Transplacental transfer of cobalt and chromium in patients with metal-on-metal hip arthroplasty

A CONTROLLED STUDY

H. Ziaee,
J. Daniel,
A. K. Datta,
S. Blunt,
D. J. W. McMinn

From The McMinn Centre, and Birmingham Women's Healthcare NHS Trust, Birmingham, England

Metal-on-metal bearings are being increasingly used in young patients. The potential adverse effects of systemic metal ion elevation are the subject of ongoing investigation. The purpose of this study was to investigate whether cobalt and chromium ions cross the placenta of pregnant women with a metal-on-metal hip resurfacing and reach the developing fetus. Whole blood levels were estimated using high-resolution inductively-coupled plasma mass spectrometry.

Our findings showed that cobalt and chromium are able to cross the placenta in the study patients with metal-on-metal hip resurfacings and in control subjects without any metal implants. In the study group the mean concentrations of cobalt and chromium in the maternal blood were 1.39 µg/l (0.55 to 2.55) and 1.28 µg/l (0.52 to 2.39), respectively. The mean umbilical cord blood concentrations of cobalt and chromium were comparatively lower, at 0.839 µg/l (0.42 to 1.75) and 0.378 µg/l (0.14 to 1.03), respectively, and this difference was significant with respect to chromium ($p < 0.05$).

In the control group, the mean concentrations of cobalt and chromium in the maternal blood were 0.341 µg/l (0.18 to 0.54) and 0.199 µg/l (0.12 to 0.33), and in the umbilical cord blood they were 0.336 µg/l (0.17 to 0.5) and 0.194 µg/l (0.11 to 0.56), respectively. The differences between the maternal and umbilical cord blood levels in the controls were marginal, and not statistically significant ($p > 0.05$). The mean cord blood level of cobalt in the study patients was significantly greater than that in the control group ($p < 0.01$). Although the mean umbilical cord blood chromium level was nearly twice as high in the study patients (0.378 µg/l) as in the controls (0.1934 µg/l), this difference was not statistically significant. ($p > 0.05$)

The transplacental transfer rate was in excess of 95% in the controls for both metals, but only 29% for chromium and 60% for cobalt in study patients, suggesting that the placenta exerts a modulatory effect on the rate of metal ion transfer.

■ H. Ziaee, BSc(Hons), Biomedical Scientist
■ J. Daniel, FRCS, Director of Research, Staff Orthopaedic Surgeon
■ D. J. W. McMinn, FRCS, Consultant Orthopaedic Surgeon
The McMinn Centre, 25 Highfield Road, Birmingham B15 3DP, UK.

■ A. K. Datta, MD, MRCOG, Specialist Registrar
■ S. Blunt, MD, FRCOG, Consultant Obstetrician, Gynaecologist
Birmingham Women's Health Care NHS Trust, Metchley Park Road, Birmingham B15 2TG, UK.

Correspondence should be sent to Mr J. Daniel; e-mail: josephdaniel@mcminncentre.co.uk

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The low wear properties of metal-on-metal bearings[1] make them an attractive choice, especially in young patients. One consequence of using these devices is the systemic release of metal ions. Metal components are also used as femoral stems and/or acetabular backings in all types of joint replacement. The non-articular components in conventional replacements have also been shown to release metal ions,[2] although the levels detected are not as high as in metal-on-metal devices.

Cobalt and chromium are the main constituents of the alloy used in metal-on-metal bearings and are found in the water supply and in food. With modern analytical instruments they are detectable in the blood and urine of patients with metal implants as well as in control subjects without implants.[3] Current understanding of metal ion transport and excretion indicates that there is an efficient renal clearance mechanism to handle any excess. Medium-[3] to long-term studies[4] of metal ions in patients with metal-on-metal bearings do not sustain earlier fears of a progressive accumulation in patients with well-functioning devices.

