Reseach Article

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Critical Care Obstetrics and Gynecology
ISSN 2471-9803

2016
Vol.2 No.4:22

DOI: 10.4172/2471-9803.1000130

Screening for Gestational Diabetes Mellitus in Women with Twin Pregnancies

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Received date: June 25, 2016; **Accepted date:** August 1, 2016; **Published date:** August 10, 2016

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Citation: Morikawa M, Yamada T, Satoshi I, et al. Screening for gestational diabetes mellitus in women with twin pregnancies. Crit Care Obst&Gyne. 2016, 2:22.

Abstract

Background: The main purpose of screening and treatment for gestational diabetes mellitus (GDM) is to reduce dystocia arising from fetal overgrowth. This study was conducted to determine the risks of low-birth weight infants (LBWI) and overgrowth infants (OGI) defined as infants with birth weight<2,500 g and ≥3500 g, respectively in Japanese newborns.

Methods and Findings: Retrospective observational study in 9,024 twins born to 4,512 women and 127,907 singletons born at gestational week ≥ 35 at the obstetric facilities participating in a registry system in Japan. GDM was diagnosed based on the previous criteria used in Japan until 2009. In twin vs. singleton pregnancies, GDM/diabetes mellitus (DM) was diagnosed in 1.7% vs. 2.7%, birth weight was 2,356 ± 327 g vs. 2,970 ± 426 g, rate of LBWI was 68% (6,098/9,024) vs. 12% (15,189/127,907) and rate of OGI was 0.22% (10/9,024) vs. 9.9% (12,629/127,907), respectively. There were no significant differences in risk of LBWI (70% [105/150] vs. 68% [5,993/8,874]) or OGI (0.67% [1/150] vs. 0.10% [9/8,874]) between twins born to women with and without GDM/DM, respectively, while the risk of OGI (20% [673/3,413] vs. 9.6% [11,956/124,494], P = 0.000) was significantly higher among singletons born to women with than without GDM/DM, with similar risk of LBWI (11% [369/3,413] vs. 12% [14,820/124,494]).

Conclusions: The risk of OGI was extremely lower and the risk of LBWI was extremely higher in twins compared to singletons born to Japanese women. Research is needed to determine whether treatment for GDM is beneficial for women with twin pregnancies.

Keywords: Macrosomia; Birth injury; Glucose metabolism; Shoulder dystocia

Introduction

Diabetes mellitus (DM) and gestational diabetes mellitus (GDM) during pregnancy is associated with poor maternal and perinatal outcomes [1-4]; congenital malformation, preterm birth and stillbirth are significantly more common in offspring of diabetic mothers than nondiabetic mothers [1], one of the latest review suggested that maternal diabetes during pregnancy was negatively associated with cognitive development in offsprings [2], and diabetes in pregnancy is associated with fetal overgrowth leading to a serious complication, i.e., shoulder dystocia [4]. As the treatment of GDM reduces the risks of fetal overgrowth, shoulder dystocia, and caesarean delivery [5,6], screening for GDM is recommended [7] and widely practiced even in women with twin pregnancies in Japan. Thus, the main purpose of screening and treatment of GDM is to avoid fetal birth injuries derived from dystocia associated with overgrowth of the infant through reduction of birth weight. However, this inevitably increases the number of neonates with lower birth weight. A clear phenomenological association has been demonstrated by many epidemiological studies between low birth weight and increased risk of many diseases later in life, such as insulin resistance, mortality by ischaemic heart disease, metabolic syndrome, hypertension, dyslipidaemia and obesity [8-11].

The duration of gestation is significantly shorter by approximately three weeks [12], birth weight is significantly smaller [13] and the fraction of low-birth weight infants (LBWI) defined as infants with birth weight<2500 g is significantly greater in twins than in singletons [13]. The rates of fetal birth injuries derived from dystocia associated with fetal overgrowth are therefore expected to be lower in twins than in singletons. In addition, the mode of delivery is caesarean section in approximately 80% of twin pregnancies in Japan at present [14]. Therefore, the problem of twin dystocia associated with fetal overgrowth during vaginal delivery may be minimal compared to singletons. To our knowledge, there have been no reports showing a rationale for a policy of universal screening and treatment for GDM in women with twin pregnancies.

In twin pregnancies with GDM after excluding pre-existing DM compared to non-diabetic twin pregnancies, frequencies of adverse outcomes such as 5-min Apgar scores<4, preterm birth before 32 weeks gestation, and birth weight less than the 10th percentile are fewer [15] and GDM is associated with a decreased likelihood of lower 5-min Apgar score and reduced occurrence of stillbirth and neonatal deaths [16]. In addition, improved glycemic control is not associated with improved outcomes, and is associated with a higher risk of small for gestational age infants [17].

