European Journal of Biology and Medical Science Research
Vol.8, No.3, pp.28-42, June 2020
Published by ECRTD- UK
Print ISSN: ISSN 2053-406X, Online ISSN: ISSN 2053-4078

CHANGES IN BLOOD C-REACTIVE PROTEIN IN PREGNANCY AND LABOUR AMONG APPARENTLY HEALTHY PREGNANT WOMEN IN BENIN CITY

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ABSTRACT: C-*reactive protein (CRP), a very sensitive marker, has recently been associated with inflammatory conditions and their management. Pregnancy is a pro-inflammatory state associated with changes in CRP values. Proper interpretation of CRP levels in inflammatory conditions requires good knowledge of these changes. However, most studies and reference values obtained on serum CRP in pregnancy were done in developed western countries. Regional differences in the level of CRP have been reported. It was imperative, therefore, to determine local reference values for CRP in apparently healthy pregnant women in our setting to serve as nomograms. Methods: Longitudinal case-control study with 160 women who met the criteria recruited. These were divided into two arms comprising of study and control, each consisting of 80 women. Maternal serum CRP was measured with competitive immunoassay in the first and second half of pregnancy and labour as women were followed up. Specimens were also obtained for CRP from the control group. Data obtained were analysed using the SPSS version 17 and GraphPad instant 3 software. Categorical variables were expressed as absolute numbers, and percentages and the differences in proportion were analysed using the Chi-square test or Fisher exact test, while continuous variables were presented as means with standard deviations and the differences were analysed with the t-test where appropriate. The level of significance was set as $p<0.05$. Result: Revealed a progressive increase in the C reactive protein concentration as pregnancy advanced. The rise however attained maximum level during labour. Statistical significance noted for that of labour against non-pregnant as control ($p<0.05$). Conclusion: C-reactive protein levels may serve as a marker for disease severity, though non-specific. The study shows that serum concentration of C-reactive protein in normal pregnancy for women in our environment should be 82.62 ± 32.19 ng/ml. Also, levels of concentration are increased during labour compared to non-pregnant and pregnant women with a mean value of 93.46 ± 24.00 ng/ml. Therefore, it could be of prognostic value in some pregnancy-associated complications such as preterm labour, premature rupture of membrane, chorioamnionitis, pre-eclampsia and diabetes mellitus.*

KEYWORDS: C-reactive protein, pregnancy, labour.

INTRODUCTION

In Nigeria, maternal and perinatal morbidity and mortality rate are among the highest in the world (Onuh and Aisien 2004, Nafiu, Kabir et al. 2016). A significant proportion is due to pregnancy complications caused by endothelial dysfunction. These include systemic inflammation such as pre-eclampsia and eclampsia, preterm labour and premature rupture of membrane,

chorioamnionitis and septicaemia (Wang, Gu et al. 2004, Chen, Zhang et al. 2018). C reactive protein, an inflammatory marker, has been associated with several diseases with systemic inflammation, endothelial dysfunction and recently, insulin resistance arousing considerable interest worldwide(Maguire, Power et al. 2015). Several studies have analysed serum C-reactive protein at different stages of pregnancy to investigate its association with various pregnancy complications associated with endothelial dysfunction and systemic inflammation. (Teran, Escudero et al. 2005, John, Mohamed Yusof et al. 2018) However, pregnancy itself is pro-inflammatory, and changes in C reactive protein level have been documented. The appropriate interpretation of C reactive protein level in pregnancy is incumbent on done the knowledge of these temporal changes. (Zhang, Luo et al. 2018).

C reactive protein is an acute-phase protein. It was first discovered by Tillet and Francis in 1930 (Francis and Tillett 1930) as a substance in patients serum with acute inflammation when reacted with the C polysaccharide of pneumococcus and subsequently named as such. It is an acute-phase reactant produced by the hepatocytes in response to interleukin 6 and other cytokines released during inflammation, malignancy, necrotic tissues and autoimmune disorders. (Kara, Guney et al. 2019, M, A et al. 2019) Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells and some types of bacteria, thus activating the complement system. It also enhances phagocytosis by macrophages through the process of opsonisation, (Sarween, Drayson et al. 2018), therefore participating in the clearance of necrotic and apoptotic cells and modulation of the inflammatory process. (Park, Park et al. 2019).

