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SHORT COMMUNICATION

Second-trimester Maternal Serum Progesterone Levels in Turner Syndrome with and without Hydrops and in Trisomy 18

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Placental proteins, such as inhibin A and hCG and its subunits, as well as the placental steroid progesterone, are elevated in second-trimester maternal serum from cases of fetal Down syndrome. Since different cellular mechanisms are required for protein versus steroid synthesis and secretion, these data suggest that a generalized placental hypersecretory phenomenon is associated with Down syndrome. Inhibin A and hCG are also elevated in cases of Turner syndrome with hydrops, and are reduced in cases of Turner syndrome without hydrops and in trisomy 18. The objective of the present study was to determine maternal serum levels of the placental steroid progesterone in cases of Turner syndrome and trisomy 18. Twenty-one cases of trisomy 18, 10 cases of Turner syndrome without hydrops and 12 cases of Turner syndrome with hydrops were identified and each matched to five control samples.

Maternal serum progesterone levels were significantly elevated in Turner syndrome with hydrops (2.11 MoM), slightly reduced in Turner syndrome without hydrops (0.90 MoM) and modestly, though significantly, reduced in trisomy 18 (0.73 MoM). These data are similar to the patterns seen for inhibin A and hCG, suggesting that the overall synthetic and/or secretory activity of the placenta is increased in Turner syndrome with hydrops and decreased in Turner syndrome without hydrops and in trisomy 18. These data may be helpful in understanding the pathophysiological basis of serum marker patterns in these aneuploidies.

KEY WORDS: progesterone; trisomy 18; Turner syndrome; hydrops

INTRODUCTION

Fetal Down syndrome is associated with significant elevations in second-trimester maternal serum levels of several placental proteins, including human chorionic gonadotrophin (hCG) and its free subunits (summarized in Wald *et al.* (1997)), inhibin A (Canick *et al.*, 1994; Aitken *et al.*, 1996; Cuckle *et al.*, 1996; Wallace *et al.*, 1996; Wald *et al.*, 1996; Lambert-Messerlian *et al.*, 1996; Spencer *et al.*, 1996; Wenstrom *et al.*, 1997) and pregnancy-specific β-1 glycoprotein (Knight *et al.*, 1989). Progesterone is a steroid hormone produced by the placenta that is also elevated in second-trimester maternal serum of pregnancies affected with fetal Down syndrome (Knight *et al.*, 1989; Cuckle *et al.*, 1990). Since different cellular mechanisms are required for protein versus steroid synthesis and secretion, these data, taken together, suggest that a generalized placental hypersynthetic and/or hypersecretory phenomenon is associated with this aneuploidy (Chard, 1991).

Elevations in maternal serum levels of hCG (Saller *et al.*, 1992; Wenstrom *et al.*, 1994, 1996), the free β-subunit of hCG (Laundon *et al.*, 1996), and inhibin A (Lambert-Messerlian *et al.*, 1998b) have also been described in cases of fetal Turner syndrome with hydrops. In fact, because of the similarity in maternal serum analyte patterns, patients who are screen positive for Down syndrome also tend to be at increased risk of fetal Turner syndrome with hydrops (Saller *et al.*, 1992; Wenstrom *et al.*, 1994). However, the mechanism of elevated placental protein secretion in Turner syndrome with hydrops is not known. In the present study, we have examined levels of the placental steroid, progesterone, to determine if a generalized placental hypersecretory phenomenon seems to occur in Turner syndrome with hydrops, as it does in Down syndrome.

In contrast to the patterns seen in Down syndrome and Turner syndrome with hydrops, hCG (Saller *et al.*, 1992; Wenstrom *et al.*, 1994) and inhibin A (Lambert-Messerlian *et al.*, 1998b) are modestly reduced in maternal serum of cases of Turner syndrome without hydrops, suggesting that the hydropic condition, rather than the chromosome abnormality, is responsible for the increased analyte levels. In addition, hCG (Bogart *et al.*, 1987; Canick *et al.*, 1990; Palomaki *et al.*, 1992)

