

# ESHRE PGD consortium data collection VII: cycles from January to December 2004 with pregnancy follow-up to October 2005

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**The seventh report of the ESHRE PGD Consortium is presented documenting cycles collected for the calendar year 2004 and follow-up of the pregnancies and babies born subsequent to these cycles up to October 2005. Since the beginning of the data collections, there has been a steady increase in the number of cycles, pregnancies and babies reported. For data collection VII, 45 centres have participated, reporting on 3358 cycles to oocyte retrieval (OR), 679 pregnancies and 528 babies born. Five hundred and fifty nine OR were reported for chromosomal abnormalities, 113 OR for sexing for X-linked diseases, 520 OR for monogenic diseases, 2087 OR for PGS, and 79 OR for social sexing. Data VII is compared with the cumulative data for data collections I–VI.**

**Keywords:** preimplantation genetic diagnosis; preimplantation genetic screening; fluorescence *in situ* hybridization; polymerase chain reaction; ESHRE PGD Consortium

## Introduction

The ESHRE PGD Consortium was established in 1997. Six data collections on preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS–PGD for aneuploidy) have been published (ESHRE PGD Consortium Steering Committee, 1999, 2000, 2002; Sermon *et al.*, 2005, 2007; Harper *et al.*, 2006). This report summarizes data VII collected for the calendar year 2004 and the subsequent pregnancies. In contrast to previous years, in data VII cycles started and cancelled prior to oocyte retrieval (OR) were removed from the data. This information had previously been requested in an attempt to estimate the rate of cycle cancellation, but the majority of centres did not report cancelled cycles leading to an underestimation of the number of these cycles. Additionally, data VII reports on the sex requested for social sexing and gives a detailed analysis of the misdiagnoses.

## Materials and Methods

Data were collected using a FileMaker Pro 5, 6 or 8 database and consisted of files for cycle, pregnancy and baby records. The first round of data analysis was general and identified omissions and some errors. Corrections were requested from participating centres. This was followed by a more in-depth correction and analysis by expert co-authors. Records with insufficient data, e.g. with no cycle or patient identification or no clear indication, from the wrong time period, or reported after the closure of the collection period, were excluded from the calculations. Pregnancies were defined as the presence of one or more fetal hearts at ~6-week gestation. Implantation rate was defined as the number of fetal hearts per 100 embryos transferred.

## Results

Data from 45 centres were included in this report. The results are represented in tables according to an established lay-out.

**Table Ia.** Overall cycle data collection I–VI.

Indication	PGD	PGS	PGD-SS	Total
Cycles to OR	3915 <sup>a</sup>	4791	333	9039 <sup>a</sup>
Number infertile	1495	4367	42	5904
Female age	33	37	36	35
Cycles cancelled before IVF/ICSI	11	0	0	11
ART method				
IVF	466	635	118	1219
ICSI	3346	4059	199	7604
IVF + ICSI	20	28	0	48
Frozen + ICSI/IVF/unknown	54 <sup>a</sup>	19	16	89 <sup>a</sup>
Unknown	20	50	0	70
Cancelled after IVF/ICSI	247	173	15	435
Cycles to PGS/PGD	3659	4618	318	8595
FISH	2114	4618	214	6946
PCR	1545	0	104	1649
Zona breaching				
AT drilling	2144	2524	19	4687
laser drilling	1330	1870	113	3313
Mechanical	171	159	186	516
Unknown	14	65	0	79
Biopsy method				
PB biopsy	36 <sup>b</sup>	363 <sup>b</sup>	0	399 <sup>b</sup>
Cleavage aspiration	3423 <sup>b</sup>	3890 <sup>b</sup>	131	7444 <sup>b</sup>
Cleavage extrusion	160	298	187	645
Cleavage flow displacement	2	16	0	18
Blastocyst	25	0	0	25
Unknown	16	52	0	68
Embryology				
COC's	53 445	59 227	4511	117183
Inseminated	45 625	49 706	3721	99 052
Fertilized	32 697	35 138	2535	70 370
Biopsied	24 622	27 045	2067	53 734
Successfully biopsied	24 154	26 645	1966	52 765
Diagnosed	21 340	23 831	1812	46 983
Transferable	8150	8546	765	17 461
Transferred	5706	6737	541	12 984
Frozen	1033	1141	169	2343
Clinical outcome				
Cycles to ET	2882	3471	239	6592
hCG positive	893	1111	98	2102
Positive heartbeat	699	845	74	1618
Clinical pregnancy rate (% per OR/ % per ET)	18/24	18/24	22/31	18/25

AT, acid Tyrode's; COC, cumulus–oocyte complexes; ET, embryo transfer. PGD column includes PGD for chromosome abnormalities, sexing for X-linked disease and PGD for monogenic disorders.

