Original Article

First trimester predictors of adverse pregnancy outcomes

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Aim: To identify first trimester indicators of adverse pregnancy outcomes.

Method: Data were obtained from the statewide evaluation of first trimester screening for Down syndrome in Western Australia which included 22 695 pregnancies screened between August 2001 and October 2003. Screening data were linked with pregnancy outcome information from the Hospital Morbidity Database and the Birth Defects Registry. The odds ratios (OR) of adverse outcomes were analysed for combined risk incorporating maternal age, nuchal translucency (NT) and biochemical parameters and then separately for each parameter (pregnancy-associated plasma protein-A (PAPP-A), free beta human chorionic gonadotropin (β-hCG) and NT).

Results: Risk assessments for first trimester combined screening are derived from maternal age, ultrasound measurement of fetal NT, maternal serum free β-hCG and PAPP-A. Increased combined risk for Down syndrome was significantly ($P < 0.01$) associated with spontaneous loss at or before 24 weeks gestation (OR 13.51), birth defects (OR 6.58) and preterm birth at or before 32 weeks gestation (OR 3.2). Maternal serum PAPP-A below the 5th centile was associated with Down syndrome (OR 8.43), spontaneous loss before 24 weeks (OR 5.04) and later than 24 weeks (OR 4.50), preterm delivery before 32 weeks (OR 3.11) and before 37 weeks (OR 2.24). NT above the 95th centile was associated with Down syndrome (OR 43.91), birth defects (OR 4.02) and spontaneous loss before 24 weeks (OR 6.24). Low levels of free β-hCG and increased NT were less consistently associated with adverse outcomes and high levels of free β-hCG showed limited use as an indicator. The detection rates for all outcomes other than Down syndrome were less than 40%.

Conclusion: Biochemical indicators and NT that are measured during first trimester screening for Down syndrome show a number of associations with adverse outcomes, but do not show appropriate performance characteristics for screening tests. These data are consistent with the view that the individual components, specifically low PAPP-A levels alone, do not provide an effective screening tool for adverse pregnancy outcomes.

Key words: combined risk, down syndrome, PAPP-A, prenatal screening.

Introduction

The relationship between advancing maternal age and the chance of having a fetus with aneuploidy, particularly Down syndrome (trisomy 21), has been recognised for over 40 years and formed the basis for age-related screening tests.[1,2] First trimester combined screening (maternal age, fetal nuchal translucency (NT), maternal serum free beta human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein (PAPP-A)) is widely used in Australia, with a detection rate (DR) in Western Australia (WA) of 83% and screen false positive rate (FPR) of 3.7%.[3] First trimester combined screening allows time for a diagnostic test to be

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undertaken and for a decision to be made about possible termination where necessary.

Several studies have demonstrated an association between decreased first trimester PAPP-A concentrations and intrauterine growth restriction,[4–7] low birthweight,[7–10] preterm delivery,[4–6,9–11] stillbirth after 24 weeks gestation,[9,10,12] increased risk of miscarriage, pregnancy-induced hypertension and gestational diabetes.[4,5,9] Previous studies have also identified adverse obstetric outcomes associated with single markers such as increased fetal NT[13,14] and abnormal free β-hCG levels,[15] and among pregnancies identified at increased risk of Down syndrome, there was a greater risk of poor outcomes such as spontaneous abortion, placenta praevia, intrauterine fetal demise, pregnancy-induced hypertension and preterm labour.[16,17] The use of low serum PAPP-A as an additional, independent predictive marker of pregnancy outcome remains controversial. Some experts have recommended that pregnancies with low first trimester PAPP-A levels warrant increased surveillance,[10,11,18] whereas others do not support this view.[9,19–21]

PAPP-A is one of several glycoprotein proteases produced by trophoblast cells that act on insulin-like growth factor binding protein (IGFBP), specifically IGFBP-4.[22] Once IGF-I and IGF-II are released from their IGFBPs, they promote fetal growth and development through metabolic and differentiation pathways.[22] This provides a biological rationale for PAPP-A influencing feto-placental growth and development, particularly for an association between low PAPP-A and poor pregnancy outcome.

We have previously shown that pregnancies identified at increased risk of Down syndrome by first trimester combined screening tests have a positive predictive value (PPV) of 1 in 17 for Down syndrome, but 1 in 4 for a significant birth defect, including chromosomal, structural or functional conditions.[3] In this additional study, we conducted a further analysis of data collected to evaluate first trimester screening in WA to measure the level of association between first trimester combined screening and its individual components, adverse outcomes in pregnancy and to compare the associated detection and FPRs for these indicators at different percentile cut-off levels.

