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URINARY β-CORE hCG: SCREENING FOR ANEUPLOIDIES IN EARLY PREGNANCY (11–14 WEEKS' GESTATION)

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SUMMARY

Initial studies at 17–22 weeks' gestation evaluating urinary β-core human chorionic gonadotrophin (hCG) as a marker for Down's syndrome had suggested that it may have more potential than its serum counterpart. This study measured maternal urinary β-core-hCG and creatinine at 11–14 weeks' gestation in a series of 26 aneuploidies (nine trisomy 21, five trisomy 18, four 45,X0, and eight others). The normal range for β-core-hCG and β-core-hCG/creatinine was derived from 198 normal singleton pregnancies. Trisomy 18 cases ($n=5$) had low maternal urinary β-core-hCG creatinine levels (median 0·35 MOM, range 0·08–0·82 MOM), whereas the other aneuploidies had no particular pattern; in particular, the trisomy 21 cases ($n=9$) (median 1·16 MOM, range 0·3–4·74 MOM) did not differ significantly from 1 MOM. The findings imply that maternal urinary β-core-hCG is not as discriminating for Down's syndrome between 11 and 14 weeks as later on in pregnancy. © 1997 by John Wiley & Sons, Ltd.

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INTRODUCTION

Biochemical screening for Down's syndrome is established practice in many units. In the second trimester, the most discriminatory marker is human chorionic gonadotrophin (hCG) or its free β-subunit. The intact molecule is a dimer comprising a specific β-subunit covalently bound to an α-subunit common to other glycoproteins. Both maternal serum intact hCG and the free β-subunit are elevated in Down's syndrome pregnancies but the extent of the elevation is greater for free β-hCG (Spencer *et al.*, 1992; Wald *et al.*, 1993). It has been suggested that the hCG molecule is less stable in affected pregnancies, due to the presence of 'nicking' between residues 47 and 48 or 44 and 45 in the β-subunit (Rotmensch *et al.*, 1992). The major metabolic product, β-core-hCG, is excreted into the urine (Nisula *et al.*, 1989; Cole *et al.*, 1993). This, in turn, led to the hypothesis that breakdown products of the β-subunit of hCG, in particular the major metabolic product, excreted into the urine may be more elevated than the circulating molecules (Cuckle *et al.*, 1994). Initial findings [seven cases between 19 and 22 weeks (Cuckle *et al.*, 1994); 24 cases between 15 and 22 weeks (Cuckle *et al.*, 1995); 14 cases between 17 and 21 weeks (Canick *et al.*, 1995)] substantiated this postulate but a study measuring five cases between 15 and 17 weeks did not (Hayashi and Kozu, 1995). This study looks at urinary β-core-hCG earlier in pregnancy, between 11 and 14 weeks.

MATERIALS AND METHODS

Urine samples were obtained from 224 women between 68 and 101 days' gestation undergoing

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Table I—Urinary β-core-hCG and β-core-hCG/creatinine levels in the 26 aneuploidies

Gestation (weeks+days)	β-core-hCG (pmol/l)	β-core-hCG/Cr (nmol/mmol)	β-core-hCG (MOM)	β-core-hCG/Cr (MOM)	
Trisomy 21 (9 cases)					
11+5	480	120·0	0·97	1·08	
11+6	448	160·0	0·91	1·47	
12+0	5186	218·8	10·52	2·06	
12+1	100	43·5	0·20	0·42	
12+4	1347	112·3	3·06	1·16	
12+5	2489	299·9	5·66	3·19	
12+6	8896	434·0	20·22	4·74	
13+5	500	74·0	1·12	0·96	
13+6	320	22·0	0·72	0·29	
Trisomy 18 (5 cases)					
11+5	96	38·4	0·19	0·36	
12+1	40	8·33	0·08	0·08	
13+0	96	21·8	0·22	0·25	
13+0	520	44·1	1·18	0·51	
13+6	150	60·0	0·34	0·82	
Turner's 45,XO (4 cases)					
12+0	300	76·9	0·61	0·72	
12+1	700	93·3	1·42	0·90	
13+0	680	62·4	1·55	0·70	
13+2	430	71·7	0·98	0·85	
Others (8 cases)					
11+3	260	185·7	0·42	1·60	92xxxx
11+6	350	112·9	0·71	1·04	tr7
11+0	960	95·1	1·95	0·89	xxy
12+0	400	56·34	0·81	0·53	47xyt(3:9)p
12+1	740	125·42	1·50	1·21	tr13
12+5	330	80·49	0·75	0·86	tr13
13+2	460	34·3	1·05	0·41	tr2
13+2	430	61·4	0·98	0·73	47+mar

