Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

HIGHLIGHTING THE DANGERS OF METAL-ON-METAL HIP REPLACEMENTS

Summary of the impact:

Metal-on-metal hip resurfacing was developed in the 1990s to provide a long-term solution for young, active patients with hip disease. After observing severe adverse soft tissue reactions (pseudotumours) occurring in a growing percentage of patients with metal-on-metal resurfacing, researchers from the University of Oxford highlighted the problem and identified key patient, surgical and implant related risk factors. Clinical guidelines have been introduced to emphasise the risks, and several implants have been withdrawn from the market by the manufacturers. This research has led to a dramatic decrease in the use of metal-on-metal bearings in hip replacement.

Underpinning research:

Conventional total hip replacements (THR) have historically had high failure rates in young, active patients due to their functional demands. In the 1990s hip resurfacing with metal-on-metal (MoM) bearings were developed to combat this issue and became a common alternative to conventional THR in young patients. In 2008 40% of men with hip arthritis, under 55, received MoM resurfacing rather than conventional THR. Due to the success of MoM resurfacing, conventional THR also introduced MoM bearings. Worldwide over 1 million MoM bearings have now been implanted.

University of Oxford Professor, David Murray, and other surgeons at the Nuffield Orthopaedic Centre in Oxford, began implanting MoM resurfacings in 1998. Detailed data was collected on these patients, and on patients referred to the Nuffield Orthopaedic Centre with problems relating to MoM bearings. The University of Oxford researchers observed increasing numbers of patients presenting with a variety of adverse symptoms related to their MoM bearings. These patients were investigated not only with X-rays, which is the traditional method of investigating hip replacements, but also with ultrasound scans. The scans revealed that the source of the symptoms were solid or cystic soft tissue masses. Although not malignant, these lesions resembled tumours, leading Professor Murray's group to call them pseudotumours.

Although there have been occasional reports of soft tissue masses occurring after hip replacement since the 1970s, Professor Murray's group were the first to observe that with MoM bearings these were relatively common and could be invasive and highly destructive. In the group's initial study, which was published in 2008[1], the incidence of pseudotumours was higher in women than men, with 1% of all resurfacings requiring revision due to pseudotumours. Subsequent studies showed that incidence increased with time[2]. In the group's most recent study, the incidence at 10 years was approximately 1% in men and 20% in women. Asymptomatic patients with MoM resurfacings were also scanned, revealing that the overall incidence of asymptomatic pseudotumours was 4%[3]. With time, a number of asymptomatic lesions became larger, symptomatic and required revision.

In a series of studies investigating the cause of pseudotumours, the Oxford group found that the majority were caused by excessive wear[4] due to edge loading of the MoM bearing. This resulted in high levels of chromium [Cr] and cobalt [Co] metal ions in the blood. *In vitro* and histological studies suggested that metal wear particles killed the cells around the implant, resulting in extensive soft tissue destruction[5]. Clinical studies demonstrated that women under the age of 40 with hip dysplasia had a particularly high risk of developing pseudotumours[2]. Surgical risk factors included poor acetabular orientation and downsizing of the femoral head, and implant risk factors included small component size, low clearance and coverage[2]. These, and other factors, such as

greater flexibility and a different gait pattern, explain why women are more likely to edge load their resurfacings, and as a result, are at a higher risk of developing pseudotumours.

Further clinical studies demonstrated that revision of MoM resurfacing for pseudotumours had a high complication rate of 50%, due to severe soft tissue damage[6].

