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Multiple pregnancies and the risk of diabetes mellitus in postmenopausal women

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Abstract

Objective: We aimed to investigate whether the number of pregnancies during childbearing age was associated with diabetes in postmenopausal women with no history of gestational diabetes.

Methods: Our data source was the continuous National Health and Nutrition Examination Survey 1999 to 2014. We selected 9,138 postmenopausal women over 40 years old who did not have a history of gestational diabetes during pregnancy. Logistic regression analyses were applied for the association of the number of pregnancies with diabetes.

Results: We found women with $\geq$4 pregnancies had significantly greater fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), 2-hour plasma glucose, and the Homeostatic Model Assessment of Insulin Resistance than those with two to three pregnancies (all $P < 0.01$). These women also had a significantly higher prevalence of diabetes (28.4% vs 20.7%; $P < 0.001$). Using the two to three pregnancies group as the reference, we observed a positive association of log-FPG and log-HbA1c with 4 or more pregnancies after adjustment for sociodemographic, lifestyle, and reproductive factors, and body mass index (both $P < 0.05$). Compared to women with two to three pregnancies, the odds ratios for diabetes were 1.31 (95% confidence interval [CI] 1.01-1.71) for women who never got pregnant and 1.28 (95% CI 1.10-1.48) for those with at least 4 pregnancies after multivariate adjustment.

Conclusions: At least 4 pregnancies through childbearing age may be a potential risk factor for diabetes in postmenopausal women without a history of gestational diabetes.

Key Words: Diabetes mellitus – NHANES – Number of pregnancies – Postmenopausal women – Reproductive factors.

Diabetes is dramatically increasing, imposing a large economic burden on healthcare systems worldwide.[1] Globally, it has been estimated by the International Diabetes Federation that 8.2% of adults aged 20 to 79 years are living with diabetes, and this number is projected to rise beyond 592 million in 2035.[2] In the general US population, the prevalence of diabetes is even higher and has reached up to approximately 14.3%.[3] Type 2 diabetes mellitus (T2DM) is frequently not diagnosed until severe complications appear.[4] In this context, it is of great value to identify persons at risk as early as possible to initiate primary prevention or treatment.

Reproductive factors in the pathophysiology of diabetes have gained interest in the past decade. A growing body of evidence suggests that earlier age of menarche, postmenopausal status, and both shorter and longer reproductive life spans increase the risk of insulin resistance and T2DM.[5-7] Pregnancy has also long been regarded as ''diabetogenic'' due to the progressive metabolic alterations during gestation that lead to a state of insulin resistance and compensatory hyperinsulinemia.[8,9] It has been suggested that additional pregnancies may impair the ability of normal beta cell function to maintain long-term glucose homeostasis after pregnancy.[10] However, whether subsequent pregnancy is a risk factor for diabetes in later life is still debated. The Atherosclerosis Risk in Communities Study showed that grand multiparity was associated with a 27% increased risk of diabetes in White and African-American women after adjustment for a range of demographic, and lifestyle-related factors including body mass index (BMI).[11] Moreover, another Danish study also

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found an increase in the risk of diabetes with increasing parity.[12] Nevertheless, the results of recent studies were not consistent with this hypothesis.[13-15] The most recent study, which included 16,817 participants, reported that a subsequent pregnancy is not necessarily associated with an increment in diabetes risk after gestational diabetes mellitus (GDM).[15]

Concerning the discordant results that have been reported in this field, doctors may be confused over the reproductive advice that should be given to women of childbearing age. Hence, we explored the effect of multiple pregnancies on the risk of developing diabetes in a large cohort of postmenopausal women in the continuous National Health and Nutrition Examination Survey (NHANES).

METHODS

Study population

The NHANES are cross-sectional multistage, stratified, clustered probability samples of the US noninstitutionalized population conducted by the National Center for Health Statistics (NCHS), branch of the Centers for Disease Control and Prevention. Data are available from the continuous NHANES, conducted from 1999 to 2014 (data released in 2-year cycles). The NHANES protocols were approved by the NCHS institutional review board, and written informed consent was obtained from all participants.

