SCIENCE MOVING
PEOPLE
MOVING SCIENCE

The ESHRE view on PGS

Joep Geraedts

Chairman ESHRE Task Force PGS

Conflict of interest statement

I have no commercial and/or financial relationships with manufacturers of pharmaceuticals, laboratory supplies and/or medical devices.

cshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

PGD and PGS

PGD: ART used for genetic reasons

PGS: Genetic screening used to improve ART results

Different aims

- PGD aims at having a healthy child
- ART (and PGS) aim at having a child

UNESCO, 2003

ESHRE PGD Consortium Steering Committee

1997

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

ESHRE PGD Consortium - Aims

- To survey the availability of PGD
- To collect prospectively and retrospectively data on the accuracy, reliability and effectiveness of PGD
- To initiate follow-up studies of pregnancies and children born
- To produce guidelines and recommended PGD protocols
- To formulate a consensus on the use of PGD
- To educate in the science of genetics and reproduction

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Data Collection – 13 years

1. ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium (1999). Preliminary assessment of data from January 1997 to September 1998 ESHRE PGD Consortium Steering Committee. Human Reproduction, 14: 3138-3148.
2. ESHRE PGD Consortium Steering Committee (2000) ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium: data collection II (May 2000). Hum. Reprod. 15, 2673-2683.
3. ESHRE PGD Consortium Steering Committee (2002) ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium: data collection III (May 2001), Hum Reprod., 17, 233-246.
4. Sermon, K., Moutou, C., Harper, J., Geraedts, J., Scriven, P., Wilton, L., Magli, M.-C., Michiels A, Viville, S., De Die, C. (2005) ESHRE PGD Consortium data collection IV: May-December 2001, Human Reproduction, 20(1):19-34.
5. Harper, J.C, Boelaert, K, Geraedts, J., Harton, G., Kearns, WG, Moutou, C., Muntjewerff, N., Repping, S, SenGupta, S, Scriven, P.N., Traeger-Synodinos, J, Vesela, K, Wilton, L, Sermon, K.D. (2006) ESHRE PGD Consortium data collection V: Cycles from January to December 2002 with pregnancy follow-up to October 2003, Human Reproduction, 21, 3-21
6. Sermon, K.D, Michiels, A, Harton, G, Moutou, C, Repping, S, Scriven, P.N, SenGupta, S,Traeger-Synodinos, J, Vesela, K, Viville, S, Wilton, L, Harper, J.C (2007) ESHRE PGD Consortium data collection VI: Cycles from January to December 2003 with pregnancy follow-up to October 2004, Hum Reprod. 22(2):323-36
7. Harper , JC, De Die, C, Goosens, V, Harton, G, Moutou, C, Repping, S, Scriven, P., SenGupta, S.,Traeger-Synodinos, J., Viville, S., Wilton, L., Sermon, K.D. (2007) ESHRE PGD Consortium data collection VII Cycles from January to December 2004 with pregnancy follow-up to October 2005. Hum Reprod
8. Goossens, V, Harton, G, Moutou, C, Scriven, PN, Traeger-Synodinos. J, Sermon, K, Harper, JC (2008) ESHRE PGD Consortium data collection VIII: Cycles from January to December 2005 with pregnancy follow-up to October 2006, Human Reproduction, 23(12):2629-45.
9. Goossens, V, Harton, G, Moutou, C, Traeger-Synodinos, J, Van Rij, M and Harper, JC (2009) ESHRE PGD Consortium data collection IX: cycles from January to December 2006 with pregnancy follow-up to October 2007

