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ORIGINAL ARTICLE

Cost-Effectiveness of First Trimester Screening for Preterm Pre-eclampsia in Lebanon

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Abstract To estimate, for Lebanon, the financial benefit of screening for preterm pre-eclampsia (PE) at 11–13 weeks gestation combining risk factors with mean arterial pressure and maternal serum placental growth factor. Preterm PE cases delivered during 2010–2018 at Rafik Hariri University Hospital were identified from electronic records. Manual nursing notes were reviewed to confirm the diagnosis using international criteria. For each case, adverse maternal and infant events were noted and billing information extracted. A series of 1000 non-PE pregnancies were identified and billing information recorded. Published screening detection rates for a 10% false-positive rate and the proportion prevented by aspirin prophylaxis were applied to estimate the reduced cost following screening. There were a total of 17,131 deliveries including 486 (2.84%) PE and 223 (1.30%) preterm PE cases. The caesarean section rate was substantially higher for preterm PE (74%) than non-PE deliveries (36%) and 76% of infants were admitted to the Newborn Intensive Care Unit, where the average stay was 32, 21 and 8 days for deliveries before 32, 32–33 and 34–36 weeks respectively. The total cost of maternal and infant care for preterm PE was $881,206 and the average cost of an unaffected delivery $599. It was estimated that following screening the saving in treatment costs including aspirin would have been $431,665, which is $24 per woman delivering at the hospital over the nine year period. The financial savings are more than sufficient to pay for the screening test in those who are screen-positive.

Keywords Screening · Pre-eclampsia · Early pregnancy · Cost-effective · PlGF

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Introduction

Pre-eclampsia (PE) is a common cause of fetal and maternal morbidity and mortality, particularly those cases requiring delivery before 37 weeks gestation, 'preterm' PE. Low dose soluble aspirin has been demonstrated to be preventative provided treatment begins early enough in pregnancy [1] and is most effective when taken at night [2]. It is now recommended that all women identified at high risk of PE based on prior risk factors, including body mass index, parity and family history, should take aspirin daily starting before 12 weeks gestation [3–5]. However, prior factors alone are insufficient to impact prevalence [6].

A more effective approach is to identify a high-risk group by combining information on prior risk factors together with biophysical and biochemical markers determined at 11–13 weeks gestation to compute the risk of an individual pregnancy being affected [7]. Using four markers—uterine artery Doppler pulsatility index, mean arterial pressure (MAP), maternal serum pregnancy-associated plasma protein (PAPP)-A and placental growth factor (PlGF)—would result in the identification of 80–81% preterm PE and 10% of unaffected pregnancies [6, 8].

In Australia, a 'historically controlled' trial found a 55% reduction in the incidence of preterm PE after the introduction of such screening [9]. A large multi-centre

international placebo-controlled randomized trial (ASPRE) found a 62% reduction [10]; and a 95% reduction in highly compliant women without chronic hypertension [11]. Consequently, two international bodies have recently published recommendations supporting this approach [12, 13].

In countries with limited resources the introduction of a comprehensive program of first-trimester screening for preterm PE may not be affordable [14]. Uterine artery Doppler may be available but only for women presenting late in pregnancy with symptoms of PE. In these circumstances, public health planners might consider a zero-cost option whereby the financial benefit of reduced PE incidence are equal to or exceed the cost of screening. In this paper, we estimate, for Lebanon, the financial benefit of screening with only the two markers MAP and maternal serum PlGF. Blood pressure is already routinely measured in early pregnancy and the unit cost of the single serum marker is not great.

Methods

Information on the incidence of preterm PE and the cost of treatment was obtained from the records of Rafik Hariri University Hospital, Beirut, which provides medical services both locally and to other regions. The hospital has a fully automated medical information system and electronic patient health record.

All maternity records for the nine-year period from 2010 to 2018 were extracted from the system and cases classified as PE were identified. The manual nursing notes of these cases were then reviewed to establish that the pregnancy was affected by PE, according to the criteria of the International Society for the Study of Hypertension in Pregnancy [15] and the American Society of Maternal and Fetal Medicine [16].

