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Review Article

Impact of Parity on Fracture Risk after Menopause: A Systematic Review

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Abstract

Background

Pregnancy and breastfeeding cause temporal bone resorption and can play a role in clinical expression of osteoporosis disease. Objective was to estimate the association between parity and risk of osteoporotic fracture after menopause.

Methods

We performed a systematic review through a search of PubMed, Cochrane, Embase databases from January 1, 1980 through January 31, 2016. We included all studies that evaluated the link between parity and post-menopausal osteoporotic fracture using univariate and/or multivariate analysis.

Results

Among 29 studies, a positive effect of parity was found in 7/13 prospective, 1/7 transversal and 2/10 retrospective studies. Three studies out of 5 found that parity had a protective role against the risk for any fracture (HR = 0.94[0.90-0.99], OR = 0.41[0.28-0.61] and OR = 0.90[0.84-0.99]). For hip fracture, a protective effect was found in 5 studies out of 17 and concerned women with ≥2 children in two studies (OR = 0.75[0.62-0.91], RR = 0.5[0.32-0.79]). For vertebral fracture, 1 study out of 8 reported a significantly reduced risk in women with ≥2 children (HR = 0.44[0.26-0.76]). Wrist fracture risk was evaluated in 7 studies. One found a reduced risk in parous individuals (HR = 0.71[0.52-0.97]). An increased fracture risk was found in three studies. It's about Asian sub-population with ≥5 children in two studies (HR = 1.65[1.06-2.56] and RR = 2.53[1.07-6.68]). In another, a positive correlation between vertebral fracture and parity was reported (OR = 1.093[1.008-1.186]).

Conclusion

Overall, pregnancy does not seem to be associated with an increased risk of osteoporotic fracture after menopause. The negative impact of ≥5 childbirth in Asiatic sub-population requires future investigations.

Keywords: Menopause; Parity; Risk fracture

Abbreviations

HR: Hazard Ratio; OR: Odds Ratio; HR: Hazard Ratio; CI: Confidence Interval; PTHrp: Parathyroid Hormone-Related Protein; BMD: Body Mass Density

Introduction

Osteoporosis is a disease essentially bound to menopause and ageing. The growing prevalence of osteoporosis is becoming an increasingly important health problem throughout the world. The estimations state a pandemic of osteoporosis in more than 200 million people in the world among which post-menopausal women represent 30% in United States and Europe. It expresses clinically after 50 years by fractures due to low energy traumas [1]. Osteoporotic fracture is due to the conjunction of minor trauma, lowered bone mass, change in trabecular bone microarchitecture and cortical porosity [2,3]. At least, 40% of osteoporotic women will suffer from one or several fragility fractures in their life [1].

Pregnancy and breastfeeding are periods of the woman's life with important calcic loss, estimated between 200 to 300 mg daily [4]. This loss cause, in temporal way, a negative calcic balance which is stabilized by bone resorption [5]. Isolated observations of fragility fractures were especially reported in primipares. Their incidence remains underestimated and seems related to a preliminary fragility or an excessive bone resorption at the mother [6-9]. Albright and Reifenstein reported from 1948 the existence of osteoporotic fractures in two pregnant women [10].

The link between pregnancy, breastfeeding and osteoporotic fractures is not clear in the literature. The loss of bone mass during pregnancy and especially during breastfeeding varies from 1% per month to 10% during the 6 months of lactation. This phenomenon is however reversible during the weaning [5,11,12]. The accumulation of reproductive events during woman's life plays a very important role to clinical expression of osteoporotic disease. However, acquired and environmental factors as pregnancy and lactation seem to determinate the severity of osteoporotic disease [13].

For this purpose, we performed a systematic review in order to estimate the level of association between parity and risk of osteoporotic fracture after menopause.

Materials and Methods

Data source and search strategy

We conducted a review of the medical literature in order to identify

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all articles evaluating the association of parity and risk of post-menopausal fractures through a search of PubMed, Cochrane, Embase databases from January 1, 1980 through January 31, 2016 applying the following combined search keywords: (parity OR pregnancy OR lactation OR breastfeeding OR reproduction) AND (bone OR bone mineral density OR osteoporosis OR fracture). The bibliography of relevant articles was also searched. The search was restricted to English and French literature. Two reviewers (DD, GW) reviewed titles and abstracts to identify studies likely to report association between parity with fracture and subsequently obtained the full texts (Figure 1).

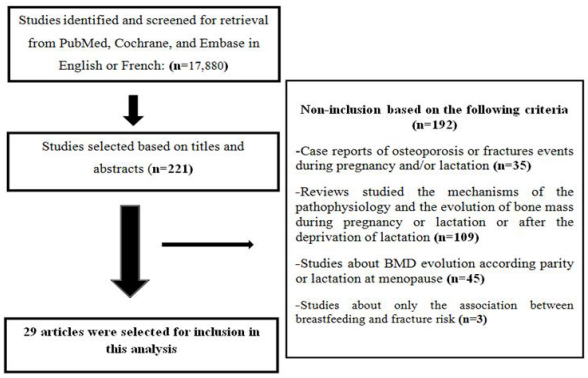

Figure 1: Studies selection process based on the inclusion and non-inclusion criteria.

