

Pre Implantation Genetic Diagnosis (PGD) Service

Glasgow Royal Infirmary

Annual Report

April 2009 - March 2010

Service Providers:

Assisted Conception Service, Royal Infirmary, Glasgow, G4 0SF

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Acknowledgements:

This report was written by Sister Walton, PGD coordinator, Assisted Conception Service (ACS), Royal Infirmary, Glasgow. All the information contained in this report was collated and analysed throughout the year by all members of the PGD service team.

1 Introduction

In vitro fertilization (IVF) offers a unique access to the oocyte and preimplantation embryo. The term “preimplantation genetic testing” describes procedures involving the removal of one or more nuclei from oocytes (polar bodies) or embryos (blastomeres or trophoctoderm cells) to test for mutations in gene sequence or chromosomal rearrangements before transferring the embryo to the patient.

“Preimplantation genetic diagnosis” (PGD) is applicable when one or both genetic parents carry a gene mutation or a balanced chromosomal rearrangement and testing is performed to determine whether that specific mutation or an unbalanced chromosomal complement has been transmitted to the oocyte or embryo.

Under the auspices of the National Services Division (NSD) of NHS Scotland, the Assisted Conception Service at Glasgow Royal Infirmary in partnership with the Duncan Guthrie Institute of Medical Genetics at Yorkhill Hospital, Glasgow provides the national service for Pre Implantation Genetic Diagnosis within Scotland.

The PGD service was established with guidance from the Department of Health, ‘Preimplantation Genetic Diagnosis (PGD) – Guiding Principles for Commissioners of NHS services.’ September 2002

2 PGD Staff Complement

Posts funded by NSD:

- PGD coordinator
- Embryologists
- Cytogeneticist

Other members of the PGD team (posts not funded by NSD):

- Medical Consultants
- Clinical Genetics Consultant
- Consultant Clinical Scientist
- Lab Manager
- Cytogeneticists
- Genetic Technologist

3 Statement of Activity

The table below shows all referrals to the PGD service from all Scottish Health Boards for the period April 2009 to March 2010. Referrals are made either via the Clinical Genetics Service or directly to the Consultants at ACS.

Health Board Area	X LINKED	TRANSLOCATIONS	OTHER e.g. SG	DNA	TOTAL
Highlands & Islands	0	1	1	0	2
Tayside	1	2	0	1	4
Lothian	0	4	0	0	4
Glasgow + Argyll & Clyde	3	9	7	2	21
Lanarkshire	1	3	1	0	5
Forth Valley	0	0	2	0	2
Ayrshire & Arran	0	1	0	0	1
Fife	0	1	0	0	1
Grampian	0	1	0	0	1
Borders	0	0	0	0	0
Orkney	0	0	0	0	0
Western Isles	0	0	0	0	0
Shetland	0	0	0	0	0
Dumfries & Galloway	0	2	0	0	2
Patients Referred	5	24	11	3	43

All of the above health boards are covered by the four Scottish Clinical Genetics Services, based in Aberdeen, Dundee, Edinburgh and Glasgow. The staff of the clinical genetics services meets twice per year and are updated regarding any developments within the PGD Service by Dr Whiteford.

4 Inclusion/exclusion criteria for the PGD service

Inclusion criteria

- The female patient should be less than 41 years of age at the time of referral
- The anti mullerian hormone level (AMH) of the female patient must be 5 pmol/L or greater
- Female body mass index (BMI) to be 35 or less.
- A stable relationship is mandatory (usually married or co habiting for > 2years)
- Both partners must have negative results when screened for the presence of HIV Hep B and Hep C in blood.
- Male sperm sample should be suitable for in vitro fertilisation (IVF) or Intra Cytoplasmic Injection (ICSI); if surgical sperm retrieval is required, the sperm needs to be placed in frozen storage before work up of probes begins.

Exclusion criteria

- Female patient 42 years of age or more at the time of referral
- The anti mullerian hormone (AMH) level of the female patient is less than 5 pmol/L
- Female body mass index (BMI) is 35 or greater.
- In a relationship for <2 years
- Either couple have positive results for HIV Hep B and Hep C status.
- Male partner azoospermia.

