Impact of Age at First Childbirth on Glucose Tolerance Status in Postmenopausal Women: The 2008–2011 Korean National Health and Nutrition Examination Survey

Jin Hwa Kim, Yun Jung, Sang Yong Kim, and Hak Yeon Bae

OBJECTIVE

The objective of the current study was to determine whether there was an association between age at first childbirth and glucose tolerance status in postmenopausal women.

RESEARCH DESIGN AND METHODS

This study was based on the data from the Korean National Health and Nutrition Examination Survey, conducted by the Korean Ministry of Health and Welfare from 2008–2011. Of 37,753 participants, data for 4,965 postmenopausal women were included in the analysis. Subjects were subdivided according to the age at first childbirth as follows: ≤19, 20–24, 25–29, and ≥30 years. Multivariate logistic regression analyses were used to identify whether there was an independent association between age at first childbirth and glucose tolerance status by adjusting for potential confounding factors.

RESULTS

The prevalence of impaired fasting glucose (IFG) and diabetes was 21.8% (1.066 of 4.965) and 15.3% (774 of 4,965), respectively. Diabetes prevalence differed significantly between the subgroups and was higher with earlier age at first childbirth: it was 10.9% in subjects aged ≥30 years and 23.8% in subjects aged ≤19 years at first childbirth. After fully adjusting for potential confounding factors, including lifestyle, sociodemographic factors, known diabetes risk factors, and reproductive factors, age at first childbirth ≤19 years was significantly associated with diabetes (odds ratio 1.492 [95% CI 1.005–2.215]). No significant associations were found between age at first childbirth and IFG.

CONCLUSIONS

Age at first childbirth influenced diabetes risk in postmenopausal women, and adolescent pregnancy was independently associated with a higher risk of diabetes in postmenopausal women.

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Department of Endocrinology and Metabolism, Chosun University Hospital, Gwangju, Republic of Korea

Corresponding author: Sang Yong Kim, diabetes@chosun.ac.kr.

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As the prevalence of diabetes increases, there is an increasing need to identify persons at risk in early life so they may benefit from early interventions to prevent diabetes later in life (1). Reproductive factors have been implicated in many health consequences for women in later life (2–4). Diabetes is associated with reproductive factors such as early menarche (5–7), early menopause (8,9), and higher parity (10–12).

Although pregnancy is a time-limited condition, childbearing can act as a medical stress test for the women through dramatic alterations in physiology and metabolism such as insulin resistance (13). The timing of childbearing has been associated with health in later life in some studies. Grundy and Holt (14) found that self-reported health among women aged 55–74 years was negatively associated with childbirth before age 23 years. Doblhammer (15) reported that women who gave childbirth before 20 years of age had a higher mortality risk at ages 50–85 years than other parous women. Another study reported an association between age at first childbirth and diabetes-related mortality in women aged 45–74 years; particularly, women who were teenage mothers were at high risk of dying from diabetes (16).

However, to our knowledge, no reports have investigated the influence of age at first childbirth on glucose tolerance status in women's later life, particularly during postmenopause. Postmenopause is related to insulin resistance and associated with risk of diabetes (17). The objective of the current study was to determine whether there was an association between age at first childbirth and glucose tolerance status in postmenopausal women.

RESEARCH DESIGN AND METHODS

Study Population

This study was based on the data from the Korea National Health and Nutrition Examination Survey (KNHANES), conducted by the Korean Ministry of Health and Welfare from 2008–2011. This survey is a cross-sectional and nationally representative study of noninstitutionalized civilians using a stratified, multistage, clustered probability sampling design. Sampling units are defined based on the data of household registries, including geographic area, sex, and age-groups. KNHANES is composed of a health interview survey, nutrition survey, and health examination survey conducted by trained investigators. All of the participants in this survey signed an informed consent form. Of the 37,753 participants in the 2008–2011 survey, we used data collected from 7,850 women who were postmenopausal. Menopause was defined as the absence of menses for 12 consecutive months. In the current study, postmenopausal women were limited to women with natural menopause. Thus, we excluded women with a history of hysterectomy (n = 911). We also excluded women with missing data for reproductive factors (n = 249), those without history of childbirth (n = 112), and those with missing or incomplete data for analysis (n = 1,613). Last, the data for 4,965 postmenopausal women were used for this analysis.

