Hyperglycemia In Pregnancy in Arab Population, Kuwait Oil Company Hospital, Kuwait

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Abstract

Background: The hyperglycemic population in pregnancy consists of two main cohorts- subjects with onset or first recognition during pregnancy (Gestational diabetes mellitus -GDM) and subjects with preexisting history of diabetes mellitus. The prevalence of GDM has been steadily increasing with the rise of obesity and unhealthy life style reaching up to 14 % annually in many countries including the United States. Hyperglycemia from any cause can seriously affect both mother and baby and increases the risk of complications during pregnancy, labor and after delivery.

Aim: We aimed to study any baseline obstetric history differences as well as labor outcomes and neonatal characteristics between the two groups, Group A- impaired glucose tolerance and recent diagnosis of pregnancy induced diabetes mellitus (n=240), and, Group B- known history of Type 2 Diabetes mellitus and already on medication (n=240).

Methods: This is a prospective, open label, double arm, observational, longitudinal registry study. The registry was launched with immediate effect in December 2012 and recruitment of subjects continued until January 2014. After fulfilling the inclusion criteria, a total of 480 subjects comprising two equal groups (Group A with a known history of type 2 diabetes mellitus and Group B with GDM) were recruited; their obstetric history captured and they were followed up on a regular basis till delivery. Mode of delivery and neonatal status especially APGAR status at birth, 5 minutes and 10 minutes were closely monitored and captured using an eCRF by the study physicians.

Results: Statistical analysis revealed a significant difference in the obstetric history-parity (p=0.000), previous abortion history (p=0.007), previous caesarean sections (p= 0.000) and type of delivery (vaginal, caesarean, vacuum (p value= 0.000, 0.000 and 0.006 respectively) while there were no statistically significant variations amongst the neonatal statuses except for higher birth weight (p=0.02) and neonatal complications (p=0.033).

Conclusion: Hyperglycemia with pregnancy is a steadily increasing problem that can seriously affect both mother and baby as shown in the present study, however, the present study did not show any significant differences in the weeks of delivery (preterm vs term). Also, the present study revealed more congenital heart problems, especially septal defects, among offspring of mothers with overt type 2 DM due to the chronicity of hyperglycemia compared with offspring of mothers with gestational diabetes.

Key words: Gestational Diabetes Mellitus, Impaired Glucose Tolerance, Type 2 Diabetes Mellitus, APGAR

Background

Kuwait has acquired a notorious place in the world ranking of metabolic disorders in the last decade, especially Diabetes Mellitus, mainly owing to the extreme climate (which makes outdoor activities less feasible) and unhealthy dietary habits. The hyperglycemic population in pregnancy consists of two main cohorts- subjects with onset or first recognition during pregnancy (Gestational diabetes mellitus -GDM) and subjects with preexisting history of diabetes mellitus.(1) Innumerous trials around the globe have dealt with the concept of impaired glucose tolerance and its effect on pregnancy and adverse outcomes. The prevalence of GDM has been steadily increasing with the rise of obesity and unhealthy life style, reaching up to 14 % annually in the United States, says Center for Disease Control (CDC).(2)

Pregnant women with gestational diabetes and impaired glucose tolerance are at high risk for pregnancy and delivery complications including infant macrosomia, neonatal hypoglycemia and caesarean delivery. (3,4) Hence, the impending necessity for a registry which compares the two hyperglycemic manifestations as GDM and known T2DM, so as to determine the effect of chronicity of hyperglycemia in pregnancy and neonatal statuses piqued our efforts. An intensive lifestyle intervention could significantly reduce incidence of diabetes. Weight loss and 150 min of physical activity per week similar in intensity to brisk walking are the most effective lifestyle intervention.(5)

Methods

This prospective, open label, double arm, observational, longitudinal registry sought the approval of its sole site (KOC hospital, Kuwait) ethics committee and gained the approval by November 2012. The registry was launched with immediate effect in December 2012 and recruitment of subjects (who complied with proper informed consent procedure) continued until January 2014. The inclusion criteria were broad, comprising 3 main points:

(a) Willingness to perform GTT (Glucose tolerance test) during 24-28 gestational weeks and follow study procedure,
(b) Women with risk factors for hyperglycemia and
(c) Signed informed consent. Exclusion criteria included any subject < 18 years of age, any underlying history of co-morbidities such as hypertension, coronary artery disease, chronic kidney disease and/ or inability to provide informed consent.

