NHS England

Clinical Commissioning Policy: Pre-implantation Genetic Diagnosis (PGD)

April 2014

Reference: E01/P/a

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Clinical Commissioning Policy: Pre-implantation Genetic Diagnosis (PGD)

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Prepared by the NHS England Clinical Reference Group for Medical Genetics

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The NHS Commissioning Board is now known as NHS England

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Policy Statement

NHS England will commission up to three cycles of Pre-implantation Genetic Diagnosis (PGD) (or a live birth whichever comes sooner) for couples who have, or are carriers of, a proven genetic disorder and who wish to avoid the birth of an affected child, in accordance with the criteria outlined in this document. This will depend on the number of previous cycles received.

In creating this policy NHS England has reviewed this clinical treatment and options for the genetic disorders for which this treatment would be considered. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

NHS England has a duty to have regard for the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012..NHS England is committed to ensuring equality of access and non-discrimination, irrespective of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex (gender) or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which they are responsible, including policy development, review and implementation.

Plain Language Summary

Pre-implantation genetic testing is a technique used to identify genetic defects in embryos created through *in vitro* fertilisation (IVF). Pre-implantation genetic diagnosis (PGD) can be offered when one or both genetic parents have, or are carriers of, a known genetic abnormality. Testing is performed on the embryos created through IVF to determine whether they are at risk of genetic disease.

This commissioning policy has been produced in order to provide and ensure equity, consistency and clarity in the commissioning of PGD services in England.

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Information on the outcome of treatments for these patients will be collected and considered to inform future reviews of this policy.

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1. Introduction

Pre-implantation genetic testing is a technique used in reproductive medicine to identify inherited genetic defects in embryos created through in vitro fertilisation (IVF). Pre-implantation genetic diagnosis (PGD) can be offered when one or both genetic parents have, or are carriers of, a known genetic abnormality; testing is performed on embryos created through IVF to determine whether they are at risk of genetic disease.

The use of PGD enables couples at risk of passing on an inherited disorder to decrease the risk of having an affected child significantly. Couples known to be at risk of transmitting genetic disorders to their children have various options to consider. These are:

- To remain childless
- To adopt a child
- To pursue gamete donation – (this process involves assisted conception techniques in which one or both parents would not be the biological parent of the child);
- To conceive naturally, and accept the risk of their child inheriting the genetic condition (this might include recurrent miscarriages of non-viable pregnancies as a result of the genetic condition)
- To conceive naturally and undergo conventional prenatal diagnosis (PND) following conception. The two commonly used post-conception diagnostic procedures are amniocentesis and chorionic villus sampling (CVS) at 16 and 11 weeks respectively. If the fetus is found to have the genetic condition of concern, the parents have to make difficult decisions about whether or not to opt for termination of the pregnancy (TOP). Termination of pregnancy is not an acceptable option for some couples.
- To undergo PGD.

PGD represents the only way for parents to have an unaffected child to whom they are both biological parents, without risking the need for termination of pregnancy. PGD is one of several reproductive options available for couples at risk of passing on a genetic condition, but the fact that the technology requires a highly skilled technical team and laboratory set up means it is significantly more expensive than the more common PND option. A very limited number of providers deliver the

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service within a strictly regulated environment. PGD forms a small part of all Assisted Reproduction Technologies; in the UK, PGD forms 0.70%[1] of all ART procedures.

The aim of a PGD service is to allow couples at significant risk of having a child with a genetic disorder, to have a child that is genetically related to them and at very low risk of being affected. Previous commissioning arrangements led to inconsistent policies on access to PGD across the country.

This commissioning policy has been produced in order to provide guidance and ensure equity, consistency and clarity in the commissioning of PGD services in England.

2. Definitions

Pre-implantation genetic diagnosis (**PGD)** is a technique that involves testing cell(s) from embryos created outside the body by IVF for a genetic disorder. Tests are carried out for the specific disorder that the embryos are known to be at significant risk of inheriting. Unaffected embryos are selected for transfer to the uterus in the hope that a normal birth will ensue.

PGD offers couples (who are usually fertile) the opportunity of having a healthy child of their own, whilst avoiding having to undergo a termination of an affected foetus detected through PND. For some people, termination of pregnancy is either unacceptable or less preferable.

