

WEB APPENDIX: Effect on Down syndrome screening performance of adjusting for values in a previous pregnancy

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I. Formulae for the distribution parameters of adjusted MoM values when current pregnancies are unaffected

Let $\{P_i; i=1,\dots,7\}$ denote the \log_{10} -MoM values in a previous unaffected pregnancy for the first trimester markers NT, free β -hCG, PAPP-A, and the second trimester markers AFP, uE₃, free β -hCG, and Inhibin-A. Also let $\{C_i; i=1,\dots,7\}$ denote the \log_{10} -MoMs for the same markers in a current unaffected pregnancy. The adjusted \log_{10} -MoM value, denoted here by AC_i , for marker i is defined by Wald *et al* (2004A) to be

$$AC_i = C_i - b_i P_i,$$

where b_i is the regression coefficient of C_i on P_i .

The \log_{10} -MoM values in a previous unaffected pregnancy were taken to have a multivariate Gaussian distribution. The value P_i has mean 0 and standard deviation σ_i . The correlation coefficient for P_i and P_j is r_{ij} . The distribution of \log_{10} -MoM values in a current unaffected pregnancy was identical.

As AC_i is a linear combination of P_i and C_i , the distribution of the adjusted \log_{10} -MoM marker values is multivariate Gaussian. The mean of AC_i is given by

$$\text{Mean}[AC_i] = \text{Mean}[C_i] - b_i \text{Mean}[P_i]. \quad (1)$$

Since the means of P_i and C_i are both 0,

$$\text{Mean}[AC_i] = 0.$$

The standard deviation of AC_i is derived as follows. The variance is

$$\text{Var}[AC_i] = \text{Var}[C_i] + b_i^2 \text{Var}[P_i] - 2b_i \text{Cov}[P_i, C_i]. \quad (2)$$

The covariance $\text{Cov}[P_i, C_i]$ can be expressed as

$$\text{Cov}[P_i, C_i] = \text{Cov}[P_i, AC_i + b_i P_i].$$

Taking $\text{Cov}[P_i, AC_i]$ to be 0 then

$$\text{Cov}[P_i, C_i] = b_i \text{Var}[P_i]$$

and equation (2) simplifies to

$$\text{Var}[AC_i] = \text{Var}[C_i] - b_i^2 \text{Var}[P_i]. \quad (3)$$

Therefore the standard deviation is

$$\text{SD}[AC_i] = \sigma_i \sqrt{(1 - b_i^2)}.$$

The correlation coefficient for AC_i and AC_j is derived as follows. The covariance has the form

$$\begin{aligned} \text{Cov}[AC_i, AC_j] &= \text{Cov}[C_i, C_j] - b_i \text{Cov}[P_i, C_j] - b_j \text{Cov}[P_j, C_i] \\ &\quad + b_i b_j \text{Cov}[P_i, P_j]. \end{aligned} \quad (4)$$

Taking $\text{Cov}[P_i, P_j]$ to be 0, then

$$\begin{aligned}\text{Cov}[P_i, C_j] &= \text{Cov}[P_i, b_j P_j + AC_j] \\ &= b_j \text{Cov}[P_i, P_j]\end{aligned}\quad (5)$$

and equation (4) simplifies to

$$\text{Cov}[AC_i, AC_j] = \text{Cov}[C_i, C_j] - b_i b_j \text{Cov}[P_i, P_j]. \quad (6)$$

Therefore the correlation coefficient is

$$\text{Cor}[AC_i, AC_j] = \frac{r_{ij}(1 - b_i b_j)}{\sqrt{(1 - b_i^2)(1 - b_j^2)}}.$$

II. Formulae for the distribution parameters of adjusted MoM values when current pregnancies are affected by Down syndrome

The \log_{10} -MoM marker values for a current affected pregnancy are taken to have a multivariate Gaussian distribution. The value C_i has mean μ_{Di} and standard deviation σ_{Di} , and the correlation coefficient for C_i and C_j is r_{Dij} .

Assume that the regression coefficients are the same as for unaffected current pregnancies and, as above, that the covariance $\text{Cov}(P_i, AC_j)$ is 0 for all i and j . It follows from equation (1) that the mean of AC_i is

$$\text{Mean}[AC_i] = \mu_{Di}.$$

It follows from equation (3) that the standard deviation of AC_i is

$$\text{SD}[AC_i] = \sqrt{\sigma_{Di}^2 - b_i \sigma_i^2}.$$

Finally, it follows from equation (6) that the correlation coefficient for AC_i and AC_j is

$$\text{Cor}[AC_i, AC_j] = \frac{r_{Dij}\sigma_{Di}\sigma_{Dj} - b_i b_j r_{ij}\sigma_i\sigma_j}{\sqrt{(\sigma_{Di}^2 - b_i^2\sigma_i^2)(\sigma_{Dj}^2 - b_j^2\sigma_j^2)}}.$$

III. Distribution parameters for adjusted and unadjusted MoM values

Table 1 Means (\log_{10} MoM) of marker levels in Down syndrome pregnancies. The means are the same for adjusted and unadjusted MoM values

Marker	Mean
Down Syndrome	
First Trimester	
NT	0.3380
Free β -hCG	0.2878
PAPP-A	-0.3768
Second Trimester	
AFP	-0.1308
uE ₃	-0.1549
Free β -hCG	0.4249
Inhibin-A	0.3384

Table 2 Standard deviations (\log_{10} MoM) of marker levels in Down syndrome and unaffected pregnancies according to adjustment for values in a previous pregnancy.