All subjects in the first trimester presenting to KOC hospital Obstetrics department were screened for a known history of T2DM and/or minimal two consecutive incidences of elevated Blood Glucose levels sufficient to meet the WHO - GDM definition.(5,6) All subjects with confirmed fasting glucose levels of $\geq$ 7.0 mmol/L or random glucose levels of $\geq$ 11.1 mmol/L in the first trimester were classified as overt / T2DM and grouped together (Group B) while those who presented with impaired glucose tolerance confirmed by a positive Oral Glucose Tolerance Test (OGTT) between 24- 28 gestational weeks were classified as GDM (Group A).(3)

Both groups had their OGTT performed and analyzed at KOC hospital laboratory. The OGTT consisted of 75 g 2-hours glucose test and was carried out after overnight fasting (10-16 hours) and at least 3 days of unrestricted diet and normal physical activity. A total of 480 subjects (Group A, n=240 and Group B, n=240) were recruited, their obstetric history captured and followed up on a regular basis till delivery. Mode of delivery and neonatal status especially APGAR status at birth, 5 minutes and 10 minutes, were closely monitored and captured using an eCRF by the study physicians.

Results

Statistical analysis:
Data were analyzed using SPSS version 12.0. A confidence interval of 5% and p- value of 0.05 were set. MANOVA and ANOVA were performed. To find significant correlations, Chi-square tests were adopted for continuous variables while Mann Whitney's U test was used for categorical variables.

Table 1 (next page) shows a significant statistical difference between Group A and B regarding obstetric history. In case of parity, Group A was comprised of comparatively higher percentages of nulliparous and primiparous subjects while multiparity was on the higher side in Group B (p= 0.000). Likewise, Group B subjects had significantly higher number of abortions (especially multiple abortions) than Group A (p= 0.007) as well as multiple caesarean sections (p=0.000). 53.3 % (n=128) in Group B were on Insulin supplementation while the rest were on oral hypoglycemic agents. All subjects in Group A were on oral hypoglycemic agents. OGTT was positive for all subjects in Group A while negative for those in Group B (probably owing to their medications).

Table 2 shows the neonatal statuses in both groups. There was statistically higher complications in Group B (p=0.033) and slightly higher birth weight (p=0.02) as compared to Group A, however there were no statistically significant differences in the APGAR scales.

Figure 1 depicts the variations in the modes of delivery for both groups. While group A had significantly higher percentage of vaginal deliveries and vacuum deliveries, group B could afford more caesarean sections (p=0.000, 0.006 and 0.000 respectively). However there were no significant differences in the weeks of delivery (preterm vs term) amongst both groups.

Table 1: Obstetric history and baseline characteristics of the two study groups

Sl no:	Criteria	Sub-classification (if any)	Group A-IGTT positive (n= 240)	Group B – IGTT negative (n= 240)	p-value
1	Live birth (mean ± S.D)		3± 2	4 ± 3	0.000**
	Live birth	Nullipara	34 (14.2%)	16 (6.7%)	
		Primipara	44 (18.3%)	32 (13.3%)	
		Multipara	162 (67.5%)	192 (80.0%)	
2	No: of abortions	None	128 (53.3%)	120 (50.0%)	0.007**
		1	74 (30.8%)	64(26.7%)	
		2-5	38 (15.8%)	56 (23.3%)	
3	No: of previous CS	None	178 (74.2%)	120 (50.0%)	0.000**
		1	32 (13.3%)	32 (13.3%)	
		≥2	30 (12.5%)	88 (36.67%)	
4	Known H/o T2DM		0 (0%)	240 (100%)	0.000**
	On Insulin treatment		0 (0%)	128 (53.3%)	0.000**
Current BSL status	IGTT	Positive	240 (100%)	0 (0%)	
		Negative	0 (0%)	240 (100%)	

