Donor Screening: clinical, infectious and genetic

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Drivers for review


UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors (2008)

Association of Biomedical Andrologists
Association of Clinical Embryologists
British Andrology Society
British Fertility Society
Royal College of Obstetricians and Gynaecologists

- Decline in the availability of donor sperm
- Removal of donor anonymity in UK (2004)
- Apparent change in UK donor profile (e.g. age)
- Increasing use of 'known donors'
- Advances in diagnostic testing
- EU Tissues and Cells Directive (2006)

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Primary aims

To protect:

- the recipients of donor sperm, egg and embryos from acquiring an infection from the donor
- any donor-conceived people from being born with an infection or acquiring a serious heritable disorder from the donor.

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The risks are real …

HIV:
Stewart *et al.*, (1985)
Araneta *et al.*, (1995)

Muscular Atrophy:
Tizzano et al., (2002)

Miscellaneous infections:
Broder *et al.*, (2007)

Fragile X:
Wirojanan *et al.*, (2008)

Cardiomyopathy:
Maron *et al.*, (2009)

Outline

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informa healthcare

UK guidelines for the medical and laboratory screening of sperm, egg and embryo donors (2008)

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Abstract
This article updates the 1999 British Andrology Society (BAS) guidelines for the screening of sperm donors and the 2000 British Fertility Society (BFS) guidelines for the screening of egg and embryo donors and combines the new recommendations into a single document. This was achieved by a multidisciplinary working group composed of representatives from the Association of Biomedical Andrologists, the Association of Clinical Embryologists, the BAS, the BFS and the Royal College of Obstetricians and Gynaecologists. The major changes to the guidelines include a requirement to consider a donor's risk of transmissible spongiform encephalopathies and the recommendation to screen for human T cell lymphotropic viruses 1 and 2. The role of nucleic amplification tests for the detection of blood borne viruses such as HIV is discussed, but it remains the recommendation that this be achieved by serological testing to detect antibody or antigen as appropriate with a quarantine period of 180 days.

Keywords: *Sperm, egg, embryo, donation, UK, guidelines*

Introduction

UK guidelines for the medical and laboratory screening of sperm donors have previously been drawn up by the British Andrology Society (BAS) (1999) with guidelines for the screening of egg and embryo donors being developed by the British Fertility Society (BFS) (Aird et al., 2000). Since the publication of each of these guidelines, the landscape of donor-assisted conception in the UK has changed markedly. Firstly, there has been a reduction in the use of donor sperm as a consequence of the increasing use of ICSI (Human Fertilisation and Embryology Authority, 2006) but also potentially through a general shortfall in the number of donors (Hamilton, 2008). There has also been increasing demand for donor eggs and the widespread development of egg sharing programmes (Simons & Ahuja, 2005). Secondly, following the removal of donor anonymity (HMSO, 2004) and the recommendations of the SEED Review (Human Fertilisation and Embryology Authority, 2005a), there has been an apparent change in the UK donor profile, particularly of sperm donors, who are now more likely to be older men (Human Fertilisation and Embryology Authority, 2005b). Thirdly, there have been major advances in the use and availability of molecular techniques to diagnose infectious diseases (Ratcliff et al., 2007) as well as increased knowledge and availability of genetic testing (McPherson, 2006). Finally, the incorporation into UK law of the EU Tissues and Cells Directive (European Union, 2006) encourages increased emphasis on the use of validated testing methods as well as introducing testing strategies not originally considered in the previous BAS and BFS Guidelines.

In response to these issues, a cross-organisational working party was formed to review the current BAS and BFS guidelines with the objective of producing a single, combined document to encompass the medical and laboratory screening of sperm, egg and

- Clinical assessment:
  - Age limit
  - Medical and surgical history
  - Reproductive and sexual history
  - Genetic History
  - Family Genetic History
  - TSE's
- Physical examination
- Screening tests
  - Karyotyping, Blood group and Rhesus
  - Autosomal recessive conditions
  - Bacterial infections
  - Blood borne viruses

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Clinical Assessment: Age

Male age effects include:

- New mutations of the paternal genome
  - Achondroplasia
  - Autism
  - Dyskinetic cerebral palsy
  - Multiple Sclerosis
  - Oral Clefts
  - Retinoblastoma
  - Schizophrenia
- Increased aneuploidy in the fetus
- Increased risk of miscarriage

De La Rochebrochard *et al.*, (2003) J. Androl., 24: 459-465

Clinical Assessment: History

Medical and Surgical

- Should include:
  - Face to face interview
  - Reference to medical records
  - Contact with family doctor
- To identify:
  - Risk factors for infection
  - High risk behaviours
  - Lifestyle issues (e.g. smoking)
  - Ability to donate

