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Pregnancy associated osteoporosis: The familial effect

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ABSTRACT

Objective. *The etiology and pathogenesis of pregnancy associated osteoporosis is unclear. Whether pregnancy has simply been an aggravating factor or is a direct etiologic cause responsible for severe bone loss needs to be elucidated.*

Methods. *In order to evaluate the contribution of familial factors to pregnancy osteoporosis, we analyzed the bone mass of 15 relatives of 5 women with pregnancy osteoporosis. Most of the patients suffered from severe back pain associated with vertebral fractures in their first pregnancy. Extensive clinical, laboratory and radiological investigations were performed to exclude secondary causes of osteoporosis. Bone mineral density measurements were performed on 15 first order family members and the results were compared with those of a control group of 20 healthy members of 5 families.*

Results. *Osteoporosis was present in 53% of the relatives of patients with pregnancy osteoporosis and in 15% of the controls ($P < 0.05$).*

Conclusion. *These results highly suggest that some patients with pregnancy associated osteoporosis have a genetic determination of low peak bone mass, and gestation, due to its association with physiological metabolic disturbances, constitutes a risk factor for the development of skeletal fractures in these patients.*

Introduction

Osteoporosis associated with pregnancy is a rare clinical condition resulting in vertebral or hip pain and fractures in young pregnant women. The clinical presentation is characterized by severe back pain associated with vertebral fractures in the third trimester of pregnancy or after delivery, and frequently in the first pregnancy (1,2). In other cases, osteoporosis affects the hip and may be associated with fracture (2). There are no clinical criteria for establishing the diagnosis of this disorder, which is based on the historical progression of events in relation to pregnancy and in the absence of other clinical underlying causes.

The etiology and pathogenesis of this disorder remains unclear. Although previous reports indicated an alteration of calcium regulatory hormones during pregnancy, there has been controversy about the presence or not of pre-existing bone disease (1, 2). Indeed, Dunne *et al.* observed a higher prevalence of fractures in the mothers of patients with pregnancy associated osteoporosis (3). But, whether pregnancy is a risk factor for osteoporosis and why only certain patients develope fractures are questions that remain unanswered.

Evidence from family studies suggests that genetic factors have a major role in the determination of bone mass and in the development of osteoporosis. The contribution of familial factors to pregnancy osteoporosis has not yet been assessed. In this report we analyzed the bone mineral density in relatives of five women with pregnancy osteoporosis, in order to evaluate the possible presence of a genetically determined pre-existing bone disease.

Patients and methods

From 1984 to 1998, 5 women with pregnancy osteoporosis were diagnosed in the Rheumatology Service of our hospital. Most of patients suffered from severe back pain, and spinal X-ray examination revealed vertebral fractures apparently related to their pregnancies. Extensive clinical and laboratory investigations were performed to exclude secondary causes of osteoporosis, especially malabsorption, hyperthyroidism, hypercortisolism or osteogenesis imperfecta.

In 15 first order family members bone mineral density (BMD) measurements were performed. There were 6 parents, including 4 mothers and 2 fathers (age range, 57-80 years), and 9 descendents including 2 brothers and 4 sisters (age range, 20-38 years), and 2 sons and 1 daughter (age range, 16-21 years). In order to assess and compare the prevalence of osteoporosis, a control group of 5 Caucasian families with a total of 20 members was included in the study. This group was composed of 7 parents, including 5 mothers and 2 fathers (age range, 54-64 years), and 13 descendants of similar ages (5 men and 8 women) (age range, 18-40 years). Healthy

families were recruited from hospital staff in the same geographical area and invited to attend the center on a voluntary basis for medical assessment. None of the relatives nor the controls reported clinical conditions related to bone loss and all of them gave their informed consent for the study. The mean age in family relatives and controls was similar (41.6 ± 23 vs 40.8 ± 14 years, P = n.s).

Bone mineral density (BMD) of the lumbar spine and femur was measured by dual X-ray absorptiometry (DPX-L, Lunar Radiation Corporation, Madison WI).The diagnosis of osteoporosis in adult relatives (> 20 year-old) was defined by a BMD in the lumbar spine or femur below -2.5 T-score, and osteopenia when BMD was below -1 T-score. In individuals younger than 20 years-old the diagnosis of osteoporosis was defined by a BMD in the lumbar spine below -2 Z-score (compared with the healthy population of similar age and gender from the same geographical area). Vertebral fracture was defined as a reduction of ≥ 20% in the anterior, middle or posterior height of the vertebral body.

The $\chi 2$ exact test, with correction for continuity, was used to compare osteoporosis frequencies between the cases and controls (patients with pregnancy associated osteoporosis were not included in the analysis). A P value of < 0.05 was considered to be significant.