www.eshre.com

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Data Collection – 13 years

- ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium (1999). Preliminary assessment of data from January 1997 to September 1998 ESHRE PGD Consortium Steering Committee. Human Reproduction, 14: 3138-3148.
- ESHRE PGD Consortium Steering Committee (2000) ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium: data collection II (May 2000). Hum. Reprod. 15, 2673-2683.
- ESHRE PGD Consortium Steering Committee (2002) ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium: data collection III (May 2001), Hum Reprod., 17, 233-246.
- Sermon, K., Moutou, C., Harper, J., Geraedts, J., Scriven, P., Wilton, L., Magli, M.-C., Michiels A, Viville, S., De Die, C. (2005) ESHRE PGD Consortium data collection IV: May-December 2001, Human Reproduction, 20(1):19-34.
- Harper, J.C, Boelaert, K, Geraedts, J., Harton, G., Kearns, WG, Moutou, C., Muntjewerff, N., Repping, S, SenGupta, S, Scriven, P.N., Traeger-Synodinos, J, Vesela, K, Wilton, L, Sermon, K.D. (2006) ESHRE PGD Consortium data collection V: Cycles from January to December 2002 with pregnancy follow-up to October 2003, Human Reproduction, 21, 3-21
- Sermon, K.D, Michiels, A, Harton, G, Moutou, C, Repping, S, Scriven, P.N, SenGupta, S,Traeger-Synodinos, J, Vesela, K, Viville, S, Wilton, L, Harper, J.C (2007) ESHRE PGD Consortium data collection VI: Cycles from January to December 2003 with pregnancy follow-up to October 2004, Hum Reprod. 22(2):323-36
- Harper , JC, De Die, C, Goosens, V, Harton, G, Moutou, C, Repping, S, Scriven, P., SenGupta, S.,Traeger-Synodinos, J., Viville, S., Wilton, L., Sermon, K.D. (2007) ESHRE PGD Consortium data collection VII Cycles from January to December 2004 with pregnancy follow-up to October 2005. Hum Reprod
- Goossens, V, Harton, G, Moutou, C, Scriven, PN, Traeger-Synodinos. J, Sermon, K, Harper, JC (2008) ESHRE PGD Consortium data collection VIII: Cycles from January to December 2005 with pregnancy follow-up to October 2006, Human Reproduction, 23(12):2629-45.
- Goossens, V, Harton, G, Moutou, C, Traeger-Synodinos, J, Van Rij, M and Harper, JC (2009) ESHRE PGD Consortium data collection IX: cycles from January to December 2006 with pregnancy follow-up to October 2007

www.eshre.com

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Data Collection I (January 1997- September 1998)

- The group indicated as ‘aneuploidy risk’ consits of patients with previous trisomy or triploidy pregnancies, age related aneuploidy or recurrent abortion.

Data Collection II (October 1998 – May 2000)

- Aneuploidy screening
- Comprised a variety of indications among which maternal age predominates. Other reasons included in this group were:
  - Repeated IVF failure
  - Recurrent spontaneous abortion

Data Collection III (May 2001)

- PGD-Aneuploidy screening (PGD-AS)
- The following groups were identified;
  - Age > 35 years
  - Recurrent IVF failure (at least 3 failed IVF attempts)
  - More than 2 miscarriages with the parents having a normal karyotype
  - Other

Data Collection IV (May – December 2001)

- The data is split up into PGD for high-risk situations and PGS

PRENATAL DIAGNOSIS
Prenat Diagn 2001; **21**: 1086–1092.
DOI: 10.1002/pd.249

Preimplantation genetic diagnosis (PGD), a collaborative activity of clinical genetic departments and IVF centres

Joep P. M. Geraedts[1]*, Joyce Harper[2], Peter Braude[3], Karen Sermon[4], Anna Veiga[5], Luca Gianaroli[6], Noelle Agan[7], Santiago Munné[8], Sue Gitlin[9], Elisabeth Blenow[10], Kylie de Boer[11], Nicole Hussey[12], Emmanuel Kanavakis[13], Soo-Huan Lee[14], Stéphane Viville[15], Lewis Krey[16], Pierre Ray[17], Serena Emiliani[18], Yung Hsien Liu[19] and Stefan Vermeulen[20]

[1]*Research Institute Growth and Development, Universiteit Maastricht, The Netherlands*
[2]*Departement of Obstetrics and Gynaecology, University College London, London, UK*
[3]*Assisted Conception Unit, St Thomas Hospital, London, UK*
[4]*Centre for Medical Genetics, Free Brussels University (VUB), Brussels, Belgium*
[5]*Instituto Dexeus, Barcelona, Spain*
[6]*SISMER, Bologna, Italy*
[7]*Department of Obstetrics and Gynaecology, Baylor College of Medicine, Houston, TX, USA*
[8]*Institute for Reproductive Medicine and Science, St Barnabas Medical Center, West Orange, NJ, USA*
[9]*Jones Institute for Reproductive Medicine, Norfolk, VI, USA*
[10]*Deptartment of Clinical Genetics, Karolinska Hospital, Stockholm, Sweden*
[11]*Sydney IVF, Sydney, Australia*
[12]*Department of Obstetrics and Gynaecology, University of Adelaide, Adelaide, Australia*
[13]*First Department of Pediatrics, Sophia's Children's Hospital, Athens, Greece*
[14]*Cha General Hospital, Pochon Cha University, Seoul, Korea*
[15]*Service de la Biologie de la Reproduction, Strasbourg, France*
[16]*New York University Medical Center, New York, NY, USA*
[17]*Hopital Necker, Paris, France*
[18]*ULB Erasme, Brussels, Belgium*
[19]*Centre for Reproductive Medicine, Kaohsiung, Taiwan*
[20]*Centre for Medical Genetics, Gent, Belgium*

