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SHORT COMMUNICATION

SCHWANGERSCHAFTS PROTEIN 1 (SP1) ADDS LITTLE TO THE AGE-RELATED DETECTION OF FETAL DOWN SYNDROME IN THE FIRST TRIMESTER OF PREGNANCY

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SUMMARY

Schwangerschafts Protein 1 (SP1), being a placental protein appearing in the maternal circulation early in pregnancy, has been investigated as a potential marker for Down syndrome in the first trimester. Our study compared SP1 levels in 15 pregnancies with a Down syndrome fetus and 97 matched controls. Although the median MoM in Down syndrome pregnancies (0·49) was lower than in controls, its use as a marker added very little to the detection rate above the maternal age alone. © 1998 John Wiley & Sons, Ltd.

KEY WORDS: SP1; β1-glycoprotein; Down syndrome; screening

INTRODUCTION

In the search for first-trimester maternal serum markers for fetal aneuploidy, many biochemical substances have been investigated. One such substance in Schwangerschafts Protein 1 (SP1). To date, four studies have appeared assessing its usefulness, all with relatively small numbers of affected fetuses (Brock *et al*., 1990; Macintosh *et al*., 1993; Bersinger *et al*., 1994; Qin *et al*., 1997). We report our findings of SP1 measurements in the sera of 15 women carrying a fetus with Down syndrome to add to the existing data.

SUBJECTS AND METHODS

From October 1990 to February 1994, maternal serum samples were taken prior to chorionic villus sampling (CVS), performed mainly for advanced maternal age. Gestational age ranged between 8 and 12 completed weeks. The serum was stored at −20°C. Serum samples were available from 15 pregnancies in which the subsequent CVS identified a fetus with Down syndrome, and from 97 controls. Controls were chosen on the basis of gestational age (within the same completed week of pregnancy), duration of storage (within three months), and maternal age (in five-year age groups).

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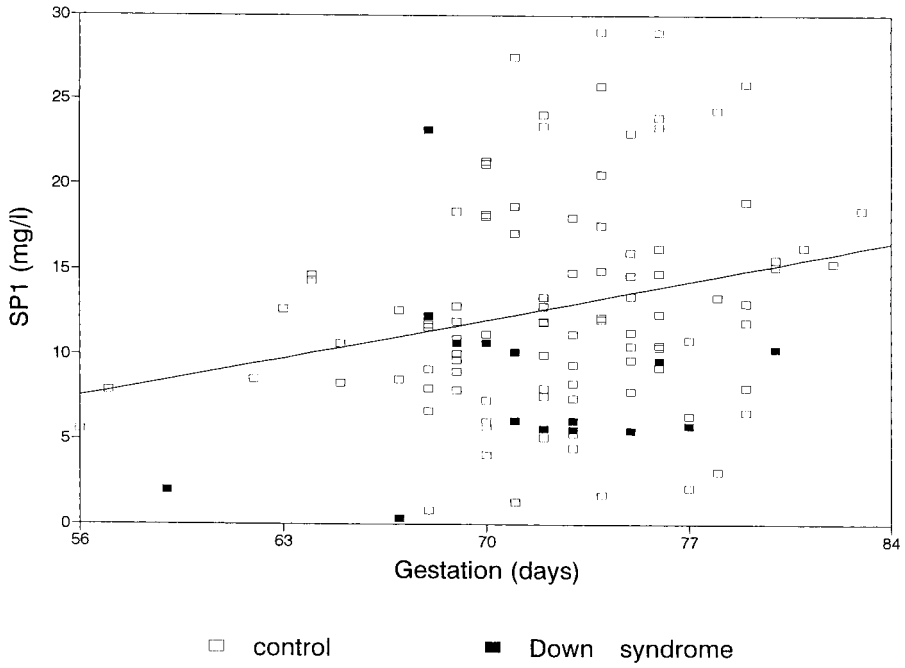

Fig. 1—Distribution of SP1 values against gestational age

SP1 was measured with a modification of a commercial radio-immunoassay (RIA-gnost SP1, Behringwerke AG, Marburg, Germany). To enhance the precision at low levels, the dilution factor of samples below 2000 ug/l was adapted appropriately. The interassay variation was 8 per cent at a level of 2900 ug/l.

