Original paper

Clinical Significance of High First Trimester C- reactive Protein in Prediction for Development of Gestational Diabetes Mellitus

Saba M. Swadi AL-Thweeni^*

^Obstetrics and Gynecology Department/ Medical college /AL- Qadisia University/ Al-Qadisia/ Iraq

Abstract

Background: GDM is glucose intolerance with onset or first recognition during pregnancy, it has been associated with not only acute increased risk for complications of pregnancy but also long-term disease risks for both mother and baby due to inflammation that plays a key role in the pathogenesis of GDM. The need of a reliable early test to diagnose and predict GDM earlier is important for development of useful intervention therapies that may impact not only on the acute but long-term health outcomes.

Objective: We performed this survey to investigate the predictive value of the of first-trimester serum CRP as screening test of gestational diabetes mellitus and, to evaluate the correlation between high CRP and body mass index (BMI).

Patients and Methods: A prospective cohort study design was conducted in AL -Qadisia City in Iraq from January 2012 to January 2015. Data for the study was collected from patients attending the department of Obstetrics and Gynaecology ,outpatient and private clinic. It included 110 low risk pregnant women at first trimester(8-13 weeks). Study was included after meeting inclusion and exclusion criteria. Venous blood was screened for plasmatic C reactive protein by CLIA system to measure C reactive protein in values with cut- off point of high level more than 3mg/L , fasting blood sugar by photometric method and in addition to routine antenatal tests. They were followed up to delivery by continue to measure fasting blood sugar between 24-28 week and after 28 week of gestation . Also for assessing of complications (10 women were lost to follow ,so only 100 women were finally available).

Results: In total, 100 low risk pregnant women at first trimester with high CRP(>3mg\L), (mean±SD 5.33±1.61), 88% of them developed GDM, 53women developed between 24-28week(early GDM, group1),35women developed >28 week(late GDM ,group2),while 12 of them remain normal(group3). CRP was significantly high in group1 comparing to group2 and group3 (mean±SD 6.383± 1.439 , p< 0.001). BMI was also significantly high in group1 comparing to group2 and group3 (100% versus14.8%). Maternal and fetal complications were significantly less frequent in women with group1 than group2 (1.88%, 11.32% and 17.14%, 28.57%) (p=0.010, 0.040) respectively.

Conclusions: We did find a significant correlation between high maternal serum CRP level at first trimester and subsequent development of gestational diabetes and also, our study showed a significant correlation between pre-pregnancy BMI and CRP in early gestational diabetic women.

Key words: C-reactive protein, gestational diabetes mellitus, body mass index, pregnancy.

Introduction

Gestational diabetes mellitus GDM , is a condition characterized by glucose intolerance during pregnancy [(1)] and those that had pre-existing diabetes which had not been diagnosed before pregnancy [(2)].

*For Correspondence: E-Mail saba.swadi1@yahoo.com

Its prevalence in pregnant women is 4.7% [3,4] . This estimate will likely increase in the future, given the alarming view.

Gestational diabetes mellitus is associated with a variety of adverse birth outcomes, including congenital anomalies, excessive fetal weight gain , polyhydroamnious , preterm labour , late stillbirth and related increases in the rate of cesarean delivery and perinatal injury. Neonatal hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia and newborn respiratory distress syndrome are also an important complications [5].

Although women with gestational diabetes mellitus (GDM) usually revert to normal status after delivery [6], GDM increases the risk for a number of long-term adverse outcomes, including progression to type 2 diabetes (T2D) in the mother [7,8] which is itself an important risk factor of cardiovascular diseases and the latter is a leading cause of death among these patients [9]. As well as increased risk of obesity, diabetes, and possibly adult cardiovascular disease in the infant [10]. Non-pharmacologic medical nutrition therapy, including dietary changes, meal planning, and increased physical activity, is recognized as the cornerstone of treatment for GDM [1].