PRENATAL DIAGNOSIS
Prenat Diagn 2001; **21**: 1086–1092.
DOI: 10.1002/pd.249

Preimplantation genetic diagnosis (PGD), a collaborative activity of clinical genetic departments and IVF centres

Joep P. M. Geraedts[1]*, Joyce Harper[2], Peter Braude[3], Karen Sermon[4], Anna Veiga[5], Luca Gianaroli[6], Noelle Agan[7], Santiago Munné[8], Sue Gitlin[9], Elisabeth Blenow[10], Kylie de Boer[11], Nicole Hussey[12], Emmanuel Kanavakis[13], Soo-Huan Lee[14], Stéphane Viville[15], Lewis Krey[16], Pierre Ray[17], Serena Emiliani[18], Yung Hsien Liu[19] and Stefan Vermeulen[20]

13 out of 20 centres offered PGS

Human Reproduction Vol.20, No.1 pp. 35–48, 2005
Advance Access publication November 11, 2004
doi:10.1093/humrep/deh579

ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'

A.R.Thornhill[1,12], C.E.deDie-Smulders[2], J.P.Geraedts[2], J.C.Harper[3], G.L.Harton[4], S.A.Lavery[5], C.Moutou[6], M.D.Robinson[7], A.G.Schmutzler[8], P.N.Scriven[9], K.D.Sermon[10] and L.Wilton[11]

[1]Section of Reproductive Endocrinology and Infertility, Mayo Clinic, College of Medicine Rochester, MN, USA, [4]Genetics and IVF Institute, Fairfax, VA, USA, [2]Department of Clinical Genetics, University Hospital Maastricht, Maastricht, The Netherlands, [3]Department of Obstetrics and Gynaecology, University College, London, [5]Institute of Obstetrics and Gynaecology, Royal Postgraduate Medical School, Hammersmith Hospital, [9]Department of Cytogenetics, and Centre for Preimplantation Genetic Diagnosis, Guy's and St. Thomas' NHS Trust, Guy's Hospital, London, [7]The Leeds PGD Centre, Assisted Conception Unit, Leeds General Infirmary, Leeds, UK, [6]Service de Biologie de la Reproduction, SIHCUS-CMCO, 19 Rue Louis Pasteur, BP120, 67303 Schiltigheim, France, [8]Section of Reproductive Medicine, University of Kiel, Germany, [10]Centre for Medical Genetics, Dutch-speaking Brussels Free University, Brussels, Belgium and [11]Melbourne IVF, 320 Victoria Parade, 3002 East Melbourne VIC, Australia

[12]To whom correspondence should be addressed at: London Fertility Centre, Cozens House, 112A Harley Street, London, W1G 7JH

Among the many educational materials produced by the European Society of Human Reproduction and Embryology (ESHRE) are guidelines. ESHRE guidelines may be developed for many reasons but their intent is always to promote best quality practices in reproductive medicine. In an era in which preimplantation genetic diagnosis (PGD) has become a reality, we must strive to maintain its efficacy and credibility by offering the safest and most effective treatment available. The dominant motivators for the development of current comprehensive guidelines for best PGD practice were (i) the absence of guidelines and/or regulation for PGD in many countries and (ii) the

Human Reproduction Vol.20, No.1 pp. 35–48, 2005
Advance Access publication November 11, 2004
doi:10.1093/humrep/deh579

ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'

A.R.Thornhill[1,12], C.E.deDie-Smulders[2], J.P.Geraedts[2], J.C.Harper[3], G.L.Harton[4], S.A.Lavery[5], C.Moutou[6], M.D.Robinson[7], A.G.Schmutzler[8], P.N.Scriven[9], K.D.Sermon[10] and L.Wilton[11]

Inclusion criteria for PGS:

- Recurrent miscarriage
- Repeated implantation failure
- Advanced maternal age (> 36 years completed years)

