

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature

By

Silvia Awor¹, Rosemary Byanyima², Benard Abola³, Annetee Nakimuli⁴, Christopher Garimoi Orach⁵, Paul Kiondo⁶, Dan Kaye⁷, Jasper Ogwal-Okeng⁸

1. Corresponding author, Department of Obstetrics and Gynecology, Faculty of Medicine Gulu University; Email: s.awor@gu.ac.ug, Tel: +256782 841168. Orcid ID: <https://orcid.org/0000-0002-9701-2264>
2. Deputy Director, Mulago National Referral Hospital, and Teaching Hospital for Makerere University, Kampala. Email: r_byanyima@hotmail.com, Orcid ID: <https://orcid.org/0000-0002-6737-9516>
3. Department of Mathematics, Faculty of Science, Gulu. University Email: benardabola@yahoo.co.uk, Orcid ID: <https://orcid.org/0000-0001-9220-7313>
4. Professor of Obstetrics and Gynaecology, Dean School of Medicine, Makerere University. Email: annettee.nakimuli@gmail.com, Orcid ID: <https://orcid.org/0000-0003-2806-0243>
5. Professor of Public Health, School of Public Health, College of Health Sciences Makerere University. Email: cgorach@musph.ac.ug, Orcid ID: <https://orcid.org/0000-0002-5209-5529>
6. Associate Professor of Obstetrics and Gynaecology, Makerere University. Email: kiondop937@gmail.com, Orcid ID: <https://orcid.org/0000-0002-8049-8843>
7. Professor of Obstetrics and Gynaecology, Makerere University and Executive Director of the Association of Gynaecologists of Uganda. Email: dkaye0700@gmail.com Orcid ID: <https://orcid.org/0000-0003-1490-859X>
8. Professor and Vice Chancellor, Lira University. Email: jogwal.okeng@gmail.com, Orcid ID: <https://orcid.org/0000-0002-1159-1307>

Abstract

Women of Afro-Caribbean racial origin are at increased risks of adverse pregnancy outcomes including preeclampsia. This is probably related to low socio-economic status among these communities. With limited resources allocated for health care, there has been a growing need to predict preeclampsia to enable frequent follow up of those at risk, for early diagnosis and treatment to minimize adverse outcomes. Risk prediction models have been developed in some parts of Africa, using maternal history and physical examination, uterine artery Doppler sonography, maternal full haemogram, liver and renal function tests with at least 50% accuracy and 70% AUC. The study concludes that routine prediction of preeclampsia in Africa is limited, although with a potential to save lives.

Key words: Maternal care, preeclampsia, prediction models, Afro-Caribbean, risk factors, Africa

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature

By

Silvia Awor¹, Rosemary Byanyima², Benard Abola³, Annette Nakimuli⁴, Christopher Garimoi Orach⁵, Paul Kiondo⁶, Dan Kaye⁷, Jasper Ogwal-Okeng⁸

Introduction

Preeclampsia (PE), a human pregnancy specific syndrome is characterized by hypertension and proteinuria (Brown, Lindheimer, de Swiet, Van Assche, & Moutquin, 2001; Myatt et al., 2014; Uganda, 2016) It is one of the leading causes of maternal death in some parts of Africa (MOH, 2017). The cause is elusive, the cure is not known and has a wide spectrum of clinical presentations (Redman, Sargent, & Staff, 2014). It is thought to result from immune maladaptation of the mother to the fetal tissue. This is thought to alter maternal blood cell count, liver and renal function tests and eventually inadequate invasion of the spiral arteries by the developing placenta (Dekker, Robillard, & Hulsey, 1998; Harmon et al., 2016; Myatt & Roberts, 2015; Powe, Levine, & Karumanchi, 2011; Prins et al., 2016; Redman, 2011; Redman et al., 2014). This will in turn hinder the normal growth of the placenta, reduce the effective surface area for exchange of nutrients between mother and baby leading to oxidative stress. This reduced surface area of functional placenta may increase the number of placental infarcts and eventually placental debris released in to maternal circulation. Increased levels of placental tissue in maternal circulation is believed to lead to maternal systemic inflammation (Dechend & Staff, 2012). This may result into endothelial injury, vasoconstriction and hypertension (Dekker et al., 1998).

During normal pregnancy, the cytotrophoblast cells emigrate from the chorionic villi to invade the inner third of the myometrium (Fisher, 2015; Powe et al., 2011). Cytotrophoblast migrate up the spiral arteries and replace, in a retrograde fashion, the maternal endothelial lining. They also insert themselves among the smooth muscle cells that form the tunica media (Fisher, 2015; Redman & Sargent, 2005) of the spiral arteries. These structural modifications of the blood vessels are associated with functional alterations, such that the spiral arteries become low resistance vessels by 18 weeks of gestation, and thus less sensitive to vasoconstrictive substances (Fisher, 2015; Redman & Sargent, 2005; Uzan, Carbonnel, Piconne, Asmar, & Ayoubi, 2011). Invasion of the venous side of the uterine circulation is minimal, sufficient to enable venous return (Fisher, 2015). As a result, the spiral arteries attain the physiologic properties that are required to perfuse the placenta adequately.

In preeclampsia, cytotrophoblast invasion of the interstitial uterine compartment is shallow in many locations including spiral arteries (Redman & Sargent, 2005). Some vessels retain portions of their endothelial lining with relatively intact muscular coats (Fisher, 2015; Powe et al., 2011; Redman & Sargent, 2005). This results into formation of constricted high resistance vessels, and endothelial dysfunction (Powe et al., 2011). And this leads to reduced blood flow to the placental bed – placental insufficiency (Elosha Eiland, 2012), and decreased oxygen tension at the placental bed (Brennan, Morton, & Davidge, 2014; Possomato-Vieira & Khalil, 2016). The resultant placental ischaemia encourages anaerobic respiration which leads to production of oxygen free radicals (Jain et al., 2014; Redman & Sargent, 2005) causing placental injury leading to increased placental debris in maternal circulation.

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

Statement of the Problem

While PE remains a major cause of maternal morbidity and mortality in Africa particularly when diagnosed late, data on the utility of Doppler sonography and maternal characteristics for early prediction of PE is limited. Doppler sonography studies revealed that reduced diastolic blood flow in the uterine arteries is associated with intrauterine growth restriction and hypertensive disorders in pregnancy (Asnafi & Hajian, 2011; Bhattacharyya Sanjoy Kumar, 2012; D. M. Gallo, Poon, Akolekar, Syngelaki, & Nicolaides, 2013; Papageorghiou et al., 2001; Papageorghiou, Yu, Erasmus, Cuckle, & Nicolaides, 2005; Trudinger, Giles, & Cook, 1985).

