Cost effectiveness analysis of a model of first trimester prediction and prevention for preterm preeclampsia against usual care

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Contribution:

What are the novel findings of this work?

A population-based program for first trimester prediction and prevention of preeclampsia will reduce both prevalence of disease and health service costs when compared to Usual Care.

What are the clinical implications of this work?

Combining first trimester prediction of preeclampsia with prophylactic intervention (low dose aspirin) has been shown to prevent disease. Translation and implementation of this program requires investment in resources for screening. This analysis supports establishment of this model of health service delivery within comparable settings.

Abstract

Objectives: Preeclampsia causes substantial maternal and neonatal mortality and morbidity. In addition to a personal impact on women, children and their families, preeclampsia has a significant economic impact on our society. Recent research suggests that a first trimester multivariate model is highly predictive of preterm (<37 weeks' gestation) preeclampsia and can be successfully combined with targeted prophylaxis (low dose aspirin) with 80% reduction in prevalence of disease. We examined the potential health outcomes and cost implications following introduction of first trimester prediction and prevention of preterm preeclampsia within a public healthcare setting when compared to Usual Care and conducted a cost-effectiveness analysis that informs health service decisions regarding implementation of such a program.

Methods: A decision analytic model was used to compare Usual Care to the proposed first trimester screening intervention within the obstetric population (n=6,822) attending two public hospitals within a metropolitan district health service in New South Wales, Australia between January 2015 and December 2016. The model worked from early pregnancy, included exposure to a variety of healthcare professionals, addressed exposure to risk assessment (Usual Care or first trimester screening) and use / compliance with low dose aspirin prescribed prophylactically for prevention of preeclampsia. All pathways culminated in six possible health outcomes ranging from no preeclampsia to maternal death. Results were presented as the number of cases of preeclampsia gained/avoided and the incremental increase/decrease in economic

costs arising from the Intervention compared to Usual Care. Significant assumptions were tested in sensitivity/uncertainty analyses.

Results: The intervention produced, across all gestational ages, 31 fewer cases of preeclampsia and reduced aggregate economic health service costs by $1,431,186 over this two-year period. None of the tested iterations of uncertainty analyses reported additional cases of preeclampsia or higher economic costs. The new intervention based on first trimester screening dominated Usual Care.

Conclusion: This cost effectiveness analysis demonstrates a reduction in prevalence of preterm preeclampsia and substantial cost savings associated with a population based program of first trimester prediction and prevention of preeclampsia and provides support for implementation of such a policy.

Introduction

Preeclampsia (PET) affects 3-8% of pregnancies and results in 60,000 maternal deaths and >500,000 preterm births worldwide each year.[1,2] This multisystem disorder requires more intensive care for mothers during pregnancy, increases long term risks of cardiovascular complications and, occasionally leaves women with life-long neurological complications.[3,4] Definitive treatment requires delivery, frequently exposing the fetus to complications of prematurity including lifelong morbidity from cerebral palsy, cognitive delay, autism and other neuro-developmental, psychomotor, behavioural and/or learning disorders.[5,6]

One recent US based study reported the health care cost burden of preeclampsia was $1.03 billion for mothers and $1.15 billion for infants; a total of $2.18 billion during the first year following birth.[7] The cost of delivery at 26 weeks' gestation ($150,000), was more than 100 times higher than a delivery at >36 weeks' gestation. A second study reported birth hospitalisation costs for maternal care increased from $8,204 to $22,702 (a 3-fold increase) and from $2,433 to $317,982 (a 14-fold increase) for neonatal care for term and very preterm deliveries respectively.[8] Lifetime medical costs of maternal stroke are estimated to be $700,000 and the ongoing cost of significant prematurity estimated at almost $60,000 per year; so, the overall economic cost is in fact even higher.[9] Prevention of preeclampsia, reducing the maternal and fetal burden of this disease, should be recognised as a public health priority.[10]

A multivariate model based on maternal history, mean arterial pressure, biochemical indices (maternal serum PaPP-A and or PlGF) and assessment of uterine artery blood flow can predict >90% of preeclampsia requiring delivery <3 weeks' gestation.[11-13] Early screening (at 11-13^{+6} weeks) allows early intervention; treatment with low dose Aspirin (150mg PO nocte) is associated with an 80% reduction in prevalence of preeclampsia leading to delivery <34 weeks and a 62% reduction in prevalence of preeclampsia <37 weeks.[14]

Studies examining the economic benefit of prediction and prevention of pre-eclampsia have reported a variety of screening strategies and endpoints and made different assumptions about screening efficacy, the effect of prophylactic intervention(s) and costs.[15-19] Many of these assumptions appear to be inaccurate based on the contemporary evidence. We present a cost-effectiveness analysis that aims to inform health service decisions regarding implementation of first trimester prediction and prevention of preterm preeclampsia. The study boundary constrains the health improvements and costs saved to those realised within six months of birth.

Materials and methods

The setting for the analysis comprised the Hunter-New England Local Health District in New South Wales, Australia. The study population comprised a subset of all women birthing at John Hunter (JHH) or Belmont Hospital between 1 January 2015 and 12 December 2016 (Table I).

