CASE REPORT

Case Report

High Chromium and Cobalt Levels in a Pregnant Patient with Bilateral Metal-on-Metal Hip Arthroplasties

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Abstract

Background Metal-on-metal bearings frequently are used in young patients leading to the concern that disseminated metals such as chromium (Cr) and cobalt (Co) as the main constituents could affect pregnancies.

Case Description We describe a 41-year-old patient with bilateral metal-on-metal hip arthroplasties, a recurrent pseudotumor, and extremely high blood levels (Cr 39 µg/L, Co 138 µg/L) at 12 gestational weeks. At different gestational weeks, maternal blood, aspirate of the pseudotumor, and amniotic fluid were analyzed for Cr and Co. Therapy with chelating agents was not recommended because the mother showed no symptoms of toxicity and the safety of chelating therapy during pregnancy is not established. At 38 weeks of gestation, a healthy male infant was delivered with elevated Cr and Co cord blood levels. At the age of 8 weeks, the infant's Cr was comparable to the cord blood level, whereas the Co decreased considerably without

treatment. At the age of 14 weeks, the infant's development was seemingly uneventful and no signs of toxicity were obvious.

Literature Review Carcinogenic, mutagenic, and teratogenic potentials of these metals have been suggested. However, we found no published clinical observations in context with pregnancies of women with hip arthroplasties using metal-on-metal implants. To our knowledge, this is the first report of such high levels of Cr and Co in a human pregnancy.

Purposes and Clinical Relevance Although we cannot generalize from one case, the seemingly uneventful outcome of this pregnancy may reassure colleagues when counseling patients with high ion levels whether to carry a pregnancy to term.

Introduction

Metal-on-metal bearings have been used frequently by orthopaedic surgeons since the 1980s, especially in young and active patients. Women have a greater incidence of congenital hip dislocation than men [10], and hip surgery can occur during childbearing age [44]. However, implantation of metal-on-metal hip devices can increase metal ion serum levels [18, 28]. This leads to the concern that disseminated metals such as chromium (Cr) and cobalt (Co) as the main constituents of the alloy used could affect pregnancies in women owing to transplacental transfer [53]. Metal-induced chromosomal changes and DNA damages might have the potential to cause carcinogenic effects in the patient and mutagenic and teratogenic effects in the offspring [21, 27].

Chromosomal changes have been seen in the peripheral blood of patients with metal-on-metal devices [13, 14, 24].

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Each author certifies that his or her institution approved or waived approval for the reporting of this case and that all investigations were conducted in conformity with ethical principles of research.

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However, the clinical consequences of these changes are unknown and to date, there is no increase in the incidence of cancer in patients receiving first-generation metal-on-metal implants [49]. Moreover, there have been no reports of suspect mutagenic or teratogenic effects in patients with second-generation metal-on-metal implants. A few studies and case reports have explored the question of pregnancy and childbirth after THA [4, 31, 32, 42, 44, 52]. These reports primarily found pregnancy and vaginal delivery can be safe after THA, although the majority of women with this type of surgery delivered by elective cesarean [31, 44]. These reports did not address the teratogenic or fetotoxic risk of the materials used. The available data are reassuring because they show that pregnancy and childbirth are not affected by the presence of a hip device [42] and pregnancy-related complications in women with THA do not differ from those in healthy women [32]. Furthermore, the integrity of the prosthesis obviously is not impaired by pregnancy and childbirth [42]. Additionally, the birth weight of the newborns reportedly is not influenced by the mothers' low weight gain during pregnancy, recommended to preserve prosthesis integrity [44].

We present a prospectively documented case of a 41-year-old primipara who underwent bilateral resurfacing with metal-on-metal Birmingham Hip Resurfacing (BHR) implants (Smith & Nephew, Memphis, TN, USA) followed by unilateral metal-on-metal THA. The patient contacted our institute at 12 weeks of gestation because of extremely high Cr and Co levels in her blood and the aspirate of a recurrent pseudotumor in her right groin. Her pregnancy course and the early postpartum period were followed at our institute.