In 1985 Trudinger and colleagues (Trudinger et al., 1985) performed Uterine artery Doppler sonography in twelve normal and 91 high risk pregnancies at 20 weeks in Sydney Australia. He found reduced end diastolic blood flow in the uterine arteries to be associated with intrauterine growth restriction and preeclampsia (Trudinger et al., 1985). This formed a baseline for uterine artery Doppler sonography for the prediction of PE and adverse pregnancy outcomes. Later Papageorghiou and colleagues (Papageorghiou et al., 2001) in United Kingdom found that for pulsatility index of uterine arteries Doppler of 1.63 for singleton pregnancies at 23 weeks in mixed populations, the overall sensitivity of detecting PE was 41%. And when delivery was below 32 weeks the sensitivity increased to 93%. When they incorporated maternal characteristics, for a false positive rate of 25% the detection rate for PE in unselected population using maternal history alone was 45.3%, with uterine artery Doppler pulsatility index 63.1% and by combining the tests it raised to 67.5% (Papageorghiou et al., 2005). However Bhattacharyya and colleagues (Bhattacharyya Sanjoy Kumar, 2012) in India found end diastolic notch, or resistive index of greater than 0.6 to have a sensitivity and specificity of 73.3% and 86.5% for high risk pregnancies, and 57.1% and 95.8% for low risk pregnancies respectively (Bhattacharyya Sanjoy Kumar, 2012).

Meanwhile Asnafi and Hajian (Asnafi & Hajian, 2011) in Iran assessed uterine artery Doppler sonography efficiency in the prediction of adverse pregnancy outcomes in high-risk pregnancies (those with history of chronic hypertension, PE, diabetes mellitus, gestational diabetes, intrauterine fetal death, history of infertility, polycystic ovarian syndrome and recurrent abortion) at 18 to 24 weeks and found PE in 48% of those with end diastolic notching as opposed to only 9% of those without end diastolic notching (Asnafi & Hajian, 2011). Furthermore, Yousuf and colleagues (Yousuf et al., 2016) in India found a laterally situated placenta predicted 52% of PE. A combination of a laterally situated placenta and an abnormal uterine artery Doppler sonography predicted 92% of PE. Similarly, Walia and colleagues (Walia, D'souza, & Gupta, 2015) in India compared roll-over test with placental localization for early prediction of preeclampsia and found a unilateral placenta at 24 weeks predicted 68% of PE, and yet none of the mothers had a positive roll-over test at that gestation age.

Gallo and colleagues (D. M. Gallo et al., 2013) in United Kingdom determined maternal characteristics that affected uterine artery Doppler sonography PI at 20 to 24 weeks and found significant independent contribution to the uterine artery Doppler flow sonography pulsatility index from gestation age, racial origin and prior history of PE or small for gestation age baby (D. M. Gallo et al., 2013). The uterine artery PI was higher in women of Afro-Caribbean origin compared to Caucasians (D. M. Gallo et al., 2013) but the investigators did not give the cut-off PI value for PE in any of the studied groups. In South Africa, Yasmin Casmod and colleagues (Yasmin Casmod, 2016) found incidence of PE was 5.8% in singleton prime gravida, and second trimester early diastolic notch predicted only 50% of cases

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

although majority (73%) of the patients were blacks in their twenties (Yasmin Casmod, 2016). Similarly, Oloyede and Iketubosin (Oloyede & Iketubosin, 2013) in Lagos Nigeria were unable to predict PE and adverse pregnancy outcomes using uterine Doppler sonography. No such study using Doppler sonography and maternal characteristics has been done for the prediction of PE in the East African Region. Many studies within mixed populations revealed PE as heterogeneous disorder. From the above review, findings from those studies are not necessarily applicable to women from Sub-Saharan Africa.

Objective

General Objective: To determine whether uterine artery Doppler ultrasonography indices, maternal history, maternal physical findings and laboratory tests predict preeclampsia and adverse pregnancy outcomes

Specific objectives

1. To determine the maternal characteristics taken during the second trimester of pregnancy with potential to predict PE
2. To determine the cut-off second trimester uterine artery Doppler Sonography PI and RI with potential to predict PE
3. To determine if selected Laboratory findings taken during the second trimester of pregnancy predict PE.

Review of Related Literature

Theories of Preeclampsia

Dekker and Robillard (Dekker G.A & Robillard P.Y, 2004) argue that the increased placental tissue in maternal circulation increases the inflammation and endothelial injury. A team of researchers (Redman & Sargent, 2003, 2005) believe poor placentation is a different disease entity from placental ischaemia. They think the degrees of immune response to the placental debris in maternal circulation determines the severity of preeclampsia (Redman & Sargent, 2003, 2005).

It is suggested that maternal exposure to sperm cells primes a woman's body for protection against preeclampsia (Sarah A. Robertson *, John J. Bromfield, & Tremellen, 2003). Semen in the genital tract triggers the influx of antigen presenting cells which then process the paternal antigens and present it to the lymphocytes in order to produce adaptive immunity (Sarah A. Robertson * et al., 2003). It is believed that there is immunological alterations found in the placental micro-environment of women who eventually develop preeclampsia (Dekker G.A & Robillard P.Y, 2004; Laresgoiti-Servitje E, 2011). Adequate cytotrophoblast invasion into the uterine spiral arteries is hindered by excessive inflammation (Laresgoiti-Servitje E, 2011) which is similar to an allograft rejection (Medawar, 1960). This results into shallow invasion of the spiral arteries hence endothelial dysfunction (Dekker G.A & Robillard P.Y, 2004).

Dekker and Robillard (Dekker G.A & Robillard P.Y, 2004) believed preeclampsia is based on a single recessive or dominant gene with incomplete penetrance. It is not clear whether maternal genetic composition is responsible for abnormal placentation or the immune maladaptation to pregnancy.

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

Other theories of preeclampsia (PE) include the genetic-conflict Theory. This states that there is an inheritable paternal other than maternal genes required for normal growth of the trophoblasts. Therefore PE may result from a maternal system unable to cope with the physiologic genetic conflict (Dekker G.A & Robillard P.Y, 2004). The very low-density lipoprotein versus toxicity preventing activity Theory observes that Free fatty acids are increased in circulation of the pregnant mothers 15 to 20 weeks before the onset of preeclampsia (Lorentzen, Endresen, Clausen, & Henriksen, 1994). This is thought to lead to endothelial injury (Arbogast, Leeper, Merrick, Olive, & Taylor, 1994). The hyper-dynamic disease model found that pregnant women who are destined to developing preeclampsia have increased cardiac output associated with a compensatory vasodilation (Bosio, McKenna, Conroy, & O'Herlihy, 1999; Shakuntala Chhabra, Jaiswal, & Singh, 2016). It is believed that the dilated systemic terminal arterioles and renal afferent arterioles may expose capillary beds to systemic pressures and increased flow rates, eventually leading to the endothelial cell injury (Bosio et al., 1999).

Blood flow to the uterus

The uterine artery is a branch of the internal iliac artery (Rock & Jones, 2008). It divides into arcuate and spiral arteries respectively (Rock & Jones, 2008). During early pregnancy, it undergoes vascular remodeling to form low resistance vessels to supply large volumes (500-650ml/min) of blood to the uterus to meet the demands of the growing fetus (Palmer et al., 1992). Therefore, inadequate remodeling is associated with reduced blood flow to the placental site (Redman et al., 2014). Uterine artery Doppler sonography measures blood flow direction, velocity, resistance and Volume (Nelson & Pretorius, 1988). Pulsatility index (PI) measures the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle (Nelson & Pretorius, 1988), while resistive index (RI) is a measure of the resistance to blood flow caused by the microvascular bed distal to the site of measurement (Nelson & Pretorius, 1988). End diastolic notch indicates reduction or cessation in blood flow through the artery at the point of measurement during diastole of the cardiac cycle (Nelson & Pretorius, 1988). This gives an idea about the placental site perfusion (Nelson & Pretorius, 1988; Redman et al., 2014). However different groups of women have different cut-off Doppler PI and RI indices (Papageorgiou et al., 2001; Prajapati & Maitra, 2013; Yasmin Casmod, 2016) making it hard to adopt a guideline from one part of the world to fit another.

Clinical Presentation of Preeclampsia

Preeclampsia can be clinically classified as mild or severe. Mild PE (Diastolic Blood pressure (Bp) < 110mmHg) is normally asymptomatic (Acharya, Brima, Burugu, & Rege, 2014; Uzan et al., 2011). Severe PE (BP >110mmHg) presents with any of the following: headache, blurring of vision, epigastric pain, seizures (Brown et al., 2001), placenta abruption (Uzan et al., 2011), HELLP syndrome (Uzan et al., 2011), difficulty in breathing (Uzan et al., 2011) disseminated intravascular coagulation (Uzan et al., 2011), acute kidney injury (Uzan et al., 2011), and increased risk of death of both the baby and the mother (Uganda, 2016; Uzan et al., 2011). Early diagnosis and delivery of the fetus is the only known cure (Myatt et al., 2014; Powe et al., 2011). The prognosis of PE depends on the gestation age and the severity of the disease (Powe et al., 2011; Uzan et al., 2011), with onset at an early gestation age carrying a worse prognosis than later onset. The recurrence rate is highest (up to 40%) in those whose

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

first PE disease manifested early (before 30 weeks of gestation) during the index pregnancy and 10% for those who got the preeclampsia near term(Uzan et al., 2011).

Risk factors for Preeclampsia and Adverse Pregnancy outcome

Risk factors include low socio-economic status, family history of hypertension, nulliparity, multiple pregnancy, obesity, chronic hypertension, women of African descent, previous personal or family history of preeclampsia, delivery of male babies and maternal age ≥ 40 years(Boyd, Tahir, Wohlfahrt, & Melbye, 2013; Dekker, 1999; Duckitt & Harrington, 2005; Khalil, Rezende, Akolekar, Syngelaki, & Nicolaides, 2013; Muto et al., 2016; Nakimuli et al., 2014; Wandabwa et al., 2010). High second trimester uterine artery Doppler resistive index, pulsatility index and early diastolic notch are also known risk factors for preeclampsia (Papageorgiou et al., 2001; Prajapati & Maitra, 2013; Trudinger et al., 1985; Yasmin Casmol, 2016). Early diagnosis and delivery of the fetus is the only known treatment(Robert K. Creasy et al., 2014) thus necessitating the need for prediction models of the disorders. In countries where screening and prediction of preeclampsia is done routinely, maternal morbidity and mortality are low (Department_of_health, 2019; Moodley & National Committee on Confidential Enquiries into Maternal Deaths, 2011; NICE, 2019, 2021).

Prediction of Preeclampsia using Maternal History and Physical Examination

In a review article by Llurba and colleagues(Llurba et al., 2009) in Madrid, the value of one step uterine artery Doppler sonography was examined at 19-22 weeks of gestation for the prediction of preeclampsia and intrauterine growth restriction. They drew receiver operating characteristic curves to compare uterine artery Doppler sonography and maternal characteristics for the prediction of preeclampsia and IUGR. For a false positive rate of 10% uterine artery Doppler mean PI identified 70.6% of pregnancies that subsequently developed PE and 73.3% of those who developed IUGR. Maternal history alone had a very low detection rate for PE and IUGR(Llurba et al., 2009). Gallo et al(D. Gallo, Poon, Fernandez, Wright, & Nicolaides, 2014) screened by maternal history and mean arterial pressure (MAP), at a false-positive rate of 10%, their detection rate of total preeclampsia was 49.3%

David Wright and colleagues(Wright, Syngelaki, Akolekar, Poon, & Nicolaides, 2015) in the United Kingdom developed a model for prediction of preeclampsia based on maternal demographic characteristics and medical history. They assumed that if the pregnancy was to continue indefinitely, all women would develop preeclampsia. They found increased risk for preeclampsia associated with advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or Antiphospholipid syndrome, family history and personal history of preeclampsia, and conception by in vitro fertilization. At a screen-positive rate of 11%, they predicted 40%, 48%, and 54% of cases of total preeclampsia and preeclampsia requiring delivery at <37 and <34 weeks' gestation, respectively.

Meanwhile Xiong and colleagues(Xiong et al., 2000) from Alberta Canada in 2000 found that maternal smoking was protective against preeclampsia. This finding was later in 2005 confirmed by Papageorgiou and colleagues (Papageorgiou et al., 2005) in the United Kingdom. However, there is limited information on smoking in women of reproductive age in Africa.

North and colleagues(North et al., 2011) found clinical risk factors for PE to be 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

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

days in the first trimester. Factors associated with reduced risk of PE 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. The area under the receiver operating characteristics curve (AUC), under internal validation, was 0.71. Addition of uterine artery Doppler indices done at 20 weeks did not improve performance (internal validation AUC 0.71). They developed a framework for specialist referral was developed based on a probability of pre-eclampsia generated by the model of at least 15% or an abnormal uterine artery Doppler waveform in a subset of women with single risk factors.

Direkvand-Moghadam *et al* (Direkvand-Moghadam, Khosravi, & Sayehmiri, 2012) found history of preeclampsia, hypertension, and infertility to be good independent predictor variables for PE using multivariate logistic regression analysis. Area under the Receiver Operation Character (AUROC) was estimated to be 0.67 (95% CI 0.59–0.67, $p < 0.01$) indicating the efficacy of the model for the prediction.

Goetzinger *et al* (Goetzinger, Tuuli, Cahill, Macones, & Odibo, 2014) found significant risk factors and their weighted scores derived from the prediction model to be chronic hypertension, history of pre-eclampsia, pre-gestational diabetes, body mass index 30kg/m^2 , bilateral UA notching, and PAPP-A MoM $< 10\text{th}$ percentile. The AUC for the risk scoring system was 0.76 (95% CI 0.69–0.83). Al-Rubaie *et al* (Al-Rubaie, Askie, Ray, Hudson, & Lord, 2016) assessed the performance of risk models and found four simple models using parity, pre-eclampsia history, race, chronic hypertension and conception method to predict early-onset pre-eclampsia achieving the highest AUC (0.76, 95% CI 0.74–0.77).

Al-Rubaie *et al* (Al-Rubaie *et al.*, 2020) developed a model (the WS model) included: maternal age, body mass index, ethnicity, multiple pregnancy, family history of pre-eclampsia, autoimmune disease, chronic hypertension and chronic renal disease. In the validation sample the model c-statistic was 0.70 (95% confidence interval 0.65–0.75) with a Hosmer-Lemeshow goodness-of-fit test p-value of 0.20. In the same study, when NICE approach was used, there was similar accuracy.

Prediction of Preeclampsia Using Uterine Artery Doppler Sonography

In the 1980s Trudinger and colleagues (Trudinger *et al.*, 1985) described uteroplacental blood flow waveforms in 12 normal and 91 complicated pregnancies starting at 20 weeks until delivery in Sydney Australia. They found reduced diastolic blood flow in the uterine arteries associated with intrauterine growth restriction and hypertensive disorders in pregnancy (Trudinger *et al.*, 1985). This study provided the baseline for more research using Doppler sonography to predict preeclampsia and adverse pregnancy outcomes. Similarly, Fleischer and colleagues (Fleischer *et al.*, 1986) assessed uterine artery Doppler velocimetry in pregnant women with hypertension in their second and third trimesters in USA. They found normal pregnancy occurred when systolic -diastolic ratio was less or equal to 2.6. A notch in the waveform would occur when the systolic-diastolic ratio was more than 2.6, and such pregnancies would be complicated by stillbirth, premature birth, intrauterine growth restriction and preeclampsia with a positive and negative predictive value of 93% and 91% respectively.

