■ INSTRUCTIONAL REVIEW: HIP

Metal-on-metal bearings

THE EVIDENCE SO FAR

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doi:10.1302/0301-620X.93B4.26429 $2.00

J Bone Joint Surg [Br] 2011;93-B:572-9.

Lately, concerns have arisen following the use of large metal-on-metal bearings in hip replacements owing to reports of catastrophic soft-tissue reactions resulting in implant failure and associated complications. This review examines the literature and contemporary presentations on current clinical dilemmas in metal-on-metal hip replacement.

The first attempt at total hip replacement (THR) took place in 1937 by Philip Wiles using stainless steel components which were fitted to the bone with bolts and screws.[1] In the 1950s McKee and Watson-Farrar[2] adopted a metal-on-metal (MoM) articulation with modified Thompson stems for THR and Ring[3] followed the same concept with his initial design. By the mid-1970s, MoM had been all but rejected in favour of Charnley's technique[4] for low-friction arthroplasty of the hip, using metal-on-polyethylene bearings. The appeal of resistance to wear conferred by MoM bearings compared with metal-on-polyethylene[5] has encouraged a trend towards the re-introduction of the MoM bearing couple. This allowed the rebirth of hip resurfacing, with the potential advantages of bone conservation, at least for the femur, to the advantage of any future revision.[6] Additionally, the possibility of a lower risk of dislocation due to larger head size and some evidence of higher levels of activity post-operatively have been attractive.[7]

Lately, reports have emerged of abnormal soft-tissue reactions to MoM THRs and hip resurfacing.[8-12] This review was prepared by the groups leading research in this field in the United Kingdom to provide a summary of the current evidence on the use of the MoM bearing as guidance to surgeons and to identify areas for further research.

Disease aetiology

The deposition of cobalt-chrome wear particles in peri-prosthetic tissues induces a spectrum of necrotic and inflammatory changes.[13] Peri-prosthetic soft-tissue lesions have been described variously as metallosis,[14] aseptic lymphocytic vasculitis-associated lesions (ALVAL),[15] adverse reaction to metal debris (ARMD)[16] and pseudotumours.[12]

Metallosis is the macroscopic staining of the soft tissues and is associated with abnormal wear, usually of the bearing surface or taper junction. The histological appearances of ALVAL[15] may occur with a range of changes from when metallosis is not evident to when there is an effusion or soft-tissue necrosis and pseudotumour formation. Pseudotumour describes a mass, which may be cystic or solid or a combination. The diagnosis is based on cross-sectional imaging or operative findings. Pseudotumours are usually, but not always, symptomatic, and histology tends to show ALVAL and tissue necrosis. The term ARMD[15,17] is an umbrella term including metallosis, ALVAL and pseudotumours. It is possible to progress through all three stages.

There appears to be no clear consensus in the literature defining the boundaries of each term, or that all metallosis develops into pseudotumours, or that ALVAL is necessarily present. It has been suggested that these abnormal soft-tissue reactions may be attributed to two aetiologies: wear-related cellular cytotoxicity and hypersensitivity.[18]

Recently, analysis of implant-derived debris from retrieved hip capsules showed that the most common metal was chromium (Cr), present as Cr(III) phosphate; this did not vary between the four manufacturers involved or the level of blood metal ions.[19] Cobalt and molybdenum were occasionally present in areas of high Cr concentration. Cobalt was normally found in a metallic state in the tissue, whereas molybdenum was found in an oxidised state. These metallic ions may have arisen from corrosion, wear, or a combination of the two. There was no evidence of Cr(VI) in the tissues.

