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Maternal weight correction of maternal serum PAPP-A and free β-hCG MoM when screening for trisomy 21 in the first trimester of pregnancy

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Objective To assess the suitability of either the log-linear or reciprocal-linear regression procedure for maternal weight correction of biochemical marker MoMs in the first trimester.

Methods Data from two prospective first-trimester OSCAR screening programmes including 32 010 women with first-trimester maternal serum-free β-hCG and PAPP-A measured by the Kryptor analyser was analysed by regression analysis to provide parameters for the log-linear and reciprocal-linear MoM correction procedures. Assessment was made by goodness of fit to the data. The impact on detection rate and false-positive rate of the different correction procedures was assessed using statistical modelling with biochemical markers alone.

Results Both log-linear and reciprocal-linear correction were shown to fit the data well. For free β-hCG, the log-linear procedure was marginally superior to the reciprocal-linear procedure ($r^2 = 0.986$ v 0.980), whilst for PAPP-A the reciprocal-linear procedure was marginally better ($r^2 = 0.991$ v 0.985). Log-linear correction reduced the variance for both markers more than did the reciprocal-linear procedure. For free β-hCG, the sd was reduced from 0.2675 to 0.2605 and for PAPP-A, it was reduced from 0.2545 to 0.2336. Correcting for maternal weight was shown to reduce the population false-positive rate from 7.0 to 6.5%, whilst maintaining the same detection rate at a risk cut-off of 1 in a 100. At individual levels, a two-fold variation in risk was demonstrated depending upon the individual's weight.

Conclusions To provide accurate individual patient-specific risks for trisomy 21, maternal weight must be taken into account and should be a mandatory data item for screening programmes. Maternal weight correction in the first trimester using free β-hCG and PAPP-A can be best achieved using the log-linear procedure.

KEY WORDS: Down syndrome; prenatal screening

INTRODUCTION

In the second trimester, it is common practice for prenatal screening programmes to adjust either analyte concentration or MoMs for a mother's weight. The logic for such adjustment is based on the fact that the placental- or fetal-derived markers tend to be more diluted in heavier women since they have a larger blood volume and conversely more concentrated in lighter women because of a smaller blood volume. Although it is argued that making correction for maternal weight reduces the population variability of the markers (Wald *et al*., 1992), in practice, the impact on detection rate and false-positive rate is very small (Wald *et al*., 1994; Reynolds *et al*., 1991).

There have been two different methods proposed for correcting second-trimester biochemical marker MoMs for maternal weight. The first procedure is based on a log-linear regression of MoM against maternal weight (Reynolds *et al*., 1991; Wald *et al*., 1981). The second procedure is based on a reciprocal-linear regression of MoM against the reciprocal of weight (Neveux *et al*., 1996). It has been suggested that this latter procedure may be a better fit to the data and a more appropriate method of correction (Neveux *et al*., 1996) although in two studies comparing the two procedures, one found no significant difference (Watt and Wald, 1998), whilst another found the reciprocal-linear regression procedure was much better at reducing the variability in screen-positive rates (Kennedy *et al*., 1999).

In moving into the first trimester, screening using maternal serum-free β-hCG and pregnancy associated plasma protein-A (PAPP-A) in conjunction with fetal nuchal translucency (NT) has achieved detection rates of 90% for a 5% false-positive rate in both retrospective (Spencer *et al*., 1999) and prospective studies at 11 to 14 weeks (Spencer *et al*., 2000a; Bindra *et al*., 2002; Spencer *et al*., 2003). Thus far, whilst limited studies have used the reciprocal-linear regression (Spencer *et al*., 2000b), no formal assessment of the two procedures has been made.

In this study, we aim to assess the suitability of either the log-linear or reciprocal-linear regression procedures for weight correction of biochemical marker MoMs in the first trimester using a large prospective data set.