The metabolic, immunological, mutagenic and carcinogenic effects of raised metal ions are not yet fully understood. Recent studies have raised the possibility of increased DNA[5] and chromosomal changes[6,7] occurring in patients with both metal-on-metal[5,6] and non-metal-on-metal[5,7] devices. As metal-on-metal bearings are being used in young patients, there is concern that mutagenic or teratogenic effects could be manifest in children conceived by these patients. The question of the potential effects on the offspring could be answered in

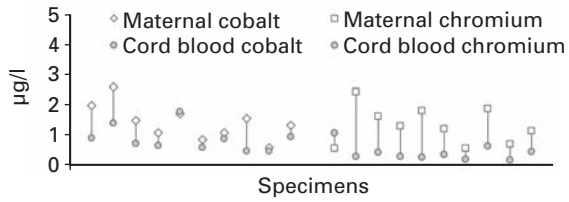

Fig. 1

Metal ion levels in whole blood specimens of patients with metal-on-metal implants.

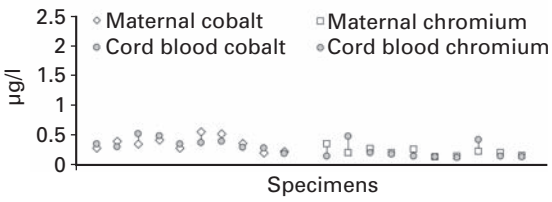

Fig. 2

Metal ion levels in whole blood specimens of subjects with no metal-on-metal implants (controls).

part if it was known whether, and to what extent, metal ions are able to transfer to the developing fetus.

The purpose of this study was to investigate whether the raised concentrations of cobalt and chromium ions in maternal blood lead to elevated levels in the umbilical cord blood of the baby, using whole blood specimens and high-resolution inductively-coupled mass spectrometry analysis.

Patients and Methods

A prospective study of metal ion levels was performed in women with metal-on-metal resurfacings and the umbilical cord blood of their babies immediately after delivery. Regional Ethics Committee approval was obtained. In the senior author's (DJWM) series of over 2700 Birmingham Hip Resurfacings (Smith and Nephew Orthopaedics Ltd, Warwick, United Kingdom) performed since 1997, there were over 100 patients of child-bearing age, all of whom were sent information about the study. From those patients who responded that they were planning a pregnancy and consented to participate, ten contacted us when they knew they were pregnant, at which stage they were sent information on the further details of the study. After obtaining informed consent, whole blood specimens were obtained from all ten patients and from the umbilical cord of their babies at the time of delivery or Caesarean section, before any intravenous fluid infusion or blood transfusion. Of these patients, nine were resident in the United Kingdom and one was from abroad. Bilateral hip resurfacing had been performed in one patient and in the remainder, unilateral hip resurfacing had been undertaken. A dysplasia acet–abular component had been required in three patients (three hips) and standard acetabular components for the remainder. The mean age of the patients was 31 years (25 to 39) and the mean duration between hip resurfacing and parturition was 53 months (11 to 119).

In order to provide normal controls, similar samples were collected after obtaining informed consent from ten patients who did not have any metallic implant, were not taking any supplements containing cobalt or chromium salts, and were registered to undergo an elective Caesarean section at the Birmingham Women's Hospital, Birmingham, United Kingdom. The mean age of the patients in the control group was 30.9 years (22 to 37). No patient in either group was known to have renal impairment. Details of the specimen collection and the measures taken to prevent contamination have been previously published. [8] A 6 ml sample of blood was drawn into each of two 6 ml Lithium sample Vacutainer tubes and stored at -18°C. The same batch of needles and tubes were used. Deionised water, flushed through two unused needles and tubes from each batch was analysed to ensure that there was no trace metal contamination from them.

The samples were stored at -18°C, batched, and sent for metal ion analysis to the Analytica AB Laboratories (Luleå, Sweden).[9] The high-resolution inductively-coupled plasma mass spectrometry instrument used was the ELEMENT (ThermoFinnigan MAT, Bremen, Germany) equipped with an ASX 500 sample changer (CETAC Technologies, Omaxa, Nebraska). A microwave digestion unit (MARS-5, CEM Microwave Corporation, Matthews, North Carolina) equipped with 12 perfluoroalcoxy-lined vessels (ACV 125) with safety rupture membranes (maximum operation pressure 1380 kPa), was used for tissue digestion. The reporting limits were 0.1 µg/l for cobalt and 0.2 µg/l for chromium.