Patients who meet the access criteria outlined in this policy are entitled to receive three NHS funded cycles of PGD.

Whilst the pre-implantation testing process may be used for other indications, its primary use under consideration in this policy is to significantly decrease the risk of having a child affected by the serious genetic condition the parents either have, or are at risk of passing on to a future child.

Completed PGD cycle with IVF/Intra-Cytoplasmic Sperm Injection (ICSI) - ovarian stimulation, egg recovery, fertilisation, embryo biopsy, genetic testing and single fresh embryo transfer. This includes the provision for future transfers of single frozen embryos where the initial procedure does not result in a viable embryo and the subsequent storage of embryos.

Abandoned PGD cycle with IVF/ICSI - Prior to egg retrieval, usually due to lack of response (where less than 3 mature follicles are present) or excessive response to gonadotrophins.

Unsuccessful cycle of PGD - includes failure of fertilisation; failure of cleavage of

[1] HFEA 2012 Fertility treatment in 2011. Trends and Figures

embryos, failure to produce any unaffected embryos or failure to conceive following embryo replacement.

An abandoned cycle will count towards the three commissioned cycles.

3. Aim and objectives

Aim

This policy document aims to specify the conditions under which PGD will be routinely commissioned by NHS England as a means of making it possible for couples at significant risk of having a child with a genetic disorder to have a child that is genetically related to them and at very low risk of being affected.

Objectives

- To reduce the variation in access to PGD
- To ensure that PGD is commissioned for those conditions for which there is acceptable evidence of clinical benefit and cost-effectiveness
- To reduce unacceptable variation in clinical practice in the conditions referred for PGD
- To promote the cost-effective use of healthcare resources

4. Criteria for commissioning

Mandatory Criteria for the Couple

- The couple must be at risk of having a child with a serious genetic condition.
- The couple must have been referred to the PGD provider by a NHS Clinical Genetics Service
- The risk of conceiving a pregnancy affected by a serious genetic condition must be 10% or more
- The couple must have received genetic counselling from a clinical geneticist or a registered genetic counsellor.

- The female partner must be under 40 years of age at the time of treatment
- The female partner must have a BMI of more than 19 and less than 30.
- Both partners must be non smokers
- There must be no living unaffected child from the current relationship.
- The HFEA must have licensed the indication for PGD.
- The test must be included in the list of UK Genetic Testing Network (UKGTN) approved tests, or be suitable for inclusion.
- The couple must not be seeking PGD primarily because they are infertile or for any other reason be unable to have children on their own.

Couples meeting the above criteria will be eligible to receive up to three (3) cycles of IVF/ICSI in conjunction with PGD, unless fertility staff feel after one or two cycles of treatment that a further cycle is not indicated for medical reasons (e.g. very poor response to ovarian hyperstimulation). Couples who have previously self funded PGD will be entitled to NHS treatment to reach a total of three (3) cycles. Where couples have previously self funded an IVF cycle in conjunction with PGD and frozen embryos exist, then they must utilise the previously frozen embryos first, before undergoing ovarian stimulation, egg retrieval and fertilisation again if the frozen embryo does not lead to a pregnancy.

NHS England will not pay for the replacement of frozen embryos created from a self funded PGD cycle.

NHS England will not commission more than three (fresh) cycles even if the patient has never had any embryos suitable for replacement or for freezing.

An abandoned cycle will count towards the three cycles.

Patients who have previously had IVF treatment without PGD will still be entitled to NHS commissioned PGD cycles if eligible.

All couples have to meet the criteria above.

Policy Exclusions

The following uses of the PGD technology are excluded from this policy.