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METHODS

Study population

At Harold Wood Hospital, Essex, and at the Fetal Medicine Centre, London, screening for chromosomal anomalies was carried out in a one-stop (OSCAR) clinic using a combination of fetal NT and maternal serum biochemistry at 11 to 14 weeks. Fetal NT and crown-rump length (CRL) were measured using standardised techniques (www.fetalmedicine.com/nuchal) by sonographers who had obtained The Fetal Medicine Foundation Certificate of Competence in the 11 to 14 weeks' scan. At the time of the ultrasound visit, a plain clotted blood sample was taken for measurement of PAPP-A and free β-hCG and after harvesting of serum, the biochemical markers were analysed using the Kryptor analytical system (Brahms AG, Berlin) with results available within 30 min of blood collection. All clinical and analytical data were stored in a fetal database (ViewPoint, Webbling, Germany) along with the outcome of pregnancy. The study group comprised unaffected pregnancies from three prospective screening studies and included 14 240 unaffected pregnancies (Bindra *et al*., 2002), 11 105 unaffected pregnancies from a second study (Spencer *et al*., 2003) and 7209 from the fourth year of prospective screening at Harold Wood Hospital. In total, the combined data set included 32 554 unaffected pregnancies of which maternal weight information in kilogram was available on 32 010 (98.3%).

From the same prospective studies, data from a total of 126 cases with trisomy 21 were also available.

The study group consisted of predominately Caucasian women (95%) with Asian, Oriental and Afro-Caribbean women representing the remaining 5%.

Data analysis

Analytical results from the unaffected pregnancies were converted to MoMs (uncorrected for maternal weight) for the respective gestation calculated from CRL using a median-regression curve derived previously. The MoMs were grouped according to maternal weight into a series of 10-kg bands from 35 to 115 kg; above 115 kg, all data were grouped into one band. For each weight band, the median MoM, median maternal weight, reciprocal median maternal weight and the number of cases were calculated. For the log-linear weight-correction procedure, the weight-correction parameters were derived from the slope and intercept of the weighted regression of median $\log_{10}$ MoM versus median weight. The square root of the number of cases in each weight band was used to weight the regression. For the reciprocal-linear weight-correction procedure, the weight-correction parameters were derived from the slope and intercept of the weighted regression of median MoM versus reciprocal median weight, weighted by square root of the number of cases in each weight band.

Weight-corrected MoMs for each marker and for each weight-correction method was determined according to the relevant correction formula. For both the unaffected and for trisomy 21 cases, biochemical risk estimates for trisomy 21 were calculated from the uncorrected and weight-corrected MoMs for each marker, and combined with maternal age. Combined NT and biochemical risk estimates were calculated similarly using the Fetal Medicine Foundation risk algorithm after incorporation of the measured NT (Snijders *et al*., 1998; Spencer *et al*., 1999). The impact of the different weight-correction procedures on detection rate and false-positive rate were assessed.

RESULTS

Table 1 shows the number of unaffected cases in each weight band along with median weight and median-free β-hCG and PAPP-A MoMs. Figures 1 and 2 show the log-linear regression plots for free β-hCG and PAPP-A. The log-linear weight correction formulae for free β-hCG and PAPP-A are thus

$$\text{Corrected free } \beta\text{-hCG MoM} = \text{free } \beta\text{-hCG MoM}/10^{(0.276-0.0040^{*}\,\text{weight})}$$

$$\text{Corrected PAPP-A MoM} = \text{PAPP-A MoM}/10^{(0.4416-0.0066^{*}\,\text{weight})}$$

Table 1—The number of unaffected cases in each weight band along with median weight and median-free β-hCG and PAPP-A MoMs

Weight band	Number	Median weight (kg)	1/Median weight	Median-free β-hCG	Median PAPP-A
35.0–44.9	658	42.73	0.0234	1.301	1.552
45.0–54.9	4814	51.43	0.0194	1.170	1.313
55.0–64.9	12 699	60.29	0.0166	1.065	1.118
65.0–74.9	7070	69.00	0.0145	0.965	0.941
75.0–84.9	3828	78.54	0.0127	0.883	0.793
85.0–94.9	1524	88.97	0.0112	0.788	0.658
95.0–104.9	822	99.24	0.0101	0.711	0.532
105.0–114.9	359	108.98	0.0092	0.701	0.461
115.0–124.9	180	119.46	0.0084	0.640	0.420
>124.9	56	135.32	0.0074	0.539	0.387
Total	32 010	66.87		1.00	1.00