RESULTS

Figure 1 shows the distribution of SP1 values against gestational age. The median multiple of the median (MoM) for Down syndrome fetuses was 0·49. The two cases with the earliest gestational age are the only cases with SP1 levels at or lower than the fifth centile of normal controls. Of the next two cases, one is at the 98th centile and one just above the 50th centile. The other 11 cases, at gestational ages of 69 days or greater, all have SP1 levels between the 10th and 50th percentile. The receiver operating characteristic curve (Fig. 2) shows that SP1 is less effective than maternal age, and adds minimal improvement to the detection rate of Down syndrome when added to the maternal age-related risk.

DISCUSSION

SP1 is a protein which appears in the maternal circulation simultaneously with hCG (Ahmed and Klopper, 1983). It is a product of the placenta having been detected in the syncytio-trophoblast using immunofluorescence. SP1 concentration increases exponentially early in pregnancy with a doubling rate of two to three days (Grudzinskas *et al.*, 1979). At seven to eight weeks' gestation the increase in SP1 slows down somewhat, and reaches a plateau at 37 weeks' gestation. There appears to be a direct relationship between plasma SP1 concentration and active placental mass (Bischof and Klopper, 1983).

Early studies investigating SP1 in threatened abortions (Schultz-Larsen and Hertz, 1978; Jandial *et al.*, 1978) suggested that SP1 was a reliable marker for predicting those pregnancies which would continue and those destined to abort. SP1 was superior in this aspect to both hCG and hPL. However, studies performed on the role of SP1 since the advent of ultrasound have shown that SP1 does not help in predicting those pregnancies that will miscarry when embryonic heart motion has been seen on ultrasound (Westergaard *et al.*, 1985; Witt *et al.*, 1990).

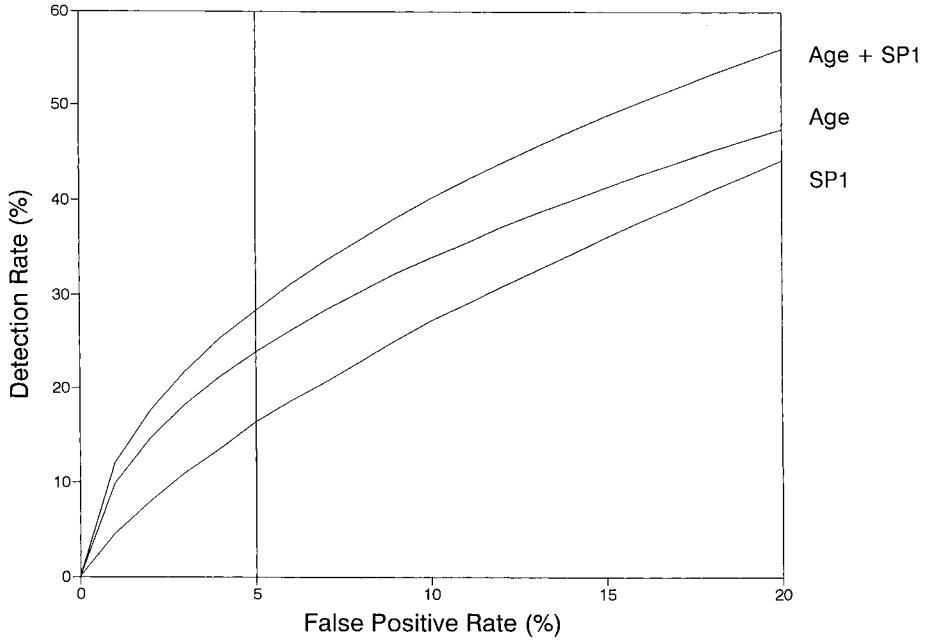

Fig. 2—The receiver operating characteristic curve comparing SP1, maternal age and the combination of these two parameters in the detection of Down syndrome fetuses

Table I—Studies of maternal SP1 levels in pregnancies affected by Down syndrome (DS) in the first trimester of pregnancy

Reference	Total number of DS pregnancies	DS pregnancies ⩽9 weeks	Time of detection	MoM of all cases
Brock *et al.* (1990)	21	9	Livebirth	0·79
Macintosh *et al.* (1993)	14	13	CVS	0·4
Brizot *et al.* (1995)	45	0	CVS or amniocentesis	0·96
Qin *et al.* (1997)	39	25	CVS or livebirth	0·27†/0·89‡
This study	15	1	CVS	0·49

*This includes the 32 Down syndrome fetuses reported in Bersinger *et al.* (1994).
†MoM of those pregnancies <10 weeks' gestation.
‡MoM of those pregnancies at 10–12 weeks' gestation.