Case reports

The main clinical characteristics of the patients are shown in Table I. In most of the patients (4 out of 5) the initial symptom was severe, invalidating back pain developed in the last trimester of pregnancy. In the remaining patient (case 5) hip pain due to transient osteoporosis of the hip was the initial complaint. In the latter case the clinical symptoms developed seven months into pregnancy. During lactation (at 4 months) the patient developed intense thoracic pain associated with vertebral fractures.

Routine investigations, including serum calcium, phosphate and alkaline phosphatase, were performed and results were normal in all patients. Hormonal studies, which included : estradiol, gonadotrophins, prolactine, urinary cortisol, thyroid function tests, didn't show abnormalities in any patient. Mesurements of calciotropic hormones included: serum 25-hydroxyvitamin D (25-OHD), 1-25-dihydroxyvitamin D (1-25-OH_2D), parathyroid hormone (PTH) and PTH-related peptide (the latter determined in only one patient), showing low 25-OHD serum concentrations in two patients (cases 1 and 5). Biochemical markers of bone turnover (serum osteocalcin and urinary hydroxyproline) were determined in 4 patients, and two of them showed slightly increased values (cases 1 and 5). It should be pointed out that these patients were referred to our center after the development of the symptoms and the hormonal studies were performed various months after delivery, from 3 months to more than one year in two patients (cases 2 and 3). Spinal X-ray films revealed various vertebral fractures in all patients (Table I), however, none of them had previous injuries or traumas severe enough to cause vertebral collapse. In addition, all the patients experienced loss of height. Lumbar and/or femoral BMD was decreased in all cases (Table II).

Family study

Age, lumbar and femoral neck BMD, as well as T scores and Z scores adjusted for age, height and weight of the patients and their relatives are reported in Table II (in individuals younger than 20 years-old only lumbar BMD and Z scores are reported). Seven of the 13 adult relatives studied had osteoporosis and 4 had osteopenia. In addition, one of the two relatives younger than 20 years old had osteoporosis. Unfortunately, in one patient (case 3) the family study was not possible. The mother of this patient suffered from forearm and ankle fractures related to minor traumas indicative of the presence of osteoporosis, however, since we did not have any densitometric measurements this case was not included in the comparative analysis. Among controls, three of the 20 subjects studied had osteoporosis (15%). As a result, the relatives of the patients with pregnancy osteoporosis showed higher frequency of osteoporosis than the control group (family relatives: 53% osteoporosis versus controls: 15 % osteoporosis, P < 0.05).

Table I. Clinical characteristics of the patients.

	case 1	case 2	case 3	case 4	case 5
Age (years)	26	36	26	36	31
Pregnancy	First	First	First	Second	First
Weight (Kg)	52	46	61	51	59
Height (cm)	156	147	162	144	165
BMI (Kg/m^2)	21.3	21.2	23.2	24.6	21.6
Symptoms*	3th trimester Back pain	3th trimester Back pain	3th trimester Back pain	3th trimester Back pain	3th trimester Hip pain + back pain in lactation
Fractures	4 vertebrae	7 vertebrae	5 vertebrae	9 vertebrae	2 vertebrae
Calcium (8.5-10.5 mg/dl)	9.7	9.2	9.2	9.3	10.3
Phosphate (2.3-4.3 mg/dl)	3.5	3.8	3.4	3.8	3.8
25-OHD (10-42 ng/ml)	7.8	ND	18	19	11
1-25-OH_2D (18-70 pg/ml)	50	ND	42	48	26
PTH (10-65 pg/ml)	48	40	25	38	22

* Development of symptoms during pregnancy. 25-OHD: 25-hydroxyvitamin D; 1-25-OH_2D: 1-25-dihydroxyvitamin D; PTH: parathyroid hormone. BMI: body mass index. () Normal values.

Discussion

Most of the patients with pregnancy associated osteoporosis included in

Table II. Bone mineral density in lumbar spine and femur in patients and family members.

	Case 1	Case 2	Case 3	Case 4	Case 5
Lumbar T score/Z score	-2.7 / -2.4	-2.17 / -1.87	-2.8 / -2.8	-4.4 / -3.9	-2.9 / -2.9
Femur T score/Z score	-2.6 / -2.4	ND	-0.8 / -0.9	-3.7 / -3.3	-2.1 / -2
	Family	Family	Family	Family	Family
Lumbar T score/Zscore	Mother (57) 0.17 / 1.34	Mother (78) -3.62 / -0.78		Mother (69) -4.28 / -2.43	Mother (66) -2.2 / -0.4
Femur T score/Z score	ND	-1.92 / 0.37		-2.06 / -0.52	-1.8 / -0.4
Lumbar Tscore/Z score	Sister (23) -1.35 / -1.28	Father (80) -2.87 / -2.07		Sister (38) -3.21 / -3.08	Father (60) -2.58 / -2.13
Femur T score/Z score	ND	-1.09 / 0.89		-2.2 / -1.96	-3.01 / -1.86
Lumbar T score/Z score	Sister (34) -0.11 / -0.01	Daughter (21) -2.54 / -2.3		Son (17) Z score -0.72	Brother (21) -1.31 / -1.64
Femur T score/Z score	-1.84 / -1.7	-1.58 / -1.56		ND	0.16 / -0.61
Lumbar T score/Z score	Sister (20) 0.17 / 1.34	Son (16) Z score -2.48			Brother (25) -3.18 /-3.08
Femur T score/Z score	ND	ND			-1.19 / -1.81

