

Association Between Parity and the Age at Menopause and Menopausal Syndrome in Northwest China

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Abstract

This study evaluated the relationships between parity and the age at menopause and menopausal syndrome among Chinese women in Gansu. A total of 7236 women aged 40 to 55 years met study eligibility criteria. The modified Kupperman Menopausal Index scale was used to assess the severity of menopausal syndrome. Cox regression was applied to estimate hazard ratio and 95% confidence interval, and logistic regression was performed to calculate odds ratio and confidence interval. The mean age at menopause was 47.91 ± 3.31 years. There is no relationship between parity and age at menopause. Women with nulliparity or multiparity seemed to have higher risks of moderate and severe menopausal syndrome. The potential beneficial effects of 1 or 2 births on menopausal syndrome were also observed by applying the multivariable logistic regression analysis, particularly in urogenital symptoms. Women with nulliparity and multiparity appeared to be at the higher risks of menopause syndrome.

Keywords

age at menopause, menopausal syndrome, parity, cross-sectional study, Kupperman Menopause Index

What We Already Know

- Parity may affect the age of menopause.
- Multiparity is related to the menopausal syndrome.

What This Article Adds

- Women with nulliparity or multiparity seemed to have higher risks of moderate and severe menopausal syndrome.
- The risk of genitourinary syndrome of menopause increased in nulliparity and the women who had 3 or more births.

Introduction

Menopause is the hallmark of loss of ovarian follicular activity, permanent cessation of menstruation, and loss of fertility. Menopausal symptoms, especially in severe conditions, are quite distressing for women and could affect their daily life and even harm their health. Women with menopause have higher risks of metabolic diseases, cognitive decline, and osteoporosis.^{1–3}

Previous studies suggested that nulliparity was associated with earlier onset of menopause.⁴ Meanwhile, a meta-analysis found that increased parity was associated with slightly later menopause age.⁵ However, confounding factors in some original research were not corrected. Other data suggested no relationship between parity and age at menopause.⁶ Few studies further analyzed the relationship between parity and age at menopause occurrence, especially in Northwest China.

Many studies reported that multiparity had an impact on the health of middle-aged women. Klingberg and colleagues showed that grand multiparous women (≥ 5 children) had

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increased risks of cardiovascular disease and myocardial infarction.⁷ Another study reported that higher parity was a risk factor for health-related quality-of-life problems in women of South Korean.⁸ A study from Japan showed that the risk of type 2 diabetes tended to increase with higher parity.⁹ Other studies suggested that higher parity was significantly associated with increased risks of cancer.^{10,11} However, low number of children may be related to high breast density.¹² Thus, birth history would influence women health and menopausal syndrome. Although the relationship between parity and menopause has been reported, the findings did not reach consistency as described earlier. Therefore, a cross-sectional survey was performed to find out whether parity could affect the age at natural menopause, the frequency, and intensity of menopausal syndrome among middle-aged women in Gansu Province of China.

This study analyzed the relationship between parity and menopausal age and menopausal syndrome to provide reproduction-related suggestions and references for future strategies of health management of perimenopausal and postmenopausal women.

Methods

Study Design and Participants

Multistage cluster random sampling method was performed in this study. The first stage: there are 13 cities/autonomous prefecture in Gansu Province, including 11 cities and 2 autonomous prefectures. According to the population and GDP per capita (data from Gansu Province Bureau of Statistics), we divided them into 9 layers (Table S1, available online). Six districts/counties were randomly selected from each layer, and a total of 54 districts/counties were selected.

In the second stage, we divided the townships/subdistricts into 9 layers according to their population and GDP per capita in 54 districts/counties selected in the first stage (Table S1, available online). We randomly selected a township/subdistrict from the first, fifth, and ninth layers, and a total of 162 townships/subdistricts were selected. The number of samples in each township/subdistrict was at least 50. The survey respondents were organized by the local village committee, neighborhood committee, and Women's Federation.

The study inclusion criteria were as follows: (1) 40 to 55 years old; (2) residents living in the area for more than 1 year; (3) no use of hormonal drugs for at least 3 months; and (4) voluntary participation in the study and signed informed consent. The exclusion criteria were as follows: (1) menopause before the age of 40 years; (2) hearing disorders; (3) cognitive disorders; (4) unilateral or bilateral hysterectomy or ovariectomy at any time; (5) a history of radiotherapy or chemotherapy; (6) pregnant or breastfeeding; and (7) menopausal hormone therapy.

Informed consent was obtained from all individual participants in the study. The Medical Ethical Committee of the First Hospital of Lanzhou University approved the study protocol (Approval Number: LDYYLL2019-20).