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Human Reproduction Vol.20, No.1 pp. 35–48, 2005
Advance Access publication November 11, 2004
doi:10.1093/humrep/deh579

ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'

A.R.Thornhill[1,12], C.E.deDie-Smulders[2], J.P.Geraedts[2], J.C.Harper[3], G.L.Harton[4], S.A.Lavery[5], C.Moutou[6], M.D.Robinson[7], A.G.Schmutzler[8], P.N.Scriven[9], K.D.Sermon[10] and L.Wilton[11]

FISH based diagnosis
PGS (*aneuploidy screening*)
For aneuploidy screening a robe set of at least 5 chromosome pairs from 13, 14, 15, 16, 18, 21, 22, X and Y is **recommended**.
Diagnosis on a single mononucleate cell is **acceptable** for PGS.

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

At least 10 RTCs on blastomeres

- Good prognosis patients: Jansen *et al.*, 2008; Mersereau *et al.*, 2008; Staessen *et al.*, 2008; Meyer *et al.*, 2009.
- Poor prognosis patients: Staessen *et al.*, 2004; Stevens *et al.*, 2004; Debrock *et al.*, 2007; Mastenbroek *et al.*, 2007; Hardarson *et al.*, 2008; Schoolcraft et al., 2009.
- These studies have all shown that PGS has not improved the delivery rate compared to a control group, and some of these studies have shown harm or had to be terminated prematurely.

cshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Explanations

- Not all chromosomes were tested;
- The biopsied blastomere is not a true representation of the embryo at the 8-cell stage because of mosaicism;
- The biopsy procedure might cause harm and negative influences on the developmental potential of the biopsied embryo.

Positions

- *American Society of Reproductive Medicine (ASRM);*
- *British Fertility Society (BFS);*
- *European Society of Human Reproduction and Embryology (ESHRE):*

have concluded that PGS as it is currently practiced does not improve the live birth rates in patients with advanced maternal age.

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

ESHRE PGD Consortium-Best Practice Guidelines for Organization of a PGD Center for Preimplantation Genetic Diagnosis/Screening (PGD/PGS)

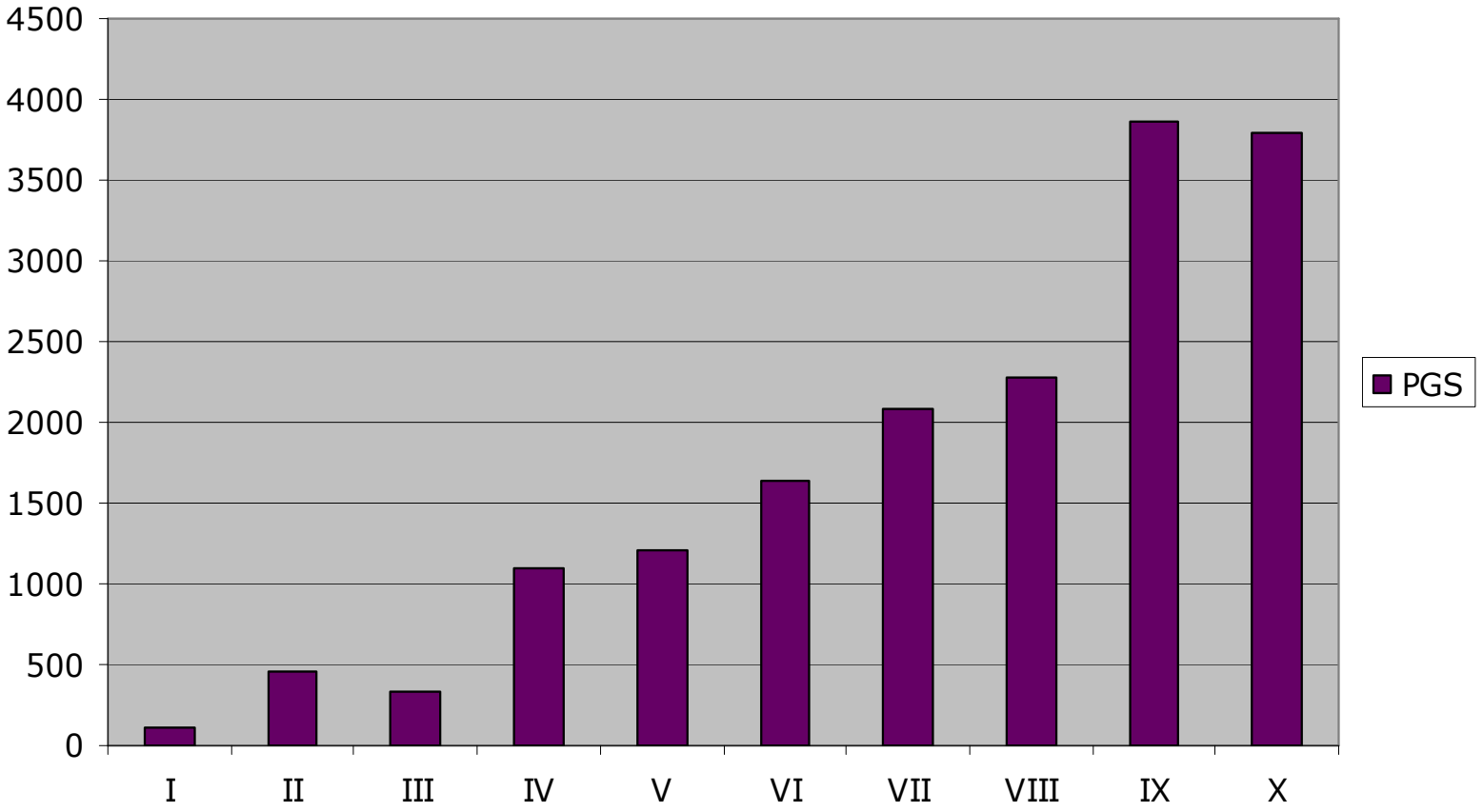
Harton, G, Braude, P, Lashwood, A, Schmutzler, A, Traeger-Synodinos, J, Wilton, L, and Harper, JC