Methods

This is a further analysis of data collected for the statewide evaluation of first trimester screening for Down syndrome and other fetal anomalies in WA.[3] This study was based on data collected on women who had a first trimester combined screening test between August 2001 and October 2003 ($N = 26\,641$) in WA which was then linked to pregnancy outcome information from the WA Midwives data collection, Birth Defects Registry, hospital morbidity data and mortality data. Data from multiple pregnancies or incomplete screens were excluded ($n = 3946$) and those without pregnancy outcome data were removed before final analysis ($n = 415$). The number of pregnancies analysed in the final screening dataset was $n = 22\,280$. The study was approved by King Edward Memorial Hospital Ethics Committee and the Confidentiality of Health Information Committee of the WA Department of Health.

The study population available for this analysis included all the above records where PAPP-A, free β-hCG and NT measurements were available. Women who had a previous fetus with a chromosomal abnormality and women with insulin-dependent diabetes mellitus were excluded from the study, leaving a cohort of 22 125. For those outcomes dependent on the calculation of gestational age, records without gestational age ($n = 68$) were excluded. Where regression analysis was adjusted for maternal weight, the cohort size was 20 076 due to absence of data on maternal weight. The dataset included Down syndrome as a fetal chromosome outcome but other aneuploidies were excluded from the final analysis.

The outcome measures that were examined included: spontaneous loss at or before 24 weeks gestation, intrauterine fetal death at longer than 24 weeks gestation, preterm birth at or before 32 weeks gestation, preterm birth before 37 weeks gestation, poor fetal growth (ICD-10-AM code O36.5), gestational hypertension, pre-eclampsia, preterm premature rupture, placenta praevia, placental abruption, gestational diabetes mellitus, neonatal death and birth defects. All outcomes were identified using administrative health records, thus excluding outcomes not requiring a hospital admission. This may result in under ascertainment, particularly in the case of spontaneous loss before 24 weeks. Poor fetal growth, gestational hypertension and pre-eclampsia, gestational diabetes mellitus, preterm premature rupture and placental disorders were identified from the mother's hospital admission records using the relevant ICD codes. Information on abortive outcomes, duration of pregnancy and live births was obtained from the midwives data collection, the Birth Defects Registry and the mother's hospital admission record.

A pregnancy at high risk of adverse outcomes was defined according to different percentile cut-offs for each indicator: highest 1%, 4% and 10% for the combined risk, lowest 1%, 5% and 10% for PAPP-A and free β-hCG and the highest 1% and 5% for free β-hCG and NT. Cut-off values for each analyte are shown in Table 1. Current practice for first trimester combined screening for Down syndrome in WA is to use a 1:300 cut-off as high risk as it approximates to the highest 4% of combined risks[3] The utility of low PAPP-A as an indicator of adverse outcomes when the combined risk was low was also examined to see if low PAPP-A (less than 5th centile or 0.40 multiple of the median (MoM)), alone adds a useful indication of adverse outcomes.

Logistic regression analysis was performed in SAS to calculate the odds (and 95% confidence intervals (CI)) of the specified adverse event occurring in the high-risk group compared to a control group where none of the specified outcomes were identified. Maternal age and weight were included as potential confounding variables. The DR and FPR were calculated in each of the high-risk categories compared to the control group. Receiver-operating characteristic (ROC) curves were produced to provide further information about the suitability of the analytes for screening the specified adverse outcomes.

Table 1 Percentile cut-off values for analytes

Percentile	Combined risk (1:n)	PAPP-A (MoM)	Free β-hCG (MoM)	Nuchal translucency (MoM)
1	56	0.25	0.24	–
4	302			–
5	–	0.40	0.37	
10	787	0.49	0.45	–
95	–		2.59	1.5
99	–		4.10	2.1

β-hCG, beta human chorionic gonadotropin.

Values for maternal serum PAPP-A and free β-hCG were calculated as multiples of the median adjusted for maternal weight and the regression analysis was adjusted for maternal age. NT was calculated in multiples of the median adjusted for gestational age. In this case, the regression analysis was adjusted for maternal age and weight. The combined risk incorporates maternal age and weight and therefore the regression analysis was not adjusted for these variables.

