

False-Negative Results in Routine Combined First-Trimester Screening for Down Syndrome in Catalonia

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Introduction

An important part of any screening protocol is to assess carefully the false-negative (FN) screening results, to improve process effectiveness. Since 2008, all pregnant women in Catalonia have been offered a combined risk assessment in the first trimester for Down Syndrome (DS) on the basis of nuchal translucency (NT) and the measurement of plasma free β -human chorionic gonadotropin (hCGb) and pregnancy-associated plasma protein-A (PAPP-A). Even though the limits of the screening are acknowledged, only a few studies have analyzed the contributing factors for FN results in first-trimester screening for fetal Down syndrome.

Objective

The aim of our study was to investigate prenatal characteristics of false negative DS cases and identify possible ways to improve the detection rate of first-trimester screening DS

Methods

We retrospectively analysed data from all pregnant women attended for routine first trimester aneuploidies screening between January 2010 and December 2012 at the 13 clinical laboratories in the public health system in Catalonia.

Measurements of hCGb and PAPP-A were made in seven laboratories using a chemiluminescence immunoassay (Immulite 2000 Siemens®) and in six laboratories using a time resolved fluorometric immunoassay (Delfia Xpress Perkin Elmer®).

Risk calculation was evaluated using three software programmes: Prisca (Siemens®), Lifecycle (Perkin Elmer®) y SsdwLab (SBP® Software). Correction factors and CRL regression equation to calculate gestational age (Robinson and Fleming 1975)¹⁵ were previously set at the same values in the three applications to avoid software-dependent differences. Serum levels of hCGb and PAPP-A were converted to MoM values using the specific medians calculated from Caucasian gestations. MoM values were corrected according to the following factors: weight, ethnicity, smoking status and diabetes. The cut-off for screen positives was 1:250.

We compared the distribution, calculating median and quartile levels, of maternal age and weight, gestational age, PAPP-A MoM, hCGb MoM, and NT MoM in true positive (TP) and false negative (FN) groups. The Mann-Whitney U test was used to compare the median values between TP and FN groups. Statistical analysis was made by an Analyse-it® software.

Results

A total of 127141 first trimester pregnancies were screened for aneuploidies in Catalonia during the studied period. There were a total of 364 DS cases in the screened population (1:349), 327 of them were confirmed TP and 37 of them were confirmed FN. Detection rate (DR) was 89.8% for a false positive rate of 3.44%.

In our study, 59,5% of all FN cases presented a SD risk between 1:250 and 1:1000. In the 40.5% remaining cases the SD risk was lower than 1:1000.

In **table 1** the median and quartile levels of maternal age and weight, gestational age, PAPP-A MoM, hCGb MoM, and NT MoM in TP and FN groups are presented. P Value of Mann-Whitney test is also shown. The difference between TP and FN groups was significant for maternal age, PAPP-A (MoM) and NT (MoM) medians.

	VP				FN				p Value
	MEDIAN (95% CI)	QUARTIL 1	QUARTIL 3	IQR	MEDIAN (95% CI)	QUARTIL 1	QUARTIL 3	IQR	
Maternal age	37.2 (36.2-37.8)	34.4	40.1	5.6	34.7 (31.5-37.0)	29.9	38.3	8.4	0.003
Maternal weight	63.0 (62.0-64.4)	57	71	14	64.0 (60.4-66.0)	59.4	67.5	8.5	0.917
Gestational age	77 (75-78)	70	83	13	79 (72-84)	70	85	15	0.515
PAPP-A MoM	0.34 (0.29-0.37)	0.22	0.52	0.3	0.56 (0.49-0.74)	0.45	0.99	0.52	<0,0001
hCGb MoM	1.63 (1.42-1.78)	1.08	2.42	1.33	1.55 (1.15-1.89)	1.13	2.23	0.99	0.623
NT MoM	1.81 (1.72-1.97)	1.35	2.52	1.19	0.96 (0.91-1.07)	0.89	1.11	0.22	<0,0001

Conclusions

This study indicates that the SD screening protocol offered to pregnant women in Catalonia has an appropriate performance, with a detection rate of 89.8% and a false positive rate of 3.44%.

Since the percentage of intermediate risk in the FN group is high, complementary strategies such as contingent screening could be applied in order to reduce the FN cases.

The data found indicate that maternal age is lower, NT is smaller and PAPP-A level is higher in the FN cases than in the VP group. The quality control in the measurement of NT and PAPP-A should be improved with the aim of reducing errors.