ORIGINAL ARTICLE

Gestational Diabetes Mellitus: Trend Assessment of Incidence and Related Risk Factors in Yazd-2008-2013

Narjes Hazar[1], Majid Jafarizadeh Malamiri[2*], Mohsen Mirzaei[3], Foroozandeh Kalantari[2], Mohammad Reza Sadeghiantafti[2], Mohammad Hassan Lotfi[4], Ali Zare[5], Masoud Rahmanian[6]

1. MD, Community Medicine Specialist, Deputy for Health Affairs, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
2. MD, Deputy for Health Affairs, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
3. MD, Department of Community Medicine, Health Monitoring Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
4. MD Ph.D. Department of Biostatistics and Epidemiology, Health Faculty, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
5. BS, Deputy for Health Affairs, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
6. MD, Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

***Correspondence:**
Majid Jafarizadeh Malamiri, MD, Deputy for Health Affairs, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
Tel: (98) 9131520374
Email: dr.jafarizadeh@gmail.com

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Abstract

Objective: Gestational Diabetes Mellitus (GDM) is an important condition in diabetes categories causing significant complications including pre-eclampsia and eclampsia among pregnant women. The aim of this study was to estimate the trend of annual GDM incidence and its risk factors in Yazd province, Iran, from 2008 to 2013.

Materials and Methods: The present study was conducted as a prospective cohort study in which all pregnant women who had attended primary health care centers were screened for GDM. Annual GDM incidence was calculated for all and also according to 5-year age groups and residential area (urban/rural). Secular trends for GDM incidence and its risk factors were also evaluated.

Results: In this study, 67320 pregnant women were screened for GDM and 5425 pregnant women were diagnosed as GDM with 6-year incidence of 8,6%. Annual incidence of GDM increased from 3.1% in 2008 to 18.9% in 2013. Assessment of crude and age-adjusted incidence across the years of follow up revealed incremental secular trend (*P*-value<0.001). Changes in GDM risk factors including maternal age and family history of diabetes were also significantly positive. GDM incidence increased in both rural and urban areas but the observed trend slopes were opposite in these different contexts.

Conclusion: Clinicians should have specific regard to pregnant women with some risk factors for timely diagnosis and treatment. Meanwhile returning to previous life style of rural area can help to decrease GDM incidence.

Keywords: Gestational diabetes mellitus, Trend, Incidence, Risk factors

Introduction

Gestational diabetes mellitus (GDM) is a condition in which blood glucose level increases during pregnancy without previous history of high blood glucose (1). GDM is an important condition in diabetes categories causing significant complications including pre-eclampsia and eclampsiaamong pregnant women (2). In addition, the risk of being large for gestational age and fetal

macrosomia, as a leading factor for increased incidence of shoulder dystocia and cesarean section, mounts in off-springs (3). Moreover, risk of developing overt diabetes increases after delivery and also in the rest of life among both affected mothers and their children (4). Therefore, prompt diagnosis and management of this condition is necessary to reduce maternal, fetal and childhood complications (5).

According to the literature, GDM incidence has been estimated between 5.8 to 12.9% in different regions around the world (6). Individual studies conducted in Iran, reported the incidence between 1.3 and 18.6 with a pooled prevalence of 3.4 % (7).

Several studies illustrated that GDM has become much more prevalent in recent years all over the world with an increasing secular trend due to older-age pregnancies along with lifestyle change consuming much more fat-reach foods and engaging less in physical activities (8). Another more important reason for this incremental grow this reduction in diagnostic cut-off points and also reliance on one instead of two abnormal tests in new diagnostic criteria (9,10).

According to our knowledge, there hasn't been conducted a comprehensive study concerning GDM incidence in Yazd province yet and therefor our knowledge is scant in this field. However, we know that GDM shares multiple risk factors with diabetes mellitus type 2 (T2DM). Moreover, the mechanisms underlying both conditions are similar including pancreas secretory malfunction and insulin resistance. Therefore, it can be hypothesized that prevalence of T2DM in a population may reflect GDM incidence in that population (11).

Islamic republic of Iran has been bearing a huge burden of T2DM. The results of Global Burdun of Disease 2010 study illustrated that diabetes had imposed a large and increasing numbers of life years lost due to death and disability on Iranian people during past two decades (12). In addition, the first National Survey of Risk Factors for Non-Communicable Diseases of Iran demonstrated that two million of the population aged 25-64 years had been affected by T2DM in 2005 (13).It has been projected that the population of afflicted individuals will increase up to 8,396,000 in 2035(14).

Yazd province is located in the center of Iran with a high prevalence of T2DM in previous years. In one comprehensive study in 1998, the prevalence of overt diabetes was estimated to be 14.5% in Yazd province (15). Another study in 2012 revealed that 16.3% of Yazd population had suffered from high blood sugar (16). Therefore, it might be expected that GDM incidence tend to be high in this province. Given the absence of reliable information on GDM status, head masters of deputy of health decided to plan and implement a universal screening program and then integrated it into primary health care (PHC). Therefore, all pregnant women without a history of T2DM had the opportunity to participate in this program. The final results of screening were used to estimate the trend of annual GDM incidence and its risk factors in Yazd province during 2008 to 2013.

Materials and Methods

This prospective cohort study was conducted in all primary health care centers and their related health houses in Yazd - Iran, during 2008-2013. All pregnant women who had attended these centers and looked for pregnancy care were eligible to include in the study. At first, the process of screening was described for pregnant women and after getting oral consent, they were enrolled. After that, pregnant women who suffered from each type of diabetes mellitus were excluded and referred to specialist to get adequate care. Otherwise, individuals' data including age, height, weight and GDM risk factors were extracted. These risk factors included age more than 30 years old, GDM history, family history of T2DM, history of hypertension, history of macrosomia (birth weight ≥ 4000gr), previous spontaneous abortion (≥2) or stillbirth, body mass index ≥ 30 kg/m2 and

history of fetal malformation in previous pregnancies. Multi- gravidity (third pregnancy or above) was also evaluated as another potential risk factor for GDM.

As most women had no reliable information on their weight before pregnancy, we asked care providers to weigh pregnant women at first visit and use that weight to calculate BMI.

After initial evaluation and risk assessment, screening tests had been done. During 2008 to mid-2012, laboratory screening tests were conducted in two steps (two-steps approach). At first step, glucose challenge test (GCT) with 50 gr glucose without fasting was done and 1-hour plasma glucose was measured. Each pregnant woman who had one or more aforementioned risk factors would undergo laboratory test at initial visit. Otherwise, screening at 24th-28th weeks of gestational age would be considered. One hour plasma glucose less than 130 mg/dl considered normal and GCT was repeated in pregnant women with at least one risk factor at 24-28th weeks. Those with plasma glucose ≥ 200 were diagnosed as GDM. Individuals with plasma glucose between 130 and 199 mg/dl were considered as suspected cases and had to undergo 100gr, 3-hour OGTT as the second step laboratory test. Interpretation of the results was established using the Carpenter and Coustan criteria (17). Pregnant women with at least two abnormal laboratory values were diagnosed as GDM. Those with one abnormal result would reevaluated one month later and would considered to be affected with GDM if at least two out-range values were detected. Because available glucose had produced as monohydrate type, pregnant women were provided with 55 gr or 110 gr glucose when GCT or OGTT had to be done respectively. At the middle of 2012, screening protocol was changed. According to this protocol, non-diabetic pregnant women should be assessed for GDM using FBS at initial visit. If the result of FBS had been 126 or more, pregnant woman would have been reevaluated and that person had been considered to be affected by DM2 if second test result had been 126 or above. These patients were referred to specialist in order to get advanced care. Pregnant women with FBS between 92 and 125 were diagnosed as GDM patients. Individuals with FBS less than 92 were assessed for GDM risk factors. In the presence of at least one risk factor, a 75 gr, 2-hour OGTT should be exploited as soon as possible. If at least one out of three results was out of range based on IADPSG criteria (FBS≥92, 1-hour BS≥180, 2-hour BS≥153), pregnant woman was considered to be afflicted with GDM. Otherwise, and in pregnant women without any risk factor, evaluation using OGTT was performed at 24–28 weeks of gestation and the diagnosis was established based on IADPSG criteria. Pregnant women were provided with 82.5 gr monohydrate glucose in this phase. All blood glucose measurements in both phases were performed in PHC laboratories using spectrophotometric methods.

Statistical analysis

Mean ± SD for continuous variables and frequencies for categorical variables were calculated. Annually incidence for GDM was calculated for all and also according to 5-year age groups and residential area (urban/rural). In addition, age adjustment was performed using WHO reference population (18) to eliminate the impacts of age differences between populations and make calculated incidence more comparable across the years (19) and then secular trend of age-adjusted incidence was evaluated.

Moreover, GDM risk factors' prevalence was evaluated for any significant trend across the years 2008-2013.

The analysis was performed using Stata version 12. Other statistical analysis was conducted inSPSS version 22. P-values less than 0.05 were considered to be statistically significant.

Results

In this study, 67320 pregnant women were screened for GDM from 2008 to 2013. Out of

them, 268 pregnant women had been diagnosed with DM type 2beforepregnancy or at initial evaluation during pregnancy. In addition, 2150 individuals experienced abortion before the time considered for prompt GDM diagnosis. Finally, 64902 pregnant women with mean age of 26.33 ± 5.3 years fulfilled eligibility criteria and entered the study (Table 1). During 6 years, 5425 pregnant women were diagnosed as GDM and 6-year incidence was 8,6%.The in cidence was 4.3% for first protocol and 19.4% for second one. Annual incidence of GDM increased from 3.1% in 2008 to 18.9% in 2013 and secular trend was statistically significant (*P*-value<0.001). As changing the protocol had let significant effects on GDM incidence, we decided to evaluate the annual trend of incidence for the first four years to assess the pattern of change regardless of protocol modification impacts. The results of analysis illustrated that changes of crude incidence was significantly positive in the passage of time.

After calculation of annual age-adjusted incidence of GDM the steady rise remained, as the trend increased during first three years but mildly decreased in forth year and then continued to increase with the slope similar to non-age adjusted incidence (Fig 1). In this phase of analysis, secular trend remained statistically significant for the first four years and also total years of follow up (*P*-value for trend <0.001). Evaluation of secular trend of GDM incidence in each age group also indicated a significant rise in GDM incidence in all age groups through aforementioned period (Table 2, Fig 2).

GDM incidence increased in both rural and urban areas during this 6-year period (*P*-value for trend <0.001), but the observed trend slopes were opposite in these different contexts during first three intervals as the trend was increasing in rural and decreasing in urban areas. Moreover, GDM incidence overtook in rural compared with urban area during last two intervals. (Table 3, Fig 3).

Changes in GDM risk factors across 6 years were also assessed. Observed changes in maternal age and family history of T2DM were significantly positive. Previous history of spontaneous abortion (2≤), history of GDM and multi-gravidity initially decreased and then increased through mentioned period of time. Previous macrosomia, previous congenital defect and stillbirth didn't change significantly across these years (Table 4).

Discussion

The present study was conducted in all primary health care centers and their related health houses in Yazd, Iran. The study population was all pregnant women who attended these centers to get perinatal care. Two screening protocols used in present study had been developed based on the latest available protocols in addition to diabetes management experts' opinion and the final versions had been approved by deputy of health affiliated to Shahid Sadooghi University of Medical Sciences, Yazd. In both protocols, recommendations had been developed in accordance with recommendations of American College of Obstetricians and Gynecologists (20) and similar to The Korea Society of Obstetrics and Gynecology (21) that advised to assess risk factors of GDM at initial prenatal care visit and perform screening tests for high risk pregnant women as soon as possible. At the time of developing first protocol, the most recommended screening method was performing Glucose Challenge Test (GCT) using 50 gram glucose followed by 3-hour Oral Glucose Tolerance Test (OGTT) using 100 gram glucose, in the case of GCT abnormality (two-steps approach) (22). A few years later, some guidelines changed their recommended screening laboratory tests to FPG for all pregnant women at first prenatal visit followed by 75-gr, 2 hour OGTT in 24^{th}-28^{th} gestational week if necessary (23). As this method seemed to be more practical and also acceptable for pregnant women, head masters of the cohort study decided to revise the method of screening in accordance with new protocol. In this way, they also took experts' opinion in the

field and employed the new method with some changes for the case of FPG ≤ 92, according to the recommendations of American College of Obstetricians and Gynecologists (20) and experts' opinion in the field.

According to the literature, using75-gr, 2 hour OGTT instead of two-steps approach may treble (10)or even quadruple (9) the incidence of GDM among screened pregnant women. In our study, the incidence with second protocol was around 4 times higher than the incidence with first protocol which was in accordance with the literature.

GDM incidence was estimated 8.6 % during six years of follow up. Between 2007-2009, another study was conducted by Soheilikhah and colleagues (24) on 1071 pregnant women who had attended two prenatal care centers in Yazd city, the capital of Yazd province and GDM was detected among 10.2% of study members which was higher than present study. The justification on this difference is not clear but reliance on only two referral centers and using different protocol for diagnosis in the

Table 1. Distribution of GDM affected women according to year, residential area and Age-group

Variable	Categories	GDM N (%)	Non-GDM N	Total
Year	2008	289 (3.1)	9076	9365
	2009	377 (3.7)	9939	10316
	2010	411 (4)	9766	10177
	2011	482 (4.5)	10331	10318
	2012	1319 (14.1)	8014	9333
	2013	2461 (18.9)	10533	12994
Residence	Rural	900 (7.7)	10755	11655
	Urban	4524 (8.8)	47157	51681
Age-group	< 25	1432 (5.6)	24023	25455
	25 -29	1599 (7.6)	19579	21178
	30-34	1470 (12.7)	10084	11554
	35-39	736 (17.1)	3573	4309
	≥ 40	184 (24.5)	567	751

Data are presented as frequency (percent)

Table 2. GDM incidence secular trend by age group

Age-group	2008	2009	2010	2011	2012	2013	*P*-value for trend
< 25	1.6	1.7	2.2	2.2	11.1	14.3	< 0.001
25 -29	2.9	3.2	2.9	4.1	11.9	17.2	< 0.001
30-34	5.7	5.5	6.7	7	18.5	25	< 0.001
35-39	6.9	12.3	12.4	9.8	25.3	28.9	< 0.001
> 40	10.1	16.7	17.7	17.7	36.7	41.6	< 0.001

Np-trend test has been done

Table 3. GDM incidence secular trend by residential area

Residential area	2008	2009	2010	2011	2012	2013	*P*-value for trend
Rural	2.4	2.7	3.1	4.1	16.8	19.6	< 0.001
Urban	3.3	3.9	4.2	4.5	13.6	18.8	< 0.001

Np-trend test has been done

Table 4. GDM incidence secular trend by different risk factors

Variable	2008	2009	2010	2011	2012	2013	*P*-value for trend
Age (Mean ± SD)	25.96 ± 5.2	26.13 ± 5.2	26.17 ± 5.2	26.35 ± 5.3	26.54 ± 5.3	26.73 ± 5.4	<0.001
Age > 30 (%)	18.9	20	19.8	21	22.4	23.7	<0.001
Family history of T2DM (%)	19.5	20.6	22.5	23.5	24	23.3	<0.001
HTN history (%)	1.2	0.9	0.8	1	0.9	0.8	0.039
Multi-gravidity (%)	23.5	23.4	22.8	23.5	25.1	27.5	<0.001
GDM history (%)	0.5	0.3	0.5	0.5	0.7	0.9	<0.001
Abortion history	2.6	2.2	2	1.9	2.1	2.1	0.036
Stillbirth history (%)	1.1	1	0.7	0.7	0.8	1	0.186
Macrosomia history	0.6	0.4	0.5	0.6	0.7	0.6	0.118
Congenital malformation history (%)	0.5	0.6	0.5	0.6	0.7	0.6	0.187

Np-trend test has been done

study of Soheilikhah and colleagues could be considered as the reasons of higher observed incidence.

In current study, the incidence of GDM experienced a significant secular trend, increased from 3.1 in 2008 to 18.9 in 2013.During 2007 to 2010, the pattern of change in GDM incidence was evaluated among nearly all pregnant women in South Korea (21). The screening protocol used for GDM diagnosis was as similar as the first protocol used in present study. Similar to our study, a significant positive change in annual incidence was observed in that region, from 3.86 in 2007 to 11.83 in 2010.Moreover, four American studies were also developed to assess annual trend of GDM (11). They ran universal screening among all pregnant women through 8 to 11 consecutive years (11). Although their screening and diagnostic protocols were different, they all found that the prevalence of GDM had been significantly increased in the USA.

The common fact in all of these studies is that the incidence of GDM has been increasing through the passage of time. There is no clear and distinct justification for this increasing secular trend. However, changing in the pattern of GDM risk factors might be considered as the predisposing factor. According to the literature, older age during pregnancy make mothers much more susceptible to be affected by GDM (25-27). In present study, pregnant women in higher age groups were much more affected in comparison with their counterparts in younger age groups. In addition, the average maternal age had been increased during six years of follow up. However, evaluation of age-standardized incidence revealed that the incidence has been increased during these years and the secular trend was significantly incremental. These findings illustrate that older age during pregnancy has not been a contributory factor to annual incidence increment and there are some other factors playing a significant role.

One of the risk factors is the presence of positive diabetes mellitus history in first-degree relatives (28-30). It is demonstrated that presence of family history of DM may increase GDM risk up to 2.2 folds (31). In current study, there was a significant incremental trend in the annual prevalence of positive family history of DM among pregnant women. Therefore, it may be hypothesized that this important risk factor is a contributory and predisposing factor in the rise of GDM annual incidence.

Another major risk factor for GDM is obesity. Nowadays, overweight and obesity get much more prevalent due to this fact that communities have encountered with life style change phenomenon in which people have tend to consume much more high caloric foods and do less physical activity(32). Obesity is classified among insulin resistance induced factors (33) which leads to GDM increase among pregnant women. Prevalence of obesity in Iran has been alarming in recent years (34). As an example, a cohort study was conducted in Tehran, the capital city of Iran, in three time sections from 1999 to 2008 in which obesity prevalence among women older than 20 years was 31,5 in 1999-2000, 37,7 in 2002-2005 and 38,6 in 2006-2008 and the trend was significantly incremental (35). In addition, three studies based on STEPs design were implemented in the whole country in 2007, 2008 and 2009 and the final data was analyzed at provincial level in Yazd (36-38). Final results illustrated that the prevalence of obesity in women aged 15-64 years was 19.9, 20.2 and 23.5 respectively. In current study, we didn't have access to most of women's weights before pregnancy and therefore, we were unable to evaluate obesity prevalence trend during the study period. However, observed trend of obesity in other studies might let us hypothesize that obesity has been one of the predisposing factors of GDM increase during years of follow up.

Different studies demonstrated that the history of GDM in previous pregnancies may be an important risk factor of existence GDM in

current pregnancy (29,39). As present study demonstrated, the prevalence of GDM history had a significant positive secular trend through the years of study and this finding make this sense that GDM history could be a predisposing factor to observed incremental trend.

There is some evidence that multi-parity (childbearing more than two times) is another risk factor for GDM (21) but the evidence on multi-gravidity is scant. In our study, multi-gravidity had been decreasing at first and then it started to increase during last three time-intervals. It can be assumed that multi-gravidity has been one of the predisposing factors of GDM during four last years of follow up.

In present study, GDM incidence trend was compared between rural and urban areas. This comparison revealed that GDM incidence was incremental in both regions except the slope of trend was increasing in rural areas and decreasing in urban settings. In recent decades, inhabitants of rural areas tend to use motorized transportation more than ever and also, enthusiasm to participate in agricultural and animal husbandry activities has been diminished. Moreover, usage of prepared and unhealthy foods has been increasing in recent years. These factors contribute to increase obesity among Iranian especially rural people which is a major risk factor in GDM (40).

Conclusions

Annual incidence of GDM increased through the study period. The secular trend was increasing in both rural and urban area. Moreover, the observed changes for some GDM related risk factors were also incremental. These findings suggest that we should have specific regard to pregnant women with some risk factors in order to provide them with timely diagnosis and treatment. Meanwhile, it seems that returning to previous conventional life style of rural area can help us to prevent or decrease GDM incidence.

Conflict of interest

All the authors declare that they have no conflict of interest.

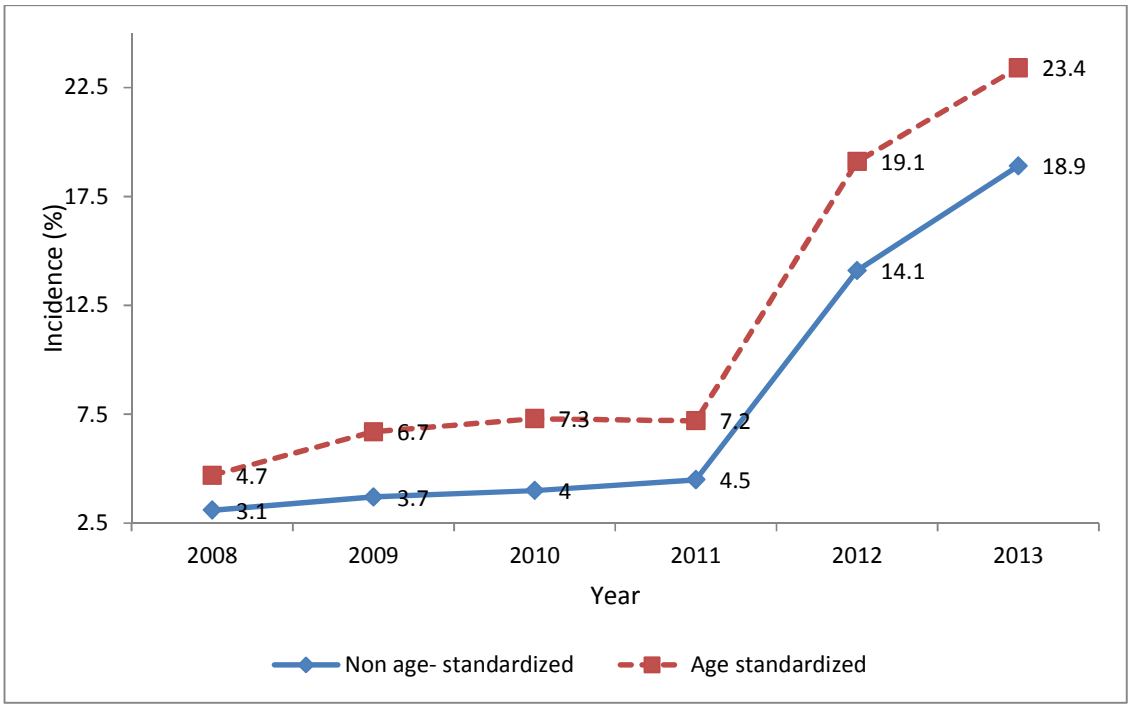

Figure 1. Crude Rate and Age Standardized Rate of GDM incidence

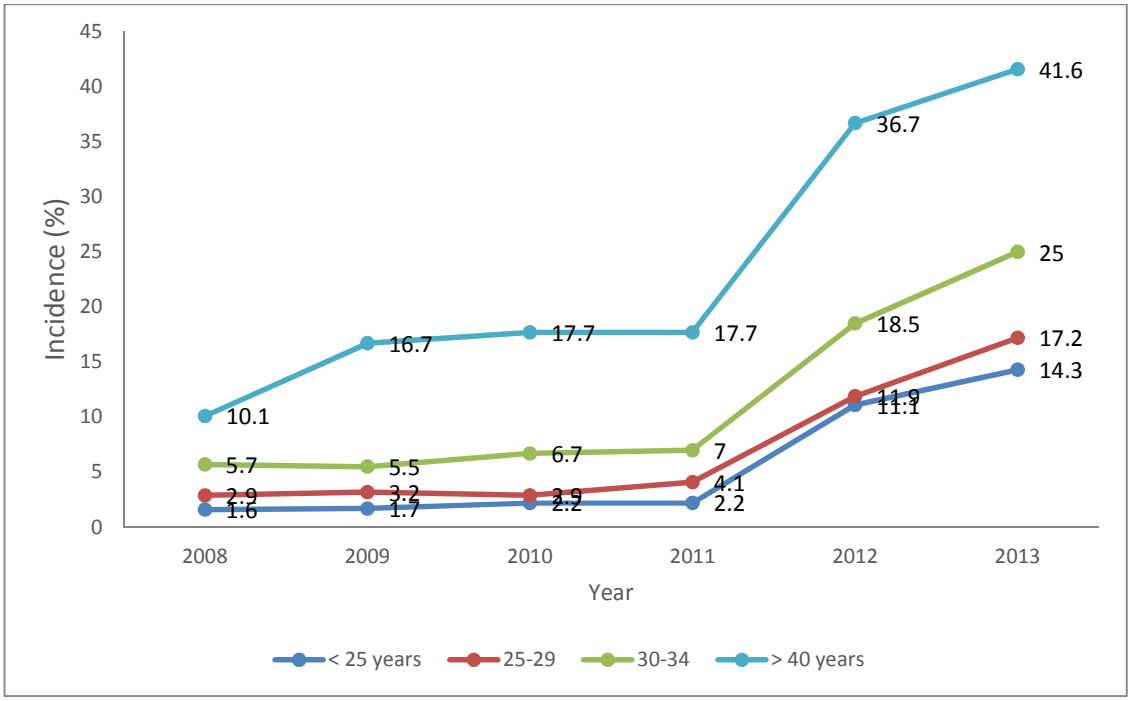

Figure 2. GDM incidence secular trend by age group

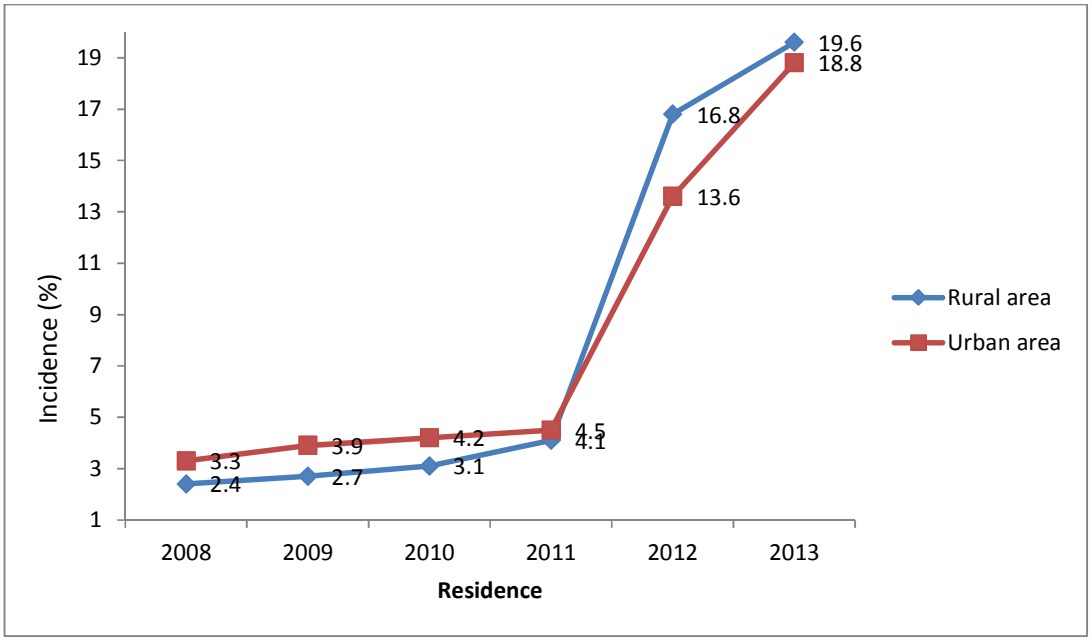

Figure 3. GDM incidence secular trend by residential area

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