The reaction to excess metal wear debris, with its association with increased blood metal ions, has been implicated in soft-tissue reactions.[17,20] Edge loading due to implant malposition and shallow acetabular components are thought to cause a failure of lubrication and to contribute to excessive wear.[21] Excess wear particles were traditionally thought to induce a dose-dependent local cytotoxic response and bring about tissue destruction.[22] More recently, in relation to the Articular Surface Replacement implant (ASR; DePuy, Leeds, United Kingdom), data suggests that tissue destruction is not dose dependent and may be caused by a true vasculitis.[23]

Cell-mediated hypersensitivity has been implicated as a cause of tissue damage in the presence of low wear.[13,18] Subsequently, features suggestive of perivascular lymphocyte infiltration resembling a type IV hypersensitivity reaction have been described.[24] However, as a cause of ALVAL this remains controversial, with others suggesting that true hypersensitivity is relatively rare and most cases of ALVAL can be explained by excessive wear.[9,25] It has been proposed that the incidence of hypersensitivity has been overstated when revisions for soft-tissue reactions have failed to demonstrate a problem with the bearing surface.[25] Recently corrosion was found on the retrieved cemented femoral components of a failed Ultima MoM THR (DePuy) without significant wear of the bearing surface.[26]

It is important to note that Willert et al[15] described the histological features of ALVAL in non-MoM bearing designs as well. This, together with a number of reports[13,27] that show ALVAL associated with a variety of causes of failure, may suggest that it is a physiological response to metal wear debris, which occurs to some degree in all implanted metal femoral components.

Local adverse effects of metal debris and pathogenesis

MoM wear leads to the release of a combination of metal ions and nanoparticles. The relative surface area and biological activity usually increase as particle size diminishes. This probably explains the difference in biological activity between cobalt-chromium in bulk form and nanoparticle form, which is the likely cause of adverse inflammatory reactions. Metal particles are considerably smaller than debris from conventional metal-on-polyethylene bearings, with the result that the total number of particles released from MoM bearings is more than two orders of magnitude higher than that found with conventional bearings.[28,29] The resultant increased surface area of metal particles leads to greater potential for corrosion and biological activity.

The wear debris is phagocytosed by macrophages and giant cells. Once in the acidic intramedullary environment of the lysosomes, the cobalt-chrome particles are subject to corrosion, producing high intracellular levels of ions, particularly cobalt, which cause cell death. In excess, this debris may cause a response within the tissue and subsequent osteolysis and aseptic loosening of the implants. It has been shown that, following phagocytosis of metal particles, the osteoblastic activity of the cell is impaired which may contribute to the cellular events that occur during aseptic loosening and soft-tissue destruction.[30]

Systemic effects of metal debris, carcinogenesis and teratogenesis

Metals such as cobalt, chromium, molybdenum and nickel are important trace elements required for normal physiology.[31] They are naturally acquired in the diet, and are present in the systemic circulation and excreted in the urine. Following MoM THR and resurfacing, the concentration of metal ions in the blood increases,[32,33] and long-term studies have shown that these elevated levels persist throughout the period of implantation and become grossly elevated when the implant becomes loose.[34,35] The systemic dissemination of metal particles to solid organs has also been shown.[36]

The exposure to cobalt and chromium has changed as a result of implant design. The particles are smaller (nanoparticles) and more numerous, and in some patients the metal levels may be higher and there may be increased corrosion.[17,26,37] Much of our knowledge about the clinical actions of these metals has come from external exposures in industry or the environment.[37] In contrast, the orthopaedic exposure is internal and hence different in that it bypasses many of the body's natural defences.[38]

Chromium most commonly exists in three forms, Cr(VI), Cr(III) and Cr(0) (metallic). Cr(VI), as either particles or ions, is an established respiratory carcinogen.[39,40] Much is understood about its genotoxicity through disturbances to DNA.[41] However, despite much research, the mechanisms by which it causes cancer are complex and elusive.[42] Cr(III) is less reactive but can damage DNA in tissue culture studies.[43] However, most studies of external exposure (e.g., oral) in animals have yielded negative results. Cobalt compounds, both soluble and particulate, cause lung cancer in animals, but the epidemiology in humans is not regarded as conclusive because of co-exposure to other carcinogens. It can act in conjunction with other metals such as tungsten to increase carcinogenesis.[44]

Little has been reported about the clinical effects of raised metal ions. However, an Alaskan patient with a poorly performing resurfacing arthroplasty developed neurological and cardiac symptoms which improved following removal of the implant.[45]

Concern remains about the long-term effects of raised metal ions and systemic dissemination, which can be divided into immune mediated and genotoxic.

