Defective endometrial prostaglandin synthesis in IVF patients with repeated implantation

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**Study objective:** To define the role of prostaglandins in the endometrium of patients with repeated failure of embryo implantation. Design: Case-control study. Setting: In-vitro Fertilization (IVF) Unit at a university hospital.

**Patients:** 34 women, comprising of 19 patients with repeated IVF failure and 15 controls with proven fertility. Interventions: Endometrial expression levels of the enzymes responsible for the prostaglandin synthesis were compared between the two groups. Main outcome measures: \(\text{cPLA}_2\alpha\) activity was assessed by Western blot. Expression of COX-2, \(\text{sPLA}_2\text{IIA}, \text{sPLA}_2\text{IB}, \text{sPLA}_2\text{V}, \text{Glypican-1}, \text{PGES}, \text{EP}\) and \(\text{LPA}_3\) was measured by real-time PCR.

**Results:** Patients displaying recurrent implantation failure expressed reduced levels of \(\text{cPLA}_2\alpha\) and COX-2 as compared to fertile controls. In response to this deficiency, \(\text{sPLA}_2\text{IIA}\) was found to be overexpressed. Interestingly, \(\text{LPA}_3\), which is known to converge on the \(\text{cPLA}_2\text{-AA-COX-PGs}\) signaling pathway, was also decreased in these patients.

**Conclusions:** Prostaglandin synthesis appears to be disrupted in patients with repeated IVF failure as compared to fertile controls. We therefore suggest that reduced prostaglandin synthesis in the human endometrium may lead to poor endometrial receptivity.
Unique Primary Ovarian Dysfunction Contributes to the Hypogonadism in Women with Prader-Willi Syndrome

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Introduction: Prader-Willi syndrome (PWS) is a heterogeneous genetic disorder associated with intellectual and emotional disabilities, hyperphagia and hypogonadism. Many of the typical features of PWS have been attributed to hypothalamic dysfunction. The aims of our study were to characterize the reproductive hormone profile and investigate the etiology of hypogonadism in women with PWS.

Patients/ Methods: Ten women aged 23±5.5y with PWS and 10 age and BMI matched controls were included. Blood samples were drawn and abdominal ultrasounds were performed on days 2-4 of spontaneous cycles or at random from amenorrheic women. Anti-Mullerian hormone (AMH), inhibin-B (INB), gonadotropins, sex-steroids, TSH, prolactin, ovarian volume and antral follicles count (AFC) in PWS women were compared with results from controls and the reference ranges.

Results: Compared to controls, PWS women had lower INB (mean ± SD, 17.6±12.8 vs. 110.6±54.5pg/mL, P=0.0002) and AMH levels (1.18±0.86 vs. 3.53±2.42ng/mL, P=0.01). INB levels were exceptionally low in all PWS women, but individual AMH levels overlapped with the levels in the controls. Ovarian volume (3.7±2.3 vs 30.5±28.8ml, p=0.03) and AFC (6.4±6.9 vs. 14.0±8.2, p=0.01) were lower in the PWS group compared to the controls. Three PWS patients had abnormally high FSH levels while only one had hypogonadotropic hypogonadism.

Conclusions: Our results suggest a unique follicular stage-specific insult in women with PWS. Thus, primary ovarian dysfunction is a major component of hypogonadism in PWS.
Arrested Puberty in PWS Males: Evidence for a Unique Sertoli Cell Defect

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Introduction: Recent studies challenge the assumption that hypogonadism in Prader-Willi Syndrome (PWS) is due only to hypothalamic dysfunction. The objectives of this study were to characterize sexual development and reproductive hormones in PWS males and investigate the etiology of hypogonadism in this syndrome.

Patients: Physical examination and blood sampling were performed on 37 PWS males, ages 4 months to 32 years.

Results: All had a history of undescended testes, age at orchiopexy ranged from 2 months to 6 years. Pubertal signs were variable, but none achieved full genital development. Anti-Mullerian hormone (AMH) levels in PWS boys were near the lower limits of normal, decreasing from 44.4 ± 17.8 ng/ml (mean ± SD) in young children to 5.9 ± 4.7 ng/ml in adolescents, similar to normal males. In contrast, inhibin B (INB) was consistently low (27.1 ± 36.1 pg/ml) or undetectable in all age groups. In adult males FSH levels were high (20.3 ± 18.3 IU/L), LH levels were normal (4.2 ± 4.3 IU/L) and testosterone levels were low (1.87 ± 1.17 ng/ml). Only two adults had hypogonadotropic hypogonadism (HH) with undetectable levels of LH and FSH. The two men with HH had high AMH levels (34.9 and 36.7 ng/ml), unlike the other 9 adults whose AMH levels were low (2.6 ± 2.1 ng/ml). DHEAS (1.06 ± 0.30 ng/ml) and D4A (281.1 ± 143.6 mcg/dl) in adult PWS were normal.

Conclusions: In most males with PWS, normal adrenarche is followed by pubertal arrest. Normal LH, high FSH, low testosterone, borderline and variably low AMH, together with extremely low levels of INB in all patients suggest that a unique Sertoli cell defect is the major contributor to hypogonadism in most PWS men.
Early Pubertal Onset in Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency

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Introduction: Diminished cortisol synthesis in patients with congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency results in increased ACTH secretion that in-turn enhances adrenal androgen production. Hyperandrogenism in childhood may cause premature pubarche, advance bone age (BA), accelerated growth and consequently short final height. Whether patients with CAH exhibit early true puberty is a matter of debate. The aim of the current study was to assess pubertal characteristics and growth patterns in children with CAH.

Patients/ Methods: Fifty-five subjects (33F/22M) with CAH (22, SW, 15, SV, 18 NC) (age 2.8 to 33.5 years, mean 14.9 ± 7.3 SDS) were enrolled. The design was a retrospectively longitudinal study. All subjects underwent genetic analysis of the CYP21 gene.

Results: The most common mutation in the entire group was V281L (22%) followed by I2splice (21%), I172N (14%), 8del (11%) and others (32%). The mean age of onset of pubarche was earlier in females 5.6 ± 2.3 (range, 1.9-10.0) compared to males 7.3 ±2.4 years (1.8-11.3) in all forms of CAH. Onset of pubarche was earlier in SV (5.0 ±2.6, 1.8-11.3) compared to SW (6.9 ± 1.6, 3-9.6) and NC (7.1± 2.4, 1.8-11.3) forms. Mean BA was advanced by 2.3± 2.1 (0-9.0) years at pubertal onset in all forms and was more advanced in SV 3.4± 5.6 (1.9-10.0) compared to NC (1.9± 2.1, 0-8.0) and SW (1.8± 1.8, 0-5.0). Increased 17-hydroxyprogesterone (17OHP) (ng/ml) was shown at pubertal onset (54 ± 80, 1.1-410) indicating poor control. In females, despite early onset of telarche (8.9 ± 2.1 (2.8-11), the mean age of menarche was within the normal range 12.5± 1.9 years, though highly variable (range, 9-16.5). High variability in onset of gonadarche was shown in males as well (10.5± 1.5, 8.2-13). Seven patients were treated with LHRH-analogs due to early onset of puberty. Low final height was shown in both females 155.7±9.0 (144-178) cm and males 164.4 ±8.0 (144-174).

Conclusions: Our results indicate that onset of puberty is earlier in children with CAH and patients with SV form are at higher risk for earlier pubarche and advanced BA compared to the other forms. The earlier timing of pubertal onset plays a critical role in final height attainment. Earlier diagnosis in children with SV form, stricter control and future medical therapy such as aromatase inhibitors may delay pubertal onset and improve the final height attainment in these patients.
Normometabolic Obesity: A Much Overrated Entity Which Vanishes With Age in a Gender Related Manner.

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Introduction: Recent evidence indicates many obese individuals are metabolically healthy (Arch. Int. Med. 2008, 168: 1609-16, 1617-24). Because in these reports from the US and Germany, subjects with single cardiometabolic abnormalities such as hypertension or fatty liver were classified as "metabolically healthy" and because overweight subjects were also included in the analyses, we re-examined the prevalence of truly normometabolic obesity among 323 consecutive obese subjects attending our obesity clinic.

Patients/Methods: We examined 323 obese subjects, whose age ranged from 18 to 78y and BMI from 30.4 to 72kg/m². To be considered metabolically healthy, subjects had to be free of any of the components of the metabolic syndrome including diabetes or impaired fasting glucose, high blood pressure (BP ≤140/80mmHg off blood pressure lowering drugs), hypertriglyceridemia (≥150mg%), low HDL (≤40mg% in men, 50mg% in women). Increased waist circumference was discarded from the classification criteria so as not to label nearly all obese subjects as "metabolically impaired".

Results: Only 58 of the 323 obese subjects (18%) were found to be metabolically healthy. The normometabolic subjects were not different from the metabolically impaired individuals with respect to BMI (41.1±0.9 vs. 42.8±0.5kg/m², P=NS), but had lower waist circumference (114±2 vs. 120±1cm, P=0.011), lower waist to hip ratio (0.87±0.01 vs. 0.93±0.01, P<0.0001) and lower total cholesterol levels (183±5 vs. 203±5mg%, P=0.008). The metabolically healthy group was also younger (36.8±1.4 vs. 45.1±0.8yrs, P<0.0001) and included a higher fraction of females relative to males: 20% of obese females but only 10% of obese males had metabolically benign obesity. Additionally, blood pressure in the metabolically healthy obese subjects was markedly lower than in the metabolically impaired subjects (120/75 vs. 140/86 mmHg, P<0.0001). Overall, the fraction of the metabolically healthy obese subjects decreased with age, declining gradually from 27.5% for those under the age of 40y to 21.3% at the age range of 40-49y, diminishing further to 8% at 50-59y, eventually reaching 0% in subjects whose age was 60 or higher. Moreover, less than 3% of the obese men at the age of 40y or older were metabolically healthy.

Conclusions: metabolically benign obesity does occur but is seen predominantly in younger subjects, particularly in individuals under the age of 40y and decreases as a function of age thereafter, practically disappearing by the age of 60. Further, obese men are more likely to harbor components of the metabolic syndrome relatively early on, such that the absence of metabolic derangements in obese males older than 40 y is unusual.
Maternally Inherited ABCC8 Mutation and a Normal Paternal ABCC8 Gene in a Case of Severe Neonatal Hyperinsulinism

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Introduction: Congenital Hyperinsulinism (CHI), caused mostly by mutations in ABCC8 gene, may appear as either focal or diffuse pancreatic lesions. Focal CHI is probably caused by a mutation in the paternal allele coinciding with the loss of the distal short arm of maternal chromosome 11, including the ABCC8 gene. We present an unusual case of a maternally inherited CHI.

Patients/Methods: A day old girl to non consanguineous parents developed severe hypoglycemia with hyperinsulinemia, responsive initially to continuous glucose infusion and then to G-tube feeding, diazoxide and somatostatin. A maternal aunt and cousin (confirmed to carry a heterozygous in-frame insertion ABCC8 gene mutation) had similar phenotypes as neonates.

Results: DNA was extracted from the patient, her parents, grandfather, another affected cousin and her mother. For the patient, all coding exons and exon/intron boundaries of KCNJ11 and ABCC8, coding for Kir6.2 and SUR1 components of K+ATP channel were sequenced. A heterozygous in-frame insertion mutation in exon 37 of the ABCC8 gene was found in the patient and her unaffected mother, which was identical to the one present in their affected relative. No other maternal or paternal mutations were identified. Co-transfection of Kir6.2 and the mutant SUR1 in COSm6 cells demonstrated severe channel dysfunction and only minimal current when exposed to MgADP (<10% of wild type).

Conclusions: This is the first maternally inherited ABCC8 heterozygous mutation reported in familial CHI. The mutation causes significant K+ channel dysfunction in expression studies. These findings exclude classical recessive, dominant or paternal UPD (uniparental disomy, focal-HI) inheritance and suggest the possibility of a novel mechanism for genetic CHI.
Hearing Deficits in Patients with Congenital IGF-1 and GH Deficiencies

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Introduction: The aim of the study was to investigate the auditory functions of untreated and treated patients with Laron Syndrome (LS) as well as with hGH deletion, both with congenital IGF-I deficiency.

Patients/ Methods: The LS group comprised 11 LS patients: 5 untreated adults (2M, 3F, 44-56y), one late IGF-I treated girl (15y), and 5 patients (4F, 1M, 7-32y) in whom IGF-I treatment had been started in infancy. The hGH del. group comprised 5 patients: 1 untreated patient (58y) and 4 treated patients (2M, 2F, 27-48y). Auditory tests included: Behavioral audiogram for pure-tones in air and bone conduction, Speech reception threshold and speech discrimination, middle ear functions using tympanometry and stapedial acoustic reflexes, transient and distortion product otoacoustic emissions for assessing the integrity of the outer hair cells situated in the cochlea, auditory brainstem responses to high stimuli to evaluate neural synchronization alone the auditory pathway up to the midbrain. Loudness discomfort level (hyperacusis) was assessed by the loudness dynamic range and a questionnaire for hyperacusis and tinnitus.

Results: The 5 untreated LS adult patients and 1 girl with LS in whom IGF-I therapy was started in age 9y had significant hearing loss, and so did the untreated patient with hGH del. Most had low frequency cochlear hearing loss with or without high frequency impairment. Unexpectedly, in most of those patients, acoustic reflex could not be evoked even to the most provocative stimuli (white noise). Auditory neural conduction as manifested in auditory brainstem responses was intact, pointing to cochlear hearing loss without retro-cochlear involvement. In all of the untreated and late treated LS patients, and untreated patient with hGH del., symptoms of hyperacusis and tinnitus were noted. Contrary, in all 5 LS patients in whom IGF-I replacement treatment was started between ages 2-3½, the auditory tests were normal. Similarly, the 4 patients with hGH del. in whom treatment with hGH started between ages 1¹⁄₁₂-6⅓ had exhibit normal auditory function.

Conclusions: untreated patients with congenital IGF deficiency (LS and hGH del.) suffer from low frequency cochlear hearing loss and absence of acoustic reflex. Those defects were absence in patients with an initiation of IGF-I or hGH treatments at an early age proving the reversibility of congenital IGF-I deficiency induced hearing loss.