Table I: Study and target population

This economic analysis compares *Usual Care* to the proposed *Screening Intervention*. Usual Care closely reflects the actual healthcare within the Hunter New England Local Health District (HNELHD). Under Usual Care, GPs first screen women and designate an appropriate model of care for low and high-risk pregnancies (Figure 1). Women are determined to be at increased risk of preeclampsia if they have one high-risk factor for this condition.[20] Pregnant women at increased risk of preeclampsia at their first GP appointment are encouraged to take 100mg of Aspirin daily from 12 weeks until birth, in line with the SOMANZ guideline.[21] The proposed intervention changes the screening process to a first trimester test that combines maternal characteristics with biochemical and biophysical markers, performed alongside traditional combined first trimester screening (cFTS) for aneuploidy at 11-13^{+6} weeks' gestation.[11,22] Women who screen high-risk are prescribed low dose 150mg Aspirin (nocte) for prophylaxis against preeclampsia.[14,23]

A decision analytic model was utilised to conduct a simulated cost-effectiveness analysis (Figure 1).[24] The decision tree was developed using Microsoft Excel with reference to best practice guidelines. [24-27] Monetary values are reported in 2018 Australian Dollars. The decision tree comprises a seven-stage probability model (Figure 1). The model reflects the natural history of a mean average pregnancy including the models of care for mothers with and without risk factors for preeclampsia. For both Usual Care and the Intervention, the expected cost/health outcome comprises the sum of the cost / health outcome of each consequence weighted by the probability of that consequence. [27] The consequences that were considered and costed were a normal pregnancy outcome, delivery for preeclampsia at <34 weeks, delivery for preeclampsia at 35-36 weeks, delivery for preeclampsia ≥37 weeks, maternal eclampsia and maternal death.

The model structure remains consistent for both the Usual Care and the Screening Intervention arms. The first bifurcation of the model reflects the fact that a percentage of pregnant women did not attend a GP prior to 14 weeks' gestation and would be unaffected by the proposed intervention. The second bifurcation accounts for the choice between the two arms of the simulation; Usual Care or the Screening Intervention. The third bifurcation reflects the assessment of women as being at high risk or low risk of preeclampsia for the respective screening method. The next bifurcation accounts for the accuracy (Positive Predictive Value / Negative Predictive Value) of the respective screening procedures. Women categorised as being at high risk of preeclampsia prior to 14 weeks are referred into an obstetrician-directed High-Risk antenatal pathway. Women categorised as a low risk of preeclampsia are

referred to a midwife-led Low Risk antenatal pathway. A proportion of women in each cohort are inaccurately assessed, but the significant health considerations lie with high-risk women assessed as low risk. The next bifurcation in the low-risk arm reflects that under Usual Care standard midwife procedures may identify some misdiagnosed women and redirect them to a high-risk antenatal pathway. Women who are not identified as high risk either through the GP screening or the midwifery screening progress proceed along the Low-Risk antenatal pathway, even if they are incorrectly assessed.

The latter bifurcations of the model reflect whether women receive prophylactic Aspirin, either from medical direction or community prevalence. The subsequent bifurcation accounts for different levels of treatment compliance and allows for the realisation of different preventative benefits for PET[11]. Community prevalence was assumed to incorporate compliance. The model incorporates a temporal aspect that enables late identification of a higher risk of PET to be identified through the Low-Risk antenatal pathway and redirected to a High-Risk treatment pathway. All pathways culminate in a health outcome status profile comprising six health states ranging from No PET/Eclampsia to Maternal Death.

Figure 1: Decision tree and sequence of events (Usual Care versus Intervention)

Table II: Transition probability estimates

The transition probabilities are provided in Table II and Supplementary Table A. The assumed probabilities remain consistent between arms for the proportion of pregnant women who booked their GP appointment prior to 14 weeks' gestation and therefore were potentially captured with the new screening procedure. To account for some endemic treatment, the measured Aspirin prevalence for the Booked and Unbooked cohorts were derived respectively from HNELHD data and assumed to reflect a combined treatment and compliance probability. The compliance rate for high-risk women identified late was also held consistent.

The majority of transition probabilities for Usual Care were derived from HNELHD data for the study population using the eMaternity patient database.[28] Women deemed at High Risk for PET were identified in line with ACOG/US Preventative Services Taskforce guidelines.[20] Approximately 9.3% of these women subsequently developed PET, which is broadly consistent with other studies.[20] Within the study population, 12.9% of those assessed High Risk were prescribed prophylactic Aspirin treatment. For Usual Care, this assumption was applied to all high-risk cohorts irrespective of the screening accuracy or whether the women progressed to develop PET. Treatment compliance for women prescribed Aspirin (69%) accounts for the evidence that poor compliance inhibits the potential PET health gains from improved screening alone.[29] The Midwife screening procedure conducted as part of the Low-Risk antenatal pathway was assumed to identify 23% of women who were in fact high risk and re-direct this cohort into a late-identification High-Risk antenatal pathway.[30]

Within the model, the primary benefit arising from the new Screening Intervention would be to re-direct more patients to an appropriate treatment path. The transition probabilities for the potential Screening Intervention comprise different assumptions in directing patients to alternative antenatal pathways, the treatment that these population subsequently receive, their compliance levels and their respective health outcomes. Where possible, these assumptions were derived from meta-analyses[31], but mainly from individual published trials. The highest level of evidence was sourced for each assumption and tested within the sensitivity analysis. Under the intervention, a probability of high-risk assessment of 10.68% was adopted reflecting the results of the ASPRE trial[11], adjusted for the prevalence of preeclampsia within this sub-population. The positive predictive value of this assessment, 10.10%, was calculated by applying the results of the ASPRE trial to the local prevalence distribution by gestation cohort. Further details are provided in the Supplementary Methods. Prescription levels for Aspirin treatment were assumed to be higher founded on local pilot evidence.[23] Moderately higher treatment compliance rates under the new screening regime were also adopted founded on trial evidence.[11]

