Joint UKBTS / NIBSC Professional Advisory Committee ([1])
Summary Sheet

1. Paper for the JPAC meeting on:	10/3/11
2. Date submitted:	17 February 2011
3. Title (including version no.):	Recommendations on a change to the Donor Selection Guidance for Trying to Conceive
4. Author(s):	Dr Philip Yate, Dr Sue Barnes
5. Brief summary:	Currently there is a difference between the donor selection guidance for Infertility /Trying to conceive between Whole Blood and Component Donors which has always allowed recipients of donated sperm, eggs and embryos to continue as blood donors and the guidance for Tissues donors which consider these to be a vCJD risk and therefore exclude recipients. This raises the issue of the safety of these tissues. Dr Yates has reviewed the literature on Sperm infectivity, in light of his paper and the reality of sperm exposure in female donors it would seem unreasonable to exclude sperm donation recipients from blood or tissue donation. In January 2010 a paper (attached) suggesting that there was evidence of prion in the ovary and uterus of a vCJD victim in the US. This would suggest that egg and embryo recipient donors should be excluded from Blood and Tissue donation. The drug Metrodin HP was withdrawn in 2003 as a vCJD precaution, advice was sought as to the background to the withdrawal and if other drugs were affected from N Goulding at the MHRA. On the basis of the advice received the SAC CSD on 9/12/10 recommended amending the DSG guidance on Trying to Conceive to exclude donors who have had Metrodin in the past. Draft Change notification attached.
6. Action required by the Joint Professional Advisory Committee: (What do you want JPAC to do in response to this paper?) e.g. • endorse a specific recommendation • advise where there is a choice of possible actions • advise on priorities within the work plan • provide a steer on policy	Enclose recommendations
7. Any other relevant information:	

Allogeneic reproductive tissue recipients and the possibility of vCJD transmission

Background

Prior to June 2010 the Whole Blood and Components Donor Selection Guidelines had an entry for 'Infertility' which did not specifically mention donated reproductive tissue. The updated version of the blood donor guidelines released in June 2010 replaced the entry for 'Infertility' with a new entry entitled 'Trying to conceive'. This entry has a new discretionary clause which states "Even if treatment included donated sperm, eggs or embryos, accept."

This raises questions as to both the status and safety of reproductive tissues.

The status of reproductive tissues

In Europe *Directive 2004/23/EC* applies to tissues and cells including haematopoietic peripheral blood, umbilical-cord (blood) and bone marrow stem cells, reproductive cells (eggs, sperm), foetal tissue and cells, and adult and embryonic stem cells. It specifically excludes blood and blood products and organs.

In the USA the donation of semen, oocytes and embryos are regulated by the FDA and are covered by the FDA document *"Guidance for Industry: Eligibility determination for donors of human cells, tissues and cellular and tissue based products (HCT/Ps)"*.

So in both Europe and the USA tissue and cell donations, including reproductive cells, are treated identically.

In the UK the regulation of human tissues and cells for human application is part of the remit of the Human Tissue Authority (HTA). However the remit does not include mature gametes and embryos (which are covered by the Human Fertilisation and Embryology Authority) but does include immature gametes. The HTA are also not responsible for organ donation other than the specific role of consent.

In the UK reproductive cells (sperm, ova, embryos created in vitro and immature ovarian or testicular tissue) are included in the remit of the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO). This Committee replaced the former Advisory Committee on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation (MSBT) whose remit did not include reproductive tissue.

The status of sperm, eggs and embryos are important because both the Whole Blood and Components Donor Selection Guidelines and the Living and Deceased Tissue Donor Guidelines exclude recipients who have had an allogeneic human tissue or organ transplant since 01/01/1980. The SAC-T and SAC-CSD have interpreted the status of reproductive tissue recipients

differently resulting in the discrepancy that whilst potential blood donors would be accepted potential tissue donors would be rejected.

The safety of reproductive tissue

Irrespective of whether sperm, eggs or embryos are classified as 'tissues' or not, what evidence is there to confirm or refute the possibility of prion infection via reproductive tissue?