In the 1990s North and colleagues (North, Ferrier, Long, Townend, & Kincaid-Smith, 1994) found the best screening for PE and small for gestational age (SGA) babies to be a RI (resistive index) or abdominal circumference (AC) above the 90th percentile. Konchak and colleagues (Konchak, Bernstein, & Capeless, 1995) found an elevated uterine RI associated with an increased risk for PE and SGA. A uterine artery notch was associated with an

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

increased risk of PE, preterm birth and SGA (Konchak et al., 1995). Bower and colleagues (Bower, Kingdom, & Campbell, 1998) found a PI of 1.5 had a sensitivity of 100% and positive predictive value of 55% while predicting adverse pregnancy outcomes, which included PE and SGA.

In the 2000s, Papageorghiou and colleagues (Papageorghiou et al., 2001) did a multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler flow sonography at 23 weeks of gestation in the United Kingdom. They found the 95th percentile for the pulsatility index for uterine arteries of the women studied was 1.63. Those pulsatility index above the 1.63 had a sensitivity and specificity of 69% and 95.2% respectively for prediction of preeclampsia (Papageorghiou et al., 2001). In addition, Papageorghiou and colleagues (Papageorghiou et al., 2005) repeated a multicenter prospective cohort study to assess the risk for the development of PE by maternal characteristics and second trimester uterine artery Doppler sonography. PE occurred in 2.2% of their study population with blacks and obese women more at risk. They found for a false positive rate of 25% the detection rate for preeclampsia using maternal history alone was 45.3%, with uterine artery Doppler flow pulsatility index was 63.1% and by combining the tests it raised to 67.5% (Papageorghiou et al., 2005).

Asnafi and Hajian (Asnafi & Hajian, 2011) assessed uterine artery Doppler sonography efficiency in the prediction of adverse pregnancy outcomes in high-risk pregnancies (those with history of chronic hypertension, preeclampsia, diabetes mellitus, gestational diabetes, intrauterine fetal death, infertility, polycystic ovarian syndrome and recurrent abortion) at 18 to 24 weeks in Iran. They found preeclampsia in 48% of those with end diastolic notching as opposed to only 9% of those without end diastolic notching (Asnafi & Hajian, 2011). Similarly Bhattacharyya and colleagues (Bhattacharyya Sanjoy Kumar, 2012) did uterine artery Doppler flow sonography in pregnant women at 24 to 26 weeks in India. They found that a unilateral or bilateral end diastolic notch, or a resistive index of greater than 0.6 had a sensitivity and specificity of 73.3% and 86.5% of high risk pregnancies, and of low risk pregnancies were 57.1% and 95.8% respectively (Bhattacharyya Sanjoy Kumar, 2012). However, they did not give the cut-off of their pulsatility index.

Poon and colleagues (Poon et al., 2013) in the United Kingdom examined the role of second trimester uterine artery Doppler flow sonography in the prediction of still births. They found that the uterine artery Doppler Pulsatility index (PI) Multiples of the Median (MoM) was above the 90th percentile in 80.6% of the still births with preeclampsia, placental abruption and small for gestation age.

Meanwhile Yousuf and colleagues (Yousuf et al., 2016) in India determined whether placental laterality and an abnormal second trimester uterine artery Doppler flow sonography was predictive of Preeclampsia. They found that a laterally situated placenta predicted 52% of preeclampsia. A combination of a laterally situated placenta and an abnormal uterine artery Doppler flow sonography predicted 92% of preeclampsia.

Yasmin Casmod and colleagues (Yasmin Casmod, 2016) did uterine artery Doppler flow sonography in the first, second and third trimesters of pregnancy in South Africa in 2008 to 2010. They found that incidence of preeclampsia was 5.8% and second trimester early diastolic notch predicted only 50% of cases. The majority (73%) of the patients were blacks in their twenties (Yasmin Casmod, 2016). However, Oloyede and Iketubosin (Iketubosin, 2013) in Lagos, Nigeria studied the Uterine artery Doppler flow in the second trimester of pregnancy to predict adverse pregnancy outcomes. They found no statistically significant

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

difference in uterine Doppler flow between those who had normal and adverse pregnancy outcomes.

Wright *et al* (Wright *et al.*, 2015) developed a model showing increased risk for PE provided by advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, family history and personal history of PE and conception by in vitro fertilization. The risk for PE decreases with increasing maternal height and in parous women with no previous PE; in the later, the protective effect, which is inversely related to the inter-pregnancy interval, persists beyond 15 years. At screen positive rate of 11%, as defined by NICE, the new model predicted 40%, 48% and 54% of cases of total PE and PE requiring delivery at <37 and <34 weeks' gestation, respectively, which were significantly higher than the respective values of 35%, 40% and 44% achieved by application of NICE guidelines.

Prediction of preeclampsia using full haemogram, liver and renal function tests

In a review article by Duckitt *et al* (Duckitt & Harrington, 2005) controlled cohort studies showed that the risk of pre-eclampsia is increased in women with a previous history of pre-eclampsia and in those with antiphospholipid antibodies, pre-existing diabetes, multiple (twin) pregnancy, nulliparity, family history, raised blood pressure (diastolic ≥ 80 mm Hg) at booking, raised body mass index before pregnancy (2.47, 1.66 to 3.67) or at booking, or maternal age ≥ 40 . Individual studies show that risk is also increased with an interval of 10 years or more since a previous pregnancy, autoimmune disease, renal disease, and chronic hypertension.

De Kat *et al* (De Kat, Hirst, Woodward, Kennedy, & Peters, 2019) summarized risk factors and models for prediction of preeclampsia. Black race stood out as a major risk factor in all the studies where the communities had a mixed race. Studies by Al-Rubaie *et al* (Al-Rubaie *et al.*, 2016) achieved the highest area under curve (AUC) for prediction of preeclampsia at 76% using maternal history. When uric acid, urea thrombocytes, hematocrit, AST and leukocytes were included into logistic regression model, Delic *et al* (Delic & Stefanovic, 2010) correctly classified 83.8% patients with preeclampsia. Elevated levels of AST alone was also predictive of preeclampsia (Mei-Dan, Wiznitzer, Sergienko, Hallak, & Sheiner, 2013). An albumin level < 3.3 g/dl had an adjusted risk ratio of 1.87 for the development of preeclampsia (Martell-Claros *et al.*, 2019). Yucel *et al* (Yucel & Ustun, 2017) predicted preeclampsia using mean platelet volume (MPV) and plateletcrit (PCT) with AUC of 64.1% and 71.2% respectively. Jhee *et al* (Jhee *et al.*, 2019) used a combination of laboratory tests (serum urea, aspartate aminotransferase (AST), ALT, creatinine, and hemoglobin levels) to predict preeclampsia with area under curve (AUC) above 57%.