All calibration and internal standard solutions were prepared by gradual dilutions of single-element standard solutions (1000 µg/ml and 10 000 µg/ml 1, SPEX Plasma Standards, Edison, New Jersey and Promochem AB, Ulricehamm, Sweden). Analytical-grade nitric acid (Merck, Darmstadt, Germany) was used after additional purification by sub-boiling distillation in a quartz still. A three-stage water purification system from an ion-exchange column (SeraDest; ELGA Berkefeld, GMBH, Celle, Germany), Milli-Q water purification system (Millipore Milli-Q, Bedford, New Jersey) and sub-boiling distillation in Teflon stills (Savilex Corporations, Minnetonka, Minnesota) were used to produce distilled deionised water. This was used to dilute samples, blanks and standards. The following certified reference materials are routinely prepared and analysed with clinical samples: A-13 Bovine Blood (IAEA), Seronorm Trace elements Serum/Urine (SERO AS, Billingstad, Norway). All statistical calculations were per-

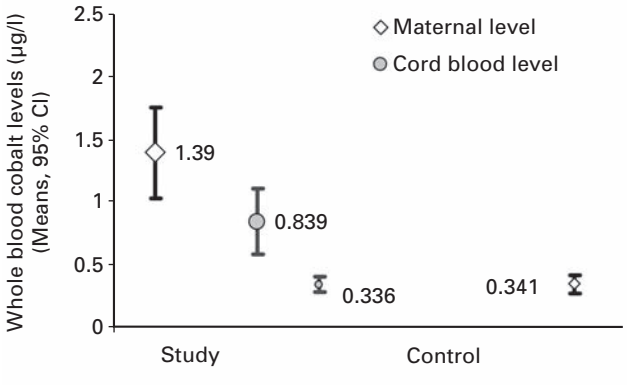

Fig. 3

Cobalt levels in the study patients with metal-on-metal implants and in the control subjects.

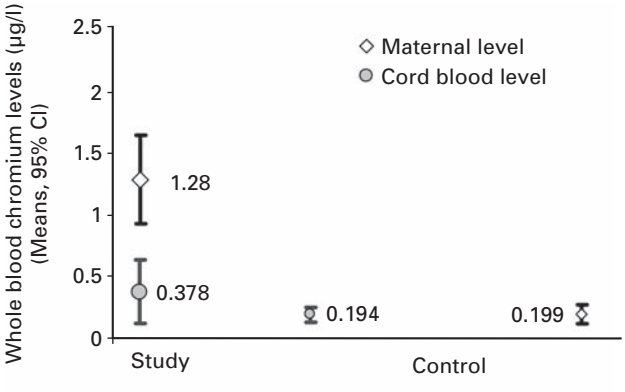

Fig. 4

Chromium levels in the study patients with metal-on-metal implants and in the control subjects.

formed using Microsoft Excel 2003, and the 95% confidence interval (CI) was used as a measure of statistical significance of the difference of the means. A p-value of less than or equal to 0.05 was considered to be significant.

Results

Cobalt and chromium metal ions were detected in all the maternal and umbilical cord blood specimens in both the study and the control groups (Figs 1 and 2). No congenital abnormality was found in any of the babies in either group.

In the study group the mean concentrations (± 95% confidence intervals) of cobalt and chromium in the maternal blood were 1.39 µg/l ± 0.36) and 1.28 µg/l ± 0.38) respectively (Figs 3 and 4). Mean maternal chromium was significantly higher ($p < 0.01$) compared with the cord blood chromium (0.378 µg/l ± 0.17), while with cobalt, the difference between the mean maternal and cord blood levels (0.839 µg/l ± 0.26) was not statistically significant ($p > 0.05$). Pearson's method showed a positive correlation ($R^2 = 0.39$) for cobalt between the maternal blood levels and the corresponding umbilical cord blood levels. We did not find a correlation between maternal and cord levels of chromium ($R^2 = 0.03$). All umbilical cord blood levels in the study group were lower than the maternal levels, except the cobalt level in one specimen and the chromium level in another.

In the control group the mean concentration (± 95% confidence intervals), of cobalt in the maternal blood was 0.341 µg/l ± 0.04 and in the cord blood 0.336 µg/l ± 0.06 (Fig. 3). The mean level of chromium in the control group was 0.199 µg/l ± 0.04 for maternal blood and 0.194 µg/l ± 0.08 µg/l for cord blood (Fig. 4). With respect to both metals the differences between the mean maternal and cord blood levels were marginal, and not statistically significant ($p > 0.5$).