Study selection criteria

To be eligible for inclusion in this systematic review, studies had to meet the following criteria:

I. Having a human prospective, retrospective, case control or cross sectional design;
II. Including a female population of premenopausal, menopausal or postmenopausal status;
III. All fractures diagnosis had to be based on clinical and/or imaging studies (radiography, bone densitometry, scanner);
IV. Having result of study evaluating the risk for one or overall fractures according to parity and expressed results with univariate and/or multivariate adjusted OR (Odds Ratio) or HR (Hazard Ratio) or RR (Relative Risk) with a Confidence Interval (CI) of 95%, with or without p value.

We excluded papers reporting case reports, reviews, commentaries and letters, studies about mechanisms of Pathophysiology and evolution of bone mass during pregnancy or lactation or after deprivation of lactation as well as animal's experimental studies, studies about only Body Mass Density (BMD) evolution according to parity or lactation at menopause, studies about only the association between breastfeeding and fracture risk, studies in which the criteria of evaluation were not sufficient. Studies where fractures or low bone mass were due to hematological or endocrinological diseases (pex multiple myeloma, hyperparathyroidism, Cushing disease etc.,) or were medically induced (use of corticoids or…) were also excluded.

Data extraction and quality assessment

Two investigators (DD, AA) reviewed independently each eligible manuscript and extracted data on general characteristics of each study including first author's name, year of publication, study design, setting and follow up. We present data also as far as characteristics of studied population (sample size, age, and menopausal status when given) and compared groups as well as data concerning the studied outcome and the type of the statistical analysis (univariate and/or multivariate analysis) used for the extraction of the main outcomes. Studies were also organized regarding methodology and quality of proof. A label ranging from A to C was attached to each publication. According to French recommendation, a grade A is established on a scientific proof established by one studies of strong level of proof for example comparative tests randomized of strong power and without major bias, meta analysis of randomized controlled essays, analyzes of decision based on well led studies. A grade B is based on a scientific assumption supplied by studies of intermediate level of proof: for example, comparative tests randomized by low power, well led not randomized comparative studies, cohort studies. A recommendation of grade C is established on studies of lesser level of proof for example, case control studies, series of case [14]. When available, ethnic origins were taken in account.

Results

Characteristics of the included studies

A total of 17,880 studies were found through literature search. The majority of them (17,659) were excluded based on title and abstract. From the 221 remaining studies, 29 studies were chosen to be evaluated in this systematic review based on full text (Figure 1).

Twenty nine studies presented data of association between parity and risk of fracture. Twelve studies included European population, eight studies North American population, one study South American population and two others a maghrebian population. Four studies were conducted in an Asiatic population and finally two studies in an Australian population. The follow up period varied from 1 to 29 years.

The risk of fracture was studied in 13 prospective, 7 transversal and 10 retrospective studies. Among these studies, 12 were grade B and 16 grade C. The publication of Petersen et al., [15] gives one part of prospective results (grade B) and one part of transversal results (grade C). It is about 17 studies examined the risk for hip's fracture, 8 the risk for vertebral's fracture, 7 the risk for wrist's fracture and 5 the risk for all fracture (Table 1 and Figure 2).

Characteristics of the included population

A total of 253,587 women were included in the 29 studies. It's about 6,149 (2.42%) women at premenopausal status and 247,438 (97.58%) at postmenopausal status. In this population, 52,375 women were Europeans (20.65%), 190,225 North Americans (75.01%), 1,855 South Americans (0.73%), 6,092 Asians (2.4%), 1,402 Australians (0.55%) and 1,638 Maghrebian (0.64%). It's about 221,632 parous, 30,013 nulliparous.

Main results of studies (Figure 2)

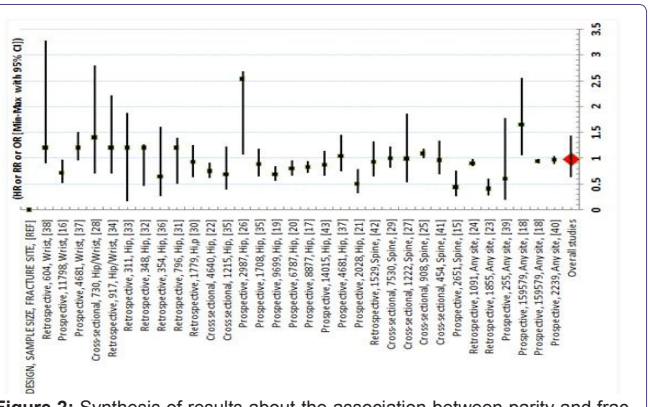

Figure 2: Synthesis of results about the association between parity and fracture risk in post-menopausal women.

Abbreviation: Min = Minimum; Max = Maximum; HR = Hazard Ratio; OR = Odds Ratio; CI = Confidence Interval; REF = Reference