Ovary

Human data

Annex 1 of the 2006 *'WHO guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies'* shows no evidence of abnormal prion in either ovarian or uterine tissue.

However, in 2009 the presence of protease-resistant prion protein PrP^{res} was detected for the first time in the ovary and uterus of a vCJD patient in the USA.

Multiorgan detection and characterization of protease-resistant prion protein in a case of vCJD examined in the United States
Notari et al
PLoS ONE January 2010 / volume 5 / Issue 1 / e8765

Sperm

Human data

Annex 1 of the 2006 *'WHO guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies'* shows no evidence of abnormal prion in the prostate, epididymis, seminal vesicle or semen.

High levels of the 'prion-like' protein Doppel (Dp1) have also been demonstrated in both Sertoli cells and spermatozoa in humans.

The human "prion-like" protein Doppel is expressed in both Sertoli cells and spermatozoa.
K Peoc'h et al
Journal of Biochemical Chemistry 277, 45, 43071-43078 (2002)

Animal data

The presence of high levels of normal cellular prion protein ($PrP^{C)}$ has been demonstrated in sheep semen, mainly derived from the epididymal fluid but also from the sperm membrane. However the authors were not able to detect PrP^{Res} after proteinase K treatment of scrapie-infected ram seminal fluid. Nor has it been possible to transmit prion infection to scrapie-susceptible transgenic mice using semen from infected rams. This would suggest the absence of PrP^{Sc} and probable absence of infectivity. It has been postulated that the absence of infectivity may reflect the lack of transconformation of the

prion protein in the genital tract due to either the specific biomechanical properties of the different glycosylated and truncated forms present or the high level of protection by the testicular and epididymal blood barrier or the lack of one or more (unidentified) co-factors needed for the conversion of PrP^{C} to PrP^{Sc}.

Prion Protein is secreted in soluble forms in epididymal fluid and proteolytically processed and transported in seminal plasma
JL Gatti et al
Biology of Reproduction, 67, 393-400 (2002)

Semen from scrapie-infected rams does not transmit prion to transgenic mice
JL Gatti et al
Reproduction 135, 415-418 (2008)

Expert opinion

A survey of international experts on either prions/prion disease or donor sperm/cryobanking as to the risk of vCJD transmission via semen/donor spermatozoa. 45 out of 104 replied. The consensus opinion was that the risk of transmission was < 1:10,000,000 even for UK men.

Is there a real risk of transmitting variant Creutzfeldt-Jacob disease by donor sperm insemination?
D Mortimer & CLR Barratt
Reproductive Biomedicine Online 2006, 13 (6), 778-790

FDA position on reproductive tissue donors

Even though no evidence exists for sexual transmission of prion disease, and despite a number of requests from sperm banks in the USA in recent years, the FDA continues to exclude all men from being sperm donors if they are regarded as a "TSE risk".

The Transmissible Spongioform Encephalopathies Advisory Committee meeting on 28/29 October 2010 identified current criteria that would render an HCT/P (human cells, tissues and cellular and tissue based products) donor ineligible as a result of TSE risk. These include

1. has spent >3 months in the UK during the period 1980-1996
2. has spent >5 years in Europe since 1980
3. has received any transfusion of blood or components in the UK or France from 1980 - present

Examples of HCT/Ps specifically included semen, oocytes and embryos to which the donor contributed spermatozoa or oocyte.

Conclusion

The finding of protease-resistant prion protein PrP^{res} in the ovary and uterus of a vCJD patient should exclude recipients of both ova and embryos from being

donors of either blood or tissue (as applies to recipients of all other tissue and cells)

Question still to be answered.

In view of both the lack of evidence of infectivity in semen in animal models and the natural exposure of the majority of female donors to semen through sexual intercourse, should sperm donors be a special exemption to the general exclusion criteria relating to recipients of allogeneic tissues or cells?