Pathophysiology of GDM :

In pregnancy, the placenta (the blood source for the baby) produces hormones that help the baby grow and develop. Some of these hormones block the action of the mother's insulin which is called insulin resistance.

During pregnancy, to keep the blood glucose levels normal, mothers need to make 2 to 3 times the normal amount of insulin due to this insulin resistance. If the body is unable to produce the extra insulin or becomes more resistant, gestational diabetes develops. When the baby requirements fall, glucose levels return to normal and diabetes usually disappears [7].

Risk factors for gestational diabetes:

As has already been stated, the risk factors for GDM share similarities with those for type 2 diabetes. The traditional, and most cited, risk factors for GDM are high maternal age, weight and parity (which are often correlated), a family history of type 2 diabetes and the previous birth of a macrosomic baby [11]. Of the more recently described risk factors, high or low maternal birth weights [12] .

Pregnancy and Gestational Diabetes Screening :

All pregnant women should be screened for gestational diabetes during their pregnancy. Screening may be done by taking the woman's medical history and examining certain risk factors, but an oral glucose tolerance test is also recommended [13].

What is the aim of Oral Glucose Tolerance Test for Gestational Diabetes?

The oral glucose tolerance test is used to screen for gestational diabetes. Gestational diabetes is a specific type of diabetes that can develop in some women late in pregnancy (usually after the 24th week). Women who develop this complication do not have diabetes before becoming pregnant.

When should Oral Glucose Tolerance Test Performed?

The test is generally given between the 24th and 28th week of pregnancy. If women have had gestational diabetes before, or if the health care provider is concerned about the risk of developing gestational diabetes, the test may be performed before the 13th week of pregnancy.[13]

Diagnosis of Gestational Diabetes:

GDM diagnosed by WHO 2006 if one or more of the following criteria are met:

- fasting plasma glucose ≥ 7.0 mmol/l (126 mg/ dl)
- 2-hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) following a 75g oral glucose load
- random plasma glucose ≥ 11.1 mmol/l (200 mg/ dl) in the presence of diabetes symptoms [14].

Now days it seems that GDM-affected women are more prone to metabolic

syndrome (MS) too [15,16]. Inflammation may be the missing link between GDM , type 2 diabetes and MS, as it is associated with insulin resistance [17].

It has been indicated that increased inflammation is an independent risk factor for the development of type 2 DM [18,19].

It has become increasingly evident that endocrine/metabolic hormones such as leptin, adiponectin, resist in, prion-flammatory mediators including C-reactive protein (CRP) are strongly linked with abnormal carbohydrate metabolism [17] .

In recent times a number of first trimester studies have shown association of different biomarkers with the development of GDM. These include elevated serum or plasma C reactive protein [15].

Recent studies have focused on C-reactive protein (CRP) more than other inflammatory markers. CRP is a protein that is synthesized by liver which is then secreted into circulation. It is a critical component of the immune system and is one of the acute phase proteins that is increased during systemic inflammation.[15]

However , even CRP levels tend to rise during pregnancy [20] since there is evidence that normal pregnancy itself stimulates the maternal inflammatory response and CRP levels are elevated in healthy pregnant women [21], but this rise will occur during late second and third trimester. On average, CRP levels tend to be normal or low level during first trimester similar to non-pregnant healthy adult women (0.2-3mg/L) [20] . The cut-point for diagnosis of high first trimester CRP level was defined as CRP>3 mg/dl [22].