For each confirmed case, information was extracted from the system on: mode of delivery (caesarean section or vaginal); the number of days the mother stayed in hospital; fetal and neonatal death; admission to the Newborn Intensive Care Unit (NICU); and number of days spent in the unit. For cases where the delivery was before 37 weeks gestation, all items billed for maternal or infant care during and following delivery were recorded. Costs were expressed in United States dollars after conversion from Lebanese pounds using [17]. The severity of preterm PE, and the consequent cost, is known to be related to the gestation of delivery. Therefore, separate costs were computed for three gestational groups: before 32 weeks; 32–33 weeks; and 34–36 weeks gestation.

A series of 1000 non-PE cases delivered in the year 2016 were selected at random with 500 having a caesarean section and 500 a normal vaginal delivery. Billing information was extracted and the average cost of the type of delivery was computed. The cost of a non-PE delivery was the average of these two costs weighted by the proportion having a caesarean section among all maternities during the study period.

The expected reduction in preterm PE cases following the screening with MAP and maternal serum PlGF was derived from published detection and false-positive rates according to the gestation of delivery in two large studies [6, 8]. The effect of aspirin on detected cases according to the gestation of delivery was from the ASPRE trial [10].

For cases delivered before 32 weeks, the estimated detection rate in one study was 88%; [6] for those delivered preterm and at term in another study the rates were 68% and 40% respectively [8]. The false-positive rate was 10% [6, 8]. In the ASPRE trial the observed reduction in preeclampsia incidence among those randomised to aspirin compared with the placebo group was 82% and 62% in deliveries before 34 and before 37 weeks respectively and, by subtraction, 48% at 34–36 weeks [10].

The current total cost of preterm PE was computed and compared with the cost expected after screening. For each gestational group the expected cost was calculated from the expected reduction in cases which were assumed to cost the same *per capo* as current preterm PE deliveries, plus for the prevented cases of a non-PE delivery. Additionally, the cost of aspirin treatment for those with positive screening results was estimated to be $7.20 [18]. The total saving was calculated and divided by the total number of deliveries over the study period. This represents the amount available to fund screening and aspirin in a zero-cost scenario.

Results

There were a total of 17,131 deliveries at Rafik Hariri University Hospital in 2010–2018. Of these 486 (2.84%) were confirmed to have PE. The rate varied according to nationality: Syrian 2.48% (232/9367); Lebanese 2.90% (190/6563); and others 5.66 (68/1201). Over the nine-year period, there were 6233 pregnancies delivered by caesarean section (36%).

There were 223 preterm PE cases, a rate of 1.30%; Fig. 1 shows the distribution of gestational ages at delivery. The median gestation was 33 weeks; a total of 82 (37%) delivered before 32 weeks, 37 (17%) at 32–33 weeks and 104 (47%) at 34–36 weeks. The remaining 16,908 pregnancies without preterm PE were classified as unaffected for the purposes of this analysis.

Table 1 shows adverse maternal and fetal outcomes in the three broad groups of preterm PE cases and for comparison, the cases delivering at 37 weeks or later. The

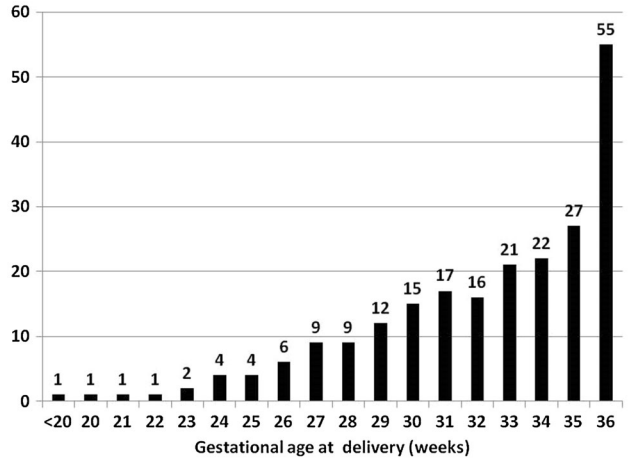

Fig. 1 Distribution of gestational age at preterm delivery with pre-eclampsia (weeks)

caesarean section rate was substantially higher for the preterm PE compared with the term cases, although this did not vary substantially between the three preterm gestational groups. Nevertheless, the average length of stay (LOS) in hospital for mothers was higher for the two earliest groups.