When compared to other markers of acute inflammation such as erythrocyte sedimentation rate, caeruloplasmin, haptoglobin and White blood cell count, C-reactive protein, has the unique property of being rapidly produced within 2 hours of an acute insult, rising to 50,000-fold within 6 hours of acute inflammation and reaching a peak at about 48 hours after the onset of an insult. (Sproston and Ashworth 2018, Denney, Waters et al. 2019) Similarly, because of its relatively short half-life of about 18 hours, its concentration rapidly declines following the resolution of the insult making it an ideal marker for early detection, monitoring of the progress of inflammatory conditions and response to pharmacological treatment within the body. (Sproston, El Mohtadi et al. 2018, Kianpour, Saadatmand et al. 2019) However, because there are large numbers of different conditions that can increase C-reactive protein production, an elevated C-reactive protein level does not diagnose a specific disease; instead, it provides support for the presence of inflammatory disease. (Chen, Zhang et al. 2018, Sproston, El Mohtadi et al. 2018) Measuring of blood C-reactive protein level, therefore, is a sensitive but nonspecific screening method for infectious and inflammatory diseases. (Chen, Zhang et al. 2018) While acute elevation in C-reactive protein has generally been accepted as an index of acute inflammation, the more subtle elevation of C-reactive protein has been proposed as an indication of biological ageing, which is a non-inflammatory condition. (Asadi, Faraji et al. 2019, Huang, Tian et al. 2020) .

Recently developed highly sensitive enzyme-linked immunosorbent assays (ELISA), have lowered the discriminatory range for serum C reactive protein values from 10mg/L to <1mg/L. It has proven highly valuable in detecting subclinical elevation in serum C reactive protein

level(Alyas, Roohi et al. 2019); a condition recently identified as a marker of endothelial damage, atherogenesis and cardiovascular disease in non-pregnant patients(Kong, Wang et al. 2018, Tanz, Stuart et al. 2018). These methods unlike conventional C reactive protein assay, allow for accurate measurement of a very low level of serum C reactive protein and permit the investigation of normal serum C reactive protein in apparently healthy individuals as a nomogram(Sproston and Ashworth 2018). Normal systemic C reactive protein levels classified as less than 5 mg/l with the average for sedentary or general population assay level estimated as less than 2 mg/l(Chen, Zhang et al. 2018). There is no difference in serum concentration between male and female genders, and neither is there a diurnal nor a nocturnal seasonal variation in serum C reactive protein level (Kianpour, Saadatmand et al. 2019). It is also not generally affected by dietary intake (Ragsdale, Kuzawa et al. 2019). However, body mass index (BMI), exercise, race, ingestion of caffeine, long term use of multivitamin, long term use of oral contraceptive pills, hormone replacement therapy, along with pregnancy and labour have all been noted to affect C reactive protein levels in the absence of inflammation (Vecchie, Bonaventura et al. 2018, Huang, Tian et al. 2020).

The place of C reactive protein in the evaluation of cardiovascular diseases has been demonstrated in the literature (Vecchie, Bonaventura et al. 2018, Kianpour, Saadatmand et al. 2019). Its screening and diagnostic role in some pregnancy complications such as preterm labour, premature rupture of membrane, chorioamnionitis, preeclampsia/eclampsia and gestational diabetes have been established in most developed countries (Chen, Zhang et al. 2018, Raio, Bersinger et al. 2019). Unfortunately, many of these diseases are of particular health importance to Sub Saharan Africa. Paradoxically, there is the paucity of studies in sub-Saharan Africa where the burden of these diseases/complications seem to be highest worldwide, contributing significantly to the high perinatal and maternal morbidities and mortality rates in this region (Olopade and Lawoyin 2008, Vecchie, Bonaventura et al. 2018).

In a few studies done in this part of the world, the interpretation of results has been a challenge due to lack of consensus on the reference value (Costello, Osrin et al. 2004, Denney, Waters et al. 2019). Thus, the need for studies becomes imperative. Therefore, make for ease of interpretation and proper utilization of C reactive protein as a marker to detect and manage the full range of inflammatory obstetric conditions in Nigeria.

CRP is a simple inflammatory marker is a sensitive tool whose properties play a vital role in obstetrics and gynaecology. Though its uses are still evolving, it is quite evident that it has a critical role in many inflammatory conditions worldwide and even more importantly, in the tropics. With the racial differences highlighted in the literature(Maguire, Power et al. 2015, Mertens, Muys et al. 2019), importation of values used overseas may interpret CRP erroneous in our environment. Until proper studies highlighting the normal range of CRP in uncomplicated pregnancies, CRP may not be useful for clinical management of many of the diseases we contend within sub-Saharan Africa (Asadi, Faraji et al. 2019). For paucity of such studies in our environment, it is therefore essential to establish the changes in the values of CRP associated with pregnancy, labour and puerperium.

MATERIALS AND METHODS

The study was conducted at the Obstetrics and Gynaecology Department of the University of Benin Teaching Hospital, Benin City. The University of Benin Teaching Hospital serves as a major referral centre for Edo, Delta, Kogi and Ondo States with an annual birth rate of about 2500 deliveries. Patients usually referred from general hospitals, government-owned health centres, private hospitals and from other departments in the hospital. The patients are generally from different socioeconomic settings, and a significant number educated.

Study Design

It Was A Longitudinal case-control study on pregnant women with healthy, uncomplicated pregnancies selected equally from the first and second halves of pregnancy and during labour in the University of Benin Teaching Hospital. Equal numbers of normal non-pregnant women in the reproductive age group were also selected to form a control group.

Selection of Subjects

Potential subjects who met the inclusion criteria were selected. These were women with singleton foetus with an uncomplicated pregnancy. These patients had a history of excluding infection in 2 weeks. Examination to exclude fever, tachycardia, BP monitoring and a detailed obstetric examination and a vaginal examination to exclude vaginal discharge. White blood cell count done was within the normal range, and both medical and obstetric pathologies excluded. While for those weighing more than 90kg or who met the criteria for screening for GDM had OGTT screening at contact and 28 weeks.

Calculation of Sample Size

The calculation is as shown below using the formula for calculating sample size for a longitudinal study comparing two groups across time.

$$N = \frac{2(z\alpha + z\beta)^2(1+(n-1)\rho)}{n[(\mu 1-\mu 2)/\sigma]2}$$

- σ^2 is the assumed common variance in the two groups
- $\mu 1 - \mu 2$ is the difference in means of the two groups
- n is the number of time points
- ρ is the assumed correlation of the repeated measures
- $z\alpha = 1.96$ 2-tailed .05 hypothesis test
- $z\beta = .842$ power = .8
- effect size $(\mu 1 - \mu 2)/\sigma = .5$
- n = 3 time points
- $\rho = .6$ correlation of repeated measures

$$N = \frac{2(1.96+0.842)^2(1+(3-1)\times 0.6)}{2\times(0.5)^2}$$

$$= \frac{(15.70241)(2.2)}{(2)(0.25)}$$

= 69.09

i.e. approximately 70 subjects for study and another 70 women for control.
With an attrition rate of 10%, about 80 patients per group required.

Ethical Considerations

Approval for this study obtained from the Research Ethical Committee of the University of Benin Teaching Hospital. Also, the study carefully explained to the patients and informed consent obtained before being recruited into the study. The right of patients to or not to participate was respected.

Data Management

The generated database was analysed with a personal computer using the SPSS version 20 and Graph Pad In stat 3. Categorical variables expressed as absolute numbers, and percentages and the differences in proportion was analysed using the Chi-square test where appropriate. In contrast, continuous variables presented as means with standard deviations and the variations analysed with the *t*-test and Analysis of Variance (ANOVA). The level of significance was set at $p<0.05$. The researchers provided funding for the study.

RESULTS

This study included 80 pregnant women and 80 non-pregnant women. Table 1 summarizes the demographic characteristics of patients studied and listed normal range and mean value of CRP in the first, second halves of pregnancy and normal range and mean value of CRP in labour. There were no statistically significant differences in the serum CRP in pregnant females when compared to the control group. (Table 2). The mean and standard deviation of CRP at I^{st} and 2^{nd} halves of pregnancy (MEAN PREG) was 82.62 ± 32.19, and that of labour was 93.46 ± 24.00, while that of non-pregnant as control was 81.20 ±32.96. The variations recorded in the CRP across these categories, when subjected to one-way analysis of variance (ANOVA) indicated a state of significant difference ($p<0.05$). Further tests (Duncan multiple ranges) to test the source of the difference showed that the mean value of CRP recorded during labour was significantly higher ($p = 0.02$) than those of mean pregnancy against the control (CRP). The Duncan multiple ranges further indicated that the mean level of CRP recorded during the first and second half of pregnancy was not statistically different from each other. The BMI categories adopted from Japan Society for the Study of Obesity (2008). The CRP tested using the non-parametric analysis of variance (Kruskal-Wallis). None of the samples fell into the underweight group (>18.5). The variations observed across the categories when subjected to *Kruskal-Wallis* tests indicated a state of insignificant difference ($p = 0.936$). Hence, we can conclude that BMI exhibits (causes) no significant change in CRP (Table 3).

The linear regression analysis performed to determine the relationship between maternal weight and CRP during pregnancy. It showed that the sign of the coefficient of weight is negative; this implies that CRP in pregnancy decreases as weight in pregnancy increases. Furthermore, the coefficient of determination was very low at 0.002; therefore, only about 0.2% of the variation in the CRP data was explained by maternal weight, while the remaining 99.98% was left unaccounted. Therefore, maternal weight is not a useful predictor of CRP in pregnancy.

The individual statistical significance of the independent variable as indicated by the t-statistics, shows that maternal weight did not pass the significant test at 5% level of significance with t statistic value of -0.426. Implies that maternal weight did not contribute significantly to CRP in pregnancy during the period studied. The Durbin – Watson statistics test value of 1.89 could be approximated to 2.0 indicating the absence of serial autocorrelation in the model; hence the findings of the model could be relied upon (Table 4).

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Table 1: Normal range and mean value of CRP in the first and second halves of pregnancy and labour