Patients and Method

This study was conducted as a prospective cohort design from January 2012 to January 2015 at Maternity and Pediatrics teaching hospital in AL_Qadisia city, Iraq. Among patients who attended the antenatal care , outpatients and private clinic in the first trimester (gestational age was based on the date of last menstrual period and confirmed by first trimester ultrasound scan). All subjects gave written informed consent for participation in the study which was approved by the local ethics committee . We considered the ethical issues and described to recruited subjects for the study and obtained the consent to take blood samples. From their medical records, we got some information including maternal age, height, pre-pregnancy weight, reproductive and medical histories, and pre-pregnancy body mass index BMI (kg/m2) and entered them in analysis of the data as covariates. Maternal height and weight were measured by standard methods and body mass index (BMI) was calculated by dividing the weight in kilograms by the height in meters to the power of two. Pre-pregnancy weight was obtained by history. After exclusion of:

1. Major uterine or fetal anomalies and maternal diseases that may alter the immune response including any infective or inflammatory process.
2. Known diabetics or history of GDM in past pregnancy.
3. The level of CRP at first trimester (<3mg\L) .
4. Other associated endocrine diseases like , thyroid or adrenal disease
5. Women taking corticosteroid therapy
6. Restriction of intrauterine growth, placenta previa, pregnancy induced hypertension and twin pregnancy.

We include 110 low risk women with high first trimester CRP (>3mg/L) **,** forty-seven percent of the women were primigravidas and the mean age of women in the study was 30+-5.83. Lowest body mass index (BMI) was 19 kg/m**2** and the highest 30 kg/m**2**. All women were tested for presence and level of CRP in blood, fasting blood sugar, in addition to the standard antenatal tests of first trimester. All assays were performed in a single private laboratory to increase reliability and minimize the variance between

laboratories. Ten women were lost to follow-up and the records of only 100 women were finally available. These women were continue to follow up in the antenatal clinic and underwent fasting blood sugar every two weeks starting from 24 weeks of gestation and till the time of delivery. CRP was tested by the chemiluminescent immunoassay (CLIA) test kit. This test kit is standardized to detect CRP concentrations of approximately 3 mg/L or higher in diluted serum samples as a cut point of high test [23]. Maternal fasting plasma samples were collected in10-mL tubes, Plasma glucose concentrations were measured in certified clinical laboratories using photometric method [24]. After diagnosis of GDM depending on fasting blood sugar[14] the study sample divided into 3 groups(gruop1 those women developed early GDM between 24_28 weeks,group2 those women developed late GDM>28 weeks and group3 those women did not developed GDM and considered normal, we continue to follow all these women till delivery to assess for maternal and perinatal complications.

Statistical analysis

Data were analyzed using SPSS (Chicago version 20) and Microsoft Office Excel 2010. Numeric variables were expressed as mean ±SD while nominal data were expressed as number and percent. One way ANOVA and post hoc LSD test was used to compare mean CRP among groups. Chi-square test was used to compare frequency distribution among groups. P-value was considered significant when it was less than or equal to 0.05.

Results

Mean age of women enrolled in the present study was 30.48±5.83 years. Median parity of patients was 2 with a range of 0 to 5. Mean body mass index (BMI) was 24.80±3.15 kg/m2. Mean fasting blood sugar (FBS) in the 1st trimester was 94.08±8.51 mg/dl. Mean CRP in the first trimester was 5.33±1.61, as shown in table 1.

Table 1. Characteristics of the study sample

Parameter*	Mean	SD	Median (range)
Age	30.48	5.83	
Parity			2.00(0-5)
BMI	24.80	3.15	
FBS1sttrimester	94.08	8.51	
CRP1sttrimester	5.33	1.61	

After follow up of women enrolled in the present study, 53 pregnant lady (53%) developed gestational diabetes at 24-28 weeks gestation. Those women were regarded as having early gestational DM(group1). Another group, consisting of 35 women, developed gestational DM after 28 weeks gestation. Those ladies were regarded as having late gestational DM(group2). twelve women did not develop DM till end of pregnancy and subsequently classified as being normal(group3), as shown in table 2.

Mean serum CRP was significantly higher in patients with early gestational DM(group1) than that of normal one(group3) (highly significant difference; P<0.001).on the other hand mean CRP of patients with late gestational DM(group2) was not significantly different from that of normal one (group3) (P>0.05). Even though, patients with early gestational DM (group1) showed a significantly higher serum CRP than patient with late gestational DM(group2) (P<0.001), as shown in table 2.