Kasyap *et al* (Kashyap, Saxena, Khullar, Sawhney, & Vasishta, 2006) studied the Role of anion gap and different electrolytes in hypertension during pregnancy and found Mean serum sodium, chloride and bicarbonate level (133.26 ± 13.1 , 104.97 ± 11.37 , and 22.01 ± 4.66 mEq/l, respectively) were significantly higher in proteinuric hypertensive women as compared to controls (125.85 ± 10.4 , 101.90 ± 6.3 , 19.34 ± 3.21 mEq/l, respectively) whereas anion gap level (6.28 ± 16.147) was non-significantly higher in proteinuric hypertensive as compared to normotensive (4.61 ± 11.84). They however could not confirm whether these findings could be used for prediction purposes, and at what gestation age these electrolytes start getting deranged.

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

Rodriguez and colleagues (Rodriguez, Masaki, Mestman, Kumar, & Rude, 1988) screened 88 normotensive gravid women between 24 and 34 weeks of gestation for the presence of micro-albuminuria and urinary calcium excretion (calcium/creatinine ratio). PE subsequently developed in 83% of participants with a high level of micro-albuminuria and a low calcium/creatinine ratio. They concluded that changes in renal function are present in gravid women who are otherwise free of symptoms in whom preeclampsia will eventually develop, and recommended testing for micro-albuminuria and a calcium/creatinine ratio for predicting development of preeclampsia.

Vahdat and colleagues (Vahdat, Kashanian, Sariri, & Mehdinia, 2012) found mean urine calcium of pre-eclamptic women was significantly lower than normotensive women, and mean calcium to creatinine ratio was significantly lower in pre-eclamptic women. This finding was repeated by Ozcan and colleagues (Ozcan, Kaleli, Ozeren, Turan, & Zorlu, 1995). They concluded that urine calcium and calcium to creatinine ratio may be used as a screening test for the prediction of preeclampsia.

Sultana and colleagues (Sultana et al., 2012) found serum calcium levels in the 1st and 2nd trimesters of gestation were significantly higher compared to the Controls. In 3rd the value was significantly lower compared to the Controls and of 1st and 2nd trimesters. Serum phosphate levels in three trimesters did not show statistically significant difference compared to the Controls and among the pregnancy groups.

Ortner and colleagues (Ortner et al., 2015) found mean base excess was similar in preeclamptic- and healthy pregnant women. In preeclampsia, there were greater offsetting contributions to the base excess, in the form of hyperchloraemia and hypoalbuminaemia. Quantitative analysis in healthy pregnancy revealed respiratory and hypoalbuminaemic alkalosis that was metabolically offset by acidosis, secondary to unmeasured anions and dilution (Ortner et al., 2015).

In the 1980s it was known that a fall in the platelet count and a rise in uric acid levels were signs of PE (Fay, Bromham, Brooks, & Gebiski, 1985). However, these were not yet used as predictive tools for PE. Yucel and Ustan (Yucel & Ustun, 2017) evaluated the changes in neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ration (PLR), mean platelet volume (MPV), red cell distribution width (RDW) and plateletcrit (PCT) in preeclampsia and their use in predicting the severity of preeclampsia in Istanbul Turkey. They found RDW and MPV were statistically higher in the preeclampsia group, meanwhile PLR and PCT were lower in those with severe preeclampsia. They concluded MPV or PCT may be a useful clinical marker to predict severe Preeclampsia.

Similarly Girling and Dow (Girling, Dow, & Smith, 1997) did a cross sectional study in London in 1997 and found that the liver enzymes in normal pregnant women were lower than the reference values used for Non-pregnant women, whereas for those with preeclampsia were much higher. However, they did not use these values as predictive tools. In a systematic review by Thangaratinam and colleagues (Thangaratinam et al., 2011) in 2006, they found Uric acid levels in women with preeclampsia is a poor predictor of maternal and fetal outcomes. This study was done in women with the diagnosis of preeclampsia and no comparison was made with the normal pregnant group.

Darkwa and colleagues (Owusu Darkwa et al., 2017) in Ghana found serum sodium and potassium were significantly reduced in preeclamptics compared to normotensive pregnant women. They concluded that changes in these electrolytes may be used for prediction of preeclampsia. Ekun and colleagues (Ekun, Olawumi, Makwe, & Ogidi, 2018) found the plasma sodium, total protein, and albumin in preeclamptic group significantly

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

decreased compared with control the control group. There was significant increase in microalbuminuria, plasma potassium, urea, creatinine, uric acid levels, serum AST, and ALT activities in preeclamptic group. These parameters may be used for prediction of PE.

Conclusion of the review of literature

A prediction model is used to screen mothers during antenatal care before they are sick, and contribute to the reduction of these maternal deaths by prediction of preeclampsia, leading to a more frequent follow up visits for those at risk, early detection and management. Whereas routine screening for adverse pregnancy outcomes is on-going in the antenatal clinics within communities in the global north, there are no tools developed and tested for screening of preeclampsia among communities in most communities in the global south.

Recommendations

Ultrasound machines are available, and physical examination is non-invasive, yet very informative to the expectant mother about the health status and structure of their unborn babies. However obstetric ultrasound scan is not routinely done in pregnancy (Ministry of Health Uganda, 2016) although over 93% of the pregnant women come into contact with a skilled health care provider at least once during their antenatal visits (Uganda Bureau of statistics, 2011). A good history taking and physical examination for every mother during antenatal care can bring out all the maternal characteristics. Complete blood count, renal and liver function tests are easily available in most hospitals and laboratories. It is easy to roll-out these tests to lower-level health facilities and clinics. With the available information, mothers and caretakers are counseled appropriately on what to expect from the findings of their screening process during antenatal care. High-risk pregnancies are referred to the few specialist health care providers. The extra vigilance given to high-risk women may perhaps lead to early diagnosis and treatment of PE, and in turn, prevent and or reduce maternal morbidity and mortality.

