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Congenital adrenal hyperplasia, *CYP21A2* deficiency: clinical and physiological aspects of pregnancy, screening and growth

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ABSTRACT

The subjects dealt with in this thesis are clinical aspects of congenital adrenal hyperplasia (CAH), such as neonatal screening, growth and the incidence of CAH during the last century in Sweden. In addition, we have used CAH as a model system to study possible prenatal effects of androgen exposure on growth and gestational length.

Gestational age at birth correlated with *CYP21A2* genotype in girls ($P < 0.01$), but not in boys with CAH (n = 109; 62 females, 47 males) (Paper I). The exact number of gestational days was known in 66 patients (37 females, 29 males). The pregnancy was longer for females with the most severe form, null genotype, 285.7 days, than for I172N, 273.9 days ($P < 0.01$) or V281L, 274.7 days ($P < 0.05$), indicating that higher androgen levels in severe forms could explain this effect. No differences between genotypes were seen in CAH males, possibly because testicular androgen production is high in normal male foetuses and adrenal androgens therefore may not have an additional effect. The cortisol deficiency is equal in CAH girls and boys, making this deficiency a less likely explanation.

Birth weight standard deviation score (SDS) corrected for gestational age in children with CAH (n = 73; 43 females, 30 males) did not differ from that of the reference population (mean, CI 95%: 0.0, -0.3 to 0.3, and 0.2, −0.2 to 0.6, for boys and girls, respectively) (Paper II). Nor did the birth weight differ between *CYP21A2* genotype groups ($P > 0.05$). In 29 46,XY females with complete androgen insensitivity syndrome (CAIS), the mean birth weight SDS was similar to that of reference boys (mean, CI 95%: 0.1, -0.2 to 0.4) and higher than the reference of females (mean, CI 95%: 0.4, 0.1 to 0.7, $P = 0.02$). Hence, these results indicate that gestational age at birth, but not prenatal growth, is affected by androgen exposure.

In a retrospective, population-based cohort study we investigated the apparent incidence of CAH in Sweden between 1910 and 2011 (Paper III). We identified 606 patients with known *CYP21A2* genotype in 490 cases (81%). The female:male ratio was 1.25:1 for the whole cohort, but close to 1 in patients detected in the screening. The number of diagnosed patients increased dramatically in the 1960s and 1970s. The proportion of salt-wasting (SW) CAH compared to milder forms increased in both sexes after the introduction of neonatal screening from 114/242 to 165/292 ($P < 0.05$). The milder forms were diagnosed more often in females. This means that both boys and girls with SW CAH were missed before screening and that screening for CAH does not only increase the number of detected boys with SW CAH as previously thought, but also of girls.

The neonatal screening for CAH in Sweden was studied from the start in 1986 to 2011 (Paper IV). A total of 2 737 932 neonates (99.8% of all live births) had been screened. No cases with evident SW CAH had been missed, sensitivity 100%. The sensitivity was lower in the simple virilising form, 79%, and non-classical CAH, 32%. The positive predictive value was higher in full-term infants, 25.1%, than in pre-terms, 1.4% ($P < 0.001$). The recall rate was lower in full-terms, 0.03%, than in pre-term infants, 0.57% ($P < 0.001$). An analysis of all publications describing neonatal screening programmes since 1996 revealed that the screening sensitivity correlated negatively with the duration of follow-up ($P = 0.034$). In contrast to current reports, our study shows that neonatal screening is effective in identifying SW CAH.

Growth in CAH was studied in a prospective, observational cohort study including all children born or diagnosed with CAH between 1989 and 1994, 80 patients (46 females, 34 males). Most children were treated with a glucocorticoid dose within the recommended 10–15 mg/m2 body surface area. Corrected final height correlated with CYP21A2 genotype ($P = 0.012$). An important finding was that the corrected final height SDS was lower in patients who had been treated with the addition of prednisolone, -1.1 ± 1.0, than in those who had been treated with cortisone acetate and/or hydrocortisone alone, -0.60 ± 1.0 ($P < 0.05$). Furthermore, body mass index at 18 years of age was higher in patients treated with prednisolone, 25.3 ± 4.7 kg/m2, compared to 23.4 ± 4.5 kg/m2 ($P < 0.05$). Hence, the results suggest that treatment with prednisolone should be avoided in growing subjects with CAH.

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