Other Options

- If a patient does not meet the entrance criteria for the PGD service, other options may be discussed. e.g. adoption, egg donation.
- Couple suitable for single gene – If they are eligible to be referred to Guy's & St Thomas or Edinburgh then all referrals and applications for assistance with travelling and accommodation expenses are made by Dr Whiteford.

Changes to criteria

There is a multidisciplinary advisory panel being established within Scotland, which will include members with expertise in the field of ethics and in the future this group will assess all patients' suitability for PGD treatment.

5 Treatment that ACS is currently licensed to provide by the Human Fertilisation and Embryology Authority (HFEA)

X- linked disorders:

Alports Syndrome
Adrenoleukodystrophy
Androgen Insensitivity Syndrome
Barths Syndrome
Brueton Agammaglobulinemia Tyrosine Kinase
Charot Marie Tooth Disorder – X linked
Duchenne Muscular Dystrophy
Fabry Disease
Fragile X – (PGH at other centres now being advised)
Haemophilia IX
Haemophilia VIII
Hunter Syndrome
X linked Hydrocephalus
Incontinentia Pigmenti
Lesch Nyhan Syndrome
X linked Lymphoproliferative Disorder
X linked Macular Dystrophy
Ornithine Transcarbamylase Deficiency

Chromosomal conditions:

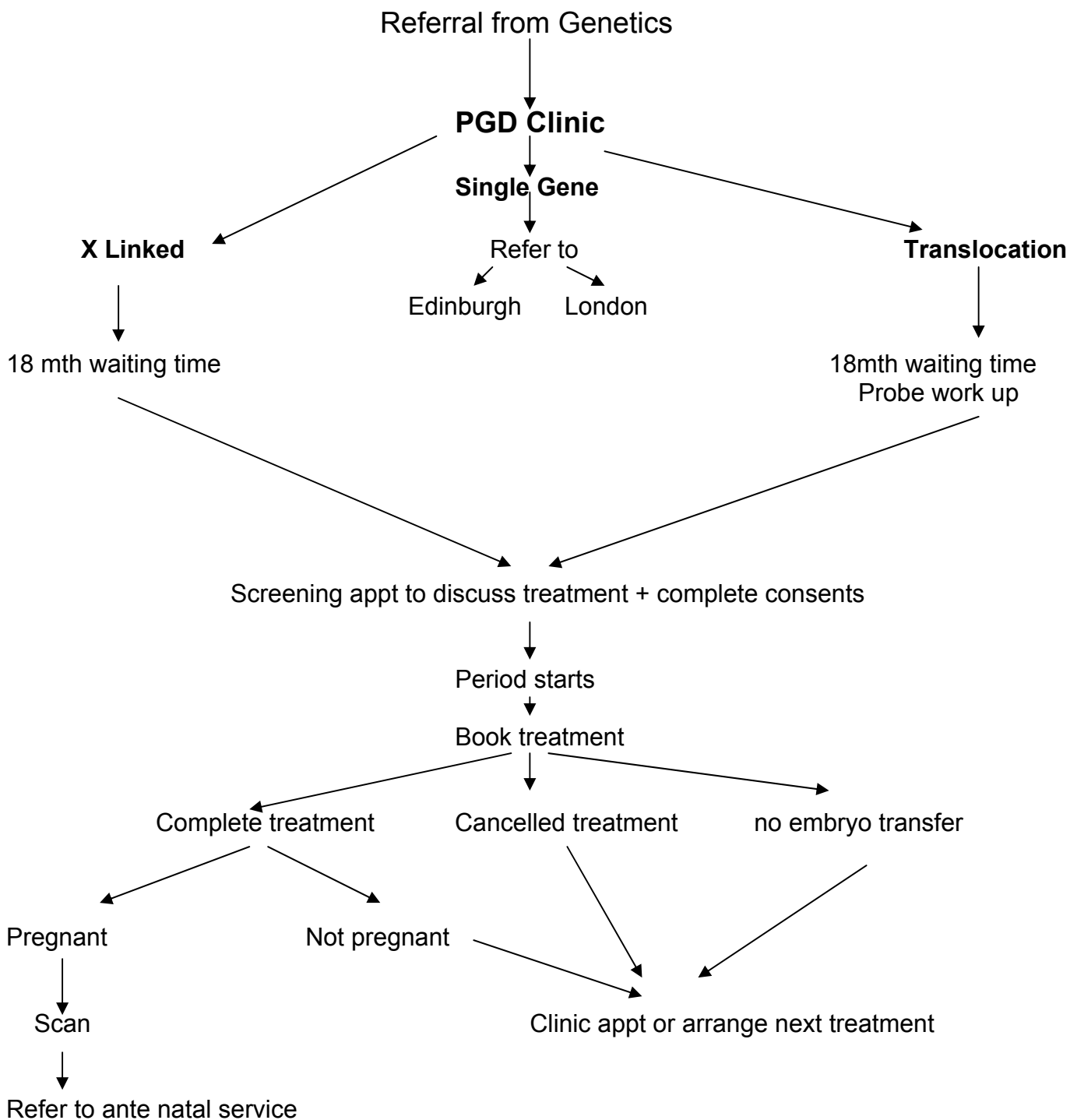
Chromosomal Rearrangements
Trisomy 21

Changes to applying for a License

At the end of 2009 the Human Fertilisation Embryology Authority changed the procedure by which centres should apply for additional PGD licenses, such that the PGD service does not need to send a new application for each specific condition, but instead a check is made to see if the specific condition is already licensed by the HFEA. All relevant information is available on-line at www.hfea.gov.uk/pgd-screening.html

When treating a new condition for the first time, the consultant will inform HFEA.

6 Referral pathway summary



7 Treatment Activity

Details of the 24 treatment cycles arranged (15 for translocations, 5 for X-linked and 4 for frozen embryo transfers) and biopsy information for them are as follows:

Treatment for Translocations

Stage of treatment	Numbers
Treatment cycles booked	15
Cancelled by patient before stimulation	2
Treatment cycles started	13
Cancelled before retrieval	1
Treatment completed with embryo transfer	6
Embryos frozen; not biopsied	1
No embryo transfer after biopsy	5
No embryos for biopsy	0
Clinical Pregnancies achieved	4

Treatment for X Linked

Stage of treatment	Numbers
Treatment cycles booked	5
Treatment cycles started	5
Treatment completed with embryo transfer	1
Embryos frozen; not biopsied	2
No embryo transfer after biopsy	2
No embryos for biopsy	0
Pregnancies achieved	0

Treatment for Frozen Embryo Transfer

Stage of treatment	Numbers
Treatment cycles booked	4
Treatment cycles started	4
Treatment completed with embryo transfer	3
No embryo transfer after biopsy	1
Pregnancies achieved	0

Biopsy Information

Quoted figures are for the period April 09 to March 10 on all the oocytes (eggs) collected and embryos (fertilized eggs) suitable for biopsy.

Number of oocytes collected	171
Number of embryos biopsied	103
Number of embryos suitable for transfer	32
Number of embryos transferred	20

8 Pregnancy Rate

From treatment cycles started

Translocation treatments started	13
X-linked treatments started	5
Total treatments started	18
Successful pregnancies	4
Clinical Pregnancy rate	22.2%

From treatment cycles that included embryo transfer

Translocation completed with embryo transfer	6
X-linked treatments completed with embryo transfer	1
Frozen embryo treatment completed with embryo transfer	3
Total treatments completed with embryo transfer	10
Successful pregnancies	4
Clinical Pregnancy rate	40%

Successful pregnancy outcomes:

July 2009 - Twins (1Male + 1 Female) – healthy, no problems identified

February 2010 - Male – healthy, no problems identified

March 2010 – Female – healthy, no problems identified

9 PGD Cytogenetic Probe Assessments

Completed probe assessments

For the period April 2009 to March 2010, PGD probe assessments were completed for 19 patients:

- 12 reciprocal translocation carriers,
- 6 Robertsonian translocation carriers,
- 1 recurrent digynic triploidy

From the date of the PGD clinic appointment to completion of PGD probe assessment, average turnaround time was:

- 10.5 months (range 3-17 months) for a reciprocal translocation/structural abnormality,
- 2 months for a common Robertsonian translocation,
- 6 months for rarer Robertsonian translocations.

(This represents an improvement over the previous 12 month's turnaround times which were:

- 14 months (range 10-23 months) for a reciprocal translocation/structural abnormality
- 4.5 months for a common Robertsonian translocation.)