First author, journal, year of publication, reference, grade of recommendation	Type of the studies, setting	Effect of parity and/or lactation on fracture	Sample size, menopausal status, age in years (mean ± DS or median)	Follow-up (years)	Compared groups	Studied outcome	Results: [incidence, (HR or OR or RR (95% CI), p value]	Conclusion
Mori et al., Bone, [16] **Grade B**	Prospective, (The Study of Women's Health Across the Nation), United-State	All fracture	2239, (1210 premenopausal and 1017 postmenopausal), (46.0±2.0)	15.7	- 2239 parous for 1 to 3 children	- Incidence of fractures on the whole studied population - Adjusted[1] HR in compared groups for fracture risk	- 15.9% - Parity per additional childbirth: 0.97(0.89-1.05), p = nd	Parity is not associated with fracture risk
Cauley et al., J Bone Miner Res, [17] **Grade B**	Prospective, (Women's Health Initiative study), United-State	All fracture	159579, postmenopausal, (50-79)	8±2.6	144094 parous vs. 15485 nulliparous*	Adjusted[2] HR for fractures risk across ethnicity (White, Black, Hispanic, Asian and American Indian)	2-4 children: 0.94(0.90-0.99), 1.10(0.82-1.46), 0.85(0.60-1.20), 1.25(0.84-1.87), 1.09(0.35-3.42), p = nd ≥5 children: 0.95(0.90-1.00), 1.13(0.84-1.54), 0.81(0.56-1.16), 1.65(1.06-2.56), 1.43(0.44-4.61), p = nd	Parity is associated to a lower risk for fracture in white parous with 2-4 children and a higher risk for fracture in asian parous with ≥5 children
Paganini-Hill et al., J Womens Health, [18] ***Grade B***	Prospective, (The Leisure World Cohort Study), United-State	Hip, wrist and spine fractures	8877, postmenopausal, (73±7.4)	20	6549 parous vs. 2308 nulliparous	- Incidence of hip, wrist, spine fracture on whole studied population - Adjusted[3] HR in compared groups for hip, wrist, spine fracture risk	0.83(0.72-0.95), 0.91(nd), 0.98(nd), p = nd	Parity is associated to a significant lower risk for hip fracture
Taylor et al., J Am Geriatr Soc, [19] ***Grade B***	Prospective, (Study of Osteoporotic Fractures), United State	Hip fracture	6787, postmenopausal, (73.3±4.9)	10.1±3.2	5558 parous* vs. 1229 nulliparous	- Incidence of hip fracture on whole studied population -Adjusted[4] HR in compared groups (with and without BMD) for hip fracture risk	8.9% With BMD: b1.28(1.06-1.55) Without BMD : 1.25(1.04-1.51) p = nd	Nulliparity is associated to a significant higher risk for hip fracture
Hillier et al., J Bone Miner Res, [20] **Grade B**	Prospective, (Study of Osteoporotic Fractures), United-State	Non traumatic hip, spine, and wrist fractures	9699, postmenopausal, (72.9±5.6 for nulliparous and 71±5.2 for parous)	3	7864 parous* vs. 1835 nulliparous	- Incident of hip, spine and wrist fracture on whole studied population - Adjusted[5] HR in compared groups (with and without BMD) for hip, spine and wrist fracture risk	6.1%, 4%, 6.5% With BMD : 1.44(1.17-1.78), 1.14(0.85-1.52) and 0.86(0.69-1.09) Without BMD : 1.44(1.17-1.78), 1.09(0.82-1.45) and 0.87(0.69-1.09), p = nd	Nulliparity is associated to a significant higher risk for hip fracture
Bjørnerem et al., J Bone Miner Res, [21] **Grade B**	Prospective, (Tromsø Study), Norway	Hip and wrist fractures	4681, postmenopausal, (63.9)	14.5	- 4230 parous vs. 451 nulliparous*	- Incidence of hip, fragility and wrist fractures on the whole studied population - Adjusted[6] HR in compared groups for hip and wrist fracture risk	9.4%, 13.2% 1.04(0.75-1.46), p = 0.89; and 1.20(0.96-1.51), p = 0.80	-Parity is not associated to the risk for hip and wrist fracture
Kauppi et al., Osteoporosis Int, [22] **Grade B**	Prospective, (Mini-Finland Health Survey study), Finland	Hip fracture	2028, postmenopausal, (63.2±9.2)	17	1633 parous vs. 395 nulliparous*	- Incidence of hip fracture on the whole studied population - Adjusted[7] RR in compared groups for hip fracture risk	6.5% 1-2 children: 0.85(0.55-1.32) ≥3 children: 0.5(0.32-0.79) p = nd	Only parity ≥3 birth is associated to a significant lower risk of hip fracture
Trémollieres et al., J Bone Miner Res, [23] **Grade B**	Prospective, (Menopause et Os Cohort Study), French	Spine and hip fractures	2651, (756 premenopausal and 1895 postmenopausal, (54±4)	13.4	2416 parous vs. 235 nulliparous*	-Incidence of fracture on the whole studied population - BMD adjusted[8] HR in compared groups for spine and hip fracture risk	15.6% 2 children: 0.68(0.42-1.11) and 0.66(0.36-1.22), ≥3 children: 0.44(0.26-0.76) and 0.52(0.27-1.00), p = nd	Only parity ≥3 birth is associated to a significant lower risk for spine fracture

