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Effect of Serum High Sensitivity C – Reactive Protein on Pregnancy Outcome in Obese Pregnant Women

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Abstract

Objective: To find out association of serum high sensitivity C - reactive protein (hs-CRP) level with pre-pregnancy weight and adverse pregnancy outcomes in obese pregnant women and in non-obese pregnant women.

Methods: A comparative study was carried out in the Department of Physiology, king George`s Medical University, Lucknow, during the period of November 2017 to June 2018.. A total of 83 pregnant women of age range 20 – 40 years in their 1st trimester were recruited in the study. ELISA method was used to measure Serum C-reactive protein. Independent t-test and correlation analysis was carried out for Data analysis. P value up to 0.05 was considered significant.

Results: Low grade systemic inflammation at more advanced level were considered in obese pregnant women, as we found the significantly higher Serum C - reactive protein concentrations ($P<0.001$) in obese pregnant women as compared to control group (9.1 ± 0.12 mg /L vs 4.3 ± 0.16 mg /L).

Conclusion: In obese pregnant women, BMI is associated with high serum C-reactive protein concentration and these findings highlight a state of low grade systemic inflammation

Keywords: BMI, C-reactive protein, ELISA, Gestational age, Inflammation marker, Obesity

Introduction

The increasing maternal obesity results in adverse outcomes for both mother and fetuses. Maternal pregnancy related risks like gestational diabetes and preeclampsia increases. On the other hand fetus is also at risk for preterm birth with low birth weight and stillbirth.

According to the **Barker hypothesis** [1], low birth weight is related to the risk of developing disease later in life.

Fetuses physiology and metabolism [2] may permanently adapted to the supply of nutrients which are crossing the placenta whether a decrease or increase amount, during intrauterine life.

Adipose tissue are main fat depots in the body. Due to excessive adipose tissue in obese pregnant mother there are large amount of metabolic and vascular abnormalities that could collectively increases the risk of maternal complications.

Circulating CRP level is strongly associated with raised triglycerides in adipose tissue as it is considered as source of subclinical inflammation [3, 4]. Weight gain during second and third trimesters of pregnancy is also associated with elevated CRP level [5].

Maternal systemic inflammation during early pregnancy might contribute to develop adverse pregnancy outcome. C-reactive protein (CRP), has a role in the innate immunity system similar to immunoglobulin G (IgG). Based on epidemiological evidences it has been established that pathological conditions due to systemic inflammations, worsening the pregnancy outcomes are associated with elevated CRP in serum.

C-reactive protein (CRP) was discovered by **Tillett and Francis in 1930** as a substance of acute inflammation, [6] that are synthesized mainly by liver in response to various interleukins (IL-1 &6) and other biomarkers. Raised CRP will be associated with increased production of ROS [reactive oxygen species], non-specific marker of inflammation, decreased antioxidant levels, lung and other organ damage.

The term high sensitive / high sensitivity C-reactive protein (hs-CRP) refers to the lower detection limit of the assay, otherwise, it is similar to routine CRP in both structure and function. CRP is traditionally measured down to concentrations of 3-5 mg/L, whereas hs-CRP measures down to levels around 0.3 mg/L. This improved sensitivity of hs-CRP can be used to detect even low-grade inflammation.

So we can use hs-CRP as a marker of low grade inflammation in early pregnancy and can predict adverse pregnancy outcome. In this way , in future doctors will be able to plan appropriate preventive therapies within time.

Materials And Methods

The Prospective Observational Study was conducted in the Department of Physiology, Obstetrics and Gynaecology and Pathology of King George's Medical University, Lucknow, Uttar Pradesh from November 2017 to June 2018.

Pregnant females of reproductive age years, who came for ante-natal check-up in obstetrics and gynaecology department, KGMU Lucknow, were selected as study population, after taking ethical clearance from University ethical committee and following exclusion criteria. A written informed consent was also taken from each participant on prescribed consent form obtained from research cell.