<sup>a</sup>Includes two cycles with PGD on frozen embryos only. These cycles were not counted in the cycles with OR. <sup>b</sup>Four cycles had polar body biopsy and cleavage stage biopsy.

Accompanying text is deliberately concise, and seven tables are only available in an electronic version: Table IIc with the list of abnormal karyotypes carried by the patients undergoing PGD, Table IIIc with the list of X-linked diseases for which sexing was carried out, Table IVc with the list of monogenic diseases for which PGD was carried out, Tables VIIa (data I–VI) and VIIb (data VII) with the complications of pregnancy and Tables XIIa (data I–VI) and XIIb (data VII) with the congenital malformations and the neonatal complications. An overview of all cycles collected previously in data collections I–VI can be found in Table Ia, whereas an overview of the current data collection can be found in Table Ib.

For all indications for PGD/PGS, ICSI was the most often used method of fertilization and cleavage stage aspiration was the most commonly used method of biopsy. Overall, zona drilling was more commonly performed using a laser

**Table Ib.** Overall cycle data collection VII.

Indication	PGD	PGS	PGD-SS	Total
Cycles to OR	1192	2087	79	3358
Number infertile	490	1963	0	2453
Female age	33	36	38	36
Cancelled before IVF/ICSI	4	0	0	4
ART method				
IVF	100	150	5	255
ICSI	1066	1878	74	3018
IVF + ICSI	5	51	0	56
Frozen + ICSI	17	8	0	25
Cancelled after IVF/ICSI	81	76	1	158
Cycles to PGS/PGD	1107	2011	78	3196
FISH	608	2011	0	2619
PCR	499	0	78	577
Zona breaching				
AT drilling	416	414	0	830
laser drilling	650	1271	1	1922
Mechanical	41	326	77	444
Biopsy method				
PB biopsy	4	344	0	348
Cleavage aspiration	1050	1587	1	2638
Cleavage extrusion	41	80	77	198
Blastocyst	4	0	0	4
PB and cleavage	8	0	0	8
Embryology				
COC's	16 715	24 029	1220	41 964
Inseminated	14 131	19 317	949	34 397
Fertilized	10 016	13 711	644	24 371
Biopsied	7407	11 751	478	19 636
Successfully biopsied	7364	11 605	461	19 430
Diagnosed	6713	10 938	445	18 096
Transferable	2429	4002	113	6642
Transferred	1515	2641	92	4248
Frozen	333	515	25	893
Clinical outcome				
Cycles to ET	837	1500	49	2386
hCG positive	269	501	20	790
Positive heartbeat	213	372	15	604
Clinical pregnancy rate (% per OR/ % per ET)	18/25	18/25	19/31	18/25
Number of fetal heartbeats	263	465	21	749
% Implantation rate (fetal heartbeats/ 100 embryos transferred)	17	18	23	17

PGD column includes PGD for chromosome abnormalities, sexing for X-linked disease and PGD for monogenic disorders.

but for some indications, such as chromosome abnormalities, acid Tyrode's was used more often (one centre that carries out a large proportion of the cycles for chromosome abnormalities used acid Tyrode's).

### **PGD cycles for chromosomal abnormalities**

Tables IIa and IIb summarize the 1633 and 559 cycles to OR collected for data collection I–VI and VII, respectively. As for previous years, data VII showed that PGD for reciprocal translocations was performed more often than for Robertsonian translocations or other types of chromosome abnormalities. For data VII, 8083 oocytes were collected, 61% (4955/8083) fertilized, 76% (3769/4955) embryos were biopsied and 99% (3745/3769) embryos were successfully biopsied. Of the embryos successfully biopsied, 93% (3485/3745) gave a diagnostic result, of which only 25% (863/3485) were transferable. From 559 OR procedures, only 64% (359/559) resulted in an embryo transfer procedure. This is in agreement with previous data showing that a high level of chromosomally abnormal