All four measures of adverse fetal outcome were associated with the gestation of delivery. The combined fetal and neonatal loss rates steadily declined across the four PE gestational groups. Excluding the intrauterine fetal deaths, there was a steady reduction in the average LOS in hospital according to gestation of delivery. NICU admission rate was highest for the two earliest groups and the average LOS in the NICU reduced with gestation.

In the sample of 500 non-PE pregnancies delivered by caesarean section, the billing average cost was $944 and for the 500 vaginal deliveries, it was $405. Since over the nine-year period 36% of pregnancies delivered by caesarean section, the average cost was estimated to be $944 * 36% + $405 * 64%, or $599.

Table 2 Maternal and infant costs in preterm pre-eclampsia cases, current and expected with screening

	Gestation of delivery (weeks)			Total
	< 32	32–33	34–36	
Current[†]				
Maternal	$128,772	$36,455	$110,870	
Infant	$360,501	$133,338	$111,270	
Both	$489,273	$169,793	$222,140	$881,206
Expected with screening				
Remaining cases*	$136,996	$98,480	$148,834	
Prevented cases[‡]	$35,365	$9308	$20,558	
Both	$172,361	$107,788	$169,392	$449,541

[†]Based on total observed billings

*After aspirin treatment in women with screen-positive results using MAP and maternal serum PlGF

[‡]Based on the average cost of a non-PE delivery

Table 2 shows the current total billing cost of the 223 preterm PE cases and compares this with the cost expected after the introduction of routine screening with MAP and maternal serum PlGF. In those delivering before 32 weeks gestation, the expected reduction in PE cases after screening was estimated by the detection rate in this group [6] multiplied by the effect of aspirin on incidence before 34 weeks [10] which was 72% (88% * 82%). The median gestational age for PE cases delivered before 32 and before 34 weeks were 29 and 30 weeks respectively, not a substantial difference (Fig. 1). Similarly, for those delivering at 32–33 weeks, the published detection rate for all preterm PE [8] was assumed to apply, since the overall median gestation was 33 weeks. And the effect of aspirin on preterm cases [10] was assumed to apply yielding an expected reduction of 42% (68% * 62%). For those delivering at 34–36 weeks the average (54%) for the published detection

Table 1 Adverse maternal and infant outcomes in pre-eclampsia cases according to gestation at delivery

	Gestation of delivery (weeks)			
	< 32	32–33	34–36	37+
Maternal				
Caesarean section rate*	66% (54/82)	69% (27/39)	71% (74/104)	49% (128/263)
Average LOS (days)	7.3	6.5	5.6	5.6
Infant				
Loss rate* (IUFD + NND)	55% (19 + 26)	16% (4 + 2)	9.6% (9 + 1)	5.7% (9 + 6)
Infant excluding IUFD				
Average LOS (days)	23.3	19.2	7.1	3.3
NICU rate*	81% (51/63)	82% (27/33)	43% (41/95)	15% (39/254)
Average LOS in NICU (days)	33.2	23.7	13.3	9.1

LOS length of stay in hospital, *IUFD* intra-uterine fetal death, *NND* neonatal death

*Unknown for some cases

rates in cases delivering before and after 37 weeks (68% and 40% respectively [8]), was assumed to apply to yield a reduction of 33% (54% * 48%). The overall number of true positive cases requiring aspirin treatment would be 153 (82 * 88% + 37 * 68% + 104 * 54%).

The screening was estimated to reduce the cost of treating preterm PE by $431,665 ($881,206–$449,541), which is $25 per woman attending the Rafik Hariri University Hospital over the 9-year period ($431,665/17,131). The cost of aspirin prophylaxis among the 153 true-positives and 1691 false-positives (10% * [17,131–233]) would total $13,320 so that the reduction in total costs would be $24 per woman ([$431,665–$13,320]/17,131).

Discussion

The current analysis shows that a policy of routine screening for preterm preeclampsia at 11 weeks gestation using MAP and maternal serum PlGF followed by low dose soluble aspirin would be cost-effective in Lebanon. The savings in the cost of maternal and infant treatment of PE, associated primarily with a high caesarean section rate and an extended infant stay in NICU would be more than sufficient to fund the cost of routine maternal serum PlGF testing.