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

References

- Acharya, A., Brima, W., Burugu, S., & Rege, T. (2014). Prediction of preeclampsia-bench to bedside. *Curr Hypertens Rep*, 16(11), 491. doi:10.1007/s11906-014-0491-3
- Al-Rubaie, Z. T. A., Hudson, H. M., Jenkins, G., Mahmoud, I., Ray, J. G., Askie, L. M., & Lord, S. J. (2020). Prediction of pre-eclampsia in nulliparous women using routinely collected maternal characteristics: a model development and validation study. *BMC pregnancy and childbirth*, 20(1), 23. doi:10.1186/s12884-019-2712-x
- Al-Rubaie, Z. T. A., Askie, L. M., Ray, J. G., Hudson, H. M., & Lord, S. J. (2016). The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology*, 123(9), 1441-1452. doi:10.1111/1471-0528.14029
- Arbogast, B. W., Leeper, S. C., Merrick, R. D., Olive, K. E., & Taylor, R. N. (1994). Which plasma factors bring about disturbance of endothelial function in pre-eclampsia? *The Lancet*, 343(8893), 340-341. doi:https://doi.org/10.1016/S0140-6736(94)91169-X
- Asnafi, N., & Hajian, K. (2011). Mid-trimester uterine artery Doppler ultrasound as a predictor of adverse obstetric outcome in high-risk pregnancy. *Taiwan J Obstet Gynecol*, 50(1), 29-32. doi:10.1016/j.tjog.2009.08.002
- Bhattacharyya Sanjoy Kumar, K. S., Kabiraj Sankar Prasad. (2012). Prediction of Preeclampsia by Midtrimester Uterine Artery Doppler Velocimetry in High-Risk and Low-Risk Women. *The Journal of Obstetrics and Gynecology of India*, 62(3), 297 - 300. doi:DOI 10.1007/s13224-012-0219-8
- Bosio, P. M., McKenna, P. J., Conroy, R., & O'Herlihy, C. (1999). Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecol*, 94(6), 978-984. doi:10.1016/s0029-7844(99)00430-5
- Bower, S., Kingdom, J., & Campbell, S. (1998). Objective and subjective assessment of abnormal uterine artery Doppler flow velocity waveforms. *Ultrasound Obstet Gynecol*, 12(4), 260-264. doi:10.1046/j.1469-0705.1998.12040260.x
- Boyd, H. A., Tahir, H., Wohlfahrt, J., & Melbye, M. (2013). Associations of personal and family preeclampsia history with the risk of early-, intermediate- and late-onset preeclampsia. *Am J Epidemiol*, 178(11), 1611-1619. doi:10.1093/aje/kwt189
- Brennan, L. J., Morton, J. S., & Davidge, S. T. (2014). Vascular dysfunction in preeclampsia. *Microcirculation*, 21(1), 4-14. doi:10.1111/micc.12079
- Brown, M. A., Lindheimer, M. D., de Swiet, M., Van Assche, A., & Moutquin, J. M. (2001). The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy*, 20(1), IX-XIV. doi:10.1081/PRG-100104165
- De Kat, A. C., Hirst, J., Woodward, M., Kennedy, S., & Peters, S. A. (2019). Prediction models for preeclampsia: A systematic review. *Pregnancy Hypertens*, 16, 48-66. doi:10.1016/j.preghy.2019.03.005
- Dechend, R., & Staff, A. C. (2012). Placenta Messages to the Mother. *Hypertension*, 59(2), 191-193. doi:10.1161/hypertensionaha.111.184861
- Dekker G.A., & Robillard P.Y. (2004). Preeclampsia: A Couple's Disease with Maternal and Fetal Manifestations. *Current Pharmaceutical Design*, 10(000-000).

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

- Dekker, G. A. (1999). Risk factors for preeclampsia. *Clin Obstet Gynecol*, 42(3), 422-435. doi:10.1097/00003081-199909000-00002
- Dekker, G. A., Robillard, P. Y., & Hulsey, T. C. (1998). Immune maladaptation in the etiology of preeclampsia: a review of corroborative epidemiologic studies. *Obstet Gynecol Surv*, 53(6), 377-382. doi:10.1097/00006254-199806000-00023
- Delic, R., & Stefanovic, M. (2010). Optimal laboratory panel for predicting preeclampsia. *J Matern Fetal Neonatal Med*, 23(1), 96-102. doi:10.3109/14767050903156643
- Department_of_health. (2019). *Pregnancy Care Guidelines*. online: Australian government Retrieved from <https://www.health.gov.au/resources/pregnancy-care-guidelines/part-d-clinical-assessments/risk-of-pre-eclampsia#264-practice-summary-preeclampsia>
- Direkvand-Moghadam, A., Khosravi, A., & Sayehmiri, K. (2012). Predictive factors for preeclampsia in pregnant women: a univariate and multivariate logistic regression analysis. *Acta Biochim Pol*, 59(4), 673-677. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/23198281>
- Duckitt, K., & Harrington, D. (2005). Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ*, 330(7491), 565. doi:10.1136/bmj.38380.674340.E0
- Ekun, O. A., Olawumi, O. M., Makwe, C. C., & Ogidi, N. O. (2018). Biochemical Assessment of Renal and Liver Function among Preeclamptics in Lagos Metropolis. *Int J Reprod Med*, 2018, 1594182. doi:10.1155/2018/1594182
- Elosha Eiland, C. N., and Marquetta Faulkner. (2012). Preeclampsia. *Journal of Pregnancy*, 2012, 7.
- Fay, R. A., Bromham, D. R., Brooks, J. A., & Gebiski, V. J. (1985). Platelets and uric acid in the prediction of preeclampsia. *Am J Obstet Gynecol*, 152(8), 1038-1039. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/4025450>
- Fisher, S. J. (2015). Why is placentation abnormal in preeclampsia? *Am J Obstet Gynecol*, 213(4 Suppl), S115-122. doi:10.1016/j.ajog.2015.08.042
- Fleischer, A., Schulman, H., Farmakides, G., Bracero, L., Grunfeld, L., Rochelson, B., & Koenigsberg, M. (1986). Uterine artery Doppler velocimetry in pregnant women with hypertension. *Am J Obstet Gynecol*, 154(4), 806-813. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3515946
- Gallo, D., Poon, L. C., Fernandez, M., Wright, D., & Nicolaides, K. H. (2014). Prediction of preeclampsia by mean arterial pressure at 11-13 and 20-24 weeks' gestation. *Fetal Diagn Ther*, 36(1), 28-37. doi:10.1159/000360287
- Gallo, D. M., Poon, L. C., Akolekar, R., Syngelaki, A., & Nicolaides, K. H. (2013). Prediction of preeclampsia by uterine artery Doppler at 20-24 weeks' gestation. *Fetal Diagn Ther*, 34(4), 241-247. doi:10.1159/000356171
- Girling, J. C., Dow, E., & Smith, J. H. (1997). Liver function tests in pre-eclampsia: importance of comparison with a reference range derived for normal pregnancy. *Br J Obstet Gynaecol*, 104(2), 246-250. doi:10.1111/j.1471-0528.1997.tb11054.x
- Goetzinger, K. R., Tuuli, M. G., Cahill, A. G., Macones, G. A., & Odibo, A. O. (2014). Development and validation of a risk factor scoring system for first-trimester prediction of preeclampsia. *Am J Perinatol*, 31(12), 1049-1056. doi:10.1055/s-0034-1371705