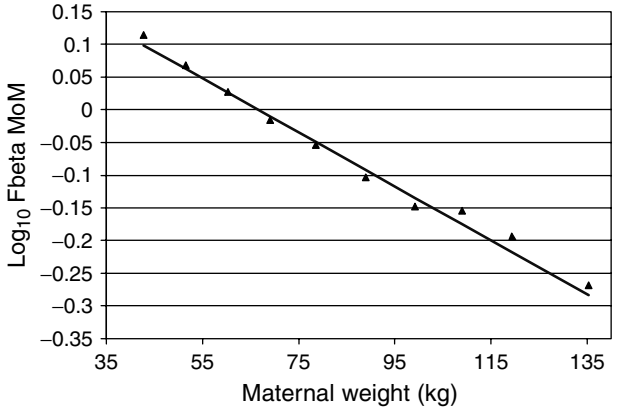

Figure 1—Log-Linear regression of median-free β-hCG MoM on median maternal weight (▲ individual group median, solid line is the weighted regression line)

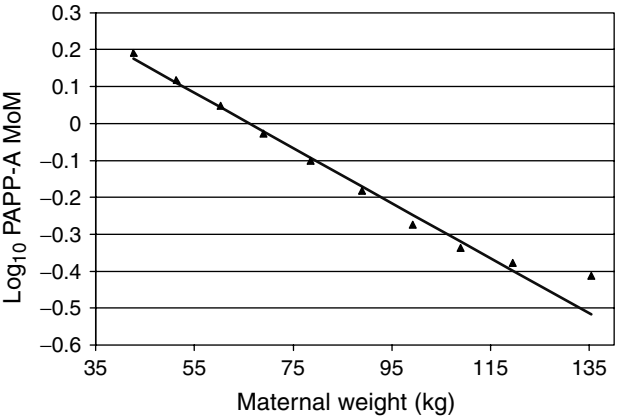

Figure 2—Log-linear regression of median PAPP-A MoM on median maternal weight (▲ individual group median, solid line is the weighted regression line)

Figures 3 and 4 show the reciprocal-linear regression plots for free β-hCG and PAPP-A. The reciprocal-linear weight correction formulae for free β-hCG and PAPP-A are thus

$$\text{Corrected free } \beta\text{-hCG MoM} = \text{free } \beta\text{-hCG MoM}/((46.875 * 1/\text{weight}) + 0.271)$$

$$\text{Corrected PAPP-A MoM} = \text{PAPP-A MoM}/((79.858 * 1/\text{weight}) - 0.230)$$

A comparison of the two fitting methods shows that both methods fit the data well, although the log-linear method appears marginally superior to the reciprocal-linear method for free β-hCG ($r^2 = 0.986$ compared with 0.980), whilst for PAPP-A the reciprocal-linear method is marginally superior to the log-linear method ($r^2 = 0.991$ compared with 0.985). Figures 5 and 6 plot the log-median free β-hCG and PAPP-A against maternal weight in each weight band along with the log-linear and reciprocal-linear regression lines again showing a better fit in the tails for reciprocal-linear with PAPP-A and for log-linear with free β-hCG.

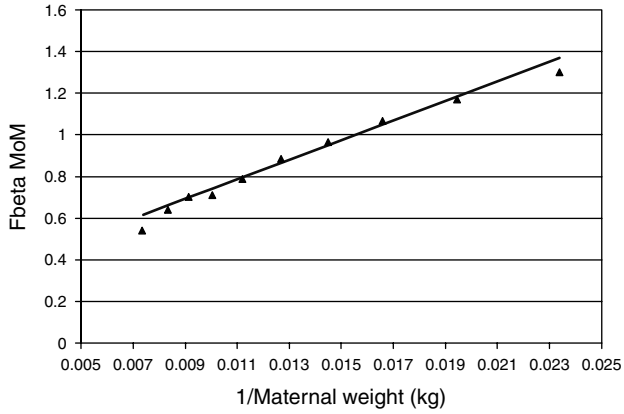

Figure 3—Linear-reciprocal regression of median-free β-hCG MoM on reciprocal median maternal weight (▲ individual group median, solid line is the weighted regression line)

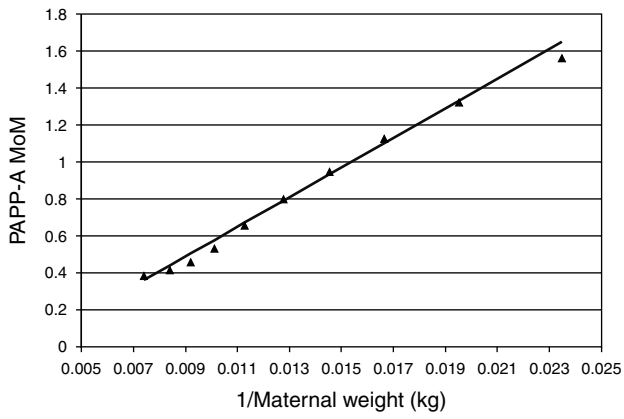

Figure 4—Linear-reciprocal regression of median PAPP-A MoM on reciprocal median maternal weight (▲ individual group median, solid line is the weighted regression line)