In total, there were 9,555 postmenopausal women aged 40 years and older. Women with self-reported gestational diabetes (n = 224) were excluded from this analysis. Also excluded were those with missing information on the number of pregnancies (n = 192) and diabetes (n = 1). After these exclusions, 9,138 postmenopausal women remained for the final analysis.

Measurements

The data were collected via an interview conducted at home and a visit to a mobile examination center. A standardized questionnaire was used to collect information on age, sex, race/ethnicity, education level, and annual household income. Race/ethnicity was categorized into Mexican American, other-Hispanic White, other-Hispanic Black, and other races. Education was categorized as less than a high school education, high school graduate, and education beyond high school. Current smoking was defined as having smoked at least 100 cigarettes in one's lifetime and currently smoking cigarettes. BMI was calculated as weight (kg) divided by the square of height (m^2). Additionally, oral contraceptive use, and use of hormone therapy (HT) were derived from the reproductive health data using questionnaires ''Have you ever taken birth control pills for any reason?'', and ''Have you ever used female hormones such as estrogen and progesterone?''. Age at menarche and age at menopause were assessed by self-report.

Glycated hemoglobin (HbA1c) level was analyzed in whole blood samples with high-performance liquid chromatography. Although different equipment was used over time, calibration of HbA1c was not necessary according to NHANES recommendations.[16] An oral glucose tolerance test was performed using 75 g of glucose, followed by venipuncture to measure 2-hour plasma glucose (2-h PG). In NHANES 1999 to 2004, plasma glucose was measured at the University of Missouri-Columbia with a Roche Cobas Mira instrument. It was measured at the University of Minnesota using a Roche/Hitachi 911 instrument in 2005 to 2006 and a Roche Modular P chemistry analyzer in 2007 to 2012. In NHANES 2013 to 2014, plasma glucose was measured using a Roche/Hitachi Cobas C chemistry analyzer at the University of Missouri-Columbia. Fasting insulin was analyzed using Merocodia Insulin ELISA kits.

Definition of variables

Our primary outcome was diabetes. Diabetes was defined as a previous diagnosis by physician, a HbA1c level of 6.5% or more, a fasting plasma glucose (FPG) level of 7.0 mmol/L (126 mg/dL) or more, or a 2-h PG level of 11.1 mmol/L (200 mg/dL) or more. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated as fasting glucose (mmol/L) $\times$ fasting insulin (μU/mL)/22.5. Our primary exposure was history of pregnancy, and this was assessed in two separate manners: as a self-reported dichotomous variable assessed from the reproductive health data file of the questionnaire, ''Ever been pregnant?'', and as a continuous variable from the same data file of the questionnaire asking, ''How many times have you been pregnant?''. In both instances, these include all pregnancies including live births, and also miscarriages, stillbirths, tubal pregnancies, and abortions. Postmenopausal women were categorized into four groups according to their number of pregnancies during their childbearing age: 2 to 3 (reference), 0, 1, and $\geq$4 times.

Statistical analysis

IBM SPSS Statistics, version 22 (IBM Corp), was used to perform all analyses. Two-tailed $P < 0.05$ was considered statistically significant. The continuous variables were summarized as the mean $\pm$ SD or median (25th and 75th percentile) based on their distribution style, and the categorical variables were summarized as a percentage (%). The Kolmogorov-Smirnov test was applied to test for normality. We used Student's *t* test for continuous variables with a normal distribution, Mann-Whitney *U* test for continuous variables with a skewed distribution, and the Pearson chi-square test for categorical variables to compare the characteristics of the study sample. To account for multiple comparisons, least significant difference was used.

The association between the number of pregnancies (independent variable) and the parameters of glucose metabolism (dependent variable) were assessed via linear regression. Model 1 was unadjusted. Model 2 included age, race, and educational level. Model 3 was further adjusted for annual household income, current smoking, BMI, physical activity, age of menarche, age of menopause, use of HT, oral contraceptive use and NHANES cycle. Educational level and annual household income are important socioeconomic factors that are closely associated with number of pregnancies and diabetes.[17] Age of menarche, age of menopause, use of HT, and oral contraceptive use are reproductive factors that have been gradually revealed to be associated with diabetes.[5-7] HbA1c, FPG, 2-h PG, and HOMA-IR were normalized by logarithmic transformation because of their skewed distributions. The results were reported as unstandardized coefficients and standard errors.