Questionnaire and Physician Examination

The questionnaire was designed and composed of (1) demographic data, including birth year, marital status, educational background attainment, employment status, and family monthly income; (2) details on menstrual and reproductive history, including age at menarche, age at first and last pregnancy, age at first and last childbearing, number of pregnancies and history of abortion, menopausal status, parity, breastfeeding, and menopausal age collected via personal interviews; and (3) the modified Kupperman Index (KMI) scoring scale.¹³ Height and weight were measured and recorded.

The modified KMI score to evaluate 13 menopausal symptoms included hot flashes and sweating, paresthesia, insomnia, irritability, depression, dizziness, fatigue, joint pain myalgia, headache, palpitations, formication, sexual complaints, and urinary symptoms. The KMI scale consisted of 13 items assessing menopausal symptoms, which were divided into the following 3 subscales: (1) somatic symptoms, including hot flashes, paresthesia, insomnia, vertigo, fatigue, muscle/joint pain, headache, palpitations, and formication; (2) psychological symptoms, including mood swings and melancholia; and (3) urogenital symptoms, including sexual and urinary problems. They were divided into 4 grades (0-3 points) according to severity: 0, no symptoms; 1, mild; 2, moderate; and 3, severe. The weighted score was 4 point each for hot flashes and sweating; 2 points each for paresthesia, insomnia, irritability, sexual life abnormality, and urinary infection; and 1 point each for other symptoms. Total score = score of each symptom \times weighted coefficient. The morbidity of menopausal syndrome was calculated using a KMI score cutoff of ≥ 7 , which was the diagnostic criterion. The menopausal syndrome was considered mild with KMI scores of 7 to 15 points, moderate with KMI scores of 16 to 30, and severe with KMI scores of >30 .

Criteria for Premenopause, Perimenopause, and Postmenopause

According to the Stages of Reproductive Aging Workshop criteria classification, the standard stages were as follows¹⁴: (1) premenopause characterized by minor changes in cycle length, particularly decreasing length of the menstrual cycle, and regular menstrual cycles with ≥ 12 menstruations during the last 12 months; (2) perimenopause characterized by a variable cycle length (persistent 7 or more difference in the length of consecutive cycles), missed 2 or more cycles, and an episode of amenorrhea

lasting more than 60 days during the last 12 months; and (3) postmenopause characterized by no menstrual bleeding during the last 12 months (at least 12 months of amenorrhea).

Quality Control

All investigators were uniformly trained on physical measurement methods, questionnaire explanation, and notes on completing the questionnaire. All the interviewees completed the survey in a face-to-face manner. The questionnaire was collected on the spot after completion and uniformly numbered in the order of site and recall questionnaire. The data were imputed into the Epidata database by one investigator and one statistician. The data were checked to avoid inconsistency.

Estimation of Sample Size and Statistical Analysis

Data from previous studies suggested that 75% of midlife women suffered from menopause syndrome.¹⁵ The parameters of incidence were set at 75%, accuracy at 0.05, and bilateral confidence intervals (CIs) at 95%. Furthermore, the minimum sample size of each layer was considered as 128 with 30% enlargement to reduce the sampling error, and the final number of women to be recruited was about 9000.

The statistical analysis was performed using SPSS 24.0 version. The continuous quantitative variables were expressed as mean \pm standard deviation ($\bar{x} \pm s$). The qualitative variables were expressed as medians and percentages. Chi-square test and analysis of variance were used to compare categorical and continuous data, respectively. Nonnormal distribution data were represented by median (25%, 75%), and nonparametric tests were used. Median and mean age at natural menopause were evaluated using nonparametric Kaplan-Meier cumulative survivorship estimates. Cox regression was applied to estimate the hazard ratio and 95% CI of the relationship between parity and age at menopause, and logistic regression model was used to calculate the odds ratio (OR) and CI of effects of parity on menopausal syndrome. *P* value $< .05$ indicated a statistically significant difference.

Results

A total of 8500 women agreed to enroll in the study, and 8446 questionnaires were reclaimed, with 508 ineffective questionnaires, including 379 cases of incomplete demographic information, 67 cases of age < 40 years, and 62 cases of similar surveys, and hence removed. In addition, 702 questionnaires were excluded for reasons of surgical menopause and incomplete or error information on menstruation and birth history. A total of 7236 women who completed the questionnaires were included in the study. The response rate was 99.36%.