Results

The median maternal age in the screened population was 31 years (range 14–47 years) compared to 29 years for all West Australian mothers giving birth during the same period.[23] One in five women screened was aged 35 years or older and 51% of babies identified with Down syndrome through screening were within this age group. The median gestation at the time of the ultrasound scan was 12 weeks and four days (range 70–101 days) and 12 weeks and three days (range 62–100 days) for blood collection. Body weights were available for 90% of women, with a median of 65 kg (range 33–160 kg) and 10% of women weighed 100 kg or more. Two laboratories generated the biochemistry data, using either Kryptor-Brahms (92%) or Wallac (8%) assays, and medians for free β-hCG and PAPP-A were 0.94 and 1.01 MoMs, respectively. The median NT was 1.5 mm (range 0.1–12 mm).

The incidence of the adverse outcomes per 100 pregnancies measured in this study is given in Table 2. Our results demonstrate the association between low maternal serum PAPP-A and a range of adverse pregnancy outcomes including birth defects, poor fetal growth, spontaneous loss less than 24 weeks, preterm delivery before 32 weeks, premature rupture of membranes, gestational hypertension and pre-eclampsia, although the relationships are much weaker than that seen for Down syndrome (Tables 2 and 3).

An increased combined risk for Down syndrome is also associated with increased risk of spontaneous loss before 24 weeks, poor fetal growth, premature rupture of membranes, preterm delivery, birth defects and gestational hypertension. Among those with increased combined risk for Down syndrome, 12% (230) had PAPP-A results below the 10th centile.

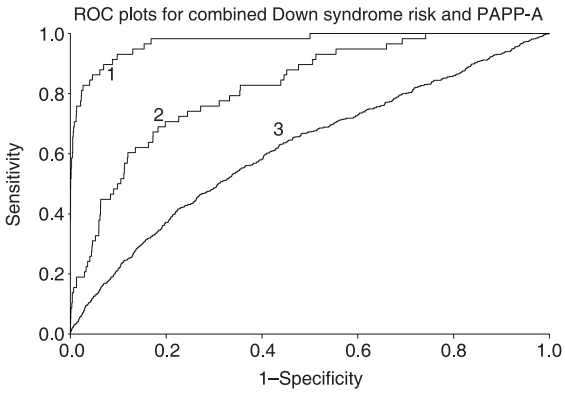

Figure 1 Receiver-operating characteristic (ROC) plots for (1) the combined risk assessment of Down syndrome (area under the curve, AUC= 0.9), (2) serum pregnancy-associated plasma protein (PAPP-A) level in the prediction of Down syndrome pregnancies (AUC = 0.8); (3) PAPP-A level in the prediction of intrauterine growth retardation (AUC = 0.62).

Low levels of free β-hCG and increased NT were less consistently associated with adverse outcomes and high levels of free β-hCG showed limited use as a stand alone indicator (Table 3).

Levels of PAPP-A below the 5th centile cut-off, in the absence of an increased combined risk, showed a similar association with adverse outcomes as when cases with increased combined risk were included. The associated PPVs were 15% and less.

This finding is reinforced by the ROC curves shown in Fig. 1. The most accurate screening test as shown by the ROC curves is that of the combined risk for Down syndrome with an area under the curve (AUC) of 0.9, followed by PAPP-A risk for Down syndrome with an AUC of 0.8. The next most accurate tests were those for spontaneous loss before 24 weeks (combined risk: AUC 0.65, PAPP-A: AUC 0.67) followed by birth defects (combined risk: AUC 0.65, PAPP-A: AUC 0.60) and for intrauterine growth retardation (PAPP-A: AUC 0.62). In all other cases, the AUC values for the combined risk and low PAPP-A were between 0.5 and 0.6. The ROC curve for spontaneous loss before 24 weeks has not been plotted due to the small number of cases in our dataset.

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Table 2 Performance characteristics of pregnancy-associated plasma protein (PAPP-A) and combined risks for selected outcomes