To consider the diabetes probability model, binary logistic regression analysis was applied. Data were reported as the odds ratio (OR) and 95% confidence interval (CI). The models were the same as those used for the linear regression analysis.

Sensitivity analysis

In the sensitivity analysis, our exposure became those pregnancies with live births, which was assessed from the reproductive health data file of the questionnaire, ''How many deliveries resulted in a live birth?''. In addition, we conducted sensitivity analysis by using one or two pregnancies as the reference. Finally, in NHANES 2011 to 2012 and NHANES 2013 to 2014, the diabetes file of the questionnaire consisted of the family history of diabetes, which is one of the important confounders. Hence, we further adjusted for family history of diabetes and reanalyzed our results using the NHANES 2011 to 2014 data.

RESULTS

General characteristics of postmenopausal women stratified by number of pregnancies in their childbearing age

In all, 9,138 postmenopausal women met our selection criteria of being ≥40 years old and having documented reproductive history and diabetes information. Of these 9,138 postmenopausal women, 3,646 reported being pregnant two to three times, 610 reported never being pregnant, and 4,052 reported being pregnant at least four times during their childbearing age. The general characteristics of these postmenopausal women are presented in Table 1.

Compared with those who had two to three pregnancies, women who reported being pregnant at least four times were older, were more likely to be Mexican American and less likely to be non-Hispanic white, had a lower educational level, and less annual household income. These women also had significantly greater BMI, FPG, HbA1c, 2-hour PG, and

TABLE 1. *General characteristics of postmenopausal women according to number of pregnancies*

	Number of pregnancies			
	2-3	0	1	≥4
N	3,646	610	830	4,052
Age, y	64 ± 11	64 ± 11	64 ± 11	66 ± 10[c]
Race, %				
Mexican American	10.2	8.2	8.0[a]	22.1[c]
Other Hispanic	6.9	7.1	6.6	8.0
Non-Hispanic white	57.6	59.3	58.4	43.3[c]
Non-Hispanic black	20.1	18.4	23.5[a]	21.2
Other race	5.2	7.0	3.5[a]	5.4
Education level, %				
<High school	23.4	18.9[a]	22.0	44.8[c]
High school	27.6	20.0[c]	26.9	23.5[c]
>High school	49.0	61.1[c]	51.1	31.7[c]
Annual household income, %				
Under $25,000	31.1	33.2	32.1	41.3[c]
$25,000-$54,999	30.8	27.8	27.0	30.7
$55,000 and over	38.1	39.0	40.8	28.0[c]
Current smoker, %	41.2	37.4	48.0[c]	39.6
BMI, kg/m^2	28.3 (24.5-33.0)	27.9 (23.9-33.2)	27.6 (23.6-32.8)[a]	29.0 (25.1-33.6)[c]
BMI categories, %				
Normal	28.0	30.7	33.7[b]	24.3[c]
Overweight	32.1	31.3	28.8	32.2
Obese	39.9	38.0	37.5	43.5[b]
Age of menarche, y	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)
Age of menopause, y	46 (40-51)	47 (40-51)	46 (40-50)	47 (40-51)
Oral contraceptive use, %	59.2	44.5[c]	54.9[a]	51.9[c]
Use of HT, %	43.7	37.5[b]	45.3	35.0[c]
FPG, mmol/L	5.61 (5.22-6.22)	5.64 (5.16-6.47)	5.55 (5.16-6.11)	5.72 (5.27-6.50)[c]
2-h PG, mmol/L	6.66 (5.55-8.60)	6.61 (5.15-9.01)	6.72 (5.47-8.80)	7.16 (5.77-9.22)[b]
HbA1c, %	5.60 (5.30-6.00)	5.60 (5.40-6.10)	5.60 (5.30-5.90)[a]	5.70 (5.40-6.10)[c]
HOMA-IR	2.40 (1.39-4.41)	2.31 (1.43-4.52)	2.29 (1.40-3.81)	2.70 (1.64-4.83)[c]

Data were summarized as the mean ± SD or median (interquartile range) for continuous variables based on their distribution style or as a number with proportion for categorical variables.
FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment index of insulin resistance; HT, hormone therapy; 2-hour PG, 2-hour plasma glucose.
Overweight and obese adults were defined based upon BMI measures of 25-29.9 kg/m^2 and ≥30 kg/m^2, respectively.
[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$, vs number of pregnancies 2-3 group.