- Preimplantation genetic screening (PGS) is currently controversial. Opinions of laboratory specialists and clinicians interested in PGD and PGS have been taken into account in this document. While current evidence suggests that PGS at cleavage stages may be ineffective, there are still questions as to whether PGS at the blastocyst stage or on polar bodies might show improved delivery rates.

From document at the ESHRE website

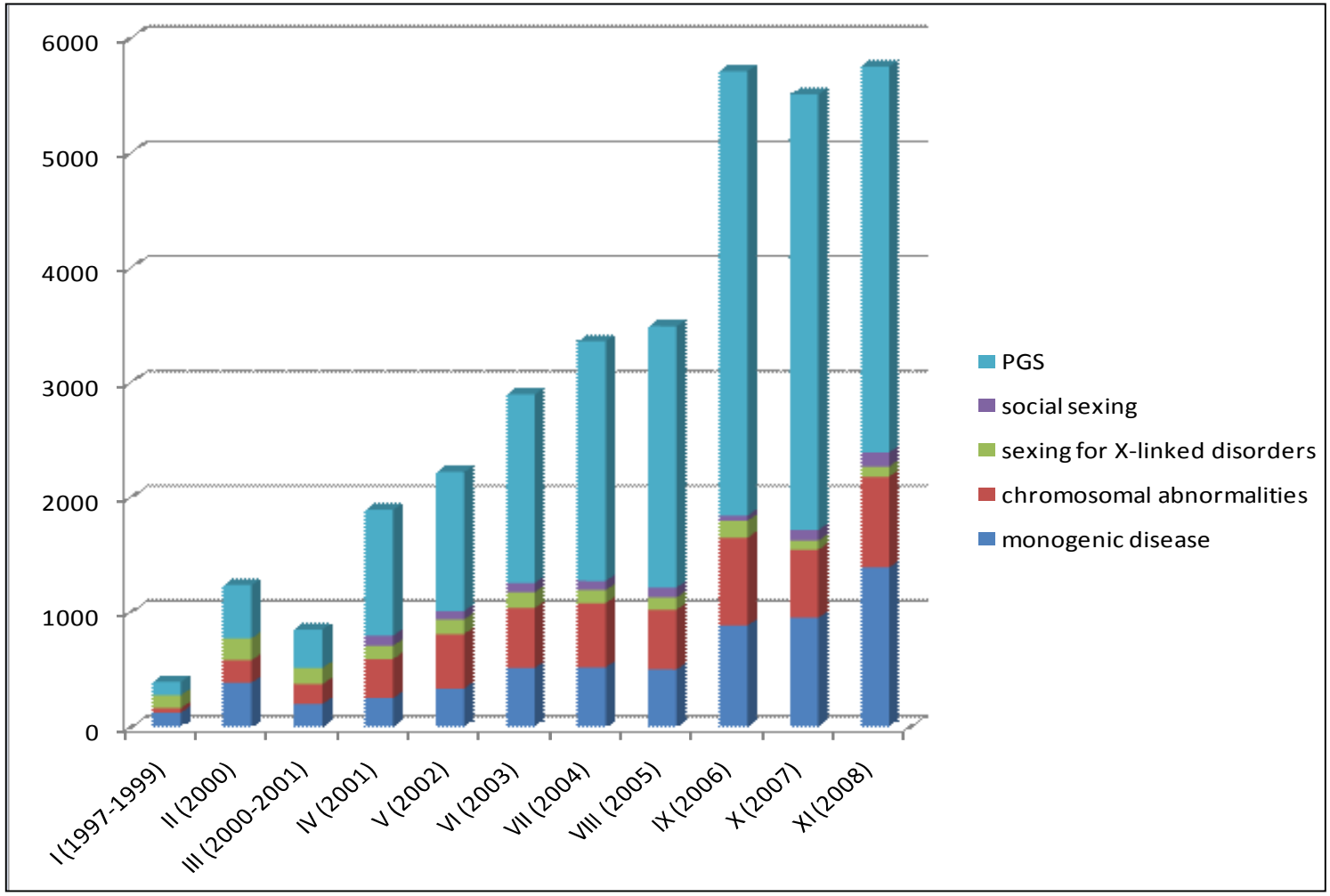
eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Evolution of cycle data (I)



cshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Evolution of cycle data (II)



Alternatives

- Trophectoderm biopsy:
  - Advantages: both maternal and paternal abnormalities can be studied and it does not touch the future embryo.
  - Disadvantages: not very much time available for the analysis, there is mosaicism, be it less than at the 8-cell stage. The trophectoderm might not be representative for the inner cell mass.
- Polar body biopsy:
  - Advantages: No mosaicism. Does not touch the future embryo. Allowed in Germany, Austria and Switzerland.
  - Disadvantage: Only maternal abnormalities.

Origin of non-disjunction in human autosomal trisomies

Chromosome	#Cases	Maternal (%)	Paternal (%
13	42	37 (88.1)	5 (11.9)
15	17	15 (88.2)	2 (11.8)
16	56	56 (100.0)	0 (0.0)
18	176	161 (91.5)	15 (8.5)
21	880	805 (91.5)	75 (8.5)

Adapted from Nicolaidis & Petersen (1998)

ESHRE PGS task force (established 2007)

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Human Reproduction, Vol.25, No.3 pp. 575–577, 2010
Advanced Access publication on December 23, 2009 doi:10.1093/humrep/dep446

human reproduction DEBATE

What next for preimplantation genetic screening? A polar body approach!

Joep Geraedts[1,11], John Collins[2], Luca Gianaroli[3], Veerle Goossens[4], Alan Handyside[5], Joyce Harper[6], Markus Montag[7], Sjoerd Repping[8,9], and Andreas Schmutzler[10]

Aims of ESHRE PGS study

- to show that the analysis of both polar bodies can be completed within a time period that allows for fresh transfer;
- to ensure the reliable identification of the chromosomal status of an oocyte in at least 90% of polar body biopsy attempts;
- to test the feasibility of a multicentre randomized trial based on the technology used in the pilot study.

