ORIGINAL ARTICLE

Maternal Factors Associated with Preeclampsia among Asians: Systematic Review of Large Cohort Studies

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Abstract

Background: Maternal mortality is still a major problem in developing countries. In 2015, World Health Organization estimated the Maternal Mortality Rate (MMR) in developing countries was as high as 239 per 100,000 live births, while it was as low as 12 in developed countries. According to the data, this indicates the failure of many developing countries in achieving Millennium Development Goals (MDG), nevertheless the awareness of which is still low. Moreover, maternal death also immensely affects the growth and development of a child, which can lead to a reduced child's life quality. In fact, 25% of maternal deaths are caused by Preeclampsia, hence it is still a global burden, and has to be controlled to achieve Sustainable Development Goals in 2030. In addition, a population-specific systematic review of maternal factors associated with preeclampsia among Asian has not been done before. **Aim**: This study reports a systematic review to identify factors associated with preeclampsia among Asian in order to reduce its incidence through increasing awareness and screening quality of preeclampsia. **Material and method:** A systematic review was conducted on cohort studies concerning the factors associated with preeclampsia among Asian. Cohort studies were chosen as it is a time-based study, therefore compatible to identify the risk of preeclampsia, based on pathogenesis during pregnancy time. 6133 records, related with preeclampsia among Asian, were found from *Pubmed*. We exclude publications that did not meet inclusion criteria (n = 6037), then which meet exclusion criteria (n = 81). Finally, three reviewers extracted data from total included study (n = 15) and we assested the studies with STROBE statement to show the quality of each studies. **Results:** There were 375.622 participants among 15 studies. The studies show that factors associated with preeclampsia are: maternal BMI, maternal weight gain during pregnancy, maternal age, history of gestational hypertension and preecalmpsia, diabetes mellitus, gravida and parrity, etc. Risk factors with highest odd ratio are pre-gestational obese (OR: 7.85); chronic hypertension (OR: 7.174); and previous history of gestational hypertension or preeclampsia (OR: 8.85). On the other hand, weight gain below IOM in overweight pre-gestational weight (OR: 0.76), isolated anti TPO antibody (OR: 0.7), normal BMI with BPD >90 (OR: 0.86), and maternal weight gain <10kg (OR: 0.5) are shown to be protective factors of preeclampsia. Furthermore, maternal BMI, history of gestational hypertension and preeclampsia are risk factors of preeclampsia which most discussed and could be a complex issues among Asian countries. **Conclusion:** From this systematic review,

maternal BMI (overweight and obese), inappropriate maternal weight gain, and history of pre-gestational hypertension and preeclampsia, were proven to be the highest risk of preeclampsia among Asian women. Other risks of which are maternal age, mother's education, mother activity, DM and hypothyroidism. With this knowledge, we aim this review to improve the quality of preeclampsia screening and awareness of physicians and mothers regarding the problem or even develop a practical evidence based list of risk factors related to preeclampsia among Asian, which can be assesed by health care worker.

Keywords: *preeclampsia, body mass index, maternal age, hypertension, history of preeclampsia*

Background

Preeclampsia is a potentially dangerous pregnancy complication caused by vascular endothelial malfunction disorder. As the highest contributor in maternal mortality, preeclampsia is still a global burden, especially in developing countries. In fact, every day, at least 76,000 from 290,000 deaths, translating to 25% of all deaths of mothers all over the world, are accounted to preeclampsia. In 2015, World Health Organization estimated the Maternal Mortality Rate in developing countries was as high as 239 per 100,000 live births, while it was as low as 12 in developed countries. The significance of the problem is also shown in data of maternal death risk, which is 1 in 180 in developing countries, compared to 1 in 4900 in developed countries.[1] This huge gap was then worsen by the data that many developing countries failed to achieve Millennium Development Goals (MDGs) in reducing maternal mortality rate. Our beloved homeland, Indonesia, for example, still has the MMR twice the initial expected number, which is of 305 deaths compared to 102 deaths per 100,000 live births. This indicates the lack of knowledge and awareness towards the causes of maternal death.[2]

Moreover, maternal death also deeply affects the growth and development of a child. Without the presence of a well-built mother and child attachment, the establishment of cognitive, physical, social, and emotional capacity of a child could be impaired. Not only affecting the family, preeclampsia also causing disadvantages to the country. Treatment of preeclampsia in the United States has cost more than 2.18 billion US dollar per year. With the MMR significantly higher in developing countries, it can be conceived how developing countries are economically burdened.[3]

In addition, a population-specific systematic review of maternal factors associated with preeclampsia among Asian has not been done before. Our systematic review stands as the new strategy to reduce MMR in Sustainable Development Goals, and agenda that serves as a continuation of MDGs, to 70 deaths per 100,000 live births.

