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Erythrocyte sedimentation rate as a simple test to predict late-stage pregnancy complications of women in low-resource settings

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Abstract: **Hypertension is the most common medical problem encountered during pregnancy, complicating 2-3% of pregnancies. Hypertension, also known as high blood pressure is defined as a blood pressure reading of 140/90 or above. WHO estimates the incidence of PIH to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%). In Nigeria, prevalence ranges between 2% and 16.7% in different zones. In our study, an assessment of the effect of certain blood rheological variables on the blood pressure of pregnant women was undertaken. One hundred and sixty eight women in advanced stages of pregnancy were assessed, using fifty non-pregnant women as control subjects. The result showed that there is a significant association between Erythrocyte sedimentation rate (ESR) and blood pressure changes in pregnancy. There was also a significant association between ESR and parity. The study suggests that inflammatory processes triggered off during the first pregnancy may become exacerbated in subsequent pregnancies in multiparous pregnant women. The study shows that ESR levels may be used in predicting possible development of pregnancy-induced complications in pregnant women, especially during the early third trimester in low-income countries where access to adequate health facilities may be difficult.**

Keywords: **Hypertension, ESR.**

1. INTRODUCTION

Pregnancy is a state in which the physiological status of an expectant mother changes progressively as the pregnancy advances. These changes represent a positive preparation and adaptation to accommodate and support the developing foetus. Alterations in pregnancy haemodynamics start early in pregnancy and are maintained to the third semester. Generally, abnormalities in whole blood viscosity have been implicated in hypertension (Devereux *et al*., 2000). Chronic hypertension develops before 20 weeks of pregnancy or lasts more than 12 weeks after delivery. Gestational hypertension develops after 20 weeks of pregnancy. Unlike pre-eclampsia, affected women do not have protein in their urine and the condition usually goes away after delivery. Occasionally, chronic or gestational hypertension leads to pre-eclampsia, a serious condition characterized by high blood pressure and protein in urine after 20 weeks of pregnancy. Pre-eclampsia not only causes high blood pressure, but also affects other parts in the mother's body such as the kidney, liver and blood vessels (Braun, 2003). Sometimes an early delivery is needed to prevent potentially life-threatening complications for both mother and fetus.

In normal pregnancies, most rheological parameters are reduced by about 10% to 20% due to physiological haemodilution and plasma expansion (Thorburn *et al.*, 1982). In normal pregnancy, it has been reported that fibrinogen level rises, red cell aggregation increases and red cell deformability falls (Gronowski *et al*., 2004). These are factors that all contribute to hyperviscosity or a decreased rate of blood flow and a raise in the erythrocyte sedimentation rate (ESR). In a study,

adverse outcome of pregnancy pre-eclampsia was found to coincide with haemo-concentration and over-activation of blood coagulation, both of which alter blood rheology (Gronowski *et al*., 2004). Sugam *et al*., (1982) proved that a coincidental increase in RBC aggregation and haemoconcentration may potentially derogate blood flow in the materno-foetal unit. Slowing down of blood flow tends to activate and promote blood coagulation activities in the affected patient.

While it is easier to monitor those pregnant women with pre-existing high blood pressure, pregnancy-induced hypertension may develop suddenly as the pregnancy advances; and for women in underserved, remote communities, complications such as pre-eclampsia or eclampsia among others may develop, threatening the lives of both mother and child while immediate medical attention required in such emergencies may be far-fetched. On the contrary, marked rheological changes do not occur suddenly and are usually measurable. If certain parameters of blood rheology could be used as predictors of pregnancy outcome then this could possibly permit selective and early monitoring of a potential increase in blood pressure before fatality occurs. This is particularly important in underserved communities in which access to good health-care may be difficult.

Urinalysis and particularly the protein fraction thereof, has been used to predict the likelihood of a pregnant woman developing pre-eclampsia. An additional test to predict potential complications before harm occurs in both mother and child is desirable. Moreover, the blood is a better reflector of the physiological changes in the body than the urine. In this study, a few haemorheological variables were assessed for their efficacy to determine the true rheological status of pregnant women.