Changes in the lymphocyte count have been reported in patients with MoM hip replacements.[46,47] Reduced peripheral blood counts of T (especially) and B lymphocytes were noted. One possible explanation for the low levels of T cells in the circulation and high numbers in the tissues[15,27,48,49] involves the compartmentalisation of T cells into the tissues, as occurs in rheumatoid arthritis. The

signal for this could be metal wear debris, but as yet the initiating substance has not been identified.

The Committee on Mutogenicity has reported that internal exposure to orthopaedic metals is associated with increased genotoxicity.[50] Patients with worn metal-on-polyethylene implants and co-exposure to polyethylene and cement show increased aneuploidy if the femoral component is made of titanium alloy, and increased chromosome translocations and aneuploidy if it is made of cobalt-chrome.[51] Patients with well-functioning MoM implants having smaller particles and no polyethylene show mainly aneuploidy.[52] These differences in biological reactions are reflected in tissue culture studies.[53,54]

The risk of cancer after exposure to orthopaedic implants has not in general taken into account the dose, the nature or the form of the metal. A meta-analysis by Onega, Baron and MacKenzie[55] comprising 1 435 356 person-years of follow-up, and a recent analysis by Visuri et al[56] of 310 341 person-years, have shown no overall increase in cancers after joint replacement. Some cancers were less numerous, such as cancers of the lung and bowel, whereas others were more common, such as prostatic cancers. Those showing a reduction have been suggested to be the result of reduced smoking in patients fit for surgery and the use of non-steroidal inflammatory drugs. The Onega study[55] suggested a late increase in melanoma and cancers of the bladder, kidney and oropharynx, which raises the question whether the increased cancers are related to metal exposure.[57]

There are three good reasons for continuing surveillance. First, as Visuri et al[56] noted, the mean follow-up has been short (11 years), compared to the latency for some tumours (20 to 40 years). Secondly, the evidence suggests a shift in the distribution of cancer which may or may not be related to metal exposure. Thirdly, the exposures are changing. If the exposing agent can alter the immune response from a macrophage-led aseptic loosening associated with metal-on-polyethylene implants, to a lymphocytic soft-tissue response in MoM implants, then the possibility of other, more long-term effects should not be discounted.

As MoM bearings are often used in younger patients, the teratogenic potential of metal ions needs to be considered. Exposure to metal ions such as chromium and cobalt induces teratogenicity in animal studies,[58,59] but there is little evidence of its impact on human embryos. Brodner et al[60] concluded that there was no passage of cobalt and chromium ions from maternal to fetal blood at the time of delivery. In contrast, Ziaee et al[61] published evidence of transplacental transfer of cobalt and chromium, but highlighted a possible modulatory effect exerted by the placenta. However, no mothers had abnormal levels of metal ions, so the modulation effect has not been examined in mothers with poorly performing implants.

It may therefore be concluded that although the theoretical risk of teratogenicity with MoM bearings may exist, there remain insufficient clinical data to confirm this in humans.

What is the frequency of adverse metal reactions?

There is generally a low incidence of symptomatic adverse soft-tissue reactions after hip resurfacing or MoM THR, but certain implants have been associated with a higher incidence. The prevalence of adverse soft-tissue reactions following MoM THR has only recently been described.

A long-term follow-up of the Metasul (Zimmer, Winterthur, Switzerland) reported no adverse reactions to metal debris and pseudotumours, with a survival rate of 94.4% at a mean of 12.3 years.[62] However, in another study the Metasul MoM THR showed a rate of ALVAL of 5% at ten years.[63]

A contemporary report on the ASR large-head MoM THR showed a rate of ARMD of 6% at a mean of 41 months,[17] which has risen to 18% on further review. A similar incidence of ARMD has been reported independently using the same prosthesis.[64]

In relation to hip resurfacing, the incidence of adverse soft-tissue reactions such as pseudotumours has been quoted to range from 0.3% to 3.4% at a maximum mean follow-up of 7.1 years.[8,17,65,66] An incidence of pseudotumour-related revision surgery of 1.8% was reported in a series of 1419 resurfacings.[67] The incidence was very low in men and higher in women, particularly those under 40 years old. This latter observation relates to many factors, such as small size, a pre-operative diagnosis of dysplasia, a gender difference in the range of movement and in head-neck ratio. The incidence of asymptomatic pseudotumours is unknown, but has been estimated at 4%.[10] However, these patients were not truly asymptomatic as they have lower functional scores.

