

## MOTHERISK ROUNDS

# Does Treatment With Bisphosphonates Endanger the Human Pregnancy?

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## Abstract

Bisphosphonates are clinically used in the treatment of various bone diseases including corticosteroid-induced osteoporosis, hypercalcemia associated with malignancy, and osteogenesis imperfecta. They are therefore often used in women of childbearing age, but little is known about their possible effects on the human embryo and fetus. Animal studies have revealed unfavourable effects of bisphosphonate treatment on the fetus, mainly in the skeleton. Since bisphosphonates are retained for a long time in the human skeleton, concerns have been raised that even pre-pregnancy administration of bisphosphonates may result in embryofetal exposure and alter fetal bone modelling. To obtain current information on the risks and safety of bisphosphonate use in pregnancy, we performed a systematic search of the Medline and Embase databases, from 1950 and 1974, respectively, to September 2008. Fifty-one cases of exposure to bisphosphonates before or during pregnancy were identified; none of them described any skeletal abnormalities or other congenital malformations in the infants. The bisphosphonates used were alendronate (32 cases), pamidronate (11), etidronate (5), risedronate (2), and zoledronic acid (1).

Although in theory bisphosphonates may affect bone modelling and development in the fetus, the 51 cases reported to date did not detect such pathology.

## Résumé

Les bisphosphonates sont utilisés en clinique pour la prise en charge de diverses pathologies osseuses, y compris l'ostéoporose provoquée par des corticostéroïdes, l'hypercalcémie associée à une malignité et l'ostéogenèse imparfaite. Ils sont donc souvent utilisés chez les femmes en âge de procréer; cependant, nous ne disposons que de peu de données au sujet de leurs effets possibles sur l'embryon et le fœtus humains. Des études menées chez l'animal ont révélé que le traitement aux bisphosphonates exerçait des effets défavorables sur le fœtus, principalement au niveau du squelette. Puisque les bisphosphonates demeurent longtemps au sein du squelette humain, le fait que même l'administration pré-grossesse de bisphosphonates puisse entraîner une exposition embryofœtale et altérer le modelage osseux fœtal a suscité des préoccupations. Afin d'obtenir des renseignements à jour au sujet des risques et de l'innocuité de l'utilisation de bisphosphonates pendant la grossesse, nous avons mené des recherches systématiques au sein des bases de données Medline et Embase, à partir de 1950 et de 1974, respectivement, jusqu'à septembre 2008. Cinquante et un cas d'exposition aux bisphosphonates avant ou pendant la grossesse ont été identifiés; aucun d'entre eux ne décrivait quelque anomalie squelettique ou autre malformation congénitale que ce soit chez les nouveau-nés. Les bisphosphonates utilisés étaient les

suivants : alendronate (32 cas), pamidronate (11 cas), étidronate (5 cas), risédronate (2 cas) et acide zolédronique (1 cas).

Bien que, en théorie, les bisphosphonates puissent affecter le développement et le modelage osseux chez le fœtus, les 51 cas signalés à ce jour n'ont pas mis au jour une telle pathologie.

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## INTRODUCTION

Bisphosphonates are synthetic analogues of pyrophosphate that inhibit bone resorption. The classical pharmacological effects of bisphosphonates appear to be the result of two key properties: their affinity for bone mineral and their inhibitory effects on osteoclasts.<sup>1</sup> Bisphosphonates inhibit bone resorption by being selectively taken up and adsorbed to mineral surfaces in bone, where they interfere with the action of the bone-resorbing osteoclasts. Bisphosphonates are rapidly cleared from blood, with 20% to 80% being deposited in the skeleton.<sup>2</sup> As long as bisphosphonates remain incorporated into the bone matrix, these drugs are not pharmacologically active.

The release of bisphosphonate from bone can occur through bone remodelling and resorption. It has been shown that the urinary excretion of small amounts of bisphosphonate can be measured over many weeks or months after stopping treatment because of the release from skeleton.<sup>3</sup> This means that bisphosphonate is present in the circulation and available for reuptake into bone for prolonged periods, and this is probably responsible for their ongoing pharmacological action.<sup>1</sup> The long skeletal retention time of these agents allows intermittent administration, and the most potent drugs (e.g., zoledronic acid) may be effective when administered as infrequently as once per year.