- Non medical gender selection e.g. for the purpose of family balancing. This is illegal in the United Kingdom (UK).[1]
- Human Leucocyte Antigen (HLA) typing to produce a donor sibling for a child requiring an allogeneic stem cell transplant[2]. This will be governed by the NHS England research policy[3]. (Considered experimental has been deleted)

- Using PGD to address infertility or to prevent miscarriages of unknown aetiology.[4]
- Pre-implantation Genetic Screening (PGS). Here, genetic testing is used to screen embryos for various abnormalities in chromosomes, typically the number of chromosomes (chromosomal aneuploidies).[5]

PGD versus PGS

PGD should NOT be confused with Pre-implantation Genetic Screening (PGS) mentioned above. The widespread use of PGS without evidence of its ability to improve delivery rates has been reported as a problem in the field of IVF.[6]

In PGS, no specific genetic diagnosis is tested for. The parents are presumed to be chromosomally normal and the test is used to look for abnormalities in chromosome numbers. The main indications suggested for PGS are advanced maternal age (usually defined as maternal age over 37 or 38 years), repeated implantation failure (usually defined as three or more failed embryo transfer procedures involving high-quality embryos), repeated miscarriage (RM) in patients with normal karyotypes (usually at least three previous miscarriages) and severe male factor infertility.[7]

Since 2004[8] there have been 11 randomised controlled trials (RCTs), mainly for advanced maternal age, which have shown no benefit of performing PGS. In a systematic review and meta-analysis of the RCTs for PGS, the authors have reported there is no evidence of a beneficial effect of PGS as currently applied on the live birth rate after IVF. On the contrary, for women of advanced maternal age PGS significantly lowers the live birth rate from 26% after IVF without PGS, to between 13% and 23% using PGS.[9].

In the absence of evidence of its clinical and cost effectiveness, there is no intention to support the introduction of PGS into NHS clinical practice.

5. Patient pathway

Patients requiring PGD should be referred first to their Regional Clinical Genetics Service. Patients will be referred from a Clinical Genetics Service to a licensed PGD provider, where an initial outpatient appointment (a screening appointment) will be arranged to discuss whether a PGD might be possible, an explanation of the process and also to assess the couple's suitability for treatment.

Both the clinical genetics service and the PGD provider will be required to ensure the patient meets the agreed criteria for accessing the PGD service. Once it has been agreed that the couple meet the criteria, and the couple after a discussion of their reproductive options choose PGD as an option to pursue, up to three cycles of

treatment will be offered with a full review after each cycle.

If it is decided after an unsuccessful cycle, that the treatment is unlikely to benefit the couple, further treatment should not be offered.

6. Governance arrangements

NHS England expects that robust mechanisms will be put in place to support clinical governance to comply with the HFEA Code of Practice.

1. The centre must have a valid HFEA licence which includes the provision of PGD, and abide by the HFEA regulations for PGD testing. The HFEA provides details of licensed PGD clinics online.[10] NHS England will monitor the inspection reports provided by the HFEA and will discuss the findings with the providers where appropriate.
2. The laboratory where the genetic test is being carried out must have current Clinical Pathology Accreditation (CPA). See appendix 1 for the list of licensed PGD providers that have current CPA accreditation.
3. There must be an existing licence to carry out that test from the HFEA or the PGD clinic must apply for and receive a licence prior to treatment if that condition is not currently licensed.

In addition to the approval of the HFEA, clinics must make their own judgement about whether PGD is appropriate treatment for a particular couple, using guidance contained in the HFEA's Code of Practice.

For NHS England to purchase PGD services from a Provider, the PGD Provider would have to be licensed by the HFEA and utilise a laboratory that has demonstrated compliance with ISO:15189 standards as assessed and accredited by CPA/UKAS.

Not all the licensed or CPA accredited PGD Providers in appendix 1 currently have contracts with NHS England. The NHS England area teams should be contacted to find out which ones they have contracts with.

7. Epidemiology and needs assessment

Epidemiology

An epidemiological description of each of the more than 200 conditions currently licensed by the HFEA for PGD use is not practical.

Referrals for PGD

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At present information on patients who have been referred for PGD is not recorded. However information from Guy's Hospital in London indicates about a quarter of the patients (25%) referred for PGD proceed to treatment after they have been provided with information about the process, chance of success, outcomes and alternatives.[11] The Centre for Reproductive Health in London reports a PGD take up rate of 50%.[12]

Utilisation of PGD – (NHS and Privately funded PGD cycles)

Data from the HFEA on the number of PGD cycles that took place shows a steady increase in the utilisation of the PGD technology as evidenced by the number of PGD cycles taking place. There is considerable year on year fluctuation in the level of increase as shown in table 1 below. Between 2004 and 2011 there has been a 358% increase in the number of PGD cycles carried out. Assuming that the international flow of patients is minimal and all the PGD cycles were for UK residents, this puts the utilisation rate at 7.7 per million population for the UK in 2011.