What is the importance of implant position?

There appears to be a strong positive correlation between high inclination angles of the acetabular component and revision.[68-70] The resultant edge loading provokes accelerated wear, with particle release. A hip simulator analysis has also found significantly higher *in vitro* wear rates at higher acetabular component inclination angles.[71]

The effect of version of the acetabular component is harder to study, partly because it is more difficult to measure,[72] but there may be adverse reactions with greater anteversion,[17] with some designs being more vulnerable to malpositioning (Fig. 1).[73] This was not confirmed in a CT study of acetabular component anteversion and wear rate in failed hips.[74] Elsewhere, no association was found between anteversion of the acetabular component and blood metal ion levels.[75]

It has been proposed that optimal positioning of the acetabular component in resurfacing is approximately 20° anteversion with an inclination of 45°.[76,77] A fourfold reduction in the incidence of pseudotumours when acetabular components are optimally positioned within 10° of this recommended orientation has been reported.[77]

What is the importance of implant size?

In MoM hip resurfacing there is strong evidence to suggest that smaller components are associated with increased

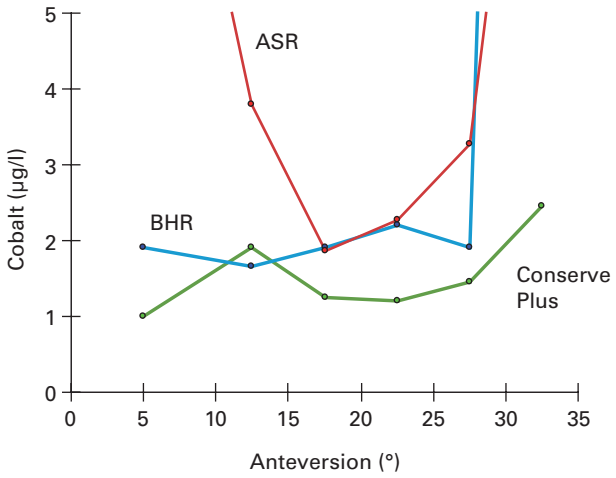

Fig. 1

The influence of anteversion of the acetabular component on serum levels of cobalt ions (ASR, Articular Surface Replacement (DePuy); BHR, Birmingham Hip Resurfacing (Smith & Nephew); Conserve Plus (Wright Medical Technologies)).

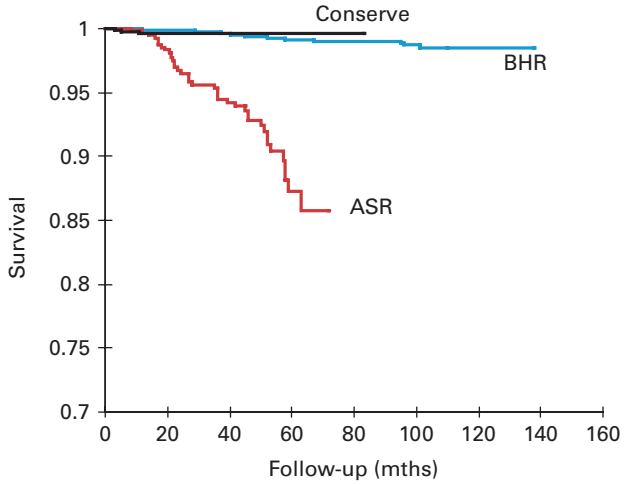

Fig. 2

Kaplan-Meier survival analysis of three versions of hip resurfacing, with failure related to adverse reactions to metal debris only (ASR, Articular Surface Replacement (DePuy); BHR, Birmingham Hip Resurfacing (Smith & Nephew); Conserve Plus (Wright Medical Technologies)).

metal wear debris owing to poorer fluid lubrication.[71] This is compounded by the reduction of the arc of cover in smaller components. Furthermore, a reduced head-neck ratio may give rise to increased edge loading and subsequent wear. The overall effect is to cause accelerated wear and precipitate revision.[67,70,78]

With regard to the femoral component in hip resurfacing, smaller sizes are associated with an increased risk of complications, such as fracture of the femoral neck.[71] It is thought that as the stem size remains constant as the size of the component decreases, the stem contributes to a greater proportion of the total stiffness, and increases the stress shielding, leading to fracture. The role of cement penetration with a greater load per unit area in smaller femoral components has also been implicated in this mode of failure.

In MoM THR, there have been descriptions of impingement between the acetabular and femoral components leading to wear and soft-tissue metal reactions.[79,80] Reducing the size of the femoral component to conserve acetabular bone will reduce the head-neck ratio. This will restrict the range of movement and increase the risk of impingement. It has been reported that a large reduction in the head-neck ratio in women is associated with a higher risk of pseudotumour.[76]

What is the significance of gender?

There is higher incidence of pseudotumours following MoM resurfacing in women.[67] This may in part be specific to anatomical differences, but may be confounded by differences in size between men and women.

Are all metal-on-metal resurfacings equal?

The design of resurfacing implants is suggested to make an important contribution to early failure. This has been observed in outcome reports comparing the ASR surface replacement, the Birmingham resurfacing (BHR; Smith and Nephew, Warwick, United Kingdom) and the ASR THR. The ASR implants performed worst.[17] This may relate to the lower diametrical clearance and the sub-hemispherical acetabular design of this implant, which might give rise to edge loading and increased wear. In a multicentre study using three different resurfacings in 4000 cases, Langton et al[81] showed a difference in failures related to ARMD with the BHR, Conserve Plus (Wright Medical, Arlington, Tennessee) and ASR designs (Fig. 2). Similarly, figures from the Australian Joint Registry identified a relationship between a higher age and gender-adjusted, revision secondary to fracture and type of prosthesis, with the ASR, Durom (Zimmer) and Recap (Biomet, Bridgend, United Kingdom) implants showing increased failure compared with the BHR.[78]

Is there a difference between the effect of resurfacing and large-head MoM THR?

The evidence at present is unclear, but there are concerns that the extra junction of the head and trunnion could exacerbate the problems of MoM bearings.

A randomised controlled trial comparing the use of large-head MoM THR to MoM resurfacing described a higher concentration of blood cobalt and chromium ions in the THR group. These findings did not correlate with any trend in terms of quality of life. A possible confounding factor in this study was the modular neck in the THR, which may be associated with wear at the neck-stem junction, raising concerns about the role of the trunnion in the production of metal ions.[82] A retrieval analysis of 240 MoM hip components comparing modular THR with hip resurfacing found similar rates of wear in the two groups.[83] More recently, The North Tees Hospital in the United

Kingdom presented results showing that with the ASR design the failure rate of large-head MoM THR exceeds that of the hip resurfacing version.[84] Interestingly, in the THR group the cobalt levels in the blood were raised in preference to chromium.

The larger heads were more prone to failure, but a lack of wear was found despite the implant failing with the histological features of ALVAL. This may represent mechanical wear of the taper, reiterating concerns from earlier studies (Fig. 3).[84]

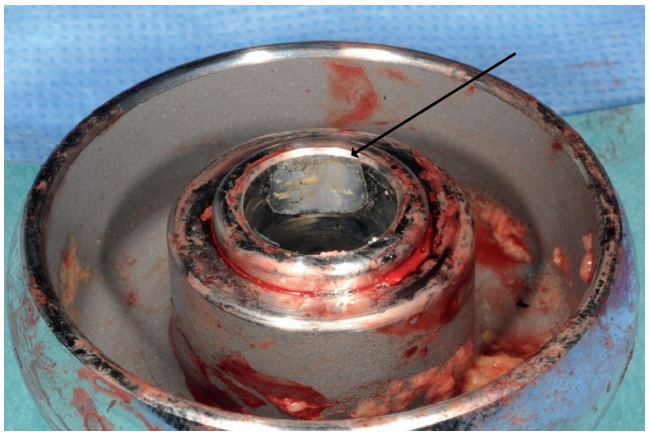

Fig. 3

Photograph of a worn taper from an explanted modular head of a metal-on-metal total hip replacement. The arrow shows the small area of normally preserved taper in the shape of a thumbprint.