IGTT = impaired glucose tolerance test, T2DM= type 2 diabetes mellitus

Figure 1: Types of delivery (percentages) in both groups

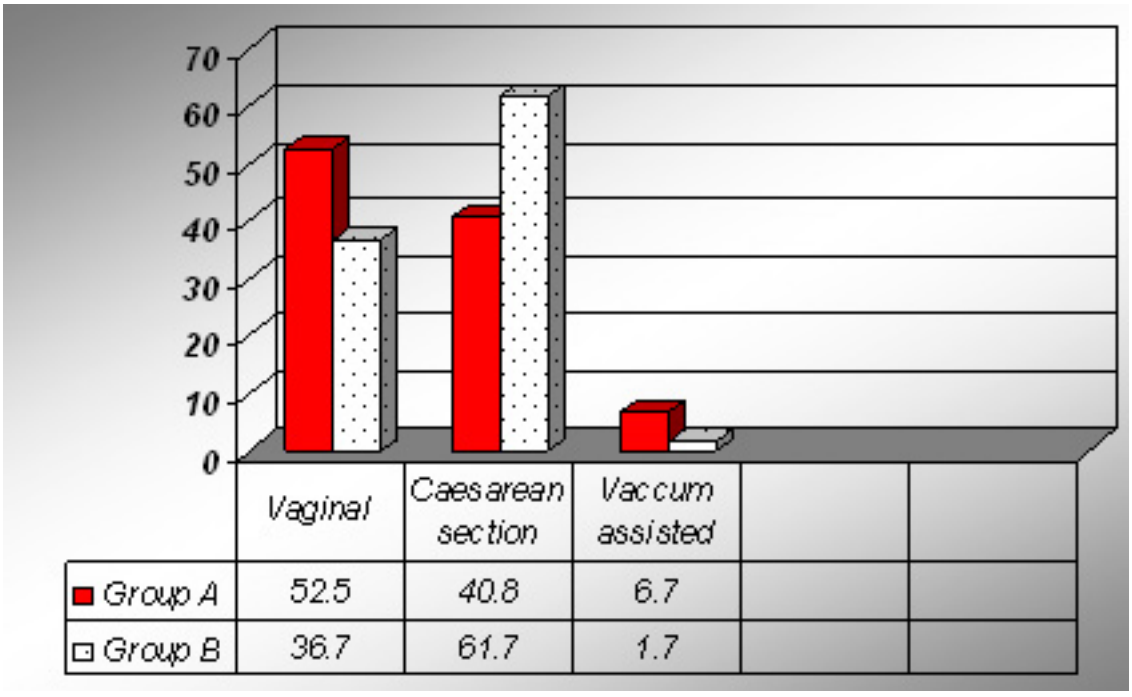

Table 2: Neonatal status

Sl no.	Criteria	Sub-classification (if any)	Group A-IGTT positive (n= 240)	Group B – IGTT negative (n= 240)	P-value
1	Birth weight				
	Average		3.22 ± 0.60	3.37 ±0.72	0.02*
	Classification of birth weight	Low	20 (8.3%)	20 (8.3%)	0.346
		Normal	208 (86.7%)	200 (83.3%)	
		High	12 (5.0%)	20 (8.3%)	
2	Abnormal birth weight		32 (13.3%)	40 (16.7%)	0.307
	APGAR				
a)	APGAR score on birth	Mean	7.72 ± 1.48	7.62 ±1.83	0.511
		Normal	220 (91.7%)	212(88.3%)	0.304
		Low	12 (5.0%)	16 (6.7%)	
		Critical	4 (1.7%)	8 (3.3%)	
		Nil	4 (1.7%)	4 (1.7%)	
b)	APGAR after 5 minutes	Mean	8.75 ± 1.30	8.50 ±1.74	0.075
		Normal	234 (97.5%)	224(93.3%)	0.150
		Low	2 (0.8%)	8 (3.3%)	
		Critical	0 (0%)	4 (1.7%)	
		Nil	4 (1.7%)	4 (1.7%)	
c)	APGAR after 10 minutes	Mean	9.57 ± 1.37	9.30 ± 1.78	0.066
		Normal	234 (97.5%)	232 (96.7%)	0.522
		Low	2 (0.8%)	0	
		Critical	0	4 (1.7%)	
		Nil	4 (1.7%)	4 (1.7%)	
3	NEONATAL COMPLICATIONS				
a	Complications present		48 (20.0%)	68 (28.3%)	0.033*
b	Type of complications				
c	Expired	Total	4 (1.7%)	4 (1.7%)	
		Still born	2 (0.8%)	0	
		Macerated	2 (0.8%)	0	
d	Cord vessel abnormalities		4 (1.7%)	0	
e	Septal defects	Total	2 (0.8%)	8 (3.3%)	
		ASD	2 (0.8%)	4(1.7%)	
		VSD	0	4 (1.7%)	
		ASD and VSD	0	4 (1.7%)	
f	Patent ductus arteriosus		2 (0.8%)	4 (1.7%)	
	Patent foramen ovale(PFO)		2 (0.8%)	4 (1.7%)	
g	Potter's syndrome		0	4 (1.7%)	
h	Polycythemia vera		2 (0.8%)	0	
i	Respiratory disorders	RDS	2 (0.8%)	4 (1.7%)	
		TTN	8 (3.3%)	8 (3.3%)	
		Cyanosis	8 (3.3%)	0	
		Ventilated	6 (2.5%)	12 (5.0%)	
		Incubated	0	0	
j	Shoulder dystocia		2 (0.8%)	0	
k	Caput medusa		0	4 (1.7%)	