Characteristics of the Study Population

The baseline demographics of the 7236 participants are summarized in Table S2, available online. Furthermore, 60 were nulliparous women; 3500 had 2 births and 327 had ≥ 4 births, accounting for 48.40% and 4.46%, respectively. The rates of women educated beyond high school with 3 and 4 births were significantly higher than the rates of those with 1 birth (92.65% and 97.86% vs 44%, $P < .001$). The proportions of low income and residence in rural areas were the highest in women with ≥ 4 births (53.82%, $P < .001$, and 66.06%, $P < .001$, respectively). The age at first delivery was significantly lower in women with ≥ 4 births than in those with 1 birth (21.39 ± 2.32 vs 25.54 ± 2.88 , $P < .001$).

Effects of Parity on the Age at Menopause

The Kaplan-Meier analysis indicated that the median age at menopause was 48 years and the mean age at menopause was 47.91 ± 3.31 years. Moreover, 1673 women experienced menopause. A trend of increased mean age at menopause was observed with the increased parities ($F = 4.794$; $P = .001$). The median age at menopause was 3 years earlier among women with nulliparity than among women with ≥ 4 births (median: 46 vs 49). Women with 1 birth had a higher risk of menopause (hazard ratio = 1.322; 95% CI = 1.072-1.629). After adjustment for confounding factors, no relationship was observed between parity and the age at menopause ($P = .595$; Table S3, available online).

The Kaplan-Meier estimates are shown in Figure 1. Women with higher parity had a higher risk of menopause ($\chi^2 = 12.042$; $P = .017$). However, the Cox regression analysis showed that the relationships were not significant after adjustment for body mass index, marital status, residential location, ethnicity, educational level, age at menarche, age at menopause, age at first delivery, age at last delivery, history of induced labor, ectopic pregnancy, and breastfeeding ($P = .488$; Figure S1, available online).

Relationship Between Parity and the Severity of Menopausal Syndrome

Figure S2 (available online) shows that, excluding nulliparous women, the rest of the group had a significant increase of proportions in the moderate and severe menopausal syndrome with a higher parity ($\chi^2 = 289.079$; $P < .001$). The proportions of moderate (50.5%) and severe syndrome (17.1%) were highest in women with ≥ 4 births. The prevalence of severe syndrome was higher in nulliparous women than in those with 1 or 2 births (8.3% vs 4.3% and 7.6%).

After adjustment for confounding factors, a lower risk of moderate and severe syndrome was found among women with 1 birth (OR = 0.534; 95% CI = 0.330-0.863) and those with 2 births (OR = 0.360; 95% CI = 0.187-0.693) and 3 births (OR = 0.540; 95% CI = 0.317-0.922), respectively, compared with those with ≥ 4 births (Table 1).

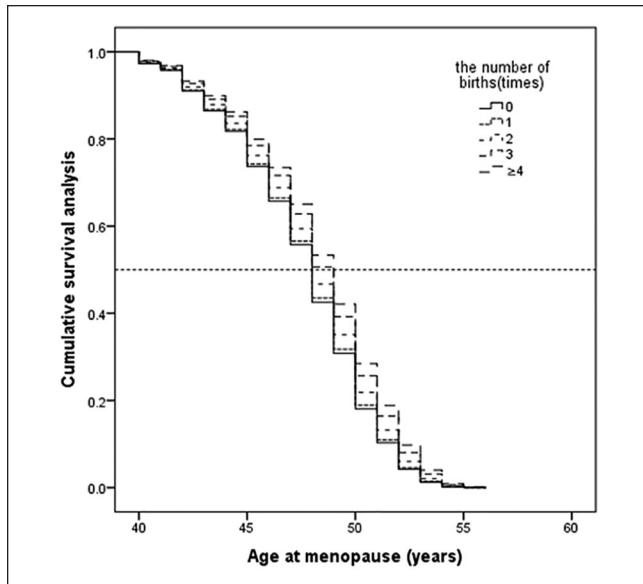


Figure 1. Kaplan-Meier curve of the effect of parity on the age at menopause. Women with higher parity had a higher risk of menopause ($\chi^2 = 12.042$; $P = .017$).

Relationship Between Parity and 3 Main Menopausal Syndromes

The risk of somatic and psychological symptoms increased with the higher parity, but the difference was not found to be statistically significant on applying the multivariable logistic regression analysis. Compared with women ≥ 4 births, women with 1 and 2 births had a lower risk for urogenital symptoms (Table 2).