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

- Harmon, A. C., Cornelius, D. C., Amaral, L. M., Faulkner, J. L., Cunningham, M. W., Jr., Wallace, K., & LaMarca, B. (2016). The role of inflammation in the pathology of preeclampsia. *Clin Sci (Lond)*, 130(6), 409-419. doi:10.1042/CS20150702
- Iketubosin, O. A. O. F. (2013). Uterine artery Doppler study in second trimester of pregnancy. *Pan African Medical Journal*. doi:doi:10.11604/pamj.2013.15.87.2321
- Jain, A., Schneider, H., Aliyev, E., Soydemir, F., Baumann, M., Surbek, D., . . . Albrecht, C. (2014). Hypoxic treatment of human dual placental perfusion induces a preeclampsia-like inflammatory response. *Lab Invest*, 94(8), 873-880. doi:10.1038/labinvest.2014.76
- Jhee, J. H., Lee, S., Park, Y., Lee, S. E., Kim, Y. A., Kang, S.-W., . . . Park, J. T. (2019). Prediction model development of late-onset preeclampsia using machine learning-based methods. *PLoS One*, 14(8), e0221202-e0221202. doi:10.1371/journal.pone.0221202
- Kashyap, M. K., Saxena, S. V., Khullar, M., Sawhney, H., & Vasishta, K. (2006). Role of anion gap and different electrolytes in hypertension during pregnancy (preeclampsia). *Mol Cell Biochem*, 282(1-2), 157-167. doi:10.1007/s11010-006-1739-2
- Khalil, A., Rezende, J., Akolekar, R., Syngelaki, A., & Nicolaides, K. H. (2013). Maternal racial origin and adverse pregnancy outcome: a cohort study. *Ultrasound Obstet Gynecol*, 41(3), 278-285. doi:10.1002/uog.12313
- Konchak, P. S., Bernstein, I. M., & Capeless, E. L. (1995). Uterine artery Doppler velocimetry in the detection of adverse obstetric outcomes in women with unexplained elevated maternal serum alpha-fetoprotein levels. *Am J Obstet Gynecol*, 173(4), 1115-1119. doi:10.1016/0002-9378(95)91336-x
- Laresgoiti-Servitje E, G.-L. N., Olson DM. (2011). An immunological insight into the origins of pre-eclampsia. *Hum Reprod Update.*, 17(2).
- Llurba, E., Carreras, E., Gratacos, E., Juan, M., Astor, J., Vives, A., . . . Cabero, L. (2009). Maternal history and uterine artery Doppler in the assessment of risk for development of early- and late-onset preeclampsia and intrauterine growth restriction. *Obstet Gynecol Int*, 2009, 275613. doi:10.1155/2009/275613
- Lorentzen, B., Endresen, M. J., Clausen, T., & Henriksen, T. (1994). Fasting Serum Free Fatty Acids and Triglycerides are Increased Before 20 Weeks of Gestation in Women who Later Develop Preeclampsia. *Hypertension in Pregnancy*, 13(1), 103-109. doi:10.3109/10641959409084177
- Martell-Claros, N., Abad-Cardiel, M., García-Donaire, J., De Los Santos, C., Gonzalez, V., Fuentes, M., . . . Sosa, L. (2019). HYPOALBUMINEMIA AS A RISK FACTOR OF PREECLAMPSIA- ECLAMPSIA IN HIGH RISK PREGNANCY. *Journal of Hypertension*, 37, e240. doi:10.1097/01.hjh.0000573076.28399.b1
- Medawar, P. (1960). Nobel lecture.
- Mei-Dan, E., Wiznitzer, A., Sergienko, R., Hallak, M., & Sheiner, E. (2013). Prediction of preeclampsia: liver function tests during the first 20 gestational weeks. *J Matern Fetal Neonatal Med*, 26(3), 250-253. doi:10.3109/14767058.2012.733771
- Ministry of Health Uganda. (2016). *Uganda Clinical guidelines* (December 2016 ed.). Kampala: Ministry of Health.
- MOH. (2017). *Maternal and Perinatal Death Surveillance and Response Guidelines*. Kampala
- Moodley, J., & National Committee on Confidential Enquiries into Maternal Deaths, N. D. o. S. A. (2011). Maternal deaths associated with hypertension in South Africa: lessons to

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

- learn from the Saving Mothers report, 2005-2007. *Cardiovasc J Afr*, 22(1), 31-35. doi:CVJ-21.026
10.5830/cvja-2010-042
- Muto, H., Yamamoto, R., Ishii, K., Kakubari, R., Takaoka, S., Mabuchi, A., & Mitsuda, N. (2016). Risk assessment of hypertensive disorders in pregnancy with maternal characteristics in early gestation: A single-center cohort study. *Taiwan J Obstet Gynecol*, 55(3), 341-345. doi:10.1016/j.tjog.2016.04.009
- Myatt, L., Redman, C. W., Staff, A. C., Hansson, S., Wilson, M. L., Laivuori, H., . . . Global Pregnancy, C. (2014). Strategy for standardization of preeclampsia research study design. *Hypertension*, 63(6), 1293-1301. doi:10.1161/HYPERTENSIONAHA.113.02664
- Myatt, L., & Roberts, J. M. (2015). Preeclampsia: Syndrome or Disease? *Curr Hypertens Rep*, 17(11), 83. doi:10.1007/s11906-015-0595-4
- Nakimuli, A., Chazara, O., Byamugisha, J., Elliott, A. M., Kaleebu, P., Mirembe, F., & Moffett, A. (2014). Pregnancy, parturition and preeclampsia in women of African ancestry. *Am J Obstet Gynecol*, 210(6), 510-520 e511. doi:10.1016/j.ajog.2013.10.879
- Nelson, T. R., & Pretorius, D. H. (1988). The Doppler signal: where does it come from and what does it mean? *AJR Am J Roentgenol*, 151(3), 439-447. doi:10.2214/ajr.151.3.439
- NICE. (2019). <Hypertension in pregnancy_ diagnosis and management.pdf>. 55.
- NICE. (2021). <hypertension-in-pregnancy-reducing-the-risk-of-hypertensive-disorders-before-and-during-pregnancy.pdf>.
- North, R. A., Ferrier, C., Long, D., Townend, K., & Kincaid-Smith, P. (1994). Uterine artery Doppler flow velocity waveforms in the second trimester for the prediction of preeclampsia and fetal growth retardation. *Obstet Gynecol*, 83(3), 378-386. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8127529>
- North, R. A., McCowan, L. M., Dekker, G. A., Poston, L., Chan, E. H., Stewart, A. W., . . . Kenny, L. C. (2011). Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ*, 342, d1875. doi:10.1136/bmj.d1875
- Oloyede, O. A., & Iketubosin, F. (2013). Uterine artery Doppler study in second trimester of pregnancy. *Pan African Medical Journal*. doi:doi:10.11604/pamj.2013.15.87.2321
- Ortner, C. M., Combrinck, B., Allie, S., Story, D., Landau, R., Cain, K., & Dyer, R. A. (2015). Strong ion and weak acid analysis in severe preeclampsia: potential clinical significance†. *BJA: British Journal of Anaesthesia*, 115(2), 275-284. doi:10.1093/bja/aev221
- Owusu Darkwa, E., Djagbletey, R., Antwi-Boasiako, C., Aryee, G., Sottie, D., & Akowuah, A. (2017). Serum sodium and potassium levels in preeclampsia: A case-control study in a large tertiary hospital in Ghana. *Cogent Medicine*, 4(1), 1376898. doi:10.1080/2331205X.2017.1376898
- Ozcan, T., Kaleli, B., Ozeren, M., Turan, C., & Zorlu, G. (1995). Urinary calcium to creatinine ratio for predicting preeclampsia. *Am J Perinatol*, 12(5), 349-351. doi:10.1055/s-2007-994494
- Palmer, S. K., Zamudio, S., Coffin, C., Parker, S., Stamm, E., & Moore, L. G. (1992). Quantitative estimation of human uterine artery blood flow and pelvic blood flow redistribution in pregnancy. *Obstet Gynecol*, 80(6), 1000-1006. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/1448242>