	Sensitivity	False positive rate	PPV	NPV	Incidence per 100 women screened
PAPP-A ≤ 5th centile					
Birth defects	11.66	4.15	13.32	95.21	4.19
Down syndrome	25.86	4.15	2.09	99.74	0.27
Poor fetal growth	10.55	4.15	8.70	96.62	2.87
Spontaneous fetal loss < 24 weeks	17.39	4.12	0.57	99.88	0.10
Spontaneous fetal loss > 24 weeks	16.07	4.12	1.27	99.71	0.25
Preterm delivery < 32 weeks	11.65	4.12	4.26	98.57	1.21
Preterm delivery < 37 weeks	8.74	4.12	16.73	91.72	7.26
Neonatal death	13.10	4.15	2.09	99.74	0.38
Premature rupture of membranes	7.93	4.15	4.48	97.70	1.88
Placenta praevia	96.70	95.85	1.60	98.74	1.23
Placental abruption	13.60	4.15	1.95	99.46	0.47
Gestational diabetes mellitus	6.53	4.15	6.64	95.78	3.48
Gestational hypertension	6.46	4.15	11.68	92.35	6.53
Pre-eclampsia	9.13	4.15	7.86	96.46	2.98
Combined risk ≤ 1:300					
Birth defects	17.39	3.13	23.30	95.55	4.19
Down syndrome	82.8	3.13	8.5	100.00	0.27
Poor fetal growth	5.51	3.13	6.19	96.48	2.87
Spontaneous fetal loss < 24 weeks	30.43	3.14	1.30	99.90	0.10
Spontaneous fetal loss > 24 weeks	7.14	3.14	0.75	99.68	0.25
Preterm delivery < 32 weeks	9.40	3.14	4.5	98.55	1.21
Preterm delivery < 37 weeks	5.68	3.14	14.65	91.55	7.26
Neonatal death	9.14	3.13	1.12	99.53	0.38
Premature rupture of membranes	6.49	3.13	4.85	97.69	1.88
Placenta praevia	3.30	3.13	1.67	98.42	1.23
Placental abruption	4.85	3.13	0.93	99.41	0.47
Gestational diabetes mellitus	4.05	3.13	5.53	95.72	3.48
Gestational hypertension	4.59	3.13	11.07	92.28	6.53
Pre-eclampsia	4.57	3.13	5.36	96.32	2.98

NPV, negative predictive value; PPV, positive predictive value.

Discussion

The pattern of increased fetal NT, normal to elevated maternal serum free β-hCG and low PAPP-A levels has been highly effective in first trimester screening programs for Down syndrome[24] and other fetal aneuploidies.[12]

Use of the combined risk as a predictor of Down syndrome was the only indicator to show suitable performance characteristics for a screening test with a DR of 83% and FPR of 3.7%. The best DR for an adverse outcome other than Down syndrome was 43.5% for the top 10% of combined risk as a predictor of spontaneous loss before 24 weeks and this had an associated FPR of 8.6%.

An increased rate of pregnancy loss before 24 weeks[9,21] and gestational hypertension[20] has previously been associated with free β-hCG levels below the 5th centile, but we were unable to confirm these findings. On the other hand, the association we observed with NT above the 95th centile and spontaneous fetal loss is consistent with previous studies.[6,9,21,25]

Using similar screening protocols as in the current study, Breathnach *et al.*[26] were able to detect 78% of pregnancies with non-Down syndrome aneuploidies such as trisomy 13, 18, Turner's syndrome and other trisomies. However, we restricted our focus to cases of Down syndrome since there were too few cases of non-Down syndrome aneuploidies identified in our dataset.

At each cut-off level (1st, 5th and 10th centile), we observed a consistent, significant association between PAPP-A and poor fetal growth, spontaneous fetal loss, preterm delivery and pre-eclampsia. We also observed a trend for the odds ratios (OR) to increase as PAPP-A levels decreased from the 10th to below the 5th and 1st centiles. Previous studies found that low PAPP-A levels were associated with spontaneous fetal loss,[5,8–10] preterm delivery[4–6,9–11] and pre-eclampsia,[4–6,8,9,11] and that PAPP-A results below 1st and 5th centiles were associated with increased risk of intrauterine growth retardation.[6,7,11] Our results do not support earlier findings of low PAPP-A being significantly associated with placenta praevia[16] or gestational diabetes.[4,5,9]

Inconsistent associations have previously been reported between first trimester free β-hCG and PAPP-A levels with adverse pregnancy outcome. Our results demonstrated a significantly increased risk of preterm birth when PAPP-A is below the 5th centile, confirming several previous studies,[4–6,9–11] but in contrast to others.[8,18,20] Our results were consistent with others demonstrating that low PAPP-A