Discussion

This study evaluated the relationship between parity and the age at menopause, as well as menopausal syndrome among Chinese women in Gansu. Although the mean age at menopause was associated with the increased parity, the relationship between parity, and age at menopause was not found to be significant. Women with nulliparity and multiparity seemed to have higher risks of moderate and severe menopausal syndrome. However, the potential beneficial effects of 1 or 2 births on menopausal syndromes were observed by applying multivariable logistic regression analysis, particularly in urogenital symptoms.

Relationship Between Parity and the Age at Menopause

Menopause is an important milestone for midlife women because it represents loss of fertility and transition to post-reproductive life. In the present study, the mean age at menopause was 47.91 years, which was a little earlier compared with that in other provinces in China⁴ or in developed

countries, such as Australia¹⁶ and America.⁶ It was speculated that the participant (40-55 years) bias might have partly led to the results. Meanwhile, Gansu Province is located in Northwest China and its lower economic level may influence the onset of menopause.

Compared with other studies, this study showed that the relationship between parity and age at menopause was attenuated by adjustment for confounding factors. However, other studies found that higher parity was associated with older age at menopause⁵ and nulliparity was associated with increased risks of premature and early menopause.⁴ It was speculated that parity and fewer cumulative menstrual cycles in parous women might be associated with a larger reserve of oocytes and longer exposure to estrogen.¹⁷ Importantly, it was found that infertile patients had similar Anti-Mullerian Hormone (AMH) levels and Antral Follicle Count (AFC) compared with controls with no history of infertility in an age-adjusted linear regression analysis,¹⁸ confirming results of the present study. However, the study participants were aged < 40 years old. It was believed that ethnicity, living environment, economy, geography, diet characteristics, smoking, physical activity, individual characteristics, and sample size might be factors leading to inconsistent results. This study was based on the province's large sample size, representing the overall situation in Gansu Province and lead to credible results.

Relationship Between Parity and Severity of Menopausal Symptoms

The present study showed that the risk of moderate and severe menopausal syndrome increased in women ≥ 3 births; nulliparous women had a higher risk of severe syndrome compared with those having 1 or 2 births, which was in agreement with previous findings that multiparity aggravated menopausal symptoms.^{4,8} Several potential reasons accounted for this relation, it was quite possible that parous women might not get enough postpartum nursing and adequate nutrition after delivery. Meanwhile, multiparous women were at a younger age at first gravidity and delivery, that the organ systems were not able to meet the increased physiological demands of pregnancy in younger mothers.¹⁹ It was also difficult to raise more children due to the lack of financial supports and burdens of labor work. Moreover, infertile women were significantly more likely to report severely decreased libido and more than twice as likely to report severe vaginal dryness,²⁰ which was similar to findings of the present study.

A lower risk of urogenital symptoms was found in women with 1 and 2 births compared with nulliparous and multiparous (3 and ≥ 4 births) women. Previous studies on the factors associated with reproduction and menopausal symptoms indicated that increased parity was truly related to urogenital symptoms. Botlero and colleagues reported that the risk of developing stress incontinence increased with obesity

Table 1. Multivariable Logistic Regression Analysis of the Effects of Parity on the Menopausal Syndrome^a.

Parity	Mild (n = 2147)		Moderate (n = 2930)		Severe (n = 572)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
0	0.493 (0.232-1.048)	0.762 (0.321-1.810)	0.190 (0.090-0.401) ^b	0.434 (0.187-1.004)	0.164 (0.056-0.480) ^b	0.601 (0.178-2.028)
1	0.534 (0.351-0.811) ^b	0.936 (0.556-1.575)	0.252 (0.172-0.368) ^b	0.534 (0.330-0.863) ^b	0.092 (0.057-0.147) ^b	0.360 (0.187-0.693) ^b
2	0.755 (0.498-1.145)	1.042 (0.657-0.653)	0.429 (0.294-0.624) ^b	0.682 (0.447-1.039)	0.235 (0.151-0.367) ^b	0.540 (0.317-0.922) ^b
3	0.761 (0.486-1.192)	0.900 (0.564-1.436)	0.674 (0.450-1.009)	0.826 (0.541-1.262)	0.547 (0.340-0.881) ^b	0.772 (0.461-1.291)
≥4						

^aData are given as odds ratio (95% confidence interval).

^bP < .05, adjusted for age, body mass index, marital status, residential location, ethnicity, educational level, age at menarche, age at first delivery, age at last delivery, history of induced labor, ectopic pregnancy, the number of pregnancy and abortion, breastfeeding time, and menopausal period.

Table 2. Multivariable Logistic Regression Analysis of the Relationship Between Parity and 3 Main Menopausal Syndromes^a.