Mean BMI of patients with early gestational DM (group1) was significantly higher than that of normal subjects(group3) and patients with late gestational DM(group2), as shown in figure 1and table 3.

Maternal and fetal complications were significantly less frequent in women with early gestational DM(group1) than late gestational DM(group2), as shown in table 4.

Table 2. Classification of study sample according to FBS after follow up

Groups	No. (%)	Mean CRP	SD
Normal (group3)	12 (12)	4.058	0.624
Early gestational diabetes(group1)	53 (53)	6.383	1.439
Late gestational diabetes(group2)	35 (35)	4.180	0.791
total	100 (100)	5.333	1.613

P1: Early versus normal (<0.001)
P2: late versus normal (0.757)
P3: Early versus late (<0.001)

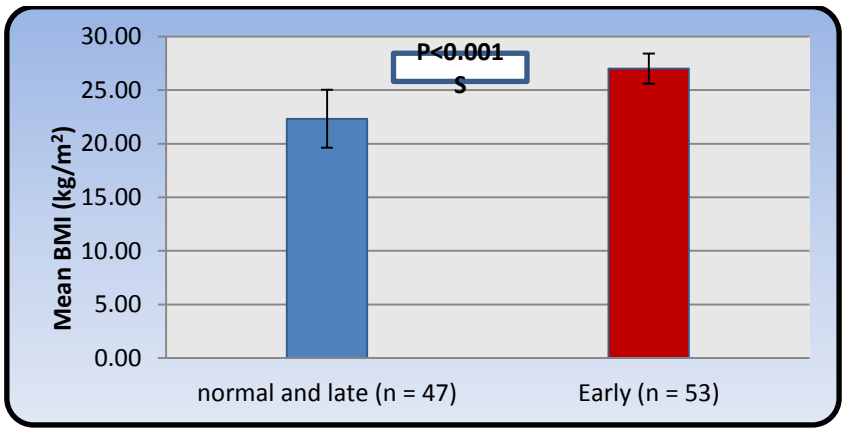

Figure 1. Comparison of mean BMI between Early gestational DM(group1) and rest of pregnant women

Table 3. Frequency of overweight and obesity in women enrolled in the present study

	Normal and late (n =47) (group3and group2)		Early (n = 53) (group1)		Total (n = 100)	
BMI	No.	%	No.	%	No.	%
Normal	40	85.11	0	0.00	40	40.00
Overweight or obese	7	14.89	53	100.00	60	60.00
Total	47	100.00	53	100.00	100	100.00

P<0.001

Table 4. Maternal and fetal complications in patients with early(group1) and late (group2)gestational diabetes

Complications	Early Gestational DM(group1) (n=53)	Late Gestational DM(group2) (n=35)	P-value
Maternal complications*	1 (1.88%)	6 (17.14%)	0.010
Fetal complications**	6 (11.32%)	10 (28.57%)	0.040

*preterm labour ,increase rate of cesarean delivery ,shoulder dystocia and perineal injury . **macrosomia ,polyhydroamnious,late stillbirth and preterm labour and its complications.

Discussion

Gestational diabetes mellitus (GDM) usually manifests itself in the latter half of pregnancy and is characterized by carbohydrate intolerance of variable severity. The presence of GDM has implications for both the mother and the baby. Perinatal morbidity includes macrosomia, hypoglycaemia, hyperbilirubinaemia and respiratory distress syndrome, which in turn may generate subsequent complications [25]. Longer term consequences for the offspring may

include obesity and diabetes independent of genetic factors [26]. For the mother, there is an increased risk of overt Type 2 diabetes later in life [27]. If GDM is diagnosed, women will usually be counseled and advised to adopt a healthy lifestyle for the duration of their pregnancy and where it is deed appropriate, women may also be required to undergo pharmacologic or insulin therapy.