Measurement and Classification of Variables

Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA 225; seca Deutschland, Hamburg, Germany) while the participants were in the upright position. Body weight was measured to the nearest 0.1 kg on a balanced scale (GL-6000-20; CAS, Seoul, Korea). BMI was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference (WC) was measured midway between the costal margin and the iliac crest at the end of a normal expiration. Blood pressure (BP) was measured from the right arm using a standard mercury sphygmomanometer (Baumanometer; WA Baum Co., Copiague, NY) after 5 min of rest in the sitting position. The mean value of two separate BP measurements was used for analysis. Venous blood samples were obtained after a minimum fasting time of 8 h. Fasting plasma glucose (FPG) was measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan).

Self-reported questionnaires were administered to determine smoking status, alcohol drinking, family income, education level, residential area, regular exercise, and total energy intake. Residential area was categorized according to the Korean administrative district as an urban or rural area. Regular exercise was indicated as "yes" when the subject did moderate exercise on a regular basis (for $>$30 min at a time and more than five times per week). Known hypertension and dyslipidemia were defined as having treatment or being diagnosed by a physician. Subjects were also asked to recall reproductive factors, including age at menarche, age at menopause, number of pregnancies, age at first childbirth, oral contraceptive use, and hormone replacement therapy.

Statistical Analyses

Complex sample analysis was applied to the KNHANES data to weight all values following the recommendations from the Korea Centers for Diabetes Control and Prevention. Continuous variables are reported as the mean $\pm$ SD, and categorical variables are reported as weighted percentages. The comparisons among groups were performed using the t test for continuous variables, and the χ^2 test was used for categorical variables.

For data analysis, subjects were categorized into three groups according to glucose tolerance status: diabetes was defined as FPG $\geq$126 mg/dL, the use of insulin or antidiabetes medication, or being diagnosed with diabetes by a physician. Impaired fasting glucose (IFG) was defined as 100 mg/dL $\leq$FPG $<$126 mg/dL. Normal glucose tolerance (NGT) was defined as FPG $<$100 mg/dL and no history of the use of insulin or antidiabetes medication and no history of being diagnosed with diabetes by a physician. Subjects were also subdivided into four groups according to their age at first childbirth: $\leq$19, 20–24, 25–29, and $\geq$30 years.

Multivariate logistic regression analyses were used to measure the association between age at first childbirth and diabetes by evaluating the odds ratio (OR) after adjusting for potential confounding factors that were associated with an increased risk of diabetes . Analyses were adjusted for potential confounders in a series of models. Covariates were added to the

model: first, we added age and lifestyle behaviors (smoking status, alcohol drinking, and total energy intake), then sociodemographic factors (family income and education), then known diabetes risk factors (hypertension history, systolic BP, BMI, and WC), and finally reproductive factors (age at menarche, number of pregnancies, and hormone replacement therapy). In the analyses, age at first childbirth was entered as a categorical variable with age at first childbirth between 25 and 29 years taken as a reference because there were too many individual first childbirth ages.

Last, we assessed for interactions with key covariates by inclusion cross-product terms. Interaction between age and age at first childbirth was also assessed to confirm whether the association between age at first childbirth and glucose tolerance status differed by ages.

Statistical analyses were performed using SPSS software (version 18.0; SPSS Inc.), and a P value of <0.05 was considered to be statistically significant.

RESULTS

The basic patient characteristics are shown in Table 1. The mean age was 62.81 ± 0.19 years. The prevalence of IFG and diabetes was 21.8% (1.066 of 4.965) and 15.3% (774 of 4,965), respectively. As expected, subjects with IFG or diabetes were more likely to have higher BMI, WC, systolic BP, and FPG, history of hypertension, and history of dyslipidemia than those with NGT. Lower family income and education level were more common among subjects with IFG or diabetes. No