Bisphosphonates have been established as the primary treatment for bone diseases associated with excessive resorption.<sup>1,4</sup> They are principally used in the treatment of osteoporosis, Paget's disease, myeloma, bony metastases, and hypercalcemia of malignancy in adults, but there has been increasing and successful application in pediatric bone

**Key Words:** Bisphosphonates, pregnancy

diseases, notably osteogenesis imperfecta. The widespread and long-term use of bisphosphonates in clinical medicine increases the possibility that these compounds will be used in women of childbearing age, including pregnant women. Because of their long persistence and slow release from bone, it has been suggested that even pre-pregnancy administration of bisphosphonates may alter fetal bone modelling and reduce the amount of resorbable bone calcium available to the fetus during the third trimester.<sup>5,6</sup>

## **METHODS**

In order to summarize current knowledge about the safety and risks of bisphosphonate use in women of reproductive age, we searched the Medline database for articles published between 1950 and September 2008, and the Embase database for articles published between 1974 and September 2008 to identify reports of bisphosphonate use before or during pregnancy.

## **RESULTS**

### **Animal Studies**

In rats, subcutaneously administered alendronate was found to cross the placenta, accumulate in the fetal skeleton, decrease fetal weight, and decrease bone growth.<sup>6</sup> Rat studies have also shown that high-dose bisphosphonate therapy during pregnancy can result in shortening of diaphyseal bone, increased diaphyseal trabecular volume, and a reduction in bone marrow volume in the fetus.<sup>6</sup> Reproduction toxicity studies in rats and rabbits with pamidronate at daily doses about 10 times higher than the recommended human therapeutic dose produced maternal toxicity, embryoletality or severe general underdevelopment and a marked skeletal retardation of the fetuses.<sup>5</sup>

Bisphosphonate toxicity in pregnant rats was associated with symptomatic hypocalcemia in the dams during the later stages of pregnancy, as well as prolongation of parturition and fetal demise.<sup>5,7</sup> Neonatal deaths were due to protracted deliveries rather than a direct effect of bisphosphonates on the pups. The presumption is that uterine muscle activity, which is calcium-dependent, is disordered in the face of a low serum calcium concentration. Fortunately, women taking bisphosphonates do not experience significant hypocalcemia, which was the cause of the adverse effects in these studies.

There have been no reports of congenital abnormalities associated with use of alendronate and pamidronate in animal teratology studies.

### **Human Pregnancy Experience**

It is not known whether bisphosphonates cross the human placenta, but the molecular weight of most bisphosphonates is relatively low, and transplacental passage could

be expected. Information about human pregnancies following bisphosphonate use is limited and comprises several case reports and case series with 51 pregnancies in total.<sup>8-14,17-19</sup>

One case report described a pregnancy in which a 49-year-old woman who had been amenorrheic for two years used alendronate 10 mg/day orally for presumed postmenopausal osteoporosis.<sup>8</sup> She was unaware of the pregnancy until labour began. An apparently normal female infant with a birth weight of 2390 g (50th centile) was born at 36 weeks' gestation. Laboratory tests (phosphate, alkaline phosphatase and ionized calcium) were within normal limits. Dual x-rays of the infant's skull and wrists revealed normal bone structure and density without abnormal calcification. At one year of age, the infant's weight was 8 kg (10th centile) and her height was 73 cm (50th centile), but other aspects of her physical and psychomotor development were normal.

Another report of 15 pregnancies exposed to different bisphosphonates from one to three months prior to pregnancy (6 patients), or during the first trimester (9 patients), found no congenital anomalies in 14 live births.<sup>9</sup> There was one miscarriage and one case of unrelated Apert syndrome.

In a case series of 24 pregnancies with pre-pregnancy or early pregnancy exposure to alendronate, there were 19 live-born infants and five miscarriages.<sup>10</sup> No major congenital anomalies were found among the offspring. The authors found lower mean gestational age at birth, reduced mean birth weight and an increased rate of miscarriage in pregnancies exposed to alendronate than in controls; although this may be related to the maternal disease responsible for osteoporosis and to the concomitant use of medications, especially glucocorticoids (taken by 13 of the 24 women), an effect of alendronate could not be excluded.

