Metal Ion Levels in Maternal and Placental Blood Following Metal-on-Metal Arthroplasty

Running Title: Maternal and Placental Metal Ion Levels

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Abstract

Background: There has been a resurgence in the interest and use of metal-on-metal (MOM) bearing surfaces in hip arthroplasty. However, concerns remain regarding elevated metal levels in blood and urine and possible effect on the fetus of a pregnant female with a MOM bearing surface.

Purpose: The purpose of this study is to compare metal concentrations in maternal and fetal serum in subjects with MOM hip arthroplasty to subjects without metal-containing implants.

Methods: Maternal and umbilical cord blood was obtained from three patients with a MOM hip arthroplasty and seven patients without implants who served as controls. Maternal and placental serum metal levels were tested using inductively-coupled plasma-mass spectrometry. The serum concentrations of titanium, nickel, cobalt, and chromium were measured. Intergroup comparisons were made independent of the means with use of the Wilcoxon-Mann-Whitney test. Correlations were established with use of the Spearman rank-order correlation test.

Results: Mothers with implants have statistically significant elevations in serum Cr and Co levels in comparison to control mothers. Babies from mothers with implants have statistically significant elevations in serum Co and Cr levels in comparison to control babies.

Conclusions: The Cr and Co serum levels obtained from both mothers with implants and the offspring of mothers with implants are elevated in comparison to the control maternal and offspring levels.

Clinical Relevance: Circulating Co and Cr degradation products from metal on metal bearings cross the placental barrier. Clinicians and women of child-bearing age should be cognizant of these findings when considering the use of metal-on-metal bearing couples.

Level of Evidence: Level III

Introduction

There has been a resurgence in the interest and use of metal-on-metal bearing surfaces in total hip arthroplasty (THA).[1] Further, recent literature has advocated metal-on-metal resurfacing procedures in select patient populations[15]. Specifically, young, active individuals are considered the ideal candidates. [3] Proposed benefits for the use of metal-on-metal bearing surfaces include reduced wear and the prevention of osteolysis.[2]

Concerns, however, remain regarding elevated metal ion levels in blood and urine. Several studies have shown that DNA and chromosomal changes can occur in patients with both metal-on-metal and non-metal-on-metal devices .[12,13,14] The carcinogenicity of elevated metal ions is also still unknown.[4] It also is unclear if elevated metal ion levels can adversely affect the developing fetus in pregnant female patients with metal-on-metal bearing surfaces. To help answer this question, it is critical to determine whether metal ions are able to cross the placenta into the developing fetus.

Substances cross the placenta by one of four methods: passive diffusion, facilitated diffusion, active transfer, and receptor-mediated endocytosis.[1] Passive diffusion is the most substantial transfer method and is limited by the molecular weight of a substance. Facilitated diffusion is a mechanism by which specific transport proteins allow a substance to pass down its concentration gradient into the fetus. Active transport, on the other hand, uses energy to move substances against a concentration gradient. Receptor-mediated endocytosis is a process by which certain substances are ingested using a specific receptor-ligand interaction to transport across the placenta.[15] The purpose of our study is to determine if metal ions can cross the placenta by

determining metal ion concentrations in maternal and neonate serum in subjects with metal-on-metal total hip arthroplasties.

Materials and Methods

Ten patients were prospectively enrolled in this study. All patients provided informed consent and agreed to maternal and umbilical cord blood sampling. The study was approved by the Human Investigation Committees at Rush University Medical Center. Seven of the ten patients did not have an implant and served as controls. The remaining three patients had either a metal-on-metal unilateral primary THA or unilateral metal-on-metal hip resurfacing arthroplasty and no other metal implant in the body. For all subjects, maternal and umbilical cord blood was obtained at the time of delivery.

Implant Group Demographics

The three women in the implant group had a mean age of 32.3 years (range, 23 to 39) at the time of delivery. The first patient had post-traumatic osteoarthritis and underwent right THA using a modular metal on metal 60mm acetabular component, a 36 mm cobalt chrome head, and a cementless, titanium proximally porous coated femoral component (Pinnacle and Summitt, DePuy, Warsaw, IN). Her infant was born two years post-operatively. The second patient had a diagnosis of degenerative osteoarthritis secondary to developmental dysplasia of the hip and underwent a hybrid metal-on-metal hip resurfacing with a monoblock 50 mm cup and 40 mm cobalt chrome head (Conserve Plus, Wright Medical, Arlington, TN). She gave birth to her infant six years after her arthroplasty. The third patient also had a diagnosis of degenerative osteoarthritis secondary to developmental dysplasia of the hip and underwent hip resurfacing

with a 54 mm monoblock cup and 44 mm cobalt chrome head (Conserve Plus). Her infant was born four years after her resurfacing arthroplasty. All of the infants were born healthy and the deliveries were uneventful.

