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Mini Review

We Need More Aggressive Early Antenatal Care for Preeclampsia in Low Resource Primary Care Setting

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Abstract

Preeclampsia even though is still number one lady killer, until recently the pathophysiology is not completely understood and hence the management is only screening, low dose aspirin and induce labor. The problems are so big, with so little options: Screening is so expensive, multi-markers and not user friendly. Antenatal care are voluntary and if suffered from PE, the pregnancy will be induced at 37 week of pregnancy.

We propose new model of antenatal Care through aggressive management by active HRP findings, Low dose aspirin, closed mentoring and maternity waiting homes not waiting in the clinic and let the couples make voluntary antenatal care.

There will be 7 maternal characteristics items(age, previous PE, born as IUGR baby, first degree relative, interpregnancy interval, primpaternity, history of medical disorders) and two biophysical markers (Body Mass Index, Mean Arterial Pressure) as candidates for markers as high risk pregnancy for preeclampsia.

Keywords: *Preeclampsia; Aggressive Management ANC; Active HRP Findings; Low Dose Aspirin; Closed Mentoring; Maternity Waiting Home*

Abbreviation

ANC: Ante-Natal Care; BMI: Body Mass Index; EOP: Early Onset Preeclampsia; HRP: High Risk Pregnancy; HPP: Hemorrhagic Post Partum; IUGR: Intra Uterine Growth Restriction; LDA: Low Dose Aspirin; PE: Preeclampsia; LOP: Late Onset Preeclampsia; MAP: Mean Arterial Pressure; MWH: Maternity Waiting Home

"In a war that you cannot win, you don't want a general who fights to the point of total annihilation. You want someone who knows how to fight for territory that can be won and how to surrender it when it can't, someone who understands that the damage is greatest if all you do is battle to the bitter end" Atul Gawande - Being Mortal: Medicine And What Matters In The End [1].

Introduction

There are some considerations to the above title - We Need More Aggressive Early Antenatal Care for Preeclampsia in Low Resource Primary Care Setting - even most of the professional organization [2-10] and papers [11-17] do not recommend simple early prediction for preeclampsia as follow: 1. PE remains one of the top five causes of maternal and perinatal mortality worldwide. Data from several

writers estimate that PE claims the lives of more than 70,000 women per year and more than 500,000 of their fetuses and newborns: meaning the loss of 1600 lives/day. More than 99% of these losses occur in low- and middle-income countries. For every woman who dies, it is estimated that another 20 suffer a life-altering morbidity. In the last ten years PE remained the largest proportion of maternal deaths [3-9]. 2. The low accuracy of Doppler velocimetry in PE prediction [18]. 3. At Dr Soetomo General Hospital, PE alone and PE in combined with HPP and heart disease in pregnancy were the largest proportion of maternal deaths for many years [19,20]. 4. While advanced research in developed countries and copied by expert in developing countries - no causal factors found and no better clinical advantage for this disease until now [21-25]. 5. Low Dose Aspirin is the only drug available and affordable for PE prevention [10,23,26,27]. 6. There are many screening methods that can only be done at secondary/tertiary setting and very expensive [2-18]. 7. Primary care setting has different positions - can be considered as opportunity, compare with the hospital such as first visit, early gestational age, almost no emergency cases. 8. In low resource setting with low education patients - low sensitivity low specificity of a method must be balanced with high mortality and morbidity rate in PE.

So, there are very big problems, not completely understood the cause, expensive screening test can predicts about 90% of early-onset PE, but does not predict term PE and has a very low positive predictive value. Its cost effectiveness - even in developed countries - is still under debate, little efforts that can be done in first trimester - low resource setting. From my point of view, some papers have little partiality to trying to look for the best medicine for the poor in the low resource primary care setting who most likely face this disease. Those papers may allow decision makers, professional organization, consider not to take action immediately while mothers suffer from the disease - too late and too little premise, because of waiting the best evidence - not best available facilities. We have to treat this disease as Number One Priority/Enemy - the same with HPP and treat it differently compare to post-term pregnancy, PROM, or other obstetric disorders. We have to treat preeclampsia and HPP not just by business as usual.

We propose more aggressive method, active finding for high risk pregnancy, LDA, continuous mentoring and maternity waiting homes to manage PE in low resource primary setting.

Preeclampsia

August [27] defined Preeclampsia (PE) as a syndrome characterized by the new onset of hypertension plus proteinuria, end-organ dysfunction, or both after 20 weeks of gestation in a previously normotensive woman. According to Poon., *et al.* [10] - the ISSHP [17] defined PE as systolic blood pressure at ≥ 140 mm Hg and/or diastolic blood pressure at ≥ 90 mm Hg on at least two occasions measured 4 hours apart in previously normotensive women and is accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation.

