Lack of Hirsutism in an XX Woman With History of Hyperandrogenism and Oligomenorrhea: Two Coexisting Disorders or Novel Syndrome of Androgen Insensitivity?

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Polycystic ovary syndrome (PCOS) is one of the most common causes of infertility in women, and its etiologies have not been clearly elucidated. Non-classical congenital adrenal hyperplasia (NC-CAH) with mild to moderate enzyme deficiency of 21-hydroxylase due to bi-allelic mutations in its gene (*CYP21A2*) is a cause of secondary PCOS that should always be considered. Common clinical features of NC-CAH include menstrual irregularities, hirsutism, acne, advanced bone age with accelerated linear growth, and short stature, associated with hyperandrogenism. Androgen insensitivity syndrome (AIS) is another cause of hyperandrogenism due to lack of response to androgen typically in genetic male (XY) presenting with female physical characteristics, most commonly due to a mutation in the androgen receptor (*AR*) gene on the X chromosome. Here, we present a 61 years old woman, with a diagnosis of PCOS based on oligomenorrhea and high testosterone ~90 pg/mL at age 18, meeting both NIH and Rotterdam PCOS diagnostic criteria. She took oral contraceptive pills only for one year, despite continued menstrual irregularities. After age 42, her menstrual cycles became and remained regular without further intervention until menopause at age 51, while her testosterone levels fluctuated between 80 and 250 pg/mL. After menopause, her testosterone levels drastically increased to >350 pg/mL. The patient has been recommended, but reluctant to undergo oophorectomy for enlarged non-cystic ovaries. Other potentially related clinical features include the presence of a pituitary adenoma, and a thyroid nodule. She has no notable adrenal mass or myelolipoma. Patient is lean and well-fit, at 5'11" and 151 lb. The most puzzling feature has been a lack of virilization and hirsutism. During laboratory evaluation, high 17-hydroxyprogesterone was identified, and NC-CAH became a potential etiology of PCOS, but this did not explain the lack of apparent virilization. The finding of unimpressive levels of DHEA implied that this pathway probably was unlikely the major cause of high testosterone. Investigation for hyperandrogenism focusing on AIS revealed normal female karyotype XX, and no identifiable mutations or abnormal copy number in *AR*. The findings thus far have provided no unifying diagnosis for her clinical features, especially for androgen insensitivity, and additional studies are being performed. Assessment of other genes recently reported to be associated with AIS is being performed as well as genetic confirmation of NC-CAH by analyzing *CYP21A2*. Steroid 5-alpha reductase 2 (*SRD5A2*), whose mutations and polymorphism interestingly are associated with AIS and PCOS, respectively, and nuclear receptor subfamily 5, group A, member 1 (*NR5A1*) is another gene associated with AIS. It remains to be determined whether she has AIS as a coexisting disorder with NC-CAH or a novel syndrome with a feature of androgen insensitivity.

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Need for Screening Triglyceride Levels in Women on Oral Contraceptives

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Introduction: Oral contraceptive pills (OCPs) are the most used form of reversible contraceptives by women. Major risks are cardiovascular but OCPs also cause secondary hypertriglyceridemia (HTG) through effects of estrogen, which decreases hepatic triglyceride lipase and lipoprotein lipase activity. This causes increased triglycerides, cholesterol and free fatty acids,[1] which then in turn can lead to life-threatening acute pancreatitis.

Case Description: A 23-year-old morbidly obese (BMI 38.2 mg/kg^2) female presented with severe epigastric pain, nausea and vomiting. She had a history of mild intermittent asthma, recently diagnosed pre-diabetes and recently started on OCPs. Initial labs were consistent with diabetic ketoacidosis with glucose 528 mg/dL (65-115 mg/dL), anion gap 21 mEq/L (5-15 mEq), and beta-hydroxybutyrate 2.00 mmol/L (0.02-0.27 mmol/L); and acute pancreatitis with triglyceride 4,425 mg/dL (30-200 mg/dL) and lipase >600 U/L (8-78 UL), confirmed on imaging.

She rapidly deteriorated, developing acute hypoxemic respiratory distress requiring intubation and distributive shock requiring three vasopressors. She progressed into multi-organ failure with acute respiratory distress syndrome, ischemic liver and acute renal failure despite insulin drip, colloidal fluid resuscitation, continuous veno-venous hemofiltration and high positive end-exploratory pressures. She developed rhabdomyolysis, followed by abdominal compartment syndrome requiring decompressive laparotomy that resulted in large volume blood loss and retroperitoneal necrosis needing multiple laparotomies. Ultimately, she became non-responsive off sedation, attributed to malignant cerebral edema that progressed to brain herniation.

While HTG was likely the cause of her pancreatitis, she had normal triglyceride levels on prior routine lab work while not on OCPs.

Discussion: Severe acute pancreatitis is a life-threatening complication of HTG which may be precipitated by use of OCPs. We believe that there is a need for more research in this field and even propose periodic monitoring of HTG in women taking OCPs given the severity of the consequences. While there are currently no guidelines for monitoring lipid levels in women on OCP, appropriate clinical awareness of physicians prescribing OCPs to patients may prevent fatal outcomes.

References: 1. Stumpf, M., Kluthcovsky, A., Okamoto, J., Schrut, G., Cajoeiro, P., Chacra, A. and Bizeli, R. (2018). Acute pancreatitis secondary to oral contraceptive-induced hypertriglyceridemia: a case report. Gynecological Endocrinology, 34(11), pp.930-932.

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Ovarian Hyperthecosis: Hyperandrogenism in a Post-Menopausal Woman

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