Four groups have investigated SP1 as a marker for fetal aneuploidy (see Table I). Brock *et al.* (1990) measured SP1 in serum (at 7–14 weeks' gestation) of 21 women who subsequently delivered a Down syndrome infant. The median (MoM) for Down syndrome fetuses was 0·79. Macintosh *et al.* (1993) reported their results on 14 fetuses with Down syndrome detected by chorionic villus sampling (CVS). The gestational age at time of blood sampling ranged from 6–12 weeks, with the majority of the cases of Down syndrome being less than nine weeks' gestation. Their median MoM for SP1 was 0·4. For a five per cent screen positive rate they detected 46 per cent of Down syndrome pregnancies, and with a combination of age and SP1, detected 50 per cent of affected fetuses. Bersinger *et al.* (1994) examined the sera from 29 women carrying a fetus with Down syndrome, collected between 10 and 13 weeks' gestation prior to CVS being performed. They found the median (MoM) for SP1 in Down syndrome to be 0·94 between 10–11 weeks, and 0·68 between 12–13 weeks. In an extension of this study, the same group reported a median MoM of 0·96 for

gestational ages ranging from 10–13 weeks (Brizot *et al*., 1995). Qin *et al*. (1997) reported the results of SP1 estimations on the sera of 156 women carrying a fetus with Down syndrome, 39 of them at less than 14 weeks' gestation. The median MoM for the 25 samples taken between five and nine weeks' gestation was 0·27. For the 14 samples between 10 and 12 weeks', the median MoM was 0·89, which was not significantly different from the controls.

Our results show that SP1 was below the normal median for the majority of Down syndrome fetuses. However, only 16·2 per cent of affected fetuses would have been detected at a five per cent false-positive rate. Using the maternal age-related risk alone, given the pregnant population distribution in the north of the Netherlands in 1990, 23·7 per cent of pregnancies carrying a Down syndrome fetus would have been detected. By adding these two parameters the detection rate only increased to 28·2 per cent. The average gestational age at the time of blood sampling in our study was greater than that of Macintosh *et al*. (1993), which could explain our less-promising results. Fourteen of the 15 Down syndrome samples we tested were from pregnancies greater than nine weeks' gestation. Before 70 days' gestation, with a false-positive rate of five per cent, three of the six cases would have been detected by SP1 alone; after 70 days, none at all. Although the numbers are small, these data are consistent with Bersinger *et al*. (1994) and Qin *et al*. (1997). The data all seem to suggest that SP1 may be a reasonable marker for a Down syndrome fetus at gestations less than 10 weeks, but has very little discriminatory power between 10 and 13 weeks' gestation. Although our study did not address the early second trimester, the study of Qin *et al*. (1997) suggests a renewed role for SP1 after 14 weeks' gestation, when a raised SP1 level is more common in Down syndrome pregnancies.

Why Down syndrome pregnancies have lower levels of SP1 prior to nine weeks' gestation is unclear; the assumption that the lower SP1 values are due to impending abortion is not borne out by the studies mentioned above. Perhaps aneuploid pregnancies do not have the initial rapid increase in SP1 noted in the first seven to eight weeks in normal pregnancies, but experience a more steady increase, catching up only after eight weeks, and then apparently overshooting the mark after 14 weeks' gestation. This still does not explain the very high levels seen in two women between 9 and 10 weeks' gestation in our study. For whatever reason, SP1 appears to be an ineffective marker for Down syndrome in the gestational window between 10 and 14 weeks.

If SP1 is to be used in first-trimester screening, then it would appear to be most useful in the very early weeks (i.e., nine weeks' gestation or less). In any first-trimester Down syndrome screening programme, it needs to be remembered that many aneuploid pregnancies abort spontaneously and the earlier they are detected the greater that likelihood is (Snijders *et al*., 1994; Macintosh *et al*., 1995). Hence, before SP1 is considered for use as an *early* marker for Down syndrome, more information will be required regarding SP1 levels in aneuploid prgnancies destined to miscarry. Longitudinal data on SP1 levels in individual affected pregnancies may help our understanding of the changes seen across gestation.

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