Gonadotrophin stimulation in children with abnormal sexual development

S. K. GARG, P. K. BAND YOPADHYAY, B. RAM

Summary
Plasma levels of testosterone were measured by radioimmunoassay before and after 3 days' administration of human chorionic gonadotrophin (HCG) 2000 IU/d in 34 prepubertal boys (6 normal, 3 with anorchia, 5 with micro penis, 8 with cryptorchidism, 6 with hypogonadotrophic hypogonadism and 6 with hypospadias). The increase in plasma testosterone value ranged from 2.4 nmol/l to 10.5 nmol/l in normal boys. There was negligible \( P > 0.05 \) response in boys with anorchia compared with normal children. Subjects with micropenis showed a subnormal response \( P > 0.05 \). Children with cryptorchidism showed a normal increase in testosterone levels \( P > 0.05 \), but in those with hypogonadotrophic hypogonadism and hypospadias the increase was variable \( (1.2 - 8.8 \text{ nmol/l}) \). Although the HCG stimulation test is not diagnostic in the majority of the sexual disorders, it appears to be sensitive for diagnosing anorchia.

Plasma testosterone is becoming more widely used to evaluate testicular function. During fetal life the testes secrete testosterone, which is responsible for development of the external genitalia. Leydig cells, which are present at birth in normal testes, regress during the first year of life and are not usually recognisable on histological examination until puberty. Stimulation of Leydig cells with human chorionic gonadotrophin (HCG) is necessary when investigating prepubertal subjects. Numerous reports have appeared on the use of the HCG stimulation test in boys with anorchia. The test has also been used to investigate boys with cryptorchidism or delayed puberty and to study testicular function in hermaphrodites and subjects with sex chromosome disorders, microphallus and hypogonadotrophic hypogonadism. The clinical value of the test is still uncertain in many of the latter group. The present study describes the plasma testosterone value before and after HCG stimulation in 6 normal boys and 28 subjects with various abnormalities of the external genitalia.

Subjects and methods
Thirty-four prepubertal boys (6 with normal genitalia, 3 with anorchia, 5 with micro penis, 6 with hypospadias, 8 with cryptorchidism and 6 with hypogonadotrophic hypogonadism) were included in the study. All were in the stage P1 of puberty. A detailed history of ingestion of drugs antenally and family history were recorded. Testicular volume on both sides varied between 1 and 3 ml (Prader's orchidometer) in all subjects except those with cryptorchidism in whom the size of the descended testes was 2 - 3 ml. All the hidden testes (unilateral/bilateral) were intra-abdominal. The testes could not be identified even at exploratory surgery in anorchia, and these subjects were investigated after surgery. Subjects with micropenis had underdeveloped scrotum in which testicular tissue could be felt. All 6 patients with hypospadias had the urethral opening at the base of the penis and 1 had retracted testes. The diagnosis of hypogonadotrophic hypogonadism was confirmed in these 6 patients by low basal and stimulable (gonadotrophin-releasing hormone 50 \( \mu g \) gonadotrophin (luteinising hormone (LH) and follicle-stimulating hormone (FSH)) levels and none had any neurosurgical interference; 3 had anosmia and 1 had hyposmia but none had any skeletal abnormalities. In all 34 subjects Barr body examinations on buccal smears were normal. General and systemic examination was essentially normal in all subjects. Details for each group are given in Table I.

Each subject received HCG 2000 IU (Professi) intramuscularly for 3 consecutive days. Blood samples were drawn before the first injection and approximately 24 hours after the last injection of HCG. Sera, separated at room temperature after clotting, were frozen and stored at \(-20°C\) until assayed.

Plasma testosterone levels were estimated by radio-immunoassay using antiserum supplied by the World Health Organisation (batch No. K8885) and \(^3\)H-testosterone as tracer; separation of bound and free hormone was done with dextran charcoal. Basal gonadotrophin (LH, FSH), prolactin (PRL) and oestradiol (E\(_2\)) values were also estimated by radio-immunoassay.

Results
Basal levels of testosterone in normal individuals ranged from 0.9 nmol/l to 5.5 nmol/l (Fig. 1). The rise in plasma testosterone after HCG stimulation ranged from 2.4 nmol/l to 10.5 nmol/l, with an average increase of 3.11 nmol/l (Table I). The basal testosterone levels in anorchia were 0.72 ± 0.61 nmol/l, which was not statistically significant in comparison with normal controls \( P > 0.05 \). After stimulation with HCG the rise in testosterone level was 1.08 ± 0.19 nmol/l, which was significantly different when compared with normal subjects \( P < 0.05 \).

The mean basal concentrations of testosterone and after HCG stimulation in other groups (micro penis, cryptorchidism, and cryptorchidism with hypospadias, anorchia and micropenis) were significantly different from normal controls \( P < 0.05 \).