Reproductive and Sexual

- Should include:
  - Face to face interview
  - Reference to medical records
  - Contact with family doctor
- To identify
  - History of previous STI's (e.g. genital warts)
  - High risk sexual behaviour
  - Unprotected intercourse
  - Multiple partners

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Clinical Assessment: Genetic History

The donor should not have any significant heritable condition which include:

- Familial diseases with a major genetic component:
  e.g. cleft lip or palate, congenital hip dislocation, clubfoot, hypospadias
- Any significant Mendelian disorders:
  e.g. albinism, hemophilia, hemoglobin disorders, neurofibromatosis
- Familial diseases with a known or reliably indicated genetic component:
  e.g. debilitating asthma, juvenile diabetes mellitus, epileptic disorder
- A chromosomal arrangement that may result in unbalanced gametes.
- Be heterozygous for an autosomal recessive gene:
  e.g. Cystic fibrosis, α^0 or β-Thalassaemia, sickle cell, Tay-Sachs disease

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Clinical Assessment: Genetic History

The donor should ordinarily not:

- Be heterozygous for an autosomal recessive gene known to be prevalent in the donor's ethnic background:
  - Cystic fibrosis
  - Glucose-6-phosphate dehydrogenase deficiency
  - α^0 or β-Thalassaemia
  - Sickle cell disease
  - Tay-Sachs disease

  But, in exceptional circumstances (known donation) these may not necessarily be contraindications for donation provided that all parties are fully-informed and the view of an appropriately qualified clinical geneticist is obtained.

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Clinical Assessment: Family Genetic History

The donor's genetic parents, siblings and offspring should be free of:

- Familial diseases with a major genetic component:
  - e.g. cleft lip or palate, congenital hip dislocation, clubfoot, hypospadias
- Non-trivial disorders showing Mendelian inheritance:
  - e.g. autosomal dominant or X-linked disorders such as Huntington's disease
  - E.g. autosomal recessive disease with high frequency in the population (e.g. Cystic Fibrosis)
- A chromosomal abnormality (unless the donor has a normal karyotype)
- A history of mitochondiral disorders is only relevant to egg donation!

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Transmissible Spongiform Encephalopathies

- Previous UK guidance made no mention of TSE's such as Creutzfelt-Jacob disease (CJD).
- UK Advisory Committee on Dangerous Pathogens and the Spongiform Encephalopathy Advisory Committee (2003) makes no mention of semen, gametes or embryos.
- US Food and Drug Administration (2004) excludes any man from donating sperm if they:
  - spent more than 3 months in the UK during the period 1980-1996; or
  - more than 5 years (cumulatively) in any EU country since 1980.
- European Union Directive 2006/17/EC makes no specific mention of TSEs and reproductive tissues and cells.

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Transmissible Spongiform Encephalopathies

Given the indeterminate risk of transmitting TSEs through sperm, egg and embryo donation, it is suggested that donors should not be accepted who have:

- Been diagnosed with a prion-related disease or have first degree family members similarly diagnosed;
- Undergone invasive neurosurgial procedures;
- Received human pituitary-derived growth hormone, cornea, sclera or dura mater.

Since, there are no agreed means of identifying risk-factors of testing potential donors to exclude those at risk of developing variant CJD, these criteria seemed a realistic safeguard without having a significant bearing on donor recruitment.

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Physical Examination

Physical examination should be carried out by an appropriately trained clinician to assist in the detection of:

- Inherent congenital abnormalities (e.g. hypospadias)
- Evidence of high risk behaviour (e.g. intravenous drug abuse)
- Sexually transmitted infections (e.g. urethral discharge or genital warts)

Because there are currently no validated test methods to detect human papilloma virus or herpes simplex virus, the physical examination of males should include an examination to detect any genital warts or sores associated with these infections

Genital warts and herpes should again be excluded at end of donation by physical examination and medical history.

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Screening Tests

Karyotyping

All donors should be screened:

- Frequency of balanced translocations is <2 per 1,000. (Evans *et al.,* 1978).
- Cytogenetic abnormalities can be detected during screening of sperm donors. (Ravel *et al.,* 2006).

A donor found to have a significant chromosomal abnormality should be rejected.

Blood Group and Rhesus

- The use of donor gametes and embryos creates the potential for rhesus incompatibility.
- All donors should have their blood group and rhesus status recorded for matching purposes when required.

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Screening Tests: Autosomal Recessive Conditions

Potential donors should ordinarily screen negative for the following conditions according to their ethnic background:

- Cystic fibrosis (e.g. Caucasian)
- α^0 or β-Thalassaemia (e.g. Mediterranean, Middle East, Indian subcontinent)
- Sickle cell disease (e.g. African and Afro Caribbean)
- Tay-Sachs disease (e.g. Jews of Eastern European descent)

In exceptional circumstances (known donation) donors who screen positive may be accepted after consultation with an appropriately qualified clinical geneticist or consultant hematologist (as appropriate).

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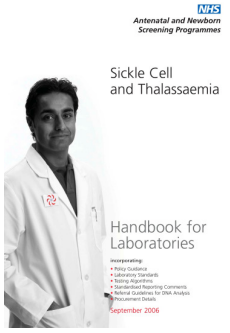
Screening Tests: Autosomal Recessive Conditions

http://www.ukgtn.nhs.uk



http://sct.screening.nhs.uk

Screening Tests: Bacterial Infections

- Prior to donation, donors should screen negative for:
  - Syphilis (*Treponema pallidum*)
  - Gonorrhoea (*Neisseria gonorrhoea*)
  - Chlamydia (*Chlamydia trachomatis*)
- Screening should be carried out in consultation with a GUM physician.
- Testing should be performed by an accredited laboratory.
- Tests should be repeated every 6 months throughout donation and,
  - Gonorrhoea and Chlamydia immediately after last donation
  - Syphilis one month later
- British Association for Sexual Health and HIV guidelines should be followed (http://www.bashh.org).

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Screening Tests: Bacterial Infections

(for asymptomatic heterosexual men)

Site or specimen	Gonorrhoea	Chlamydia	Syphilis
Urethra	culture	NAAT	n/a
Rectum	n/a	n/a	n/a
Oropharynx	n/a	n/a	n/a
Urine	NAAT (if no urethral specimen)	NAAT	n/a
Blood	n/a	n/a	EIA

http://www.bashh.org

Screening Tests: Cytomegalovirus

- CMV is a common infectious agent of urine, saliva & genital secretions.
- In healthy individuals is well tolerated & largely asymptomatic.
- Infection in pregnancy may lead to deafness & mental retardation in the neonate.
- Approx 500 babies per year born in UK following CMV infection.
- BAS (1999) suggested CMV positive donors should not be accepted.
- There is currently a shortfall in the number of UK sperm donors.
- Many use CMV positive donors to treat CMV positive women.

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Screening Tests: Cytomegalovirus

Prospective sperm donors should continue to be screened for the presence of cytomegalovirus IgG and IgM antibodies using the appropriate serological test, noting that:

- is always preferable to recruit CMV-negative donors (i.e., those who are IgG and IgM negative). If there are sufficient numbers of CMV-negative individuals willing to donate then CMV-positive donors should not be recruited.
- In situations where insufficient CMV-negative donors are available, CMV IgG positive (IgM negative) donors may be recruited but their use should be limited to CMV IgG positive recipients.
- individuals who are CMV positive with IgM antibodies, indicating an active infection, should defer donation.
- a donor who is initially seronegative and who seroconverts whilst donating must not be used for treatment purposes. The screening timetable and quarantine period (if applicable) must therefore take account of this.

The decision to treat a patient with a seropositive donor should be a matter of clinical judgement.

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Screening Tests: Other Blood Borne Viruses

- Prior to donation, donors should screen negative for:
  - Human Immunodeficiency Virus (HIV) 1 & 2
  - Human T cell lymphotropic viruses (HTLV) 1 & 2
  - Hepatitis B & C
- Screening should be carried out in consultation with a suitably experienced virologist and testing should be performed by an accredited laboratory.
- BAS (1999) guidelines and HFEA Code of Practice stated a requirement for a 6 month quarantine period.
- EU Directive suggests that if NAAT tests were performed that a repeat test was not required and by inference that quarantine was not necessary.

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Screening Tests: Other Blood Borne Viruses

- Sperm donors could be at higher risk than blood donors because fewer restrictions apply.
- HIV NAATs were unlicenced for diagnostic use, being quantitative assays designed to monitor disease progression.
- Specialised knowledge is required to interpret NAAT test result.
- There is no data to confirm whether a NAAT that was negative for HIV in plasma would necessarily be negative for HIV in semen, although natural history studies have suggested a good correlation.
- The precautionary principle should apply unless their was good reason to override it.

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Screening Tests: Other Blood Borne Viruses

Therefore:

- It is recommended that the detection of blood-borne viruses in sperm, egg and embryo donors should continue to be carried out by using serological testing to detect antibody or antigen as appropriate.
- Donated samples should continue to be quarantined for at least 180 days.

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2010 Review

- Key topic areas so far:
  - Age limits
  - CMV
  - NAAT testing for BBV's
  - Developments in genetic testing
- But suggestions are welcome.

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