During this time, increased surveillance of the pregnancy is undertaken to help ameliorate the consequent maternal and fetal morbidity associated with GDM. The clinical importance of this surveillance is highlighted by recent published findings that demonstrate that even mild hyperglycaemia over a prolonged period is associated with numerous adverse perinatal outcomes [28].

Therefore, there is a growing need to diagnose and manage pregnancy-induced diabetes earlier if the short-term and long-term risks to the fetus are to be minimized , and it is important to recognize that by the time GDM is diagnosed in the late second or early third trimester of pregnancy, the 'pathology' is probably established and that reversal of the potential adverse perinatal outcomes may be limited. Numerous GDM risk-factor assessments have been attempted during first trimester pregnancy such as

family history of GDM and/or diabetes, fasting plasma glucose, 1-h glucose challenge test [29], oral glucose tolerance test [30] and hemoglobin A1c [31], and although some have been able to provide a good negative predictive measure for subsequent GDM [32], all tests suffer from poor positive predictive values and are of limited-efficacy.

The second and third trimesters of pregnancy represent a physiological type of insulin resistance [33]. Insulin resistance is associated with dysfunction of endothelial and inflammation as well as increased production of cytokines by adipose tissue and CRP, a sensitive marker of inflammation, by the liver. [34]. A G Taba´k1,2, M Kivima¨ki1 et al (2010) studies show that high C-reactive protein (CRP) levels predict diabetes type 2 [35].

Gestational diabetes is a biochemical and epidemiological condition similar to type 2 diabetes [36], so pro-inflammatory cytokines such as CRP may be associated with GDM. In our study of a middle-aged pregnant women, we observed elevated first trimester CRP levels in people who developed gestational diabetes , and the risk of developing GDM was earlier(24-28weeks) among women with highest CRP level, these findings are consistent with Wolf et al [17] found that CRP concentrations in the first trimester predicted the development of GDM in the ongoing pregnancy and first trimester CRP levels were significantly increased among women who subsequently developed first GDM compared with control subjects (3.1 vs. 2.1 mg/l, $P < 0.01$). The risk of developing GDM among women in the highest CRP tertile compared with the lowest tertile was 3.2 (95% CI 1.2-8.8). After adjusting for age, race/ethnicity, smoking, parity, blood pressure, and gestational age at CRP sampling, the risk of developing GDM among women in the highest compared with the lowest tertile was 3.6 (95% CI 1.2-11.4).

Bhattacharya Sudhindra Mohan [37] study shows that C-reactive protein in early months as an inflammatory marker is not a dependable screening test for gestational diabetes developing in later months of pregnancy, and these finding are disagree with our findings. Also, in our study CRP concentrations correlated with BMI before pregnancy in women who early developed gestational diabetes. This result is consistent with the study of Leipold et al [38] that showed a significant correlation between pre-pregnancy BMI and CRP level.

In our study the maternal and fetal complications were significantly less frequent in women with early gestational DM than late gestational DM ,we can explain this result , the early detection and

intervention of GDM the less the complications . This result consistent with Crowther, et al., 2005, Landon, et al., 2009 [39,40] study which show that early detection and intensive intervention therapy can significantly reduce maternal and fetal morbidity .However if we study each complication alone we can get low rate of complications in late group comparing to the reported rates.

Conclusion and recommendation

Screening for glucose intolerance during pregnancy provides an opportunity to offer management to those women diagnosed with gestational diabetes mellitus. However, there is a need to diagnose gestational diabetes early to minimize exposure of the developing fetus to suboptimal conditions and prevent perinatal complications and their sequelae. From our study we identify potential proinflammatory biomarkers based on first trimester CRP for impending gestational diabetes that appear in the plasma before impaired glucose tolerance.These results are more significant in women with high BMI. The development of such test will provide data that better informs clinical decision-making and patient management that will not only directly benefit the immediate pregnancy, but will also help mitigate the longer-term ramifications of these conditions for both mother and baby. larger randomized controlled trials are needed to confirm the clinical usefulness of this proinflammatory marker as early predictor for developing gestational diabetes mellitus.