Pathophysiology of preeclampsia is not completely understood, there are many differences between experts such as Karumanchi [25] proposed that in PE, the cytotrophoblast infiltrates the decidual portion of the spiral arteries, but fails to penetrate the myometrial portion thus, the vessels remain narrow, resulting in hypoperfusion and ischemia, that in turn appears to elaborate antiangiogenic proteins, inflammatory cytokines into the maternal bloodstream that result in maternal endothelial dysfunction. While Dekker and his group [23] found that lack of remodelling is more linked to IUGR not PE, evidenced by SCOPE studies: 'SGA with abnormal uterine artery Doppler velocity waveforms' associated with < 6 months of sexual relationship and a large percentage of preeclampsia, currently encountered in a Western setting, is term preeclampsia without any indication of lack of spiral artery remodelling.

According to Dekker [23], treatment of established disease is akin to a scenario best described as 'an attempt to save the ship that is already sinking', the disease cannot be cured and propose that progress in this area will have to come from early prevention. August [27] also stated that since there is no curative treatment other than delivery, an intervention that could prevent preeclampsia would have a significant impact on maternal and infant health worldwide. Poon., *et al.* [10] stated that the quest to effectively predict PE in the first

trimester of pregnancy so that necessary measures can be initiated early enough to improve placentation and thus prevent or at least reduce the frequency of its occurrence. According to Norwitz and Bellusi [17], high-risk status based on obstetric and medical risk factors in early pregnancy do not accurately distinguish women who will go on to develop preeclampsia from those who will not (i.e. the positive predictive value is low). Sibai, Dekker, and Kupferminc [21] stated that women at risk are identified on the basis of epidemiological and clinical risk factors, treatment is still prenatal care, timely diagnosis, proper management, and timely delivery.

Ideal screening methods that represent good predictive value

Some writers stated different requirements, Levine [11]: simple, rapid, noninvasive, inexpensive, easy to perform early in gestation, and impose minimal discomfort or risk. The technology should be widely available, and the results valid, reliable, and reproducible. Useful prediction of preeclampsia would also require a very high likelihood ratio for a positive test (> 15) as well as a very low likelihood ratio for a negative result (less than 0.1). Kosack., *et al.* [28] suggested the ASSURED model stands for: Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users - that can be used as a benchmark for identifying the most appropriate diagnostic tests for resource-constrained setting. Norwitz stated that a test would need very high sensitivity and specificity to accurately predict or exclude the development of the disease.

Pessimistic or optimistic

Most of the writers/professional organization less optimistic about the future of screening PE in first trimester in low resource primary care health center or should use combination of biophysical incl maternal history and biomarkers. ACOG [9]: Regardless of the parameters used, screening for preeclampsia in low risk women is associated with very low positive predictive values ranging from 8% to 33%. Magee - FIGO [6]: Currently, there is no single predictor of pre-eclampsia among women at either low or increased risk of pre-eclampsia that is ready for introduction into clinical practice. Norwitz [17]: tests are not sufficiently accurate, the overall methodological quality of available studies was generally poor. Poon, Nicolaides stated [13]: Effective screening for the development of early onset preeclampsia (PE) can be provided in the first-trimester of pregnancy. Screening by a combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, maternal serum pregnancy-associated plasma protein-A and placental growth factor can identify about 95% of cases of early onset PE for a false-positive rate of 10%. USPSTF(7): inadequate evidence on the effectiveness of risk prediction tools (e.g. clinical indicators, serum markers, or uterine artery pulsatility index) that would support different screening strategies for predicting preeclampsia. Zhang., *et al.* [16] in 3270 pregnancies combined mean arterial pressure (MAP), serum placental growth factor (PLGF) and pregnancy associated plasma protein A (PAPP-A) found that at 10% false positive rate, detection rates of early and late preeclampsia were 87.50 and 48.57%. Reddy., *et al*. [15]: A combined first trimester screening model for pre-eclampsia that includes maternal history, mean arterial pressure, uterine artery Doppler and PlGF has been shown to be the most effective at identifying the population at greatest risk of pre-eclampsia. Kenny., *et al.* [5] in nulliparous women, combining multiple biomarkers and clinical data provided modest prediction of preeclampsia. Dekker [23] preeclampsia is a heterogeneous syndrome, not one test will predict all types of preeclampsia, and not one type of treatment will prevent all preeclampsia.