Cr=creatinine.

prenatal diagnosis. The indications for prenatal diagnosis were advanced maternal age or increased nuchal translucency. The maternal ages ranged from 20 to 42 years. All pregnancies were singleton and viable at the onset of the study. Crown–rump length (CRL) was measured in 222 cases. The samples were stored at −40°C until assayed for β-core-hCG and creatinine. The β-core-hCG assay used was a modification of a previously published radioimmunoassay method (Lee *et al.*, 1991). Creatinine was measured by the Jaffe method, using a Monarch 200 centrifugal analyser. The β-core-hCG concentration was expressed in nmol/mmol creatinine. The β-core-hCG/creatinine values in 198 unaffected singleton pregnancies were used to define the normal levels for the appropriate gestations (range 68–101 days). Gestational age was based on ultrasound measurement of the CRL or the biparietal diameter and this was used to determine the normal range of assay values. Gestation was based on menstrual history in the 26 aneuploidies. The latter was to avoid introducing any bias due to apparent potential reduction in gestational age in aneuploidies when estimated from the CRL, especially in trisomy 18 cases (Macintosh *et al.*, 1995). The calculations were also performed using CRL gestation for the aneuploidies.

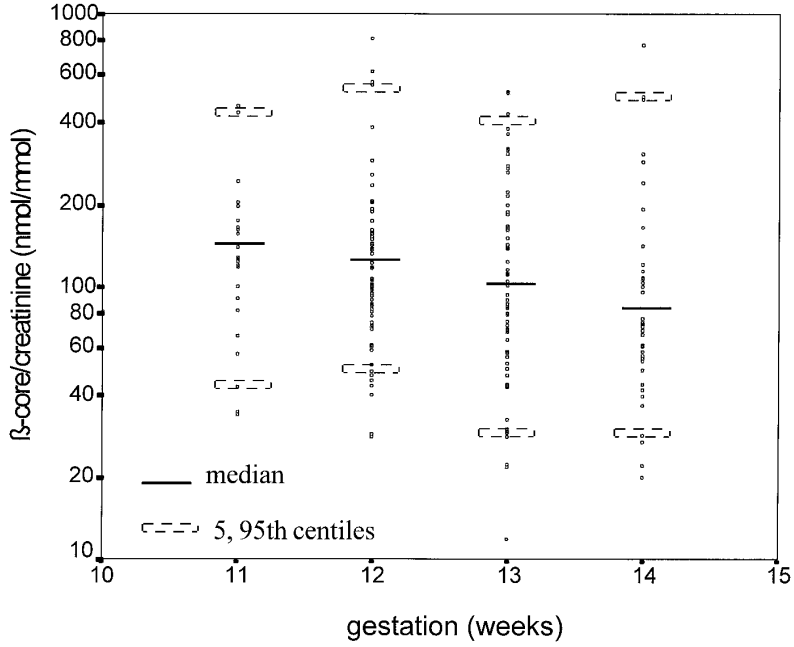

Fig. 1—Maternal urinary β-core-hCG/creatinine concentration according to gestational age expressed to the nearest completed week in the 198 unaffected pregnancies. The median values and the fifth and 95th centiles are shown by the bars

RESULTS

Clinical details of the 26 aneuploidies are given in Table I. The median of the unaffected cases of β-core-hCG/creatinine according to gestation is shown in Fig. 1 and in keeping with standard practice, all data were expressed as multiples of the normal median (MOM). The β-core-hCG concentrations in all 224 samples according to gestation and karyotype is shown in Fig. 2. The individual values in the 26 aneuploidies are shown in Table I. The median β-core-hCG and β-core-hCG/creatinine values were inversely related to the gestation in weeks in the unaffected samples (median β-core-hCG = − 17.23 weeks + 313 based on the median values of β-core-hCG, 680 at 11 weeks; 493 at 12 weeks; 440 at 13 weeks; 445 at 14 weeks) and for β-core-hCG/creatinine (124 at 11 weeks; 107 at 12 weeks; 87 at 13 weeks; 73 at 14 weeks). The urinary β-core-hCG/creatinine values expressed in MOM is plotted according to karyotype in Fig. 2. There is a tendency for trisomy 18 to have low urinary β-core-hCG/creatinine levels (median 0·35 MOM, range 0·08–0·82 MOM) and for trisomy 21 to have raised values (median 1·16 MOM, range 0·3–4·74 MOM). There was no particular pattern with the other aneuploidies. The results were unaltered by the method of dating gestational age (menstrual history or scan) used for the aneuploidies.

DISCUSSION

Initial findings were significantly elevated maternal urinary β-core-hCG/creatinine levels (median 6·02 MOM) in 24 cases of Down's syndrome between 15 and 22 weeks' gestation. This was also confirmed by Canick *et al.* (1995) (median 5·34 MOM, 14 cases between 17 and 21 weeks). Canick also compared serum hCG and urinary β-core-hCG/creatinine levels and found that in all 14 cases the urinary β-core-hCG/creatinine level was higher than the comparable maternal serum hCG level. There has been one study (Hayashi and Kozu, 1995) which failed to find such elevated levels of urinary β-core-hCG/creatinine (median 1·33 MOM, five cases between 15 and 17 weeks).

This study measured urinary β-core-hCG/creatinine in Down's syndrome pregnancies as early as 11–14 weeks' gestation. Preliminary results do not show the same degree of elevation of levels

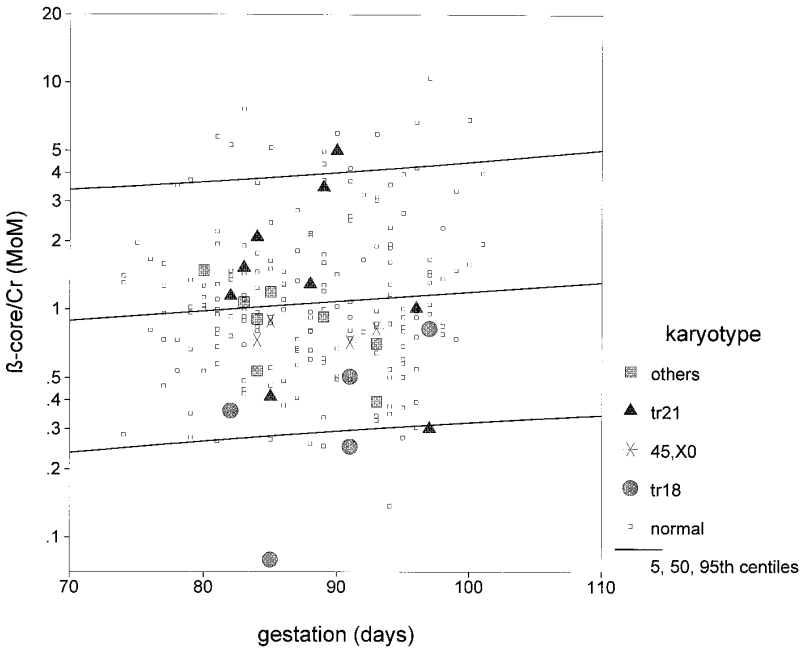

Fig. 2—Maternal urinary β-core-hCG/creatinine concentration in unaffected pregnancies (n=198); trisomy 21 (n=9); trisomy 18 (n=5); 45,X0 (n=4), and others (n=8) according to gestational age (weeks 11–14). The median and the fifth and 95th centiles for the unaffected pregnancies are shown

at this stage (median 1·16 MOM) compared with the 15–22 weeks study. There was a single 11-week sample in the Cuckle *et al.* study which was 1·01 MOM, the lowest value of the 24 cases and this is consistent with our measurements. The other samples failing to demonstrate such marked elevation were taken between 15 and 17 weeks' gestation (Hayashi and Kozu, 1995). The implications from this are that the phenomenon of extremely high urinary β-core-hCG/creatinine seen in Down's syndrome may occur only in the late second trimester.

There are nine reported values of urinary β-core-hCG/creatinine in trisomy 18 pregnancies (Cuckle *et al.*, 1995; Canick *et al.*, 1995; Hayashi and Kozu, 1995). Three of these nine samples were measured between 11 and 14 weeks and are in agreement with this study in finding reduced levels.

Because of the limited number of samples from aneuploidies and the problems of determining the median value for unaffected pregnancies, no final conclusion can be reached concerning the merits of urinary β-core-hCG/creatinine at 11–14 weeks but its discriminating ability as a marker for Down's syndrome is very likely to be less than in later pregnancy.

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