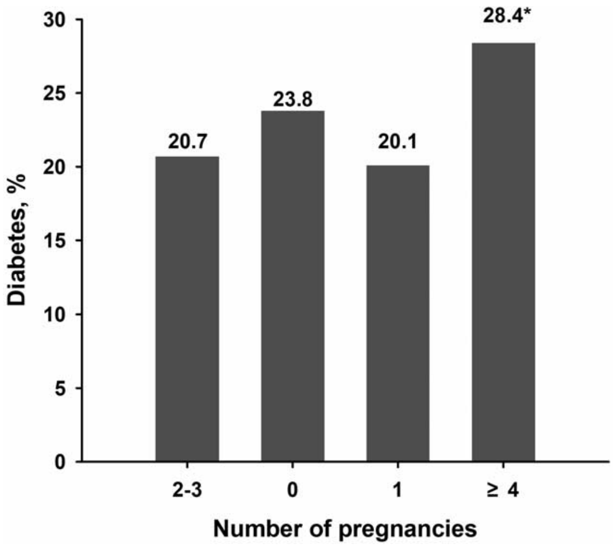

FIG. 1. The prevalence of diabetes according to number of pregnancies in postmenopausal women. *$P < 0.05$, vs women with two to three pregnancies.

HOMA-IR (all $P < 0.01$). In addition, women who reported never being pregnant had a higher educational level and annual household income. These women were less likely to use oral contraceptives and HT ($P < 0.01$).

Prevalence of diabetes stratified by number of pregnancies in their childbearing age

As shown in Fig. 1, the prevalence of diabetes was significantly higher in women with at least four pregnancies than in those with two to three pregnancies (28.4% vs 20.7%; $P < 0.001$). Women who reported never being pregnant also had higher diabetes prevalence than those with two to three pregnancies, though the significance was marginal (23.8% vs 20.7%; $P = 0.086$).

Association between the number of pregnancies and the parameters of glucose metabolism

Table 2 gives the results of the association between the number of pregnancies and the parameters of glucose metabolism. Using the two to three pregnancies group as the reference, we observed a significant association of log-FPG, log-HbA1c, log 2-hour PG, and log-HOMA-IR with four or more pregnancies in the unadjusted model (Table 2, model 1). Further adjustments for socioeconomic, lifestyle, and reproductive factors and BMI attenuated such association, but there was still significance in log-FPG and log-HbA1c (Table 2, model 2).

Association between number of pregnancies and diabetes

Table 3 provides the association between the number of pregnancies and diabetes. In the unadjusted model, those with four or more pregnancies were at higher risk of diabetes (OR 1.52, 95% CI 1.36-1.68). After adjustment for age, race, educational level, annual household income, current smoking, BMI, physical activity, age of menarche, age of menopause, use of HT, oral contraceptive use, and NHANES cycle, an increase in the odds of having diabetes was seen in women with no pregnancy (OR 1.31, 95% CI 1.01-1.71) and those who had at least four pregnancies (OR 1.28, 95% CI 1.10-1.48).

TABLE 2. *Association between number of pregnancies (independent variable) and parameters of glucose metabolism (dependent variable): linear regression*