Table 1—Characteristics of the study population

	Total	NGT	IFG	Diabetes	*P* value
N (%)	4,965	3,125 (62.9)	1,066 (21.8)	774 (15.3)	
Age (years)	62.81 ± 0.19	61.68 ± 0.23	63.63 ± 0.37	66.24 ± 0.39	<0.001
BMI (kg/m^2)	24.22 ± 0.05	23.74 ± 0.65	24.89 ± 0.11	25.27 ± 0.13	<0.001
WC (cm)	82.45 ± 0.18	80.82 ± 0.22	84.27 ± 0.32	86.60 ± 0.39	<0.001
SBP (mmHg)	126.11 ± 0.365	123.89 ± 0.43	129.03 ± 0.67	131.09 ± 0.78	<0.001
DBP (mmHg)	77.17 ± 0.19	76.89 ± 0.24	78.52 ± 0.34	76.42 ± 0.42	<0.001
FPG (mg/dL)	101.21 ± 0.42	90.08 ± 0.13	107.12 ± 0.24	138.54 ± 1.88	<0.001
Smoking (%)					0.027
Never	91.1	91.3	89.9	91.7	
Past	2.1	2.4	1.1	2.1	
Current	6.9	6.3	9.0	6.2	
Alcohol drinking (%)					0.002
None	51.1	49.0	50.6	60.6	
≤1/week	42.9	44.9	42.8	34.9	
2–3/week	3.9	4.1	4.3	2.9	
≥4/week	2.0	2.0	2.3	1.6	
Family income[a] (%)					<0.001
<100	30.8	27.7	34.6	38.3	
100–199	20.4	20.2	20.2	22.0	
200–299	15.6	16.4	13.6	15.0	
≥300	33.2	35.8	31.7	24.6	
Less than high school education (%)	77.4	73.9	80.5	87.6	<0.001
Residence in urban area (%)	64.1	64.3	62.8	65.5	0.590
Regular exercise,[b] yes (%)	13.1	13.5	13.6	10.9	0.257
Total energy intake (kcal)	1,571.93 ± 12.40	1,596.47 ± 14.21	1,563.69 ± 28.32	1,482.88 ± 28.66	<0.001
Known hypertension (%)	39.1	31.0	45.2	63.7	<0.001
Known dyslipidemia (%)	12.8	9.8	13.7	24.2	<0.001
Age at menarche (years)	15.95 ± 0.04	15.87 ± 0.05	16.05 ± 0.07	16.09 ± 0.09	0.041
Age at menopause (years)	49.31 ± 0.07	49.34 ± 0.09	49.48 ± 0.17	48.94 ± 0.21	0.130
Pregnancies (*n*)	5.14 ± 0.017	5.06 ± 0.28	5.04 ± 0.08	5.60 ± 0.09	<0.001
OC, ever (%)	22.2	21.6	21.5	25.8	0.123
HRT, ever (%)	14.5	16.7	11.1	10.3	<0.001
Age at first childbirth (years)	23.68 ± 0.06	23.92 ± 0.08	23.51 ± 0.13	22.94 ± 0.15	<0.001
Age-group at first childbirth (%)					<0.001
≤19 years	9.7	8.2	10.2	15.0	
20–24 years	52.9	51.5	54.1	57.4	
25–29 years	31.9	34.0	31.7	23.7	
≥30 years	5.4	6.3	4.0	3.9	

Data are mean ± SD for continuous variables and weighted percentages for categorical variables. DBP, diastolic BP; HRT, hormone replacement therapy; OC, oral contraceptive; SBP, systolic BP. [a]Unit is 1,000 Korean wons/month. [b]Regular exercise was indicated as "yes" when the subject did moderate exercise on a regular basis (for >30 min at a time and more than five times per week).

significant differences were found for the residential area and regular exercise among each subgroups.

The mean age at first childbirth was 23.68 ± 0.06 years. Subjects with IFG or diabetes were more likely to be younger at first childbirth and to be ≤19 years at first childbirth than those with NGT. The number of pregnancies and age at menarche were more likely to be higher in subjects with diabetes. No significant differences were found for the age at menopause and oral contraceptive use among each subgroups.