Control Demographics

Seven women and their infants served as controls with a mean age of 32.1 years (range, 24–37 years) at the time of delivery. None of the control women had a history of renal impairment, inherited genetic disorders, or metal implants.

Collection of Specimens

Blood was collected into S-Monovettte syringes using the multi-adapter (Sarsedt, Priceton, N.J.) and an infusion set (Butterly, Abbott, Abbott Park, IL or Vacutainer® Brand Safety-Lok™ Blood collection set, Becton Dickinson Franklin Lakes, NJ). Three ten-milliliter syringes were drawn and each syringe was labeled to indicate the sequence of collection. The first ten milliliters were drawn to rinse the needle and adapter, as a precautionary measure. Blood was allowed to clot naturally and than centrifuged at 1850 times gravity for thirty minutes separating samples into cell and serum fractions which were stored in labeled vials at -80 ºC until analysis. All manipulations of the specimens following collection were carried out in a class-100 environment provided by a SterilGuard Biological Safety Cabinet (Baker, Sanford, MN) using class-100 gloves (Oak Technical, Ravenna, OH) to minimize atmospheric and manual contamination.

Metal Analysis

Maternal and umbilical cord serum metal ion levels were tested using inductively coupled plasma mass spectrometry (ICP-MS). The high-resolution sector field inductively-coupled plasma mass spectrometry instrument used was the ELEMENT2 (Thermo-Fisher Scientific GmBH, Bremen, Germany) equipped with an SC-E2 autosampler, Teflon™ nebulizer and spray chamber, sapphire injector (Elemental Scientific Inc Omaha, Nebraska) and platinum cones (R.A.Chilton, Chester UK and Spectron INC , Ventura, CA). The serum concentrations of titanium, nickel, cobalt, and chromium were measured. The detection limits in nanograms per milliliter (parts per billion) were 0.015 for chromium, 0.04 for cobalt, 0.2 for titanium, and 0.17 for nickel. By convention, concentrations below the detection limit were approximated as one-half of the detection limit.

All calibration and internal standard solutions were prepared by gradual dilutions of single-element standard solutions (1000 ug/ml from High Purity Standards, Charleston, SC). Purified water, 18 megΩ, was provided from a Milli-Q water purification system (Academic A10, Millipore, Bedford, New Jersey) and high purity acids, Ultrex® II, nitric and hydrochloric were purchased from Mallinckrodt Baker (Phillipsburg, NJ). These were used to dilute samples, blanks, and standards. The certified reference material Seronorm Trace elements (SERO AS, Billingstad, Norway) were routinely analyzed with samples. The method of additions was employed for sample analysis.

Statistical Analysis

SPSS for Windows (Version 16) was used for data management and statistical analysis. Because the data had statistically nonnormal distributions, nonparametric statistical methods were used. It was not possible to obtain statistical normality by transforming the data. The Mann-Whitney

test was done separately for mothers and infants to compare the implant and control groups with respect to serum metal ion levels. The Friedman test was done separately for the implant and control groups to compare mothers and infants with respect to serum metal ion levels. Scatterplots and Pearson correlations were obtained separately for the implant and control groups to investigate relationships between maternal and infant serum metal ion levels. A 0.05 significance level was used for all statistical analyses. No one-sided tests were done.

Results

Table I shows the serum metal ion levels for the study groups. The implant-group mothers had significantly higher chromium and cobalt levels than did the control mothers with mean chromium levels of 1.870 ng/ml versus 0.163 ng/ml ($p = 0.017$) and mean cobalt levels of 0.972 ng/ml versus 0.206 ng/ml ($p = 0.017$). All of the control maternal chromium and cobalt levels were lower than the implant-group There were no significant differences detected between the implant-group and control mothers with respect to serum titanium or nickel levels with the numbers of patients available for study.

Table I. Serum metal ion levels (ng/ml) for mothers and infants in implant and control groups