	1st half of preg. Mean CRP (range) [ng/ml]		**2nd half of preg. Mean CRP (range) [ng/ml]**		**Labour Mean CRP (range) [ng/ml]**		**p-Value**
Age (years)							p>0.05
< 19	42.95 ± 3.46	(40.5 – 45.4)	43.45 ± 4.17	(40.5 – 46.4)	48.95 ± 2.06	(47.5 – 50.4)	
20-24	75.74 ± 33.41	(20.0 – 106.9)	78.51 ± 34.37	(20.5 – 107.9)	87.79 ± 35.84	(30.5 – 119.5)	
25-29	84.95 ± 33.60	(10.4 – 115.0)	84.84 ± 33.31	(10.5 – 110.2)	91.26 ± 34.21	(12.5 – 115.8)	
30-34	80.48 ± 30.97	(25.0 – 110.5)	80.89 ± 30.65	(25.8 – 111.0)	87.42 ± 33.21	(25.0 – 115.9)	
≥ 35	77.44 ± 32.28	(21.0 – 110.1)	77.88 ± 32.66	(22.0 – 111.1)	82.44 ± 33.64	(23.1 – 120.3)	
Parity							p>0.05
P 0	81.11 ± 27.31	(40.0 – 115.0)	79.35 ± 25.19	(40.5 – 100.6)	91.96 ± 29.46	(47.5 – 120.3)	
P 1-4	79.63 ± 32.91	(10.4 – 110.5)	81.00 ± 33.14	(10.5 – 111.1)	85.36 ± 34.40	(12.5 – 115.9)	
P5 and above	59.02 ± 43.97	(30.5 – 109.7)	56.57 ± 46.89	(28.5 – 110.7)	62.36 ± 42.81	(37.0 – 111.8)	
LOE							p>0.05
No formal ed.	30.00 ± 0.0		35.56 ± 0.00		46.90 ± 0.00		
Pry	86.78 ± 26.99	(12.0 – 115.0)	87.06 ± 27.11	(10.5 – 111.1)	93.62 ± 29.09	(14.5 – 119.5)	
Secondary	77.08 ± 32.59	(21.0 – 110.5)	76.33 ± 32.69	(22.0 – 110.7)	84.05 ± 35.05	(23.1 – 120.3)	
Tertiary	73.34 ± 36.01	(10.4 – 109.2)	74.39 ± 36.27	(11.4 – 110.2)	79.20 ± 37.10	(12.5 – 115.4)	
Social Status							p>0.05
1	83.55 ± 28.95	(30.2 – 108.7)	84.41 ± 29.13	(31.2 – 109.7)	92.55 ± 29.53	(32.3 – 115.3)	
2	74.15 ± 35.36	(10.4 – 109.5)	75.51 ± 35.43	(11.4 – 110.2)	79.26 ± 37.87	(12.5 – 120.3)	
3	69.06 ± 36.86	(20.0 – 110.0)	69.25 ± 37.70	(20.5 – 111.0)	74.49 ± 36.76	(23.1 – 115.7)	
4	83.00 ± 27.79	(29.3 – 110.5)	84.60 ± 28.01	(28.5 – 107.9)	92.56 ± 31.17	(31.4 – 119.5)	
5	84.00 ± 32.49	(12.0 – 115.0)	82.57 ± 31.70	(10.5 – 111.1)	89.46 ± 32.57	(14.5 – 115.7)	

LOE = Level of Education
Social Class using Olusanya *et al*.

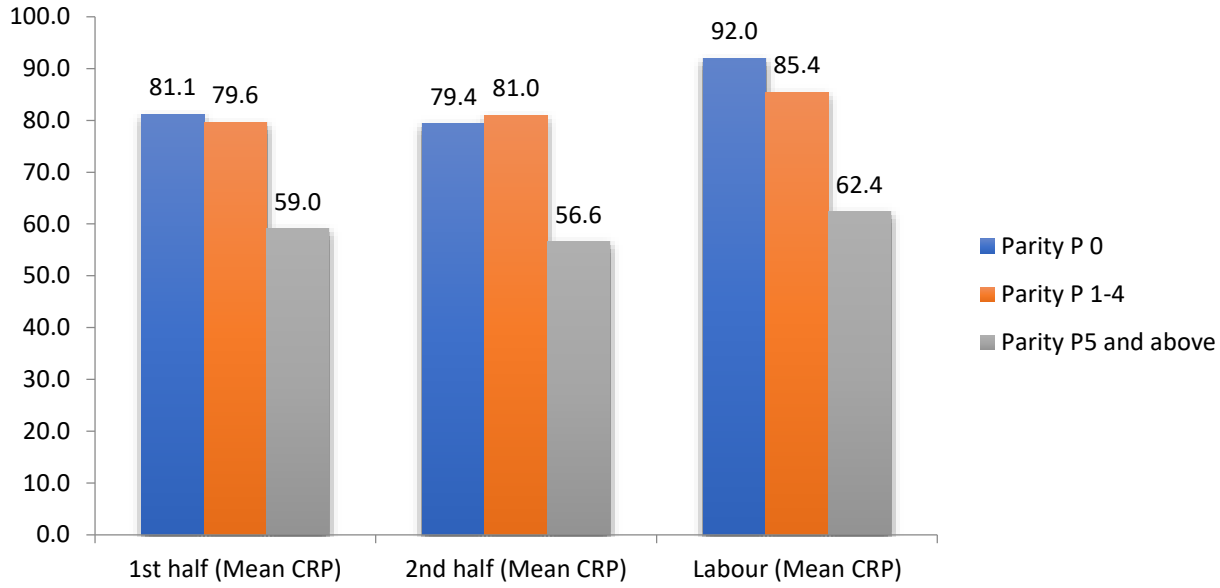

Fig. 2. The distribution of mean CRP by the respondents' parity.

