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Maternal body weight and first trimester screening for chromosomal anomalies.

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Abstract

Prenatal risk ratios for Down syndrome adjust for maternal weight because maternal serum biomarker levels decrease with increasing maternal weight. This is accomplished by converting serum biomarker values into a multiple of the expected median (MOM) for women of the same gestational age. Weight is frequently not recorded and the impact of using MOMs not adjusted for weight for calculating risk ratios is unknown. The aim of this study is to examine the effect of missing weight on first trimester Down syndrome risk ratios by comparing risk ratios calculated using weight-unadjusted-and –adjusted MOMs. Findings at the population level indicate that the impact of not correcting for maternal weight on first trimester screening results for chromosomal anomalies would lead to 84 per 10,000 pregnancies changing from negative to positive and 56 per 10,000 pregnancies changing from positive to negative.

Pregnancy screening for chromosomal anomalies currently involves determining individual risks using information from maternal characteristics, ultrasound measurements and maternal serum biomarkers.[1] Because maternal serum biomarker levels decrease with increasing maternal weight[2] each biomarker concentration is adjusted for weight by converting values into a multiple of the expected median (MOM) for women of the same gestational age.[3] However, maternal weight is not always recorded. The impact of not correcting for weight on first trimester screening results has not been quantified. A recent Canadian study found that, of women with a weight discrepancy of >5 pounds (lbs) (2.3 kg) and within 50 units of the risk cut-off, the chance of a screening result changing ranged from 33-43%. However, among women with a Down syndrome infant, weight discrepancies of up to 15 lbs (~ 8 kg) made no difference.[4] One possible explanation is that correction for weight does not alter screening results when abnormal serum biomarkers levels are pronounced. A limitation of this study was that it examined the impact of theoretical weight values without considering corresponding changes to serum biomarkers that, in reality, would occur parallel to varying weight scenarios. Therefore, the aims of this study were to quantify the proportion of pregnancies with unrecorded weight, assess whether weight is missing at random and compare weight unadjusted- and –adjusted risk ratios and screening results for chromosomal anomalies, using women's actual body weight values obtained from a separate source.

This cohort study included women with singleton pregnancies who received antenatal and obstetric services from public hospitals in the Northern Sydney Central Coast Health Area, Australia and had a blood sample analysed as part of first trimester screening between November 2006 and December 2009. Variables from the laboratory database, collected at the time of screening, included: maternal age, weight, gestational age and serum biomarkers free hCG and

PAPP-A. Antenatal and birth data for the study region was recorded in an electronic obstetric surveillance system. Information from the obstetric database used in this study included: self-reported pre-pregnancy weight and height, parity, smoking status during pregnancy, chorionic villus sampling < 20 weeks, amniocentesis <20 weeks, any birth defect and birth outcome. Body mass index (BMI; kg/m^2) was calculated using maternal weight and height from the obstetric database and categorised using international standards.[5] Record linkage was used to combine women's information from the laboratory and obstetric databases with only de-identified data made available to researchers. The study was approved by the Human Research Ethics Committee of Northern Sydney Central Coast Health (LNR/11/HAWKE/254).

For women where weight was not recorded, the laboratory's algorithms and parameters were used to convert biomarker concentrations of free β-hCG and PAPP-A into two adjusted multiple of the expected median (MoM) values: i) adjusted for gestational age only (replicating the result given in the absence of maternal weight); and ii) adjusted for gestational age and maternal weight ascertained from the obstetric database. Crump-rump length (CRL) and nuchal translucency thickness (NT) were not available in the laboratory database, thus, average population estimates were applied and kept constant in the risk ratio calculations (CRL=59 mm; NT=1.8 mm).[6] MoM values, ultrasound measurements and maternal characteristics were then manually entered into the Fetal Medicine Foundation (FMF) First Trimester Screening Program® (Astraia, Munich, Germany) to determine weight unadjusted- and-adjusted risk ratios for chromosomal anomalies Trisomy 21 (Down syndrome), Trisomy 18 and Trisomy 13. The background risk based on maternal age produced by the (FMF)-Software for interpreting the adjusted risk ratio was used to determine the impact of weight-adjusted-and-unadjusted MoM values on risk ratios. The clinical cut-offs applied to risk ratios were 1:350 for Trisomy 21, 1:50

for Trisomy 18 and 1:50 for Trisomy 13. Descriptive statistics were used to compare women with recorded and unrecorded weight values and to examine risk ratios and screening results using explanatory factors. All analyses were conducted using SAS, version 9.3 (SAS Institute, Cary, NC, USA) and P-value <0.05 was considered statistically significant.