This retrospective observational study was conducted to determine the risks of low-birth weight infants (LBWI) and overgrowth infants (OGI) defined as infants with birth weight<2,500 g and ≥3500 g, respectively in diabetic (pre-existing DM and GDM) Japanese women with singleton and twin pregnancies.

Materials and Methods

This study was conducted after receiving approval from the Institutional Review Board of the Hokkaido University Hospital.

Study population

The study population consisted of 127,907 and 4,512 women with singleton and twin pregnancies, respectively, who gave birth at gestational week (GW) ≥ 35, and were registered in the Japan Society of Obstetrics and Gynecology Successive Pregnancy Birth Registry System (JSOG registry system) over the three-year period between 2007 and 2009. Although 192,254 and 7,900 women with singleton and twin pregnancies at GW ≥ 22 were registered in this system over the three-year period, corresponding to 6.0% and 18.0% of all singleton and twin pregnancies occurring in Japan during this period, respectively, we excluded 64,347 women with singleton pregnancies and 3,388 women with twin pregnancies because of GW at delivery<35, missing data on age, parity, body height, pre-pregnancy body weight, gestational week at delivery, birth weight of infant, Apgar scores and/or sex of the infant. Finally, the numbers of women with singleton (n = 127,907) and twin pregnancies (n = 4,512) accounted for 67% and 57% of all singleton and twin pregnancies, respectively, registered in the JSOG registry system during the study period. In this population, the diagnosis of hyperglycaemia, including DM and GDM, was based on the previous criteria used in Japan until 2009 [18]. Thus, this population included both pre-existing DM and GDM diagnosed in the current pregnancy. The OGI was defined as an infant with birth weight ≥ 3500 g. LBWI was defined as an infant with birth weight<2500 g in this study.

Statistical analyses were performed using the statistical software IBM SPSS Statistics, version 19.0 (SPSS Inc., Chicago, IL). The data are presented as the means ± SD or median [range]. Fisher's exact test was used to compare the frequencies among categorical data. In all analyses, P<0.05 was taken to indicate statistical significance.

Results

There were significant differences in many demographic characteristics between women with singleton and twin pregnancies due to the relatively large number of subjects included in the study. However, clinically important differences relevant to the present topic included infant birth weight (2,356 ± 327 vs. 2,970 ± 426 g for twins and singletons, respectively) and the rates of caesarean section (80% vs. 27% for twins and singletons, respectively) and hyperglycaemia (1.7% vs. 2.7% for twin and singleton pregnancies, respectively) (**Table 1**). The mean birth weight of twins (2,356 g) corresponded to approximately 80% of that for singletons (2,970 g). The frequency of infants with Apgar score<8 at 5 min did not differ between the two groups, but perinatal mortality rate was significantly lower in twins than in singletons.

Table 1 Demographic characteristics of the JSOG cohort.

	Twin	Singleton	P-value
Number of women	4512	127907	
Nullipara	2721 (60.3%)	67244 (52.6%)	<0.0001
Age (years)	31.7 ± 4.8	31.5 ± 5.1	0.0390
≤19	33 (0.7%)	1528 (1.2%)	0.0031
20-24	306 (6.8%)	10418 (8.1%)	0.0009
25-29	1052 (23.3%)	30845 (24.1%)	0.2217
30-34	1781 (39.5%)	47209 (36.9%)	0.0005
35-39	1150 (25.5%)	31140 (24.3%)	0.0808
≥40	190 (4.2%)	6767 (5.3%)	0.0011
Pre-pregnancy BMI (kg/m2)	21.0 ± 3.3	21.2 ± 3.7	0.0004
≤18.4	783 (17.4%)	23049 (18.0%)	0.2611
18.5-24.9	3294 (73.0%)	90081 (70.4%)	0.0002
≥25.0	435 (9.6%)	14777 (11.6%)	<0.0001
Gestational week at delivery	36.6 ± 1.0	38.7 ± 1.4	<0.0001
35	642 (14.2%)	2992 (2.3%)	<0.0001
36	1329 (29.5%)	5314 (4.2%)	<0.0001
37	1935 (42.9%)	18176 (14.2%)	<0.0001
38	514 (11.4%)	28675 (22.4%)	<0.0001

39	69 (1.5%)	31725 (24.8%)	<0.0001
40	22 (0.5%)	28728 (22.5%)	<0.0001
≥41	1 (0.02%)	12297 (9.6%)	<0.0001
Birth weight	2356 ± 327	2970 ± 426	<0.0001
Caesarean delivery	3624 (80.3%)	34943 (27.3%)	<0.0001
Female infant	4544 (50.5%)	62210 (48.6%)	0.0016
Male infant	4480 (49.6%)	65687 (51.4%)	0.0016
Apgar score at 5-min<8	166 (1.8%)	2319 (1.8%)	0.8384
Perinatal mortality#	24 (0.27%)	601 (0.47%)	0.0045
Stillbirth	15 (0.17%)	350 (0.27%)	0.0567
Early neonatal death*	9 (0.10%)	251 (0.20%)	0.0440
GDM/DM	75 (1.7%)	3413 (2.7%)	<0.0001
Data are expressed as the means ± SD; *: Death within 7 days of life; #: Including stillbirth and early neonatal death within 7 days of life.			

