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Outcome of pregnancy with new onset proteinuria and progression to pre-eclampsia: A retrospective analysis

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ABSTRACT

Objective: To examine maternal and neonatal outcomes of gestational proteinuria, and to identify maternal characteristics for progression to pre-eclampsia.

Study design: Retrospective cohort. Included all pregnant women who delivered between Jan 2014–Feb 2017 with new onset proteinuria in a single obstetric unit. Demographic, maternal and neonatal outcomes were compared.

Results: Eighteen (25%) out of 73 women with new onset gestational proteinuria developed pre-eclampsia. The incidence of gestational proteinuria was 0.54%. Compared with women that remained normotensive, those that developed hypertension had delivery at earlier gestation ($p = .02$), increased risk of fetal growth restriction ($p = .01$) and lower newborn birthweight ($p = .002$). Maximal proteinuria and fetal growth restriction were independent factors associated with development of pre-eclampsia. In particular, high proteinuria level ≥ 2 g/d constitute a major predictor for progression ($p = .03$).

Conclusion: Increased vigilance for antenatal surveillance is important in women with gestational proteinuria as a substantial portion progress to pre-eclampsia. Serial growth scan and proteinuria assay are suggested to predict possible pre-eclampsia development.

1. Introduction

Proteinuria during pregnancy can be physiological due to combination of increased glomerular filtration rate, increased permeability of the glomerular baseline membrane, and reduced tubular reabsorption of filtered protein in pregnancy. However, proteinuria is also a cardinal feature of pre-eclampsia, which is a leading cause of maternal and neonatal morbidity and mortality worldwide [1]. In the past, outcome of isolated gestational proteinuria (IGP), i.e. proteinuria without hypertension, was believed to be favorable [2]. However, in recent years, there has been growing evidence that IGP was part of the pre-eclampsia continuum.

At molecular level, excessive placental secretion of anti-angiogenic proteins such as soluble fms-like tyrosine kinase 1 and soluble endoglin into maternal blood were believed to cause widespread endothelial dysfunction. Features of pre-eclampsia were ascribed to generalized endothelial dysfunction, for example, proteinuria resulted from increased vascular permeability and hypertension caused by disturbed endothelial control of vasculature [3]. Holston et al. in 2009 reported a modest and transient imbalance of circulating anti-angiogenic factors in patients with gestational proteinuria [4]. This finding supported the hypothesis that IGP could be a mild variant form of pre-eclampsia.

Nevertheless, at clinical level, the relationship of IGP with pre-eclampsia had not been fully understood. According to a national incidence study using the UK Obstetric Surveillance system involving 299 UK hospitals, 214 cases met the criteria for eclampsia in year 2005–2006 [5]. One week before the eclamptic fit, 38% had established pre-eclampsia, 10% had hypertension without proteinuria, and another 8% had proteinuria without hypertension, inferring an intimate relationship between IGP and pre-eclampsia. Morikawa et al. was the first to report women exhibiting proteinuria in the absence of hypertension later developed high blood pressure and were diagnosed pre-eclampsia [6]. In this study, we aimed to compare maternal and neonatal outcomes in gestational proteinuria and those who progress to proteinuria-preceding pre-eclampsia (P-PE) and to recognize maternal characteristics to predict such progression.

2. Methods

This retrospective cohort was conducted in a single obstetric center in Hong Kong. We identified all women who delivered in the unit from Jan 2014–Feb 2017 with new onset proteinuria during their antenatal

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Table 1
Maternal characteristics and pregnancy outcome.