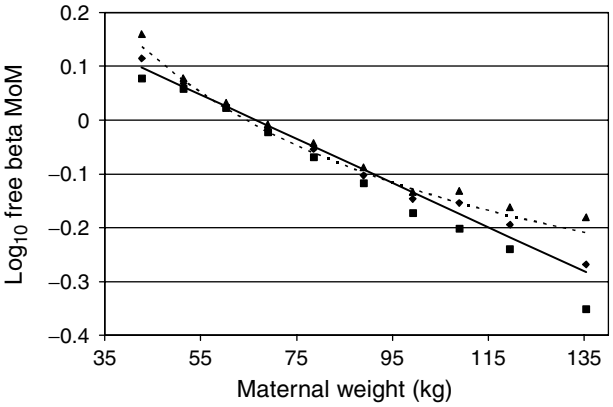

Figure 5—Plot of median free-β-hCG MoM (♦) for each maternal weight band against median maternal weight. Log-linear regression line is shown as a solid line with the linear-reciprocal regression shown as the dotted line. ▲ represents the 95% and ■ the 5% confidence intervals

To assess the impact on first-trimester screening of using no weight correction, log-linear correction or reciprocal-linear correction, we retrospectively calculated

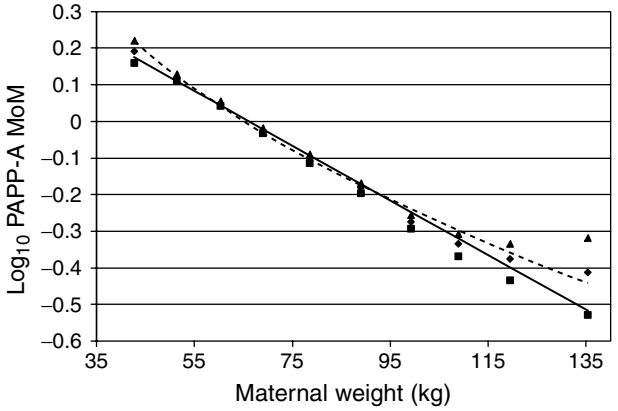

Figure 6—Plot of median PAPP-A MoM (♦) for each maternal weight band against median maternal weight. Log-linear regression line is shown as a solid line with the linear-reciprocal regression shown as the dotted line. ▲ represents the 95% and ■ the 5% confidence intervals

Table 2—False-positive rate and detection rate using a 1 in 100 risk cut-off for biochemistry and maternal age when screening using different weight-correction methods. Number of unaffected cases = 32 010, number of trisomy 21 cases = 126

Correction method		Biochemistry/ age only (number at risk (%))
No weight correction	False-positive rate (%)	2241 (7.0%)
	Detection rate (%)	84 (67%)
Log-linear	False-positive rate (%)	2094 (6.5%)
	Detection rate (%)	84 (67%)
Reciprocal-linear	False-positive rate (%)	2259 (7.1%)
	Detection rate (%)	84 (67%)

the risk for trisomy 21 using biochemistry and maternal age. Table 2 shows the false-positive rate and detection rate using a 1 in 100 risk cut-off for biochemistry and maternal age. The results show that correction for maternal weight using the log-linear procedure results in a marginal reduction in population false-positive rates with little or no impact on population-detection rates.

For the log-linear procedure, two cases with trisomy 21 classified as low risk using no weight correction were re-classified as high risk and two cases classified as high risk were re-classified as low risk on weight correction. For unaffected pregnancies, 54 cases classified as low risk using no weight correction were re-classified as high risk and 201 cases classified as high risk were re-classified as low risk on weight correction.

For the reciprocal-linear procedure, two cases with trisomy 21 classified as low risk using no weight correction were re-classified as high risk and two cases classified as high risk were re-classified as low risk on weight correction. For unaffected pregnancies, 219 cases classified as low risk using no weight correction were re-classified as high risk and 201 classified as low risk were re-classified as high risk after weight correction.