Case Report

A 41-year-old primipara (height 168 cm, weight 72 kg) with bilateral metal-on-metal hip implants contacted our institute in January 2010 after 12 weeks of gestation concerning extremely high Cr and Co blood levels. In June 2005 she had a right hip arthroplasty with a BHR implant because of arthrosis secondary to untreated hip dysplasia. In December 2005 she presented with palpable swelling in her right groin, which was repeatedly aspirated. In 2007, she underwent resurfacing arthroplasty of her left hip for dysplasia without complications. Owing to persisting pain of her right hip, MRI was performed in 2008 which showed a fluid collection of $10 \times 3 \times 3$ cm, primarily located ventrally to the femoral neck. As a result of chronic pain accompanied by substantial atrophy of the right femoral neck (Fig. 1), the patient underwent revision surgery in August 2009 at which time a cementless conventional metal-on-metal implant was used in the THA (Fig. 2) (44 mm implant; Wright Medical Technology, Inc,

Fig. 1 A radiograph obtained after bilateral arthroplasties using BHR prostheses (Smith & Nephew, Memphis, TN, USA) shows atrophy of the right femoral neck as compared with the left.

Fig. 2 Four years later, revision surgery was done without replacing the BHR cup. A THA with a conventional metal-on-metal prosthesis with a 44-mm femoral head (Wright Medical Technology, Inc, Arlington, TN, USA) was implanted.

Arlington, TN, USA) without replacing the cup. The excised recurrent pseudotumor was a solid mass, white to grayish, $1 \times 3 \times 2$ cm, rich in granulated and necrotic tissue, infiltrations of lymphocytes and plasma cells indicative for a hypersensitivity reaction, and birefringent wear debris. Owing to a leg-length difference of 1.3 cm, a second revision surgery was done 8 days later; a larger-shaft prosthesis was implanted. Approximately 3 months later, at 7 weeks of gestation, she again had a painful pseudotumor developed at the same location. During pregnancy, when sitting, she sustained three posterior dislocations of the right hip that were reduced under general

anesthesia. However, she swam and cycled regularly. Fetal ultrasound identified no malformations or other abnormalities. A healthy male infant was delivered by cesarean section at 38 weeks of gestation (Table 1). Whole blood, aspirate samples of the pseudotumor, and amniotic fluid were analyzed for Cr and Co using inductively coupled plasma mass spectrometry (ICP-MS) at gestational weeks 7, 15, and 18, and at delivery, revealing elevated metal ion levels for all investigated compartments (Table 2). The patient's renal function was normal. The infant's endocrine functions and results of the structured pediatric examination program including hearing tests performed at Day 4 and Week 5 revealed no abnormalities. The mother initially breastfed her child, then stopped owing to low milk production. At the age of 8 weeks, the infant's Cr was comparable to the cord blood level, whereas the Co considerably decreased without treatment (Table 2). At 14 weeks, the infant's development was apparently uneventful and the hip ultrasound was normal. Revision

surgery with a metal-on-polyethylene implant of the mother's right hip is planned for the future, as she still has pain and recurrent dislocations.

Discussion

To our knowledge, this is the first report of such high levels of Cr and Co during a human pregnancy. Implantation of metal-on-metal hip devices can lead to an increase in metal ion serum levels, especially if mechanical dysfunction occurs. Some studies report an increase of Cr and Co levels in patients with metal-on-metal hip implants. The postoperative metal ion values of our patient exceed the values reported by other investigators more than 100-fold (Table 3). Renal impairment might cause increased metal ion levels but was excluded for our patient.

For industrial exposure to Co and Cr, health effects include: (1) impairment of cardiac, renal, and the male reproductive systems; (2) greater incidence of inflammatory and other immune reactions; and (3) development of lung cancer after long-term exposure to Cr (VI) [22]. Local inflammatory and other immunologic reactions in periprosthetic tissues also have been reported [22]. Inflammatory and necrotic changes in addition to a presumed delayed hypersensitivity response to CoCr particles might lead to the formation of pseudotumors [30, 50]. However, there is less information regarding systemic effects and the long-term effects of elevated Cr and Co levels from surgical implants are unknown. At concentrations equivalent to those found in the blood of patients with well-functioning metal hip prostheses, DNA double-strand breaks were caused by Cr (VI) and nanoparticles of CoCr alloy, the latter ones also inducing chromosome aberrations [36], however, Cr (VI) is rapidly reduced to its trivalent form after cellular uptake [17] and, as reviewed by Afolaranmi et al., Cr- and Co-induced carcinogenesis remain theoretical as no data have been published to suggest any definite pathologic effects [1]. In our patient, Cr and Co were determined using ICP-MS that quantifies the overall metal content, thus information regarding the oxidation state could not be obtained.

Acute or chronic poisoning can lead to numerous clinical symptoms such as visual loss, hearing disturbance, and lower limb hyposthenia as described in a female patient with a metallic hip prosthesis and raised concentrations of Cr and Co in blood, plasma, urine, and cerebrospinal fluid. Chelating treatment with edetic acid decreased metal ion concentrations, but neurologic symptoms improved only after resection arthroplasty [37]. Other case reports describe hypothyroidism, peripheral neuropathy, cardiomyopathy [35], impairment of hearing and sight, numbness in the feet, and dermatitis on the head and neck, with

Table 1. Neonatal characteristics

Parameter	Value
Birth weight	2840 g
Length	48 cm
Head circumference	33.5 cm
Apgar score (1, 5, and 10 minutes)	9/10/10
Umbilical artery pH	7.4

Table 2. Concentration of Cr and Co in blood, aspirate of the pseudotumor, and amniotic fluid

Compartment and time of measurement	Cr (μg/L)	Co (μg/L)
Maternal blood	39	138
Seventh week of gestation		
Aspirate of the pseudotumor	1011	258
Seventh week of gestation		
Maternal blood	33	139
Fifteenth week of gestation		
Amniotic fluid	6	20
Eighteenth week of gestation		
Maternal blood	20	143
Thirty-eighth week of gestation (delivery)		
Cord blood	2.1*	75**
Thirty-eighth week of gestation (delivery)		
Infant blood	2.5	13
Age of 8 weeks		

Normal range (blood) = Cr < 1 μg/L, Co < 4 μg/L; measurements were performed on whole blood using quadrupole ICP-MS (XSeries 2 ICP-MS, Thermo Scientific, Dreieich, Germany); cord blood levels were * 10.5% for chromium and **52.4% for cobalt of the maternal values at delivery; Cr = chromium; Co = cobalt.

Table 3. Co and Cr levels reported in selected studies after use of metal-on-metal hip implants.