Comparison of Clinical Characteristics and Glucose Tolerance Status Among Age-at-First-Childbirth Subgroups

Table 2 shows the characteristics of the subjects stratified into four groups by age at first childbirth. Subjects with earlier age at first childbirth were older; had higher BMI, WC, systolic BP, and FPG; and had had more pregnancies than those with later age at first childbirth. In addition, subjects with earlier age at first childbirth were more likely to have lower family income and education level.

Diabetes prevalence differed significantly between the subgroups and was higher with earlier age at first childbirth: this prevalence was 10.9% in subjects aged ≥30 years at first childbirth and 23.8% in subjects aged ≤19 years at first childbirth (Table 2). However, IFG prevalence was not significantly different between the subgroups, although it was higher with earlier age at first childbirth: it was 16.2% in subjects aged ≥30 years at first childbirth and 22.9% in subjects aged ≤19 years at first childbirth (Table 2).

Relationship Between Age at First Childbirth and Diabetes

Table 3 shows the results of the logistic regression analyses designed to examine the relationship between age at first childbirth and diabetes. In the unadjusted model, age at first childbirth 20–24 years and age at first childbirth ≤19 years were significantly associated with diabetes (OR 1.553 [95% CI 1.244–1.938] and OR 2.435 [1.742–3.404], respectively) compared with age at first childbirth 25–29 years. After further multivariable adjustment for age and lifestyle behaviors, the ORs were attenuated but remained significant (age at first childbirth 20–24 years: OR 1.346 [1.065–1.702]; age at first childbirth ≤19 years: OR 1.671

Table 2—Characteristics of the study population according to age at first childbirth

	Age at first childbirth (years)				
	≤19	20–24	25–29	≥30	*P* value
n	494	2,720	1,516	235	
Age (years)	70.04 ± 0.58	63.67 ± 0.24	59.74 ± 0.25	59.56 ± 0.80	<0.001
BMI (kg/m^2)	24.65 ± 0.17	24.37 ± 0.07	23.96 ± 0.09	23.59 ± 0.25	<0.001
WC (cm)	84.77 ± 0.49	83.13 ± 0.22	81.17 ± 0.29	79.31 ± 0.70	<0.001
SBP (mmHg)	130.23 ± 0.91	126.42 ± 0.46	124.83 ± 0.60	123.36 ± 1.78	<0.001
DBP (mmHg)	76.46 ± 0.48	77.01 ± 0.25	77.75 ± 0.32	76.72 ± 0.93	0.088
FPG (mg/dL)	105.00 ± 1.82	102.37 ± 0.63	98.78 ± 0.61	97.50 ± 1.38	<0.001
Smoking (%)					<0.001
Never	81.2	91.9	93.6	85.9	
Past	3.9	2.0	1.9	1.4	
Current	15.0	6.2	4.5	10.1	
Alcohol drinking (%)					0.008
None	59.4	50.4	49.2	54.8	
≤1/week	34.0	43.1	46.0	38.6	
2–3/week	2.9	4.4	3.4	4.9	
≥4/week	3.8	2.1	1.4	1.7	
Family income[a] (%)					<0.001
<100	48.6	35.8	20.0	14.4	
100–199	21.7	21.3	17.8	24.9	
200–299	9.8	14.3	18.6	20.4	
≥300	20.0	28.6	43.6	40.3	
Less than high school education (%)	98.0	86.3	60.3	54.5	<0.001
Total energy intake (kcal)	1,377.67 ± 29.35	1,567.23 ± 15.50	1,624.81 ± 20.64	1,652.49 ± 59.91	<0.001
Known hypertension (%)	56.3	39.9	34.3	28.3	<0.001
Known dyslipidemia (%)	9.1	13.0	13.4	14.9	0.184
Age at menarche (years)	15.76 ± 0.08	16.17 ± 0.04	15.68 ± 0.07	15.67 ± 0.15	<0.001
Pregnancies (*n*)	6.32 ± 0.14	5.29 ± 0.05	4.83 ± 0.54	3.29 ± 0.12	<0.001
HRT, ever (%)	7.6	12.8	17.9	23.2	<0.001
IFG (%)	22.9	22.3	21.7	16.2	0.257
Diabetes (%)	23.8	16.6	11.4	10.9	<0.001

Data are mean ± SD for continuous variables and weighted percentages for categorical variables. DBP, diastolic BP; HRT, hormone replacement therapy; SBP, systolic BP. [a]Unit is 1,000 Korean wons/month.