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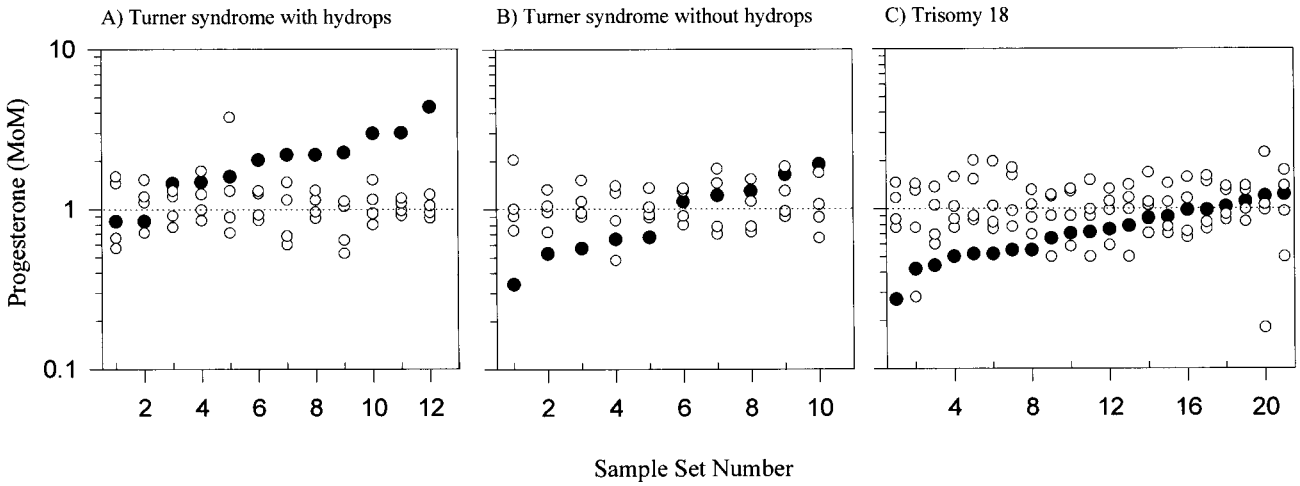

Fig. 1—Second-trimester maternal serum progesterone levels in cases of Turner syndrome with (A) and without hydrops (B) and in trisomy 18 (C). A median value was calculated for each set of five unaffected samples, and all data for each set are expressed in multiples of the median (MoM). The MoM value for each case (●) is shown relative to its matched controls (○), and the fifth control value for each set, the median, is represented as the horizontal dotted line at 1.0 MoM

and inhibin A (Aitken *et al.*, 1996; Lambert-Messerlian *et al.*, 1998b) are low in cases of trisomy 18. Therefore, we have examined levels of maternal serum progesterone in trisomy 18 and Turner syndrome cases with and without hydrops to determine whether this placental steroid is synthesized and secreted in the same pattern as observed for placental proteins.

METHODS

Second-trimester maternal serum samples (15–20 completed weeks of gestation) from 21 cases of trisomy 18 and 22 cases of Turner syndrome (12 with hydrops) were retrieved from freezer storage at Women and Infants, and Strong Memorial Hospitals. All cases of trisomy 18 and Turner syndrome were identified by cytogenetic analysis at the respective institutions. These cases were previously described in detail (Lambert-Messerlian *et al.*, 1998b). Each case was matched for completed week of gestation and duration of freezer storage (± 1 week) to five control samples from unaffected pregnancies. Samples were assayed for progesterone using a chemiluminescent competitive immunoassay from Diagnostic Products Laboratories, Los Angeles, CA. Inter- and intra-assay coefficients of variation were less than 15 per cent. Levels of AFP, uE3, hCG and inhibin A were also measured in each sample, either at the time of sample receipt for second-trimester prenatal screening or retrospectively at the time of the present study.

RESULTS

Although there was no effect of duration of freezer storage on maternal serum progesterone levels, there was a small, but significant, positive correlation between increasing gestational age and levels of progesterone ($r=0.2$, $p<0.05$). Therefore, data were analysed as case/control sets using matched rank analysis.

Maternal serum progesterone levels were elevated in Turner syndrome with hydrops ($p<0.01$). The median value in Turner syndrome with hydrops was 2.11 MoM (Fig. 1(A)). In contrast, maternal serum progesterone levels were marginally reduced in cases of Turner syndrome without hydrops (median=0.90 MoM, Fig. 1(B)), although this reduction was not significant. Maternal serum progesterone levels were moderately, and significantly, reduced in cases of trisomy 18 ($p<0.01$). The median value in trisomy 18 was 0.73 MoM (Fig. 1(C)).