The minimum sample size was determined using a statistical formula that is $n=z^2p*q/d^2$ for P value of 0.02% and 95% of confidence interval. [7] Calculated minimum sample size was 62. However to increase the power of the study, the maximum sample size was increased by 83. Total 120 women with singleton gestation were recruited in this study.

The height was measured with the rigid stadiometer and first weight were measured by portable scale with minimal clothing and without footwear, for each woman, and BMI (kg/m2) was calculated at first and at subsequent visits.

All the enrolled women were categorized into four sub-groups according to their 1st trimester BMI as follows: Underweight ($\leq$18.5 kg/m^2), Normal weight (18.5-23.0 kg/m^2), Overweight (23.1-25.0 kg/m^2), Obese (>25 kg/m^2). The group with normal BMI (18.5-23.0 kg/m2) was used as the reference group for the analysis. The patients were followed up to delivery.

ELISA (enzyme linked immune-sorbant assay) method was used to estimate the serum C - reactive protein. ELISA uses two highly specific monoclonal antibodies: one is specific for CRP and immobilized onto the microwell plate and another monoclonal antibody specific for a different region of CRP is conjugated to horse radish peroxidase (HRP).

Now, CRP from the sample and standards was allowed to bind to the plate, washed, and subsequently incubated with the HRP conjugate. The enzyme substrate was added after a second washing step. The stopping solution was added to terminate the enzymatic reaction. The absorbance was measured on a microtiter plate reader. The intensity of the colour formed by the enzymatic reaction is directly proportional to the concentration of CRP in the sample. A set of standards was used to plot a

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standard curve from which the amount of CRP in patient samples and controls were directly read.

Data analysis were carried out by SPSS version 21.0. The numeric variables like age and C - reactive protein level were analyzed by use of independent sample t-test. Whereas, the correlation between C - reactive protein and BMI were calculated by using Pearson's correlation co-efficient (r) .

Normal range-- dynamic range (approximately 0.05–500 mg/L) low risk (<1.0 mg/L), average risk (1.0-3.0 mg/L), and high risk (>3.0 mg/L). [Bıro A. et al. "Studies on the interactions between C-reactive protein and complement proteins" Immunology 2007]

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Results

During the study period, 120 women were booked for antenatal care, out of which, 83 met the eligibility criteria and were recruited into the study. At the time of enrollment in the study, all the females were in the reproductive age group (range 20-40 years) and mean age was 28.27±4.82 year Range of height, weight and BMI of the females enrolled in the study ranged from 139-165 cms, 40-80 kgs, 16.65-36.73 kg/m^2 respectively while mean values of above anthropometric variables were 149.07±5.64 cms, 55.46±8.29 kg and 25.11±4.35 kg/m^2

Table 1: Demographic Profile of Mothers present in the study (n=83)

SN	Characteristics	Mean ±SD;(range)
1.	Mean Age ± SD,(Range) in years	28.27±4.82 ;(20-40)
2.	Mean Height ±SD, (range) (cm)	149.07±5.64 ;(139-165)
3.	Mean Weight ±SD, (range) (kg)	55.46±8.29; (40-80)
4.	Mean BMI ±SD, (range) (kg/m^2)	25.11±4.35 ;(16.65-36.73)

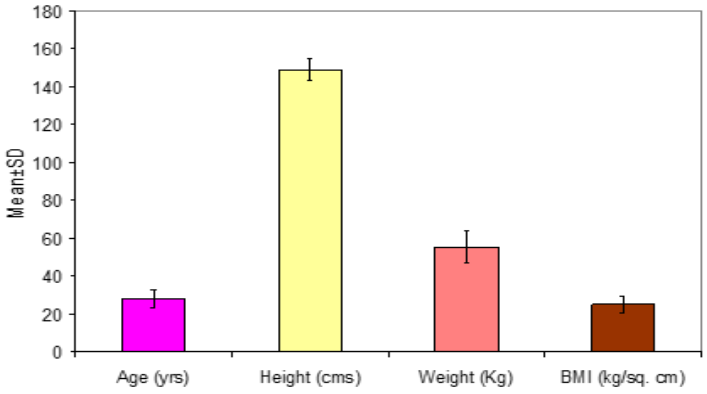

Fig. 1: Bar Diagram depicting mean age, height, weight and BMI of study population