2. MATERIALS AND METHODS

This was an observational study carried out in Abeokuta, Ogun State of Nigeria. The study was undertaken among pregnant women presenting for ante-natal clinic at Oba Ademola State Hospital, Ijemo, Abeokuta. Abeokuta is a fairly urban area hosting the above-named maternity hospital. The majority of subjects are traders or artisans while a very low percentage are civil servants. 168 pregnant women were enlisted for the study.

The demographic data of the subjects were obtained by questionnaire after an informed consent for the study had been obtained from each subject. The study lasted for five months, with an average of twenty samples being collected on each antenatal clinic day (holding every fortnight). Samples obtained were subsequently analyzed in the laboratory. Control subjects consisted of 50 apparently healthy non-pregnant women and analysis of control specimens was carried out in the fifth month.

52 of the study subjects were in the late stage of the second trimester while 116 were in the third trimester. All pregnant women attending ante-natal clinic, whose pregnancy was up to 4 months were included. Exclusion criteria consisted of non-pregnant women, women in the early stages (less than 4 months) of pregnancy and pregnant women with severe organic diseases and those with sexually transmitted infections.

Specimen collection: five millilitres (5mls) of venous blood sample was collected from each subject using sterile disposable needle and syringe. Two millilitres (2mls) each of blood specimen was dispensed into properly labelled bottle containing Ethylene Diamine Tetra-acetic Acid (EDTA) and also into a plain specimen bottle. The remaining 1ml of blood was dispensed into a properly labelled specimen bottle containing 3.8% Trisodium citrate at a ratio of one volume of anticoagulant to nine volumes of whole blood.

3. SPECIMEN ANALYSIS

Blood pressure for each subject was taken at the point of blood specimen collection. Haematocrit determinations were carried out by centrifuging blood collected into microhaematocrit tubes from the EDTA bottle in a haematocrit centrifuge at 5,000rpm for five minutes.

The Erythrocyte Sedimentation Rate (ESR) was done for each subject by the Westergren method using blood from the trisodium citrate bottle. Briefly, whole blood from citrate anticoagulant bottle was drawn into a Westergren tube and kept in the ESR stand in a vertical position for the red blood cells to sediment. Result for each specimen was read after 1 hour. The total serum protein was carried out by analyzing serum obtained from the plain bottles by the Biuret method (SeraPak), while the serum albumin was determined by the Bromo-Cresol Green method. The optical density (O.D) of the tests for each specimen was read spectrophotometrically at 460nm and 620nm respectively after incubation. The serum globulin level was determined by deduction of the albumin value from the serum total protein.

4. DATA ANALYSIS

The data generated from this study was collated and analyzed statistically using the chi-square test. The p-value for the chi-square test to determine the level of significance was set at 0.05. Appropriate tables were set up which were then converted to charts, while charts were plotted to illustrate the results obtained.

5. RESULTS

The demographic data revealed a majority of pregnant women (47.6%) falling within the age bracket 26-30 years. The mean age of study subjects is 21 years. Multiparous women (women who have had a baby or more previously) numbered 87 out of the 164 subjects, while 75 (45%) were first time pregnancies (nulliparous). Two subjects did not disclose this required information. One hundred and twenty (73.8%) of the total number had total serum protein values within the range 6.0-8.0g/dl, whereas two (2) subjects representing 1.2% fell below this level. Twenty (20) other subjects (11.9%) exceeded the 8.0g/dl acceptable upper limit of the reference range. Ninety-nine (99) pregnant women (59%) had erythrocyte sedimentation rate (ESR) values greater than 20mm/hr (Westergren); the remaining 67 women had ESR values between 1mm/hr and 20mm/hr, a range considered to be the acceptable for normal, non-pregnant women of child-bearing age. The majority of women were found to be anaemic. 67 subjects (39%) had haematocrit values lower than 30%. Another 65 women had PCV values in the range 30% - 34% while only thirty-four (20.7%) had haematocrit values between 35% and 44%.

Of all the parameters tested (Haematocrit, Serum total protein, Albumin and ESR) to determine their relationship with the blood pressure of pregnant women, only the Erythrocyte Sedimentation Rate (ESR) had a significant association with blood pressure changes in pregnancy, ($p<0.05$). Sixty-eight (40%) women, out of the total 88 subjects who were multiparous had blood pressure above the normal range (i.e a systolic that is 140 and above, or a diastolic of 100 and above or having both combined). Forty-two of the seventy-four nulliparous or first time pregnant women had normal blood pressure, while the remaining thirty-two had blood pressure above the normal range. In general, forty (23.8%) pregnant women had blood pressure values that are above the normal. The rest of the lot, 128 in number had blood pressure values that were within normal limits. Among this number, only fourteen women had a history of high blood pressure predating pregnancy. It was also observed that parity had a significant effect on the pregnant women's blood pressure, ($p<0.05$). Parity also had a significant effect on the erythrocyte sedimentation rate (ESR), ($p<0.05$). On the contrary, parity did not have any significant effect on any of the other parameters.

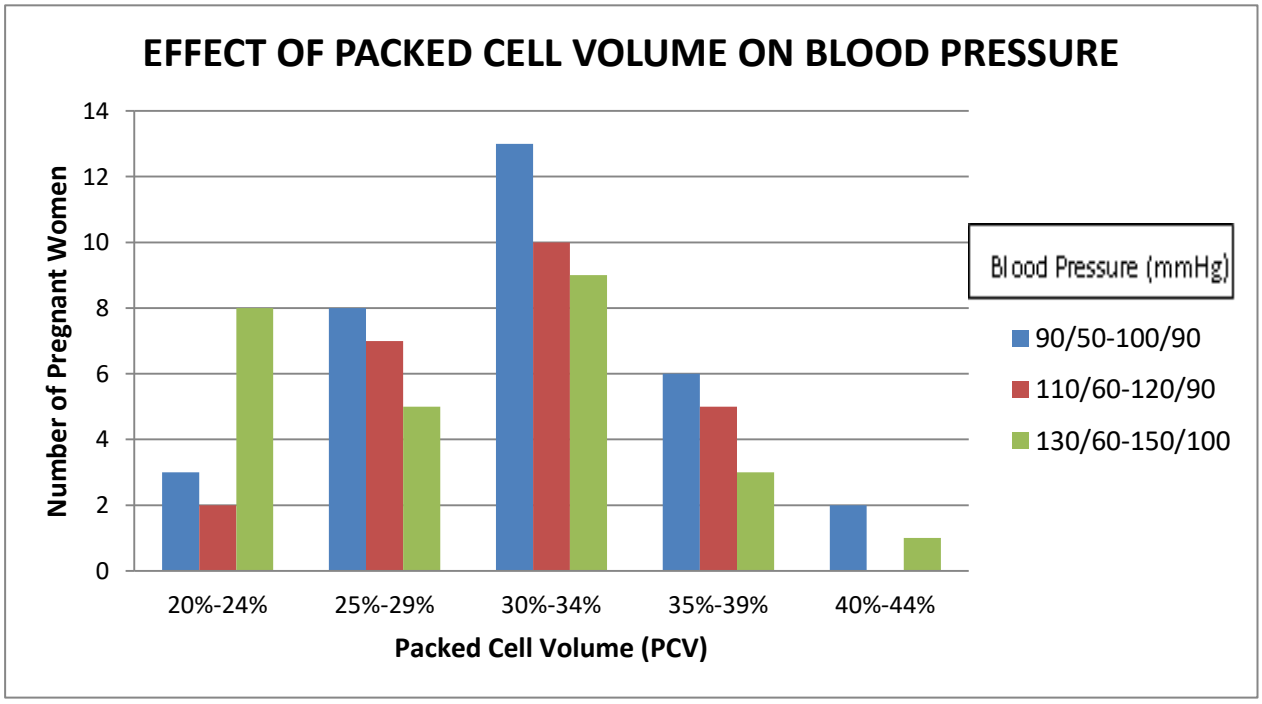

Fig. 1 The effect of Haematocrit on Blood Pressure measurement

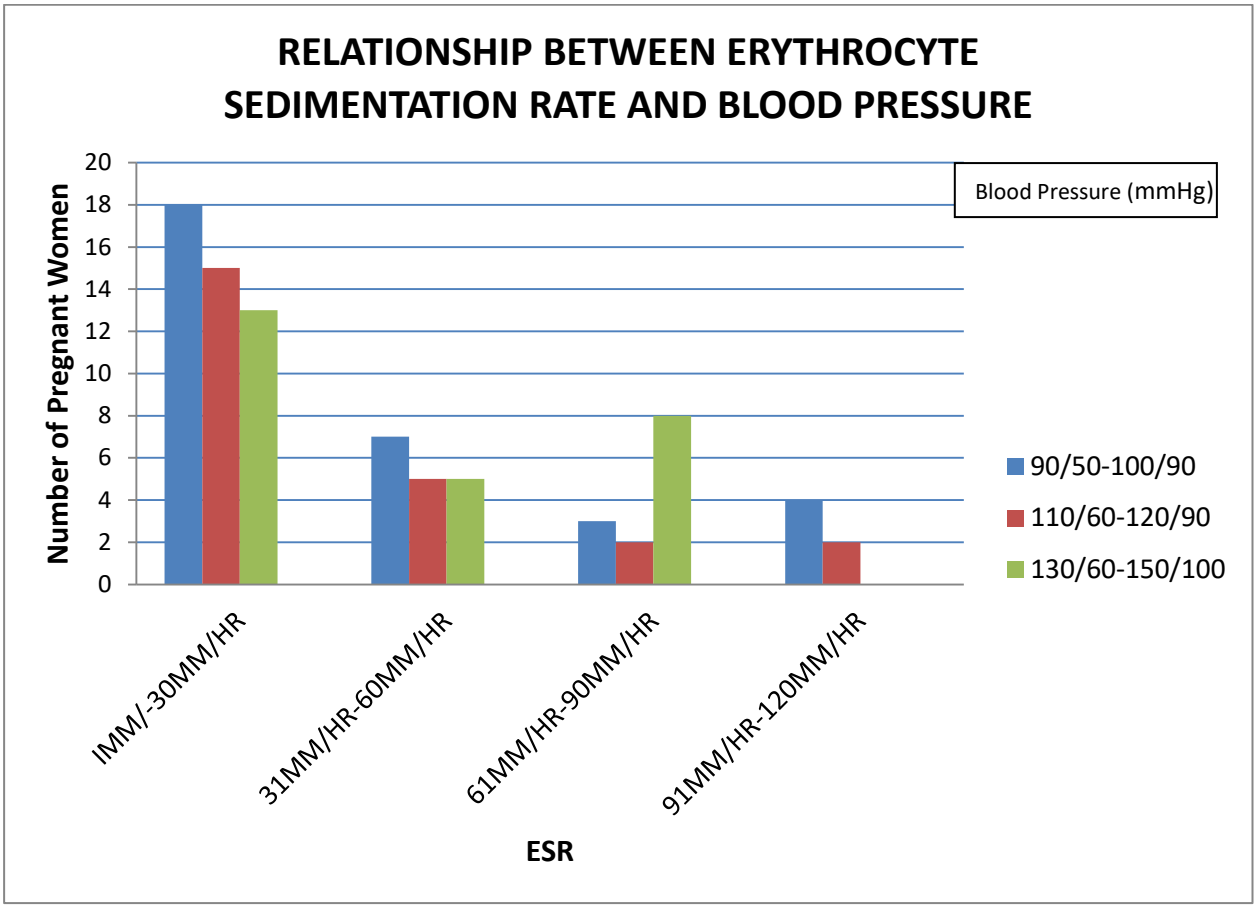

Fig.2 The relationship between ESR and Blood Pressure

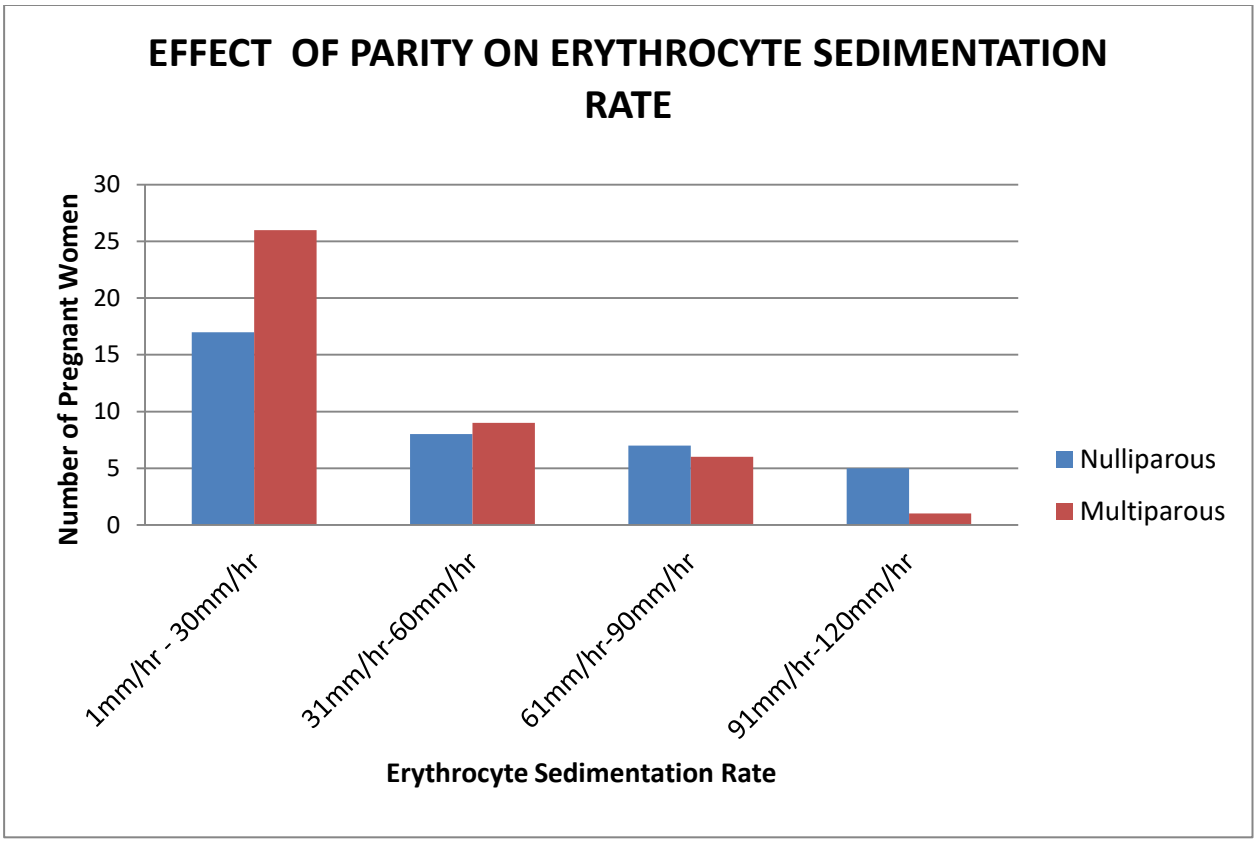

Fig.3 The effect of parity on Erythrocyte Sedimentation Rate measurement

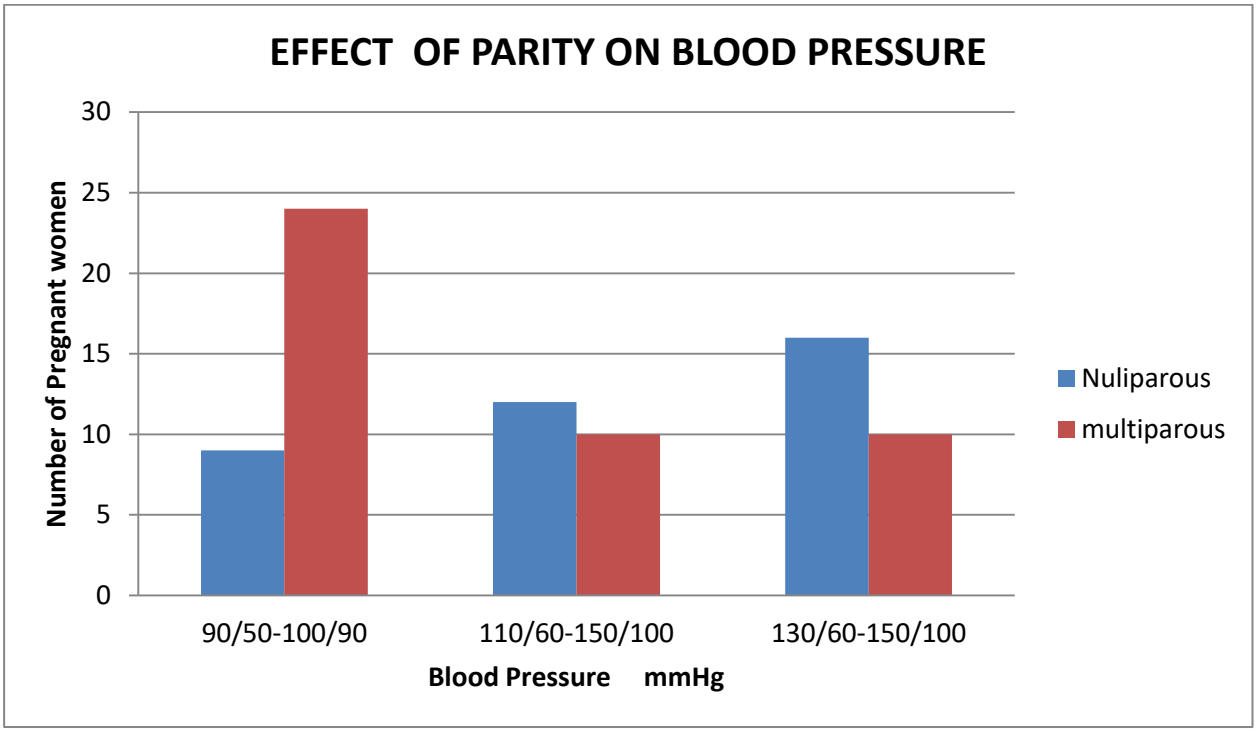

Fig. 4 The effect of Parity on Blood Pressure measurement

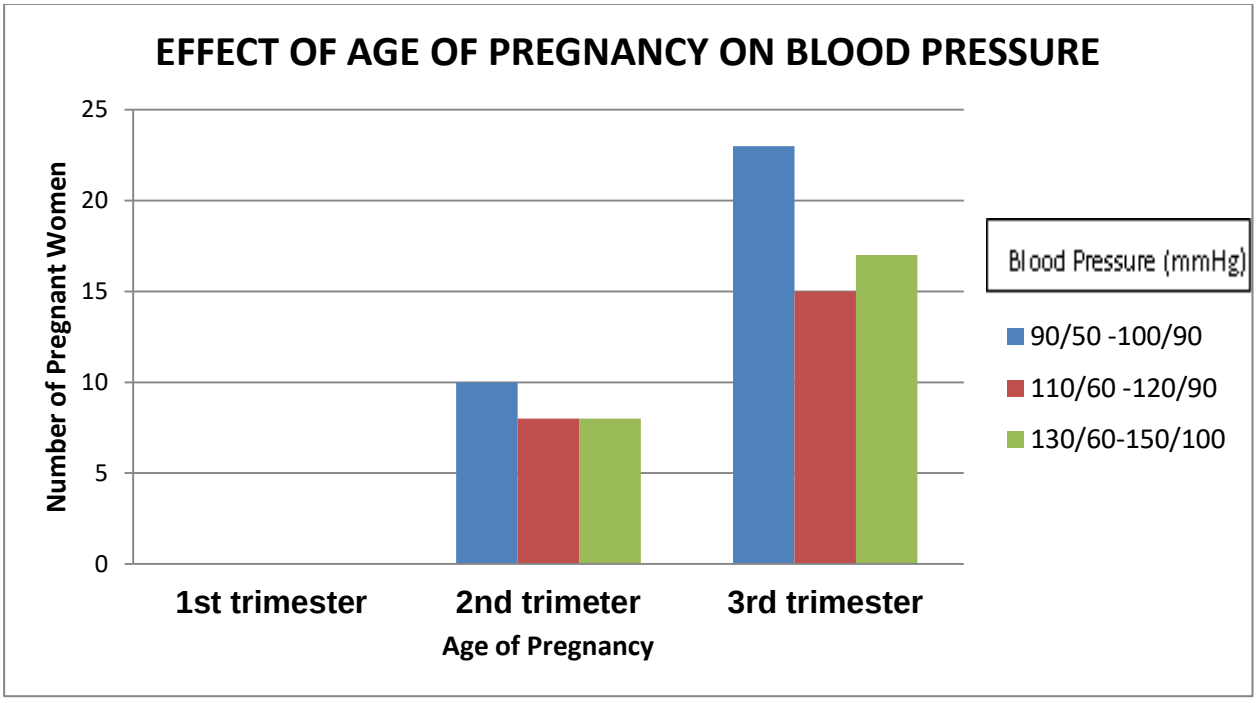

Fig. 5 The effect of gestational age on the measurement of Blood Pressure

6. DISCUSSION

During pregnancy there are large scale changes of physiological function affecting all body systems. These changes represent a positive preparation to accommodate the developing foetus. However, some of these changes exert deleterious effects on maternal health. This study was initiated to