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Zoledronic acid for the treatment of pregnancy-associated femoral head necrosis: A case report

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ABSTRACT

Introduction: The management of pregnancy-associated femoral necrosis is controversial. Conservative management may eventually lead to hip replacement.
Case: A 40-year-old woman developed necrosis of the left hip during her first pregnancy. Treatment with zoledronic acid three months after delivery resulted in rapid reduction of the necrotic area. The patient's second pregnancy shortly afterwards had no complications. A magnetic resonance scan three years later documented complete resolution.
Conclusion: Femoral head necrosis should be suspected in the differential diagnosis of pain in pregnancy. Zoledronic acid given in the early stages prevented progression to hip arthritis in this case.
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1. Introduction

Worldwide, there are annually some 20,000–30,000 new cases of avascular femoral head necrosis (FHN) [1]. As it usually affects young, active individuals, the consequent early hip arthrosis represents an important social and economic burden, despite its low prevalence.

The necrotic zone is clearly detectable on magnetic resonance imaging (MRI), making diagnosis easy and unequivocal. The pathological process leading to FHN involves impaired blood supply, but the etiology is debatable and likely multifactorial. The most important causative factors include steroid therapy, alcohol use, and trauma [2]. Since the first description by Pfeifer in 1957 [3], fewer than 100 cases of pregnancy-associated FHN have been reported. Management is mainly conservative, based on lifestyle changes and restricted weight bearing. Other treatments rely mostly on surgery: vascularized or non-vascularized grafts, osteotomy, core decompression, drilling, arthroplasty, and, most recently, cell therapy [4,5]. Among non-operative strategies, electric stimulation and shockwaves have been employed, and one case of oral bisphosphonate administration is reported in the literature [6]. A summary of the available literature is presented in Table 1 [3–36].

We here report the case of a patient who developed FHN during her first pregnancy, was successfully treated with a single intravenous infusion of zoledronic acid, and did not relapse during a second pregnancy that followed shortly afterwards.

2. Case Presentation

A Caucasian woman, 40 years old, developed FHN during her first pregnancy. Pain in her left hip began in the 27th week of pregnancy; the patient ascribed it to the increased weight bearing associated with late gestation. Physical examination revealed an antalgic gait and limitation in hip-motion ranges.

Her medical history was insignificant and she had no known risk factors for osteonecrosis. Alcohol intake was low (1–2 drinks per week) before pregnancy and had been discontinued during pregnancy. Delivery was natural but due to the hip pain the patient was not able to push properly and the delivery was mechanically forced. Notwithstanding the persistent pain and mobility limitation, the patient refused any specific treatment during the first 3 months of lactation. An MRI scan one month after delivery revealed a large necrotic area in the left femoral head and no signs of osteoarthritis (Fig. 1, panel A). At the same time, baseline biochemistry (including complete blood count, ESR, PTH, vitamin D, both serum and 24 h urine calcium levels) was within normal ranges except for PTH, which was suppressed as a consequence of the physiological secretion of PTH-related peptide during lactation. Accordingly, serum calcium was slightly elevated. DXA scans showed osteoporotic values at the lumbar spine (L2-L4 T-score −2.7 SD) as well as at the femoral neck and the proximal femur (−2.6 and −2.5 SD, respectively). Pain was treated with steroids (prednisone 25 mg/day for 7 days) and paracetamol (1000 mg as needed), but without improvement. Intravenous treatment with zoledronic acid 5 mg was performed 3 months after delivery (i.e. 4 months after symptom onset). The patient discontinued lactation for one week after the infusion.

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Table 1
Osteonecrosis of the femoral head in pregnancy.

Year	Author [Ref]	N cases/site	Study type	Age	Associated condition/s	Treatment	Outcome
1957	Pfeifer [3]	1/BIL	CR	26	Toxemia	No	ND
1962	Jacobs [7]	2(1/BIL)	CR	24–25	ND		ND
1964	Patterson [8]	1	Retrospective (1935–1960)	ND	ND	ND	ND
1965	Burrows [9]	1			Thrombopenia/prednisone		ND
1968	Griffiths [10]	2	CR	18–29	Sickle cell anemia (one pt)		ND
1970	McCollum [11]	2	CR	ND			ND
1971	Louyot [12]	3	CR	ND			ND
1972	Kay [13]	2	CR	29–36	Aplastic anemia and prednisone (one pt)	No	ND
1980	Zolla-Pazner [14]	1/L	CR	35	None	ND	ND
1981	Hattori [15]	1/R	CR	28	None	Bone graft (tibial cortical bone)	FU: gradual recovery
1982	Arlet [16]	7 (3/BIL)	CR	21–40		Drilling/core decompression	FU (1-14 yrs): 3 bad, 3 good, 1 lost at FU
1982	Cheng [17]	7	CR	27–45	None	5 conservative 1 drilling 1 ND	5 improvement 1 OA progression (conservative treatment) 1 lost at FU
1984	Pellicci [18]	3	CR	ND	None	1 core decompression	ND
1988	Myllynen [19]	2	CR	ND	None	Needle aspiration/lifestyle changes	Complete recovery at 1 yr
1988	Rose-Pittet [20]	2	CR	ND	ND	ND	ND
1990	Van den Veyver [21]	1/R	CR	ND	None	Drilling	Complete recovery
1991	Lausten [22]	1/L	CR	24	None	No	AP at 30 months. FU (3 yrs) good function
1994	Caniggia [23]	2	CR	ND	Oral contraceptives 4 and 6 yrs	No	ND
1999	Hasegawa [24]	1/BIL	CR	31	hMG-hCG	Transtrochanteric posterior rotational osteotomy	Recovery at 10 months
1999	Montella [25]	13/L (4/BIL)	CR	25–41	None	11 free vascularized fibular graft 1 core decompression 1 osteotomy	FU (24-35mos): −9 improvement −1 total AP (bil) −1 no improve (core decomp) −1 lost at FU −1 osteotomy (ND at FU)
1999	Spencer [26]	1/R	CR	37	High dose steroid (6 courses: betamethasone 12 mg/24 h	Core decompression	Full recovery
2000	Scher [27]	3	CR (letter)	ND	ND	1 intertrochanteric osteotomy 2 arthrotomy (misdiagnosis)	ND
2001	Gribble [28]	1R	CR	ND	None (2nd pregnancy)	Conservative	Resolution at 6 months
2005	Vandenbussche [29]	1BIL	CR	36	hMG-hCG	No	FU (4 yrs): progression and total AP
2006	Sen [30]	1 L	CR	32	None (2nd pregnancy)	Conservative & analgesics	AP
2007	Steib-Furno [31]	1	CR in prospective & retrospective study 1990–2005	40	None	No	Secondary OA
2008	Ugwonali [32]	4BIL	CR			Operative and non operative: -anti inflammatory medications -pulsating electromagnetic field -core decompression - AP	ND
2009	Van der Valk [33]	1/BIL	CR	25	Sickle cell β thalassemia	No	ND
2011	Lin [34]	2BIL	CR	26–27	None	Core decompression (one pt)	ND
2014	Bhardwaj [35]	–	Literature review				
2016	Nassar [6]	1	CR	38	None	Physical, oral BP & shockwaves	Marked clinical improvement
2016	Wood [4]	1	CR & literature rev	34	Hypothyroidism	Total AP	Good clinical results
2017	Hernigou [36]	436	Cross-over			Observational	
2018	Hernigou [5]	145				Cell therapy (MSC)	FU 8-25 yrs.: low conversion rate to AP

AP = hip arthroplasty; BIL = bilateral; BP = bisphosphonates; CR = Case Report; FU = follow up; L = left; MSC = mesenchymal stem cell; ND = no data; OA = osteoarthritis; R = right.

Cholecalciferol (7500 IU/weekly) and calcium carbonate (1000 mg/day) supplements were continued for the duration of lactation (6 months).

A striking resolution of edema was evident on an MRI scan done 3 months after the treatment (Fig. 1, panel B). Reduction in pain and improvement in mobility were also marked and continued during the course of follow-up.

One year after delivery, the patient became pregnant again. As she knew she was at risk of FHN, she ensured she rested properly during the day. Nonetheless, she developed pain, although she did not take