Table 1: No of PGD Cycles (Fresh and Frozen) in UK from 2004 – 2011

Calendar Year	No of PGD cycles carried out	%age increase in cycles from previous year	PGD cycles per million UK population
2004	95		1.6
2005	134	41%	2.2
2006	184	37%	3.0
2007	198	8%	3.2
2008	214	8%	3.5
2009	288	35%	4.7
2010	373	30%	6.0
2011	435	14%	7.7
Source of information: HFEA annual reports. Population Information from ONS			

Overall, there is evidence that indicates historic demand for PGD was highest in south east England with the London population having had a significantly higher demand than the rest of the country. The rate for London in 2011/12 was 10.1 per million population.

Potential Need

Using the incidence and prevalence of the top 20 indications for which PGD had been requested in south east England (which together had accounted for 95% of the total requests), an estimated 5,000 couples could be eligible for PGD every year[13]. However, these couples, who could be regarded as having a need, may for various reasons not necessarily choose to proceed with PGD treatment. Evidence from the literature and practice indicates that whilst natural conception and PND was the most common reproductive choice for many of these couples in the past, PGD is increasingly being seen as a first choice. The profile of couples who choose PGD generally shows couples from these four main categories:

- Couples at high risk of having a child affected by a genetically-caused disease or malformation;
- Couples at high genetic risk who have undergone "conventional" prenatal diagnosis and who terminated recurrent pregnancies after an affected foetus was found;
- Couples at risk of giving birth to a child affected by a genetically-caused disease or malformation and who object to termination of pregnancy.
- Couples who have an affected child.

Published literature indicates that when PGD costs are met by public funding or mandated insurance coverage, demand for PGD steadily increases. Belgium introduced full reimbursement of all ART including PGD in 2003 and currently has PGD utilisation rates of about 28 per million population[2]. France[14] also has a fully public funded PGD programme and reported a 15% increase in utilisation rates between 2007 and 2008. In the USA, states with mandated insurance cover have PGD utilisation rates twice that of states without mandated insurance cover. It is therefore anticipated that PGD utilisation rates for England would have increased following implementation of a national policy in April 2013. An audit is planned in April 2014 after the first full year of implementing this policy.

8. Evidence base

[2] Reported rate for Belgium is 33 per million population. However, their local report indicates 15% of their PGD activity is for foreigners. Thus the utilisation rate for local population is calculated as 28 per million population.

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The effectiveness of PGD in reducing the reproductive risk by successfully identifying and only transferring healthy embryos

The aim of PGD technology is to ensure the embryo transferred is free from the genetic condition for which the test is applied. Information about the effectiveness of PGD in reducing the risk of passing on a genetic disease compared with a couple getting pregnant spontaneously is based on observational studies, with the largest case series being that from the European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium.[15, 16]. In its most recent report, information is provided on over 10,000 PGD cycles that took place between January 1997 and December 2008.[17]

The two main techniques used in the PGD process to identify embryos at risk of the genetic disease being tested for are Polymerase Chain Reaction (PCR) and Fluorescence in situ hybridisation (FISH). If these tests wrongly identify an affected embryo as normal and the embryo results in an affected pregnancy, the false negative test is generally termed a misdiagnosis.[18].

The cumulative number following PGD performed between 1997 and 2008 has been reported in the ESHRE case series as about 0.2%. i.e. about 2 in a 1,000 as shown in table 2 below.

Table 2:Misdiagnosis reported in the ESHRE1997 - 2008 data

Indication	**No of PGD cycles that proceeded to embryo transfer**	**No of misdiagnosis reported to ESHRE consortium**	**% misdiagnosis**
Chromosomal abnormalities	2731	3	0.11%
Single Gene Disorders	3727	10	0.27%
Sexing only for X-linked disease	880	4	0.45%
Overall PGD	7338	17	0.23%

Twelve of these false negatives were after PCR testing and the remaining three (3) after FISH testing. The majority of the misdiagnoses for PCR testing (9/12)

occurred prior to 2001 and were mainly in single gene disorders. PCR assays have since become increasingly technically advanced. In the last three years for which data is available i.e. 2006 – 2008, no PCR misdiagnoses have been reported in the 3,424 PGD cycles for single gene disorders carried out in this time.