Table III: Summary of health outcome profiles

The primary health outcome for the economic analysis comprised cases of early-onset preeclampsia avoided. Preeclampsia was defined according to the guidelines of the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) [21]. Health outcomes were segmented further in the model to account for the significantly skewed

distribution where a small percentage of the target population incur the most severe health outcomes and the largest costs. The assumed health outcome profiles for the respective health pathways (Figure 1) in the model are detailed in Table III. The profiles vary according to the prevalence of PET within the given sub-population, their potential to develop preterm PET, their treatment with Aspirin, or non-treatment respectively, and their compliance with treatment. Profiles that reflect the unbooked pathways or unaffected by these considerations were held consistent for both Usual Care and the Intervention arms. The methods to derive the respective PET health outcome profiles are detailed in the Supplementary Methods.

Table IV: Intervention costs (Incremental additional costs per patient compared to Usual Care)

Table V: Implementation costs (Aggregate costs to implement the intervention in the setting for the respective patient numbers)

The model incorporates the net intervention costs compared to Usual Care and the costs to implement the change in screening practice. Applied to the intervention arm only, intervention costs capture the additional marginal cost per person. Intervention costs include the additional labour, equipment and services required per patient to deliver first trimester screening for preeclampsia alongside scheduled cFTS. The categories, unit cost and volume of each component is detailed in Table IV for both all women screened (AUD 43.00 per patient) and for women assessed High Risk (an

additional AUD 6.26 per patient) respectively. The assumptions were derived from pilots of the new screening procedure at maternity clinics in Sydney and Newcastle, Australia. The aggregate costs to implement the new intervention are detailed in Table V. These costs include the establishment of new procedures within the screening clinic, staff training and establishment of the referral system. Costs were derived from pilot implementation of the intervention in the same setting.

Table VI: Total costs per woman by antenatal pathway for the period from the initial GP consult to four weeks pre-birth

Compared to Usual Care, the Screening Intervention directs women into alternative antenatal health pathways (Figure 1), which holds implications for the net operational costs to deliver antenatal care. Antenatal costs include primary care, midwife and/or obstetrician consultation, pathology, imaging and pharmaceutical costs grouped into the respective antenatal pathways (Table VI and Supplementary Tables B, C, D and E).

Table VII: Aggregate late antenatal, intra-partum and post-partum costs per event by health outcome status & uncertainty range / profile

Health service costs incurred for the late antenatal, intra-partum and post-partum period to six months post-birth, were calculated directly from individual data for every hospital service event provided during the study period. Costs were derived for women categorised, on the basis of their health outcomes, into one of the six designated health

outcomes (Supplementary Table F). For women not affected by PET, costs were estimated from a random sample of 250 individuals without any evidence of PET-related symptoms or treatment. The inclusion/exclusion criteria, for this low-risk cohort, were designed to reflect the health profile of the study cohort should the screening intervention prevent cases of preterm PET. That is, not all women are assumed to have a low-risk pregnancy, given other potential morbidities. Average costs by health outcome status, and standard deviations for the sensitivity analysis, are provided in Table VII. For the early antenatal period, the per patient cost were held consistent between Usual Care and the intervention. Aggregate costs varied between arms based on the number of women realising the alternative health outcomes in line with their pregnancy and healthcare pathway. Costs were not escalated or discounted for the study period, given the limited timeframe (24 months) and the lack of evidence regarding health service productivity gains or the specific time of patient costs. The effect of this assumption on the results would be to marginally reduce the costs and was considered negligible compared to other assumptions.

The results are presented as the number of cases of preeclampsia gained/avoided and the incremental increase/decrease in economic costs arising from the Intervention compared to Usual Care. The sensitivity of the results to the assumptions was assessed using a univariate deterministic sensitivity analysis. The uncertainty of the results to the significant parameter assumptions were tested using a probabilistic sensitivity analysis. The parameter ranges and assumed distributions are detailed in Tables II, III, VI and VII. Uncertainty parameters for the transition probability estimates were modelled using 500 iterations of a simulation of 1,000 random allocations to the

original mean estimates. Uncertainty parameters for each alternative health outcome profile were modelled using 500 iterations of a simulation of 10,000 random allocations. Uncertainty parameters and the appropriate distribution were derived from original data for the aggregate late antenatal, intra-partum and post-partum costs. The Monte Carlo simulations were undertaken using the Excel add-in Ersatz (http://www.epigear.com).

Ethics approval for the patient data utilised for this research was provided by the Hunter-New England Local Health District Human Research Ethics Committee (AU201704-05).

Results

The central analysis using the mean point estimates for all assumptions found that first trimester screening with early prophylactic intervention dominates usual care. That is, the intervention produced approximately 31 fewer total cases of PET and reduced aggregate economic costs within the health service for the study population over the study period by $1,431,186 (Table VIII). These results are considered conservative because: the study boundary excludes the potential longer term health gains and net savings following six-month post birth assessment; the health outcome measure of cases of PET avoided does not account for the improved level of severity within the total e.g. fewer <34 weeks gestation (Table IX); and some assumptions are considered conservative e.g. 70.6% treatment compliance for women assessed high risk, whereas pilot evidence currently finds that compliance could be markedly higher.