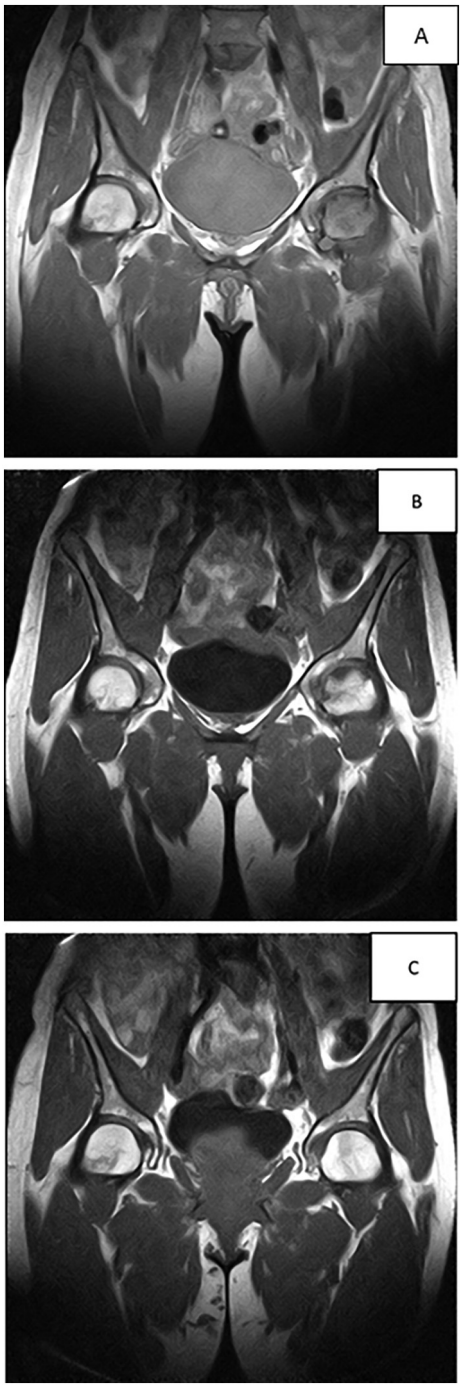

Fig. 1. Magnetic resonance imaging. Panel A - Before treatment: large necrotic area in the head and neck of the left femur. Panel A – Follow-up at 3 months: normalized signal in the head and neck of the left femur. Small residual subcortical hypointense area. Panel C - Follow-up at 23 months: minimal hypointense band at the anterior inner cortical limitans.

analgesic medications. Delivery was without complications and an MRI scan 3 months later, i.e. 23 months after the treatment with zoledronic acid, showed complete resolution (Fig. 1, panel C). A final MRI scan confirmed the result one year later, i.e. at 3-year follow-up (data not shown).

3. Discussion

We report a case of pregnancy-associated FHN successfully treated with a single intravenous administration of 5 mg zoledronic acid. The outcome persisted over time notwithstanding the patient undergoing two steroid cycles and undertaking a second pregnancy, not planned at the time of the treatment.

Osteonecrosis of the femoral head must always be taken into account in the differential diagnosis of hip pain in pregnancy [35]. This complication was reported for the first time by Pfeifer in 1957 [3] but to date only scattered cases and a single study with a meaningful sample size are available in the scientific literature [36]. Little is known about the underlying mechanism. Among the different risk factors involved, weight increase/mechanical stress, hormonal changes, reduced mobility, and coagulation impairment [37] have been proposed, but the causative role of each factor is difficult to establish and it is possible they all contribute to induce the necrosis. It is important to highlight that pregnancy-associated FHN has a well-defined cause-effect relationship, with a coinciding onset, progressive evolution, and a lack of other causes. Sporadic cases of pregnancy-associated FHN as a possible complication of steroids, human gonadotropin (hMG-hCG) drugs, or contraceptive medications are reported. Our patient did not undergo previous or concomitant treatment and she avoided alcohol. A short course of steroid treatment followed the development of FHN; therefore we can regard this case a clear-cut example of the effectiveness of injectable aminobisphosphonates in gestational osteonecrosis of the hip. Moreover, it is one of the rare cases in the literature describing the effectiveness of a treatment throughout the duration of a second pregnancy.

The differential diagnosis of osteonecrosis includes transient osteoporosis of the hip (TOH) and bone marrow edema syndrome (BMES) [38]. MRI can usually discriminate between these diseases, but at early stages the diagnosis remains controversial, as subchondral lesions, which have been demonstrated to be highly predictive of FHN [39], may be limited and not as clearly evident as at advanced stages. No X-ray was taken at that time. MRI was performed only after delivery, i.e. three months after pain onset. The radiologist diagnosed osteonecrosis and described an irregular profile of the anterior femoral head, but did not stage the disease according to the ARCO classification [40]. As mentioned, the patient was osteoporotic and FHN has been demonstrated to be associated with low bone mass [41]. A shortened course to recovery is reported by using bisphosphonates in TOH. It must be also pointed out that although the disease may resolve with conservative therapy, it predisposes the patient to fracture or avascular necrosis [38]. We do not know exactly when the edema had begun; however, the pain was severe and functional impairment was extremely limiting, particularly for a person who had just become a mother. We felt it was important to start treatment as promptly as possible.