Marker	Unadjusted	Adjusted
Down Syndrome		
First Trimester		
NT	0.2313	0.2308
Free β -hCG	0.2569	0.2216
PAPP-A	0.2802	0.2599
Second Trimester		
AFP	0.1398	0.1275
uE ₃	0.1238	0.1202
Free β -hCG	0.2965	0.2760
Inhibin-A	0.2679	0.2547
Unaffected		
First Trimester		
NT (11 completed weeks)	0.1439	0.1430
Free β -hCG	0.2651	0.2311
PAPP-A	0.2495	0.2264
Second trimester		
AFP	0.1399	0.1276
uE ₃	0.1142	0.1103
Free β -hCG	0.2577	0.2339
Inhibin-A	0.2078	0.1904

Table 3 Correlation coefficients between marker levels in Down syndrome pregnancies according to adjustment for values in a previous pregnancy

	Unadjusted						Adjusted					
	First Trimester			Second Trimester			First Trimester			Second Trimester		
	NT	Free β -hCG	PAPP-A	AFP	uE ₃	Free β -hCG	NT	Free β -hCG	PAPP-A	AFP	uE ₃	Free β -hCG
First trimester												
Free β -hCG	0.1080						0.1270					
PAPP-A	-0.1506	-0.0692					-0.1613	-0.1195				
Second trimester												
AFP	0.0809	0.0697	0.0660				0.0892	0.0842	0.0570			
uE ₃	0.0695	-0.3666	0.3712	-0.1903			0.0707	-0.4340	0.4002	-0.1455		
Free β -hCG	0.1471	0.7797	-0.3004	0.1981	-0.4356		0.1600	0.7960	-0.3578	0.2161	-0.4763	
Inhibin-A	0.1854	0.2909	-0.1842	0.1770	-0.3276	0.4384	0.1966	0.2985	-0.2120	0.1743	-0.3479	0.4430

Table 4 Correlation coefficients between marker levels in unaffected pregnancies according to adjustment for values in a previous pregnancy

	Unadjusted						Adjusted					
	First Trimester			Second Trimester			First Trimester			Second Trimester		
	NT	Free β -hCG	PAPP-A	AFP	uE ₃	Free β -hCG	NT	Free β -hCG	PAPP-A	AFP	uE ₃	Free β -hCG
First trimester												
Free β -hCG	-0.0391						-0.0427					
PAPP-A	-0.0516	0.1395					-0.0546	0.1400				
Second trimester												
AFP	-0.0095	0.0167	0.1160				-0.1000	0.0168	0.1160			
uE ₃	0.0596	-0.0255	0.1213	0.2010			0.0603	-0.0264	0.1233	0.2010		
Free β -hCG	-0.0604	0.7605	0.0627	0.0974	-0.0585		-0.0639	0.7635	0.0627	0.0974	-0.0595	
Inhibin-A	-0.0499	0.2937	0.0237	0.2033	-0.0875	0.4092	-0.0524	0.2956	0.0237	0.2033	-0.0886	0.4093

IV Results for complete adjustment of marker values for those in a previous pregnancy

Table 5 Screening performance in women who have had a previously screened pregnancy according to whether serum marker levels are MoM adjusted or completely adjusted for those in the previous pregnancy

Screening test	Adjustment	DR(%) for a FPR of			FPR(%) for a DR of	
		1%	3%	5%	75%	85%
Triple	MoM	59	73	80	3.5	7.9
	Complete	60	73	80	3.5	7.7
Quadruple	MoM	68	80	85	1.9	4.9
	Complete	68	80	85	1.8	4.9
Combined	MoM	75	83	87	1.1	3.7
	Complete	75	84	88	1.1	3.6
Serum Integrated	MoM	76	85	89	0.9	2.9
	Complete	76	85	89	0.9	2.9
Integrated	MoM	88	93	95	0.2	0.7
	Complete	88	93	95	0.2	0.7

DR: Detection rate

FPR: False positive rate

Table 6 Screening performance in women who have had a previous false-positive screening result according to whether serum markers are MoM adjusted or completely adjusted for those in a previous pregnancy, and according to risk cut-off

Screening test	Adjustment	Risk cut-off of 1:150		Risk cut-off of 1:250	
		DR(%)	FPR(%)	DR(%)	FPR(%)
Triple	MoM	85	6.8	89	9.8
	Complete	86	7.2	89	9.9
Quadruple	MoM	87	5.0	90	7.6
	Complete	88	5.5	90	7.9
Combined	MoM	88	5.0	91	7.5
	Complete	89	5.2	91	7.7
Serum Integrated	MoM	88	3.8	91	5.9
	Complete	89	4.2	92	6.2
Integrated	MoM	93	2.5	95	3.7
	Complete	93	2.7	95	3.9

IV Results for adjusting NT MoM values for those in a previous pregnancy

Table 7 Screening performance in women who have had a previously screened pregnancy according to whether serum marker levels are adjusted or serum marker and NT values are adjusted for those in the previous pregnancy

Screening test	Adjustment	DR(%) for a FPR of			FPR(%) for a DR of	
		1%	3%	5%	75%	85%
Combined	Serum	75	83	87	1.1	3.7
	Serum + NT	75	84	87	1.0	3.6
Integrated	Serum	88	93	95	0.2	0.7
	Serum + NT	88	93	95	0.1	0.6

Table 9 Screening performance in women who have had a previous false-positive screening result according to whether serum markers are adjusted or serum marker and NT levels are adjusted for those in a previous pregnancy

Screening test	Adjustment	Risk cut-off of 1:150		Risk cut-off of 1:250	
		DR(%)	FPR(%)	DR(%)	FPR(%)
Combined	Serum	88	5.0	91	7.5
	Serum+NT	88	4.0	90	6.3
Integrated	Serum	93	2.5	95	3.7
	Serum+NT	92	2.1	94	3.2