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Effect of parity on bone mineral density: A systematic review and meta-analysis

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ABSTRACT

Introduction: Parity has been suggested as a possible factor affecting bone health in women. However, study results on its association with bone mineral density are conflicting.
Methods: PubMed, EMBASE, the Cochrane Library, and Korean online databases were searched using the terms "parity" and "bone mineral density", in May 2016. Two independent reviewers extracted the mean and standard deviation of bone mineral density measurements of the femoral neck, spine, and total hip in nulliparous and parous healthy women.
Results: Among the initial 10,146 studies, 10 articles comprising 24,771 women met the inclusion criteria. The overall effect of parity on bone mineral density was positive (mean difference = 5.97 mg/cm^2; 95% CI 2.37 to 9.57; $P = 0.001$). The effect appears site-specific as parity was not significantly associated with the bone mineral density of the femoral neck ($P = 0.09$) and lumbar spine ($P = 0.17$), but parous women had significantly higher bone mineral density of the total hip compared to nulliparous women (mean difference = 5.98 mg/cm^2; 95% CI 1.72 to 10.24; $P = 0.006$). No obvious heterogeneity existed among the included studies (femoral neck $I^2 = 0\%$; spine $I^2 = 31\%$; total hip $I^2 = 0\%$).
Conclusion: Parity has a positive effect on bone in healthy, community-dwelling women and its effect appears site-specific.

1. Introduction

Osteoporosis, a skeletal disorder characterized by decreased bone strength, is a global health issue affecting millions of people around the world. With the aging population, morbidity and mortality from fractures owing to low bone mineral density (BMD) continue to increase, contributing to a greater socio-economic burden [1]. Thus, efforts to screen individuals at risk for osteoporosis, and to identify and address various risk factors are necessary.

During pregnancy, significant changes in calcium metabolism occur and thus, it has been suggested that it may have a long-term effect on bone health in women. However, the association between parity and BMD in women remains unclear and mixed results have been published with regard to whether parity has a positive [2–11], negative [12–25] or no [26–36] correlation with BMD. A recently published meta-analysis reported that increasing parity is associated with reduced hip fracture risk in postmenopausal women [37]. However, no meta-analysis has assessed the effect on BMD in healthy, community-dwelling women of all ages, both pre- and postmenopausal. As BMD can predict fracture risk in health population, we used BMD as our outcome measure in conducting the meta-analysis [38,39]. The conflicting results of individual studies were pooled to assess the effect of parity on bone health in healthy women of all ages and menopausal status.

2. Material and methods

2.1. Search strategy and study selection

PubMed, EMBASE, the Cochrane Library, and Korean online databases (KISS and KoreaMed) were searched in May 2016, using keywords such as "parity" and "bone mineral density", without restriction of the publication date (For full search strategy, see Supplementary Table 1). Electronic searches were supplemented by manual searching of reference lists of review articles and original research papers. All English and non-English articles, theses, and abstracts were screened, with foreign papers translated; however, none of the non-English papers

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contained relevant data and, thus, were not included in our study. The last search was run on August 3, 2016. When appropriate data were not available from the articles, the corresponding authors were contacted for data acquisition.

2.2. Study quality assessment

Methodological quality was assessed using a modified form of Newcastle-Ottawa Quality Assessment Scale (NOS) [40] adapted for cross-sectional studies. A maximum of six stars could be awarded for each study with three stars for selection of the study groups, one star for comparability of the groups and one star for ascertainment of outcome of interest. We defined score of 3 or less as 'poor' quality and >3 as 'good' quality, and used the quality score in subgroup analysis following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guideline [41].

2.3. Inclusion and exclusion criteria

Studies were considered eligible if they (1) evaluated the association between parity and BMD in population-based samples, (2) measured BMD using dual energy X-ray absorptiometry (DXA) and expressed in mg/cm^2, and (3) had outcomes available for both nulliparous and parous groups, with sample size provided for each group. Subjects were excluded if they had BMD at sites other than the femoral neck, lumbar spine and hip or, if there was insufficient data to permit meta-analysis e.g. standard deviation, standard error or 95% confidence interval lacking.

2.4. Data extraction

Two reviewers independently confirmed the eligibility of studies and collected data from the selected studies. Means and SD of BMD measurements at the femoral neck, spine, and total hip were extracted. If the studies lacked SD estimates but provided SE or CI, SD was estimated in accordance with the recommendations of the Cochrane Handbook [42]. When BMD values were given for multiple parity groups, the values were combined using the formulae provided in the Cochrane Handbook [42]. BMD values adjusted for age and/or BMI were used, if available.

2.5. Statistical methods

The analyzed outcomes were BMD of the femoral neck, lumbar spine, and hip. Both fixed- and random-effects meta-analyses were performed and if heterogeneity was high, random effects model was used. Heterogeneity was assessed using I^2 and χ^2 statistics, with $I^2 > 50\%$ and χ^2 P-values of <0.10 used as a threshold indicating significant heterogeneity. Publication bias was assessed using a funnel plot and Egger's test. Sensitivity analyses were conducted to investigate the sources of heterogeneity. Subgroup analyses were conducted according to the participant characteristics (i.e. menopausal status, mean age) and study characteristics (i.e. study location, sample size, and publication year). All tests were two tailed, and a P value < 0.05 was considered statistically significant. Data were analyzed using Review Manager (RevMan) V.5.3 (Nordic Cochrane Center, Copenhagen, Denmark).

3. Results

Initially, 10,146 studies were identified, of which 9,782 were excluded by title and/or abstract screening. Of the 364 initially retrieved studies, 131 were identified as eligible for full-text review. After exclusion, 10 articles [28,32,43–50] were included for final analysis (Fig. 1).

The characteristics of the included studies are summarized in Table 1. Three studies were conducted in the USA, two in the UK, one in Denmark, one in Australia, one in Mexico, one in Morocco, and one in Sri Lanka. The publication date ranged from 1991 to 2009. All studies were cross sectional, except for two, which were prospective follow-up studies [44,45]. In Hansen, et al.'s study (1991) [44], BMD values were only available for a later date, i.e. 1989 and not 1977, and thus, 1989 values were used; in Hillier, et al.'s study (2003) [45], data provided was cross sectional. Two studies [28,32] included only premenopausal women, four [43,47–49] included both pre- and postmenopausal women, and three [44–46] included only postmenopausal women. One study [50] did not provide the menopausal status of participants; however, for the purpose of analysis, they were considered postmenopausal as the participant age ranged from 50 to 54. The total population size ranged from 36 to 9,699, with the number of women in the nulliparous group ranging from 6 to 1,835 and that in the parous group ranging from 15 to 7,864. BMD at the spine was measured in all of the included studies, BMD at the femoral neck was measured in seven studies, and BMD at the total hip was measured in four studies. Unadjusted BMD values were used in all except four studies, with three studies [45,47,48] using age- and weight/BMI-adjusted values and one study [46] using age-adjusted values (Table 1).

The quality score of the included studies are shown in Table 2. The NOS scores ranged from 3 to 6, and the mean score was 4.2 (SD = 1.1). Overall, the studies were of relatively high methodological quality, except three studies [28,32,49] which were categorized as poor quality studies. The main area of concern was comparability of studies.

The visual inspection of the funnel plot did not indicate publication bias supported by Egger's test (femoral neck, $P = 0.414$; spine, $P = 0.247$; total hip, $P = 0.546$; see Supplementary Fig. 1A, B, C) for further details). As only one of the ten studies included fewer than 50 participants, the possibility of small study effects is unlikely. Small study effects is a generic term used to describe phenomenon where studies with small sample sizes sometimes show different, often larger, treatment effects than those with large sample size [51].

Fig. 2 shows the results of the meta-analysis. No obvious between-study heterogeneity was found among the included studies for the femoral neck and total hip (femoral neck, $I^2 = 0\%$; spine, $I^2 = 55\%$; total hip, $I^2 = 0\%$). Parity was not significantly associated with BMD at the femoral neck ($P = 0.09$) and lumbar spine ($P = 0.17$). However, compared to nulliparous women, parous women had a significantly higher BMD at the total hip (mean difference = 5.98 mg/cm^2; 95% CI 1.72 to 10.24; $P = 0.006$). The overall effect of parity on BMD was also positive (mean difference = 7.90 mg/cm^2; 95% CI 0.62 to 15.17; $P = 0.03$). However, as the assessment of the overall effect is based on BMD values from same studies for different measurement sites, such results should be interpreted with caution.

The results of the subgroup analyses stratified by participant characteristics, study location, publication year and study quality are shown in Table 3. The effect of parity on BMD of the spine was more pronounced in women with mean age < 50 years old (33.06 [10.79 to 55.33], $P = 0.004$) compared to women with mean age ≥ 50 years old (5.72 [−13.58 to 25.02], $P = 0.56$). Similarly, although statistically non-significant, the pooled estimate of mean differences appear substantially larger in premenopausal women than in postmenopausal women (femoral neck: 29.68 [−42.26 to 101.61], $P = 0.42$ vs. 6.11 [−21.51 to 33.73], $P = 0.66$; spine: 20.69 [−44.83 to 86.21], $P = 0.54$ vs. 0.26 [−8.27 to 8.79], $P = 0.95$). However, no statistically significant differences between subgroups were observed for all subgroups analyzed.

For BMD of the total hip, significant mean differences in BMD of the total hip were observed in studies on postmenopausal women and conducted in the US; however, such results are attributable to Hillier, et al.'s (2007) study, which had a substantially larger sample size compared with those of other included studies. Although subgroup analyses according to study size (<30 subjects versus ≥30) and year of publication (before 2000 versus 2000 and later) were planned, such analyses were not possible as all studies had >30 subjects and all were published after 2000. Subgroup analyses by mean number of parity could not be performed owing to insufficient data in the included studies.