assess certain rheological parameters and their relationship with the blood pressure of women in pregnancy. The parameters assessed in this study include the haematocrit, the serum proteins and the erythrocyte sedimentation rate (ESR). Certain rheological variables have been known to affect blood pressure changes in individuals. Among these are: the diameter of the blood vessel, haematocrit level, serum protein concentration, serum fibrinogen level and the viscosity of the blood at any point in time (Koenig *et al.*, 1998). Of particular importance

is the contribution of plasma fibrinogen, being a factor that determines to a great extent, the plasma viscosity and its ability to contribute a small portion to serum protein concentrations. Reports from different workers show that there is hyperfibrinogenaemia in pregnant women (Wright *et al.,* 1988*;* Kanetas *et al.*, 2001*;* Salawu and Durosinmi, 2001). According to Chace *et al*., (2003), plasma concentration of fibrinogen increases approximately 65% in pregnancy and this contributes to the increased sedimentation rate. The increased concentration of fibrinogen could be due to enhanced synthesis and utilization in the utero-placental circulation or hormonal changes or both, with oestrogen in particular being in high concentration (Harkness, 1971). The increased fibrinogen concentration in this condition is therefore expected to lead to increased plasma viscosity. However, changes in the concentration of one or more of the plasma protein fractions could also lead to a change in plasma viscosity and thus plays a significant role in haemorheology (Harkness, 1971).

In this study, we found that there was a mean increase in ESR during pregnancy. These results reiterate the already established belief that erythrocyte sedimentation rate increases during pregnancy. From previous research works, it has been found that gestational age and haemoglobin concentration both significantly influenced erythrocyte sedimentation rate (van den Broer and Letsky, 2001).

The erythrocyte sedimentation rate is one of the measurements of the acute phase response (Koller *et al.,* 1980). It is helpful in detecting the presence of inflammation and its response to treatment. It is influenced by anaemia, which may be present in inflammatory diseases, and by the proteins of the acute phase response, factors which are both commonly present in pregnancy. In this study, we were able to determine only the haematocrit, the serum protein concentration and the erythrocyte sedimentation rate (ESR) as an indirect assessment of blood viscosity since a direct assay of viscosity and plasma fibrinogen was not possible as a result of resource constraints. ESR assessment in this wise is reasonable since the key protein responsible for viscosity is fibrinogen and the same fibrinogen is mainly responsible for ESR changes in disease conditions. In this study, the ESR of the subjects had a significant effect on blood pressure changes in pregnancy ($p<0.05$). This implies that ESR as a test could be used to predict the possibility of significant changes in blood pressure during pregnancy.