The 4 misdiagnoses reported for X-linked disorders happened a time when PCR was used to determine the diagnosis. FISH technology has now superseded the older PCR technology for sexing since 2005. For the most recent data available, ESHRE series X[19] and XI[20], again no misdiagnoses are reported.

In summary, the evidence indicates the incidence of misdiagnosis after PGD is very low.

The effectiveness of PGD in producing a live birth

The most recent ESHRE data reports[21] that out of 2,235 PGD cycles that went on to oocyte retrieval, there were 413 deliveries. The live birth rate of 18.4% for the most recent data year reflects the findings in a large study of 2753 unselected consecutive cycles carried out 1498 couples in Belgium[22] and reported a live birth rate of 17% per cycle.

The 2009 UK data from the HFEA reports a higher live birth rate after PGD of 34.7%. However as evidenced in the 2008 data from the HFEA, there are significant differences in the live birth outcome depending on the age of the patient as shown in table 3.

Table 3: Live birth rate for pre-implantation genetic diagnosis vrs IVF cycles, United Kingdom, 2010

Age of woman (years)	**PGD Live birth rate (%)***	**2010 IVF live birth rate (%)**
Less than 35	30.4	32.2
35 to 37	32.1	27.7
38 to 39	-	20.8
40 to 42	-	13.6
43 to 44	-	5.0
Over 44	-	1.9
Total	31.6	25.6

Some individual PGD centres report higher live birth rates for PGD as shown in table 4 below. The rates shown do not take into consideration the number of twin pregnancies (which is not regarded as a good outcome following IVF or PGD because of the increased risk of antenatal and neonatal complications).

Table 4: Live birth rates for PGD cycles in year ending Q4 2011- UK [3]

PGD Centre	Fresh cycles	Live Birth	LB %
Assisted Reproduction & Gynaecology Centre (ARGC), London	8	4	50%
Birmingham Women's Hospital	4	2	50%
CARE Nottingham	32	11	34%
Centre for Reproductive & Genetic Health (UCH), London	41	8	20%
Edinburgh ACU	18	1	16%
Glasgow Royal Infirmary	20	6	30%
Guy's Hospital, London	181	61	34%
IVF Hammersmith, London	18	2	11%
Newcastle Fertility Centre at Life	3	1	33%
Oxford Fertility Unit	18	3	17%

[3] NHS England does not currently commission PGD from all the Providers listed in Table 4 as not all of them are currently utilising laboratories with CPA accreditation. The NHS England offices in the relevant region should be contacted to find out which of the PGD Providers they have contracts with.

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The Bridge Centre, London	20	4	20%
Overall for PGD in UK	**364**	**104**	**29%**

In summary, the live birth rate after PGD is similar to that after IVF. Some individual PGD providers report higher live birth rates.

The cost-effectiveness of the PGD technology

A single study[23] in the United States has assessed whether the use of PGD for carrier couples of cystic fibrosis to prevent the birth of a child with cystic fibrosis represents a cost saving to society.

A Markov model was applied to couples in which both partners were cystic fibrosis carriers. The authors calculated the net benefit of giving birth to a child as the present value of lifetime earnings minus lifetime medical costs. The annual average medical costs for cystic fibrosis reported in this USA study was $20,331 (£12,918[4]).

The authors report the net benefit of PGD over normal conception for PGD in a woman age less than 35 years is $182,000 (£115,631). For women aged 35 – 40 years, the net benefit was $114,000 (£72,431.36). There was no benefit for women over 40. The net benefit varied with age, the maximum number of PGD cycles, whether or not couples were "allowed" to conceive naturally whilst undergoing PGD and if the outcome was a twin delivery.

The authors conclude PGD provides a cost saving to society when used by carrier couples of cystic fibrosis and recommend PGD should be offered for the prevention of an affected child.