Hundrup et al., Eur J Epidemiol, [24] **Grade B**	Prospective, Denmark, The Danish Nurse Cohort Study	Hip fracture	14015 postmenopausal, (≥50)	6	11120 parous vs 2762 nulliparous*	- Non adjusted HR in compared groups for hip fracture risk	0.87 (0.66-1.15), p = 0.323	Parity is not associated to the risk for hip and wrist fracture
Naves et al., Osteoporosis Int, [25] **Grade B**	Prospective, (European Vertebral Osteoporosis Study), Spain	Vertebral and no vertebral osteoporotic fractures	255, postmenopausal, (65±9)	8	- 212 Parous vs. 38 nulliparous*	- Incident of osteoporotic fracture on the whole studied population - Adjusted[9] OR in compared groups for osteoporotic fracture risk	12.1% 0.60(0.20-1.78)	Parity is not associated with the risk for osteoporotic fracture
Petersen et al., Ann Epidemiol, [15] **Grade B**	Prospective, (The Danish Twin Survey Study), Denmark	Hip fracture	1708, postmenopausal, 75 (66-99)	29.11	- 523 parous 1-2 birth* vs. 293 nulliparous and vs. 352 parous 3-4 birth	-Incidence of hip fracture on whole studied population - Non adjusted HR in compared groups for hip fracture risk	18.7% Nulliparity: 1.28(0.98-1.68) 3-4 children: 0.88(0.65-1.19), p = nd	Parity is not associated to the risk for hip fracture
Honkanen et al., Osteoporosis Int, [26] **Grade B**	Prospective, (Kuopio Osteoporosis Risk Factor and Prevention Study), Finland	Distal forearm fracture	11798, (3775 premenopausal and 8023 postmenopausal), (52.3±2.9)	5	10488 parous vs. 1310 nulliparous*	-Incidence of forearm fracture on whole studied population - Adjusted[10] HR in compared groups for distal forearm fracture risk	3.1% 0.71(0.52-0.97), p = 0.031	Parity is associated to a significant lower risk for distal forearm fracture
Fujiwara et al., J Bone Miner Res, [27] Grade B	Prospective, (Adult Health Study), Japan	Hip fracture	2987, postmenopausal, (58.6±11.6)	14	1353 parous 1-2 children* vs. 254 nulliparous and vs. 923 parous 3-4 children and vs. 403 parous ≥5 children	Adjusted[11] RR in compared groups for hip fracture risk	Nulliparity: 2.31(0.60-7.76) 3-4 children: 1.26(0.51-3.39) ≥5 children: 2.53(1.07-6.68), p = nd	Parity ≥5 children is associated to a higher risk for hip fracture
Hwang et al., Osteoporos Int, [28] **Grade C**	Cross-sectional, (Korea National Health and Nutrition Examination Survey) South Korea	Vertebral fracture	1222 postmenopausal, (62.8±8.8)	2	444 parous <3 births* vs 778 parous ≥3 births	Adjusted[12] OR in compared groups for hip fracture risk	0.999 (0.537-1.861)	Parity is not associated with a risk of vertebral fracture
Lambrinoudaki et al., Spine J, [29] **Grade C**	Cross-sectional study, Greece	Vertebral fracture	454, postmenopausal, (56.8±7.1)	5	378 parous vs. 68 nulliparous	Non adjusted OR in compared groups for vertebral fracture risk	Parity per one extra child : 0.968(0.69-1.34), p = 0.847	Parity is not associated to the risk for vertebral fracture
Maghraoui et al., Bone, [30] **Grade C**	Cross-sectional study, Marocco	Vertebral fracture	908, postmenopausal, (60.9±7.7)	3	(nd) parous vs. (nd) nulliparous*	- Percentage of vertebral fracture on the whole studied population - Non adjusted OR in compared groups for vertebral fracture risk	42% 1.093(1.008-1.186), p = 0.031	Parity is associated to a significant higher risk for vertebral fracture
Allali et al., Maturitas, [31] **Grade C**	Cross-sectional, Marocco	Osteoporotic peripheral fracture	730, postmenopausal, (59.4±7.6)	nd	663 parous vs 67 nulliparous*	Adjusted[13] OR in compared groups for osteoporotic peripheral fracture risk	1-3 children: 1.40(0.70-2.80), p = 0.3 4-5 children: 1.10(0.53-2.28), p=0.7 ≥6 children: 0.85(0.39-1.80), p = 0.6	Parity is not associated to the risk for peripheral fracture
Petersen et al., Ann Epidemiol, [15] **Grade C**	Cross sectional, (The Longitudinal Study of Aging Danish Twins 1995), Denmark	Hip fracture	1215, postmenopausal, 80 (75-98)	18	-531 parous 1-2 birth* vs. 226 nulliparous and vs. 355 parous 3-4 birth	- Percentage of hip fracture on whole studied population - Non adjusted OR in compared groups for hip fracture risk	77.3% Nulliparity: 1.18(0.69-2.02) 3-4 children: 0.69(0.39-1.23), p = nd	Parity is not associated to the risk for hip fracture
Michaelsson et al., Am J Epidemiol, [32] **Grade C**	Cross sectional, case-control study, Sweden	Hip fracture	4640, postmenopausal, (72.5±6.8 in cases and 70.5±7.7 in controls)	3	-3848 parous vs. 792 nulliparous*	- Percentage of hip fracture on whole studied population - Adjusted[14] OR in compared groups for hip fracture risk	28.6% 1 child: 0.90(0.73-1.12), 2 children: 0.75(0.62-0.91), 3 children: 0.80(0.66-0.98), p = nd	Parity ≥2 children is protective for hip fracture

O'Neill et al., Osteoporos Int, [33] **Grade C**	Cross-sectional, (European Vertebral Osteoporosis Study), United-Kingdom	Vertebral deformity	7530, post-menopausal, (67.3±7.9 in cases and 62.6±7.9 in controls)	Nd	- 6398 parous vs. 1132 nulliparous*	Adjusted[15] OR in compared groups for vertebral deformity	1.00(0.82-1.23), p = nd	Parity is not associated to the risk for vertebral deformity
Shin et al., J Bone Miner Metab, [34] **Grade C**	Retrospective, (Ansung community cohort study), Korea	Vertebral fracture	1529, (314 premeno-pausal and 1215 post-menopausal), (59.1±8.7)	2	687 parous ≥4 births vs. 809 parous <4 births*	- Percentage of vertebral fracture on the whole studied population - Age adjusted OR in compared groups for vertebral fracture risk	14.8% 0.93(0.65-1.32), p = nd	Parity is not associated to the risk for vertebral fracture
Wengreen et al., Osteoporos Int, [35] **Grade C**	Retrospective, Case control study, (Utah Study of Nutrition and Bone Health), United State	Hip fracture	1779, post-menopausal, (76.7±9.1)	5	1624 parous vs.155 nullip-arous*	- Percentage of hip fracture on whole studied population - Adjusted[16] OR in compared groups for hip fracture risk	49.5% 0.93(0.63-1.25), p = nd	Parity is not associated to the risk for hip fracture
Huo et al., Osteoporos Int, [36] **Grade C**	Retrospective, Case control study, China	Hip fracture	354, post-menopausal, (67.1±8.3)	2	- 115 parous 1-2 birth* vs. 83 parous ≥5 birth and vs. 18 nulliparous	- Percentage of hip fracture on whole studied population - Adjusted[17] OR in compared groups for hip fracture risk	33.3% Nulliparity: 0.79(0.19 -3.25) ≥5 children: 0.64(0.26-1.61), p = 0.49	Parity is not associated to the risk of fracture
Cure-Cure et al., Int J Gynae-col Obstet, [37] **Grade C**	Retrospective, Columbia	All fracture	1855, post-menopausal, (61.3±-8.3)	5	1612 parous vs. 243 nullip-arous*	- Percentage of frac-ture on whole studied population - Non adjusted OR in compared groups for all fracture risk	22.9% 0.41(0.28-0.61), p<0.000002	Parity is as-sociated with a significant lower risk for fracture
Parazzini et al., J Epidemiol Community Health, [38] **Grade C**	Retrospective, Cross sectional, (Italian case control study), Italia	Hip fracture	796, post-menopausal, (66)	10	632 Parous vs. 164 nullip-arous*	Adjusted[18] OR in compared groups for hip fracture risk	0.8(0.5-1.4), p = 0.22	Parity is not associated to a risk for hip fracture
Hoffman et al., Osteoporosis Int, [39] **Grade C**	Retrospective, case-control study, United-State	Hip fracture	348, post-menopausal, (≥50)	3	- 233 parous vs. 115 nullip-arous*	- Percentage of hip fracture on whole studied population - Adjusted[19] OR in compared groups for hip fracture risk	50% 0.76(0.46-1.27), p = nd	Parity is not associated to the risk for hip fracture
Nguyen et al., J Clin Endocrinol Metab, [40] **Grade C**	Retrospective, (Dubbo Osteopo-rosis Epidemiology Study), Australia	Atraumatic fracture	1091, post-menopausal, (70±7.2)	5	990 parous* vs. 101 nullip-arous	Adjusted[20] OR in com-pared groups for no traumatic fracture risk	1.10(1.01-1.19), p<0.01	Nulliparity is associated to a significant higher risk for atraumatic fracture
Mallmin et al., Osteoporosis Int, [41] **Grade C**	Retrospective, case-control study, Sweden	Distal forearm fracture	604, (94 pre-menopausal and 510 post-menopausal), (62.8±10.1)	1	- 515 parous vs. 89 nullipa-rous*	Adjusted[21] OR in com-pared group for distal forearm fracture	1.72(0.90-3.28), p = nd	-Parity is not associated to the risk for forearm fracture
Cumming et al., Int J Epidemiol, [42] **Grade C**	Retrospective, case-control study, Australia	Hip fracture	311, post-menopausal, (≥65)	2	- 246 parous vs. 65 nullipa-rous*	- Percentage of hip fracture on whole studied population - Adjusted[22] OR in compared groups for hip fracture risk	55.9% 0.56(0.17-1.88), p = nd	Parity is not associated to the risk for hip fracture
Alderman et al., Am J Epidemiol, [43] **Grade C**	Retrospective, case-control study, United-State	Hip and forearm fractures	917, post-menopausal, (50-74)	5	- 734 parous vs. 183 nullip-arous*	- Percentage of frac-ture on whole studied population - Adjusted[23] OR in compared groups for hip and forearm fracture risk	38.7% 1.2(0.7-2.22), p = nd	Parity is not associated to the risk for hip and forearm fractures

Table 1: Synthesis of the data of the studies having estimated the association between parity and fracture risk in post-menopausal women.

Abbreviations: HR = Hazard Ratio; OR = Odds Ratio; RR = Relative Risk; nd = no data; BMD = Bone Mineral Density; BMD: Bone Mass Density

***** Table 1 legend

[1]Adjusted for age, race/ethnicity, menopausal transition stage, body mass index, smoking status, smoking pack-years, alcohol consumption level, physical activity level, employment status, diabetes, hyperthyroidism, current use of supplementary calcium, current use of supplementary vitamin D, prior use of sex steroid hormones, prior use birth control pills, prior use of Depo-Provera injection, current or prior use of oral corticosteroids, current use of proton pump inhibitors, other bone-adverse medications, and study site.

[2]Adjusted for age, years since menopause, education, living with a partner, height, weight, caffeine intake, smoking, fracture history, parental fracture history, falls, current HT use (5yr), corticosteroid use (>2 years), sedative/ anxiolytics use, arthritis, depression, health status, and parity.

[3]Adjusted for age and others variables: for hip fracture (history of fracture, BMI, diabetes, glaucoma, smoking, vitamin A supplement use, attitude and having been pregnant), for wrist fracture (history of fracture, BMI, heart attack, alcohol consumption, vitamin A supplement use, cola intake and hysterectomy), for spine fracture (history of fracture, BMI, blood pressure medication, nonprescription pain medication, smoking, exercise, and attitude.

