMCID: PMC3477027.

This is a cross-sectional study examining insulin-glucose dynamics in 18 early adolescent, first-degree female relatives of women with PCOS and 21 healthy, age-matched control adolescents without PCOS close relatives. The adolescent girls underwent anthropometric measurements, steroid profiling and frequently sampled Intravenous Glucose Tolerance Test (IVGTT), while Homeostasis Model Assessment (HOMA) index, Glucose Disposal Index (GDI), Acute Insulin Response (AIR) and Quantitative insulin sensitivity check index (QUICKI) were derived from IVGTT results. Adolescent girls with PCOS close relatives showed higher mean HOMA and lower GDI with no differences in mean age or BMI Z-score between the adolescent groups. The higher HOMA possibly reflects lowered insulin sensitivity and lower GDI may indicate poorer beta-cell function. These results suggest the presence of multiple risk factors for type 2 diabetes in early adolescent first-degree relatives of women with PCOS prior to onset of PCOS.

PCOS – Ovary

Tosi F, Negri C, Perrone F, Dorizzi R, Castello R, Bonora E, Moghetti P. Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2012 May;97(5):1712-9. PubMed PMID: 22419715.

As more evidence is reported in the literature, understanding of the direct and stimulatory effects of PCOS-associated hyperinsulinemia on ovarian androgen secretion is becoming clearer. This interesting study from the group in Verona, Italy, supports the concept that overproduction of insulin itself may stimulate ovarian androgen excess. Subjects with PCOS were well controlled as the adrenal contribution of androgens was suppressed during the hyperinsulinemic euglycemic clamp technique. High levels of insulin were required, supporting the finding of insulin resistance in these normal weight women, with significant ovarian androgen production induced by the high insulin. The prolonged 17-hour study, producing chronic rather than acute hyperinsulinemia, is more reflective of the PCOS condition. Improvement in insulin resistance with the use of insulin-sensitizing medication, lifestyle modification or both allows these patients to take direct control of their syndrome. Lowering of ovarian androgens may enhance their reproductive outcomes by correcting hyperinsulinemia and normalizing ovarian function, or at least by improving their response to ovulation induction and assisted reproduction. These subjects were nearly all of normal weight, which underscores the importance of screening all PCOS patients for insulin resistance and impaired glucose tolerance, and to subsequently consider insulin sensitization management in their fertility care.

PCOS – Pregnancy Complications

Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Bloigu R, Puukka K, Ruokonen A, Tapanainen JS. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. J Clin Endocrinol Metab. 2012 May;97(5):1492-500. PubMed PMID: 22419702.

The authors investigated whether metformin decreases the early miscarriage rate and improves the pregnancy rates (PR) and live-birth rates (LBR) in PCOS in this multicenter, randomized (1:1), double-blind, placebo-controlled study. Three hundred twenty women with PCOS and anovulatory infertility were randomized to metformin (n = 160, Diformin; obese women, 1000 mg two times daily; nonobese subjects, 500 mg + 1000 mg daily) or identical doses of placebo (n = 160). After 3 months of treatment, another appropriate infertility treatment was combined, if necessary. If pregnancy occurred, metformin/placebo was continued up to 12 weeks of gestation. Miscarriage rates were low and similar in the two groups (metformin 15.2% vs. placebo 17.9%, P = 0.8). Intent-to-treat analysis showed that metformin significantly improved PR and LBR (vs. placebo) in the whole study population (PR: 53.6 vs. 40.4%, P = 0.006; LBR: 41.9 vs. 28.8%, P = 0.014) and PR in obese women (49.0 vs. 31.4%, P = 0.04), and there was a similar trend in nonobese (PR:58.6 vs. 47.6%, P = 0.09; LBR: 46.7 vs. 34.5%, P = 0.09) and in obese women with regard to LBR (35.7 vs. 21.9%, P = 0.07). Cox regression analysis showed that metformin plus standard infertility treatment increased the chance of pregnancy 1.6 times (HR 1.6, 95% CI 1.13-2.27). They concluded that obese women with anovulatory infertility benefit from 3 months pretreatment with metformin and its combination with routine ovulation induction agents thereafter.