The model is only relevant to PGD for cystic fibrosis. The main limitation in generalising this study to the setting in England is that the costs reported in the study and the lifetime earnings in England would differ significantly. Also nearly all the higher benefit from PGD reported is shown in the sensitivity analysis to be based on the higher probability of healthy twins with consequent high lifetime earnings. Valuing twins the same as singletons reduced the net benefit of PGD in women under 35 years to $1,800 (£1,143).

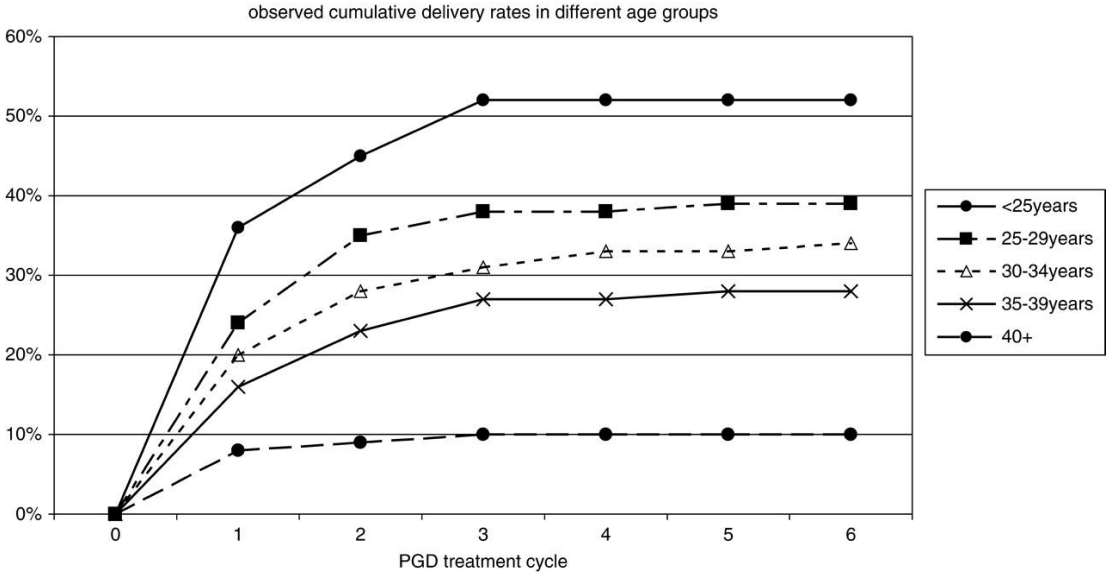
In summary, there is a significant gap in the literature on the cost effectiveness of PGD for even the most common indications.

Limits to the PGD treatment cycles

[4] Currency convertor - $1=£0.635335
http://www.xe.com/ucc/convert/?Amount=182000&From=USD&To=GBP

In a prospective observational study of PGD in 1,498 couples, Verpoest et al[24] report the observed cumulative delivery rates depended on the age of the patient and increased consistently for the first three cycles then levelled off after the third cycle as shown in figure 4.1.

Figure 1: Observed cumulative delivery rates post PGD by age groups



In summary, there is some evidence that delivery rates consistently improve with the first three cycles of PGD.

BMI >30

Being overweight or obese is associated with decreased pregnancy rates, increased requirement for gonadotrophins and a higher miscarriage rate. An elevated BMI is also associated with increased technical difficulty during egg collection and an increased obstetric risk. Obesity decreases successful pregnancy rates in both natural and assisted conception cycles, with fertility being partially restored if weight loss can be achieved.[25, 26, 27]

Smoking

Smoking has in various studies been reported to be associated with lower fertility rates, result in adverse obstetrical outcomes including spontaneous abortion[28], placenta praevia[29, 30], placental abruption[31], preterm birth[32], stillbirth[33], fetal growth restriction[34], low birth weight[35, 36], sudden infant death syndrome[37] and a higher

risk of IVF failures.[38, 39]

Age: The female partner should be under 40 years of age at the time of treatment

In addition to the natural decline in fertility with age[40], increasing maternal age has been shown to be one of the major factors that affect the outcome of IVF[41] and PGD[42] cycles. Studies reporting the outcome of IVF show the cumulative life birth rate significantly decreases with increasing maternal age. Stern et al.[43] have reported the cumulative live-birth rate after three cycles was 60.1% for ages<35 years and declined steadily to 8.5% for ages>or=43 years. Similar findings have been reported more recently[44] in a large review of assisted reproduction cycles. By the third cycle, the conservative and optimal estimates of live-birth rates with autologous oocytes had declined from 63.3% and 74.6%, respectively, for women younger than 31 years of age to 18.6% and 27.8% for those 41 or 42 years of age and to 6.6% and 11.3% for those 43 years of age or older.