Objective

To identify factors associated with preeclampsia among Asian in order to reduce its incidence through increasing awareness and screening quality of preeclampsia

Method

We conducted a systematic review of large cohort studies concerning the factors associated with preeclampsia among Asian. Cohort studies were chosen, as it is a time-period approach, due to it's compatibility to identify the risk of preeclampsia based on its pathogenesis during a definite pregnancy time.

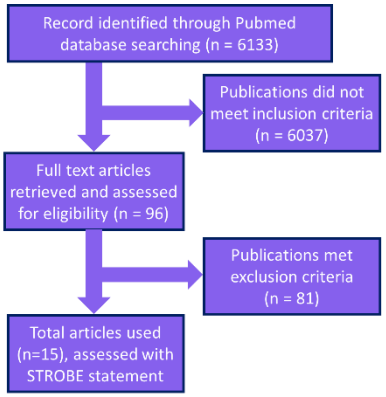

Figure 1. Conceptual Framework

From *Pubmed* Database, 6133 records were identified from all time until October 2017. For the search strategy we used combinations of several terms: "preeclampsia OR pre-eclampsia OR PE", "risk factor OR factor OR risk", "Asian OR Asia", "cohort OR prospective study OR retrospective study". We only included prospective and retrospective cohort studies identifying the risk factor of preeclampsia with Asian as the spesific population sample. We excluded the study which is not written in English and the study which published not in Asia region due to the reason that Asian who lived outside the continent might have changed their life style distinctively. Studies identifying biomolecular or genetic factor were also excluded, because we would like to identify factor which is common, preventable and can be altered in order to reduce the number of preeclampsia. Then, 6037 publications that did not meet inclusion criteria and another 81 publications that met the exclusion criteria were excluded, resulting in the final 15 total included studies [Figure 1].

Furthermore, data from the total included studies were extracted and assessed with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement spesificaly for cohort study to show the quality of each publications. Data extraction and STROBE statement assessment was done by three reviewers, which had been equalized and trained in using STROBE Statment as assessing tool. In addition, each study was assessed and evaluated three times by different reviewer in order to reduce human error and bias of data extraction or STROBE statement assessment.

We abstracted information from the publications on: study design, location of study, sample size, gestational age, mean age of sample, method of analysis, outcome (associated factor and its odd ratio). As mentioned before, quality of each cohort study we assessed them with STROBE statement, so they could be qualitatively compared with equal assessment.

Result

Characteristic of Included Studies

The total participants included in this systematic review were 375.622 from 15 studies. This included studies are summarised in [Table 1].

Risk factors of preeclampsia that are most discussed in the studies and problematic in Asia are maternal BMI and history of gestational hypertension and preeclampsia. The Odd Ratios of the risk factors are 7.85 and 8.85, respectively, causing both factors to have highest OR compared to another factors. Other risk factor that has high OR is chronic hypertension (OR: 7.174). On the other hand, the protective factors of preeclampsia are weight gain below IOM in overweight pre-gestational weight (OR: 0.76), isolated anti-TPO antibody, normal BMI, BPD >90 (ORs: 0.86), maternal weight gain <10 kg and maternal weight gain ≥ 16 kg (ORs: 0.6) [Figure 2]. In addition, The best study of which, according to STROBE Statement, is a 2015-publication by Li X et al. The study scores 20.4 out of maximum 22 points.

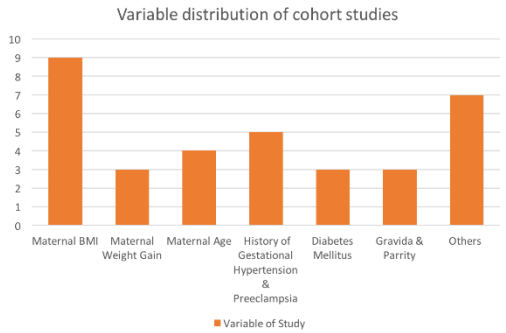

Figure 2. Bar Diagram of Variable Distribution of Cohort Studies

Discussion

Preeclampsia is described as an pregnancy-specific syndrome which could affect every organ system virtually. It is characterised by hypertension which could damage to another organ system, most often the kidneys, then cause proteinuria which also manifest as oedema in both of hands and feet. According to summarised result of included studies in [Table 1], preeclampsia is well-known as a multifactorial disorder. There are several factors associated with preeclampsia, nevertheless we will discuss the top-3 factors related to occurrence of preeclampsia among Asian.