[4]Adjusted for total hip BMD, age, any previous fracture since age 50, history of maternal hip fracture after age 50, Parkinson's disease, type II diabetes mellitus, lowest quartile for distant depth perception, BMI, height at age 25, walking speed, digit symbol test number completed.

[5]Adjusted for age, weight, height, maternal history of hip fracture, fracture of any bone after age 50, self-reported, on feet ≤4h/day, uses arms to stand from chair, history of diabetes, current calcium intake, current estrogen use, low frequency contrast sensitivity, resting pulse rate, and the interactions of self-reported health with on feet ≤4h/day

[6]HR adjusted for age, height, BMI (body mass index), smoking, alcohol use, physical activity, history of diabetes and previous wrist or hip fracture, use of hormone replacement therapy, and length of education

[7]Adjusted for age, age at last menstrual period, level of education, BMI, vitamin D status, parity, alcohol consumption, smoking history, leisure time physical activity and self-rated health.

[8]Adjusted for age, BMI, use of bisphosphonates, raloxifene or ranelate (past and present), use of estroprogestinic preparations (past and present), serum 25OHD levels, and number of pregnancies and presence of densitometric osteoporosis.

[9]Adjustment by age, handgrip strength, femoral neck BMD, prevalent vertebral fracture and the history of falls in the follow-up.

[10]Adjusted for age, postmenopausal, body mass index, dairy calcium intake, hormone replacement therapy during follow-up, Wrist fracture history, parity.

[11]Adjusted for age, BMI, milk intake, alcohol intake, menarche, parity.

[12]Adjusted for age, BMI, age at menarche, duration of menopause, systolic blood pressure, GFR, PTH, 25(OH)D3, oral contraceptive use, HTN, DM, physical activity, alcohol and smoking status , number of deliveries, and age at first and last delivery.

[13]Adjustment for age (OR, 1.06; 95% CI, 0.97-1.15), BMI (OR, 1.01; 95% CI, 0.99-1.03), age at menopause (OR, 0.96; 95% CI, 0.89–1.04), time since menopause: (OR, 0.94; 95% CI, 0.87-1.02), wearing veil (OR, 1.02; 95% CI, 0.69-1.53) and total femoral BMD (OR, 0.13; 95% CI, 0.038-0.4).

[14]Adjusted for age (=54, 55-59, 60-64, 65-69, 70-74, and =75 years), hormone replacement therapy (never, former, and current use), oral contraceptive use (never and ever use), and body mass index (by quintiles)

[15]Adjusted for center, age, body mass index and smoking.

[16]Adjusted for age, education, BMI, history of estrogen use, age at menopause, history of oral contraceptive use, history of endometriosis, smoking status, vitamin D receptor genotype, lifetime physical activity, diabetes status, and history of breastfeeding.

[17]Adjusted for age, height, education, BMI, years lived in rural area, occupation, standing activities prior retirement, dietary calcium intake, breastfeeding and parity

[18]Adjusted for age, education, BMI, smoking status and estrogen replacement therapy.

[19]Adjusted for hospital of recruitment, age group, and age and body mass index.

[20]Adjusted for age, weight parity, estrogen exposure, hysterectomy.

[21]Adjusted for BMI, education, daily physical activity, leisure time activity, smoking, nulliparity, duration of HRT, menopausal discomfort, age at menopause.

[22]Adjustment for age, Body mass index, history of hormone replacement therapy use, current use of psychotropic medications, current smoking status, current dairy product consumption, score on mental state questionnaire, current physical activity and health status (number of self-report illnesses)

[23]Adjusted for attained for age, country and occupational group.

Association between parity and fracture risk: Ten studies found that multiparity had a protective role against the risk for fracture (IC 95% variation of RR = [0.32-0.79], HR = [0.26-0.99] and OR = [0.28-0.99]). Seven of them were prospective [17-20,22,23,26] with a follow up between 3-20 years, one cross sectional [32] and two retrospective [37,40]. These results were found by multivariate adjusted analysis in eight studies [18-20,22,26,32,40]. Only three studies found a significant increased risk for vertebral fracture in Moroccan women (OR = 1.09, IC 95% [1.00-1.18], p = 0.031), [30] all fracture in Asian's North Americans parous with five or more children (HR = 1.65, IC 95% = [1.06-2.56]) [17] and hip fracture in Japanese parous with five or more children (RR = 2.53, IC 95% = [1.07-6.68]) [27]. In one study [17] the multivariate adjusted risk for osteoporotic fractures was lower in white women with 2-4 children (HR = 0.94, IC 95% = [0.90-0.99]), and higher in Asian's North American women with 5 or more children (HR = 1.65, IC 95% = [1.06-2.56]) compared to nulliparous. The rest of 16 studies [15,16,21,24,25,28,29,31,33-36,38,39,41,42] found no statistical association between fracture and parity (Table 1 and Figure 2). It is necessary to note that no study on the American, European and Australian populations found a negative effect of the parity on the bone after the menopause. The only studies having found a higher risk for fracture resulted from an evaluation on the Asiatic or North African populations [17,27,30] (Table 2).

