

## Association of Elevated Serum Ferritin Levels in Early Pregnancy and the Risk of Development of Gestational Diabetes Mellitus

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### Abstract

**Background:** Gestational diabetes mellitus (GDM) is an important cause of perinatal mortality and morbidity. The fact that the Asian Indian phenotype is at high risk for development of metabolic syndrome and its complications like GDM necessitates early diagnosis. The role of serum ferritin as an inflammatory marker is used in this study and its levels are measured in early pregnancy to predict the risk of developing GDM, thereby making it as a tool for early diagnosis and prevention of maternal and fetal morbidity and mortality.

**Methods:** 75 antenatal women with gestational age less than 14 weeks attending out-patient department (OPD) of Obstetrics and Gynaecology at Government General Hospital (GGH), Guntur between December 2019 and December 2020. Samples obtained to measure serum ferritin level by fully automated bidirectionally interfaced chemi-luminescence immunoassay. Serum ferritin levels measured are groups in quintiles (<30, 30-60, 60-90 and >90 ng/ml). Patients underwent oral glucose challenge test (OGCT) with 75g glucose at 24-28 weeks and 32-34 weeks of gestation. All the women included in the study were followed up to monitor the risk of developing GDM.

**Results:** 22 (29.3%) women were diagnosed with GDM. Among these 22 women, 10 were started with insulin, 7 with medical nutrition therapy (MNT) and 5 were started with Metformin. In the 10 women started on insulin, 3 had serum ferritin levels >90 ng/ml.

**Conclusion:** High ferritin can be regarded as a significant risk factor for the development of gestational diabetes. Though significant association was seen in this study between high serum ferritin and risk of developing GDM, further prospective cohort studies are required to confirm the results.

**Keywords:** Serum ferritin, gestational diabetes mellitus

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## Background

The incidence of gestational diabetes mellitus (GDM) widely varies from 0.5 to 42% of all pregnancies [1]. Early diagnosis of GDM using OGTT is done before 14 weeks of gestational age. No tests are available before this gestational age, which can predict the development of GDM. The complications occurring due to GDM are preventable if screening and diagnosis is done at an early stage as possible. Ferritin is a major iron storage protein and also a positive acute phase reactant, which increases in the presence of various acute and chronic disease conditions. Studies have shown significant relation between higher serum ferritin levels and risk of development of insulin resistance states like GDM [2-9]. Shimin and colleagues in a systematic review revealed that increased risk of GDM is significantly associated with greater levels of ferritin [10]. This study is undertaken to look into the predictability of GDM in our South Indian cohort using serum ferritin levels.

## Materials and Methods

This was a prospective analytical study conducted on 75 pregnant women aged 19 to 35 years with singleton pregnancy of gestational age less than 14 weeks attending the antenatal OPD of GGH,

Guntur between December 1st 2019 and December 1<sup>st</sup> 2020. Women with previous history of diabetes, cardiovascular, haematological, rheumatological, autoimmune conditions or infections that could interfere with the tests, or those who refused consent, were excluded from the study. Venous blood samples were obtained before 14 weeks of gestation to measure serum ferritin level by fully automated bidirectionally interfaced chemi-luminescence immunoassay. Serum ferritin levels measured were groups in quintiles (<30, 30-60, 60-90 and >90 ng/ml). These women underwent OGCT with 75g glucose at 24-28 weeks and 32-34 weeks of gestation. Pregnant women were considered to have GDM if 2 or more of the four values exceeded those described in Carpenter and Coustin criteria (ADA 2009). IBM SPSS Version 28 for windows was used to do statistical analysis.

## Results

Out of the 75 women included in the study, 14 (18.7%) were aged 19-22 years, 44 (58.7%) were aged 23-26 years and 17 (22.6%) were aged 27-30 years. The serum ferritin in these women was as depicted in table 1.

**Table 1: Serum Ferritin in Pregnant Women of Different Ages**

Age (in yrs.)	Pregnant women	S. Ferritin (ng/ml)			
		< 30	30 -60	60-90	> 90
19-22	14	5(36)	4(29)	5(36)	0
23-26	44	13(30)	18(41)	12(27)	1 (2)
27-30	17	2(12)	6(35)	4(24)	5(29)
Total	75	20	28	21	6
Chi Square test P<0.016, Significant					

Of the 22 women with GDM, 4 were aged 19-22 years (29% of the age group), 7 were aged 23-26 (16% of the age group) and 11 were aged 27-30 (65% of that age group). Majority of GDM cases fall in the age group of 27-30 years, which is significant.

Among the 75 pregnant women, 22 were multiparous (29.3%). There was no significant association of parity with either ferritin levels or the presence of GDM.

In the study, risk factors like PCOS, previous history of GDM, family history of diabetes or previous history of a big baby were significantly associated with

increased ferritin levels, as seen in table 2.

**Table 2: Effect of Risk Factors of GDM on Serum Ferritin**

Risk factor	No. of women	S. Ferritin (ng/ml)			
		< 30	30 -60	60-90	> 90
PCOS	6	0	2(33)	3(50)	1(16.7)
Previous GDM	5	0	0	1(20)	4(80)
Previous big baby	2	0	1(50)	1(50)	0
Family h/o DM	5	0	0	4(80)	1(20)
Chi Square test P<0.001, Highly Significant					

All women having serum ferritin levels >90 ng/ml and majority of the women having ferritin levels 60-90 ng/ml developed GDM. The p-value is <0.001. There is a significant association between GDM and increased serum ferritin levels in the study population, as shown in table 3.

**Table 3: Association between Serum Ferritin Levels and GDM**

S. Ferritin (ng/ml)	Women	GDM	
		Yes	No
<30	20	0	20(100)
30 -60	28	4(14)	24(86)
60 -90	21	12(57)	9(43)
>90	6	6(100)	0
<b>Total</b>	75	22	53
Chi Square test P<0.001, Highly Significant			

Moreover, majority of the women who had elevated serum ferritin levels (>60 ng/ml) who developed GDM had the need for insulin. The association is significant, as evident from table 4.

**Table 4: Serum Ferritin Levels in Women with GDM Treated with Various Approaches**

Outcome	GDM Rx	S. Ferritin (ng/ml)			
		< 30	30 -60	60-90	> 90
<b>Insulin</b>	10	0	1(10)	6(60)	3(30)
<b>MNT</b>	7	0	2(28.6)	4(57.1)	1(14.3)
<b>Total</b>	17	0	3	10	4
Chi Square test P<0.001, Highly Significant					

## Discussion

The study looked into the association of elevated serum ferritin levels with the development of GDM. The reference range for serum ferritin levels in pregnant women was 12-150 ng/ml. In this study, only six women had serum ferritin values above 90 ng/ml. This implies that the study group had serum ferritin levels less than normal ferritin range, reflecting their poor iron stores and prevalence of iron

deficiency, in spite of good hemoglobin levels. Hence the upper limit of serum ferritin was not considered as the cut off value.

Insulin resistance plays a key role in GDM and there is systemic inflammation, as indicated by higher levels of C-reactive protein and interleukin-6. Adipocytes in adipose tissue can secrete pro-inflammatory cytokines in obesity. Elevated serum ferritin levels have been

found in many chronic inflammation related diseases.

In The Camden Study by Xinhua Chen et al [2], which was one of the earliest and largest studies on this association, women who developed GDM during pregnancy had higher serum ferritin concentrations ( $131.11 \pm 17.00$  pmol/l) than women who did not develop GDM ( $87.53 \pm 2.15$  pmol/l,  $P < 0.001$ ).

In another large prospective study by S Soheilykhah et al (3), 32% in the GDM group and 25.2% of normal subjects exhibited high ferritin levels ( $p=0.01$ ). The risk of GDM with these high levels of ferritin was 1.4-fold higher than that for subjects with lower concentrations.

In a case-control study of 350 GDM cases and 349 non-GDM controls conducted in participants from the Danish National Birth Cohort, plasma concentrations of ferritin in early pregnancy were significantly higher in GDM cases than in controls[4].

Zein and co-workers in a prospective observational study from Lebanon observed that ferritin level in early pregnancy was significantly correlated to glucose level after OGTT at 1-hr and 2-hr [5].

Amiri from Iran showed that high ferritin levels (greater than 80 ng/ml) increased the risk of gestational diabetes to 2.4-fold [95% CI= 2.4(0.83-6.9)]  $p=0.01$  [6].

Some small prospective observational studies from India showed a similar association [7]. Elevated serum ferritin level is associated with increased incidence of GDM irrespective of other risk factors [8].

Though our study had reciprocated similar findings, the limitation was that the study population was small as serum ferritin tests are costlier and not readily available. Fetal outcome and maternal outcome have also not been studied, due to logistic reasons. [9, 10]

## Conclusion

The study confirms the association of elevated proinflammatory markers like serum ferritin with the development of GDM, and this could be a step forward in looking for other such markers and dose-response relationships in further studies to identify women at risk much earlier and intervene appropriately.

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