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REVIEW

Does the use of bisphosphonates during pregnancy affect fetal outcomes? A systematic review

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Abstract

Purpose This systematic review aimed to determine the effects of maternal exposure to bisphosphonates (BPs) during pregnancy on neonatal outcomes. It aimed to disclosfe the impact of BPs on neonates and identify aspects that require further investigation.

Methods A comprehensive search of PubMed, Science Direct, LILACS, EMBASE, and Web of Science was conducted until August 2022, with no time restrictions. The selection criteria included studies published in English that evaluated pregnant women who were exposed to BPs.

Results From an initial pool of 2169 studies, 13 met the inclusion criteria for this systematic review. These studies collectively included 106 women (108 pregnancies) who were exposed to BPs either before orduring pregnancy. A summary of the key characteristics of the selected studies and the risk of bias assessment are provided. Exposure to BPs occurs at various stages of pregnancy, with different indications for BP treatment. The most frequently reported neonatal outcomes were spontaneous abortion, congenital malformations, hypocalcemia, preterm birth, and low birth weight.

Conclusion Although previous reports have linked BPs before or during pregnancy with adverse neonatal outcomes, these associations should be interpreted with caution. Given the complexity of these findings, further research is necessary to provide more definitive insights to guide clinical decisions regarding the use of BPs in pregnant women.

Keywords Pregnancy · Bisphosphonate · Embryonic and fetal development

Introduction

Bisphosphonates (BPs) have long been used for various therapeutic purposes. They were introduced as pharmaceuticals over three decades ago and extensive data have been collected on their potential benefits and associated risks. BPs are part of several pharmacological strategies used to treat and prevent bone-related conditions, with osteoporosis being the most common target condition. In addition, they are used to manage conditions such as Paget's disease, hypercalcemia, and osteogenesis imperfecta and to prevent bone metastasis. As analogues of pyrophosphate, BPs inhibit bone resorption by diminishing osteoclastic activity, thereby reducing the bone remodeling rate and contributing to the overall bone mass accretion [1–4].

First-generation, non-nitrogen-containing BPs (etidronate, clodronate, and tiludronate) share structural similarity with pyrophosphate, allowing easy internalization by osteoclasts. This interaction renders newly synthesized adenosine triphosphate (ATP) non-hydrolysable, leading to

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its intracellular accumulation and the prevention of ATP-dependent processes, ultimately causing osteoclast apoptosis [1, 2]. Second-generation BPs, the nitrogen-containing molecules alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid, work through different mechanisms, primarily by inhibiting the mevalonate pathway, which is essential for cellular function by binding to farnesyl pyrophosphate synthase [1, 2].

Owing to their pharmacokinetic properties, BPs have long half-lives and accumulate in the bone tissue, especially at active remodeling sites [3, 5]. In addition, the use of BPs during pregnancy or the pregestational period has raised significant biosafety concerns [6]. Not only do BPs have the capability to cross the placental barrier, potentially affecting fetal skeletal development and ultimately impacting fetal viability, but it is also imperative to consider their underexplored effects on the placenta and their subsequent influence on uterine artery flowmetry. This aspect is particularly pertinent in clinical contexts given that uterine artery flowmetry is a critical area of ongoing research with significant implications for maternal and fetal health [7].

However, very few in vivo studies using mammals have been conducted given the associated ethical constraints. Patlas et al. [8], in their seminal study on pregnant rats, described skeletal alterations in offspring exposed to alendronate during pregnancy, including reduced fetal weight and impaired bone growth. Graepel et al. [9] reported severe outcomes from high doses of pamidronate in pregnant rats and rabbits, including increased maternal and embryonic toxicity and generalized fetal skeletal underdevelopment. However, it is worth to mention that the administered doses were ten times higher than the usual clinical doses recommended for humans. Minsker et al. [10] reported that alendronate induces hypocalcemia in gestating rats, leading to complications during parturition and increased fetal mortality without developmental defects in the offspring. To date, the literature has reported no congenital abnormalities in offspring that are incompatible with survival.

In the context of human pregnancy, clinical and observational studies have suggested the potential impact of BPs on fetal development and labor timing [11, 12]. However, establishing a cause-and-effect relationship is challenging. One factor contributing to the potential complexity of these findings is the question of whether the observed outcomes are primarily attributed to BP effects or influenced by the underlying medical condition under treatment. Adding to this complexity is the wide range of therapeutic regimens and doses contingent on the pathology being treated and its severity. The diversity of therapeutic approaches makes it challenging to accurately discern eventual dose-dependent effects, further highlighting the need for a comprehensive investigation.

Interestingly, to the best of our knowledge, no previous systematic reviews have been conducted within the scope of this subject. This underscores the novelty and importance of the present study, which aimed to shed light on the underexplored impact of BPs during pregnancy on fetal development.