**Table IIa.** PGD for chromosomal abnormalities, data collection I–VI.

Indication	Robertsonian translocation, male carrier	Robertsonian translocations, female carrier	Reciprocal, male carrier	Reciprocal, female carrier	Sex chromosome aneuploidy	Other	Total
Cycles to OR	268	213	424	438	171	119	1633
Number infertile	239	104	251	197	155	65	1011
Female age	36	33	34	34	34	33	33
Cancelled before IVF/ICSI	0	0	1	0	5	1	7
ART method							
IVF	11	29	49	114	18	33	254
ICSI	250	178	358	310	147	83	1326
IVF + ICSI	2	2	2	5	0	1	12
Frozen + ICSI/unknown	4	4	13	9	1	1	32
Unknown	1	0	1	0	0	0	2
Cancelled after IVF/ICSI	21	13	34	33	10	5	116
Cycles to PGD	247	200	389	405	156	113	1510
Zona breaching							
AT drilling	160	132	277	305	83	73	1030
Laser drilling	86	63	93	88	46	32	408
Mechanical	1	5	19	12	27	8	72
Biopsy method							
Polar body biopsy	1	4	0	3	0	0	8
Cleavage aspiration	240	189	360	376	156	109	1430
Cleavage extrusion	6	7	24	22	0	4	63
Cleavage flow displacement	0	0	1	1	0	0	2
Blastocyst	0	0	4	3	0	0	7
Embryology							
COC's	3930	2992	6296	6438	2077	1485	23 218
Inseminated	3315	2498	5328	5616	1702	1310	19 769
Fertilized	2276	1827	3854	4202	1210	903	14 272
Biopsied	1509	1466	3036	3373	852	712	10 948
Successfully biopsied	1477	1443	2986	3320	839	694	10 759
Diagnosed	1282	1312	2724	3080	757	626	9781
Transferable	498	407	567	640	359	226	2697
Transferred	358	315	482	544	255	165	2119
Frozen	46	28	17	25	24	18	158
Clinical outcome							
Cycles to ET	190	163	258	280	126	84	1101
hCG positive	61	49	71	76	36	21	314
Positive heartbeat	52	38	53	58	23	18	242
Clinical pregnancy rate (% per OR/% per ET)	19/27	18/23	13/21	13/21	13/18	15/21	15/22

embryos are found in these patients. A positive hCG was obtained in 109 cycles, with a positive heartbeat in 90 cycles (16% per OR (90/559) and 25% per ET (90/359)). This gave an implantation rate of 19% (115/614). These pregnancy rates were similar to the previous data collections.

#### **PGD cycles for sexing for X-linked diseases**

Tables IIIa and IIIb summarize the 703 and 113 cycles to OR collected for data collection I–VI and VII, respectively. As for previous years, FISH was used more than PCR (only one cycle by PCR). For data VII, 1504 oocytes were collected, 63% (830/1311) fertilized, 74% (617/830) embryos were biopsied and 99% (608/617) were successfully biopsied. Of the embryos successfully biopsied, 93% (564/608) gave a diagnostic result, of which only 32% (183/564) were transferable (female). From 113 OR procedures, only 67% (76/113) resulted in an embryo transfer procedure. A positive hCG was obtained in 26 cycles, with a positive heartbeat in 20 cycles (18% per OR (20/113) and 26% per ET (20/76)). This gave an implantation rate of 17% (20/120). These pregnancy rates were similar to the previous data collections.

#### **PGD for monogenic diseases**

Tables IVa and IVb summarize the 1579 and 520 cycles to OR collected for data collection I–VI and VII, respectively. The most common indications for PGD for autosomal recessive diseases were cystic fibrosis (51 cycles),  $\beta$ -thalassemia (38 cycles, plus five cycles for  $\beta$ -thalassemia with HLA typing), spinal muscular atrophy (SMA) (36 cycles) and sickle cell anaemia (12 cycles, plus seven cycles for sickle cell/ $\beta$ -thalassemia and four cycles with HLA typing). There were four cycles for two independent disorders; SMA combined with retinitis pigmentosa. The most common indications in the group of autosomal dominant diseases were myotonic dystrophy type I (80 cycles), Huntington disease (56 cycles), Neurofibromatosis type I (18 cycles) and adenomatous polyposis coli (12 cycles). The most common indications where a specific diagnosis of X-linked diseases was carried out were for fragile X syndrome (FRAXA) (37 cycles), Duchenne muscular dystrophy (DMD) (19 cycles), and haemophilia (8 cycles). PGD cycles for an additional 53 monogenic diseases were initiated in 133 cycles, (included under 'others' in Table IVb), and they are listed in Table IVc. Besides the cycles for  $\beta$ -thalassemia or