Of 2, 411 women with singleton pregnancies that underwent first trimester screening, 368 (15.3%) had no recorded weight. Women with unrecorded weight, compared to those with weight records, were more likely to be younger [mean (SD) 32.2 ± 4.8 vs. 32.9 ± 5.1, p=0.003] and, using data from the obstetric database, have a lower mean body weight (62.4 ± 12.2 vs. 64.2 ± 13.8, p=0.05) and BMI (23.3 ± 4.4 vs. 23.9 ±5.2, p=0.04). The proportion of women with and without weight records that were underweight (6.2% vs. 7.3%), normal weight (60.8% vs. 63.9%), overweight (18.8% vs. 16.3%) and obese (9.5% vs. 7.6%) were not significantly different, nor were they different by parity, smoking during pregnancy, testing < 20 weeks for chronic villus sampling or amniocentesis, reporting of any birth defect or stillbirths.

Comparison between weight unadjusted and adjusted risk ratios among women with no recorded laboratory weight found discrepancies in 28 women. There were 11 (3.1%) women, all of whom were underweight or normal weight, where, compared to the background risk, the risk ratio of a chromosomal anomaly was lower based on the weight-unadjusted risk ratio and higher based on the weight-adjusted risk ratio. There were 17 (4.8%) women, all of whom were overweight or obese, where, compared to the background risk, the risk ratio of a chromosomal anomaly was higher based on the weight-unadjusted risk ratio and lower based on the weight-adjusted risk ratio. After applying clinical cut-offs, only a total of 5 women had a discrepancy in screening result; all except one were negative when uncorrected for weight and positive when corrected for weight. All 5 women had live births with no reported birth defects.

For Trisomy 21 both risk ratios identified a negative screening result for 333 (93.3%) women and a positive screening result for 20 (5.6%) women. Two women (0.6%) had a positive screening result that would only have been identified using the weight-adjusted risk ratio. These latter two cases of underweight and normal weight women aged 26 and 35 years did not undergo chronic villus sampling or amniocentesis. Two overweight/obese women (0.6%) aged 28 and 36 years only had a positive screening result when the risk ratio that was uncorrected for weight was used, one of which had an amniocentesis. For Trisomy 18, both risk ratios identified a negative screening result for 355 (99.4%) women and a positive screening result for 1 (0.3%) woman. One woman (0.3%) had a positive screening result that would only have been identified using the weight-adjusted risk ratio. This latter case was a 42 year-old underweight woman with no chronic villus sampling or amniocentesis. For Trisomy 13, there was complete concordance; 356 (99.7%) women had a negative screening result and 1 normal weight woman had a positive result with no reported birth defects or adverse outcomes.

Correlation between maternal body weight collected in the laboratory (mean ± SD: 65.8 ± 14.0) and obstetric databases (64.0 ± 13.6) showed a high level of agreement (ρ=0.97, p<0.0001). The mean (95% CI) discrepancy in body weight between the two databases was -1.3 kg (-1.5, -1.2). Maternal age was not correlated to body weight ascertained from the obstetric (ρ=0.02, p=0.41) or laboratory (ρ=0.02, p=0.30) databases.

In summary, this study found that maternal weight is commonly not recorded and that weight information is not missing at random. Findings suggest that monitoring and evaluation of data is necessary for quality control. Of assurance, weight in this study population was more frequently reported in higher risk women (i.e. older and heavier) suggesting that screening centers are aware of the importance of these factors. Importantly, for the majority of women, correcting for weight

made no difference to screening results for chromosomal anomalies. Findings indicate smaller differences than the 5-15 pounds hypothesized by Huang et al. In a small number of cases, correction for weight changed the screening result. Maternal weight information is routinely available and since it can be important, healthcare providers should be informed that this information must be provided for accurate results. At the population level this would impact 84 per 10,000 pregnancies changing from negative to positive and 56 per 10,000 pregnancies changing from positive to negative.

There are some study limitations. The laboratory database did not have ultrasound measurements because in this study region blood collection usually precedes the appointment date for the nuchal translucency ultrasound. This allows biomarker results to be known on the day on the ultrasound visit so that the healthcare provider can calculate risk ratios and deliver screening results to women and their families in person along with any additional counseling or support. Other limitations include use of data on 'any birth defects' as a proxy for chromosomal anomalies and use of self-reported pre-pregnancy body weight measurements instead of direct measurements as the reference source. However, our analysis found that weight records in the laboratory database were highly correlated with self-reported values from the obstetric database.

In conclusion, not correcting for maternal weight in first trimester screening may lead to under- and over-identification of screening results of chromosomal anomalies. The importance of correcting for maternal body weight applies to current screening programs and the impact should be examined further with the potential new maternal plasma DNA screening.[7]

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Contribution to authorship

AK, NN and CLR developed the concept and design of the study. AK, NN, VT and JM assisted with data acquisition and the software program to run risk ratio analyses. AK conducted the analysis and was responsible for drafting the manuscript which was approved by all authors. All authors revised the manuscript for important intellectual content, contributed to the interpretation of data and had final approval of the manuscript to be published.

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