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

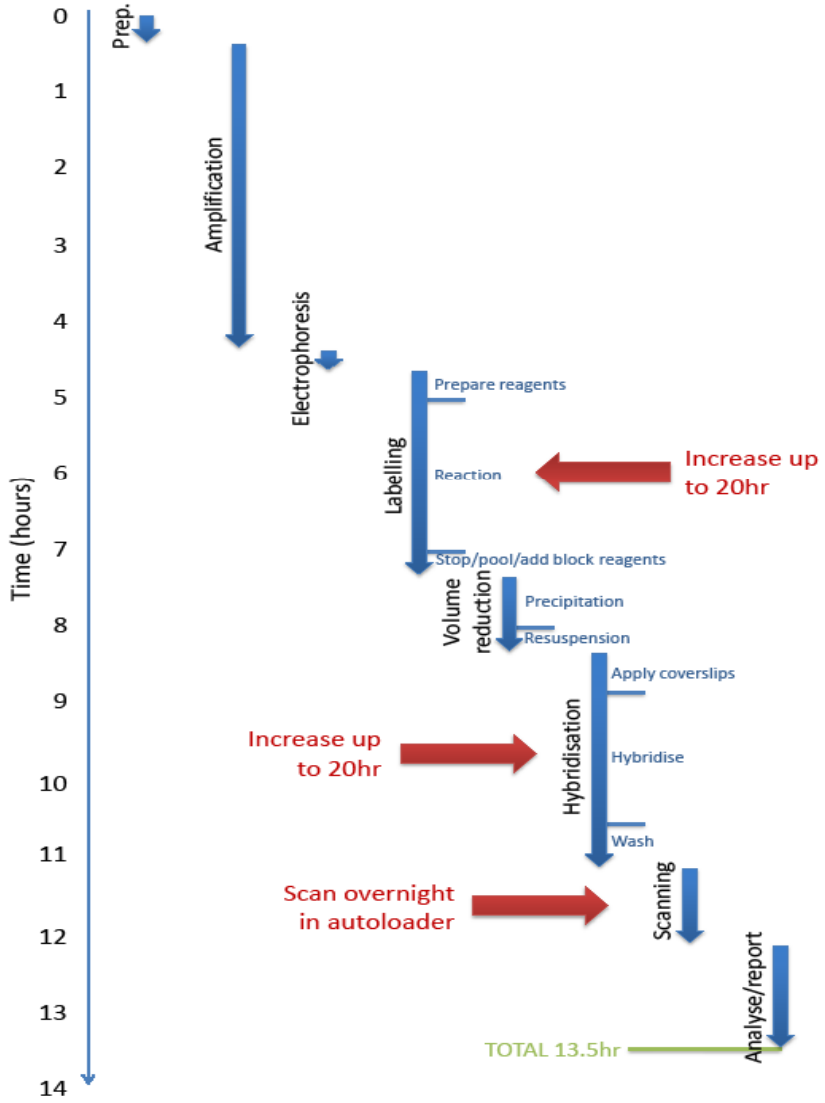
Aims of proof of principle study

- to show that the analysis of both polar bodies can be completed within a time period that allows for fresh transfer;
- to ensure the reliable identification of the chromosomal status of an oocyte in at least 90% of polar body biopsy attempts;
- to test the feasibility of a multicentre randomized trial based on the technology used in the pilot study.

Materials & Methods

- Two centres (Bologna and Bonn)
- All mature metaphase II oocytes fertilised by ICSI
- First and second polar body biopsied simultaneously
- Both polar bodies analysed separately for chromosome aneuploidy by array CGH (24sure; BlueGnome)

Protocol timings



cshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Patient characteristics

Number of patients 41
Number of cycles 42
Average age 40.0
Average number of zygotes 5.5
Total number of zygotes 226

Results (predicted oocytes)

Total number biopsied	226	
Total number result PB1 and 2	191	*85%*
Euploid	43	*23%*
Aneuploid	148	*77%*

Concordance analysis

- Concordance rate ploidy status 89%
- 125/140 oocyte - PB 1 and 2 combinations concordant
- 15/140 oocyte - PB 1 and 2 combinations discordant
- All discordant cases aneuploid PBs and a normal chromosomal complement in the oocyte

Clinical results

19/42 cycles (45 %) only aneuploid oocyte	
23/42 cycles with ≥ 1 euploid oocyte	
Cycles with fresh transfer	23
Transfers total	24
Pregnancy (+hCG)	9
Clinical pregnancy	8
Ongoing pregnancy rate per cycle:	19 %
Ongoing pregnancy rate per transfer:	33.3 %

cshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Conclusions

- This is the first critical assessment of 23 chromosome testing of PB 1 + 2 and oocyte using array CGH;
- It has been shown that the analysis of both polar bodies can be completed within 12-13 hours and allows for fresh transfer;
- The reliable identification of the chromosomal status of an oocyte is possible in almost 90% of polar body biopsy attempts;
- The feasibility of a multicentre randomized trial based on the technology used in the pilot study should be tested.

Acknowledgements

Steering Committees from 1997 to 2010

Markus Montag

Cristina Magli

Sjoerd Repping

Alan Handyside

Catherine Staessen

Katerina Vesela

ESHRE PGS Task Force

Joyce Harper

Andreas Schmutzler

John Collins

Veerle Goossens

Luca Gianaroli

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE