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Journal of Current Trends in Women's Health & Complications

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Research Article

The Utility of Serum Fructosamine in Diagnosis of Gestational Diabetes

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Abstract

Different organizations use variable glucose criteria for diagnosis of gestational diabetes. American College of Obstetricians Gynecologists, and American Diabetes Association recommend 2 step testing: 1) 1-hour oral glucose tolerance test (OGTT) with glucose level 1-hour after 50gm glucose ingestion any time during the day. 2) 3-hour OGTT with 100gm glucose ingestion after overnight fast with glucose level during 1-hour OGTT ≥140 mg/dl. Many women shun 3-hour OGTT because of requirement of preparation with least daily intake of 150gm of carbohydrates for 3 days as well as nausea and/or vomiting during prior OGTT.

Methods:

Random glucose, Fructosamine (mcM/l) and HbA1c (%) were determined at 24-30 weeks in 202 pregnant women, age 24-40 years with 1-hour OGTT and 3-hour OGTT with abnormal 1-hour OGTT, and 21 age matched non-pregnant women.

Results:

Fructosamine in non-diabetic pregnant women (192±1) were lower ($p<0.01$) than age matched non-pregnant cohort (224±5). Threshold Fructosamine level between groups was 198. Fructosamine in 29 of 57 pregnant women with abnormal 1-hour but normal 3-hour OGTT were <198, similar to non-diabetic pregnant women. Fructosamine in 28 pregnant women with abnormal 3-hour OGTT ranged between 173 to 228. Sensitivity and Specificity indices were 88% (CI 95%, 83-94; $p<0.001$) and 89% (CI 95%, 83-98; $p<0.001$) respectively. Amongst 5 of 7 women with abnormal 3-hour OGTT, Fructosamine were <198 while being >198 in other 2 women.

Conclusion:

Fructosamine may be as or more accurate than OGTTs because of documentation of false positive 3-hour OGTT in some women. Moreover, it is a simpler and more convenient test because of not requiring fasting, glucose ingestion and preparation.

Keywords: Fructosamine, Gestational Diabetes, Glucose tolerance test, Hemoglobin A1c (HbA1c)

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Received Date: 13 Dec, 2024
Accepted Date: 16 Dec, 2024
Published Date: 02 Jan, 2025

Introduction

All organizations recommend OGTT with variable glucose criteria for diagnosis of gestational diabetes (GDM). American college of Obstetricians and Gynecologists (ACOG) and American Diabetes Association (ADA) recommend 2 step testing: 1) 1-hour oral glucose tolerance test (1-hour OGTT) involves determination of glucose level 1-hour after 50gm glucose ingestion at any time during the day. 2) 3-hour glucose tolerance test (3-hour OGTT) is completed with 100gm glucose ingestion after an overnight fast in pregnant women with glucose level of 1-hour OGTT is ≥140 mg/dl [1,2]. Preparation with least daily intake of 150gm of carbohydrates for 3 days prior to testing is recommended, though not frequently undertaken before testing for 3-hour OGTT. Moreover, many women are reluctant to undergo OGTT testing because of intolerance to glucose ingestion as well as the required preparation. Finally, determination of Hemoglobin A1c (HbA1c) is recommended for diagnosis of diabetes in non-pregnant adults, though not in diagnosis of GDM [3]. We believe that HbA1c is not recommended for diagnosis of GDM since it denotes average

blood glucose over 3 months' period. Glucose metabolism is continually evolving, even during the normal pregnancy lasting about 9 months, and hence may not be accurate. In contrast, serum Fructosamine concentration expresses average blood glucose over 3 weeks and may therefore be accurate. We recently documented serum Fructosamine concentration as an alternative diagnostic test for GDM confirmed by continuous glucose monitoring for 2 weeks as suggested in a recent study [4,5]. The pregnant woman vehemently refused OGTT because of nausea and vomiting during 1-hour OGTT. In another case study, we demonstrated that 3-hour OGTT was false positive as documented by lack of a single blood sugar ≥140 mg/dl during continuous glucose monitoring for 2 weeks [6]. In both subjects, serum Fructosamine levels were < 198 and almost identical diurnal glycemic profiles documented by CGM. Therefore, we examined utility of serum Fructosamine as a screening test for diagnosis of GDM although it has not been recommended by ADA [3].