Parity	Somatic scorings ≥4 (n = 5898)		Psychological scorings ≥1 (n = 4748)		Urogenital scorings ≥1 (n = 4476)	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
0	0.394 (0.197-0.788) ^b	0.616 (0.291-1.306)	0.396 (0.224-0.698) ^b	0.352 (0.119-1.041)	0.476 (0.269-0.843) ^b	0.641 (0.354-1.160)
1	0.383 (0.266-0.550) ^b	0.718 (0.458-1.125)	0.503 (0.386-0.656) ^b	0.532 (0.277-1.082)	0.455 (0.350-0.591) ^b	0.621 (0.471-0.818) ^b
2	0.563 (0.393-0.809) ^b	0.797 (0.539-1.179)	0.634 (0.488-0.823) ^b	0.765 (0.464-1.262)	0.552 (0.427-0.715) ^b	0.725 (0.555-0.947) ^b
3	0.821 (0.555-1.216)	0.902 (0.598-1.359)	0.798 (0.601-1.059)	1.078 (0.648-1.793)	0.708 (0.535-0.935) ^b	0.767 (0.575-1.022)
≥4						

^aData are given as odds ratio (95% confidence interval).

^bP < .05, adjusted for age, body mass index, marital status, residential location, ethnicity, educational level, age at menarche, age at first delivery, age at last delivery, history of induced labor, ectopic pregnancy, the number of pregnancy and abortion, breastfeeding time, and menopausal period.

and parity.²¹ One population-based survey in China showed multiple pregnancies were more risky than single pregnancy for developing urinary incontinence.²² Women scoring positive on the infertility index were significantly more likely to report severely decreased libido and more than twice as likely to report severe vaginal dryness in multivariable models.²³ Yeniel and colleagues showed that vaginal delivery was an independent risk factor for prolapse with an OR of 2.92 (95% CI = 1.19-7.17) compared with nulliparity.²⁴ Awwad and colleagues found that clinically significant pelvic organ prolapse was found in 3.6% of nulliparous, 6.5% of primiparous, 22.7% of secondiparous, 32.9% of triparous, and 46.8% of tetraparous women.²⁵ It was thought that the determinants of experiencing menopausal symptoms were complex, representing biological, psychological, and social factors. The prevalence of sexual problems and urinary symptoms in the present study was 48.89% and 33.4%, respectively, both accounting for 61.86% (data not shown), which was lower than the prevalence of 79.1% to 83% reported in other studies.^{26,27} The European REVIVE survey, which included the largest cohort of postmenopausal women studied to date, confirmed that vulvovaginal atrophy was frequent but still underdiagnosed and undertreated.²⁸ The American Journal of Obstetrics and Gynecology reported genitourinary syndrome of menopause affects more than 50% of postmenopausal women.²⁹

A large number of factors result in an independent relationship between parity and urogenital symptoms. A previous study demonstrated that vaginal delivery was at a greater

risks of presenting with urinary incontinence because of structural changes in the pelvic floor and repeated injury to the muscles, nerves, and connective tissue of the pelvic floor during childbirths.³⁰ Furthermore, the participants in the present study had a low education level and resided in economically backward areas. Therefore, they lacked antepartum and postpartum care and guidance, leading to sexual problems and urinary symptoms.³¹

Investigations on birth limits had been conducted in China for 40 years. The nulliparity women are usually infertile or choose to remain childless. And women with multiple births reside in remote rural areas had a lower educational level and live by physical labor.³² Therefore, higher parity is probably a result of lower income and deficient educational background, which contribute to higher rate of menopausal syndrome and are in fact not reasons for severe menopausal syndrome. This may be due to the fact that women with higher parity are often found in low-income families with deficient educational background, which was consistent with this study.

Limitations

This study, being a cross-sectional study, adopted multi-stage cluster random sampling method to reduce the selective bias with enough samples, while it had several potential limitations. First, information about parity and the age at menopause was obtained using self-reported questionnaires, leading to recall bias and a lack of a validity check.

Second, the study did not exclude all the confounding effects of the natural aging process that might influence the experience of symptoms. Further randomized, controlled, prospective studies are needed to substantiate the relationship between multiparity and menopausal syndrome.

Conclusions

This study suggested relationships between parity and the age at menopause and menopausal syndrome, which was particularly specific to Chinese women in Gansu. Together, the data both supported and extended the current understanding of the parity as a factor contributing to a woman's experience of menopausal symptomatology. However, further higher quality prospective studies should be conducted to confirm the relationship between parity and menopause, which might serve as a valid tool for practitioners to consider when counseling their premenopausal patients about the incidence and severity of menopause.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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