Materials and methods

Protocol and registration

This systematic review protocol was registered with the Open Science Framework (under https://doi.org/10.17605/OSF.IO/KE36U). This study followed the ethical standards of the Institutional and National Research Committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Inclusion criteria

This review focuses on studies that examined the effects of bisphosphonate exposure on pregnant women. The inclusion criteria followed the PICOS (population, intervention, comparison, outcome, and study design) framework, specifically targeting studies enrolling women undergoing BP therapy before or during pregnancy that resulted in fetal exposure. The primary outcome of interest was the adverse neonatal outcomes associated with maternal BP exposure.

Exclusion criteria

The following types of studies were excluded: reviews, editorials, letters, personal opinions, book chapters, conference abstracts, experimental in vitro or in vivo studies, studies not available in English, and studies involving oncological patients.

Study selection

Studies were identified through searches of the following electronic databases: PubMed, Science Direct, LILACS, EMBASE, and Web of Science, with an additional gray literature search on Google Scholar. The search strategy is described in Appendix S1 in the manuscript. No time restrictions were applied, and only articles in English were considered. All the searches were completed in August 2022. Reference lists of the included articles were also considered for additional pertinent studies that were not identified in the database searches. Duplicate references were removed using the reference manager software (Mendeley Desktop, Elsevier, New York).

Risk of bias within studies

The Joanna Briggs Institute Critical Appraisal Checklist for Case Series [13] was used to evaluate study quality. The scoring was discussed among reviewers and a decision about the methodology was applied according to the following categorization: studies were deemed to have a "high risk of bias" if their analysis scored below 49%; a "moderate risk of bias" for scores between 50 and 69%; and a "low risk of bias" for scores above 70%.

Summary measures

The primary goal of this systematic review was to investigate adverse neonatal outcomes associated with maternal BP exposure. All outcome measurements were considered in this review.

Results

In phase 1, 2169 articles were identified from the selected databases. After removing duplicates, 1918 articles remained. After evaluating the titles and abstracts, 1852 studies were excluded, and 66 articles were selected for further consideration. An additional 10 articles were included in the manual search of the reference lists. Subsequently, a comprehensive assessment of the articles selected in phase 1 was performed. This methodology led to the inclusion of 13 studies for this systematic review. A flowchart of the selection methodology is shown in Fig. 1.

Study characteristics

This review included 13 studies involving 106 women (108 pregnancies) exposed to BPs either before or during pregnancy. The number of cases in each study ranged from 1 [14, 15] to 36 [16]. Studies have been conducted in various countries, including Argentina [14], Australia [17], Canada [11, 18], France [16], Israel [12, 15], Italy [19], Serbia [20], South Korea [11], Taiwan [21], and the UK [22–24]. All studies were written in English between 2003 and 2018. Details of the selected studies are listed in Table 1. Two studies [12, 16] included control groups, totaling 882 pregnant women who were not exposed to BPs.

Evaluation of risk of bias

All 13 studies were submitted to the Joanna Briggs Institute's Critical Appraisal Checklist for Case Series [13]. Two