What do plain radiographs, ultrasound, MRI and CT offer?

Imaging plays an important role in aiding the diagnosis of early implant failure and soft-tissue complications. We suggest that the various modalities are combined in a diagnostic protocol for the assessment of symptomatic patients. We are unaware of any published literature quoting the sensitivity and specificity of the different modalities in relation to the diagnosis of adverse metal reactions and implant failure.

Artefact-reduction MRI, 3D-CT measurements and blood metal ion measurements have been reported in the diagnosis of unexplained hip pain following resurfacing. The useful role of each modality in determining the cause of implant failure was highlighted.[85] Plain radiographs using EBRA may be used to define the position of the implant in those at risk of developing pseudotumours.[86] The advantages of this technique are the lower radiation, the fact that the imaging can be performed in a physiological standing position, and the greater availability. Additionally, aseptic loosening and fracture of the femoral neck can be readily seen, although not necessarily related to underlying soft-tissue reactions. However, the validity of plain radiographs may be compromised by large-diameter metal femoral heads because the acetabular rim is obscured.[72]

Three-dimensional CT might also have an important role in evaluating component malposition[87] and reveal early focal osteolysis.[88]

Metal artefact reduction series (MARS) MRI analysis may be useful in delineating soft-tissue abnormalities and mass lesions when plain radiographs are normal.[89] However, because of metal artefacts small lesions directly adjacent to the implants may be overlooked. Accordingly, ultrasonography may be useful when small underlying soft-tissue lesions are suspected.[12,90] This would also allow identification of the lesion as either solid or cystic, and also guide aspiration for histological analysis.

Is there an accepted cut-off level for blood metal ion levels?

The identification of high serum levels of metal ions is an indication that the hip is functioning poorly. However, there is currently no accepted cut-off level.

Detectable levels of metal in the serum and urine of patients with THRs have been described in the early literature.[91] At five years in a well-functioning MoM implant a higher concentration of serum cobalt ions has been described compared to pre-operative levels. There was a peak in the six- to 12-month period post-operatively.[92] The cobalt and chromium ion concentrations in whole blood remained significantly higher at six years than pre-operatively, with peak levels of 1.26 μg/l and 2.41 μg/l, respectively, reported at one year.[32] There is overall consensus that the blood cobalt or chromium level of a well-functioning MoM hip is approximately 2 μg/l (which is equivalent to 2 parts per billion (ppb)) and 2 ng/ml, respectively. For bilateral hip resurfacings, this is raised to approximately 3 μg/l,[84] and also for patients with renal failure.

There is a correlation between the metal ion concentrations of serum and joint aspirate and component wear. The same work concluded that serum chromium ion levels of > 17 μg/l and serum cobalt ion levels of > 19 μg/l are likely to be associated with metallosis.[93] Other authors have reported similar findings.[10] Additionally, elevated metal ion levels have been used to identify patients with ARMD.[17]

It may thus be presumed that raised metal ion levels up to a certain level is a feature of MoM bearings and does not necessarily represent underlying pathogenesis. However, higher levels may herald an adverse change. Hart et al[74] showed that blood levels of cobalt were doubled in painful hips compared with well-functioning hips. They also used data from well-functioning MoM hips and the statistical definition of an outlier (third quartile + 2 × interquartile range) to define a cut-off level of 7 μg/l for either cobalt or chromium.[47] They presented a specificity and sensitivity analysis of these levels to predict failure of MoM hips that showed a 90% specificity but only a 50% sensitivity. These levels have been adopted by the United Kingdom, Medicines and Healthcare Products Regulatory Agency for their safety alert published in April 2010.[94]

In another study, using 4 μg/l as a cut-off increased the detection of ARMD cases from 75% to 90%.[95]

Importantly, the detection of ARMD pseudotumours was less satisfactory in MoM THRs, as the tapers often release metal debris when they fail.