ND: Not done. ( ): Age.

this report showed a high prevalence of osteoporosis among their relatives. This finding highly suggests that in some patients pregnancy osteoporosis is a pre-existing bone disease where the gestation, due to its association with physiological metabolic disturbances, constitutes a risk factor for the development of skeletal fractures.

In all cases vertebral compression fractures developed shortly during the last trimester of pregnancy or after delivery, suggesting a causal relationship. Although it could be argued that vertebral fractures in these patients might have been present before pregnancy, none of them experienced previous injuries or traumas severe enough to cause vertebral collapse. In addition, clinical symptoms, ie, severe and invalidating back pain developed late in pregnancy associated with loss of height, highly suggest that vertebral fractures were developed during pregnancy. Indeed, this is the most frequent form of manifestation of pregnancy osteoporosis in previous clinical studies (2,3). It remains unclear whether pregnancy has simply been an aggravating factor disclosing a latent disease in a patient with an underlying osteoporosis or if it is a direct etiologic cause responsible for severe bone loss. Although the amount of bone density change with pregnancy is controversial, it has been shown that about 30g of calcium (3% of total body calcium) may be lost during normal pregnancy, mostly in the last trimester of pregnancy to provide normal bone mineralization for the developing foetus (4). In confirmation of this, recent studies have shown nearly 4% of bone mass loss during pregnancy (5,6). In addition, the calcium demand from the maternal skeleton increases during lactation. Thus, approximately 6% of bone in the lumbar spine is lost over a six-month period in lactating women (7-9). These amounts of bone loss are probably clinically insignificant in healthy women but in patients with pre-existing low bone mass may trigger the clinical manifestations of the osteoporotic syndrome. Similarly during pregnancy and lactation, other clinical conditions such as corticosteroid therapy or organ transplantation may induce a rapid initial bone loss of similar magnitude (10). The early bone loss period in these situations when the patient has a previous low bone mass may develop into skeletal fractures.

Although the etiology and pathogenesis of pregnancy osteoporosis remains obscure, gestation is considered to be a physiological state of stress to maternal calcium metabolism. In this situation, the calcium demand could be addressed by compensatory mechanisms including increased intestinal calcium absorption, renal conservation of calcium, or calcium mobilization from the maternal skeleton (4). Thus, a marked increase in bone turnover has been associated with pregnancy and lactation, which return to normal after weaning (5, 6, 8, 9, 11). The studies on physiological changes of calciotropic hormones during pregnancy are controversial. Serum levels of 1-25-OH_2D increase with the calcium demand of pregnancy, which is believed to be responsible, in part, for the improvement in calcium absorption. Modifications in serum PTH levels have been also described, with later studies indicating either no significant variation or a decrease of PTH levels with gestation (6). Other factors such as the PTH related peptide (PTHrp) or the insulin-like growth factor I (IGF-I), have also been implicated in the bone remodeling of this process (4-6, 12).

It has been suggested that in pregnancy associated osteoporosis there is a failure in the calcium regulating hormones. In this sense, isolated cases of pregnancy osteoporosis have been related to a failure to increase serum levels of 1-25-OH_2D as expected in normal pregnancy (1,2), or even to increase serum PTHrp levels (13). Nevertheless, the clinical significance of these observations remains to be fully appreciated.

In the present series, hormonal tests were normal in all patients. However, since this condition is mostly self-limiting, a rapid reversal of the metabolic abnormalities after delivery can not be totally ruled out (1, 2, 14). It should be pointed out that biochemical and hormonal studies were performed various months after the onset of symptoms in

most patients. The lack of early recognition of this condition and the delayed referral is a common finding also present in previous studies, which frequently causes a considerable delay between symptoms and laboratory investigations (2,3). Interestingly, most of the patients showed the presence of osteoporosis in most family members studied, suggesting a pre-existing pathological condition of genetic cause in some of these patients. Indeed, Dunne et al (3) indicated a higher prevalence of fractures in mothers of patients with pregnancy osteoporosis, and Carbone *et al.* (15) reported the existence of osteopenia in the siblings of two patients with pregnancy associated osteoporosis.

In conclusion, whatever the explanation for bone loss during pregnancy, our findings suggest that osteoporotic fractures that occur in pregnancy may be associated with a pre-existing low peak bone mass in some of these patients. Familial influences of genetic origin may contribute to the development of osteoporosis in these patients.

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