References

1. Reader DM. Medical Nutrition Therapy and Lifestyle Interventions. *Diabetes Care.* July 2007 2007;30(Supplement 2):S188-S193.
2. Hapo Study Cooperative Research Group
3. Hossein-Nezhad A, Maghbooli Z, Vassigh AR, et al: Prevalence of gestational diabetes mellitus and pregnancy outcomes in Iranian women. Taiwan J Obstet Gynecol 2007, 46:236–241.
4. Kim C, Newton KM, Knopp RH: Gestational diabetes and the incidence of type 2 diabetes. Diabetes Care 2002, 25:1862–1868.
5. Reece EA. The fetal and maternal consequences of gestational diabetes mellitus. *J Matern Fetal Neonatal Med.* Mar 2010;23:199-203.
6. Metzger BE, Cho NH, Roston SM, et al: Prepregnancy weight and antepartum insulin secretion predict glucose tolerance five years after gestational diabetes mellitus. Diabetes Care 1993, 16:1598–1605.
7. Gilmartin AB, Ural SH & Repke JT (2008) Gestational diabetes mellitus. Rev Obstet Gynecol 1, 129–134.
8. Ben-Haroush A, Yogev Y & Hod M (2004) Epidemiology of gestational diabetes mellitus and its association with type 2 diabetes. Diabet Med 21, 103–113.
9. Kannel WB, McGee DL: Diabetes and cardiovascular disease: the Framingham study. JAMA 1979, 241:2035–8.
10. The Cardiovascular Health Study. Diabetes 2001, 50:2384–2389.
11. Feig DS, Zinman B, Wang X, Hux JE: Risk of development of diabetes mellitus after diagnosis of gestational diabetes. CMAJ 2008,
12. Innes KE, Byers TE, Marshall JA, et al. (2002) Association of a woman's own birth weight with subsequent risk for gestational diabetes. JAMA 287, 2534–2544.
13. O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 1964; 13:278-285.
14. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. WHO/NCD/NCS/99.2 ed. Geneva: World Health Organization; 1999.
15. Di Cianni G, Lencioni C, Volpe L, et al: C-reactive protein and metabolic syndrome in women with previous gestational diabetes. Diabetes Metab Res Rev 2007, 23:135–140.
16. Ferraz TB, Motta RS, Ferraz CL, et al: C-reactive protein and components of diabetes. Diabetes Res Clin Pract 2007, 78(1):23–29
17. Wolf M, Sandler L, Hsu K, et al: First-trimester C-reactive protein and subsequent gestational diabetes. Diabetes Care 2003, 26:819–24.
18. Barzilay JI, Abraham L, Heckbert SR, et al: The relation of markers of inflammation to the development of glucose disorders in the elderly:
19. Pradhan AD, Cook NR, Buring JE, et al: C-reactive protein is independently associated with fasting insulin in non diabetic women.