Table VIII: Summary results: Intervention compared to Usual Care, Cases of PET Avoided & Total Net Costs, mean point estimates for study population, for study period

Table IX: Intervention compared to Usual Care - Cases of PET prevented, total and by health outcome category

The uncertainty analysis demonstrates that none of the iterations produced a result with additional cases of PET or higher economic costs (Figure 2). That is, the first trimester screening intervention dominates usual care under most rational assumption

ranges, with both a reduction in the prevalence of disease and a reduction in the overall cost burden to the health service.

Figure 2: Results of the probabilistic uncertainty analysis on the cost-effectiveness plane, Intervention versus Usual Care, and mean point estimate (black diamond)

Consistent with the uncertainty analysis, the results from the univariate sensitivity analyses demonstrate that none of the changes to the key parameter assumptions changes the dominance of the proposed screening intervention over usual care. Of the 62 assumptions tested, only a few generated notable effects on the outcome measures (Figures 3a & 3b). Logically, the total number of PET cases avoided was most sensitive to accuracy of the new screening intervention (positive predictive value). The model accounted for the fact that some of the women did not engage with the health service until after the potential for the treatment to be effective. The results were partially sensitive to both this factor and the assumed aspirin treatment effect size (Figure 3a).

The mean estimates for total net economic costs were most sensitive to the assumption for health services costs incurred during the late antenatal, intra-partum and post-partum period, particularly for cases of PET with gestation < *34 weeks* and *34 to 36.6 weeks (*Figure 3b*)*. The estimates for these costs have a high level of certainty given their derivation from health service event data for 100% of the respective sub-population. The health outcome profile assumptions also had a moderate effect upon total costs, given their direction of women into higher cost pathways (Figure 3b). In line with the outcomes, the accuracy of the new screening intervention, as demonstrated by

the positive predictive value, had a moderate effect on the economic costs, as did the prophylactic effect of early treatment with aspirin.

Figure 3a: Results of univariate sensitivity analysis – Effect of changes in input assumptions to the estimate for total cases of PET avoided

Figure 3b: Results of univariate sensitivity analysis – Effect of changes in input assumptions to the estimate for total net economic costs

Discussion

This cost-effectiveness analysis demonstrates that implementation of a program of first trimester prediction and prevention of preterm preeclampsia has the potential to reduce the prevalence of disease and reduce the overall cost burden of managing this adverse outcome. This intervention clearly dominates Usual Care and the findings are strongly supportive of investment in this new model of care. In a maternity unit delivering approximately 3,500 infants per year, implementation of a comprehensive screening policy could result in the delivery of 14 fewer preeclamptic infants <37 weeks' gestation with a net economic gain of $715,000 per year.

This analysis is dominated by neonatal cost savings made in relation to the reduction in prevalence of preterm preeclampsia. The cost-effectiveness model recently proposed by Mallampati *et al.* (2019) was dominated by similar factors – but we note several assumptions in this analysis that led to a failure to recognize the value of this new intervention.[19] Mallampati *et al.* underestimated the impact of first trimester screening on prevalence of preterm pre-eclampsia, underestimated the costs associated with preterm delivery and most significantly, failed to account for the substantial reduction in the rate of extreme preterm delivery, a cohort that necessarily incurs markedly higher healthcare costs.[7,8,13,14,23]

In our practice, additional costs of screening are incremental as women are already offered a first trimester screen for aneuploidy. The level of savings on neonatal care do, however, also make the analysis favorable in circumstances where no first trimester

screening program is currently in place and where formal investment in equipment and human resource would be needed to run such a service. Using the model, we have calculated a 'break-even' point of AUD280 per patient. Interestingly, this is well above the costs of first trimester screening recently proposed by Mallampati *et al.*[19] The model could also be adjusted to evaluate alternative methods of screening, such as a combination of maternal history and mean arterial pressure, which have been advocated in some low-resource settings, although it is important to recognize that the evidence base for prediction and prophylactic intervention with these more limited screening tools is incomplete.[32]

Aspirin is recognized as having value for prophylaxis against pre-eclampsia and the current standard of care promotes use in women deemed high-risk of this disease. [20] The analysis of our own data showed that approximately 5% of women had one or more high-risk factors but only 12.9% of these women were prescribed aspirin in early pregnancy. These findings are consistent with other Australian studies; Helou *et al.* (2017) retrospectively reviewed a cohort of women who developed preeclampsia during the course of pregnancy and reported that only 23% of those who had risk factors had been prescribed aspirin antenatally.[30] Shanmugalingham *et al*. (2018) recently demonstrated that compliance remains an issue even amongst women who have had previous affected pregnancies, reporting a compliance rate of 69%.[29] A secondary analysis of the ASPRE trial has demonstrated the importance of compliance, reporting preterm preeclampsia rates of 0.9% and 3.3% in high-risk women who were compliant (took >90% of tables) or were not compliant respectively.[13] First trimester screening may impact compliance in two ways; first, it formalizes the

screening process, improving performance of clinicians in risk assessment and second, a high risk result reinforces the potential for risk, improving uptake of the intervention.[33]

Shmueli et al. (2012) and Ortved *et al*. (2019) examined cost-effectiveness of first trimester models of prediction and prevention in Israeli and Canadian settings.[16,17] The Israeli analysis included an additional biomarker for screening (PP13) but assumed a similar sensitivity in screening for preterm preeclampsia (90%).[17] They did however assume less impact of intervention (30% reduction in prevalence for pre-eclampsia <34 weeks). The Canadian group modelled screening and intervention according to the Fetal Medicine Foundation algorithm but, in comparison to our local data, may have underestimated costs of preterm delivery and neonatal care.[16] Both groups concluded that first trimester screening was of value, with the potential to prevent a significant proportion of cases of early preeclampsia and significant cost savings to the health care system.