The mean cord blood level of cobalt in the study patients (0.839 µg/l ± 0.26) was significantly greater ($p < 0.01$) than that in the control group (0.336 µg/l ± 0.06). The difference of mean cord blood chromium between the study (0.378 µg/l ± 0.17) and control (0.194 µg/l ± 0.08) groups was not statistically significant ($p > 0.05$).

Discussion

Cobalt and chromium are essential trace elements. Cobalt is needed for the synthesis of cyanocobalamin (vitamin B_{12}). However, excessive administration of cobalt is believed to produce goitre and possibly cardiomyopathy. Chromium is part of the metabolic pathway that produces a cellular response to insulin and the uptake of glucose. It is therefore essential for all the energy functions of the cell. Animal experiments suggest the possibility of teratogenicity following the administration of various metals,[10] including chromium.[11] Chromosomal changes have been seen in patients with metal-on-metal[6] devices and also with conventional bearing devices,[7] and the possibility of DNA damage in laboratory experiments[5] has been reported. Others have found no correlation between these changes and elevations of cobalt and chromium levels.[6,12] Such changes have the potential to cause carcinogenic effects in the subjects and mutagenic and teratogenic effects in the offspring. It is also known that there are mechanisms in the body that monitor and repair metal-induced DNA changes, and there are systems that protect against their effects.[15]

First-generation metal-on-metal hip replacements were used during the 1960s and 1970s.[14] Long-term studies on patients with these historic replacements have shown that there is no increase in the incidence of cancer in them compared with the general population.[15] Over 400 000 second-generation metal-on-metal devices have been implanted since the late 1980s, and several patients have reported having had babies in the years following implantation. There have been no published reports of mutagenic/

teratogenic effects in these patients, nor have there been such reports in those treated with the earlier metal-on-metal hip replacements. The question of the possibility of such effects on the developing fetus could be answered in part if it were known whether metal ions are transferred across the placenta.

A recent study[16] of the transplacental transfer of metal ions in patients with metal-on-metal hip devices led to the conclusion that the elevated ion levels in maternal blood do not lead to raised levels in the umbilical cord blood, and that the placenta acts as an effective barrier to metal ions released from these devices. This would imply that the rapidly dividing and differentiating tissues in the developing fetus are not exposed to the elevated metal ion levels and are therefore not subject to the potential adverse effects predicted by the laboratory experiments.

However, that study[16] was based on a study of serum levels in three subjects using graphite furnace atomic absorption spectrometry, which may not be adequate to detect metal ions at very low levels. Graphite furnace atomic absorption spectrometry and other conventional analytical techniques are not as sensitive as high-resolution inductively-coupled plasma mass spectrometry[17] to measure the low metal ion concentrations expected in whole blood. Although MacDonald, Brodner and Jacobs[18] suggest serum analysis to monitor metal exposure, their recommendation is based on 'the relative ease of serum analysis' rather than on an investigation of the sensitivity or reliability of serum analysis. Another study[19] with a large series of concurrent specimens shows serum to be less reliable than whole blood as a surrogate marker of systemic metal exposure. In fact, in their study, Brodner et al[16] could not detect metal ions in two of the three maternal serum samples and all of the three babies' serum specimens at the time of delivery.

Study group (mothers with metal-on-metal devices). The relative levels of metal ions in the maternal and umbilical cord blood in the study group patients reveal that the placenta does exert a modulatory effect on the transfer of metal ions. The cord blood levels of cobalt and chromium in these patients was only 60.4% and 29.4% of the mean maternal blood levels, respectively (Figs 3 and 4). The mean difference between maternal and umbilical cord chromium levels was statistically significant ($p < 0.005$), although the corresponding difference for cobalt did not reach statistical significance. This might be because of the small numbers of patients in the study.

Control group (mothers with no metal devices). In the control group the mean cobalt level in the umbilical cord blood was 98.5% of the mean maternal cobalt level (Fig. 3). With respect to chromium, the mean cord blood level was 97.2% of the mean maternal level (Fig. 4). The differences between the mean maternal and cord blood levels were not statistically significant with respect to either cobalt or chromium. This suggests that, far from acting as a barrier, there is an almost-free passage of these ions across the placental barrier at the levels expected in the normal population.