Our target of 12 months for completion of cytogenetic probe assessments for reciprocal translocations/structural abnormalities was achieved in 9 out of 13 (69%) cases

Our target of 6 months for completion of cytogenetic probe assessments for common Robertsonian translocations was achieved in all cases

Probe assessments currently in progress/waiting to be started

PGD probe assessments are currently being carried out for 4 patients:

- 1 insertional translocation carrier
- 1 pericentric inversion carrier
- 1 reciprocal translocation carrier
- 1 Robertsonian translocation carrier.

PGD probe assessments for 6 patients have yet to be started

10 Clinical Audit Programme

Performance data from the Department of Cytogenetics, Institute of Medical Genetics, Yorkhill Hospital, Glasgow

Following embryo biopsy FISH diagnosis, investigation of non-transferred embryos is performed as an essential quality control measure to ensure that the biopsy diagnosis was correct and to assess FISH error rates:

- false negative rate (i.e. embryos with a normal biopsy diagnosis but abnormal on follow up)
- false positive rate (i.e. embryos with an abnormal biopsy diagnosis but a normal follow up result)

For X-linked conditions (embryo sexing)*:

Number of embryos biopsied	152
Number of non-transferred embryos available for follow up	112
Normal (biopsy)/Abnormal (follow up)	5
False negative rate	5/152 or 3.3%
Abnormal (biopsy)/Normal (follow up)	7
False positive rate	7/152 or 4.6%

For structural rearrangements*

Number of embryos biopsied	184
Number of non-transferred embryos available for follow up	144
Normal (biopsy)/Abnormal (follow up)	1
False negative rate	1/184 or 0.5%
Abnormal (biopsy)/Normal (follow up)	9
False positive rate	9/184 or 4.9%

* calculated using data collected from October 2002 - March 2010

European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium - FISH Based PGD Embryo Follow up Study

To date there has been very little published data on PGD embryo follow up studies and therefore no opportunity for centres to fully assess their error/misdiagnosis rates.

However, this year, the ESHRE PGD Consortium is conducting a study on non-transferred embryos that have undergone FISH analysis during a PGD cycle. Our centre is participating in this study by submitting data on a minimum of 30 embryo follow ups.

The study aims to provide a more complete evaluation of the potential rate of misdiagnosis by identifying the rate of discordance between clinical PGD analysis and embryo follow-up results. The study should also identify likely reasons of discordance e.g. protocol-related parameters, embryo quality, embryo biology, and highlight criteria for optimizing clinical PGD results. The results of the study are expected to be published in July 2010.

Cytogenetic European Quality Assessment (CEQA) Scheme

Our registration for the CEQA scheme was accepted in June 2009, allowing us to participate in their annual PGD EQA scheme. The EQA scheme is comprised of two parts:

- Part 1 involved carrying out PGD cytogenetic probe assessments and submitting written reports for two case scenarios; carrier of a t(10;11) reciprocal translocation and carrier of a 14;21 Robertsonian translocation.
- Part 2 involved online FISH analysis of biopsied embryos from the above cases and submission of reports including embryo diagnosis and recommendations for embryo transfer.

Laboratory performance is scored on analysis, written description and interpretation.

Individual laboratory reports were issued by CEQA in December 2009. Our laboratory achieved a satisfactory performance with a score of 18 out of 18.

Participation in CEQA PGD 2010 commences week beginning 31st May.

Performance data from the Embryology laboratory, Assisted Conception Service, Royal Infirmary, Glasgow