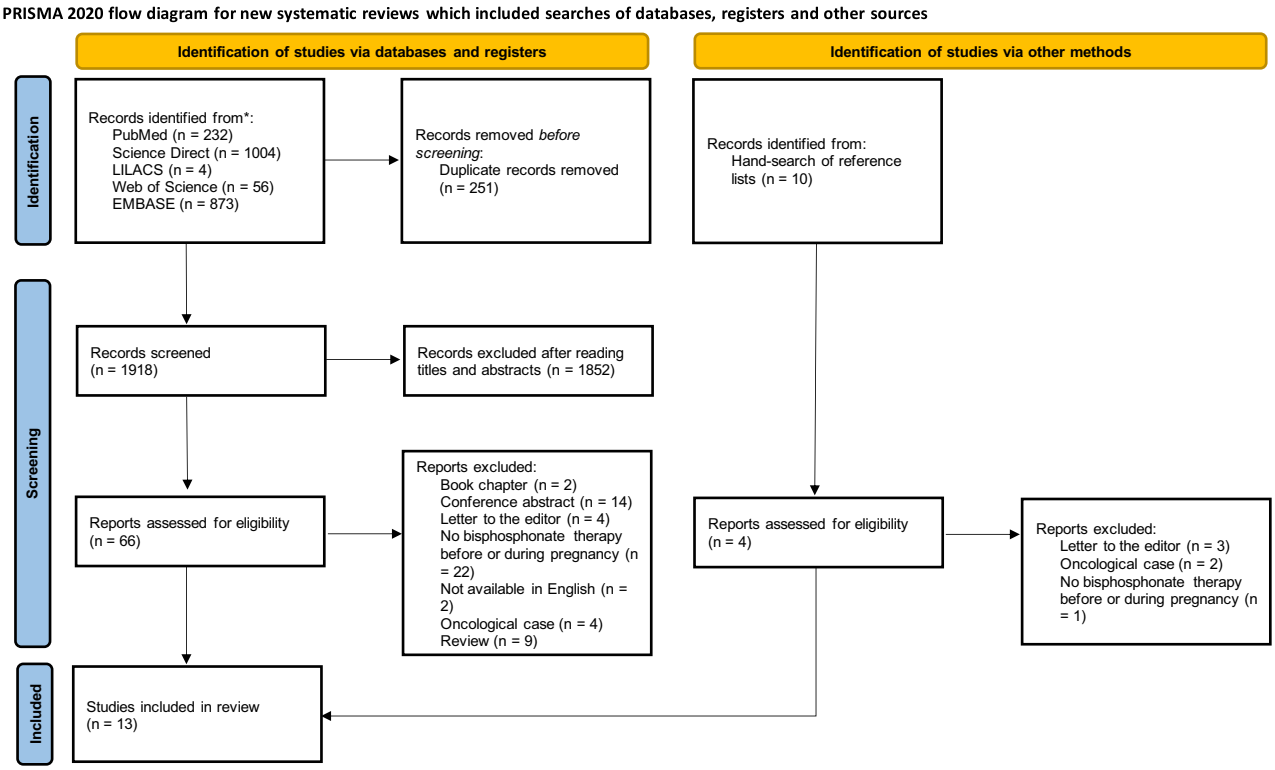

Fig. 1 Flow diagram of literature search and selection criteria adapted from PRISMA

Table 1 Description of articles features

Author	Country	Study design	Bisphosphonate	Age (years)	Duration of administration	Indication	Gestational age at delivery (weeks)	Birth weight (grams)	Adverse neonatal outcomes
Athimulam et al. [23]	UK	Case report; two cases	Alendronate (dose not reported)	34	Until pregnancy	Pregnancy-associated osteoporosis	**36**	**-**	**-**
Barrera et al. [22]	UK	Observational cohort ($n=13.643$); one case	Risedronate (dose not reported)	-	First trimester	-	-	-	None
Biswas et al. [24]	UK	Observational cohort ($n=11.916$); two cases	Alendronate (dose not reported)	-	First trimester in one case Patient stopped taking alendronate 2 months prior to becoming pregnant in the other case	-	-	-	None
Chan and Zacharin [17]	Australia	Case report; four cases	Case 1: pamidronate 3 mg/kg i.v. every 4–6 months for 4 years (cumulative dose, 7.5 mg/kg/yr) Case 2, pregnancy 1: pamidronate 3 mg/kg i.v. every 4–6 months for 2.2 years (cumulative dose, 9 mg/kg/yr) Case 3, pregnancy 2: pamidronate therapy not restarted after pregnancy 1 Case 4: pamidronate 1 mg/kg i.v. every 2 months for 2.2 years (cumulative dose, 6 mg/kg/yr)	29.5	Discontinued 3 months before pregnancy Last dose 3 months before pregnancy Last dose 4 years before the second pregnancy Discontinued 21 months before pregnancy	McCune–Albright syndrome Fibrous lower limb dysplasia Fibrous lower limb dysplasia Osteogenesis imperfecta	38 Full-term Full-term 34	2500 - - 2270	- - - Hypercalcemia (10.8 mg/dL), hyperphosphatemia (6.66 mg/dL), low femoral BMD (0.127)
Chen et al. [21]	Taiwan	Case report; one case (two pregnancies)	Case 1: Pamidronate 15 mg i.v. monthly, for 3 years Case 2: 6 months after the delivery, she started pamidronate 30 mg i.v. monthly, for 1 year. Then, started oral alendronate 70 mg/week	26 30	Last dose 1 month before pregnancy Last dose 4 months before her second pregnancy,	Osteogenesis imperfecta	38 37	3838 2840	None
Koren et al. [15]	Israel	Case report; one case	Pamidronate 90 mg given in three divided doses	38	Third trimester	Humoral hypercalcemia	35	-	Hypocalcemia

Table 1 (continued)

Author	Country	Study design	Bisphosphonate	Age (years)	Duration of administration	Indication	Gestational age at delivery (weeks)	Birth weight (grams)	Adverse neonatal outcomes
Levy et al. [11]	Canada and South Korea	Cohort; 21 cases	Alendronate ($n=12$), etidronate ($n=5$), risedronate ($n=2$) and pamidronate ($n=2$). (dose not reported)	-	Fifteen patients in the bisphosphonate group had first-trimester exposure, and 6 patients discontinued the bisphosphonates within 3 months prior to conception	Primary osteoporosis ($n=5$), osteoporosis associated with cancer ($n=1$), and osteoporosis secondary to corticosteroid use such as inflammatory bowel disease and SLE* ($n=15$)	38.7 ± 1.9 mean ± SD	3100 ± 300 mean ± SD	Apert syndrome, premature birth, jaundice, low birth weight
Losada et al. [19]	Italy	Case series; 10 cases	Alendronate, clodronate, neridronate and pamidronate (Dose not reported)	35	Before and during pregnancy	Corticoid induced osteoporosis ($n=7$), osteoporosis ($n=1$), pelvic fracture ($n=1$), and femoral avascular necrosis ($n=1$)	38, mean	2890, mean	One spontaneous abortion (10%), 2 congenital malformations (20%), 1 ventricular septal defect (exposed to clodronic acid) and 1 kidney and cardiac malformation (exposed to alendronate), 1 premature birth, and 1 distress syndrome
Mastaglia et al. [14]	Argentina	Case report; one case	Pamidronate 240 mg i.v. given in four divided doses	21	Last infusion during the first trimester of pregnancy	Type 1 Gaucher's disease	37	2230	Low birth weight
Munns et al. [18]	Canada	Case report; two cases	Case 1: pamidronate at a dose of 1 mg/kg on each of 3 consecutive days every 4 months. A total cumulative pamidronate dose of 49.5 mg/kg (9 mg/kg/year) Case 2: cyclical intravenous pamidronate from 12.5 to 17.8 years of age. A total cumulative pamidronate dose of 48 mg/kg (9 mg/kg/year)	17.4	Until pregnancy Until pregnancy	Osteogenesis imperfecta Osteogenesis imperfecta	37 38	3600 2860	Hypocalcemia Bilateral talipes equinovarus