Study	Implant	Analytic technique	Sample	Followup (years)	Median Co level [µg/L]	Median Cr level [µg/L]
Coleman et al. [9]	C cast alloy (unilateral and bilateral)	NAA	Whole blood	1	6.5*	3.9*
Jacobs et al. [20]	McKee-Farrar (unilateral)	AAS	Serum	25	0.9*	1.3*
Brodner et al. [5]	Metasul® (unilateral)	AAS	Serum	1	1.1	–
Schaffer et al. [41]	Sikomet-SM21 (unilateral)	AAS	Whole blood	1–3	1.5	2.2
Skipor et al. [43]	Conserve Plus® (unilateral)	AAS	Serum	0.25	1.3*	1.9*
				1	1.1*	1.8*
Brodner et al. [6]	Metasul® (unilateral)	AAS	Serum	5	0.7	–
Clarke et al. [8]	Ultima® (unilateral)	ICP-MS	Serum	1.7	1.3	1
	BHR (unilateral)	ICP-MS	Serum	1.3	2.1	2.6
	Cormet™ (unilateral)	ICP-MS	Serum	1.3	3.0	4.2
MacDonald et al. [29]	M2a (unilateral)	ICP-MS	RBC	2	1.1	2.5
Savarino et al. [40]	Metasul® (unilateral)	AAS	Serum	2	0.88	0.85
				4.3	0.81	0.86
Witzleb et al. [51]	Metasul® (unilateral and bilateral)	AAS	Serum	0.25	2.2	0.8
Allan et al. [2]	Cormet™ (unilateral)	ICP-MS	Serum	0.5	2.6	3.7
				1	3.3	4.4
				2	2.1	3.6
Grubl et al. [16]	Metasul® (unilateral)	AAS	Serum	10	0.75	0.95
Antoniou et al. [3]	Ultamet (unilateral)	ICP-MS	Serum	0.5	1.8	0.25
				1	2.3	0.4
Lazennec et al. [26]	Metasul®	AAS	Serum	1	1.4/1.7**	2.2/2.6**
				3	1.7/2.3	2.1/2.6
				5	1.3/2.8	1.7/2.8
				7	1.7/1.9	1.4/2.4
				9	1.6/2	1.5/3
de Souza et al. [11]	Cormet™ (unilateral and bilateral)	AAS / ICP-MS	Serum	0.5	3.1*	3.7*
				1	4.7*	5.4*
				1.5	4.6*	5.9*
				5	3.8*	4*
				10	5.1*	6.1*
Garbuz et al. [15]	Durom (Resurfacing) (unilateral)	ICP-MS	Serum	1	0.5	0.8
				2	0.5	0.8
	Durom (THA) (unilateral)			1	5.1	2.1
				2	5.4	2.9
Imanishi et al. [19]	Ultamet (unilateral)	ICP-MS	Serum	0.25	0.7	0.6
				1	1.1	0.8
Vendittoli et al. [48]	Durom (unilateral)	ICP-MS	Whole blood	0.25	0.9*	2*
				1	0.7*	1.6*
				2	0.6*	1.4*
Kim et al. [23]	Conserve Plus® (unilateral)	ICP-MS	Serum	1	1.0	2.0
				2	1.1	1.6

Table 3. continued

Study	Implant	Analytic technique	Sample	Followup (years)	Median Co level [μg/L]	Median Cr level [μg/L]
Lavigne et al. [25]	BHR (unilateral)	ICP-MS	Whole blood	0.25	1.0	1.2
				1	1.3	1.4
				2	1.9	1.9
	M2a (unilateral)		0.25	0.5	0.9	
			1	0.7	0.8	
			2	0.7	1.1	
	ASR™ XL (unilateral)		0.25	0.7	0.9	
			1	0.9	1.1	
			2	1.3	1.3	
	Durom (unilateral)		0.25	1.2	1.0	
			1	2.3	1.0	
			2	2.7	1.3	
Moroni et al. [33]	BHR (unilateral)	AAS	Serum	2	1.2*	2.2*
				5	1.1*	2.3*
	Metasul (unilateral)		Serum	2	1.3*	1.8*
				5	1.4*	1.9*
Nikolaou et al. [34]	Metasul® (unilateral)	ICP-MS	Whole blood	1–3	2.2	0.4
				4–5	2.9	0.7
				6–7	2.3	0.7
				> 7	2.3	0.4
Hasegawa et al. [18]	Cormet™ (unilateral)	ICP-MS	Serum	0.25	1.4	1.4
				1	2.3	2.1
				2	2.3	1.6
Current study	BHR (bilateral)/ BHR + THA	ICP-MS	Whole blood	4.3	138	39
				4.5	139	33
				5	143	20