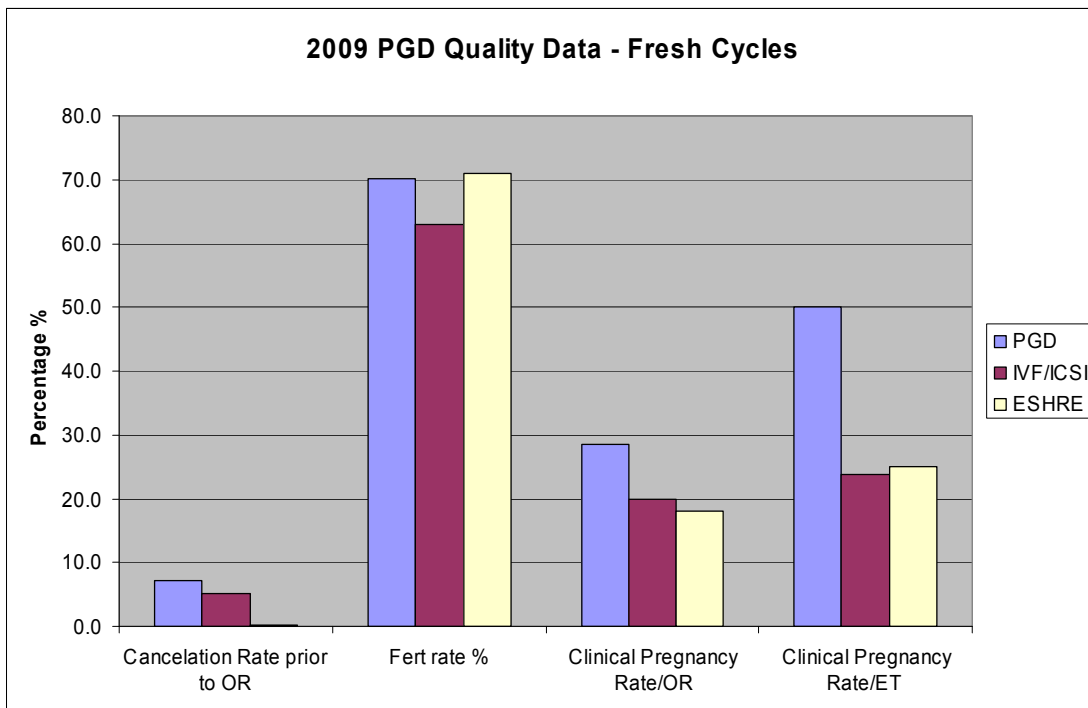
Data for all PGD cycles completed in 2009:

Total number of cases	17
Number of fresh biopsy cases	15
Number of frozen/thawed cases	2
Cases requiring 2 cell biopsy for Genetics	1
Number of 2PN embryos available	107
Number of embryos biopsied	94 (88%)
Number of embryos damaged	0
Number of blastomeres damaged	0
Number of embryos suitable for transfer	27 (28%)
Number of embryos transferred	18
Number of cases reaching embryo transfer	11 (65%)
Number of positive hCG results per embryo transfer	3 (27%)
Number of clinical pregnancies per embryo transfer	3 (27%)

Data for transport of samples from ACS to Medical Genetics since October 2002

Total number of slides transported	728
Clinical analysis	413
Confirmational analysis	315
Number of slides damaged in transit	0

Comparison of 2009 PGD data to unit averages and ESHRE PGD consortium data



Benchmarking

The PGD service, GRI is now using the ESHRE criteria for benchmarking the quality of service provided. In addition, FileMaker Pro 10 software has been acquired and installed meaning that the PGD service data will be submitted to ESHRE via their website. (The data for 2008 has already been submitted and will be reported at the consortium in July 2010).

11 Waiting time information

Waiting times

The time period from receipt of a referral letter to the arranging of a clinic appointment is currently about 8 weeks. Waiting times (in months) to begin treatment can be summarised as follows:

	1 st treatment cycle	2nd treatment cycle	3 rd treatment cycle	Frozen embryo transfer
X Linked	16-18	6-8	8-12	3-4
Translocations	16-18	6-8	8-12	3-4

Number of patients currently waiting to start treatment

There are currently 29 patients waiting to start treatment distributed as follows:

	1 st treatment cycle	2nd treatment cycle	3 rd treatment cycle	Frozen embryo transfer
X Linked	1	2	3	0
Translocations	13	5	5	0
Totals	14	7	8	0

NB: as of March 2010, 7 patients are wishing to delay their treatment for a variety of reasons and they are not included in the above figures.

12 Quality of Care Issues

National Service Division (NSD), NHS Scotland

NSD has a fundamental role in promoting, developing and maintaining the PGD service in Scotland. To help NSD achieve this, the PGD service at GRI provides reports about the service's performance on a six monthly and annual basis

Equality and Diversity

In early 2009, ACS, GRI was audited by Greater Glasgow and Clyde Health Board's 'Equality Impact Assessment for Frontline Patient Services' team. Compliance with the following was assessed:

- Ethnicity
- Disability
- Sexual Orientation
- Religion and Belief
- Age (Children/young/older people)
- Social class
- Socio-Economic status
- Additional marginalisation

In October 2009, the Equality Impact Assessment team produced a report of ACS's compliance rate with required regulations, which was largely favourable. ACS's Quality Manager dealt with the few minor points which needed a response, to the satisfaction of the Equality Impact Assessment team.