Table 3—OR (95% CI) for diabetes according to age at first childbirth

	≤19 years	20–24 years	25–29 years (reference)	≥30 years
Diabetes				
Model 1	2.435 (1.742–3.404)*	1.553 (1.244–1.938)*	1.00	0.954 (0.561–1.623)
Model 2	1.671 (1.148–2.432)*	1.346 (1.065–1.702)*	1.00	0.954 (0.557–1.634)
Model 3	1.533 (1.048–2.242)*	1.243 (0.972–1.589)	1.00	0.959 (0.560–1.642)
Model 4	1.501 (1.010–2.229)*	1.225 (0.941–1.594)	1.00	1.077 (0.615–1.888)
Model 5	1.492 (1.005–2.215)*	1.219 (0.936–1.587)	1.00	1.085 (0.617–1.907)

Model 1: unadjusted. Model 2: adjusted for age and lifestyle behaviors (smoking status, alcohol drinking, and total energy intake). Model 3: model 2 plus sociodemographic factors (family income and education). Model 4: model 3 plus diabetes risk factors (known hypertension, systolic BP, BMI, and WC). Model 5: model 4 plus reproductive factors (age at menarche, number of pregnancies, and hormone replacement therapy). *$P < 0.05$.

[1.148–2.432]). After adjustment for the previous factors as well as for sociodemographic factors, age at first childbirth 20–24 years was no longer significantly associated with diabetes (1.243 [0.972–1.589]) but remained significant in subjects aged ≤19 years at first childbirth (1.533 [1.048–2.242]). These independent associations remained after adjustment for the known diabetes risk factors in addition to the above factors (age at first childbirth ≤19 years: 1.501 [1.010–2.229]). After further adjustment for reproductive factors, the association remained significant in subjects aged ≤19 years at first childbirth (1.492 [1.005–2.215]). There were no significant association between other reproductive factors on model 5 and diabetes (Table 4).

In the above analyses, there were no significant interactions by any covariates including age and age at first childbirth for any glucose tolerance status (all $P > 0.05$).

CONCLUSIONS

In this study, adolescent pregnancy (age at first childbirth ≤19 years) was independently associated with a higher risk of diabetes in postmenopausal women, after adjustment for multiple potential confounding variables. We did not find a significant association between age at first childbirth and prevalence of IFG. To our knowledge, this is the first large population-based study to explore the association between age at first childbirth and glucose tolerance status in postmenopausal women. Our results indicate long-term effects of age at first childbirth on incident diabetes.

As this study had a cross-sectional design, it was not possible to determine which mechanisms connect adolescent pregnancy and increasing risk of diabetes. Several possibilities may be suggested.

First, the effect of estrogen activity can vary depending on the physiology of the woman at a given age (18). Deleterious outcomes can occur in an organism that is not physiologically prepared for such activity. An early start of estrogen exposure, such as an early age at menarche, can have an adverse effect on glucose tolerance, leading to increase diabetes risk (5–7). Pregnancy during adolescence may therefore be correlated with the earlier exposure of biologically immature organs to a high dose of estrogen (19), which can induce subtle, deleterious changes in glucose metabolism. These changes could be sustained, leading to increased risk of diabetes in later life when the cumulative effects of aging diminish the reserves of an already vulnerable organ, or menopause state–related insulin resistance status triggers increased glucose level.

Second, during pregnancy, nearly every organ of the mother's body must work harder to meet the demands of the developing fetus (13,19). It is possible that an organ system is unable to meet the increased physiological demands of pregnancy in an adolescent mother, who is still growing and has not completed her own physical growth. These can be induced gestational syndromes, including diabetes (20–23). It is generally assumed that pregnancy-associated insulin resistance resolves after parturition, though some of the components reappear in later life (24).