AAS = atomic absorption spectrophotometry; ICP-MS = inductively coupled plasma mass spectrometry; NAA = neutron activation analysis; RBC = red blood cells; * mean Co levels reported; **metal ion levels reported for unilateral/bilateral metal-on-metal hip replacements, respectively; ASR XL, Ultamet (DePuy, Warsaw, IN, USA); BHR, Birmingham Hip Resurfacing, Sikomet (Smith & Nephew, Memphis, TN, USA); CormetTM (Corin Surgical, Cirencester, UK); Conserve Plus[®] (Wright Medical Technology, Arlington, TN, USA); Durom, Metasul[®] (Zimmer GmbH, Winterthur, Switzerland); M2a (Biomet, Warsaw, IN, USA); Ultima[®] (Johnson & Johnson, Leeds, UK).

improving clinical symptoms after revision surgery [45]. Cardiovascular, neurologic, and endocrine problems also were observed in five patients owing to remarkably high Co concentrations attributable to their prosthetic hip [46, 47]. Occult or future toxic effects related to cobaltism for the mother and the infant in our study cannot completely be ruled out.

There is concern regarding potential effects on the unborn. However, reports of adverse effects of elevated metal ion levels in human pregnancies are limited. Ziaee et al. [53] verified that Cr and Co cross the placenta in pregnant women with metal-on-metal hip resurfacings and in the control group of pregnant women without any metal implants. In contrast to the control group in which the differences between the mean maternal and cord blood levels were marginal, in the study group, cord blood levels of Cr and Co were 29.4% and 60.4% of the maternal blood

levels, respectively. This led to the suggestion that the placenta does not act as a total barrier, but rather exerts a modulatory effect on the transfer of these essential trace elements that also are required by the developing fetus. None of the children reported in the study by Ziaee et al. had congenital anomalies [53]. Regarding our case, the contents of Cr and Co in the amniotic fluid and in the cord blood were much lower than that in the maternal blood corresponding to transplacental transfer rates of 10.5% for Cr and 52.4% for Co (Table 2), which is consistent with the observations of Ziaee et al. [53] and those of Rudge et al. [38], who estimated a transplacental transfer of 45% for Co in 62 paired samples of maternal and cord blood. Even in the presence of much higher maternal levels, as was the case for our patient, than that reported by Ziaee et al. [53] (mean maternal blood Cr 1.28 μg/L, mean maternal blood Co 1.39 μg/L), the threshold for the

placental modulatory effects obviously is not exceeded. In a more recent study, teratogenic effects also were not observed in three pregnant patients with metal-on-metal hip resurfacings, although there was a transplacental passage of less than 25% Cr and approximately 50% Co [12]. In yet another study of three pregnant women with metal-on-metal implants and slightly elevated serum levels, Cr and Co could not be detected in the umbilical cord sera [7]. However, in that study, metal ions were determined using graphite furnace atomic absorption spectrometry, which is not as sensitive as high-resolution ICP-MS used by Ziaee et al. [53] and which might contribute to the different findings.

Because our patient showed no neurotoxic symptoms or other signs of intoxication and developmental toxicity has not yet been suspected in human pregnancies, we did not recommend chelating therapy. Moreover, efficacy of chelating therapy in patients with elevated metal ions resulting from surgical implants is unclear and deficiency of essential trace elements, especially copper and zinc, is possible. However, although the chelating agent 2,3-dimercaptopropane-1-sulfonate is reportedly not teratogenic in laboratory animal experiments [39], there are no data regarding possible adverse reproductive effects in human pregnancies. Thus, we do not recommend chelating therapy in general for pregnant women with increased metal ion levels because of prosthesis wear but such a choice would need to be individualized.

We cannot generalize from one patient, but given the lack of documented reports on pregnant women exposed to extremely elevated Cr and Co levels, the seemingly uneventful outcome of this pregnancy may reassure colleagues when counseling patients with high ion levels whether to carry a pregnancy to term.

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