ASD= atrial septal defect,
VSD= ventricular septal defect,
RDS= respiratory distress syndrome,
TTN= transient tachycardia in new born

Discussion

The aim of our registry was to identify any key differences between T2DM and GDM cases, and the related delivery complications and neonatal statuses. As opposed to the meta- analysis reports of 14 studies done by Hai-Qing Wang, Han-Lin Lai, Yi Li et al in 2015(8), our study did not show any significant risk effect for impaired Glucose tolerance as a predictor for Large for Gestational Age (LGA). Fetal growth is mainly dependent on interactions of maternal and fetal endocrine statuses and genetic predispositions. Higher amount of maternal blood sugar levels in turn exposes the fetus to higher levels of glucose leading to fetal lipogenesis and excessive growth.(9) In our study, it was shown that the average birth weight was statistically higher in known diabetics than gestational diabetics.

Earlier studies have proved that achievement of glucose control in women with at least one OGTT value decreased adverse neonatal outcomes to near baseline level.(10,11,12) However our study has shown that chronicity of hyperglycemic status significantly increases adverse neonatal outcomes (p=0.033).

Recent studies have confirmed in mouse models that maternal type 2 diabetes mellitus causes heart defects in the developing embryo manifested with oxidative stress, endoplasmic reticulum stress, and excessive apoptosis in heart cells.(13) Our trial has shown that though congenital heart defects (especially septal defects) were common in both groups of offspring of females with either overt diabetes or gestational diabetes, but more frequent among the offspring of mothers with overt T2DM (8% vs 2%, in Group B and Group A respectively).

Even though the differences between APGAR scores at birth, 5 minutes and 10 minutes weren't statistically significant, it was noted that while those in Group A born with low scores recovered rapidly, the recovery was late in group B.

New meta-analysis done by Jared T. Rockner et al (14) from 25 studies has shown that women with 1 abnormal value on 3- h, 100 g OGTT have a significantly increased risk for poor outcomes comparable with women who have gestational diabetes mellitus. Even though our study hasn't included any similar subjects we have been able to conclude that though both groups require good management, more care needs to be given to those with previous history of T2DM even if their OGTT is negative. Along with medications, dietary control and exercise shall make for better management. (15)

Conclusion

Hyperglycemia with pregnancy is a steadily increasing problem that can seriously affect both mother and baby as shown in the present study, however, there were no significant differences in the weeks of delivery (preterm vs term) amongst this group of people. However our study has shown that chronicity of hyperglycemic status significantly increases adverse neonatal outcomes especially in regards to septal defects. The limitation of the study lies in the fact that this was a single centre trial with no randomization. Also, a thorough analysis of all baseline characteristics and clinical presentations, as well as adverse event log needs to be maintained.

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