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RESEARCH LETTER

Second-trimester maternal serum screening for Down syndrome in twin-to-twin transfusion syndrome

Nathalie Sermondade[1], Sophie Dreux[1], Jean-François Oury[2] and Françoise Muller[1,3]*

[1]*Service de Biochimie-Hormonologie, Hôpital Robert Debré, AP-HP, Paris, France*
[2]*Service de Gynécologie Obstétrique, Hôpital Robert Debré, AP-HP, Paris, France*
[3]*Université Paris Ile de France Ouest, France*

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Prenatal Down syndrome screening is widely used, based on risk calculation combining maternal age, second- or first-trimester maternal serum markers and nuchal translucency (NT) measurement. Many confounding factors have been studied for maternal serum markers distribution, such as maternal weight, maternal smoking and twin pregnancies (Cuckle, 2000; Wald and Rish, 2005). Correlation between markers and pregnancy outcome or foetal pathology such as pre-eclampsia, chromosomal anomalies, foetal death, foetal hydrops, small for gestational age and prematurity have also been reported. In twin pregnancies, maternal serum Down syndrome screening is fraught with difficulties (Garchet-Beaudron *et al*., 2008), among which that markers distribution depends on chorionicity (Muller *et al*., 2003). About 20% of twin pregnancies are monochorionic (MC), which can be complicated by twin-to-twin transfusion syndrome (TTTS) in 10% to 20% of cases.

The aim of our study was to evaluate whether maternal serum markers are different when a MC twin pregnancy is secondary complicated by TTTS and to analyse whether the difference depends on the severity of TTTS.

This retrospective study concerned 3606 maternal serums twin pregnancies included in routine second-trimester Down syndrome screening (14–21 weeks of amenorrhea), of which 493 were MC. Cases with unrelated severe abnormal outcome (miscarriage, foetal death, aneuploidies, foetal malformations) were excluded ($n = 53$). TTTS was observed in 60 cases (12%). Alpha-fetoprotein (AFP) and free β-human chorionic gonadotrophin (hCG) (Dual kit PerkinElmer, Turku, Finland) were assessed using the AutoDELFIA automatic immunoassay system (PerkinElmer, Turku, Finland) and expressed in multiples of median (MoM). This MoM was first corrected by factors corresponding to maternal weight and smoking status. This corrected MoM was divided by factors that we previously defined for MC twin pregnancies, 2.1 for AFP and 2.16 for free β-hCG (Muller *et al*., 2003).

Marker values were compared between MC twins complicated by TTTS and those with normal outcome (Mann–Whitney).

Table 1 reports the results of Down syndrome screening markers. A significant difference ($P = 0.0016$) was observed for free β-hCG MoM values between MC twins with versus without TTTS (1.39 vs 0.98). Using a 2.5 MoM–free β-hCG cutoff, the sensitivity and the 1-specificity to predict TTTS were 24% and 9.3%, respectively. The difference observed in AFP MoMs between MC pregnancies complicated or not by TTTS (1.15 vs 0.99) did not reach statistical significance ($P = 0.20$).

When TTTS cases were divided into two groups depending on the outcome (at least one alive infant, $n = 32$, vs both infants dead, $n = 28$), higher free β-hCG levels were noted in the cases with worse outcome (1.23 vs 1.47 MoM); the difference, however, did not reach significance.

The relation between maternal serum Down syndrome markers and TTTS has not been previously studied. TTTS is due to unbalanced blood flow through placental anastomoses (Denbow *et al*., 2000), but the detailed mechanism leading to its complex foetal cardiovascular and renal disturbances remains unclear (Mahieu-Caputo *et al*., 2003). Despite advances in perinatal management (Senat *et al*., 2004), TTTS still carries a high risk of both foetal and neonatal mortality and morbidity. In the present study, we observed that free β-hCG is significantly higher (1.39 MoM vs 0.98) when a MC twin pregnancy is subsequently complicated by TTTS, particularly when a poor outcome is observed (1.47 MoM). The non-significant difference in free β-hCG levels according to severity of outcome is probably due to the small number of cases. Sebire *et al*. (1997) similarly observed discordance in foetal nuchal translucency in MC twins destined to develop severe TTTS. Sensitivity (38%) and specificity (9%) of a NT > 95th percentile were similar to those we have observed for maternal serum markers.

*Correspondence to: Françoise Muller, Biochimie Hormonologie, Hôpital Robert Debré, 48, Bd Sérurier, 75019, Paris, France.
E-mail: francoise.muller@rdb.aphp.fr

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Table 1—MoM values of maternal serum markers in MC twin pregnancies with and without TTTS

	Twin pregnancies	MC without TTTS	MC with TTTS	*P* (with vs without TTTS)
n	3606	380	60	
AFP median MoM (range)	1 (0.37–23.69)	0.99 (0.32–2.88)	1.15 (0.50–4.50)	0.20
β-hCG median MoM (range)	1 (0.12–13.4)	0.98 (0.21–27.3)	1.39 (0.29–5.71)	0.0016

AFP, Alpha-fetoprotein; hCG, human chorionic gonadotrophin; MC, monochorionic; MoM, multiples of median; TTTS, twin-to-twin transfusion syndrome.

The higher value of MoM-free β-hCG can probably be explained by the placental oedema observed in TTTS. The relation between placental oedema and hCG was observed in Down syndrome in which hCG was statistically higher when the foetus presented with hydrops (2.51 MoM vs 4.07) (Benn *et al*., 2002), and in Turner syndrome in which total hCG was 0.66 MoM in nonhydropic noncystic Turner cases versus 3.29 in hydropic cases (Benn and Ying, 2004).

In conclusion, second-trimester maternal serum–free β-hCG is significantly higher in MC twin pregnancies, which subsequently develop TTTS. Placental oedema may explain this difference. The poor sensitivity and specificity of the test, however, does not allow to firmly identify the at-risk patients.

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