DISCUSSION

In the second-trimester of pregnancy, the placental steroid progesterone appears to be secreted in a pattern similar to the placental proteins, hCG and inhibin A, in fetal Turner syndrome and in Down syndrome. Previous reports describe a two-fold elevation in hCG and inhibin A (summarized in Wald *et al.* (1997)) and a 20 per cent increase in progesterone levels (Knight *et al.*, 1989; Cuckle *et al.*, 1990) in maternal serum of cases of fetal Down syndrome. These analytes are also elevated in Turner syndrome with hydrops, with a four-fold increase in hCG and inhibin A (Lambert-Messerlian *et al.*, 1998b), and a two-fold increase in progesterone.

The present progesterone data add to a growing list of analytes that are derived from the placenta and elevated in second-trimester maternal serum samples from Down syndrome and Turner syndrome with hydrops. Our present results, in combination with previous reports, support the hypothesis presented by Chard (1991) suggesting that a generalized placental hypersecretory activity occurs in Down syndrome, and perhaps in Turner syndrome with hydrops. In Down

syndrome, in addition to elevations in second-trimester maternal serum levels of hCG and its subunits, inhibin and progesterone, levels of pregnancy-specific β-1 glycoprotein (SP-1) are, on average, 47 per cent higher in Down syndrome pregnancy (Wald *et al*., 1997). At first glance levels of pregnancy associated plasma protein A (PAPP-A) appear to be an exception to this observation, with second-trimester levels unaffected (0.97 MoM) in Down syndrome pregnancy. However, since first trimester levels of PAPP-A are extremely low (0.38 MoM) (Wald *et al*., 1997), one may infer that the recovery of PAPP-A levels in the second-trimester actually reflects increased second-trimester synthesis and/or secretion. Note that analytes derived from fetal rather than placental origin, such as alpha fetoprotein and unconjugated oestriol, are reduced in second-trimester maternal serum samples from Down syndrome (Wald *et al*., 1997) and Turner syndrome (Saller *et al*., 1992) pregnancy.

The elevation of maternal serum progesterone in Turner syndrome with hydrops, like the elevations of hCG (Saller *et al*., 1996; Knowles and Flett 1994) and inhibin A levels, appears to be secondary to the hydropic condition rather than a direct result of the aneuploidy, since elevations are not seen in Turner syndrome without hydrops. In fact, levels of progesterone are somewhat decreased in Turner syndrome without hydrops as well as in trisomy 18, again consistent with the patterns of hCG and inhibin A secretion in these cases (Saller *et al*., 1992; Wenstrom *et al*., 1994; Lambert-Messerlian *et al*., 1998b). In Turner syndrome without hydrops, modest reductions occur in maternal serum levels of inhibin A, hCG (Lambert-Messerlian *et al*., 1998b) and progesterone (0.90 MoM). In trisomy 18, maternal serum hCG levels are much lower (0.13–0.30 MoM) (Bogart *et al*., 1987; Canick *et al*., 1990; Palomaki *et al*., 1992; Aitken *et al*., 1996; Lambert-Messerlian *et al*., 1998b) than those of either inhibin A (median = 0.84–0.88 MoM) (Aitken *et al*., 1996; Lambert-Messerlian *et al*., 1998b) or progesterone (median = 0.73 MoM). These data suggest that a generalized placental hyposecretory and/or hyposynthetic state may be associated with Turner syndrome without hydrops and with trisomy 18.

The mechanism of placental hypersecretion in Down syndrome and Turner syndrome is unknown. Some evidence suggests that increased placental synthesis may accompany or be responsible for the apparent hypersecretory phenomenon observed in Down syndrome. For example, cultured trophoblasts from cases of Down syndrome secreted 10 times more hCG than age-matched control cells, and the mRNA levels for both the α and β-subunits of hCG were increased in Down syndrome placental tissues (Eldar-Geva *et al*., 1995). In addition, the placental content of hCG as well as SP1 was elevated in Down syndrome cases (Newby *et al*., 1997). The mRNA for the α-subunit of inhibin A was significantly increased in Down syndrome placental tissues in comparison with tissues from unaffected pregnancies (Lambert-Messerlian *et al*., 1998a). Whether altered placental synthesis of inhibin A or hCG accompanies the maternal serum changes in these analytes is not known for Turner syndrome, and placental progesterone synthesis has yet to be studied in Down syndrome, Turner syndrome or in trisomy 18.

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