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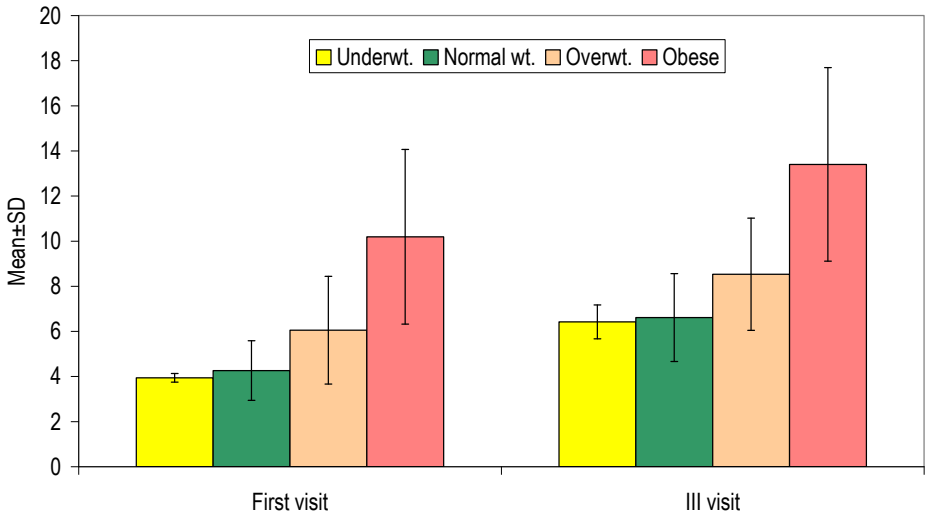

Fig. 2: Comparison of Mean CRP levels among different maternal BMI categories at first and third visits

An incremental trend of CRP levels with BMI (Nutritional status) was observed at first visit (enrolment), which was also found to be maintained at third visit. [Fig.2] Association of CRP levels and BMI were found to be statistically significant at enrolment (first visit) and at third visit.

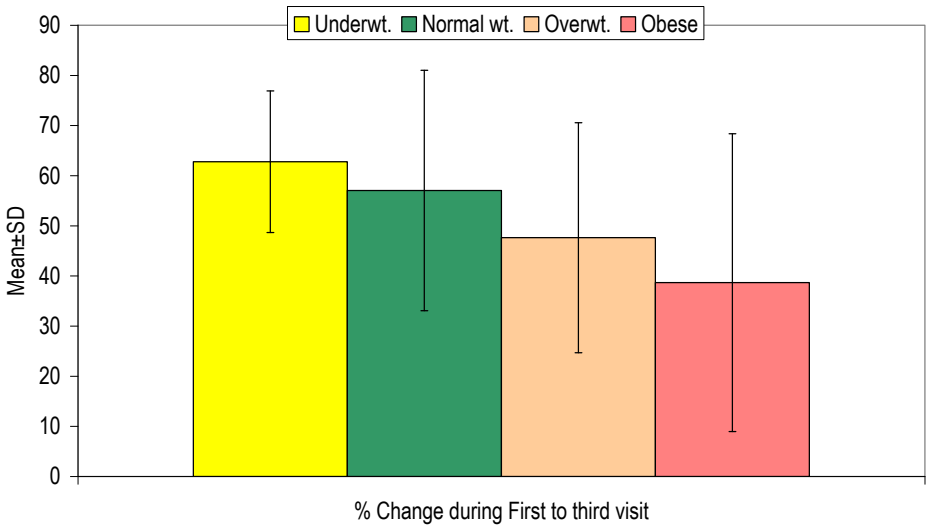

Fig. 3: Comparison of % Change in CRP levels among different maternal BMI categories between first and third visits

Maximum % change in CRP levels was observed among Underweight (62.77±14.12%) followed by Normal weight (57.04±23.97%), Overweight (47.62±22.93%) and minimum among obese (38.66±29.70%),because there was already high CRP levels in obese women, that's why % change in CRP levels was found minimum among them.