Population	References	Type of studies, Main criteria, simple size	Results: [incidence, (HR or OR or RR with 95% CI)]
North American	Mori et al. [16]	Prospective, Parity and all fracture, 2239	HR = 0.97(0.89-1.05)
	Cauley et al. [17]	Prospective, Parity and all fracture, 159579	White (2-4 children): HR = 0.94(0.90-0.99) Asian (≥5 children): HR = 1.65(1.06-2.56)
	Wengreen et al. [35]	Retrospective, Parity and hip fracture, 1779	OR = 0.93(0.63-1.25)
	Paganini-Hill et al. [18]	Prospective, Parity and hip fracture, 8877	HR = 0.83(0.72-0.95)
	Taylor et al. [19]	Prospective, Parity and hip fracture, 6787	HR = 0.80(0.66- 0.96)
	Hillier et al. [20]	Prospective, Parity and hip fracture, 9699	HR = 0.69(0.56-0.85)
	Hoffman et al. [39]	Retrospective, Parity and hip fracture, 348	OR = 0.76(0.46-1.27)
	Alderman et al. [43]	Retrospective, Parity and hip or wrist fracture, 917	OR = 1.20(0.70-2.22)
European	Lambrinoudaki et al. [29]	Cross-sectional, Parity and spine fracture, 454	OR = 0.96(0.69-1.34)
	Kauppi et al. [22]	Prospective, Parity ≥3 children and hip fracture, 2028	RR = 0.50(0.32-0.79)
	Bjørnerem et al. [21]	Prospective, Parity and (hip, wrist) fracture, 4681	HR = 1.04(0.75-1.46), HR = 1.20(0.96-1.51)
	Trémollières et al. [23]	Prospective, Parity ≥3 children and spine fracture, 2651	HR = 0.44(0.26-0.76)
	Hundrup et al. [24]	Prospective, Parity and hip fracture, 14015	HR = 0.87(0.66–1.15)
	Naves et al. [25]	Prospective, Parity and osteoporotic fracture, 255	OR = 0.60(0.20-1.78)
	Petersen et al. [15]	Prospective, Parity and hip fracture, 1708	HR = 0.88(0.65-1.19)
	Petersen et al. [15]	Cross sectional, Parity and hip fracture, 1215	OR = 0.69(0.39-1.23)
	Michaelsson et al. [32]	Cross sectional, Parity ≥2 children and hip fracture, 4640	OR = 0.75(0.62-0.91)
	Honkanen et al. [26]	Prospective, Parity and wrist fracture, 11798	HR = 0.71(0.52-0.97)
	O'Neill et al. [33]	Cross-sectional, Parity and spine fracture, 7530	OR = 1.00(0.82-1.23)
	Parazzini et al. [38]	Retrospective, Parity and hip fracture, 796	OR = 0.80(0.50-1.40)
	Mallmin et al. [41]	Retrospective, Parity and wrist fracture, 604	OR = 1.72(0.90-3.28)
Asiatic	Hwang et al. [28]	Cross-sectional, Parity ≥3 children and spine fracture, 1222	OR = 0.99(0.53–1.86)
	Shin et al. [34]	Retrospective, Parity and spine fracture, 1529	OR = 0.93(0.65-1.32)
	Huo et al. [36]	Retrospective, Parity and all fracture, 354	OR = 0.64(0.26-1.61)
	Fujiwara et al. [27]	Prospective, Parity ≥5 children and hip fracture, 2987	RR = 2.53(1.07-6.68)
Maghrebian	Maghraoui et al. [30]	Cross-sectional, Parity and spine fracture, 908	OR = 1.09(1.008-1.18)
	Allali et al. [31]	Cross-sectional, Parity and peripheral fracture, 730	OR = 1.40(0.70-2.80)
South American	Cure-Cure et al. [37]	Retrospective, Parity and all fracture, 1855	OR = 0.41(0.28-0.61)
Australian	Nguyen et al. [40]	Retrospective, Parity and all fracture, 1091	OR = 0.90(0.84-0.99)
	Cumming et al. [42]	Retrospective, Parity and hip fracture, 311	OR = 0.56(0.17-1.88)

Table 2: Association of fracture risk and parity according the ethnicity.

Abbreviation: HR = Hazard Ratio; OR = Odds Ratio; RR = Relative Risk

Association between parity and hip fracture risk: Data concerning hip fracture risk were included in 17 studies [15,18-24,27,31,32,35,36,38,39,42,43]. Five studies [18-20,22,32] found a statistically significant reduced risk for hip fracture in parous compared to nulliparous (IC 95% variation of RR = [0.32-0.79], HR = [0.56-0.96] and OR = [0.62-0.98]). This result was confirmed by multivariate analysis in all studies. This reduced risk concerned especially women with two or more children in two studies [22,32] with an OR = 0.75[0.62-0.91] and RR = 0.5[0.32-0.79]. However, an increased risk for hip fracture was found in one prospective study concerned women with five or more children in Japanese postmenopausal population [27].

Association between parity and vertebral fracture risk: Eight studies evaluated the association of vertebral fracture to parity [16,18,20,28-30,33,34]. One of them [23] found a significant reduced risk for vertebral fracture in French women with three or more children (OR = 0.44[0.26-0.76]). However, one study found a significant increase risk for vertebral fracture in post-menopausal Moroccan parous population with an OR = 1.093[1.008-1.186] [30].

Association between parity and wrist fracture risk: Seven studies examined the risk for wrist fracture [18,20,21,26,31,41,43]. One of these studies [26] found that the risk for wrist fracture was reduced in parous compared to nulliparous (IC 95% variation of HR = 71[0.52-0.97]). This result was confirmed by a multivariate analysis.