**Table IIIb.** PGD for chromosomal abnormalities, data collection VII.

Indication	Robertsonian translocation, male carrier	Robertsonian translocations, female carrier	Reciprocal, male carrier	Reciprocal, female carrier	Sex chromosome aneuploidy	Other	Total
Cycles to OR	97	57	167	163	34	41	559
Number infertile	77	35	115	104	33	19	383
Female age	32	33	33	33	31	33	33
Cancelled before IVF/ICSI	0	0	2	0	0	1	3
ART method							
IVF	5	9	17	36	1	5	73
ICSI	91	47	144	116	33	34	465
IVF + ICSI	0	0	0	2	0	1	3
ICSI + frozen	1	1	4	9	0	0	15
Cancelled after IVF/ICSI	2	2	14	21	4	1	44
Cycles to PGD	95	55	151	142	30	39	512
Zona breaching							
AT drilling	38	27	72	84	11	21	253
Laser drilling	54	28	75	53	17	14	241
Mechanical	3	0	4	5	2	4	18
Biopsy method							
Polar body	0	1	0	2	0	0	3
Cleavage aspiration	92	47	149	135	27	33	483
Cleavage extrusion	3	7	2	5	3	6	26
Embryology							
COC's	1464	798	2297	2384	526	614	8083
Inseminated	1219	653	1962	2049	435	527	6845
Fertilized	842	487	1342	1552	317	415	4955
Biopsied	627	386	1026	1197	200	333	3769
Successfully biopsied	620	385	1019	1190	199	332	3745
Diagnosed	573	351	964	1103	177	317	3485
Transferable	222	87	191	199	88	76	863
Transferred	130	66	152	159	49	58	614
Frozen	35	7	11	14	12	2	81
Clinical outcome							
Cycles to ET	74	40	91	96	24	34	359
hCG positive	27	18	26	25	6	7	109
Positive heartbeat	24	14	20	19	6	7	90
Clinical pregnancy rate	25/32	25/35	12/22	12/20	18/25	17/21	16/25
% per OR/ET							
Number of fetal hearts	33	17	23	28	6	8	115
% implantation rate (fetal hearts/embryos transferred)	25	26	15	18	12	14	19

sickle cell anaemia with HLA typing, HLA typing was carried out with PGD for Fanconi anaemia (1 cycle), Incontinentia Pigmenti (2 cycles), sexing (1 cycle) and Wiskott–Aldrich syndrome (1 cycle) as well as 6 cycles for HLA typing alone (in total 20 cycles involving HLA).

For data VII, 7128 oocytes were collected, 71% (4231/5975) fertilized, 71% (3021/4231) embryos were biopsied and 100% (3011/3021) were successfully biopsied. Three cycles used IVF for embryo fertilization, whereas in the remaining 517 cycles, ICSI was used. IVF is not recommended when PCR is used because sperm embedded in the zona can enter the PCR tube and contaminate the blastomere (Thornhill *et al.*, 2005). In the majority of cycles, biopsy was carried out using cleavage stage aspiration but four (0.8%) used trophoctoderm biopsy in blastocysts and one cycle used polar body biopsy. Of the embryos successfully biopsied, 88% (2664/3011) gave a diagnostic result, of which 52% (1383/2664) were transferable. From 520 OR procedures, 77% (402/520) resulted in an embryo transfer procedure. A positive hCG was obtained in 134 cycles, with a positive heartbeat in 103 cycles (20% per OR (103/520) and 26% per ET (103/402)). This gave an implantation rate

of 16% (128/781). These pregnancy rates were similar to the previous data collections.