One hundred and twenty-eight of the one hundred and sixty eight subjects had total serum protein values within the acceptable range for normal individuals. It may therefore not be wrong to conclude that pregnancy does not bring about significant increases in total serum protein. Even if it does, it is not reflected in its relationship with the erythrocyte sedimentation rate results obtained in this study. This is validated by the statistical analysis of data; ($p>0.05$). Albumin constitutes the major fraction of serum proteins. Albumin concentration falls early in pregnancy, partly due to haemodilution; a factor which is responsible for the fall in total protein concentration in pregnancy (Hytten, 1991). Moreover, albumin synthesis rate is decreased by inflammatory cytokines (Clarke *et al*., 1995)

While this study shows that there is no significant association between blood pressure in pregnancy and albumin, there is also no significant association between serum total protein and blood pressure changes in pregnancy. It is expected that serum levels of protein would be affected by the albumin constituent since albumin is the major protein in blood. The likely reason for the protein level having no impact on the woman's blood pressure would be pregnancy-associated haemodilution. In addition, the foetus also utilizes the proteins for growth as a result of which the maternal serum protein levels do not rise significantly. There is however, a significant association between globulin level in blood and blood pressure in pregnancy, ($p<0.05$). This may partly explain the association between ESR and blood pressure in pregnancy. According to Ochei and Kolhatkar, (2008), the changes in the proportion of the soluble constituents of plasma such as increased fibrinogen or globulin also results in increased rate of erythrocyte fall. Although a fibrinogen assay was not carried out on the subjects, it is known that certain serum proteins - fibrinogen for instance - do contribute to blood viscosity, and blood viscosity significantly affects an individual's blood pressure.

One hundred and thirty two persons had haematocrit levels that are below the normal range for women. Only thirty-four had haematocrit values that are normal. It is known that haematocrit values of most women fall during pregnancy due to haemodilution and increased demand for iron and other supplements by the growing foetus (Kanetas *et al*., 2001). In addition, because many women tend to suffer loss of appetite during this period, nutritional deficiency resulting in nutritional anaemia may occur. Although low levels of haematocrit values were found in this study, there is no significant association between blood pressure changes in pregnancy and haematocrit values.

Age of pregnancy also had a significant effect on blood pressure. In this study, most of the pregnancies were in the 3rd trimester. In other words, the majority of the subjects assessed were already in the late stage of pregnancy. This stage is

usually associated with significant physiological changes in the pregnant woman and severe inflammatory changes at that, thus bringing about raised tension in such women (Redman *et al*., 2010).

The individual woman's parity also affects the blood pressure going by the results obtained in this study, with the *p* value ($p<0.05$) showing a significant association between parity and blood pressure. Blood pressure is higher in women who have had one or more children than in nulliparous women. There is the likelihood that previous pregnancies might have induced inflammatory stress on the affected women which is further exacerbated by their current condition. The result in this study implies that acute phase proteins released in response to the trauma induced by the pregnancy increases with each subsequent pregnancy. The stimulus for production is likely to be pro-inflammatory cytokines such as interleukin-1, interleukin 6 and tumour necrosis factor (TNF). Therefore, a raised blood pressure may be expected in women who have had a previous pregnancy since a build-up of inflammatory cytokines increase with each subsequent pregnancy**.** Such women are therefore likely to be susceptible to blood pressure-related complications.

Taken together, this study shows that ESR measurements adequately reflect the true haemorheological status of the pregnant woman as the age of the foetus advances.

7. CONCLUSION

The blood erythrocyte sedimentation rate (ESR) may be used as an adjunct to urinalysis for predicting late-stage pregnancy complications associated with high blood pressure in low resource-settings. However, a correlative study of ESR and blood pressure changes in pregnancy would need to be undertaken to validate this suggestion.

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