Mallampati et al. were critical of other models that failed to include an evaluation of universal aspirin use.[19] On face value, this appeals due to the fact that the costs of the screening intervention are significantly higher than those of the prophylactic therapy and that this approach maximises 'screening' sensitivity. We note, however, that none of the randomised controlled trials that evaluated aspirin use in low-risk nulliparous populations showed benefit in this approach.[34-36] Meta-analysis of these trials gives a relative risk (RR) for pre-eclampsia 1.01 (95%CI: 0.68 – 1.34). We do not think it is appropriate to advocate changes to health policy founded on an economic analysis that is not supported by robust clinical evidence. The main issue with universal treatment is

likely compliance. The three trials reported compliance rates of 42-57% - which would effectively halve the impact of the intervention; Mallampati *et al.* chose to test a compliance rate of 90% in their base analysis, based on published data from a cohort that had a 50% recruitment rate to an intervention study; which may not represent the general population.[19,37] An additional issue that was not completely addressed is the potential impact of complications of aspirin therapy when universal therapy is recommended. Interesting, two of the trials reported significant increases in postpartum haemorrhage – which was not costed.[34,37] In addition, there is some evidence to suggest that aspirin may be associated with increased risks of neonatal complications such as cerebral palsy – and whilst we should be cautious in our interpretation of these data, the use of a screening process that minimizes drug exposure whilst maximizing improvement in outcome should be a priority.[38]

The strength of our study lies in the development of a model that is closely founded on data from the local population in a local health setting. We recognize, however, that caution should be used in generalizing these results, given that the parameters and intervention costs will vary in different settings. Probabilistic uncertainty analysis assumes that parameters are independent. Some of the inputs within this model will be correlated and this limitation was not explicitly addressed. Given the clear decision guidance from the results, it is unlikely that technical refinements to account for this limitation would affect the decision insight. This study limited analysis to health improvements and costs saved within six months of birth. We recognise that preeclampsia is associated with significant long-term morbidity for both mothers and infants and that overall cost savings are likely underestimated in this assessment. All

economic models necessarily represent a simplification of the real world, but this analysis has sought to incorporate all key considerations such as the potential population accessible for the intervention and the effectiveness of screening and preventative therapy and has sought to embed the majority of assumptions within a real-world setting using real-world data wherever possible.

The results of this cost effectiveness analysis provide supporting evidence for a significant reduction in prevalence of preterm preeclampsia and substantial cost savings associated with a policy of population wide first trimester prediction and prevention of preterm preeclampsia. Given that this is a pathway supported by robust clinical evidence, we suggest that this should be the approach recommended for service implementation.

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Figure legends

Figure 1 Decision tree and sequence of events (Usual Care versus Intervention)

Figure 2 Results of the probabilistic uncertainty analysis on the cost-effectiveness plane, Intervention versus Usual Care, and mean point estimate (black diamond).

Figure 3a Results of univariate sensitivity analysis – Effect of changes in input assumptions to the estimate for total cases of PET avoided

Figure 3b Results of univariate sensitivity analysis – Effect of changes in input assumptions to the estimate for total net economic costs

Supplementary legends

Supplementary methods

Supplementary Table A: Data for screening, positive/negative predictive value calculations and PET outcomes, Count, Usual Care, Study population (booked subset), January 1 2015 to December 31 2016

Supplementary Table B: Cost events for Pre-Antepartum period by Model of Care

Supplementary Table C: Cost values for Pre-Antepartum period

Supplementary Table D: Pre-Antepartum Costs: Diagnostic blood tests

Supplementary Table E: Pre-Antepartum Costs: Other diagnostic tests

Supplementary Table F: Inclusion/exclusion criteria for calculation of costs for late antenatal*, intra-partum and post-partum care.

Table I: Study and target population

Description	Population category	Count (No.)	Inclusion/Exclusion Criteria
Total Population	A	7,879	All women: birthing at JHH or Belmont Hospital; birthing between 1/1/2015 - 31/12/2016
Total births	Aa	8,078	All children: born at JHH or Belmont Hospital; born between 1/1/2015 - 31/12/2016
Study Population: Population directed to relevant clinics & exclusion of confounding complication pregnancies	B = Subset A	6,822	Booked to deliver at JHH / Belmont; excludes transfers from external regions e.g. Sydney, Central Coast, rural NSW; resident within Newcastle, Lake Macquarie or Port Stephens Local Government Areas; All singletons
Population with potential to receive intervention screening	C = Subset B	6,089	Gestation at first comprehensive assessment < 14 weeks
Count of women receiving NT scan	D = Subset of B	5,020	That is, potential to receive PET Screening < 14 weeks, if available
Population with PET (of consultation pop.)	Cc = Subset of C	119	Women identified within eMaternity with a previous history of PE

Source: eMaternity electronic medical record, Hunter New England Local Health District, NSW Health

Table II: Transition probability estimates

Model parameter	Point estimate	Unit of Analysis	Sensitivity / Uncertainty Analysis (dist, range)	Source/Rationale
Consistent assumptions				
Proportion visiting GP prior to 14 weeks gestation	89.26%	% of Pop. A	SA & UC (Normal, SD: 1.0%)	[28] ; women receiving NT scan
Background Aspirin prevalence: Booked women	1.92%	As a % of all Booked women	SA & UC (Normal, SD: 0.38%)	[28] ; Applies only to booked population in both arms
Background Aspirin prevalence: Unbooked women	1.09%	As a % of all Unbooked women	SA & UC (Normal, SD: 0.30%)	[28] ; Applies only to Unbooked population in both arms
Aspirin compliance: Late identification cohort	69%	As a % of all Booked women, identified High Risk late within Low Risk MOC	SA & UC (Normal, SD: 1.4%)	[29]; SD range calculated
Usual Care assumptions				
Proportion assessed High Risk at GP booking visit	5.11%	% of Pop. C	TP	[28 39]; Women assessed High Risk from Pop. C (n=311)
Positive predictive value of PET Screening - High Risk women	9.32%	Developed PET from High Risk subset	TP	[28 39]; Accurately assessed High Risk women (n=29)
Negative predictive value of PET Screening – Low Risk women	98.44%	As a % of women who did not develop PET from Low Risk subset	TP	[28 39]; Accurately assessed Low Risk women (n=5,688)
Prophylactic Aspirin treatment: Percentage of women prescribed Aspirin in High Risk cohort	12.86%	As a % of women in High Risk cohort	TP	[28] ; In line with ACOG guidelines
Aspirin compliance: All cohorts identified High Risk; early & late diagnosis	69.0%	As a % of booked women prescribed Aspirin	SA & UC (Normal, SD: 1.4%)	[29]; Applies to all booked women prescribed Aspirin in Usual Care; SD range calculated
Late identification (20 weeks) of High Risk profile women from low risk Midwifery MOC	23.0%	As a % of all Booked women within low risk MOC	SA & UC (Normal, SD: 1.3%)	[30]; SD range calculated
Intervention assumptions				
Proportion assessed High Risk at new Screening Intervention	10.68%	As a % of Pop. C	SA & UC (Normal, SD: 1.0%)	[11]; SD range calculated
Positive predictive value of PET Screening - Accurately	10.05%	As a % of women	SA & UC; (Normal,	[11]; Adjusted for early PET categories using [40];

Model parameter	Point estimate	Unit of Analysis	Sensitivity / Uncertainty Analysis (dist, range)	Source/Rationale
assessed High Risk women		assessed High Risk at new screening	SD: 0.9%)	Adjusted for prevalence in study sub-population [28]; SD range calculated
Negative predictive value of PET Screening – Low Risk women	99.01%	As a % of women assessed Low Risk at new screening	SA & UC; (Normal, SD: 0.4%)	[11]; Adjusted for early PET categories using [40]; Adjusted for prevalence in study sub-population [28]; SD range calculated
Prophylactic Aspirin treatment: Percentage of women prescribed Aspirin in High Risk cohort	99.90%	As a % of women correctly or incorrectly assessed High Risk	SA & UC (Normal, SD: 0.1%)	[41]; Applies to both correct/incorrect assessment branches with and without real risk of PET; In line with ACOG guidelines; SD range calculated
Late identification (20 weeks) of high-risk profile women from Low Risk Midwifery MOC	0.0%	As a % of all Booked women within low risk MOC	NA	Necessitated by intervention; redirection with later less accurate screening (compared to intervention) halted
Aspirin compliance: High Risk women (excluding late identification; Midwifery MOC)	70.60%	As a % of booked women prescribed Aspirin	SA & UC (Normal, SD: 1.5%)	[11]; Applies to booked women prescribed Aspirin in the Intervention arm (excluding Midwifery MOC) ; SD range calculated
Aspirin compliance: Late identification; Midwifery MOC only	69.0%	As a % of booked women prescribed Aspirin	SA & UC (Normal, SD: 1.4%)	[29]; Applies to all booked women in Midwifery MOC; SD range calculated

Notes: GP – General Practitioner; NT – Nuchal Translucency scan; PET – Preeclampsia/Eclampsia; TP – Total Population: Actual data for total study population; SA – Univariate sensitivity analysis; UC – Probabilistic uncertainty analysis; NA – Not applicable; SD – Standard deviation

Table III: Summary of health outcome profiles (mean point estimates* and standard deviations)

	Health outcome profiles for given health pathway/s (corresponding to Figure 1)									
Decision Tree pathway: Outcome branch code	O (Both)	N (Both)	H, I, K (Usual Care only)	H, I, K (Interventn. only)	G, J, (Usual Care only)	G, J (Interventn. only)	D, E, F, L, M (Both)	C (Both)	A (Both)	B (Both)
Decision Tree pathway: Summary description	Unbooked (Late); Unknown risk; no treatment	Unbooked (Late); Unknown risk; Aspirin	Low Risk (GP); Dev PE; No late ident/no treatment or late ident/poor compliance	Low Risk (Interv); Dev PE; No late ident / no treatment or late ident/ poor compliance	Low Risk (GP); Dev PE; late ident / Aspirin (late)	Low Risk (Interv); Dev PE; Aspirin (late)	Low Risk & High Risk; No PE; Aspirin / no treat.	High Risk; Dev PE; no treatment	High Risk; Dev PE; Aspirin (early); Good compliance	High Risk; Dev PE; Aspirin (early); Poor compliance
Mean point estimates										
None	97.46%	97.71%	0.00%	0.00%	10.00%	10.00%	100.00%	0.00%	56.10%	22.58%
PET > 37 weeks	1.13%	1.02%	57.23%	80.82%	51.51%	72.74%	0.00%	62.11%	35.62%	48.32%
PET 34 - 36+6 weeks	0.83%	0.75%	21.99%	16.66%	19.79%	14.99%	0.00%	21.28%	4.48%	16.38%
PET < 34 weeks	0.56%	0.50%	19.79%	1.86%	17.81%	1.67%	0.00%	15.96%	3.36%	12.28%
Eclampsia	0.02%	0.01%	0.73%	0.49%	0.66%	0.44%	0.00%	0.49%	0.33%	0.41%
Death	0.005%	0.005%	0.25%	0.17%	0.22%	0.15%	0.00%	0.17%	0.11%	0.14%
Standard deviations (Dirichlet distribution profile)										
None	0.17%	0.16%	0.00%	0.00%	0.28%	0.34%	0.00%	0.00%	0.48%	0.41%
PET > 37 weeks	0.11%	0.09%	0.50%	0.41%	0.52%	0.45%	0.00%	0.46%	0.42%	0.45%
PET 34 - 36+6 weeks	0.09%	0.08%	0.43%	0.39%	0.43%	0.35%	0.00%	0.38%	0.21%	0.34%
PET < 34 weeks	0.08%	0.07%	0.42%	0.00%	0.37%	0.14%	0.00%	0.38%	0.18%	0.33%
Eclampsia	0.00%	0.00%	0.09%	0.09%	0.07%	0.07%	0.00%	0.06%	0.06%	0.06%
Death	0.00%	0.00%	0.05%	0.04%	0.05%	0.04%	0.00%	0.04%	0.03%	0.07%

*Note: Some distributions do not total 100% due to rounding of percentages for publication only

Table IV: Intervention costs

Description (Additional components - *Italics*)	Additional resources	Volume	Unit Type	Cost per unit (AUD2018)	Cost per screened patient (AUD2018)	Additional assumptions
Incremental additional costs per patient screened compared to Usual Care						
Referral by GP for screening (cFTS *& PE*)	None					Referral directed to First Trimester Screening Service (FTSS) rather than private imaging provider
Nuchal Translucency (NT) scan	None					NT scan provided in Usual Care for aneuploidy screening
Doppler: Uterine Artery Pulsatility index	Labour - Sonographer time	10	minutes	$1.16	$11.64	NSW Industry Code Classification: 15RAD3102; Additional time take to assess uterine artery dopplers
	Equipment - Ultrasound machine	10	minutes	$0.17	$1.75	One ultrasound machine (AUD$145,000);utilised 52 weeks, 38 hours per week; Straight line depreciation seven years
Blood tests: Beta Human Chorionic Gonadotropin (BHCG) / Pregnancy-associated Plasma Protein A (PaPPA)	None					
Blood test: Placental Growth Factor (PlGF)	Equipment - PlGF assays	1	PlGF Assay	$15.40	$15.40	Market price: 45-48 PlGF kits pa (2% re-run rate, 5 days per week); AUD$990 per kit (excl. GST); plus instrument consumables
Maternal blood pressure	Labour - Registered Nurse / Midwife time; two times left and right	10	minutes	$0.78	$7.83	NSW Industry Code Classification: 02RMW06 (AUD$40.5079 per hour)
Maternal blood pressure	Equipment - Microlife A2 classic (two machines pa); Capital allocation per screened patient	1	per screened patient	$0.09	$0.09	Cost of blood pressures; $140 x two machines for simultaneous measures, 3,000 patients pa (Sydney LHD hospital pharmacy)

Risk calculation (data entry - addit. component)	Labour - Obstetric specialist time	5	minutes	$1.26	$6.29	NSW Industry Code Classification: Staff specialist (37STSP01)
					$43.00	**Incremental additional cost per patient (per patient screened)**
Incremental costs per patient assessed High Risk compared to Usual Care						
Interpret / discuss results with patient (Intervention - High Risk)	Labour – Obstetric specialist, additional discussion time	5	minutes	$1.26	$6.29	NSW Industry Code Classification: 37STSP01
					$6.29	**Incremental additional cost per patient (per patient assessed High Risk)**

Table V: Implementation costs (Aggregate costs to implement the intervention in the setting for the respective patient numbers)

