REVIEW
O&G Forum 2016;26:5-8

Early detection of Pre-Eclampsia

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Abstract
Pre-eclampsia is a major cause of maternal and perinatal morbidity and mortality. The current recommended screening approach is to identify risk factors from maternal history and demographic characteristics. Blood pressure and urinary proteins must be determined at every ante-natal visit. Patients with gestational hypertension and/or gestational proteinuria require increased antenatal surveillance because they have an increased risk for developing pre-eclampsia during pregnancy. We recommend that these patients be considered for management at District level. Local protocols must in place for emergency treatment and referral of patients who develop a sudden acute hypertensive emergency.

Introduction

Pre-eclampsia is an important cause of pregnancy morbidity and hypertensive disorders remain one of the leading causes of maternal death globally. More than half of the maternal deaths due to pre-eclampsia in the United Kingdom were the result of failure to identify pre-eclampsia along with a delay in responding to clinical symptoms and signs.[1] Sixty-six percent of hypertensive deaths reported to the National Committee for the Confidential Enquiry into Maternal Deaths (NCCEMD) in South Africa during the period 2011-2013 were considered avoidable.[2] Clinical manifestations may present at any time from the second trimester to the early post-partum period. In a population-based study in the central, south-western and eastern Tshwane regions, severe pre-eclampsia was the most frequent indication for emergency transfer of women with life-threatening conditions to tertiary facilities.[3] Unlike women with severe pre-eclampsia, women with mild-to-moderate disease generally have no symptoms. This indicates the need to identify risk factors at booking and to identify and react to symptoms and signs in the early stages of the disease process.

First trimester risk assessment for early onset pre-eclampsia

Early identification of women at risk would allow for implementation of preventative therapy or more intensive surveillance during the ante-natal period. Current predictive tests (maternal serum analytes and uterine artery doppler velocimetry) for pre-eclampsia are of limited value due to their low positive predictive value (PPV).[4] These tests require a large number of women to be identified as high risk and to potentially undergo intensive surveillance in order to detect one case of early-onset pre-eclampsia. Adverse effects of identifying women at risk include parental anxiety, increased frequency of ante-natal visits and additional surveillance testing. An ideal screening test would require a high sensitivity and a high PPV so that women who test positive would be at high risk of the disease. Models that include multiple predictive factors show better detection rates than those using only a single factor. However there are several limitations associated with the current models described. Many models have not been validated making them unsuitable for daily practice.[5] A systematic review of the quality of first trimester risk prediction models for pre-eclampsia has found frequent methodological deficiencies in reporting risk.[6] The authors therefore concluded that the reliability and validity of these models are of limited value. Currently no single model or test has gained widespread acceptance into clinical practice. Both the American College of Obstetricians and Gynaecologists and the Department of Health Guidelines for Maternity Care in South Africa therefore do not recommend additional screening beyond obtaining an appropriate medical history.[4,7] The following women are most susceptible to developing pre-eclampsia[7]:

- Primigravidae, in particular teenagers and elderly primigravidae
- Women of age 35 years and above
- Women with a previous pregnancy complicated by pre-eclampsia
- Women with previous abruptio placentae or intra-uterine death
- Women with multiple pregnancies
- Medical complications such as chronic hypertension, renal disorders, diabetes, connective tissue disorders or antiphospholipid syndrome
- Women who develop oedema in the mid trimester or have excessive weight gain.
- Obesity

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Screening for Pre-eclampsia after the first trimester
In a proposed new pyramid of pregnancy care, an intergrated clinic visit at 22 weeks gestation in which biochemical markers are combined with maternal factors to determine a patient-specific risk of developing pre-eclampsia. On the basis of such risk subsequent management of pregnancy including timing and content of ante-natal visits could be determined. A screening model using maternal factors and biomarkers at 19 – 24 weeks has been shown to be superior to history-based risk assessment.[8] The authors found that by adding mid-trimester uterine artery pulsatility index (UTPI), mean arterial pressure (MAP) and placental growth factor (PLGF) they could predict the development of early, intermediate or late onset pre-eclampsia. Screening by maternal factors predicted 52%, 47% and 37% of pre-eclampsia at <32, <37 and >37 weeks gestation at a false positive rate of 10%. The respective values for combined screening with maternal factors and MAP, UTPI, and PLGF were 99%, 85% and 46%.

Although such a model may help risk stratify the frequency of ante-natal visits, the risk assessment is too late to implement preventatives measures such as aspirin. This model is also probably not feasible in middle and lower income countries where resources are limited. The model will also have to be tested in different population groups.

Ante-natal care
Patients identified as high risk after history-based screening should be offered calcium supplementation and low dose aspirin from 12 weeks gestation. A meta-analysis that studied the effect of aspirin if started before 16 weeks found a 52% reduction in the risk for pre-eclampsia compared to the control group. No effect was observed when aspirin was started after 16 weeks.[9] The risk of pre-eclampsia is halved if calcium supplementation is given to women with a low dietary calcium intake.[10] Calcium also reduces the risk of preterm birth and serious morbidity.