Table 1 (continued)

Author	Country	Study design	Bisphosphonate	Age (years)	Duration of administration	Indication	Gestational age at delivery (weeks)	Birth weight (grams)	Adverse neonatal outcomes
Ornoy et al. [12]	Israel	Case–control; Test: 24 cases of women exposed to BPs, Control: 790 women exposed to non-teratogens	Alendronate (dose not reported)	-	1–6 months before pregnancy (8 women) or before and during the first 3–8 weeks of pregnancy (15 women). One woman was treated until week 21	SLE ($n=5$), familial osteoporosis ($n=4$), Takayasu arteritis ($n=2$), Behcet's disease ($n=2$), hypothyroidism ($n=2$), rheumatoid arthritis ($n=1$), psoriatic arthritis ($n=1$), disease ($n=1$), asthma ($n=1$), berylliosis ($n=1$), autoimmune hepatitis ($n=1$), early menopause ($n=1$), Laron syndrome ($n=1$), leprosy with perinatal listeria infection ($n=1$)	Alendronate group: 38, mean [36–41] IQR Control group: 40, mean [38–41] IQR	Alendronate group: 2910, mean [2650–3200] IQR Control group: 3290, mean [2946–3610] IQR	Lower gestational age at birth, reduced birth weight, and higher spontaneous abortion compared to controls ($p<0.05$)
Sokal et al. [16]	France	Case–control; Test: 36 women exposed to BPs, Control: 92 women with systemic inflammatory disorders but not exposed to BPs	23 cases with systemic disease received oral BPs: Risedronate in 15 (65.2%), alendronate in 6 (26.1%), and etidronate and unknown in 1 each (dose not reported) 13 cases with bone disease, BPs were alendronate for 9 (69.2%), pamidronate for 2 (15.4%), and etidronate, ibandronate, and risedronate for 1 each. One patient received both etidronate and alendronate. Three patients (23.1%) received intravenous BPs (pamidronate, $n=2$; ibandronate, n = 1). (dose not reported)	27 [25.5; 34] IQR 36 [33; 40] IQR	5 (13.8%) were exposed within the 6 weeks before pregnancy and 31 (86.1%) during pregnancy, mainly during the first trimester (30/31, 96.8%)	Among the exposed women, 23 had a systemic inflammatory disease, including SLE in 5 (1 with associated APS), RA in 5, isolated APS in 1, systemic vasculitis in 6 (Behçet disease, $n=3$; Takayasu's disease, $n=2$; and polyarteritis nodosa, $n=1$), and other inflammatory diseases in 6 (Crohn's disease, $n=2$; systemic sclerosis, Still's disease, pemphigus, and multiple sclerosis, $n=1$ each) 13 cases with bone diseases had heterogeneous bone disorders: osteoporosis ($n=9$, including steroid-induced osteoporosis in patients with asthma, $n=2$; Cushing disease, $n=1$), pheochromocytoma ($n=1$), and other benign disorders ($n=4$: fibrodysplasia, osteogenesis imperfecta, algodystrophy, hyperparathyroidism with hypercalcemia, $n=1$ each)	Systemic inflammatory disease exposed to BPs: 38 [36.5; 39] IQR Bone diseases exposed to BPs: 39 [36.5; 40.50] IQR Control: 38 [36.25; 39]	Systemic inflammatory disease exposed to BPs: 2.700 [2.272; 3.125] IQR Bone diseases exposed to BPs: 3.390 [2.945; 3.560] Control: 3.075 [2.542; 3.402] IQR	Systemic inflammatory disease exposed to BPs: patent ductus arteriosus, inguinal hernia, negative otoacoustic emissions, craniofacial dysmorphia, type 3 esophagus atresia, hand malformations, incomplete lung fissure, retroesophageal subclavian artery, ocular colobomatous cyst, bone maturation advance Bone diseases exposed to BPs: polycythemia, thrombocytopenia, acute fetal distress, cardiac rhythm disorders, materno-fetal infection, hyaline membrane disease, icterus, hyponatremia, enteropathy, hypotonia, apnea, gastroesophageal reflux, anemia
Vujasinovic-Stupar et al. [20]	Serbia	Case report; one case (two pregnancies exposed to BPs)	Case 1: Etidronate 400 mg daily i.v. for 2 weeks every 3 months for 1.5 years Case 2: Etidronate 400 mg daily i.v. for 2 weeks every 3 months for 2 years	33 35	Three months before conception Three months before conception	Pregnancy-associated spinal osteoporosis	40 40	- -	None None

SLE systemic lupus erythematosus

studies [11, 16] had a low risk of bias, ten studies [12, 14, 15, 17, 18, 20–24] exhibited a moderate risk of bias, and one study [19] had a high risk of bias. Further information regarding the risk of bias is presented in Table 2.

Synthesis of results

The reviewed studies included 106 women (108 pregnancies) who were exposed to BPs before or during pregnancy. The gestational age at delivery ranged from 34 [17] to 40 [12, 20] weeks, with an average of 37.87 weeks. Maternal age ranged from 17 [18] to 38 [15] years, with an average of 30.15 years, although four studies did not report the maternal age [11, 12, 22, 24]. In the control groups, gestational age at delivery ranged from 36.25 [16] to 41 [12] weeks, with an average of 39 weeks, with maternal ages ranging from 33 to 40 years [16].

Exposure to BPs occurred at various stages: before conception in 31 cases [11, 17, 21, 23, 24], during the first trimester in 63 cases [11, 12, 14, 16, 22, 24], during the second trimester in 6 cases [12, 16], during the third trimester in 5 cases [15, 16], and throughout the entire gestational period in 1 case [16]. Data regarding the exposure period are shown in Fig. 2.

The indications for BP treatment encompassed various medical conditions and included corticoid-induced osteoporosis ($n=32$), osteoporosis ($n=17$), rheumatoid arthritis ($n=6$), Behçet's disease ($n=5$), osteogenesis imperfecta ($n=5$), pregnancy-associated osteoporosis ($n=4$), Takayasu arteritis ($n=4$), asthma ($n=3$), Crohn's disease ($n=3$), fibrous dysplasia ($n=3$), hypothyroidism ($n=2$) and other disorders with one case each ($n=20$): algodystrophy, autoimmune hepatitis, berylliosis, Cushing disease, early menopause, femoral avascular necrosis, humoral hypercalcemia, hyperparathyroidism with hypercalcemia, Laron syndrome, leprosy with perinatal listeria infection, McCune Albright Syndrome, multiple sclerosis, pelvic fracture, pemphigus, pheochromocytoma, polyarteritis nodosa, psoriatic arthritis, Still's disease, systemic sclerosis, and type 1 Gaucher's disease. Two studies [22, 24] did not report the indications for BP therapy.

The most commonly prescribed BP was orally administered alendronate (55 cases, taken via oral administration) [12, 19, 21, 24]. Residronate was prescribed in 19 cases, taken via oral administration [16, 17]. Pamidronate was prescribed in 17 cases and was taken via intravenous administration [16, 17, 19]. Etidronate was prescribed to 10 patients, and both oral and intravenous administration methods were used [11, 20]. Ibandronate was prescribed in 2 cases and administered via both oral and intravenous routes [16]. Clodronate and neridronate were prescribed in 1 case each [19]. In 1 patient, the administered BP (formula and dose) was unknown [16]. A summary of the BP distribution data is shown in Fig. 3.

Regarding neonatal outcomes, birth weights ranged from 2230 [14] to 3838 g [21], with an average weight of 2927 g. Data from the control groups [12, 16] revealed that birth weight ranged from 2542 [16] to 3610 g [12], with an average of 3182 g. Adverse neonatal outcomes were reported in 39 cases, including spontaneous abortion ($n=6$) [12, 19]; congenital malformations ($n=4$) [16, 19]; hypocalcemia ($n=4$) [15, 16, 18, 21]; low birth weight ($n=3$) [11, 12, 14]; premature birth ($n=3$) [11, 12, 19]; distress syndrome ($n=2$) [16, 19]; and jaundice ($n=2$) [11, 16]. All of the following were reported in one case: anemia [16], apert syndrome [11], apnea [16], bilateral talipes equinovarus [18], cardiac rhythm disorders [16], enteropathy [16], gastroesophageal reflux [16], hyaline membrane disease [16], hypercalcemia [17], hyperphosphatemia [17], hypotonia [16], low femoral BMD [17], maternofetal infection [16], polycythemia [16], and thrombocytopenia [16]. Of the included studies, one did not report any adverse neonatal outcomes [23] and four other studies [20–22, 24] reported none.

Discussion

Summary of evidence

This systematic review assessed the adverse neonatal outcomes related to maternal exposure to bisphosphonates (BPs). The use of BPs in pregnant women is uncommon because of the generally low risk of fracture in this demographic population and limited evidence regarding their potential teratogenic effects on fetuses [25, 26]. This study included 106 women (108 pregnancies) exposed to BPs before or during pregnancy.

BPs constitute a crucial class of medications mainly used to reduce excessive bone loss in various clinical settings [26]. Therefore, despite being contraindicated during pregnancy and lactation, BPs may be unintentionally prescribed to women of childbearing age [27], with prescriptions estimated to be as high as 40% [28], because of their broad therapeutic applications and off-label use.