![Fig. 1. Plasma testosterone levels in 34 subjects before (X) and after (Y) three injections of HCG in the various groups.](image)
TABLE I. CLINICAL AND LABORATORY DATA IN THE VARIOUS GROUPS (34 SUBJECTS)

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Mean age (yrs) (range)</th>
<th>Testosterone (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td>12.5 (9.2-14.4)</td>
<td>2.12 ± 1.77*</td>
</tr>
<tr>
<td>Anorchia</td>
<td>3</td>
<td>15.5 (12.6-17.8)</td>
<td>0.72 ± 0.61</td>
</tr>
<tr>
<td>Microopenis</td>
<td>5</td>
<td>11.8 (7.8-13.4)</td>
<td>2.12 ± 1.23*</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>6</td>
<td>2.5 (0.3-3.6)</td>
<td>1.78 ± 0.85</td>
</tr>
<tr>
<td>Cryptorchidism Unilateral</td>
<td>5</td>
<td>13.2 (9.2-17.6)</td>
<td>3.4 ± 1.65</td>
</tr>
<tr>
<td>Bilateral</td>
<td>3</td>
<td>3.8 ± 1.64</td>
<td>3.73 ± 0.76</td>
</tr>
<tr>
<td>Hypogonadotropic</td>
<td></td>
<td></td>
<td>18.8 (15,6-20.4)</td>
</tr>
</tbody>
</table>

*P > 0.05.

hypogonadotropic hypogonadism and hypospadias) were not statistically different from those found in normal children. Stimulation with HCG was unable to differentiate between unilateral and bilateral cryptorchidism (P > 0.05).

Discussion

The usefulness of short-term administration of HCG as a diagnostic test in assessing Leydig cell reserve in prepubertal boys has been widely recognised.17-18 The response of testosterone to HCG increases with the onset of puberty.17 However, wide variations in the response to HCG are seen even in normal subjects.19,20 This makes the interpretation of the test difficult in an individual patient and thus limits its usefulness.

Different workers have used widely variable doses of HCG. The dose of HCG varied from 800 - 5000 IU2-15 and the period of stimulation from 3 days to 6 weeks.5,8 It is now generally believed that HCG 2000 IU/d for 3 days gives maximum stimulation.16 In the present study we used HCG 2000 IU daily intramuscularly for 3 days. It was observed that the response to HCG followed the general pattern recorded in other series16 and the present work highlights both its usefulness and its limitations.

Boys with normal genital development showed an increase in testosterone level that ranged between 2.4 nmol/l and 10.5 nmol/l. This is similar to that reported by Grant et al.14 The boys with anorchia showed a minimal response to HCG, similar to previously published series.3,9-20 The present study highlights the value of HCG stimulation test in investigating anorchia. A negative reaction to stimulation in children with suspected anorchia precludes the need for surgical exploration. Definitive conclusions are difficult to draw since the number of subjects studied was small.

Cryptorchid boys showed a good response to HCG stimulation. The usefulness of the HCG stimulation test in anorchia but definite conclusions were not possible owing to the small number of subjects in the trial. This test helps to differentiate the subject with anorchia from one with cryptorchidism. In cryptorchidism, whether unilateral or bilateral, the test response was similar. There is considerable heterogeneity among normal subjects and the different groups of patients suffering from various genital disorders. This makes the diagnostic interpretation of the test difficult.

REFERENCES


Chorio-amnionitis in relation to mode of delivery at term

G. H. MÖLLER, D. L. WOODS, A. F. MALAN, C. C. SINCLAIR-SMITH

Summary

The incidence of inflammatory changes on histological examination in the placenta, membranes and umbilical cord of 50 infants born by spontaneous vaginal delivery were compared with those of 50 infants born by elective caesarean section before the onset of labour at term. Inflammation was significantly more frequent after vaginal delivery (28%) than after caesarean section (6%). This suggests that intra-uterine bacterial colonisation is uncommon before the onset of labour and is argued that chorio-amnionitis in the vaginally delivered placenta occurred during labour.

An acute inflammatory infiltration of the placenta, membranes and umbilical cord occurs when bacteria spread from the cervix and vagina into the uterine cavity. The reported incidence of such an inflammatory response, often referred to as chorio-amnionitis, varies widely in different studies and may depend on several factors, including the duration of membrane rupture, the gestational age at the onset of labour, and the amount of obstetric intervention before delivery.

In addition to complicating labour, it has been suggested that chorio-amnionitis is a cause of labour owing to the stimulation of prostaglandin synthesis in the inflamed membranes. If chorio-amnionitis is either a cause or a complication of labour, then it should often occur in vaginal deliveries after the spontaneous onset of labour. In contrast, it should be uncommon with elective caesarean section.

To test the hypothesis that chorio-amnionitis is uncommon before the onset of labour, the incidence of acute inflammation in the placentas of infants delivered by caesarean section was compared with those of infants delivered by spontaneous vaginal delivery at term.

Material and methods

The placentas of 100 consecutive infants born at term (37 - 42 weeks) were studied. Fifty infants were born by normal vaginal delivery after the spontaneous onset of labour. The duration of membrane rupture was less than 24 hours in all infants born vaginally and none of the mothers showed clinical signs of chorio-amnionitis during labour. A further 50 infants were delivered by elective caesarean section before the onset of labour. The membranes were intact at operation. In most cases, the indication for surgery was a previous caesarean section.

The placentas were examined within 24 hours of delivery. A segment of umbilical cord, a roll of peripheral membranes and a block of chorionic plate were sampled from each placenta. The chi-square test was used in the analysis of the data.


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