Do we know the threshold for revision?

Common indications for revision surgery following MoM resurfacing include fracture, loosening/lysis, pseudotumour, metal hypersensitivity, pain, avascular necrosis and instability. There is no clear documented evidence describing the overall threshold for revision surgery. Among 397 revisions of hip resurfacings the most common indication was peri-prosthetic fracture, which accounted for 43%; metal sensitivity 28%.[96] Another series of 53 revisions included 40% due to fracture and pseudotumours represented 30%.[97] However, the recognition of the problems posed by pseudotumours may see a change in the threshold for revision with a greater emphasis on monitoring the asymptomatic patient.

Does early intervention prevent bone/soft-tissue loss: what is the outcome of revision surgery?

It is proposed that early intervention may be associated with a more favourable outcome of revision surgery. However, little is known of the natural history of soft-tissue lesions following MoM replacements. The possibility of progression has been suggested in two papers. In each case symptoms deteriorated, necessitating revision.[8,17]

Outcome following revision surgery may be influenced by the degree of tissue destruction at the time of surgery, with reports of good results in patients who underwent early revision surgery in the absence of soft-tissue destruction.[8,98,99] Poorer results have been reported in revisions for pseudotumours compared with other aetiologies.[97] Early identification and intervention seems to be the most appropriate management.

What is the minimum follow-up needed for MoM THR and resurfacing?

The current Medicines and Healthcare Products Regulatory Agency guidelines recommend annual follow-up for the first five years after MoM replacement.[94] Thereafter, annual follow-up should be reserved for symptomatic patients only. There appears to be a higher incidence of symptomatic pseudotumours during the first few years after surgery. An incidence of 1% within the first five years has been suggested.[8] Langton et al[17] described a similar early pattern of presentation, with, however, some also presenting more than five years after operation. This should probably continue beyond five years.

Conclusion

The outcomes of MoM bearing hip replacements are variable. Hip resurfacing remains a successful operation in younger men with appropriate anatomy.[100]

Soft-tissue reactions have been seen around all devices, even when well positioned and asymptomatic, but their significance is not fully understood. What is clear is that the results of all these devices depend on appropriate surgical technique and patient selection. However, these simple rules appear to be less forgiving with MoM bearings.

Current data suggest that correct surgical technique in an appropriately selected cohort of patients is associated with a low incidence of adverse soft-tissue reactions. High-risk factors for developing complications include small component sizes, female gender and significant anatomical variation due to, for example, dysplasia, where positioning the acetabular component may be difficult. In such situations the use of this bearing should be approached with caution. Patients with a high acetabular component inclination angle and a rising level of metal ions in the blood are at a high risk of requiring revision.

Although there are theoretical risks of carcinogenesis and teratogenesis, there is no evidence of this occurring in humans in relation to MoM replacements. Nevertheless, consideration should be given to these concerns, especially if the patient intends to bear children.

Metal ion studies provide a method of identifying excessive particle loads which have been associated with adverse soft-tissue responses. We advocate that serum metal ion concentrations should be measured at regular intervals in all symptomatic patients, those with malpositioned asymptomatic implants, and patients with ASR implants. A persistent rise in metal ion concentrations, irrespective of symptoms, should be investigated further with appropriate imaging.

The various imaging modalities should be combined into a protocol, with plain radiographs performed as part of routine annual follow-up. In symptomatic patients or those who are asymptomatic but have raised blood metal ion concentrations, ultrasound scanning and MARS MRI should be considered.

There must remain a low threshold for early surgical intervention where there is evidence of implant failure. If soft-tissue destruction or extensive bone loss had occurred, appropriate expertise must be available for reconstructive surgery.

While the present evidence for the use of MoM THR is unclear, it is our opinion that MoM resurfacing remains a viable option and should not be discarded because of problems related to metal reactions. The ideal candidate would be a young, active male with relatively normal anatomy. In such patients, favourable outcomes can still be expected, and provided that the patient is fully informed of the risks and benefits of the surgery, surgeons should feel confident in offering this as an option.

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