A significant concern regarding the use of BPs in pregnancy is their ability to cross the placenta [29]. BPs are also known to have a very long skeletal half-life. For example, the half-life of alendronate exceeds ten years, posing a risk of fetal exposure even after treatment cessation. Although inactive when incorporated into the bone matrix, BPs can get reactivated upon bone tissue resorption and become available in the systemic circulation [26]. Other specific osteologic therapies such as denosumab therapy are contraindicated during pregnancy, further limiting treatment options

Table 2 Risk of bias

	Athimulan et al. [23]	Barrera et al. [22]	Biswas et al. [24]	Chan and Zacharin [17]	Chen et al. [21]	Koren et al. [15]	Levy et al. [11]	Losada et al. [19]	Mastaglia et al. [14]	Munns et al. [18]	Ornoy et al. [12]	Sokal et al. [16]	Vujasinovic-Stupar et al. [20]
Were there clear criteria for inclusion in the case series?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the condition measured in a standard, reliable way for all participants included in the case series?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Were valid methods used for identification of the condition for all participants included in the case series?	Y	Y	Y	Y	Y	Y	Y	UN	Y	Y	Y	Y	Y
Did the case series have consecutive inclusion of participants?	NA	UN	UN	UN	NA	NA	UN	UN	NA	UN	UN	Y	NA
Did the case series have complete inclusion of participants?	NA	UN	UN	UN	NA	NA	Y	UN	NA	UN	UN	Y	NA
Was there clear reporting of the demographics of the participants in the study?	Y	Y	Y	N	N	N	Y	N	N	N	Y	Y	N
Was there clear reporting of clinical information of the participants?	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Were the outcomes or follow up results of cases clearly reported?	N	N	N	Y	Y	Y	N	N	Y	Y	N	Y	Y
Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	N	N	N	N	N	N	Y	N	N	N	N	Y	N
Was statistical analysis appropriate?	NA	Y	Y	Y	NA	NA	Y	N	NA	NA	Y	Y	

Y yes, *N* no, *UN* unclear, *NA* not applicable

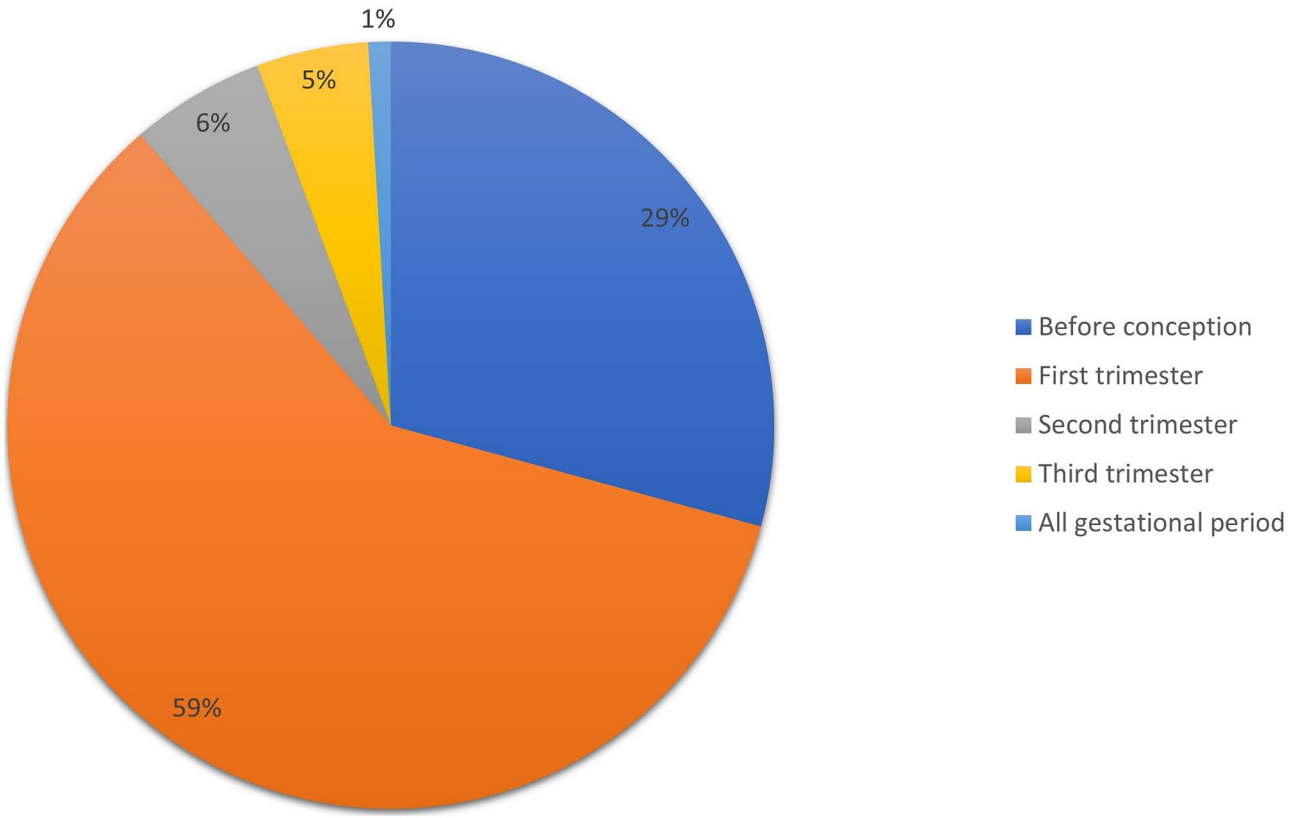

Fig. 2 Bisphosphonates exposure time

for pregnant women [27]. However, because premenopausal women have a relatively low fracture risk, pharmacological treatment for osteoporosis or low bone mineral density is generally not recommended [28].