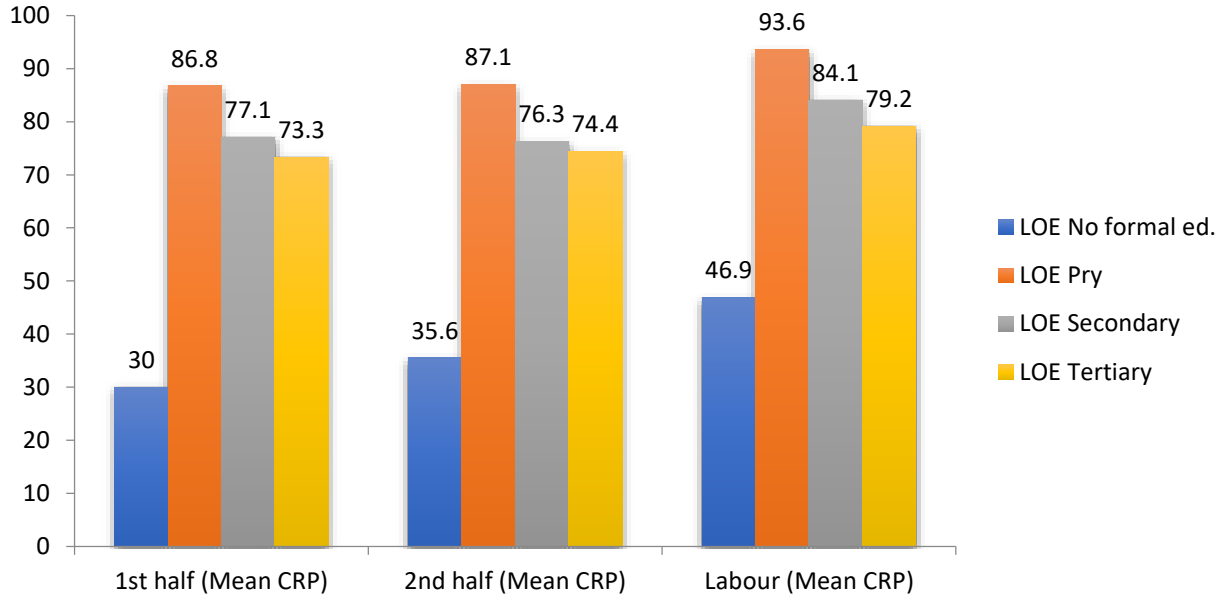

Fig. 3. The distribution of mean CRP by the respondents' level of education (LOE)