Overall, the number of PGD cycles performed for monogenic disorders between January and December 2004 represents the largest number performed in a single year so far with an increase in the number of different disorders tested. Four cycles involved more than one monogenic disorder (SMA and retinitis pigmentosa), and one cycle each for SMA, DMD and FRAXA were combined with PGS by FISH analysis. Thirteen cycles were for an autosomal recessive or specific diagnosis of an X-linked disorder combined with HLA typing. Of the 20 cycles carried out involving HLA typing, only two (Wiskott–Aldrich syndrome/HLA and sexing/HLA) resulted in a pregnancy. A shift towards PGD for inherited cancer predispositions has continued from the last data collection.

#### **Preimplantation genetic screening**

Tables Va and Vb summarize the 4791 and 2087 cycles to OR reported for data collection I–VI and VII, respectively. For data VII, 24 029 oocytes were collected, 71% (13 711/19317) fertilized, 86% (11 751/13711) embryos were biopsied

**Table IIIa.** Sexing only for X-linked disease using PCR or FISH, data collection I–VI.

	FISH	PCR	Total
Cycles to OR	638	65	703
Number infertile	103	0	103
Female age	33	29	31
ART method			
IVF	171	10	181
ICSI	461	55	516
IVF + ICSI	5	0	5
ICSI and frozen	1	0	1
Cancelled after IVF/ICSI	34 <sup>a</sup>	1 <sup>b</sup>	35 <sup>a,b</sup>
Cycles to PGD	604	64	668
Zona breaching			
AT drilling	363	52	415
Laser drilling	209	2	211
Mechanical	32	10	42
Biopsy method			
Cleavage aspiration	586	59	645
Cleavage extrusion	17	5	22
Blastocyst	1	0	1
Embryology			
COC's	8454	899	9353
Inseminated	7495	689	8184
Fertilized	5347	546	5893
Biopsied	4045	451	4496
Successfully biopsied	3935	415	4350
Diagnosed	3583	325	3908
Transferable	1258	175	1433
Transferred	907	137	1044
Frozen	210 <sup>c</sup>	57 <sup>c</sup>	267 <sup>c</sup>
Clinical outcome			
Cycles to ET	483	54	537
hCG positive	150	24	174
Positive heartbeat	120	17	137
Clinical pregnancy rate (% per OR/% per ET)	19/25 <sup>d</sup>	26/31 <sup>d</sup>	19/26 <sup>d</sup>

<sup>a</sup>Twenty seven embryos from two cycles frozen before biopsy due to hyperstimulation. <sup>b</sup>Twenty embryos frozen before biopsy. <sup>c</sup>Twenty four cycles with embryos frozen without biopsy or after failed diagnosis included. <sup>d</sup>Eleven embryos transferred removed from calculations due to lack of information regarding the number of FHB in pregnancies resulting from the transfer of those embryos.

and 99% (11 605/11751) were successfully biopsied. Of the embryos successfully biopsied, 94% (10 938/11605) gave a diagnostic result, of which only 37% (4002/10 938) were transferable. From 2087 OR procedures only 72% (1500/2087) resulted in an embryo transfer procedure. A positive hCG was obtained in 501 cycles, with a positive heartbeat in 376 cycles (18% per OR (376/2087) and 25% per ET (376/1500)). This gave an implantation rate of 18% (465/2641). These pregnancy rates were similar to the previous data collections.

The main indications were advanced maternal age (AMA) (541 OR) and repeated implantation failure (RIF) (670 OR). Three new combinations of indications were reported: patients who had experienced a previous chromosomally abnormal pregnancy, RIF combined with severe male factor infertility (SMF) and AMA combined with SMF. A large number of cycles were reported as having no indication (79 OR). All indications involving AMA showed pregnancy rates per OR below 14%. Patients with two indications involving AMA (AMA plus spontaneous abortion, AMA plus RIF and AMA plus SMF) all did poorly with a pregnancy rate per OR of <8%. Recurrent spontaneous abortion showed a relatively high pregnancy rate