References to the research:

1. Pandit, H. *et al.* Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br* **90**, 847–851 (2008). doi: 10.1302/0301-620X.90B7.20213. ***Primary paper reporting that pseudotumours occur relatively commonly after MoM resurfacing and can cause major problems.***

2. Glyn-Jones, S. *et al.* Risk factors for inflammatory pseudotumour formation following hip resurfacing. *J Bone Joint Surg Br* **91**, 1566–1574 (2009). doi: 10.1302/0301-620X.91B12.22287. ***Paper identifying the risk factors for pseudotumours after MoM resurfacing.***

3. Kwon, Y.M. *et al*. Asymptomatic pseudotumours after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. *J Arthroplasty* **26** 511-8 (2011). doi: 10.1016/j.arth.2010.05.030. ***Paper showing that patients with asymptomatic MoM resurfacings may have developed pseudotumours.***

4. Kwon, Y.M. et al. Analysis of wear of retrieved metal-on-metal hip resurfacing implants revised due to pseudotumours. *J Bone Joint Surg Br* **92** 356-61 (2010). doi: 10.1302/0301-620X.92B3.23281. ***Study demonstrating that most pseudotumours are caused by high wear due to edge loading of the MoM bearing.***

5. Kwon, Y.M. *et al.* Dose-dependent cytotoxicity of clinically relevant cobalt nanoparticles and ions on macrophages in vitro. *Biomed Mater* **4**, 025018 (2009) doi: 10.1088/1748-6041/4/2/025018. ***A paper showing that the metal wear particles kill cells.***

6. Grammatopoulos, G. *et al.* Hip resurfacings revised for inflammatory pseudotumour have a poor outcome. *J Bone Joint Surg Br* **91**, 1019–1024 (2009). doi: 10.1302/0301-620X.91B8.22562. ***Paper demonstrating that poor results are achieved following revision of MoM resurfacings for pseudotumour.***

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Details of the impact:

By demonstrating the frequency, the severity, and the risk factors for pseudotumours related to MoM hip replacements (MoMHR), this research has led to dramatic changes in clinical practice and guidelines nationally and internationally. As a result, implantation of MoM replacements has now virtually ceased. For those already implanted, routine surveillance is recommended and all patients with problems, including mild complaints, are investigated in detail. Early revision is encouraged to prevent significant soft tissue damage. This has had a significant impact on patient health, clinical guidelines and the orthopaedic industry.

Health and Patient Care

The identification of pseudotumours and the severe problems that they can cause after MoM hip replacement has led to a dramatic reduction in the use of these implants. Data from the National Joint Registry for England and Wales has shown that the use of MoM resurfacing halved between

2008 and 2010, with 40% of men under 55 having MoMHR in 2008, in comparison to 20% in 2010. It is estimated that this number has halved again in recent years[7]. The Arthritis Research UK website provides information on hip resurfacing from experts, and states that although metal-on-metal hip replacements are still being implanted, predominately in young men under the age of 50, their general use has reduced "very sharply" in the UK in recent years[8].

The full scale of the problem, identified by Professor Murray's team almost seven years ago is now clearly reflected by the National Joint Registry for England and Wales[7] and other registries[12], which all show the very high failure rates of MoM replacements. These failures are associated with considerable patient suffering and expense to the health service.

Guidelines and Policy

On the basis of the University of Oxford's research, and the research of other groups that have followed its lead, strong recommendations have been issued regarding the use of MoM replacements in the UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has issued numerous Medical Device alerts for various MoM implants. In February 2012 MHRA advised that all patients with metal-on-metal hips should be followed up annually for five years[9]. This Medical Device alert was replaced in June 2012, with updated recommendations stating that all patients with MoMHR should be followed up "annually for the life of the implant"[10].

The British Orthopaedic Association summarised the status of MoMHR in 2011, highlighting the problems of MoM replacements and supporting recommendations to follow up MoMHR and restrict its use[11]. The National Joint Registry for England and Wales also highlights the high failure rate of MoMHR[7].

Similar guidance has also been issued internationally. The Australian Orthopaedic Association National Joint Replacement Registry, highlights the high failure rate of MoMHR in its Hip and Knee Arthroplasty 2011 Annual Report[12]. The Canadian Orthopaedic Association (COA) also issued similar recommendations in February 2011[13]. In the United States, the Food and Drug Administration (FDA) also highlighted the safety risks associated with MoMHR, and made recommendations on patient monitoring[14].