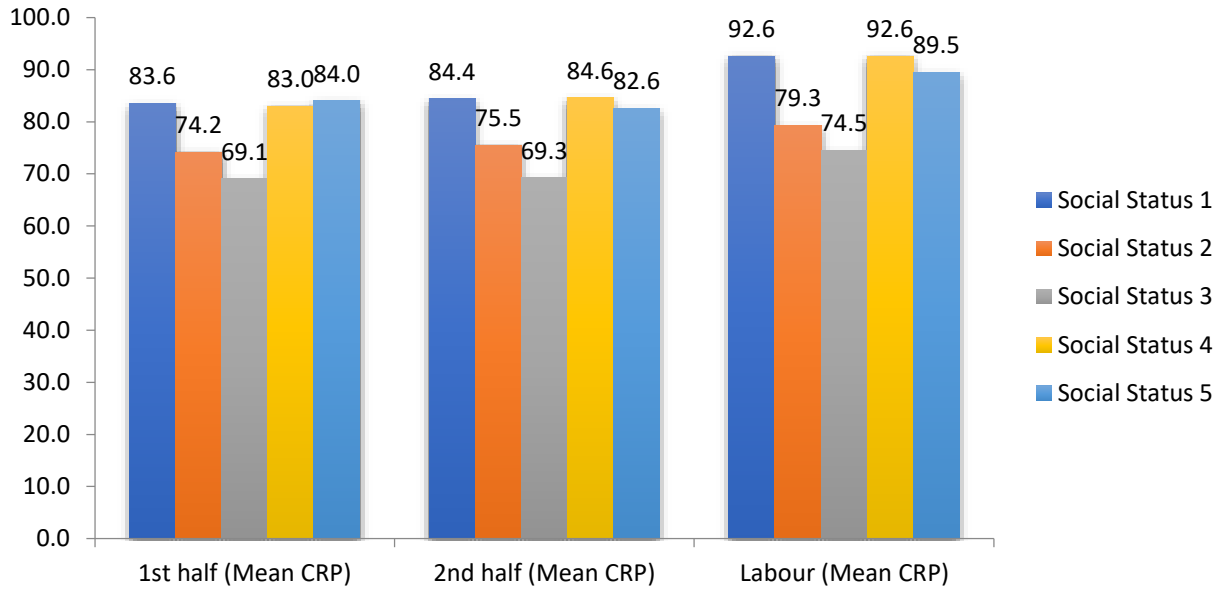

Fig. 4. The distribution of mean CRP by the respondents' social status.

Table 2: Comparison of CRP between subjects in Pregnancy, 1st trimester, second trimester and labour with Control Group

	MEAN PREG	**LABOUR**	**CONTROL**		
	Mean± SD (Min-Max)	Mean± SD (Min-Max)	Mean± SD (Min-Max)	F-Value	p-VALUE
CRP ng/ml	82.62 ^{B} ±32.19 (10.90-114.50)	93.46 ^{A} ±24.00 (12.40-126.30)	81.20 ^{B} ±32.96 (10.40-110.10)	4.00	p<0.05

p<0.05 – Significant Difference
Similar Superscript in a row – No Significant Difference

Table 3: Relationship between CRP and BMI

BMI Category (kg/m^2)	**BMI Range *(Source: Japan, 2008)***	**C-Reactive Protein Mean±SD**	**p-VALUE**
Under weight	< 18.5	-nil-	
Normal Range	18.5 to 24.99	88.26 ± 31.70	P>0.05
Overweight	25.0 to 30.0	76.62 ± 33.63	
Obese	> 30	82.91 ± 32.76	

P>0.05 = Not Significant

Table 4: Linear Regression model specifying that CRP in pregnancy is a function of maternal weight

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics		Durbin-Watson
					R Square Change	F Change	
1	.048	0.002	-0.01	33.12989	0.002	0.182	1.89

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	T-stat	Sig.
		B	Std. Error	Beta		
1	(Constant)	93.67	29.494		3.176	0.002
	WEIGHT	-0.154	0.361	-0.048	-0.426	**0.671**

DISCUSSION

Inflammation is an integral part of a healthy pregnancy process (Kara, Guney et al. 2019, Alonso-Ventura, Li et al. 2020). The activities of the inflammatory cells play a central role during implantation and decidualisation in the first few weeks of pregnancy (Chen, Zhang et al. 2018). Also, pivotal in the trigger of uterine activation culminating in successful labour and delivery (Kara, Guney et al. 2019). However, the inflammatory process is subject to some forms of regulation. Thus, create some degree of tolerance at a particular stage of pregnancy to prevent neonatal adverse outcome (Denney, Waters et al. 2019, Chudal, Brown et al. 2020). The diagnostic significance of C reactive protein has been demonstrated in several studies. In this study, we compared the serum levels of CRP of pregnant women during antenatal, labour and delivery with non-pregnant women (control).