In summary, the evidence indicates a BMI >30, Smoking and age> 39 decreases the chances of a successful ART cycle.

9. Rationale behind the policy statement

Scientific evidence shows that PGD is technically feasible for an increasing number of genetic conditions and reduces the risk of having a child affected by a specific known genetic disorder.

10. Mechanism for funding

NHS England contracts with suitably accredited providers via the relevant area team. Area teams will not pay for PGD services from providers they do not have contracts with.

11. Audit requirements

There is currently no central database to which PGD service providers report on

NHS activity. As part of this commissioning policy, PGD Service providers will provide two sets of auditable data to NHS commissioners for all the NHS PGD cycles they have provided:

Data set 1: Monthly minimum data set on the PGD cycles for that month.

Data set 2: An annual report and dataset on all patients who were referred to the PGD provider – whether they decided against PGD or went on to have treatment. This annual report should provide information on the desired primary outcome of PGD which is the birth of an unaffected baby for the cycles of the previous year. In addition to the live birth rates, reports should also cover secondary indicators such as:

- Multiple Births
- Prematurity and low birth weight
- Method of Delivery
- Misdiagnosis
- Other complications
- Acceptance of the procedures

The data fields to be reported on will be outlined in the information schedule of the Service Specification.

The data and reports will not only enable monitoring of this PGD policy but will also enable outcome information to be collected and collated to inform future PGD policy needs.

All PGD Providers with a commissioned service from NHS England will have to maintain a suitable audit trail proving compliance with all the mandatory criteria including the patients full review after completion of each cycle.

12. Documents which have informed this policy

The original policy document (2013 policy) was informed by:

- The Yorkshire and Humber PGD policy[49]
- The London SCG PGD Clinical Advisory Group PGD Access Criteria[50]
- Pre-implantation Genetic Diagnosis – A comprehensive Healthcare Needs

Assessment for South East England[51]

- The Department of Health PGD – Guiding Principles for Commissioners of NHS Services September 2002[52]

13. Links to other policies

Whilst the PGD technology requires IVF and ICSI services, the policy is NOT linked to the IVF policies of the Clinical Commissioning Groups. As previously stated, in the context of this policy, IVF and ICSI are used as part of the PGD process. They are not being used to treat existing infertility.

14. Date of next review

September 2014

15. Glossary of terms

Term	Meaning
Amniocentesis	A test that can be carried out during pregnancy to determine whether the foetus has a specific problem. It is conducted by taking and analysing a sample of amniotic fluid.
Blastocytes	Any undifferentiated embryonic cell (Lawrence, 2000: 75)
Chorionic villus sampling (CVS)	This is a test for serious foetal problems. It is available to pregnant women, particularly those with a family history of inherited disorders, or who are over 35. It's an alternative to amniocentesis (where a sample of the mother's amniotic fluid is taken for testing). CVS has the advantage that it can be done earlier than amniocentesis, at about 10 weeks after fertilisation. (NHS Direct b, 2009).
Chromosomal Abnormality	An abnormality with one or more chromosomes, or in the number of chromosomes.
Chromosome	A structure within cells that contains genetic information.
Cleavage stage embryos	This is when the fertilised cell has started to divide.
Congenital malformations	A malformation of the developing foetus. In this case it refers to those caused by genetic/chromosomal abnormalities.
Embryo	A fertilised egg.
Foetus	The unborn child after the end of the eighth week of pregnancy to the moment of birth.(NSC, 2009)
Gonadotrophins	Hormones that stimulate the function of the organs in which reproductive cells are produced (Lawrence, 2000; 254)
Human Fertlisation and Embryology Authority (HFEA).	UK's independent regulator overseeing the use of gametes and embryos in fertility treatment and research. (HFEA, c, 2009)

