OC4.3

Gender difference in genetic and diagnosis of congenital hypogonadotropic hypogonadism (CHH) in a large cohort from an Endo-ERN referral center

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Congenital hypogonadotropic hypogonadism (CHH) is a rare condition characterized by impairment of pubertal development, that can be associated with hypo/anosmia (Kallmann Syndrome, KS) or normosmia (nCHH). A genetic basis can be identified in nearly 50% of cases, with increasingly common detection of oligogenicity. CHH has a strong male predominance (MtoF ratio 5–3:1), although sex ratio for CHH in families with autosomal inheritance has been proven to be close to equal. The rationale for this epidemiologic difference is not clearly understood. Our study aims to evaluate gender differences in clinical and genetic diagnosis of CHH. 313 CHH patients with absent pubertal development, consecutively referred to our Center from 01/2016, were enrolled in this study. Data collection included clinical assessment at diagnosis and genetic analysis performed by next generation sequencing (NGS), employing a panel of 27 candidate genes (ANOS1, FGFR1, PROK2, PROK-R2, KISS1, KISS1R, GnRH, GnRHR, FGF8, TACR3, TAC3, HS6ST1, CHD7, DUSP6, FEZF1, FGF17, FLTR3, IL17RD, SEMA3A, SEMA3E, SEMA7A, SOX2, SOX10, SPRY4, WDR11, HESX1, NELF). Among 313 patients 87 were female (F) and 226 male (M) (FtoM ratio 1:2.6). 43.8% had a diagnosis of KS and 56.2% of nCHH (no significant gender difference). Rare genetic variants were found in 54.3% of patients (F 55.2% vs. M 54%). Monoallelic rare variants were found in 37.1% (F 33.3% vs. M 38.5%), biallelic monogenic rare variants in 4.2% (F 5.7 vs M 3.5%) and oligogenicity in 13.1% (16.1% vs. 11.9%), with no significant difference between sex, even after exclusion of X-linked ANOS1. Prevalence of rare variants in each candidate gene resulted in line with literature, showing no significant gender differences, except for IL17RD (F 5,7% vs. M 1,3%, *P* 0.040). Age at diagnosis was 17.2 ± 2.9 for F and 16.8 ± 3.5 for M (*P* 0.065). Presence of clinical "red flags" (family history, hypo/anosmia, micropenis, cryptorchidism, midline defects, bimanual synkinesis, renal abnormality, deafness) was significant higher in male (F 64.4% vs. M 79.2%, *P* 0.008), but not related to age at diagnosis or presence of rare variants. Nevertheless, these rates become similar after excluding micropenis and cryptorchidism, as only male manifestations. Our data confirm the male predominance in CHH but they do not allow to identify substantial differences in genetic or clinical presentation between gender, suggesting that gender gap in CHH prevalence do not depend upon variability of the underlying pathogenic mechanisms, but rather to gender specific characteristics of GnRH function or differences in diagnostic capability.

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OC4.4

Fertility outcomes in women with hypopituitarism compared to women with hypogonadotrophic hypogonadism in a single UK centre

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Objective
Previous studies have documented poor fertility results in women with hypopituitarism (HP) both in terms of pregnancy rates and outcomes. We aimed to assess ovulation induction (OI) and pregnancy outcomes in women with HP compared to women with hypogonadotrophic hypogonadism (HH) treated at University College London Hospitals.
Design
A retrospective study.
Patients
39 women with HP and 57 women with HH underwent 143 and 266 cycles of OI respectively (median age at cycle 33.5 years [interquartile range (IQR) 31.4–37.0] vs 34.3 years [IQR 32.3–36.6] respectively, $P = 0.35$).
Methods
OI was carried out by using human menopausal gonadotropin (hMG) according to a standard protocol and a 10,000 IU human chorionic gonadotropin trigger. Baseline serum oestradiol, follicle stimulating hormone, luteinizing hormone, prolactin, thyroid functions tests and insulin-like growth factor-1 were measured together with a uterine scan. Ovulation was confirmed by a mid-luteal phase progesterone of >30 nmol/l or ultrasound evidence of corpus luteum. Clinical pregnancy was defined by the presence of at least one heartbeat on an ultrasound scan.
Results
Ovulation rates were similar between women with HP and HH. Although pregnancy and live birth rates per cycle were greater in women with HP compared to women with HH (28.7% vs 16.2%, $P = 0.003$ and 17.0% vs 9.4%, $P = 0.025$ respectively), pregnancy and live birth rates per patient were similar (66.7% vs 50.9%, $P = 0.125$ and 48.6% vs 37.5%, $P = 0.286$ respectively). Foetal loss per pregnancy was not different between women HP and HH (29.3% vs 39.5%, $P = 0.323$ respectively), with a similar proportion of multiple pregnancies per live births between the 2 groups of women (HP 8.3% vs HH 20.0%, $P = 0.243$). There were no major complications in most of the deliveries. Median number of cycles to pregnancy in women with HH was 9 (Standard Error [SE] 0.0) vs 6 cycles (SE 0.8) in women with HP (Log Rank: $P = 0.001$).
Conclusions
Encouraging ovulation and pregnancy rates can be obtained in women with HP using hMG. A smaller uterine size and lack of size normalisation following standard oestrogen replacement therapy may in part explain the greater miscarriage rate compared to the general population in these women. Management in a multidisciplinary team is advised.

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OC4.5

Lower level of sexual maturation rating and reduced concentrations of reproductive hormones, luteinizing hormone, follicle stimulating hormone, testosterone and estradiol in short stature children with mutations in growth hormone secretagogue receptor 1a

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Puberty onset is sensitive to the energy reserves of the organism, especially in females where there is an association between obesity and early puberty. Studies have shown that in the presence of growth hormone secretagogue receptor 1a (GHSR1a) mutations, there is a decrease in ghrelin-mediated appetite, resulting in relatively low BMI, which contributes to the delayed onset of puberty. Furthermore, delayed puberty is observed in clinical conditions associated with low IGF1, suggesting that IGF1 also exerts stimulatory, synergistic, or permissive effects on the onset of puberty. Thus, low IGF1 levels due to a decrease in GH secretion caused by GHSR1a insufficiency may also negatively modulate the timing of puberty onset. The present study was designed to determine the level of sexual maturation rating (SMR) and the concentrations of reproductive hormones, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (T) and estradiol (E2) in normal and short stature children having GHSR1a mutations. SMR including penile length, testicular volume, pubic hair and facial hair stage for boys ($n = 21$) and breast development and pubic hair stage for girls ($n = 14$) having short stature between the ages of 2 and 14 years was measured and compared with age matched control subjects ($n = 50$). The stage of pubertal development was assessed by using the criteria described by Tanner and Whitehouse. ELISA was used for analysis of plasma LH and E2 and specific RIA systems were used for analysis of plasma FSH and T. Data were analyzed using Student's t test, ANOVA and Pearson correlation r. The results revealed a significant difference between mean penile length and testicular volume of normal boys and short stature boys at early and mid-pubertal stages. Similarly, breast development was significantly delayed in short stature girls than normal girls at early and mid-puberty. Pubic hair development in short stature girls and pubic and facial hair development in short stature boys were also significantly delayed as compared to normal girls and boys at early and mid-puberty. The levels of LH, FSH, T and E2 were higher in normal than short stature boys and girls and a significant difference was witnessed at early and mid-pubertal stages. In conclusion, SMR was higher in normal children as compared to short