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

- Papageorgiou, A. T., Yu, C. K., Bindra, R., Pandis, G., Nicolaides, K. H., & Fetal Medicine Foundation Second Trimester Screening, G. (2001). Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. *Ultrasound Obstet Gynecol*, 18(5), 441-449. doi:10.1046/j.0960-7692.2001.00572.x
- Papageorgiou, A. T., Yu, C. K., Erasmus, I. E., Cuckle, H. S., & Nicolaides, K. H. (2005). Assessment of risk for the development of pre-eclampsia by maternal characteristics and uterine artery Doppler. *BJOG*, 112(6), 703-709. doi:10.1111/j.1471-0528.2005.00519.x
- Poon, L. C., Volpe, N., Muto, B., Yu, C. K., Syngelaki, A., & Nicolaides, K. H. (2013). Second-trimester uterine artery Doppler in the prediction of stillbirths. *Fetal Diagn Ther*, 33(1), 28-35. doi:10.1159/000342109
- Possomato-Vieira, J. S., & Khalil, R. A. (2016). Mechanisms of Endothelial Dysfunction in Hypertensive Pregnancy and Preeclampsia. *Adv Pharmacol*, 77, 361-431. doi:10.1016/bs.apha.2016.04.008
- Powe, C. E., Levine, R. J., & Karumanchi, S. A. (2011). Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation*, 123(24), 2856-2869. doi:10.1161/CIRCULATIONAHA.109.853127
- Prajapati, S. R., & Maitra, N. (2013). Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler, and mean arterial pressure (a prospective study of 200 cases). *J Obstet Gynaecol India*, 63(1), 32-36. doi:10.1007/s13224-012-0239-4
- Prins, J. R., van der Hoorn, M. L., Keijser, R., Ris-Stalpers, C., van Beelen, E., Afink, G. B., . . . Scherjon, S. A. (2016). Higher decidual EBI3 and HLA-G mRNA expression in preeclampsia: Cause or consequence of preeclampsia. *Hum Immunol*, 77(1), 68-70. doi:10.1016/j.humimm.2015.10.004
- Redman, C. W. (2011). Preeclampsia: a multi-stress disorder. *Rev Med Interne*, 32 Suppl 1, S41-44. doi:10.1016/j.revmed.2011.03.331
- Redman, C. W., & Sargent, I. L. (2003). Pre-eclampsia, the placenta and the maternal systemic inflammatory response--a review. *Placenta*, 24 Suppl A, S21-27. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12842410>
- Redman, C. W., & Sargent, I. L. (2005). Latest advances in understanding preeclampsia. *Science*, 308(5728), 1592-1594. doi:10.1126/science.1111726
- Redman, C. W., Sargent, I. L., & Staff, A. C. (2014). IFPA Senior Award Lecture: making sense of pre-eclampsia - two placental causes of preeclampsia? *Placenta*, 35 Suppl, S20-25. doi:10.1016/j.placenta.2013.12.008
- Robert K. Creasy, Robert Resnik, Jay D. Iams, Charles J. Lookwood, Thomas R. Moore, & Greene, M. F. (2014). *Creasy and Resnik's maternal-fetal medicine, Principles and practice* (R. K. Creasy, R. Resnik, J. D. Iams, C. J. Lockwood, T. R. Moore, & M. F. Greene Eds. 7th ed.): Elsevier Saunders.
- Rock, J. A., & Jones, H. W. (2008). *Te Linde's Operative Gynecology* (J. A. Rock & H. W. Jones III Eds. 10th ed.): Wolters Kluwer, Lippincott, Williams & Wilkins.
- Rodriguez, M. H., Masaki, D. I., Mestman, J., Kumar, D., & Rude, R. (1988). Calcium/creatinine ratio and microalbuminuria in the prediction of preeclampsia. *Am J Obstet Gynecol*, 159(6), 1452-1455. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/3061296>

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

- Sarah A. Robertson *, John J. Bromfield, & Tremellen, K. P. (2003). Seminal ‘priming’ for protection from preeclampsia*/a unifying hypothesis. *Journal of Reproductive Immunology*, 59, 253-265.
- Shakuntala Chhabra, Jaiswal, A., & Singh, A. (2016). Prediction of Hypertensive Disorders of Pregnancy by Measuring Cardiac Output in Early Pregnancy *IBIMA Publishing Obstetrics & Gynecology: An International Journal*, 2016, 8. doi:10.5171/2016.827403
- Sultana, M., Begum, R., Akhter, Q., Lovely, N., Akhter, S., & Islam, M. (2012). Serum calcium and phosphate level in normal pregnant women. *Bangladesh Journal of Medical Science*, 11. doi:10.3329/bjms.v11i3.11732
- Thangaratinam, S., Koopmans, C. M., Iyengar, S., Zamora, J., Ismail, K., Mol, B. W. M., & Khan, K. (2011). *Accuracy of liver function tests for predicting adverse maternal and fetal outcomes in women with preeclampsia: A systematic review* (Vol. 90).
- Trudinger, B. J., Giles, W. B., & Cook, C. M. (1985). Uteroplacental blood flow velocity-time waveforms in normal and complicated pregnancy. *Br J Obstet Gynaecol*, 92(1), 39-45. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3966989
- Uganda Bureau of statistics. (2011). *Uganda Demographic and Health Survey*.
- Uganda, M. o. H. (2016). *Uganda Clinical guidelines* (December 2016 ed.). Kampala: Ministry of Health.
- Uzan, J., Carbonnel, M., Piconne, O., Asmar, R., & Ayoubi, J. M. (2011). Pre-eclampsia: pathophysiology, diagnosis, and management. *Vasc Health Risk Manag*, 7, 467-474. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21822394
- Vahdat, M., Kashanian, M., Sariri, E., & Mehdinia, M. (2012). Evaluation of the value of calcium to creatinine ratio for predicting of pre-eclampsia. *J Matern Fetal Neonatal Med*, 25(12), 2793-2794. doi:10.3109/14767058.2012.712561
- Walia, M., D’souza, A. S., & Gupta, G. (2015). Comparison between roll-over test and placental localization for early prediction of preeclampsia. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 4, 1710-1713. doi:http://dx.doi.org/10.18203/2320-1770.ijrcog20150784
- Wandabwa, J., Doyle, P., Kiondo, P., Campbell, O., Maconichie, N., & Welishe, G. (2010). Risk factors for severe pre-eclampsia and eclampsia in Mulago Hospital, Kampala, Uganda. *East Afr Med J*, 87(10), 415-424. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/23057275>
- Wright, D., Syngelaki, A., Akolekar, R., Poon, L. C., & Nicolaides, K. H. (2015). Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *American Journal of obstetrics and Gynecology*, 213(62), 1-10.
- Xiong, X., Wang, F. L., Davidge, S. T., Demianczuk, N. N., Mayes, D. C., Olson, D. M., & Saunders, L. D. (2000). Maternal smoking and preeclampsia. *J Reprod Med*, 45(9), 727-732. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11027081
- Yasmin Casmod, B. V. D., E. Nicolaou. (2016). Uterine artery Doppler screening as a predictor of pre-eclampsia. *health sa gesondheid*, 21, 391-396.

Citation: Awor, S; Byanyima, R; Abola, B; Nakimuli, A; Orach, C. G; Kiondo, P; Kaye, D & Ogwal-Okeng, J. (2022). Prediction of Preeclampsia Using Routinely Available Care: A Review of Literature. *Journal of African Interdisciplinary Studies*. 6(1), 109 – 126.

- Yousuf, S., Ahmad, A., Qadir, S., Gul, S., Tali, S. H., Shaheen, F., . . . Dar, R. (2016). Utility of Placental Laterality and Uterine Artery Doppler Abnormalities for Prediction of Preeclampsia. *J Obstet Gynaecol India*, 66(Suppl 1), 212-216. doi:10.1007/s13224-015-0837-z
- Yucel, B., & Ustun, B. (2017). Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume, red cell distribution width and plateletcrit in preeclampsia. *Pregnancy Hypertens*, 7, 29-32. doi:10.1016/j.preghy.2016.12.002