	Chromium		Cobalt		Titanium		Nickel	
Pair	**Mother**	**Infant**	**Mother**	**Infant**	**Mother**	**Infant**	**Mother**	**Infant**
Implant Group								
I-1	1.021	0.158	0.425	0.225	1.769	0.781	0.085	0.279
I-2	2.123	0.263	1.237	0.567	0.100	0.100	0.237	0.180
I-3	2.465	0.443	1.254	0.667	0.100	0.219	0.085	0.454
Mean	1.870	0.288	0.972	0.486	0.656	0.366	0.136	0.304
Control Group								
C-1	0.038	0.063	0.338	0.218	0.100	0.100	0.192	0.170
C-2	0.074	0.028	0.184	0.135	0.100	0.100	0.176	0.085
C-3	0.110	0.150	0.106	0.087	0.100	0.100	0.085	0.085
C-4	0.116	0.166	0.114	0.172	0.100	0.100	0.085	0.085
C-5	0.206	0.073	0.154	0.168	0.333	0.224	0.085	0.319
C-6	0.254	0.150	0.254	0.157	0.201	0.100	0.181	0.532
C-7	0.339	0.046	0.291	0.172	0.100	0.224	0.206	0.085
Mean	0.163	0.096	0.206	0.158	0.148	0.135	0.144	0.195

Similarly, the implant-group infants had significantly higher chromium and cobalt levels than did the control infants with mean chromium levels of 0.288 ng/ml versus 0.096 ng/ml ($p = 0.030$) and mean cobalt levels of 0.486 ng/ml versus 0.158 ng/ml ($p = 0.017$). All but one of the control infants had chromium levels that were lower than the implant-group infant chromium levels. All of the control infant cobalt levels were lower than the implant-group infant cobalt levels. No

statistically significant differences were found between the implant-group and control INFANTS with respect to serum titanium or nickel levels with the number of subjects studied.
For the implant and control groups considered separately, there were no statistically significant differences between the maternal and infant titanium levels or the maternal and infant nickel levels (put in p-value for these two comparisons). For the control group, no statistically significant differences were found between the maternal and infant chromium levels (p-value here) or the maternal and infant cobalt levels (p-value). In the implant group, however, the mother's chromium level was always higher than her infant's chromium level, and the mother's cobalt level was always higher than her infant's cobalt level. These differences reached the smallest *p*-value possible when the Friedman test is done with a sample size of 3 (p = 0.083).

In the control group, there was no correlation between the maternal and infant chromium levels, or between the maternal and infant cobalt levels. In the implant group, however, the maternal and infant chromium levels were highly correlated (Spearman's rho = 1), as were the maternal and infant cobalt levels (Spearman's rho = 1).

When the infants' chromium levels were expressed as a percentage of their mothers' chromium levels, the mean was 15.3% (range, 12.4% to18.0%) for the implant group and 84.4% (range, 13.6% to 165.7%) for the control group ($p = 0.053$). The mean infant cobalt level, expressed as a percentage of the maternal cobalt level, was 50.6% (range, 45.8% to 53.2%) for the implant group and 85.9% (range, 58.9% to 151.3%) for the control group; a significant difference (p = 0.017).

Discussion

The chromium and cobalt serum levels obtained from mothers with implants and their offspring were elevated in comparison to the control group. Further, there is a strong correlation between implant maternal cobalt and chromium levels and implant infant cobalt and chromium levels while no such correlation exists in the control group. Therefore, we have concluded that cobalt and chromium cross the placental barrier and are found at higher levels in the offspring of patients with metal-on-metal implants as a result of elevated maternal metal-ion levels. We also found that implant mothers had higher chromium and cobalt levels compared with implant babies. Implant babies had approximately 15% of the level of chromium and 50% of the level of cobalt when compared to implant maternal levels. This suggests that the placenta modulates the transfer of chromium and cobalt when these are present in higher than normal levels.

To our knowledge, only two prior studies report chromium and cobalt levels in maternal and umbilical cord sera following metal-on-metal hip arthroplasty. Brodner et al. determined the maternal serum levels of cobalt and chromium in three women who averaged 3.8 years post metal-on-metal hip arthroplasty and compared those to cobalt and chromium levels obtained from umbilical cord sera.[1] At the time of delivery, the maternal chromium concentrations were 1.6 ng/ml, 0.5 ng/ml, and 0.9 ng/ml and the cobalt concentrations were 1 ng/ml and below the detection limit in the other two.[1] Cobalt and chromium concentrations of the three umbilical cord sera were below the detection limit.[1] The authors concluded that cobalt and chromium did not cross the placenta based on their laboratory detection limits. Brodner et al., however, measured cobalt and chromium levels with atomic absorption spectrometry which had reported detection limits for cobalt and chromium in serum of 0.3 ng/ml, which is substantially higher than the

detection limit of ICP-MS, as was used in our study. The relatively high detection limitations of atomic absorption spectrometry are likely responsible for the inability to detect elevated chromium and cobalt levels in umbilical cord sera in the Brodner study.