Dr Philip Yates
Acting Chair SAC Tissues

21/01/2011

At the SAC CSD on 12/8/10 the Chair was charged with obtaining from Nigel Goulding the background to the withdrawal of Metrodin HP, this is his response:

Dear Sue,

Metrodin HP for IVF, I've attached 2 documents produced by MCA in February 2003. In one Professor Alasdair Breckenridge, Chairman of the Committee on Safety of Medicines said: *"CSM has advised the withdrawal of Metrodin HP purely as a precautionary measure. The Committee carefully considered this issue and advised that even a theoretical risk such as that associated with Metrodin HP was unacceptable given that there are alternative treatments. It is stressed that there have been no reported cases of the transmission of CJD via urine or products derived from urine."*

Also the Q&A document stated the following:

Q. Why is it being withdrawn?

A. The Committee on Safety of Medicines (CSM) continually reviews the safety of medicines that are prepared from human and animal materials, particularly with respect to any potential risk from the transmission of BSE or variant CJD (vCJD). The aim is to minimise the risk as far as possible by applying a precautionary principle to the consideration of the safety of medicines. Consistent with this aim is the CSM's advice that products that are prepared from plasma or urine sourced from any country with one or more confirmed cases of vCJD should be replaced by alternative treatments whenever practicable. Metrodin HP is prepared from urine collected in Italy, where there has been a recently confirmed case of vCJD. Since there are adequate supplies of alternative products, CSM has advised that Metrodin HP should no longer be used in the UK. It should be stressed, however, that this is a purely precautionary measure. There has been no reported case of transmission of vCJD via urine or products derived from urine.

Q. What is the risk to women who have received Metrodin HP?

A. The risk to women of contracting vCJD from Metrodin HP is incalculably small. However, the precautionary principle applies even where the risk is so small, because alternative treatments are available.

The CSM advice in 2003 was based on the position at the time that there had been no reported case of transmission of vCJD via urine or products derived from urine. However, even if the risk to women of contracting vCJD from Metrodin HP was assessed as being incalculably small, it would seem prudent to apply the precautionary principle and defer donors under these circumstances.

Regards

Nigel

Nigel Goulding
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Inspection, Enforcement & Standards Division
Medicines and Healthcare products Regulatory Agency

Date of publication:	Implementation:

Change Notification UK National Blood Services No. - 2011

Applies to all Donor Selection Guidelines.

Trying to Conceive (applies to female donors only)

Obligatory
Take care to exclude pregnancy.

Must not donate if:
a) Under investigation for infertility.

b) Less than 12 weeks after completion of treatment with clomiphene (Clomid®).

c) Less than 12 weeks after completion of treatment with tamoxifen.

d) Has ever been given human gonadotrophin of pituitary origin.

e) Has received donated eggs or embryos since 1980.

f) If donor knows that they have ever been treated with Metrodin HP® .

Discretionary
If *not known to have been treated with Metrodin HP®* but *treated* exclusively with *other* non-pituitary derived gonadotrophins and or donated sperm, accept.

See if Relevant

Prion Associated Diseases

Additional Information
The 12 week period is an additional safeguard to avoid taking a donation early in a pregnancy.

The use of human gonadotrophin of pituitary origin (follicle-stimulating hormone (FSH) and luteinizing hormone (LH)) had stopped in the UK by 1986. The situation in other countries varied so specific dates cannot be given.

There is a concern that transfer of tissues (eggs or embyros) between individuals might lead to the spread of vCJD.

Metrodin HP® was withdrawn by the Committee on Safety of Medicines in 2003 and following advice from the Medicines and Healthcare products Regulatory Authority the precautionary principle has been applied to withdraw donors who have been treated with this product. Donors treated for infertility after 2003 in the UK will not have been treated with this product.

Donors trying to conceive naturally can donate provided that they have not missed a period. Taking folic acid or other vitamin and mineral preparations is not a problem.

Update Information
This entry was last updated in:
DSG-WB Edition 203, Release ????

Reason for Change
Withdrawal of donors who have ever been treated with Metrodin HP®, donated eggs or embryos has been added.

Donor Information
If you wish to obtain more information regarding a personal medical issue please contact your National Help Line.

Please do not contact this web site for personal medical queries, as we are not in a position to provide individual answers.