In this review, the women were primarily exposed to BPs before conception (31/106, 29.2%) or during the first trimester of pregnancy (63/106, 59.4%). In most cases, BP therapy is discontinued after pregnancy, reflecting a cautious approach during pregnancy [14, 17, 18, 20–24].

Adverse neonatal outcomes were reported in 39 cases, across the included studies. The most prevalent alterations were spontaneous abortion ($n=6$), congenital malformations ($n=4$), hypocalcemia ($n=4$), preterm birth ($n=3$), and low birth weight ($n=3$), which will be discussed further.

In regards to spontaneous abortion, Ornoy et al. [12], found a significant correlation between spontaneous abortion rates and exposure to bisphosphonates (BPs)—20.8% in the BP-exposed group versus 7% in the control group. However, the overall incidence rate of spontaneous abortion in this review was 5.5%, a figure below the 10 and 20% range commonly observed in the general pregnant population [30–32]. This suggests that exposure to BPs does not significantly increase the risk of spontaneous abortion.

Congenital malformations include a wide range of structural and functional anomalies that occur during intrauterine development and are apparent at birth, potentially affecting health, development, and survival. The observed rate of congenital malformations in this study was 3.8%, slightly above the general prevalence of approximately 2–3% [33]. Notably, Sokal et al. [16] reported two cases of polymalformative syndromes, one involving premature birth (26 weeks of amenorrhoea) and the other showing malformations evocative of mycophenolate mofetil exposure syndrome. In a study by Losada et al. [19] two cases were reported: one with a ventricular septal defect and the other with kidney and cardiac malformations. Despite these findings, the diversity of malformations reported in these cases did not suggest a clear association between the malformations and BP use.

Hypocalcemia is a metabolic condition commonly encountered in newborns, particularly premature and low-birth-weight neonates. Its prevalence seems to vary and is significantly influenced by gestational age and the presence of perinatal pathology [34]. Although laboratory-related hypocalcemia is generally transitory and asymptomatic, it can escalate to a potentially life-threatening condition [35]. The increased metabolic demand of the fetus in the third trimester of pregnancy broadly results in the augmented release of calcium from the maternal skeleton, which is then transferred across the placenta. Abrupt cessation of placental calcium transfer at birth has been acknowledged