Discussion

The impact of pregnancy on the risk of osteoporotic fracture in postmenopausal women is controversial. This systematic review analyzed the results of 29 selected clinical studies concerning the relationship between the risk of osteoporotic fracture at menopause and parity during the reproductive period of women.

Only three studies, two prospectives [17,27] and one observational [30] associated parity to an increased risk of osteoporotic fracture after menopause. They involved, respectively, Asian-American, Japanese and North African populations. In all three studies, trabecular and cortical bone compartments were affected. The risk of fracture appeared in multivariate analysis to be associated with parity 5 or more

children in the two prospective series with, respectively, HR = 1.65[1.06-2.56] [18] and RR = 2.53[1.07-6.68] [27]. This increased risk should be compared with the decrease in bone mass density, because fracture risk doubles for each point reduction in T-score [44]. Early pregnancy, its impact on the acquisition of peak bone mass [45,46], poor contraceptive use and the impact of ethnic factors and/or nutritional habits (daily calcic ration) can be discussed. This negative link between parity and the fracture risk is limited to Asian women [17,27]. In all others studies in this population, even if not negative, now beneficial link is described [28,34,36]. At least, the Moroccan study show a negative link between parity and fracture risk, but exhibit methodological pitfalls: lack of control group, primary objective limited to worsening of vertebral fracture and no evaluation of osteoporotic fracture incidence [30]. In none Asiatic women, no data were support the hypothesis of a negative relationship between multiparity and fracture risk.

Ten out of the 29 studies reported a decrease in fracture risk in menopausal women that was attributable to parity. The majority of these included a Caucasian population. The risk of vertebral and non-vertebral fractures was reduced by 6% to 50% among menopausal parous compared with nulliparous women [18-20,26,37,40]. This reduced risk appears only beyond 2 to 3 pregnancies in four studies [17,22,23,32]. A reduction in the risk of vertebral fracture more than 50% (HR = 0.44[0.26-0.76]) was reported by Trémollieres et al. [23]. In case-control studies, Michaelsson et al., [32] and Hillier et al., [20] found a reduced risk of hip fracture from 8% to 10% per child in postmenopausal women. The impact on the risk of wrist fracture was specifically assessed by Honkanen et al., [26] in a large prospective study of 11 798 pre and postmenopausal women. The risk of wrist fracture in multivariate analysis was reduced by 30% (HR = 0.71[0.52-0.97]) among women with parity compared with nulliparous. The meta-analysis of Wang et al., [47] has included 10 prospective studies about parity and fracture in postmenopausal women. This paper is in accordance with our conclusion as it reports that increasing number of parity is associated with linearly reduced hip fracture risks among women. The osteoporosis fracture and hip fracture risks of parous women with at least one live birth were reduced by 11% and 26% respectively. The risk reduction for hip fracture was 12% for each one increased live birth.

These beneficial effects on all bone compartments are partly explicable by pathophysiological mechanisms and mechanical changes in bone structure. Bone loss during pregnancy and lactation are associated with hypersecretion of Parathyroid Hormone-Related Protein (PTHrp) and a fall in estrogen impregnation [48-50]. Increasing parity leads to functionally iterative estrogen deficiency. This promotes increased bone diameter by increasing periosteal apposition and endosteal resorption [51-54]. Mechanical resistance in torsion and flexion of a hollow cylinder increases exponentially with its diameter when the amount of material remains constant. This applies to the diaphyseal bone that undergoes a beneficial transformation during pregnancy, with no change in bone mass density or a slight decrease [53,55].

However, conclusions from the included studies should be examined carefully because of important heterogeneity in studies. Studies differed considerably in their sampling profiles, follow-up times, and the extent of exposure to the risk of fracture. Regardless of the bone site and the population studied, the problem of reproducibility is addressed most often in retrospective studies data. In generally data in this synthesis of the literature suggest that multiparity do not generally appear to be deleterious to bone during the menopause.

The results of these studies provide no evidence for an association between pregnancy and an increased risk of osteoporotic fracture. Referring to the aggregate risk without stratification according to the number of pregnancies, the majority of studies in this systematic review agree that there is no significant influence of parity on fracture risk after the menopause either by population or bone site [15,16,21,24,25,28,29,31,33-36,38,39,41,42]. In agreement to these results, Henderson et al., [56] reported that postmenopausal osteoporotic risk is not affected by the occurrence of multiple pregnancies during lactation in multiparous women with more than five children. Our results confirm also the findings of Karlsson et al., [11] who reported a neutral or beneficial effect of pregnancy on osteoporotic risk after the menopause. A doubt remains for Asian women in whom osteoporotic risk increase as been described for five pregnancies or more. Additional studies are needed to clarify this point.

Conclusion

According to this review, pregnancy does not seem to be associated with an increased risk of osteoporotic fracture after menopause. Most of the studies agree on the absence of a significant effect, regardless of the population and the bone site. However, a non-negligible number of studies (especially Americans, Europeans and Australians) report a protective effect in bone by increased bone diameter due to increased periosteal apposition and endosteal resorption. Contraceptive use and the impact of ethnic factors and/or nutritional habits (daily calcic ration) could also be discussed in the studies on Asiatic or African population where a negative impact was reported. According to our analysis, the types of sample chosen and the study designs used explain at least partly these differences. Other powerful and rigorous studies are required to elucidate the link between parity and osteoporotic risk especially in Asian population. They will provide a basis on which to recommend preventive practices.

Declaration

Authors' contributions

DD, MA, CB and MLS carried out research and drafted the manuscript. DD, GW, OM, SND and MLS conceived of the study and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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