The frequency of ante-natal visits for women at risk is not defined and it is also possible for women without any risk factors to develop the condition. The complete absence of ante-natal care is strongly associated with eclampsia and fetal death.[11] In a local study of pre-eclamptic near misses at Steve Biko Academic Hospital in Tshwane, South Africa, the average time between ante-natal visits and an obstetric emergency due to a hypertensive event was reported as 2.6 weeks.[12] A combined approach to ante-natal care should therefore be considered for high risk patients. A pregnant mother should be advised to visit a day-clinic, undertake home monitoring or should be examined by an occupational nurse at the work-place between scheduled ante-natal visits. Blood pressure must be measured with equipment that is accurate for the individual hypertensive pregnant woman. A cuff size of 18x36cm should be used for women with an arm circumference of 41cm or more. Proteinuria must be estimated by urinary dipsticks.

The National Institute for Clinical Excellence (NICE) recommends assessments for pre-eclampsia at weeks 16, 28, 34, 36, 38, 40 and 41 weeks for low risk healthy parous women with a singleton fetus.[13] The South African National Department of Health has revised the ante-natal schedule for low risk patients. Additional ante-natal visits have been included after a peak in maternal deaths related to pre-eclampsia was observed at 32 and 36 weeks. The recommended schedule consists of visits at booking, 20, 26, 30, 34, 36, 38, 40 and 41 weeks. Women should be informed that pre-eclampsia may develop between assessments, should be made aware of the symptoms and know how to contact their healthcare providers at all times.

The pre-eclampsia community guideline (PRECOG) recommends that women with any of the following risk factors be offered referral before 20 weeks for specialist input to their ante-natal care plan[14]:

- Previous pre-eclampsia
- Multiple pregnancy
- Underlying medical conditions such as pre-existing hypertension or booking diastolic blood pressure > 90mmHg, pre-existing renal disease or booking proteinuria or pre-existing diabetes
- Presence of antiphospholipid antibodies

Clinical signs that may precede the onset of pre-eclampsia
Organ systems that are most susceptible to inflammation and endothelial dysfunction during the pre-eclamptic disease process are: central nervous system, lungs, liver, kidneys, heart, systemic vasculature and coagulation systems.[15] Therefore clinical manifestations vary between individuals and some patients may present with proteinuria first; and develop hypertension later. There are 3 important clinical features which may precede the diagnosis of pre-eclampsia: isolated gestational proteinuria in which proteinuria precedes hypertension, gestational hypertension preceding pre-eclampsia and pre-eclampsia in which hypertension and proteinuria occur simultaneously.[16,17,18] In most cases, however, hypertension is usually the first clinical feature of pre-eclampsia.[19] If gestational hypertension develops before 34 weeks the likelihood of progression to pre-eclampsia is 15-25%.[18] Women with gestational hypertension diagnosed after 36 weeks have a 10% risk of developing pre-eclampsia. In a study by Yamada et al women with isolated gestational proteinuria had a relative risk of 13.1 (95% CI 9.2-18.5) for the development of pre-eclampsia compared with those without proteinuria.[20] The risk of pre-eclampsia among women with isolated gestational proteinuria varies between 25-34%.[20,21]

Assessments after 20 weeks gestation can be helpful in identifying the possible onset of pre-eclampsia. Symptoms and signs which may precede the diagnosis of pre-eclampsia include new hypertension and new proteinuria. Symptoms of headache, visual disturbance, epigastric pain vomiting are suggestive of imminent eclampsia. In a community setting, fetal compromise is assessed by asking women about reduced fetal movements or by assessment for a small for gestational age fetus. Patients presenting with any of the above symptoms should be assessed further for possible pre-eclampsia.

The PRECOG II guideline recommends the following for patients with new hypertension and/or new proteinuria[22]

- Admit all patients with a diastolic blood pressure of > 110mmHg or systolic blood pressure of >160mmHg.
- Consider admission of patients with diastolic blood pressure between 90-110 mmHg or systolic blood pressure between 140-160mmHg and no proteinuria on dipstix
- For patients with 1+ proteinuria, quantify by 24 hour urine collection
- Admit patients with 2+ proteinuria
- Admit women with a diastolic blood pressure of > 90mmHg and new proteinuria of 2+.
- Admit women with a diastolic blood pressure of >110 mmHg and new proteinuria of 1+
- Consider admission of women with a diastolic blood pressure of 100-109mmHg and 1+ proteinuria.
- For women with diastolic blood pressure of 90-99 mmHg and 1+ proteinuria, exclude significant proteinuria by quantification of protein in a 24-hour urine sample.
- Measure the haemoglobin, platelet count, serum creatinine and aspartate aminotransferase levels. Use pregnancy specific ranges of results to identify features of HELLP syndrome (name derived from features of: haemolysis, elevated liver enzymes and low platelet count)
- Arrange an ultrasound to determine fetal weight, amniotic fluid levels and umbilical artery Doppler measurement.
- Review all results and umbilical artery Doppler readings.
- Repeat all assessments in a week if results are normal.