Third, pregnancy is a phase when fat may accumulate rapidly and change in its distribution (25). Obesity may also be an intermediating factor between young pregnancy and later diabetes risk, as teenage pregnancies are characterized by higher weight gain compared with adult pregnancies. Some studies suggest that this excessive gestational weight gain not only contributes to adolescent obesity but also increases the risk of becoming overweight during adulthood. Adolescent mothers are at increased risk of subsequent obesity (26–28). The consequences of childbearing, which involves several role changes and stresses, can also induce unhealthy behaviors, such as a lower physical activity and a higher caloric intake (29). These sedentary lifestyle behaviors can contribute to the development of obesity. The duration of obesity is a strong risk factor for diabetes (30). Postpartum weight retention and development of obesity, especially

Table 4—OR (95% CI) for diabetes of other reproductive factors on model 5

	Diabetes
Age at menarche (years)	0.988 (0.937–1.042)
Number of pregnancies	1.001 (0.998–1.003)
Hormone replacement therapy (ever)	0.831 (0.598–1.155)

Model 5: adjusted for age, lifestyle behaviors (smoking status, alcohol drinking, and total energy intake), sociodemographic factors (family income and education), diabetes risk factors (known hypertension, systolic BP, BMI, and WC), and other reproductive factors.

abdominal obesity, in young age may confer diabetes risk by adding to the individual's cumulative exposure to obesity. However, unfortunately, no information on gestational weight gain, postpartum weight retention, and lifetime weight change was available in the current study. Additional studies are needed to explore these potential causal relationships in more detail.

Fourth, women with history of adolescent pregnancy may have higher parity. Multiparity has been suggested to be a risk factor for type 2 diabetes in later life (10–12). A previous study found that increasing parity was correlated with an early age at first childbirth (31). In the current study, subjects with earlier age at first childbirth had more pregnancies than those with later age at first childbirth. However, the association of adolescent pregnancy with diabetes remained significant after adjustment for the number of pregnancies in the current study. There was no significant association between number of pregnancies and diabetes. This finding suggests that adolescent pregnancy may itself influence glucose tolerance status via pathophysiological pathways other than those related to number of pregnancies.

Fifth, socioeconomic status might lead to both earlier age at first birth and risk of diabetes as selection effects. The effect of these selective processes certainly have varied over time and between social groups. Education, family income, and residential area were considerable confounders of the association between age at first childbirth and diabetes in the current study. The addition of these variables to the multivariable models attenuated the magnitude of association between age at first childbirth and diabetes but continued to be statistically significant in women $<$25 years of age at first childbirth. Lower socioeconomic status seems to confound or mediate that association and can also affect lifestyle behaviors and the risk of diabetes. However, these results should be interpreted with caution because our data on socioeconomic factors reflect the status at enrollment but not during the adolescent period.

The strength of our study is that it was a large population-based national representative study that considered a comprehensive range of possible confounding and mediating factors, including sociodemographic, lifestyle, anthropometric, and reproductive factors. Nevertheless, there were several limitations. The measurements were performed at a certain time in a cross-sectional design; thus, a causal relationship could not be clearly determined. For the identification and classification of glucose tolerance status, the lack of oral glucose tolerance tests and HbA_{1c} data are also an important limitation of this study, as is the fact that we had only a single measurement of FPG. Another limitation was that age at first childbirth, age at menopause, and age at menarche were based on self-report, which is prone to recall bias. However, the recall of reproductive factors is expected to be valid and reliable (32,33). We also did not have information regarding the history of gestational diabetes, live first childbirth, and sex of the offspring. We lastly should note that the adolescent environmental conditions of this study population were different from those of today's adolescents, making these results potentially less generalizable to today's women. Women in this study were likely to have experienced relatively difficult or even traumatic adolescent periods compared with today's women because that period included the Japanese colonial period, World War II, and the Korean War. These environmental realities may have further increased the risk of diabetes in this study population.

In conclusion, age at first childbirth influenced diabetes in postmenopausal women, and adolescent pregnancy was independently associated with a higher risk of diabetes in postmenopausal women. We propose that adolescent pregnancy may contribute to the development of diabetes in later life and should be considered a risk factor for diabetes. Therefore, for effective prevention of diabetes in postmenopausal women, more attention should be focused on women with adolescent pregnancy. A prospective study is needed to explore the possible causal relationship between adolescent pregnancy and later diabetes.

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