Subjects and Methods

The study was approved by institutional review board at the affiliated Des Moines University, Des Moines Iowa. Random plasma glucose, serum Fructosamine (mcM/l) and HbA1c (%) concentrations were determined at 24-30 weeks in 202 pregnant women, age range (24-40 years) with 1-hour OGTT, and 21 age matched non-pregnant women after obtaining informed consent. The same testing was repeated at the time of 3-hour OGTT in 57 pregnant women with abnormal 1-hour OGTT as expressed by plasma glucose ≥140 mg/dl. The diagnosis of GDM was established by abnormal 3-hour OGTT as adopted by current guidelines of ACOG and ADA [1,2]. Plasma glucose, serum Fructosamine and HbA1c determinations were conducted by local clinical laboratory at the medical center with well-established assays using chemical analyzer. Statistical analyses for comparisons between data in pregnant and non-pregnant women as well as women with GDM were conducted by 'Student's 't' test' and analyses of variance. Sensitivity and specificity indices were determined for Fructosamine in comparison to 3-hour OGTT. All data was reported as mean ± standard error of mean (SEM).

Results

Serum Fructosamine levels were significantly lower ($p< 0.01$) in non-diabetic pregnant women when compared with age matched non-pregnant women whereas random plasma glucose and HbA1c concentrations were not significantly different amongst groups **(Table 1).** Diagnosis of GDM was further excluded by normal 3-hour OGTT in 28 of 57 pregnant women with abnormal 1-hour OGTT on further evaluation as recommended. Fructosamine levels in this group of 28 women were not significantly different when compared with pregnant women without GDM as confirmed by normal 1-hour OGTT **(Table 2).** In pregnant women with GDM established by 3-hour OGTT, mean serum Fructosamine level was significantly greater as compared to pregnant women without GDM, though similar to non-pregnant age matched cohort (Table 2). However, there was a marked variation in Fructosamine concentrations in individual women with a range between 173 to 225 mM/l. The median Fructosamine level was 198. Thus, a significant Fructosamine overlap was noted in this group with some levels not significantly different (<198) when compared with those noted in pregnant women without GDM and others with levels (>198). Sensitivity index was 88% (confidence interval at 95%, 83-94; $p<0.001$). Specificity index was 89% (CI at 95%, 83-98; $p<0.001$). On further testing, Fructosamine levels in 3 pregnant women with abnormal 3-hour OGTT matched levels in non-diabetic pregnant women (<198) and therefore may be suggestive of false positive OGTT, while Fructosamine levels were (>198) in 2 women with both abnormal 1-hour and 3-hour OGTTs consistent with true GDM.

Discussion

This study confirms our previous observations that serum Fructosamine concentrations are subnormal and significantly lower in pregnant women without GDM when compared to pregnant women manifesting GDM [7,8]. Lowering of Fructosamine has been documented in previous reports [9-11]. However, these studies failed to assess sensitivity and specificity. Alternatively, studies assessing sensitivity and specifically were contradictory [12-14]. One report documented high sensitivity (85.8%) and low specificity (23.4% in 113 women) but without comparative data with non-pregnant women [12]. Another study described high specificity (85.7%) but low sensitivity (41.7%), while another study showed both the sensitivity (54.8%) and the specificity (48.6%) to be moderate [13,14]. Moreover, in contrast to our study, both sensitivity and specificity were examined during midterm for prediction of GDM and not for diagnosis [14]. Additionally, one study determined Fructosamine at the beginning of all three trimesters and found no women with GDM while another study failed to determine sensitivity and specificity and did not include age matched non-pregnant women [15,16]. Finally, most of these studies were conducted more than 20 years ago and therefore the assay systems used for measurement of Fructosamine were probably not as accurate as the present methodology. The progress in methodology may have contributed to the difference in the findings in our study and these reports [12-16].