Table 3 First trimester predictors of adverse pregnancy outcomes

	All outcomes		Birth defect		Down syndrome		Poor fetal growth		Pre-eclampsia	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
CR 4%	2.18**	1.90–2.51	6.52**	5.39–7.89	148.73**	74.84–295.57	1.81**	1.27–2.57	1.48	1.02–2.16
PAPP-A 5%	1.89**	1.66–2.15	3.05**	2.46–3.79	8.43**	4.63–15.34	2.71**	2.08–3.53	2.31**	1.75–3.04
Free β-hCG 5%	1.46**	1.28–2.15	1.98**	1.55–2.52	0.00	0.00	1.14	0.80–1.63	1.70	1.26–2.29
NT 95%	1.45**	1.26–1.67	4.02**	3.29–4.92	43.91**	24.58–78.43	0.84	0.54–1.3	0.70	0.44–1.11
	Spontaneous loss < 24 weeks		Spontaneous loss > 24 weeks		Preterm delivery < 32 weeks		Preterm delivery < 37 weeks		Neonatal death	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
CR 4%	13.51**	5.53–32.98	2.38	0.86–6.59	3.20**	2.10–4.88	1.86**	1.48–2.34	2.38	1.03–5.49
PAPP-A 5%	5.04**	1.71–14.88	4.50**	2.19–9.22	3.11**	2.12–4.55	2.24**	1.85–2.71	3.52**	1.86–6.67
Free β-hCG 5%	2.10	0.49–8.99	0.79	0.19–3.24	1.73	1.09–2.74	1.49**	1.21–1.84	1.35	0.55–3.35
NT 95%	6.24**	2.04–19.08	1.82	0.65–5.05	1.76	1.06–2.9	1.22	0.95–1.55	1.59	0.64–3.97
	Premature rupture		Placental praevia		Placental abruption		Gestational diabetes mellitus		Gestational hypertension	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
CR 4%	2.15**	1.44–3.21	1.06	0.54–2.06	1.58	0.64–3.9	1.31	0.90–1.89	1.49**	1.15–1.93
PAPP-A 5%	2.01**	1.40–2.89	0.80	0.41–1.57	3.65**	2.07–6.45	1.64**	1.22–2.21	1.59**	1.27–1.99
Free β-hCG 5%	1.47	0.99–2.19	0.99	0.55–1.78	0.63	0.20–2.00	1.80**	1.36–2.37	1.47	1.18–1.83
NT 95%	1.15	0.72–1.84	1.20	0.68–2.12	0.47	0.12–1.93	1.13	0.80–1.61	0.87	0.65–1.17

**Figures significant at $P < 0.01$ level

β-hCG, beta human chorionic gonadotropin; CI, confidence interval; CR, combined risk; NT, nuchal translucency; OR, odds ratio; PAPP-A, pregnancy-associated plasma protein.

results predicted hypertensive disorders,[4,5,8,9,11] which was not replicated by some smaller studies.[20,27] Consistent with other studies, we also found that PAPP-A levels below the 10th, 5th and 1st centiles were associated with spontaneous loss both before[5,8,9,21] and after 24 weeks.[9,11] Contradictory evidence may be partly explained by the smaller cohort size in some studies[8,18,20,21] compared with the larger studies.[3,9] An interesting outcome from this study has been the differences in ORs for different outcomes. While we observed that spontaneous loss before 24 weeks was best predicted by first trimester combined screening (OR 13.51) and then by NT (OR 6.24), spontaneous loss after 24 weeks was best predicted by PAPP-A falling below the 5th centile (OR 5.04). Some reports have examined whether different aetiologies are associated in a clinically useful way with different predictive markers.[28,29] Further detailed analysis, linking aetiologies to adverse outcomes might provide additional information.

Using a 5% cut-off value for PAPP-A, the PPVs (0.7–5.0) and specificity (96.8%) for spontaneous loss before or after 24 weeks and preterm delivery before 32 weeks are comparable to other studies.[6,9] Our results demonstrate that low PAPP-A has a high specificity but low PPV for these conditions compared with those at increased combined risk for Down syndrome. While it is clear from this study that cut-offs for PAPP-A (0.4 MoM), NT (1.5 MoM) or free β-hCG (0.37 MoM) will identify pregnancy cohorts with increased risks of different adverse outcomes, it is not clear how increased surveillance is likely to play a role in reducing adverse obstetric and neonatal outcomes.[30] Overall, more than 3000 pregnancies (13.4% of the study group) had a significantly increased risk of some form of adverse outcome, based on one or more parameters (PAPP-A, free β-hCG or NT). Therefore, improved mechanisms are required to select women for increased surveillance. In addition, further studies are needed to inform protocols that specify when and how frequently high-risk pregnancies should be monitored and which markers will prove most useful.[31] In our view, the current data alone do not provide sufficient evidence to be applied in routine clinical practice at this time.[32] Combinations of first trimester markers such as PAPP-A, free β-hCG, NT, ADAM12 or angiogenic factors[7,28,29] together with uterine artery Doppler studies at 22–23 weeks gestation[11,33] are likely to improve the PPV in pregnancy cohorts selected for intensive surveillance.[34]

While we observed a statistically significant association between low PAPP-A and several adverse pregnancy outcomes, the low predictive values observed do not necessarily justify more intensive surveillance in otherwise normal pregnancies. It is important to note that none of the indicators for adverse outcomes other than the combined risk for Down syndrome were suitable as a screening test.

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