Table 3—False-positive rate at different maternal weight bands with and without log-linear weight correction of the biochemical marker MoMs. Risks calculated using biochemistry and maternal age with a 1 in 100 risk cut-off

Weight band	No weight correction (%)	Log-linear weight correction (%)
35.0–44.9	5.3	5.9
45.0–54.9	4.4	5.0
55.0–64.9	6.8	6.5
65.0–74.9	7.1	6.4
75.0–84.9	7.6	6.6
85.0–94.9	8.3	6.5
95.0–104.9	10.7	6.4
105.0–114.9	13.1	6.6
115.0–124.9	15.6	6.8
>124.9	15.9	6.4
All	7.0	6.5

To further demonstrate the improvement that weight correction can bring, we assessed the impact of weight correction on the unaffected population standard deviation (sd) of $\log_{10}$ marker MoMs. In the uncorrected case, the sd for free β-hCG was 0.2675, it was 0.2602 with log-linear correction and 0.2602 with reciprocal-linear correction. In the uncorrected cases, the sd for PAPP-A was 0.2545, it was reduced to 0.2336 with log-linear correction and to 0.2354 with reciprocal-linear correction. The tightening of the distribution of marker MoMs was more noticeable for PAPP-A and particularly with the log-linear correction procedures.

When the impact of correction is assessed by individual weight bands, it can be seen that when screening using biochemistry and maternal age, log-linear correction evens out the false-positive rate across the maternal weight bands (Table 3).

Although weight correction seems to have an almost negligible impact on population detection and false-positive rates, for an individual woman, weight correction can have quite a dramatic impact on her individual patient-specific risk. Table 4 shows the biochemical risk and combined biochemistry/NT risk when making a neutral weight correction compared with what the risk would have been, given different maternal weights. The risks are calculated for a woman aged 30 years with an NT of 2.5 mm, gestation of 12 weeks 0 days, free β-hCG of 90 iu/L and PAPP-A of 1.75 iu/L. The results indicating a two-fold variation in risk clearly show the importance to the individual of having the correct adjustment made for maternal weight. This data confirms that maternal weight should become a mandatory data item for prenatal screening programmes to allow calculation of an accurate patient-specific risk.

DISCUSSION

Our analysis of the two major weight-correction procedures has shown that in the first trimester—as in the second trimester (Watt and Wald, 1998; Kennedy *et al*., 1999), there is little to choose between the

Table 4—Biochemical risk and combined biochemistry/NT risk when making a neutral weight correction compared with what the risk would have been, given different maternal weights. The risks are calculated for a woman aged 30 years with an NT of 2.5 mm, gestation of 12 weeks 0 days, free β-hCG of 90 iu/L and PAPP-A of 1.75 iu/L

Weight (kg)	Free β-hCG MoM	PAPP-A MoM	Biochemical risk (1 in)	Combined risk (1 in)
None given	2.29	0.67	236	252
35	1.67	0.41	146	156
40	1.75	0.45	162	172
45	1.83	0.48	177	189
50	1.92	0.52	194	206
55	2.01	0.56	210	224
60	2.11	0.60	226	241
65	2.21	0.65	243	259
70	2.31	0.70	259	275
75	2.42	0.76	274	292
80	2.53	0.82	288	307
85	2.65	0.88	302	321
90	2.78	0.95	314	334
95	2.91	1.03	325	346
100	3.04	1.11	334	355
105	3.19	1.20	341	363
110	3.34	1.29	346	369
115	3.50	1.39	350	373
120	3.66	1.50	351	374
125	3.83	1.62	350	373

log-linear procedure or the reciprocal-linear procedure in that both fit the data reasonably well. If anything, the log-linear procedure fits the PAPP-A data better and results in a more significant reduction in variance, hence, we would propose to use this procedure in preference to the reciprocal-linear procedure. As has been noted previously in second-trimester studies (Wald *et al*., 1992; Reynolds *et al*., 1991; Neveux *et al*., 1996; Watt and Wald, 1998; Kennedy *et al*., 1999) the impact on population-detection rate and false-positive rate is very small. However, to the individual woman presenting for prenatal screening, population-detection rates and false-positive rates are a minor consideration; what the individual wants is the best estimate of risk for her. We have shown the significant impact that non-correction for maternal weight can have on an individual's risk, altering this by some two-fold depending upon the individual's weight. Clearly, for an accurate individual patient-specific risk for trisomy 21, maternal weight must be taken into account, and items such as maternal weight should become a mandatory data item for any such screening programmes.

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