It seems that most of the writers suggested a combination of multiple markers - maternal history, biophysical and biomarkers which doesn't suit with the ASSURED model designed by Kosack WHO (18) and very expensive.

New antenatal care

Antenatal care should be started from pre-conceptional counselling, we propose that there are some women who are not eligible to get pregnant such as women with severe heart disease, morbidly obese, age more than 45 years old, infection, previous morbidly adherence placenta etc [19,20]. North., *et al.* [29] proposed international model: of the 3529 women, the ability to predict pre-eclampsia in healthy nulliparous women using clinical phenotype is modest. Clinical risk factors at 14 - 16 weeks' gestation were age, mean arterial blood

pressure, body mass index (BMI), family history of pre-eclampsia, family history of coronary heart disease, maternal birth weight, and vaginal bleeding for at least five days. Factors associated with reduced risk were a previous single miscarriage with the same partner, taking at least 12 months to conceive, high intake of fruit, cigarette smoking, and alcohol use in the first trimester. Addition of uterine artery Doppler indices did not improve performance. Nicolaides [30,31] proposed a new inverted trigonum of antenatal care which also consist of screening for preeclampsia and algorithms which combine maternal characteristics and biophysical and biochemical tests at 11 - 13 weeks. This model could potentially identify about 90, 80 and 60% of pregnancies that subsequently develop early (before 34 weeks), intermediate (34 - 37 weeks) and late (after 37 weeks) preeclampsia, with a false-positive rate of 5%.

Baschat [32] introduced the next step after classifying the risk according to multi-markers algorithm into two groups - the treatable factors such as Metabolic, Cardiovascular, Prothrombotic and non-treatable factors such as Placental and Personal factors. Ghia., *et al.* [33] and Wright., *et al.* [34] proposed almost similar models: Two-stage screening as follow 1. first-stage screening in the whole population by maternal factors alone or a combination of maternal factors, mean arterial pressure and uterine artery pulsatility index or maternal factors, mean arterial pressure and placental growth factor and 2. second-stage screening by the triple test only for a subgroup of the population selected on the basis of the risk derived from first-stage screening and found financial benefits over conducting the test for the entire population. Ghojazadeh M., *et al.* [12] in a total of 739 nulliparous women at their 24 - 28th weeks of the first pregnancy used simple combined model of demographic characteristics including maternal age, BMI, years of education and positive roll-over tests can predict preeclampsia without any cost for the patients with a sensitivity of 93% and a specificity of 80%. Hermanto TJ., *et al.* proposed OPROCOT stands for Out of the Box, Proactive, Comprehensive and Top down as an alternative options to reduce maternal death at district level [19,20,35-37].

Propose antenatal care for preeclampsia

We propose new more aggressive antenatal care specifically designed to reduce the burden of PE which consist of active finding high risk pregnancy for PE, LDA, continuous mentoring these pregnant women and maternity waiting home to prevent loss of follow up. The items for active findings consist of history taking and biophysical markers (BMI and MAP).

Items from history taking

Age [14,24,38,39]

Almost all of the writers agree that age below 20 and over 35 or 40 increase risk of preeclampsia with difference value of OR = 14. Kumaril., *et al.* [38] found that maternal age below 20 years and above 30 years is more prone for development of preeclampsia. Robillard P-Y, Dekker G., *et al.* [39] found that rising maternal ages were strictly parallel for EOP and LOP.

Previous preeclampsia [14,24,39,40]

There are some writers with large number of patients, who mentioned that previous preeclampsia increase risk recurrent preeclampsia to almost 4 times and 8 times 7 and even stated as the biggest pooled RR, Rana., *et al.* [24] stated that prior preeclampsia has RR, 8.4.

First degree relative [14,24,41,42]

It is interesting that premise previously consider as myths proven to be right - Carr., *et al*. in sister and Sherf., *et al.* with eye catching title: Like Mother Like Daughter.

Born as an IUGR baby [14,24,42,43]

Sherf., *et al*. [42] in a total of 1490 in F1, 1616 in F2, and 2311 in F3, also found that low birth weight LBW in mothers (F), was found to be a significant predictor for LBW in offspring (OR = 1.6, 95% CI 1.022.6, p = .043). Andraweera., *et al.* [43] in a total of 5,336 nulliparous women from the screening for pregnancy endpoints (SCOPE) study found that birth weight < 2,500g was associated with increased risk of PE aOR = 1.7, compared with the referent and Women born with birth weight < 2,500g and who subsequently developed overweight or

were diagnosed with obesity were at increased risk of PE aOR = 2.3.