As expected, the LBWI were significantly more likely to be born to women with twin than with singleton pregnancies (**Figure 1**). The OGI were significantly more likely to be born to women with singleton than with twin pregnancies. LBWI accounted for 70% (105/150) and 68% (5,993/8,874) of all twins born to women with and without GDM/DM, respectively. OGI accounted for only 0.67% (1/150) and 0.10% (9/8,874) of all twins born to women with and without GDM/DM, respectively. None of the twins and 0.9% (1,167/127,907) of singletons had a birth weight ≥ 4000 g. Thus, the overall frequency of OGI twins was very low, i.e., 0.11% (10/9,024), with a very high overall LBWI rate of 67.6% (6,098/9,024).

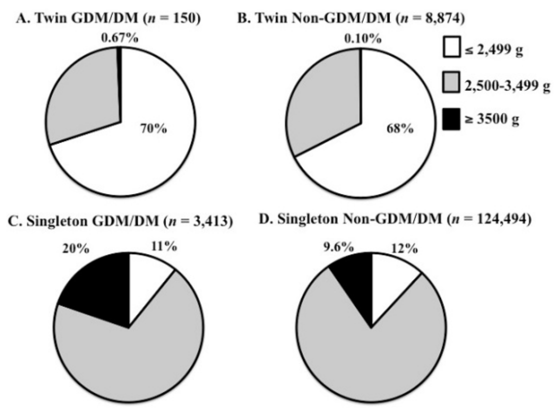

Figure 1 Distribution of birth weights according to the presence or absence of GDM/DM in singleton and twin pregnancies.

Among singletons born before or at GW 37, the risk of LBWI was consistently lower for those born to women with than without GDM/DM irrespective of GW at delivery, while among twins born before or at GW 37, the risk of LBWI was somewhat higher for twins born to women with than without GDM/DM irrespective of GW at delivery (**Figure 2**). In contrast, the risk of OGI was consistently higher for singletons born to women with than without GDM/DM irrespective of GW at delivery, while there was no significant difference in this risk between twins born to women with and without GDM/DM.

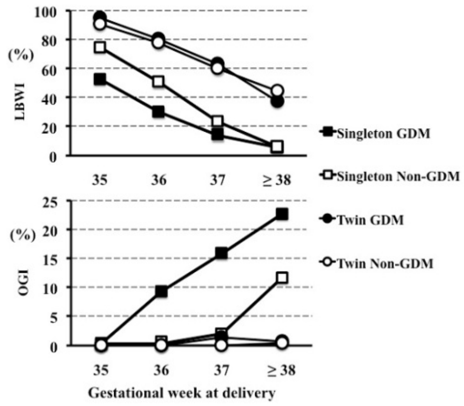

Figure 2 Fraction size of LBWI and OGI according to gestational week at delivery.

Maternal pre-pregnancy body mass index (BMI) was <20.4 kg/m^2 in 51% (4,630/9,024) and 50% (64,518/127,907) of mothers with twin and singleton pregnancies, respectively (**Table 2**). The risk of OGI born to women with BMI<20.4 and ≥20.4 did not differ significantly among twins (0.04% [2/4,630] vs. 0.18% [8/4,394], respectively, P = 0.0592), while the risk of LBWI were significantly higher for twins born to the former than the latter (71% [3,280/4,630] vs. 64% [2,818/4,394], respectively, P<0.0001). In singletons, the risk of OGI was significantly lower for those born to women with BMI<20.4 than with ≥20.4 (6.9% [4,435/64,518] vs. 13% [8,194/63,389], respectively, P<0.0001), while that of LBWI was significantly higher for those born to women with BMI<20.4 than with ≥20.4 (14% [8,713/64,518] vs. 10% [6,476/63,389], respectively, P<0.0001). Thus, the risk of OGI was very low (approximately 1 in 1,150 women), but the risk of LBWI was extremely high (>70%) for twins born to Japanese women with pre-pregnancy BMI<20.4.

Table 2 Frequency of LBWI and OGI according to maternal pre-pregnancy body mass index (BMI).