The level of CRP in pregnancy was consistently higher than that of non-pregnant women. Though, not statistically significant. This finding is consistent with earlier studies (Holingue, Owusu et al. 2018, Sproston and Ashworth 2018). The increase in CRP in pregnancy orchestrated by the growing foetus triggers the modulation of the immune system with the stages of pregnancy. The placenta development involves a well-coordinated interplay of the angiogenesis and pro-inflammatory cytokines (Raio, Bersinger et al. 2019). The process culminates in the cytokines induced and placenta secretion of CRP in gestation age-dependent manner (Zhang, Luo et al. 2018). The alteration in the interplay process could result in inflammatory outburst, associated with endothelial activation (Vecchié, Bonaventura et al. 2018). The resulted accentuation of the

CRP seen in some adverse pregnancy outcome such as preeclampsia (Raio, Bersinger et al. 2019). Though the mechanism is poorly understood, the angiogenesis and the endothelial activation may explain the place of CRP as a useful marker in the evaluation of the patients with cardiovascular disease (Denney, Waters et al. 2019, Raio, Bersinger et al. 2019). Furthermore, it may explain its role in evaluating women suffering from cardiovascular disease with a previous history of preeclampsia or pregnancy-induced hypertension (PIH) (Chen, Zhang et al. 2018, Vecchie, Bonaventura et al. 2018).

Evidence has shown that its production is not limited to the liver, but the kidneys as well(Tarim, Bağiş et al. 2005). Ghezzi et al. demonstrated the role of amniotic CRP as a marker for preterm delivery (Ghezzi, Franchi et al. 2002). Other adverse pregnancy outcomes include preterm premature rupture of membranes (PROM) and intra-amniotic infection (Borna, Mirzaie et al. 2009, Raio, Bersinger et al. 2019).

Similarly, other studies (Fischer-Suárez, Fernández-Alonso et al. 2016, Huang, Tian et al. 2020). demonstrated an increase in the level of the CRP in pregnancy with a significant increase in labour. The association of labour with the elevation of oestrogen, progesterone and prostaglandins may explain the surge (Kianpour, Saadatmand et al. 2019, Mertens, Muys et al. 2019). Giving credence to the inflammatory process involved in pregnancy and labour. Furthermore, the labour process propagates the activities of Natural killer cells (Vecchié, Bonaventura et al. 2018, Raio, Bersinger et al. 2019) resulting in increased production of IL-1 (Zhang, Luo et al. 2018, Raio, Bersinger et al. 2019). and induction of the hepatic output of C-reactive protein. Also, the production of prostaglandin necessary for cervical ripening and uterine contraction during labour may increase cytokine production and invariably increases C reactive protein production(Kong, Wang et al. 2018). CRP is an acute-phase plasma protein that responds with a rapid rise in serum concentration to infection and tissue injury (Borna, Mirzaie et al. 2009). The process of delivery by vaginal route is primarily associated with tissue injury. Thus, resulting in an exacerbated inflammatory response that extends to the immediate postpartum period (Mertens, Muys et al. 2019).

Conversely, and corroborated by other studies (Kong, Wang et al. 2018, Vecchie, Bonaventura et al. 2018, Karli, Ozdemir et al. 2019) the level of serum CRP at the various stages of pregnancy was independent of age, parity, level of education and socioeconomic status. Ageing can be associated with reduced inflammatory response and elevated inflammatory biomarkers in a phenomenon called inflammaging (Michaud, Balardy et al. 2013). In the absence of any infirmity, the inflammatory markers such as CRP tends to be within the average level.

CRP, as a valuable biomarker, has been shown in the physiological and pathological process(Vecchie, Bonaventura et al. 2018, Denney, Waters et al. 2019). More importantly, its prognostic value in pregnancy-related complications cannot be overemphasized. Therefore, it becomes imperative to establish the benchmarks in pregnancy and labour in our setting.

CONCLUSION AND RECOMMENDATION

The study reveals that the serum concentration of C reactive protein in a healthy pregnancy for women in our environment to be 82.62 ± 32.19 ng/ml. The value tends to increase during labour compared to non-pregnant and pregnant women with a mean value of 93.46 ± 24.00 ng/ml. Therefore, recommended as a prognostic tool in some pregnancy-associated complications. In particular, are cases such as preterm labour, premature rupture of membrane, chorioamnionitis, pre-eclampsia, diabetes mellitus and other similar conditions. The clinical validity of it's monitoring role may be established in more extensive randomized studies.

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