Arterioscler Thromb Vasc Biol 2003, 23:650–655.
20. Abbassi - Ghanavati M, GreerLG , Cunningham FG.Pregnancy and laboratory studies : a reference table for clinicians . Obstet Gynedcol . 2009 Dec; 114:1326-31 .PMID: 19935037.
21. Teran E, Escudero C, Moya W, Flores M, Vallance P, Lopez-Jaramillo P. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with preeclampsia. Int J GynecolObstet. 2001;75:243 – 9.
22. Ridker PM: Cardiology Patient Page. C-reactive protein: a simple test to help predict risk of heart attack and stroke. Circulation 2003,108:e81–85.
23. Mosby's manual of diagnostic and laboratory tests , 5th ed. chapter 13, P.200 , 2006.
24. Young DS. Effects of drugs on clinical laboratory tests , 5th ed. AACC Press, 2000.
25. Hod M, Merlob P, Friedman S, Schoenfeld A, Ovadia J (1991)Gestational diabetes mellitus. A survey of perinatal complicationsin the 1980s. Diabetes 40(Suppl 2):74–78.
26. Van Assche FA, Holemans K, Aerts L (2001) Long-term consequences for offspring of diabetes during pregnancy. Br Med Bull 60:173–182.
27. Mestman JH (1987) Follow-up studies in women with gestational diabetes mellitus. Springer-Verlag, New York, pp 191–198 .
28. Schafer-Graf, U. (2009). Impact of HAPO study findings on future diagnostics and therapy of gestational diabetes. Gynakol Geburtshilfliche Rundsch, Vol.49, No.4, pp. 254-258, issn 1423-0011.
29. Caliskan E, Kayikcioglu F, Ozturk N, Koc S, Haberal A (2004) A population-based risk factor scoring will decrease unnecessary testing for the diagnosis of gestational diabetes mellitus. Acta Obstet Gynecol Scand 83:524–530 .
30. Bhattacharya SM (2004) Fasting or two-hour postprandial plasma glucose levels in early months of pregnancy as screening tools for gestational diabetes mellitus developing in later months of pregnancy. J Obstet Gynaecol Res 30:333–336 .
31. Cypryk K, Czupryniak L, Wilczynski J, Lewinski A (2004) Diabetes screening after gestational diabetes mellitus: poor performance of fasting plasma glucose. Acta Diabetol 41:5–8 .
32. Nahum GG, Wilson SB, Stanislaw H (2002) Early-pregnancy glucose screening for gestational diabetes mellitus. J Reprod Med 47:656–662 .
33. Kautzky-Willer A, Prager R, Waldhausl W, Pacini G, Thomaseth K, Wagner OF, et al. Pronounced insulin resistance and inadequate beta-cell secretion characterize lean gestational diabetes during and after pregnancy. Diabetes Care 1997;20:1717.
34. Balletshofer BM, Rittig K, Enderle MD, Volk A, Maerker E, Jacob S, et al. Endothelial dysfunction is detectable in young normotensive first-degree relatives of subjects with type 2 diabetes in association with insulin resistance. Circulation 2000;101:1780–4.
35. A G Taba´k1,2, M Kivima¨ki1 et al Changes in C-reactive protein levels before type 2 diabetes and cardiovascular death: the Whitehall II study . European Journal of Endocrinology (2010) 163 89–95.
36. Thorand B, Lowel H, Schneider A, Kolb H,Meisinger C, Frohlich M, et al. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984-1998. Archives of internal medicine2003;163:93–9.
37. Bhattacharya Sudhindra Mohan C-reative protein in early months of pregnancy as a screening test for gestational diabetes mellitus developing in later months of pregnancy, J Obstet Gynecol India Vol. 56, No. 2 : March/April 2006 Pg 131-133.
38. Leipold H, Worda C, Gruber C.J, Prikoszovich T, Wagner O and Kautzky-Willer A. Gestational diabetes mellitus is associated with increased Creactive protein concentrations in the third but not second trimester European journal of clinical investigation 2005;35:752-7.
39. Crowther, C. A., Hiller, J. E., Moss, J. R., McPhee, A. J., Jeffries, W. S. & Robinson, J. S. (2005). Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl JMed,* Vol.352, No.24, pp. 2477-2486, issn 0028-4793 .
40. Landon, M. B., Spong, C. Y., Thom, E., Carpenter, M. W., Ramin, S. M., Casey, B., Wapner, R. J., Varner, M. W., Rouse, D. J., Thorp, J. M., Sciscione, A., Catalano, Anderson, G.B. & Eunice Kennedy Shriver, N. M. (2009). A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes. *New Engl J Med,* Vol.361, No.14, pp. 1339-1348, issn 0028-4793.