It is interesting to note that the affected hip was the left one, as is frequently the case in pregnancy-associated FHN. Montella [25] suggested that an asymmetry in the iliac vascularization (the left common iliac vein passes deep and is subjected to excessive compression) may be responsible for this, in accord with the higher prevalence of venous thrombosis on the left side observed in pregnant women [42].

Whatever the etiology, the necrosis is progressive and characterized by an impaired blood supply that affects bone cell viability and bone tissue metabolism. Osteoclastic resorption of necrotic bone induces demineralization, trabecular thinning and finally collapse of the joint surface with fracture of subchondral bone. An antiresorptive drug leading to retention of bone by decreasing osteoclast activity in the early stages of the disease may therefore prevent or at least slow its progression. The inhibition of resorption of the dead bone allows subsequent osteoblast colonization, thus preserving structural architecture and femoral head integrity [43]. Our patient was osteoporotic and this prompted us to employ zoledronic acid.

Bisphosphonates are used in various conditions characterized by abnormal bone remodeling. Indeed, several reports describe the clinical and radiographic beneficial effects of alendronate, neridronate, and pamidronate in the treatment of the early stages of FHN and necrosis of different etiologies in subjects of both sexes and different ages [44–47]. Cardozo reported a low level of evidence as a consequence of

the design of the studies, but the outcome was consistently positive and long-lasting [48].

Zoledronic acid is a relatively new therapy and there are a limited number of reports concerning its use. To our knowledge, no histological study regarding the effects of zoledronic acid in the treatment of FHN in humans is available in the literature. Nevertheless, a multitude of animal studies has confirmed its effectiveness in diverse experimental models of bone diseases, including osteonecrosis. Biopsies taken during the HORIZON pivotal fracture trial demonstrated active bone remodeling and higher mineral apposition rate compared with placebo after 3-year annual zoledronic acid treatment in postmenopausal women [49]. The effect of locally delivered zoledronic acid in a compromised cancellous bone site at the femoral condyles in a rabbit was reported by Arnoldi a few years ago [50]. Histological analyses demonstrated that the drug actively supported peri-implant osteogenesis, positively affecting mesenchymal cells. We believe that this mechanism can also play a role in the healing of osteonecrotic lesions.

The experimental and clinical settings of the available reports vary, making the outcomes difficult to compare. Zoledronic acid was effective in all cases but a randomized clinical trial could not find evidence of its efficacy [51]. The latter study, which did not include pregnant or lactating women nor address the issue of pregnancy-associated FHN, had not yet published when we established the treatment. We believed that our patient could benefit from the treatment because the disease was at an early stage, the genesis was straightforward and the patient osteoporotic. Indeed, the treatment was successful and the outcome in the subsequent pregnancy was also positive. The use of zoledronic acid proved safe for the first-born as well as for the fetus throughout the second pregnancy. As explained, the drug was administered after the patient had given birth, with the precaution of lactation suspension, and 32 weeks before the beginning of the second, unplanned, pregnancy. Potential concerns about the effect of zoledronic acid on pregnancy and its precise half-life in bone continue to be debated. A recent study that analyzed the data from the French Reference Centre of Teratogenic Agents that compared pregnancy and newborn outcomes in women exposed and not exposed to bisphosphonates during or in the months before pregnancy confirmed that the drug does not affect skeletal growth in humans, nor does it have teratogenic effects [52]. The slow release of the drug associated with bone resorption is probably unable to induce circulating concentrations comparable to those used in therapy. As zoledronic acid suppresses the biochemical markers of bone resorption for up to 1 year in postmenopausal women, risk for the fetus could instead be represented by hypocalcemia, which was prevented by ensuring that the patient had adequate calcium intake during the pregnancy.

4. Conclusions

Many pregnant women likely to benefit from this treatment in the early stages of FHN are discouraged from using bisphosphonates by the clamor raised around the side-effects. We have described the long-term resolution of edema, pain and functional impairment, with no side-effects, in a patient with early-stage FHN who had two pregnancies in close succession. Zoledronic acid proved effective and safe. Our observation is promising and highlights that prompt treatment may be essential to prevent total hip arthroplasty. We believe that the management of pregnancy-associated FHN deserves further investigation through appropriate clinical studies.

Contributors

Estella Musacchio conceived the idea of the case report, interpreted data, reviewed the literature, and wrote the manuscript.

Leonardo Sartori established the patient's clinical care, critically revised the manuscript, and read and approved the final version.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient Consent

The patient described in the study has given her informed consent for the case report to be published.

Provenance and Peer Review

This case report was peer reviewed.

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