	Maternal pre-pregnancy BMI (kg/m^2)			
	Overall	**<20.4**	**≥20.4**	**P-value**
No. of twins	9024	4630	4394	
LBWI	6098 (67.6%)	3280 (70.8%	2818 (64.1%)	<0.0001
OGI	10 (0.11%)	2 (0.04%)	8 (0.18%)	0.0592
No. of singletons	127907	64518	63389	

LBWI	15189 (11.9%)	8713 (13.5%)	6476 (10.2%)	<0.0001
OGI	12629 (9.9%)	4435 (6.9%)	8194 (12.9%)	<0.0001

LBWI: Low Birth Weight Infant Defined as Birth Weight<2500 g; OGI: Overgrowth Infant defined as Birth Weight ≥ 3500 g.

Discussion

The present study demonstrated that the risk of LBWI was far greater (approximately 70%), while the risk of OGI was far lower (approximately 0.1%) among twins compared to singletons (LBWI of 12% and OGI of 10% for singletons) in Japan. In addition, 80% of women with twin pregnancies underwent caesarean section in which dystocia arising from fetal overgrowth may be uncommon. Thus, the main concern may be the risk of LBWI rather than OGI among Japanese women with twin pregnancies.

As increased plasma glucose level is closely associated with increased infant birth weight [5] treatment such as dietary intervention, self-monitoring of blood glucose and insulin therapy in women with GDM/DM can reduce birth weight, numbers of neonates with birth weight>4000 g and large for gestational age and fat mass in neonates [6]. In this study, 150 twins were born to 75 women diagnosed with GDM/DM, and 70% (105/150) were LBWI. Among diabetic pregnant women, the fraction size is far greater for GDM than pre-existing DM [16,19]. It was reasonable to speculate that the number of LBWI may have increased as a result of treatment for GDM in this population.

There was indeed an appreciable risk of OGI (approximately 1 in 5 and 10 infants to women with and without GDM/DM, respectively) in singleton pregnancies. However, the risk of OGI for twins was approximately 1 in 150 and 1,000 twins to women with and without GDM/DM, respectively. The overall risk of OGI was 0.11% (10/9,024) for twins and 9.9% (12,629/127,907) for singletons. Thus, the risk of OGI for twins was approximately 1% that for singletons. In women with twin pregnancies, screening of pre-existing DM targeting women with risk factors such as family history of DM and obesity [20] may be appropriate.

The present study was conducted in a population in which diagnosis of GDM/DM was based on the previous criteria before the introduction of the new criteria proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010 [21]. It has been shown that only a minor fraction of infants with birth weight>4000 g are born to women diagnosed with GDM based on the previous criteria: <6.0% in the era of the new criteria in the USA [22] and 12% [135/1,167] (**Figure 1**) in the present study. The IADPSG recommended new criteria for GDM with the goal of diagnosing milder glucose intolerance in pregnant women as GDM [21] and the Japan Society of Obstetrics and Gynecology adopted the IADPSG criteria in May 2010. As the new criteria allow the diagnosis of GDM in women with a lesser degree of glucose intolerance, the number of women diagnosed with GDM increased by several-fold with the new criteria [18]. This implied that more women with twin pregnancies than in the present study were being given treatment for GDM currently in Japan although they had a very low risk of OGI as well as a very high risk of LBWI.

Pre-pregnancy BMI is closely associated with the development of GDM [23] and a high pre-pregnancy BMI is an independent risk factor for OGI with birth weight ≥ 4000 g [24,25]. The risk of OGI defined as an infant with birth weight ≥ 3500 g was 0.04% (2/4,630) among twins born to women with pre-pregnancy BMI<20.4 in this study. This level, i.e., 0.04%, in the risk of OGI may allow Japanese women with twin pregnancies to skip screening for GDM if they had pre-pregnancy BMI<20.4.

The prevalence of hyperglycaemia was rather higher for singleton than twin pregnancies in this study. As the risk of GDM is similar irrespective of number of fetuses among women with similar age and pre-pregnancy BMI [26,27], this difference in the prevalence of hyperglycaemia may have been distorted by a selection bias [27]; fraction of women with either advanced age ≥ 40 years or pre-pregnancy BMI ≥ 25 was significantly greater in women with singleton than twin pregnancies in this population.

In conclusion, we compared risks of OGI and LBWI in singleton vs. twin pregnancies and demonstrated that the risk of OGI was extremely lower and the risk of LBWI was extremely higher in twin than singleton pregnancies. Although absolute risks of LBWI and OGI may differ according to ethnicity, LBWI is common and OGI is less common among twins irrespective of ethnicity. Screening and treatment for GDM may be performed in twin pregnancies worldwide. When considering the risks and benefits of universal screening for GDM in twin pregnancies, we should take the risk of LBWI as well as the association between LBWI and the development of adult diseases, such as type 2 diabetes, hypertension and ischaemic heart disease [5-8] into account. Research is needed to determine whether treatment for GDM is beneficial for women with twin pregnancies.

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