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QUESTION
Are there any data on the use of pamidronate in young women prior to pregnancy and any potential harmful effects on the baby?

BACKGROUND
Pamidronate is a bisphosphonate with potent inhibitory effects on bone resorption. Approximately 50% of a dose is eliminated unchanged in the urine after 72 hours. However, the half-life related to skeletal binding sites is prolonged and in the order of 1 to 2 years but this may be less in states of high bone turnover [1]. Studies have shown that a few days after pamidronate is given the plasma concentrations are very low (approximately 0.4% of the concentration measured during a dose). Furthermore, ongoing plasma concentrations, as a result of release of pamidronate from skeletal binding sites, are extremely low [2].

ANSWER
There are very limited human data on the use of bisphosphonates, and in particular pamidronate, before or during pregnancy. It is not known whether pamidronate would cross the placenta to the human foetus, although the molecular weight is low enough (370D) that foetal exposure should be expected [1].

There are very limited data on the use of pamidronate or other bisphosphonates prior to pregnancy. Overall the data did not indicate that use prior to pregnancy was associated with teratogenicity or foetal skeletal abnormalities. The case studies are summarised below.

A case series of 3 women and 4 pregnancies discusses the use of pamidronate therapy for polyostotic fibrous dysplasia or osteogenesis imperfecta before conception [3]. The first patient received a total of 4 years of pamidronate therapy and 3 months after therapy was stopped the patient conceived. The pregnancy was uncomplicated and the patient had a normal vaginal delivery that resulted in a healthy female infant. The infant was followed for 4 years and showed normal skeletal development. The second patient received 2.2 years of pamidronate therapy and conceived 3 months after a dose. The pregnancy was uneventful and a full-term healthy infant was delivered by vaginal delivery. The baby showed normal skeletal development. The same patient became pregnant 3 years later, which also resulted in a full-term healthy infant with no skeletal anomalies. The third patient received 2 years of pamidronate therapy and conceived 21 months after it was stopped. The baby was delivered at 34 weeks gestation due to maternal ill health. The baby was healthy and showed no signs of skeletal abnormalities.

A second case report discusses 2 women that received pamidronate therapy for osteogenesis imperfecta prior to conception [4]. Both patients received pamidronate therapy for 5 or more years before conceiving, after which, therapy was stopped. Other

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than hyperemesis in one patient both pregnancies and deliveries were normal. Both offspring inherited osteogenesis imperfecta. One baby had bilateral talipes equinovarus and one had asymptomatic hypocalcaemia at 24 hours of age that had resolved by day 11. Both the mothers and the babies remained well and free of fractures at 14 and 16 months post-partum. The authors concluded that neither baby had skeletal modelling abnormalities consistent with in utero pamidronate exposure.

There are also several case reports (available in abstract form only) that describe the use of bisphosphonates for the treatment of pregnancy and lactation associated osteoporosis [5,6]. Seven patients that developed osteoporosis as a result of pregnancy and lactation, were treated with a bisphosphonate and subsequently became pregnant (one patient 3 years after therapy, timescale unknown for the remaining patients). No foetal anomalies were noted.

Another paper (available in abstract form only) reports on the use of alendronate prior to or during 24 pregnancies [7]. The authors concluded that based on the pregnancy outcome (not stated), the use of alendronate does not impose a major teratogenic risk.

There are also very limited data on the use of pamidronate or other bisphosphonates during pregnancy. These are summarised below.

There are several case reports that describe the use of pamidronate for the treatment of maternal hypercalcaemia during pregnancy [8,9]. The patients had hypercalcaemia secondary to malignancy and pamidronate was administered in the third trimester after failure of other therapy. Use was not associated with any adverse effects in the foetus.

Results from animal studies indicate that pamidronate crosses the placenta and may affect foetal skeletal development [10,11]. When pamidronate (50mg/kg orally or 6 to 15mg/kg intravenously) was given to rats and rabbits during organogenesis it was found to delay ossification. Shortening of the long bones occurred in rats after doses of 12 to 15mg/kg. Delayed and prolonged parturition was also found to occur in pamidronate treated rats, which was secondary to hypocalcaemia [11]. It should be noted that in the animal studies, pamidronate was given to the animals during pregnancy, which is a different situation to pregnancy after pamidronate therapy has ceased.

CONCLUSIONS

There are very limited data on the use of pamidronate prior to or during human pregnancy. It is likely that pamidronate crosses the human placenta. The available data are reassuring as pamidronate therapy prior to or during pregnancy has not been associated with any adverse foetal outcomes.

High doses of pamidronate given during pregnancy were associated with skeletal anomalies in animal studies. This may suggest that the potential risks to a developing foetus may be concentration related. From the pharmacokinetic data we know that approximately 50% is excreted unchanged in the urine within 72 hours with the remainder going into bone and having a skeletal half-life of one to two years. Furthermore pamidronate concentrations in the systemic circulation are very low a few days after a dose is given, while ongoing concentrations (due to release of pamidronate from skeletal binding sites) are extremely low.

The use of pamidronate in women prior to conception must be a clinical decision. It is likely that the potential risk will be very small after one to two years. However, conception shortly

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after or during therapy would not be considered grounds for termination of pregnancy and has not been associated with adverse foetal outcomes.

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