	Number of pregnancies			
	2-3	0	1	≥4
HbA1c				
Model 1	Ref.	0.004 (0.003)	−0.003 (0.003)	0.012 (0.002)[c]
Model 2	Ref.	0.006 (0.003)[a]	−0.003 (0.003)	0.007 (0.002)[c]
Model 3	Ref.	0.005 (0.004)	−0.001 (0.003)	0.005 (0.002)[a]
FPG				
Model 1	Ref.	0.014 (0.007)[a]	0.001 (0.007)	0.019 (0.004)[c]
Model 2	Ref.	0.017 (0.007)[a]	0.001 (0.007)	0.012 (0.004)[b]
Model 3	Ref.	0.017 (0.008)[a]	0.008 (0.007)	0.012 (0.005)[a]
2-h PG				
Model 1	Ref.	−0.009 (0.013)	−0.008 (0.012)	0.021 (0.008)[b]
Model 2	Ref.	0.000 (0.013)	0.000 (0.012)	0.006 (0.008)
Model 3	Ref.	0.001 (0.014)	0.017 (0.013)	0.003 (0.008)
HOMA-IR				
Model 1	Ref.	−0.004 (0.027)	−0.018 (0.026)	0.059 (0.015)[c]
Model 2	Ref.	0.003 (0.026)	−0.016 (0.026)	0.041 (0.016)[b]
Model 3	Ref.	−0.002 (0.029)	0.018 (0.027)	0.029 (0.016)

Because HbA1c, FPG, 2-h PG, and HOMA-IR were non-normally distributed, they were log-transformed.
Data were expressed as β coefficients (standard errors).
FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-IR, Homeostasis Model Assessment Index of Insulin Resistance; 2-hour PG, 2-hour plasma glucose.
Model 1 was unadjusted. Model 2 included terms for age, race, and educational level. Model 3 included terms for model 2 and included annual household income, current smoking, BMI, physical activity, age of menarche, age of menopause, use of hormone therapy, oral contraceptive use, and National Health and Nutrition Examination Survey cycle.
[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

TABLE 3. *Odd ratios of diabetes according to number of pregnancies*

	Number of pregnancies			
	2-3	0	1	≥4
Model 1	Ref.	1.19 (0.98-1.46)	0.97 (0.80-1.16)	1.52 (1.36-1.68)[c]
Model 2	Ref.	1.25 (1.02-1.54)[a]	0.97 (0.80-1.17)	1.29 (1.16-1.44)[c]
Model 3	Ref.	1.31 (1.01-1.71)[a]	1.05 (0.81-1.37)	1.28 (1.10-1.48)[b]

Model 1 was unadjusted. Model 2 included terms for age, race, and educational level. Model 3 included the terms used for model 2 and included annual household income, current smoking, BMI, physical activity, age of menarche, age of menopause, use of hormone therapy, oral contraceptive use, and National Health and Nutrition Examination Survey cycle.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

Sensitivity analysis

In the sensitivity analysis, when exposure became those pregnancies with live births, the results did not significantly change in the fully adjusted model. The ORs of diabetes were 3.03 (95% CI 1.07, 8.61) for women with no delivery and 1.44 (95% CI 1.23, 1.70) for women with at least four live births (Supplementary Table 1, http://links.lww.com/MENO/A414). Furthermore, with choosing one or two pregnancies as the reference, an increase in the odds of having diabetes was also observed, both in women with no pregnancy and in those who had at least four pregnancies (Supplementary Tables 2 and 3, http://links.lww.com/MENO/A414). Finally, further adjustment for family history of diabetes did not significantly alter the observed associations in NHANES 2011 to 2014. The ORs of diabetes were 1.70 (95% CI 1.19, 2.43) for women with no pregnancy and 1.31 (95% CI 1.05, 1.64) for women with at least four pregnancies (Supplementary Table 4, http://links.lww.com/MENO/A414).

DISCUSSION

This study provides robust evidence on the association between the number of pregnancies in childbearing age and risk of diabetes in postmenopausal women with no history of GDM. Multiple pregnancies (at least four) were associated with an increased risk of diabetes after adjustment for sociodemographic, lifestyle, and reproductive factors, as well as BMI.