Statistically significant association of %change in CRP levels during first and third visits with BMI (Nutritional status) was found. [table-2]

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Table 2: Association of Hs- CRP levels with BMI at enrolment.

SN	Variable	Under weight BMI (≤18.5 kg/m^2) (n =4)		Normal weight BMI (18.5-23.0 kg/m^2) (n=26)		Over-weight BM[(23,0-25.0 kg/m^2) (n=10)		Obese BMI (>25 kg/m^2) (n=43)		Statistical significance	
	Hs-CRP Levels	Mean	SD	Mean	SD	Mean	SD	Mean	SD	'F'	'p'
1	First visit	3.94	0.19	4.26	1.32	6.05	2.39	10.19	3.87	23.89	<0.001
2.	Third visit	6.42	0.75	6.61	1.95	8.53	2.49	13.40	4.29	24.41	<0.001
3.	% Change during I to III visit	62.77	14.12	57.04	23.97	47.62	22.93	38.66	29.70	3.06	<0.001

Discussion

C-reactive protein (CRP) is studied as an inflammatory marker [8]. It was originally discovered by **Tillett and Francis** in 1930. Positive association of BMI with serum CRP level was reported in their study by **Deghan et al** [9] and **Fain et al**[10] . In our study, we also noticed highly positive correlation (P<0.001) of BMI with serum CRP level. Studies have shown that, regardless of BMI, abdominal adiposity also has adverse effects on health,. Adiposity identified as a key factor in low-grade chronic inflammation. In our study, we observed that CRP level of obese pregnant women was significantly higher in 3rd trimester of pregnancy. A higher prevalence of low grade systemic inflammation was observed in obese pregnant women as compared with non-obese women (p= 0.001) which was indicated by higher CRP level. Our findings corroborates with the finding of **Verhaeghe et al**,[11] who reported that plasma C – reactive protein concentration in gravidas, is strongly related to body mass index. In their study, **Visser et al**,[12] also found that there was direct correlation between higher BMI and higher C-reactive protein concentration. Their results highlight the state of low grade systemic inflammation in over weight and obese persons. Our study results are in agreement with their study. **Rexrode et al**[13] suggested body mass index as the strongest predictor of elevated inflammatory markers. His study showed high association of BMI with inflammatory markers. A corroborative study by **JANE E. et al. (2002)**[14] proven that there was impaired micro-vascular endothelial function in obese pregnant women, which results in large amount of metabolic and vascular abnormalities that could collectively be responsible for the risk of maternal complications. Adverse outcomes of pregnancy such as preeclampsia and intrauterine growth retardation [15] are result of elevated levels of CRP. Different medicines like statins were used to lower CRP level in subjects without hyperlipidaemia and having increased CRP level, but any medicine which are safe during pregnancy is not yet established[16,17].

Increased risks for adverse pregnancy outcomes due to elevated inflammation during pregnancy has also been found associated with pre-pregnancy body mass index (BMI) , in a study done by **Dayeon Shin et al.(2017)**[18,19]. In conclusion, elevated CRP levels in pregnant women was due to high pre-pregnancy BMI and was associated with increased risks of pregnancy.

A study done by **Marı´a Florencia Zacarı´as et al.(2018)**[20] explains their findings, which is almost similar to our study. They stated that, physiological

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alterations occur during normal human gestation period. Pre-gestational BMI and elevated inflammation are responsible for an increased risk for adverse pregnancy outcomes for both the mother and the offspring. Higher values of C-reactive protein , extensively examined inflammatory marker, associated with adverse events, and significantly have been observed in obese mothers. [21]

Conclusion

The results of present study showed that a state of low grade systemic inflammation in obese pregnant women is strongly correlated with BMI and level of C - reactive protein level. Therefore, there is a need of proper management of weight and high CRP level in obese pregnant women during pregnancy, from early days. Some more studies are needed to properly explain the risk and awareness of developing complications in obese pregnant women to prevent the both mother and offspring from complications.

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