Once results are available, do the following:

- Treat moderate to severe hypertension. Aim to control BP at values of 135-140mmHg systolic and 85-90mmHg diastolic.[7]
- Admit if significant proteinuria is confirmed
- Admit if umbilical artery Dopplers are absent or reversed.
- Review all results and revise ante-natal care plan.

Patients with maternal symptoms or fetal signs without hypertension or proteinuria

Patients with headache, visual disturbances or epigastric pain should be investigated further

If the fetus appears small-for-gestational age or if the mother complains of reduced fetal movements consider a detailed fetal well-being ultrasound

Local recommendation

Due to the association of pre-eclampsia developing in patients with gestational hypertension and gestational proteinuria, we recommend that these patients be considered for management at District level. All patients with a blood pressure of 140/90 or more and 1+ proteinuria should be admitted for assessment. These patients will require increased surveillance during the ante-natal period. Patients with gestational hypertension should be delivered at 38 weeks to prevent the development of late-onset pre-eclampsia.

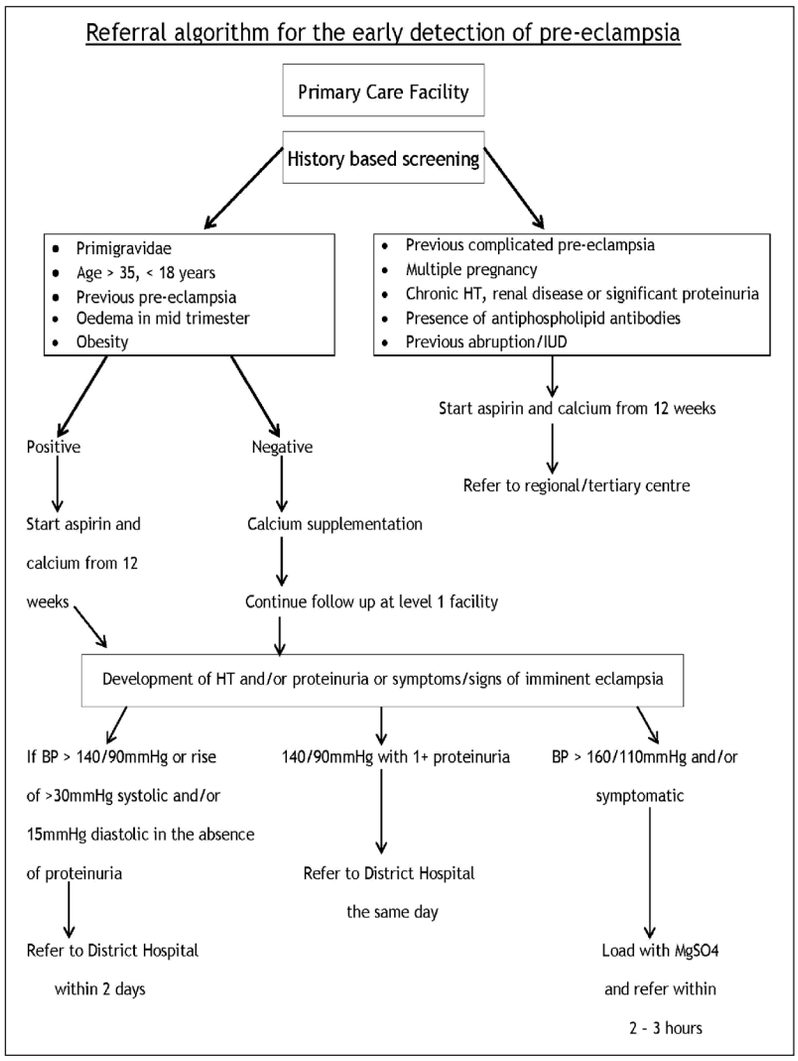
Diagnostic criteria for pre-eclampsia

The American College of Obstetricians and Gynecologist's taskforce on hypertension in pregnancy diagnostic criteria for pre-eclampsia are[23]:

- Systolic BP > 140mmHg or diastolic BP > 90mmHg on 2 occasions 4 hours apart after 20 weeks gestation in a previously normotensive patient
- If systolic BP > 160mmHg or diastolic BP > 110mmHg, confirmation within minutes is sufficient AND proteinuria > 300mg in a 24-hour urine specimen. Dipstix 1+ if a quantitative measurement is unavailable.
- New-onset hypertension without proteinuria but with new onset of any of the following is diagnostic of pre-eclampsia:
  - platelet count < 100 x 10^9/l
  - serum creatinine > 100umol/l
  - doubling of serum creatinine in the absence of other renal disease
  - liver transaminases at least twice the normal concentrations
  - pulmonary oedema
  - cerebral or visual symptoms

Conclusion

Adverse maternal outcome associated with pre-eclampsia may be reduced by implementing strategies for standardised ante-natal care surveillance and assessment. Interventions needed to identify and prevent pre-eclampsia must be explored further. Access to healthcare, distance and costs are additional obstacles faced by women in middle and lower income countries (LMIC).[24] Currently the most reliable method of identification of pre-eclampsia is early recognition of the disease during ante-natal care. However some patients may develop a sudden acute hypertensive emergency. Local protocols must be in place for emergency treatment and referral of such patients to an appropriate level of care.



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