Industry Withdrawals

DePuy, one of the largest implant manufactures for MoMHR, issued a voluntary recall of their Articular Surface Replacement ASR™ MOM Hip System in August 2010, and are funding revisions of this implant[15]. They and other companies are also involved in multi-billion dollar lawsuits[16].

Sources to corroborate the impact:

7. National Joint Registry for England and Wales. 8th Annual Report [online]. Hemel Hempstead: National Joint Registry. 2011. Available at: http://www.njrcentre.org.uk/NjrCentre/Portals/0/Documents/NJR%208th%20Annual%20Report%202011.pdf [Accessed 14 May 2013]***Data showing the reduction in MoMHR use between 2008 and 2010.***

8. Arthritis Research UK. Metal-on-metal hip replacement Q and A. 2013. Available at: http://www.arthritisresearchuk.org/arthritis-information/surgery/mom-hip-q-and-a.aspx [Accessed 14 May 2013]***An article published on the Arthritis Research UK website indicating the recent drop in MoMHR use in the UK.***

9. Medicines and Healthcare products Regulatory Agency (MHRA).All metal-on-metal (MOM) hip replacements [online] London. 2012. Available at: *http://www.mhra.gov.uk/home/groups/dts-bs/documents/medicaldevicealert/con143787.pdf* [Accessed 14 May 2013] ***Recommendations made by MHRA in February 2012, indicating that all patients with MoMHR should be followed up annually for 5 years.***

10. Medicines and Healthcare products Regulatory Agency (MHRA).All metal-on-metal (MOM) hip replacements [online] London. 2012. Available at: *http://www.mhra.gov.uk/home/groups/dts-bs/documents/medicaldevicealert/con155767.pdf [Accessed 22 May 2013]*
Updated recommendations by MHRA, released on the 25th of June 2012, stating that all patients with MoMHR should be followed up "annually for the life of the implant".

11. British Orthopaedic Association. Metal on Metal Hips [online] London. 2011. Available at: *www.boa.ac.uk/PI/Pages/Metal-on-Metal.aspx* [Accessed 15 May 2013] ***A summary of the problems related to MoMHR from The British Orthopaedic Association supporting recommendations to follow up MoMHR and restrict its use.***

12. The Australian Orthopaedic Association National Joint Replacement Registry.Hip and Knee Arthroplasty. Annual Report [online] Adelaide: University of Adelaide. 2011. Available at: http://www.surfacehippy.info/pdf/australian-nat-reg-2011.pdf [Accessed 15 May 2013]
The Australian Orthopaedic Association National Joint Replacement Registry, Hip and Knee Arthroplasty Annual Report for 2011, highlighting the high failure rate of MoMHR.

13. Canadian Orthopaedic Association. Advice to patients with metal-on-metal hips [online] Available at http://www.coa-aco.org/images/stories/library/Advice_to_Patients.pdf [Accessed 15 May 2013] ***Recommendations from The Canadian Orthopaedic Association (COA), February 2011, highlighting the high failure rate of MoMHR.***

14. medicalxpress.com. FDA probing safety of metal-on-metal hip implants [online]. 2012.Available at: http://medicalxpress.com/news/2012-06-fda-probing-safety-metal-on-metal-hip.html [Accessed 15 May 2013] ***Article about the FDA review to assess the safety risks associated with MoMHR, and make recommendations on patient monitoring.***

15. DePuy Synthes ASR™ Hip Replacement Recall Guide for Patients [online] 2013 Available at: http://www.depuy.com/asr-hip-replacement-recall [Accessed 15 May 2013] ***ASR™ Hip Replacement Recall Guide for Patients from the DePuy website.***

16. Orthopaedics One. The Case of Metal-on-Metal Implant Recalls - What Have We Learned [online] 2012.Available at: http://www.orthopaedia.com/display/Main/The+Case+of+Metal-on-Metal+Implant+Recalls+-+What+Have+We+Learned [Accessed 15 May 2013] ***Article about MoMHR recalls and lawsuits.***