In contrast, Ziaee et al. used high-resolution ICP-MS (as was done in the present study) to determine the mean concentrations of cobalt and chromium ion levels in ten maternal and umbilical cord blood samples in women with Birmingham (Smith and Nephew Ltd, Warwick, United Kingdom) hip resurfacing prostheses. Nine of those patients had a unilateral resurfacing and one patient had bilateral resurfacing prostheses. The mean resurfacing maternal age was 31 years (25 to 39) and mean duration between hip resurfacing and delivery was 53 months (11 to 119). Ten normal controls were also tested with a mean maternal age of 30.9 years (22 to 37). The authors found that the mean cord blood level of cobalt in the study patients was 0.839 ug/l, significantly higher ($p < 0.01$) than cobalt levels in the control group which measured 0.336 ug/l. The mean cord blood levels of chromium in the study and control groups were 0.378 ug/l and 0.194 ug/l respectively. Chromium levels between the two groups were not statistically significant ($p > 0.05$). Ziaee et al. also found a modulatory effect on the transfer of metal ions across the placenta in patients with metal-on-metal prostheses. They reported the levels of cobalt and chromium in offspring to be 60.4% and 29.4% maternal ion levels respectively. Control infants had mean cobalt and chromium levels 98.5% and 97.2% of mean maternal levels, respectively. The authors concluded that the placenta does not act as a barrier when ion levels are those expected in the normal population. The relative free flow of ions across the placenta in the control group is a rational finding as these are essential trace elements required by the

developing fetus. Wallach and Verch, for example, reported in an animal experiment that maternal chromium levels are depleted due to placental uptake.[12]

Ziaee et al [11] tested metal ion levels using whole blood in contrast to the use of serum as was done in our study. Daniel et al.[12] reported on the validity of serum levels as a surrogate measure of systemic exposure to metal ions in hip replacement. They suggested that serum and whole blood metal ion levels cannot be inter-converted. Metal levels in serum and whole blood may not be able to be inter-converted because metal within cells are not in dynamic equilibrium with extracellular levels. Merritt and Brown[14], for example, showed that intra- and extracellular chromium levels are widely variable. However, this finding in and of itself does not negate the validity of serum metal ion levels. Daniel et al.[12] went on to conclude that serum metal ion concentrations are not a useful surrogate measure of systemic metal ion exposure based on the wide variability seen in normalized and Bland-Altman scatterplots. Despite this conclusion a few points have been ignored. First, the Bland and Altman method is only useful when the range of differences during analysis is deemed significant or not. In other words, the results of the test depend on the user to determine significance. Another important point that was not discussed is the potential for the loss of analyte or the introduction of contaminants during whole blood analysis in contrast to serum analysis. Data from the regression lines in the study by Daniel et al[12] (Figure 3b) demonstrated that the whole blood chromium level is less that half of the serum level, suggesting a dilutional effect of the cell fraction which comprises roughly half of the volume of whole blood. This finding is at odds with the notion that measuring serum concentration fails to detect substantial stores of chromium in circulating erythrocytes and therefore is not an appropriate measure of systemic exposure. In addition, In addition, whole

blood analysis requires more processing steps providing an increased chance of contamination and variability. In our experience, serum metal ion analysis is accurate and reproducible.

The effects of metal ions on pregnant mothers and their infants are unknown. Brodner et al. found no evidence for cobalt or chromium teratogenicity in humans in literature reviews.[1] There is a paucity of available literature which studies the effects of metal ions on fetal and maternal subjects. The literature that is available is mainly limited to rodent data. Saxena et al[7]. found that chromium in the hexavalent form passed through the placenta in mice and rats which were fed high doses of potassium dichromate. Trivalent chromium on the other hand, was not found to cross the placenta.[7] In a follow-up study, Junaid et al. reported fetotoxicity in these mice and rats which were on the high dose potassium dichromate diet.[8] Cobalt was not shown to be teratogenic or cause fetotoxicity in rats given daily doses of as much as 100 mg/kg cobalt II on days 6-15 of gestation.[9]

It is important to recognize that rodent data, however, may not provide meaningful insight into the effects of metal ions in human maternal and fetal subjects. Mammalian species have significant heterogeneity in the structure and function of their placentas.[10] Rurak, for example, has shown that rodents have an additional persisting yolk sac placenta which allows the transfer of maternal immunoglobulins to the fetus. Humans, on the other hand, have a yolk sac placenta which regresses early in pregnancy.[10] Differing placental biologic function makes it difficult to extrapolate the affects of metal ions in rodents to human subjects.

In conclusion, mothers with metal on metal bearing couples and their offspring have higher chromium and cobalt levels than controls; the placenta is not a complete barrier to cobalt and chromium transport, although it seems to have a modulating effect. The affects of metal ions on maternal and fetal subjects are unknown. Clinicians and women of child-bearing age should be cognizant of these findings when considering the use of metal-on-metal bearing couples.

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