The finding that the placenta does not act as a total barrier to these elements is understandable when we realise that these essential trace elements are also required by the developing fetus for its cellular and metabolic functions. It has been reported[20] from an animal experiment that maternal chromium is actually depleted during pregnancy as a result of preferential uptake by the placentofetal unit, suggesting that the developing fetus takes up chromium for its own metabolic requirements.

Metal transfer in study group subjects compared with control group subjects. Whereas there was a fourfold elevation of mean maternal cobalt in the study patients (1.39 μg/l) compared with the control group (0.341 μg/l), the elevation in the cord blood level was only 2.5-fold (0.336 μg/l to 0.839 μg/l). With respect to chromium, a 6.5-fold elevation in the mean maternal level (from 0.199 μg/l to 1.28 μg/l) in the study patients compared with the control group leads to less than a doubling of the mean cord blood level (0.194 μg/l to 0.378 μg/l) in the study group.

The mean cord cobalt in the study group (0.839 μg/l) was significantly higher ($p < 0.01$) than that in the control group (0.336 μg/l). The mean difference in cord chromium between the study (0.378 μg/l) and control groups (0.194 μg/l) was not found to be statistically significant ($p > 0.05$), although this might be because of the small numbers in this experiment leading to a type II error. With the observed mean difference and distribution of umbilical cord chromium levels in the present study, in order to demonstrate an adequate power (0.8 or more) a sample size of 26 would be required, and we are therefore continuing to obtain data from subjects.

The differential modulatory role of the placenta with respect to the transfer of different metals has been described.[21,22] Rossipal et al[23] have shown that the platenta does exert an activating, inhibitory or concentration gradient effect on the transfer of different metals. For metals such as calcium, manganese and zinc, they reported that the placenta exhibits an active transfer mechanism, and umbilical cord levels are significantly greater than maternal levels. With others they found an inhibitory effect and with yet others a gradient effect. They found that cobalt levels in umbilical cord serum were 60% of those in the maternal serum in the normal population. In the present study we found that in the normal population the cobalt levels were almost equal in both the cord and the maternal blood (suggesting a gradient effect), whereas in the metal-on-metal group the transfer rate was 60.4% (suggesting a possible inhibitory effect), although the difference was not statistically significant ($p > 0.05$), given the limited numbers of patients studied. This inhibitory effect was even greater with chromium levels in the study group, with a transfer rate of only 29.4% and a statistically significant difference between maternal and cord levels ($p < 0.005$).

The umbilical cord has two arteries which carry blood from the fetus to the placenta and a vein which transports nutrient-enriched blood to the fetus. It could be argued that some of the differences we found are attributable to the fact that there could have been mixing of the umbilical arterial blood and venous blood in different samples. The difference between the venous and arterial concentrations is termed the consumption efficiency and indicates the rate of uptake and utilisation of the elements by the fetus. Experts[23] acknowledge that obtaining umbilical venous and arterial samples without cross-contamination is difficult. Studies[23,24] where the arteriovenous concentrations have been studied report that the consumption for different trace elements varies by a ratio ranging from -0.16 to +0.24 in normal babies. This range of difference is unlikely to affect the 1.95- to 2.5-fold elevations reported in the present study.

Metal-on-metal bearings are known to go through higher wear rates while they are run in over the first six months after implantation. During this period urine and blood studies show that there is a greater renal excretion of metal ions.[3] Our female patients who are planning a resurfacing and a pregnancy in the foreseeable future are therefore advised to have the baby before the resurfacing, or to postpone pregnancy until at least a year after the resurfacing.

We can, therefore, state that both cobalt and chromium cross the placenta, both in normal subjects without metal implants and in patients with metal-on-metal hip devices. The placenta exerts a modulatory effect on the rate of metal transfer. At low maternal metal ion levels there is a higher transfer rate than at higher maternal levels. Our data confirm the findings of earlier reports that placental modulation is different for different elements. The study also reinforces our earlier findings that studies using serum specimens[19] for metal ion analysis with a less sensitive analytical technique such as graphite furnace atomic absorption spectrometry can lead to misleading conclusions. Our study highlights the need for continued vigilance on the possible adverse effects of elevated systemic metal levels, especially in young patients with metal-on-metal hip devices.

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