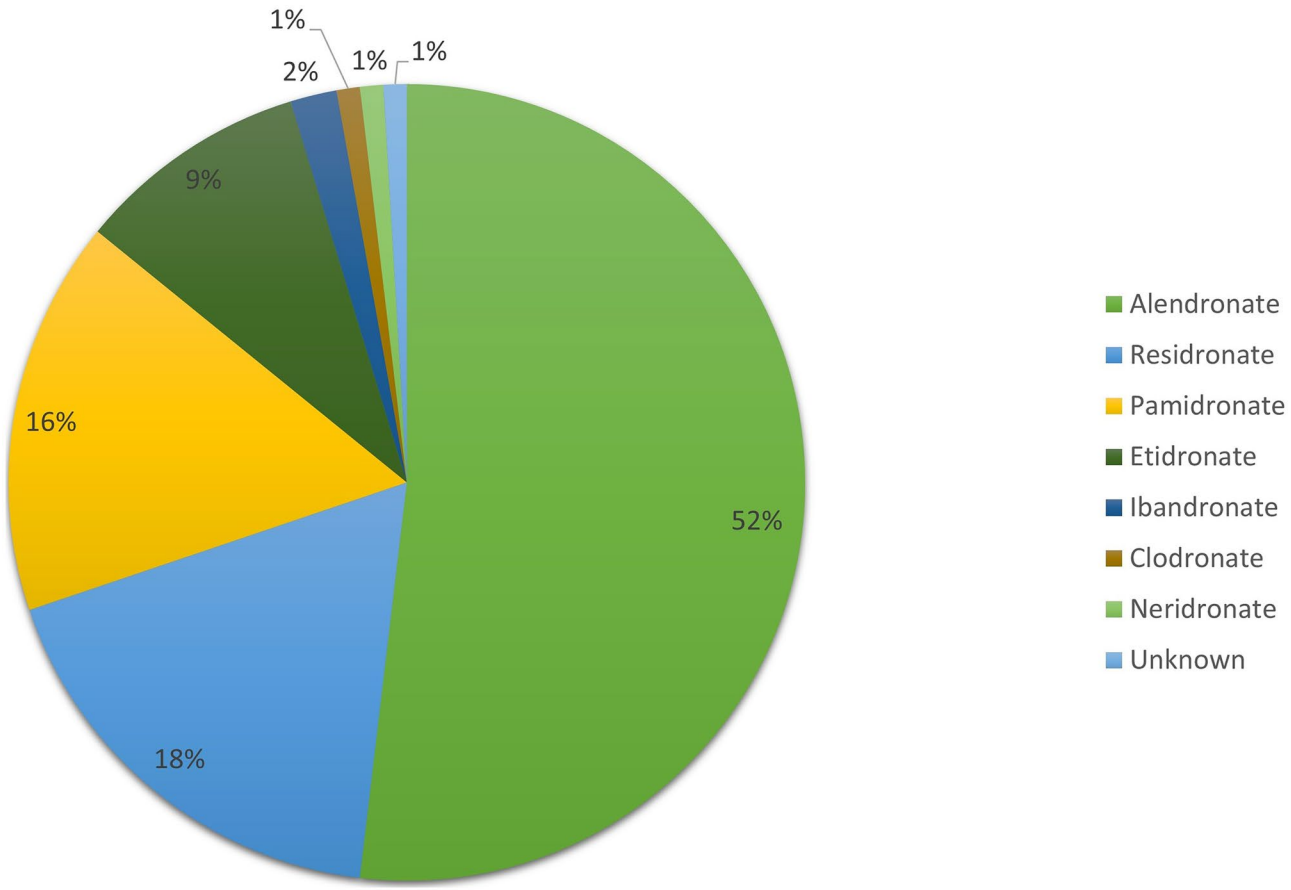

Fig. 3 Bisphosphonates distribution

as a significant factor contributing to neonatal hypocalcemia [36]. Considering that the established mechanisms of action of BPs involve the inhibition of osteoclastic bone resorption, leading to decreased calcium efflux from the skeleton, it is conceivable that BPs may contribute to neonatal hypocalcemia. This is supported by reports of low serum calcium levels in up to 40% of the patients treated with BPs. The degree of risk and severity appear to be broadly related to factors such as BPs' potency and dose as well as underlying conditions (e.g., vitamin D deficiency, hypomagnesemia, hypoparathyroidism, or renal insufficiency) [37]. Additionally, this effect was observed in the later stages of pregnancy following BP administration [16, 18], further bolstering the credibility of this hypothesis. Nevertheless, the low incidence of case reports in this review does not support an association between BP exposure and neonatal hypocalcemia.

Preterm birth, defined as birth occurring before the completion of 37 weeks of gestation, has been associated with increased morbidity and mortality outcomes compared with term births [38]. The global prevalence is approximately 10%, particularly in low- and middle-income countries [39]. In contrast, low birth weight is defined as a birth weight below 2500 g regardless of gestational age, and its general incidence ranges between 3 and 20%, with a significant geographic distribution within Africa and Asia [40]. Low birth weight is one of the most significant single risk factors for perinatal survival, early neonatal morbidity and mortality, and developmental disabilities and illnesses [41]. Ornoy et al. [12] observed significantly lower weights and gestational ages at birth in the BP-exposed group than in controls, suggesting a potential association. In addition, Sokal et al. [16] and Levy et al. [11] reported a minor tendency of BPs to lower the mean gestational age and birth weight, despite the absence of statistical significance. In this study, preterm births and birth weight were reported at a rate of 2.8%, which is consistent with the reported range in the general population. Consequently, data synthesis does not suggest a correlation between BP exposure and an increased risk of either low birth weight or preterm birth.

Limitations

This review provides significant insights into the potential effects of maternal BP exposure on neonatal outcomes.

However, this study has some significant limitations. First, the relatively small sample size (106 women and 108 pregnancies) may limit the generalisability of the findings. This sample size also makes it challenging to identify rare adverse outcomes that could be relevant to BP exposure. Additionally, the included studies often lacked comprehensive information on BP dosages, treatment protocols, specifics of concomitant pharmacological treatments, details, and severity of the underlying pathological conditions, and associated systemic conditions, all of which are critical for assessing the potential impact on neonatal outcomes. Furthermore, the inclusion of control groups in only two studies limited our ability to establish a direct cause-and-effect relationship between BP exposure and adverse neonatal outcomes.

Conclusions

Overall, despite reports of adverse neonatal outcomes, such as spontaneous abortion, congenital malformations, hypocalcemia, preterm birth, and low birth weight being the most common, evidence remains inconclusive for a direct causal relationship between exposure to BPs before or during pregnancfy and fetal alterations. The relatively low frequency of these outcomes complicates efforts in the conclusion process. Importantly, it is crucial to acknowledge the potential influence of maternal health status, including the underlying medical condition requiring BP therapy, as well as eventual associated conditions and concomitant pharmacological treatment. Therefore, the findings should be interpreted with caution. Further research is needed to investigate this connection and provide more definitive insights that can guide clinical practice and decision-making regarding the use of BPs in the realm of maternal and fetal health.

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Data availability All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Competing interests The authors declare no competing interests.

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