There have been four case reports of pregnant women with hypercalcemia from metastatic breast cancer who were given intravenous pamidronate or zoledronic acid with beneficial effect to the mothers and no serious adverse effects on the babies.<sup>11-14</sup> In the first case, a woman at 34 weeks of gestation was given pamidronate.<sup>11</sup> She delivered at 36 weeks' gestation, and the baby had a low serum calcium level at birth, but this had normalized within five days of birth. Another woman was given pamidronate at 28 weeks' gestation and delivered by Caesarean section one week later.<sup>12</sup> The baby had an elevated serum calcium level at birth, but this quickly dropped to below normal levels and remained below normal until the ninth day of life, when it became normal. In both cases, the authors were unable to ascertain if the transient neonatal hypocalcemia was due to fetal parathyroid suppression by maternal hypercalcemia or if it was a direct effect of bisphosphonate therapy.

In the third case, a woman at 28 weeks' gestation was given pamidronate and had a Caesarean section five days later.<sup>13</sup>

The baby had normal serum calcium and parathyroid hormone levels at birth, and these both remained normal.

The fourth report described a woman who received zoledronic acid during the second and third trimesters of pregnancy after undergoing chemotherapy for breast cancer during the first trimester.<sup>14</sup> She delivered a healthy girl by Caesarean section at 35 weeks' gestation. All hematological and biochemistry variables in the neonate were within the normal range. The infant was followed until the age of one year, during which time her development was normal.

None of the four infants in these reports demonstrated any skeletal abnormalities arising from bisphosphonate therapy.

There is concern that treatment of reproductive age women with bisphosphonates might result in release of the drug from bone during pregnancy years after treatment, resulting in embryofetal exposure.<sup>6,15,16</sup> Published information on whether long-term pre-pregnancy bisphosphonate exposure may alter fetal bone modelling is scarce. However, three reports of maternal and fetal outcomes after prolonged pamidronate therapy before conception, involving seven pregnancies, found no significant adverse effects.<sup>17-19</sup>

The first report described the cases of two women with osteogenesis imperfecta and their children; the young mothers had received intermittent intravenous pamidronate therapy for five years before conception.<sup>17</sup> One of the babies had transient asymptomatic hypocalcemia, and the other had bilateral talipes equinovarus. Neither infant had evidence of abnormal skeletal modelling, and both the mothers and the babies remained well and free of fractures up to 16 months post partum.

In another report, four offspring of three women, two with polyostotic fibrous dysplasia and one with osteogenesis imperfecta, were healthy with no evidence of biochemical or skeletal abnormality.<sup>18</sup> These three women were treated with IV pamidronate for 46, 26, and 19 months. Their last doses were given 3 months, 3 and 48 months (mother 2 with two babies), and 21 months before conception.

The third report was of a 30-year-old woman with idiopathic hyperphosphatasia who had been treated with cyclical intravenous pamidronate for 42 months and who had conceived one month after the last cycle.<sup>19</sup> A healthy baby was born at 36 weeks of gestation, weighing 3130 g, with normal serum calcium, phosphate, and PTH levels.

## CONCLUSION

The theoretical risk to the fetus of bone toxicity or modelling abnormality attributable to leaching of bisphosphonates from the maternal skeleton has so far not been shown in humans. On the basis of the 51 cases described above, pre-pregnancy bisphosphonate administration or inadvertent exposure during pregnancy does not appear to

represent a measurable risk to the embryo or fetus, but infants should be monitored for hypocalcemia during the first few days after birth. However, until we know whether or not bisphosphonates cross the human placenta, these drugs should be discontinued in women who are attempting to conceive or who become pregnant. Because bisphosphonates are increasingly used to treat adolescents and premenopausal women, it is clearly necessary to perform systematic studies on the outcome of pregnancy in women who, for any reason, have received bisphosphonate therapy before or during pregnancy.

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