This analysis is focused on screening for *preterm* PE. It is possible that some women at high risk of preterm PE will also be at high risk of term PE and that the aspirin treatment will also have a benefit for those cases. However, in the ASPRE trial the incidence of term PE in the aspirin and placebo arms were similar, 6.6% and 7.2% respectively [10]. This is not inconsistent with some prevention of term PE but it could be offset by cases that would have presented as preterm PE, in the absence of aspirin, having reduced severity and hence delayed onset.

The performance of PE screening protocols based on risk assessment using prior factors and pregnancy-specific markers is dependent on the distribution of risk factor in the population being screened. Detection rates for the MAP and maternal serum PlGF protocol considered here were estimated from two large multi-centre collaborative studies [6, 8]. One involved twelve centers in five countries: UK, Spain, Belgium, Greece and Italy and there is no reason to expect that the distribution of risk factors would differ in Lebanon [6]. The other, a larger study which included seven maternity hospitals in England and Wales [8], had overall performance similar to the international study.

Down syndrome screening is not widespread in Lebanon where it is generally available in the private sector. Countries with routine Down syndrome screening using the Combined test may consider introducing screening for preterm PE with a protocol of MAP and maternal serum PAPP-A which is part of the Combined test. However, this may not be the best option as this protocol is estimated to identify 7–9% fewer preterm PE cases [6, 8]. Moreover, enhancing the Combined test by the addition of PlGF leads to an increase in the Down syndrome detection rate [19–23].

Only one other study has assessed the cost of preterm PE [24]. This was carried out in California and based on the Medi-Cal fee for service schedule and reimbursement rates for private hospitals. In 2011, over 27,000 births in the state were complicated by hypertensive disorders and approximately half were paid for by Medi-Cal. Maternal and neonatal care costs were computed and the incremental cost was estimated for hypertensive disorders over and above that of a normal pregnancy. For severe preterm PE, the average incremental cost was estimated to be $13,000. In the current study the incremental cost for PE cases delivered before 32 weeks, the most severe group, was over $5000 ($489,273/82–$599). Given the disparity incomes between Lebanon and California, these are comparable amounts.

Data from the ASPRE randomized trial have been used to directly assess the impact of aspirin on the average length of stay in the NICU for preterm PE cases [25]. Those in the placebo arm of the trial admitted to the unit spent 31 days there compared with 11 days in the placebo arm, a statistically significant reduction. In the current study, the number of PE cases admitted to the NICU in the three gestational periods and expected to be detected by screening were 45 (51 * 88%), 18 (27 * 68%) and 32 (59 * 54%). These 95 cases would have an average time in NICU of 24 days [(45 * 33.2 + 18 * 23.7 + 32 * 13.3)/95]. Aspirin in screen-positive women would be expected to reduce their number to 8 (45 * 18%), 7 (18 * 38%) and 17 (32 * 52%) and reducing the average time in NICU to 7 days [(8 * 33.1 + 7 * 23.7 + 17 * 13.3)/95].

A study by Shmueli et al. [26] developed a cost–benefit model of first trimester PE screening using three markers, uAD, maternal serum PlGF and PP13. Ministry of Health prices were assigned to standard care and surveillance of pregnancies at high risk of PE, maternal hospitalization, delivery and NICU stay, and contemporary commercial prices were estimated for the screening test. A low PE incidence of 1.7% was derived from the records of one hospital and treatment using aspirin, calcium and folic acid together with intensive surveillance were assumed to prevent 30% of PE requiring delivery before 34 weeks gestation and 10% of later PE. The conclusion of the modeling exercise was that under these baseline assumptions the financial benefits would exactly equal the cost. This is consistent with the current analysis.

After decades of research, the ASPRE study demonstrated that it is now beyond doubt that first trimester

multiple marker screening for preterm PE followed by aspirin prophylaxis is effective [12, 13]. Analyses like the current study show that it is cost-effective. Health planners in all countries now need to consider how best to implement screening given their available resources.

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Compliance with ethical standards

Conflict of interest HK is an employee of HVD Life Sciences GmbH and HC is a consultant to PerkinElmer Inc; both companies provide reagents for maternal serum preeclampsia tests. Other authors have no conflict of interest.

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