	All (n = 73) (neonate = 80)	IGP (n = 55) (SD) (neonate = 61)	P = PE(n = 18) (SD) (neonate = 19)	P value; MD; 95% CI
Age	32.7 (4.6)	32.9 (4.8)	31.9 (4.2)	.44; .98; (−1.53–3.50)
Pre pregnancy BMI (kg/m^2)	23.1 (4.1)	23.2 (4.3)	22.5 (3.4)	.50; .76; (−1.46–2.98)
Primiparity	45 (61.6%)	36 (65.5%)	9 (50%)	.24
Smoker	12 (16.9%)	11 (20%)	1 (5.6%)	.15
GDM/DM in pregnancy	9 (12.3%)	9 (16.4%)	0	.07
Twin gestation	7 (9.6%)	6 (10.9%)	1 (5.6%)	.50
Previous IGP	2 (2.7%)	2 (3.6%)	0	.41
Previous pre-eclampsia	2 (2.7%)	0	2 (11.1%)	.013
Gestation at onset of proteinuria (week)	34.6 (6.8)	34.5 (7.6)	35 (3.1)	.79; −.49 (−4.18–3.20)
Proteinuria value at presentation (g/d)	1.3 (1.5)	1.1 (1.1)	1.9 (2.3)	.05; −.80; (−1.61 to .001)
Maximal proteinuria during pregnancy (g/d)	1.7 (2.0)	1.3 (1.3)	2.9 (3.0)	.003; −1.54; (−2.55 to -.53)
Increment of proteinuria (g/d)	0.4 (1.4)	0.3 (0.7)	1.0 (2.4)	.045; -.74;(−1.46 to -.002)
SBP at diagnosis (mmHg)	128 (14.2)	126.9 (14.4)	131.5 (13.4)	.23; −4.63; (-12.31 to 3.06)
DBP at diagnosis (mmHg)	76.2 (9.8)	74.8 (9.8)	80.7 (8.5)	.02; -5.96; (−11.10 to −.82)
Duration from presentation to delivery (week)	3.4 (6.4)	3.8 (7.3)	2.2 (1.3)	.36; 1.62; (−1.84 to 5.07)
Fetal growth restriction	27 (33.8%)	16 (26.2%)	11 (57.9%)	.01
Mode of delivery				
SVD	38 (47.5%)	30 (49.2%)	8 (42.1%)	.82
Instrumental	9 (11.3%)	7 (11.5%)	2 (10.5%)	
CS	33 (41.2%)	24 (39.3%)	9 (47.4%)	
Duration from proteinuria to PET (week)	NA	NA	1.6	NA
Gestation age at delivery (week)	38.0 (1.8)	38.3 (1.4)	37.2 (2.5)	.02; 1.12; (.17 to 2.08)
Iatrogenic preterm delivery before 37 weeks	8 (11%)	3 (5.5%)	5 (27.8%)	.008
Birthweight (g)	2777 (6 6 4)	2904 (6 1 6)	2369 (6 6 3)	.002; 535 (207–863)
Adjusted Birthweight (g)*		3177 (5 3 0)	2692 (4 5 7)	.001; 485 (213–757)
AS at 5 min < 7	0	0	0	–
Neonatal admission				
Nursery	46 (58.2%)	38 (62.3%)	8 (44.4%)	.20
SCBU	24 (30.4%)	18 (29.5%)	6 (33.3%)	
NICU	9 (11.4%)	5 (8.2%)	4 (22.2%)	
Stillbirth	1 (1.3%)	0	1 (5.3%)	.07

Abbreviations: BMI = body mass index. GDM = gestational diabetes. DM = diabetes mellitus. SBP = systolic blood pressure. DBP = diastolic blood pressure. SVD = spontaneous vaginal delivery. CS = caesarean section. AS = Apgar score. SCBU = special care baby unit. NICU = neonatal intensive care unit.

* Projected birthweight at term according to corresponding growth centile.

care using hospital obstetric database. Demographic data and maternal and neonatal outcomes were reviewed from medical records.

Blood pressure measurement and urine dipstick testing for detection of proteinuria were performed at each antenatal visit. Hypertension was defined as blood pressure ≥140/90 mmHg on two occasions at least 4 h apart. A spot urine protein to creatinine ratio (Spot uPCR) or 24-h urine proteinuria test would be ordered if there was 1+ or more dipstick positivity. Proteinuria was defined as Spot uPCR ≥ 0.3 mg/mg, or 24-h urine protein ≥ 0.3 g. IGP was defined as proteinuria in the absence of hypertension. Pre-eclampsia was defined as the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman. Ultrasound scans for baseline fetal growth parameters were performed for all patients at the presentation of new onset proteinuria and serial scans for interval growth were performed for those with clinical suspicion of fetal growth restriction. In our unit, it was a routine practice to offer induction for women with pre-eclampsia after 37 weeks of gestation and IGP after 38 weeks of gestation because of possible rapid progression to pre-eclampsia and associated complications. Elective caesarean section would be arranged for obstetric reason if the women agreed for earlier delivery.

Exclusion criteria included pre-existing renal disease, pre-existing proteinuria, essential hypertension, pre-existing diabetes mellitus and presence of hypertension at the time of proteinuria detection.

Demographics data including age, pre-pregnancy body mass index (BMI), primiparity, smoking status, diabetes, order of pregnancy, previous IGP/ pre-eclampsia, were obtained as they were known independent risk factors for pre-eclampsia [7]. Data relating to proteinuria, including onset gestation at diagnosis, proteinuria level and blood pressure at presentation, and maximal proteinuria values reached were also collected. The increment level of proteinuria is the difference between the maximal and the proteinuria level at presentation. Maternal outcomes examined were gestational age and mode of delivery, need of iatrogenic preterm delivery before 37 weeks, progression to pre-eclampsia and associated complications, and intensive care unit admission. Neonatal outcomes included newborn birthweight, evidence of fetal growth restriction, Apgar score at 5th minute of life, admission to neonatal intensive care unit, and intrauterine demise. Fetal growth restriction was defined as fetal weight below 10th percentile for gestational age as determined through ultrasound.

3. Sample calculation

Shira et al. reported a significantly higher maximal proteinuria level of 2.3 ± 1.9 g/day in P-PE group than IGP group 1.3 ± 1.5 g/day with a p value of .01 [8]. To achieve a power of 80% and a level of significance of 5% (two sided), a total sample size of 72 cases was required to detect a true difference in the mean proteinuria level of around 70–80% between these two groups. Our delivery rate was around 4000 per year. The incidence of gestational proteinuria was estimated to be approximately 1%, hence there would be around 40 cases of gestational proteinuria annually. Therefore we set to recruit roughly 3 years data to obtain a sufficient sample size.