Term	Meaning
In Vitro Fertilisation (IVF)	This is a process whereby eggs are removed from the ovaries and fertilised with sperm in the laboratory. It is utilised in the PGD process in order for the fertilised eggs (embryo's) to be tested for a specific genetic abnormality, with an unaffected embryo subsequently being placed in the woman's womb. (HFEA, 2009).
Intra-cytoplasmic Sperm Injection	This is a technique that can be used in IVF whereby a sperm is injected into the egg to assist in fertilisation. (NHS Direct, 2009).
Oocyte	A not yet fully developed egg cell.
Ovarian Stimulation	A technique used in IVF to assist in egg retrieval.
Pre natal diagnosis	Determining if a foetus has a specific problem, by performing a clinical test.
Pronucleate embryo	Embryo whereby two nuclei (the part of the cell that contains the DNA) from the sperm and the egg are present. (These subsequently fuse together).
The UK Genetic Testing Network (UKGTN)	This advises the NHS on genetic testing across the whole of the UK. It aims to ensure the provision of high quality equitable genetic testing services. (UKGTN A, 2009)

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Appendix 1: HFEA Licensed PGD Providers and the CPA accredited laboratories used for PGD

Region / Clinic Name	CPA Accredited laboratory used for PGD
PGD Providers in the NHS England (Northern Region)	
Care Manchester	Genesis Genetics Ltd, Nottingham
Care Sheffield	Genesis Genetics Ltd, Nottingham
PGD Providers in NHS England (Midlands and East Region)	
Care Northampton	Genesis Genetics Ltd, Nottingham
Care Nottingham	Genesis Genetics Ltd, Nottingham
Birmingham Women's Fertility Centre	Reprogenetics Limited.
PGD Providers in NHS England (London Region)	
Guy's Hospital	Department of Cytogenetics, GSTS-Pathology & DNA laboratory/Biochemical Genetics, GSTS -Pathology
Centre for Reproductive and Genetic Health (University College Hospital)	UCL Centre for PGD (EGA Institute of Women's Health UCL)
PGD Provider in NHS England (Southern Region)	
Oxford Fertility Clinic	Reprogenetics Limited.

The NHS Commissioning Board is now known as NHS England

NHS England E01/P/a
Gateway Reference 01372

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Change Notice for Published Specifications and Products developed by Clinical Reference Groups (CRG)

Amendment **to the Published Products**

Product Name	Clinical Commissioning Policy: Pre- Implantation Genetic Diagnosis (PGD)
Ref No	**E01/P/a**
CRG Lead	Frances Flinter

Description of changes required

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
	The previous policy statement was not clear about what the funded NHS cycles were for. This revised policy has stated explicitly that the NHS will fund three fresh cycles of PGD.	Section 2	Further clarification	CRG	January 2014
	A definition of an unsuccessful cycle has been included.	Section 2	Further clarification	CRG	January 2014
	Clarification to the existing criteria via questions raised through	Section 4	Further clarification	CRG	January 2014

	individual funding requests have been provided.				
	A paragraph has been included to be explicit about the fact that not all HFEA licensed PGD Providers are commissioned to provide services to NHS England.	Section 6	Further clarification	CRG	January 2014
	All tables have been updated to reflect the most recent available data on use in England. Data in the existing policy had mainly focussed on the South East England area	Section 7	Further clarification	CRG	January 2014
	All tables have been updated to reflect the most recent available data on outcomes in England	Section 8	Further clarification	CRG	January 2014
	The existing policy had a section on resource implications of the policy. This has been taken out	Section 8	Further clarification	CRG	January 2014

	to ensure consistency of formats of all the policies.				
	The rationale for the policy has been reworded to restate the reason for the policy – to decrease the risk of having a child affected by a specific known genetic disorder.	Section 9	Further clarification	CRG	January 2014
	Clarification has been provided on the funding mechanism – It will be through the NHS England Area Team the Provider is based in.	Section 10	Further clarification	CRG	January 2014
	Appendix one in the existing policy has been removed. The information contained was relevant only to South East England.		Further clarification	CRG	January 2014

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