Prior studies on the association between pregnancy and risk of diabetes in women have yielded conflicting results. A Danish study including 100,669 women showed that the risk of diabetes increased with higher parity.[12] This analysis, however, was not adjusted for BMI and other sociodemographic factors, which were found to be important confounders in other studies.[18] Similarly, an Australian study[19] and another three US studies[11,20,21] have also suggested that grand multiparity was associated with an increased risk of diabetes after adjustment for a range of demographic, and lifestyle-related factors including BMI. However, the results of recent studies have shown no association between pregnancy and diabetes.[13-15] Nevertheless, in the present study, which excluded all those with self-reported history of GDM, multiple pregnancies (at least four times) in childbearing age were still associated with diabetes in general US postmenopausal women. Intriguingly, it is worth mentioning that previous studies did not focus on postmenopausal women; thus women in those studies may have another pregnancy later in life. However, our study has included all the pregnancies in the women's entire lives, and, accordingly, might offer women in childbearing age more scientific reproductive advice.

Pregnancy, particularly the third trimester, is diabetogenic. During a normal pregnancy, gestational hormones such as placental lactogen, placental growth hormone, leptin, and insulin-like growth factor-1 cause inflammation, insulin resistance, and adaptive pancreatic β cell expansion.[22] β cells grow and proliferate dramatically in response to pregnancy,[23] and as pregnancy proceeds, insulin secretion must increase 1.5-fold for maternal euglycemia to be maintained.[12,24] This additional requirement for insulin in pregnancy could exhaust the pancreatic β cells, causing a permanent derangement of insulin secretion. While glucose homeostasis is restored to nonpregnancy levels postpartum shortly after delivery, repeated exposure to insulin resistance may result in pathological perturbations many years after childbirth. In addition, pregnancy is associated with maternal weight gain, postpartum weight retention, and changes in adipose tissue distribution, which could also increase the risk of diabetes later in life.[25,26]

It is intriguing that nonpregnancy also conferred a risk of diabetes in our analyses. It is unknown what proportion of these women suffered from involuntary infertility and what proportion made an active choice not to have children. However, involuntary infertility among nonpregnant women could be cause by conditions such as ovulation disorders and polycystic ovarian syndrome that are closely related to diabetes.[27,28] Moreover, infertile women often have high levels of anxiety, depression and psychological stress,[29] all of which are correlated to diabetes.[30] These reasons may partly explain the association we observed.

One of the highlights of this study is that we chose women with two to three pregnancies as the reference group. In our study population, the median number of pregnancies was three. A larger number of postmenopausal women reported being pregnant for two or three times in their childbearing age, at 19.4% and 20.5%, respectively. In some previous studies, researchers have chosen nonpregnancy as the reference. Considering that only a small proportion (6.7%) of women reported being never pregnant in their whole life and that pregnancy does have some protective effects on women's reproductive health such as in breast cancer,[31] it is more logical to choose women with two to three pregnancies as the reference. Of note, women with no pregnancy also had a higher prevalence of diabetes and had a higher risk of developing diabetes after multivariable adjustment.

Our study may have important implications from a clinical perspective. It indicates that multiple pregnancies reveal an underlying susceptibility to diabetes, and hence women of childbearing age should be advised that too many pregnancies may induce unfavorable metabolic outcomes after menopause. Moreover, lifestyle interventions that might prevent or delay the onset of diabetes may be suggested in predisposed women.

The strengths of this study include the strength of the NHANES survey, which is a large population-based database that allowed us to study a representative sample of American postmenopausal women. Our study also benefits from detailed information on a wide range of socioeconomic, lifestyle-related and reproductive factors, which allowed us to carry out an in-depth exploration of the observed associations. This study is not without limitations. First, the number of pregnancies was self-reported and may be subject to recall bias. Second, despite our attempt to thoroughly control for multiple confounders, residual confounding by other factors cannot be excluded. Third, because we did not have data with regard to first trimester pregnancy losses, involuntary infertility or full term deliveries only, the pregnancies in the present analysis included live births, and also miscarriages, stillbirths, tubal pregnancies, and abortions. The association of first-trimester pregnancy losses, involuntary infertility, or full-term deliveries only with diabetes warrants further investigation. Fourth, we cannot determine casual relationships in light of the cross-sectional nature of this study.

CONCLUSIONS

The present study demonstrated that in a large sample representative of the US population, multiple pregnancies ($\geq$4) during childbearing age were associated with an increased risk of diabetes in postmenopausal women without a history of GDM. This finding may provide important implications from a clinical perspective. Future prospective studies are warranted to confirm the observed associations.

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