In this study, mean Fructosamine level in women with GDM were not significantly different from non-pregnant women. This anomaly was probably because of the variability in individual levels from lower to higher than in non-pregnant women. We believe that normal or higher levels were documented in almost 50% false positive 3-hour OGTTs as shown in a study using continuous glucose monitoring for several days and in our case report [5,6].

Table 1: Serum Fructosamine, HbA1c and random or fasting glucose in pregnant women with or without GDM as documented by 1-hour and/or 3-hour OGTT and age matched non-pregnant women.

	Age	Number of Subjects	Fructosamine 200-285 mM/L	HbA1C 4.8-5.7%	Random Glucose 65-140 mg/dl	Fasting Glucose 65-100 mg/dl
Non-Pregnant	32 ± 1	21	224 ± 5	5.1 ± 0.1	84 ± 4	94 ± 2
Pregnant with GDM	32 ± 1	23	193 ± 4[ab]	5.2 ± 0.1	173 ± 6[a]	95 ± 2
Pregnant No GDM	28 ± 1	179	192 ± 1a	4.9 ± 0.2	116 ± 2[a]	85 ± 2

[a]$p<0.01$ vs non-pregnant age matched women

[b]range 173 -225 mM/l

Table 2: Serum Fructosamine, HbA1c, and random or fasting glucose concentrations in pregnant women with or without GDM as documented by 3-hour OGTT. Group with GDM is divided into 2 groups according to Fructosamine level <198 or >198 mM/l

	Age	Number of Subjects	Fructosamine 200-285 mM/L	HbA1C 4.8-5.7%	Random Glucose 65-140 mg/dl	Fasting Glucose 65-100 mg/dl
Non-Pregnant	32 ± 1	21	224 ± 5	5.1 ± 0.1	84 ± 4	94 ± 2
Pregnant NO GDM[a]	28 ± 1	179	192 ± 1[a]	4.9 ± 0.2	116 ± 2[a]	
GDM with Fructosamine <198[a]	31 ± 1	14	186 ± 3[a]	5.1 ± 0.1	166 ± 5[b]	95 ± 2
GDM with Fructosamine >198[a]	33 ± 2	9	209 ± 5[ab]	5.3 ± 0.1	187 ± 13[b]	92 ± 3

[a]p<0.01 vs non-pregnant age matched women

[b]p<0.01 vs pregnant without GDM

The exact mechanism for this finding is uncertain. However, several following speculative pathophysiologic explanations are likely as described in recent reports [8,17,18]. Additionally, lowered fasting glucose levels during pregnancy may have contributed to lower Fructosamine concentrations. However, lack of lowering of HbA1c concentrations renders this explanation improbable as well. Lack of decline in HbA1c in contrast to Fructosamine may be attributed to differences in the duration of life span of these proteins. Alternatively, glycation may have been inhibited by an antioxidant such as vitamin E present in vitamin supplement e.g. Prenatal [17]. Finally, progressively rising estrogen and progesterone levels may be probable culprits as diurnal glycemic variance has been documented to occur during normal menstrual cycles [18]. However, the data regarding Fructosamine levels during various stages of pregnancy is uncertain.

In conclusion, Fruc-tosamine may be as accurate as OGTTs in diagnosis of GDM as expressed by robust sensitivity and specificity indices when compared with 1 and 3-hour OGTTs. Importantly though, it is a simpler, more convenient and more acceptable test than OGTTs because of no requirement of fasting, glucose ingestion or preparation.

Conflict of Interest Statement
Authors have no conflict of interest. No funding.

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