Description	Resources	Volume	Unit Type	Cost per unit*	Sub-total cost (CY2018)	Additional assumptions
Local site implementation						
Development of Site Specific						
- First trimester screening questionnaire	Labor - Midwife	1	Hours	$42.02	$42.02	NSW Award: 02RMW03
- Information sheet for patients	Labor – Midwife	2	Hours	$42.02	$84.04	NSW Award: 02RMW03
- Information sheet for patients	Labor – Obstetrician	2	Hours	$75.44	$150.87	NSW Award: 37STSP01
Establishment of screening process (patient walk through)	Labor – Midwife	2	Hours	$42.02	$84.04	NSW Award: 02RMW03; Establishing infrastructure, processes for booking, assessment components, discussion of results
Centre staff training / Education						
- Obstetricians	Labor – Obstetrician	2	Hours	$75.44	$150.87	NSW Award: 37STSP01
- Sonographers	Labor - Sonographer	2	Hours	$69.86	$139.72	NSW Award: 15RAD3102
- Midwives	Labor – Midwife	2	Hours	$42.02	$84.04	NSW Award: 02RMW03
- Midwives	Labor – Obstetrician	2	Hours	$75.44	$150.87	NSW Award: 37STSP01
- Administrators	Labor – Midwife	2	Hours	$42.02	$84.04	NSW Award: 02RMW03
Weekly rounding with tertiary service clinicians	Labor – Midwife	12	Hours	$42.02	$504.23	NSW Award: 02RMW03; One hour for 12 weeks
Monthly rounding with tertiary service clinicns.	Labor – Obstetrician	3	Hours	$42.02	$126.06	NSW Award: 37STSP01; One hour for 3 months
Establishment of referral system						
Development of site specific 'Information sheet for referring clinicians'	Labor – Midwife	2	Hours	$42.02	$84.04	NSW Award: 02RMW03
Development of site specific 'Information sheet for referring clinicians'	Labor – Obstetrician	2	Hours	$75.44	$150.87	NSW Award: 37STSP01
Information sheet - Printing	Equip.– Paper/printing	6,089	per patient	$0.50	$3,044.50	Aggregate of per patient cost
Update electronic referral information and pathway (Health Pathways)	Labor – Midwife	2	Hours	$42.02	$84.04	NSW Award: 02RMW03
Update electronic referral information and	Labor – Obstetrician	2	Hours	$75.44	$150.87	NSW Award: 37STSP01

pathway (Health Pathways)						
General Practitioner (GP) Education Day	Labor – Obstetrician	8	Hours	$75.44	$603.48	MBS Code 36; Preparation time (2hrs); Presentation and question time (2 x 1hr); Two per year; GPs costs excluded as pre-committed for Continuing Professional Development req.
Small group sessions to key GP groups at their workplace	Labor – Midwife	20	Hours	$42.02	$840.38	NSW Award: 02RMW03I; Presentation/question time (20 x 1hr; Attended by 5-10 GPs per session)
Small group sessions to key GP groups at their workplace	Labor – Obstetrician	20	Hours	$75.44	$1,508.70	NSW Award: 37STSP01; Presentation/question time (20 x 1hr; Attended by 5-10 GPs per session)
Small group sessions to key GP groups at their workplace	Labor – GP	20	Hours	$249.52	$4,990.32	MBS Code 36; Presentation/question time (20 x 1hr; Attended by 5-10 GPs per session)
Monthly rounding with GP practices	Labor – Midwife	1,200	Minutes	$0.70	$840.38	20 practices x 10 minutes x six months
Total additional aggregate implementation cost					**$13,898.30**	

*Notes: Includes on-costs (16%)

Table VI: Total costs per woman by Model of Care (MOC) pathway for pre-antepartum period (period from GP consult to four weeks pre-birth)

MOC Category	Total cost per woman by MOC pathway	Univariate sensitivity range (10%)
Low Risk MOC	$682.09	$613.89 - $750.30
Late-Identification High Risk MOC	$1,001.77	$901.59 - $1,101.94
Early-Identification High Risk MOC	$1,033.90	$930.51 - $1,137.29
Unbooked	$0*	Not applicable

* Incremental analysis assumes no difference between arms

Table VII: Late antenatal*, intra-partum and post-partum costs per event by health outcome status & sensitivity assumptions

PET Health Outcome Status	Mean Costs (AUD2018)	Univariate sensitivity range (+/-10%)	Probabilistic analysis (assumed distribution and range)
No Risk	$6,525	$5,872 - $7,177	Gamma, SD - $225
PET > 37	$17,680	$15,850 - $19,373	Gamma, SD - $1,563
PET 34-36.6	$34,833	$31,349 - $38,316	Gamma, SD - $3,516
PET <34	$86,966	$78,269 - $95,663	Gamma, SD - $5,651
Eclampsia	$24,828	$22,345 - $27,311	Not applicable
Maternal Death	$49,656	$44,691 - $54,622	Not applicable

Source cost data: eMaternity electronic medical record, HNELHD; SD – Standard Deviation;
*Late antenatal - Period from the first obstetric appointment until commencement of the intra-partum period

Table VIII: Summary results: Intervention compared to Usual Care, Cases of PET Avoided & Total Net Costs, mean point estimates for study population, for study period.

Statistic	Cases of PET Avoided	Total Net Costs
Mean	31.19	($1,431,186)
Standard Deviation	2.90	($119,399)
Low	21.92	($1,874,785)
High	39.90	($1,068,365)
LCI 95%	25.16	($1,671,961)
HCI 95%	36.79	($1,210,504)

Table IX: Intervention compared to Usual Care, Outcomes – Mean estimates for Cases of PET, total and by gestation, for study population, for study period.

	Difference	
PET Health Outcome Status	Count	Percentage
No Risk	31.30	0.47%
PET > 37	(3.02)	(3.77%)
PET 34-36.6	(10.99)	(35.18%)
PET <34	(16.85)	(65.23%)
Eclampsia	(0.32)	(36.18%)
Maternal Death	(0.11)	(36.27%)