Assessment of patient's views about the PGD service

ACS, GRI gathers patient's opinions using:

- A questionnaire containing queries about all aspects of the service
- a 'suggestions box' for comments at any time
- a formal suggestions and complaints procedure

Responses to the questionnaire have been generally favourable. Recent refurbishment of the waiting room facilities was welcomed and certainly reduced the number of unfavourable comments. Two topics that did receive some unfavourable comments were:

- counselling service provision
- follow up after treatment

Given that every effort is made to emphasise to patients on several occasions throughout their treatment that counselling is available, and all patients are also given an information leaflet about ACS's counselling service, it is difficult to know how to improve matters. Similarly, the PGD coordinator at ACS routinely telephones patients to offer them a clinic appointment after treatment and in addition sends a letter asking them to contact the PGD coordinator to arrange a

clinic appointment for a discussion of their treatment with a consultant. Again it is difficult to know how to improve matters.

The questionnaire did not enquire if patients had received genetic counselling and so it has recently been revised to include a question about 'counselling facilities at the Genetics service'.

In an effort to identify means by which the quality of the service to patients may be improved, ACS's formal suggestions and complaints procedure invites patients to offer their comments, complaints or suggestions (verbally or in writing) to ACS's Consultants or Nurse Manager. Patients are also informed that they may wish to address their comments to the Patient Liaison manager of the Women and Children's Directorate of Greater Glasgow and Clyde Health Board.

During the period covered by this report, there were no verbal or written complaints from patients about the PGD service.

Clinical Risk Management

ACS has an incident reporting system (called clinical risk management) open to any members of staff to report any concerns they have about service delivery. Most of these incidents are also registered on GG&C's web based Datix system. Each incident is investigated locally (by the Quality Manager) and any potential service improvements identified are discussed with ACS's senior management before being implemented. Some time later, audits are performed to ensure that implementation has taken place and that the outcome is favourable.

Staff Meetings

The Consultants, Genetics team, Embryology team and the PGD coordinator meet regularly to discuss patient care and all aspects of the PGD service with a view to improve the service quality.

Education

Staff from both service providers are encouraged to enhance their knowledge and skills through education and study e.g.:

- Basic life support for nursing staff
- Weekly teaching sessions, either in-house or external
- British Fertility Society meetings
- European Society of Human Reproduction and Embryology meetings
- Scottish Human Reproduction and Embryology Group meetings
- Equality and Diversity study days
- British Infertility Counselling Association meetings
- The Association of Clinical Embryologists meetings
- Association for Clinical Cytogenetics Spring Conference,
- CytoChip Microarray NHS Study Day,
- 11th International Conference on Early Prenatal Diagnosis
- Scottish Gynaecology Nurses Interest Group meetings

13 Future developments

Research and development

The data collection phase of the project entitled 'The effects of biomass reduction on embryo development after biopsy of either one or two blastomeres will be completed in June 2010; the findings of the study will be collated with a view to publication. The project also facilitated the training of Dr Liza Butcher to obtain a biopsy license as of January 2010.

The requirement for this project to facilitate training of new practitioners has been superseded by a change in the law with regards the use of embryos for training purposes. From October 2009, patients no longer need to consent to a specific research project in order for their surplus embryos to be used for training purposes. This is now an option on the HFEA treatment consent forms. Furthermore, the need for external inspection of biopsy practitioners has been removed and may be carried out 'in house'. We have elected to utilise our previous biopsy practitioner (Paul Mitchell) to act as a local assessor for our embryologists currently training for a biopsy licence. We currently have a further two embryologists in training with a view to obtaining licences around May/June 2010. An increase in the number of trained biopsy practitioners to this level should help facilitate continuity of service provision.

Single Gene

At the present time, patients requiring treatment for a single gene condition are offered referral to Guys and St Thomas's Hospital, London by Dr Whiteford. Within the next 12 months some of these patients will be referred to Edinburgh as part of a pilot study.

Given that there is demand for single gene PGD service in Scotland, a business plan Has been submitted putting forward the case for centres in Glasgow and Edinburgh to provide such treatment.