Inter pregnancy interval [14,24,44,45]

Skjerven., *et al.* [44] found that: the odds ratio for PE for each one year increase in the interbirth interval was 1.12 (95 percent confidence interval, 1.11 to 1.13) in mothers, adjusting for maternal age, placental pathology, PE and parity, was found a significant predictor for low birth weight in offspring. Likewise, PE was also noted as a significant intergenerational factor following adjustments for maternal age and parity. Hercus., *et al.* [45] found that increasing birth and pregnancy intervals were associated with a significantly increased risk of developing preeclampsia in later pregnancies, with OR 1.39 at 3 years (p = 0.042) and OR 2.05 at 4 years (p = 0.002).

Primipaternity [14,22-24,45,46]

Dekker G, Robillard PY, Roberts C [22,23] in 2011 stated that paternal contribution to preeclampsia, which is demonstrated by (1) the effect of the length of the sexual relationship; (2) the concept of primipaternity versus primigravidity and (3) the existence of the so-called 'dangerous' father, as demonstrated in various large population studies. It is currently unknown how the father exerts this effect. Hercus., *et al.* [45] also found that Women with a previously normal pregnancy had a significantly increased risk of developing preeclampsia in subsequent pregnancy with a new paternity (OR 2.27). Kho., *et al.* [46] in a prospective cohort study in 2507 nulliparous women with singleton pregnancies found that short duration of sexual relationship was more common in women with preeclampsia compared with uncomplicated pregnancies (≤ 6 months 14.5% versus 6.9%, adjusted odds ratio [adjOR] 1.88; ≤ 3 months 6.9% versus 2.5%, adjOR 2.32; first intercourse 1.5% versus 0.5%, adjOR 5.75).

History of other maternal disease [14,24,39]

Bartsch., *et al.* [14] found that women with antiphospholipid antibody syndrome had the highest pooled rate of pre-eclampsia (17.3%), Chronic hypertension ranked second, both in terms of its pooled rate (16.0%) and pooled relative risk (5.1) of PE. Pregestational diabetes (pooled rate 11.0%); pooled relative risk 3.7, pre-pregnancy body mass index (BMI) > 30 7.1% and use of assisted reproductive technology (6.2%) were other prominent risk factors. Rana., *et al.* stated that major risk factors for preeclampsia were(OR > 2): Chronic hypertension (RR, 5.1), Pregestational diabetes mellitus (RR, 3.7) Multiple gestation (RR, 2.9, Pre-pregnancy BMI > 30 (RR, 2.8), Antiphospholipid syndrome (RR, 2.8), Systemic lupus erythematosus (RR, 2.5) History of stillbirth (RR, 2.4), Pre-pregnancy BMI > 25 (RR, 2.1) Nulliparity (RR, 2.1) Prior placental abruption (RR, 2.0). Interestingly, Robillard P-Y, Dekker G., *et al.* [39] found diabetes was not an independent risk factor neither for EOP or LOP.

Biophysical markers

Body mass index [14,24,39,43,47,48]

Most of the writers agreed that BMI increases the risk for preeclampsia, the bigger the higher. Barstch., *et al.* [7] found BMI ≥ 30 the pooled rate of pre-eclampsia was 5.1% (5.0% to 5.2%) and Shao., *et al.* [36] found that pre-pregnancy BMI and gestational weight gain are independent risk factors for PE. Interestingly, Robillard P-Y, Dekker G., *et al*. found that increment of BMI was only associated with LOP, diabetes was not an independent risk factor neither for EOP or LOP. Seed., *et al*. found that the risk of preeclampsia varied from 7% in obese primipara without hypertension to 30% when previous preeclampsia and chronic hypertension occurred together. A prediction model incorporating these risk factors had a sensitivity of 48 and 89% for preeclampsia delivered.

Mean arterial pressure [49-52]

Poon., *et al*. found that the detection rate of PE by log multiple of the median MAP and maternal variables was 62.5% for a false-positive rate of 10%. Gallo., *et al.* stated that performance of screening for PE by MAP is best when measurements are taken at both 11 - 13 and 20 - 24 weeks‟ gestation than at only one of these gestational ranges Wright., *et al*. suggested a model that combined information on maternal characteristics with that obtained from biomarkers and found that the contribution of biomarkers such as MAP is the additional informa-

tion they provide over that already captured in the prior mode. Tayyar., *et al*. found that the detection rate (DR), at a false-positive rate of 10%, for PE delivering < 32 weeks was 66% and 72% with screening at 12 and 22 weeks, respectively. The DR for PE delivering at 32 + 0 to 36 + 6 weeks was 54%, 56% and 81% with screening at 12, 22 and 32 weeks. The DR for PE delivering ≥ 37 weeks was 45%, 43%, 49% and 59% with screening at 12, 22, 32 and 36 weeks, respectively.