Maternal Body Mass Index

Studies have confirmed that inappropriate pre-gestational weight is associated with increased risks of preeclampsia. According to Hung TH, women with overweight and obese pre-gestational BMI carried a 3.7 fold and 7.85 fold increased risk of preeclampsia respectively.[5] Li X also showed overweight pre-gestational BMI to escalate the risk of preeclampsia by 1.98 and obese by 3.41.[6] On the other hand according to Park JH, Leung TY underweight category is less influential and tends to be a protective factor[7,8] Although, underweight pregestational BMI is a protective factor of preeclampsia, it increases risk of morbidity and mortality in infants. The positive relationship is supported by the fact that women with obese pre-gestational BMI have significantly elevated levels of IL-6 and C-reactive protein in serum, along with impaired endothelial function.[20] Currently, Asia is widely using the BMI standard based on WHO's. However, referring to that standard, obese people in Asia are prone to having a larger waist circumference than Caucasian. This implies the need of adjustment of BMI Standard in Asia.[20]

Maternal Age

Several studies have confirmed that advanced maternal age is associated with adverse pregnancy outcomes. Advanced maternal age increases the risk of preeclampsia exponentially. According to Islam MM, maternal age equal to or more than 35 years increased the risk by 3 times.[8] Li X also showed a similar increased risk by 3.34 times with maternal age above 35.[12] Moreover, in another study from Funai EF, maternal age above 40 increased the risk by 4.19 fold.[6] Maternal age is a multifactorial risk of preeclampsia, which is related with: glucose intolerance due to insulin insensitivity, abnormal lipid profile, hypertensive disorder, etc.[20]

Hypertension and History of Preeclampsia

Hypertension and history of preeclampsia have great contribution in increasing risk of preeclampsia. According to Yu S, risk of preeclampsia increase 7.714-fold in mother with chronic hypertension.[19] On other study by Taguchi T showed that previous history of hypertension and preeclampsia had 8.85

times of risk of having preeclampsia in multipara gestation.[17] Preeclampsia is initiated by placental ischemia which increases total peripheral resistance via cytokines reaction. Then, it leads hypertension and becomes preeclampsia.[20] Although patophysiology of preeclampsia remains unclear, many studies showed that incidence of preeclampsia is higher among women with previous history of hypertension and preeclampsia. Therefore, for the mother having these risks, we suggest to be more aware before having another conception and should check for ante natal care when they are pregnant.

Study Limitations

The main limitation of our review are: the uneven distribution of respondents, small number of studies, and extreme heterogeneity among Asian. The uneven distribution of respondents is caused as some Asians might have migrated outside the continent, which may not be assessed to the studies. Moreover, the study of preeclampsia among Asian is not as many as studies in Caucasians, indicating the study of which is still low with the extreme heterogeneity among Asian. Therefore, the risk factors mentioned in this review may just affect considerably in some populations which have similar/closly related culture, habit or gene.

Conclusion

From this systematic review, maternal BMI (overweight and obese), maternal age, pre-gestational hypertension and hystory of preeclampsia were proven to be the most influential and common risks of preeclampsia among Asian. Moreover, other risks of which are inappropriate maternal weight gain, low mother's education and activity, DM and hypothyroidism. With this knowledge, we aim this review to improve the quality of preeclampsia screening and awareness of physicians and mothers regarding the problem. Furthermore, we hope that this review could develop a practical evidence-based list of risk factors related to preeclampsia among Asian which can be assessed by primary health care worker.

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Table 1. Characteristics of Studies and STROBE's scoring

Author and Year of Publication	*Study Design*	*Location of Study*	*Sample Size*	*Gestational Age*	*Mean Age of Sample*	*Method of Analysis*	*Outcome*	*Strobe*
Boriboonhirun-sam D, et al. 2017.[5]	Retrospective cohort	Bangkok	300	11.3 w	34.3	Logistic regression, Chi-square, Student T-test,	Mean arterial pressure ≥105 mmHg in 24-28 weeks of gestational age (OR: 1.8)	15.8
Funai EF, et al. 2005.[6]	Retrospective cohort	Jerusalem	82 436	N/A	27	Logistic regression	Primigravida (OR:2.8); mother's education 0-4 (OR: 1.87); mothers education 5-12 (OR: 1.44) ; house wife (OR: 0.98); diabetes (OR: 5.25); maternal age 35-39 (OR: 1.68); maternal age >40 (OR: 4.19); fetal haemolytic disease (OR: 2.31)	16
Hung TH, et al. 2016.[7]	Retrospective cohort	Taipei, Taiwan	10.973	37 w	N/A	Multivariable logistic regression, Chi- square,	Pre-gestational overweight (OR:3.74); pre-gestational obese (OR: 7.85); weight gain below IOM in underweight pre-gestational weight (OR: 1.72); weight gain above IOM in underweight preg-estational weight (OR: 4.58); weight	17.3

Author and Year of Publication	*Study Design*	*Location of Study*	*Sample Size*	*Gestational Age*	*Mean Age of Sample*	*Method of Analysis*	*Outcome*	*Strobe*
							gain below IOM in normal pre-gestational weight (OR: 1.13); weight gain above IOM in normal pre-gestational weight (OR:3.65); weight gain below IOM in overweight pre-gestational weight (OR: 0.76); overweight pre-gestational weight gain in overweight pre-gestational weight (OR: 1.24)	
Islam MM, et al. 2015.[8]	Retrospective cohort	Oman	1,711	N/A	32	Chi-square test, T-test	Maternal age ≥ 35 (OR: 3)	16.6
Kumru P, et al. 2014.[9]	Cohort	Mardin, Turkey	395	10-12 w	N/A	Logistic regression, Chi-square, student T-test, Fischer's exact test	Isolated anti TPO antibody (OR: 0.7); sub-clinic hiypothyroidism (OR: 1.1); sub-clinic hypothyroidism with anti TPO (OR : 1.55)	19.6
Lee CJ, et al. 1999.[10]	Retrospective cohort	Taipei, Taiwan	29 375	20 w	20-34	Multivariate logistic regression, chi square, T-test, Fischer's exact	History of preeclampsia (OR: 6.3); multiple gestation (OR: 3.6); pregnancy body mass >24.2 (OR: 2.4); age >34 years (OR: 1.8); nulliparity (OR: 1.3); urinary tract	17

Author and Year of Publication	*Study Design*	*Location of Study*	*Sample Size*	*Gestational Age*	*Mean Age of Sample*	*Method of Analysis*	*Outcome*	*Strobe*
							infection during pregnancy (OR: 4.8); worked during pregnancy (OR: 1.9); normal BMI(OR: 0.6)	
Leung TY, et al. 2008.[11]	Retrospective cohort	Hong Kong	29.303	20 w	31	Univariate and multivariate logistic regression	BMI<18.5 (OR: 0.9) ; obesity(OR: 3.97)	19.2
LI X, et al. 2015.[12]	Retrospective cohort	Liuyang, China	6,223	N/A	N/A	Chi-square test, Fisher's exact test, univariate and multivariate logistic regression, two-tailed hypothesis test	Maternal age >35 (OR 3.34); BMI 24-28 (OR 1.98); BMI ≥ 28 (OR= 3.41); GDM (OR: 18.01); Diabetes Mellitus/renal disease/cardiac disease (OR: 4.24); fetal sex male (OR: 0.65)	20.4
Li Z, et al. 2013.[13]	Cohort	Beijing, China	193.554	N/A	N/A	Logistic regression	Age continuous (RR: 1.06); BMI continuous (RR; 1.07); factory worker (RR:1.04); other occupation (RR:1.12); junior high school (RR:1.18); prim	16.1
Marsoosi V, et al. 2011.[14]	cohort	Tehran, Iran	2219	17-24 w	27.2	Univariate and multivariablelogistic regression	BPD <10 (OR:1.04); BPD >90 (OR: 0.86)	15.2

Author and Year of Publication	*Study Design*	*Location of Study*	*Sample Size*	*Gestational Age*	*Mean Age of Sample*	*Method of Analysis*	*Outcome*	*Strobe*
Park JH, et al. 2011.[15]	Retrospective cohort	Seoul, Korea	2311	28-42 w	N/A	Univariate and multivariate logistic regression, Chi square test	BMI underweight (OR: 1.1); overweight (OR: 2.4); maternal weight gain <10kg (OR: 0.5); maternal weight gain ≥16 kg (OR:0.6)	15.9
Shetty M, et al. 2010.[16]	Cohort	India	130	28.9 ± 1.7 w	26.8 ± 3.7	Multiple logistic regression, (Chi-square test)	Working (OR: 2.63); nuliparity (OR: 4.04)	14.2
Taguchi T, et al. 2014.[17]	Retrospective cohort	Osaka, Japan	742	<14 w	N/A	Multivariable logistic regression	IN TWIN PREGNANCIES - primipara (OR: 1.77); pre-gastational BMI (OR: 1.35); family history hypertension (OR: 1.5) IN MULTIPARA PREGNANCIES - previous history of gestational hypertension or preeclampsia (OR: 8.85)	16.5
Wei YM, et al. 2015.[18]	Cohort	Beijing, China	14.451	N/A	N/A	Multivariate analysis	BMI overweight (OR: 2.26); obese (OR: 4.49); GDM with overweight (OR: 1.9); GDM with obese (OR: 1.89; non GDM with overweight (OR:	13.1

Author and Year of Publication	*Study Design*	*Location of Study*	*Sample Size*	*Gestational Age*	*Mean Age of Sample*	*Method of Analysis*	*Outcome*	*Strobe*
							2.29); nonGDM withobese (OR: 6.1)	
Yu S, et al. 2007.[19]	Retrospective cohort	Beijing, china	1.499	N/A	30.5-30.7	Chi square, fFscher exact test	Chronic hypertension(OR: 7.174) ; increasing pre-pregnancy BMI (OR: 1.131)	15