What next after active high risk pregnancy finding?

Given with thousand of islands, low awareness, very high case fatality rate, continuous mentoring for every high risk pregnant women and maternity waiting house are the best options after positive screening.

We have to learn to the results of our study on 83 maternal deaths in the year 2019 at dr Soetomo General hospital Surabaya, the result of EMAS program, maternal death mystery in Indonesia stated by Hyre and magnitude of the problems [53]. We cannot use the same method to manage PE - we have to use more aggressive method: active high risk pregnancy finding, LDA, continuous mentoring and maternity waiting house

Wild K., *et al.* [54] since the early 1990s, WHO has assessed the impact of maternity waiting homes and found the success of implementing such homes depend on the context. Vermeiden T., *et al.* [54] found that unless community awareness of preventive maternity care increases and barriers for women to stay at MWHs are overcome, these facilities will continue to be underutilized, especially among marginalized women. Ratnaningsih., *et al.* [56] with Gerdaristi mentoring program stated that the number of maternal and infant mortality from year to year decline. Nevertheless, they found several things including not maximal assistance from the volunteer and mother's level of knowledge about high-risk pregnancies are still lacking.

Number	Items	Description	Yes / No
	History		
1	Age	Below 20 over 35 years old	
2	Previous preeclampsia		
3	Born as IUGR baby	Birthweight under 2,5 kg at term	
4	First degree relative		
5	Primipaternity	New spouse	
6	Interpregnancy interval	Less than 6 month or more than 4 years	
7	History of maternal disease	SLE, Chronic hypertension, Diabetes etc.	
	Biophysical markers		
1	Body mass Index	More than 30 kg/m^2	
2	Mean Arterial Pressure	According to protocol stated by Poon and Gallo	

Table 1: *Screening PE in low resource primary setting**

**Appropriate for muligravida, IUGR: Intra Uterine Growth Restriction; SLE: Systemic Lupus Erythematosus.*

What's new in this method

1. *The items in the screening method are simpler and very much cheaper than other screening methods even though not better - accuracy must be balanced with the magnitude of the problem in low resource primary setting.*

2. *It combines screening method with LDA supplementation, closed mentoring and maternity waiting home to avoid loss of follow-up.*

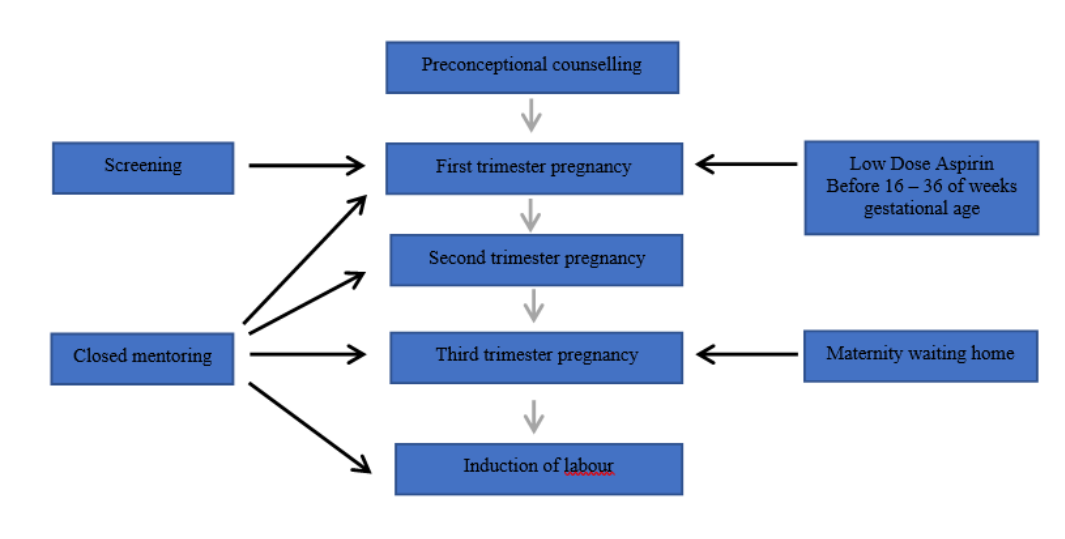

Figure 1: *Propose algorithm.*

Conclusion

Due to complexity and unknown cause of this disease, simpler and cheaper system to predict preeclampsia in first trimester even it has low sensitivity. This system consist of history taking (7 items) and simple biophysical examinations (BMI and MAP) and must be followed by LDA, closed mentoring and maternity waiting home.

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