**Table IIIb.** Sexing only for X-linked disease using PCR or FISH, data collection VII.

	FISH	PCR	Total
Cycles to OR	112	1	113
Number infertile	29	0	29
Female age	33	32	33
Cancelled before IVF/ICSI	1	0	1
ART method			
IVF	24	0	24
ICSI	85	1	86
IVF + ICSI	2	0	2
Cancelled after IVF/ICSI	15	0	15
Cycles to PGD	96	1	97
Zona breaching			
AT drilling	39	0	39
Laser drilling	55	1	56
Mechanical	2	0	2
Biopsy method			
Cleavage aspiration	87	1	88
Cleavage extrusion	9	0	9
Embryology			
COC's	1491	13	1504
Inseminated	1299	12	1311
Fertilized	820	10	830
Biopsied	610	7	617
Successfully biopsied	601	7	608
Diagnosed	560	4	564
Transferable	180	3	183
Transferred	118	2	120
Frozen	47	1	48
Clinical outcome			
Cycles to ET	75	1	76
hCG positive	26	0	26
Positive heartbeat	20	0	20
Clinical pregnancy rate (% per OR/% per ET)	18/27	0	18/26
Number fetal heartbeats	20	0	20
% implantation rate (fetal heartbeats/embryos transferred)	17	0	17

(27% per OR (72/267)) as did SMF (SMF alone; 29% per OR (56/195) and combined with RIF; 33% per OR 3/9)). Patients with no indication had a pregnancy rate of 19% per OR (15/79).

From 2087 cycles, 131 involved the biopsy of only one embryo and 190 involved the biopsy of two embryos. A large number of these cycles were for AMA. The value of PGS, if only one or two embryos are available, is debatable and possibly the best course to take is to transfer them without biopsy. Alternatively, PGS on cycles with a low number of embryos could have a diagnostic character, i.e. it could help patients to make further reproductive decisions if none of their embryos were found to be chromosomally normal.

There are repeatedly cycles with no indication and various odd indications (represented in the 'other' column) such as endometriosis, poor quality embryos, tubal disease and radiotherapy.

The Consortium has set up a working group to examine various aspects of PGS in more detail (see Discussion). There are numerous ongoing discussions about the efficacy of PGS (Harper *et al.*, 2007).

### PGD cycles for social sexing

Tables VIa and VIb summarize the 333 and 79 cycles to OR collected for data collection I–VI and VII, respectively. For data VII, 1220 oocytes were collected, 68% (644/949)

**Table IVa.** Cycles performed for single gene disorders using PCR, data collection I–VI.

	Autosomal recessive				Autosomal dominant			Specific X-sinked			Other	Total
	CF <sup>a</sup>	β-thal and β-thal + HLA	SMA	SC <sup>b</sup>	DM1	HD and HD exclus.	MS	DMD and BMD	FRAXA <sup>c</sup>	Haem		
Cycles to OR	352	182	111	31	237	214	18	60	71	30	273	1579
Number infertile	125	91	15	8	30	37	0	9	17	5	44	381
Female age	33	34	33	34	33	31	32	31	36	31	33	33
Cancelled before IVF/ICSI	0	0	0	0	3	0	0	0	0	0	1	4
Art method												
IVF	15	0	1	0	1	0	0	3	2	6	3	31
ICSI	329	181	104	31	227	210	18	54	67	22	261	1504
IVF + ICSI	0	0	0	0	1	0	0	1	0	1	0	3
Frozen + ICSI/IVF	3	1	6	0	2	1	0	2	0	1	5 <sup>d</sup>	21 <sup>d</sup>
Unknown	5	0	0	0	3	3	0	0	2	0	5	18
Cancelled after IVF/ICSI	17	16	7	1	20	7	0	1	6	0	21	96
Cycles to PGD	335	166	104	30	214	207	18	59	65	30	253 <sup>d</sup>	1481 <sup>d</sup>
Zona breaching												
AT drilling	185	111	49	16	90	73	14	28	20	21	92	699
Laser drilling	136	55	43	12	119	116	4	31	42	8	145	711
Mechanical	10	0	12	2	3	15	0	0	1	1	13	57
Unknown	4	0	0	0	2	3	0	0	2	0	3	14
Biopsy method												
Polar body biopsy	6 <sup>e</sup>	0	0	2	3	5	0	0	1	1	10 <sup>e</sup>	28 <sup>e</sup>
Cleavage aspiration	305 <sup>e</sup>	161	85	25	206	179	12	57	58	28	232 <sup>e</sup>	1348 <sup>e</sup>
Cleavage extrusion	20	5	19	3	3	19	0	0	0	1	5	75
Blastocyst	0	0	0	0	0	1	6	2	4	0	4	17
Unknown	6	0	0	0	2	3	0	0	2	0	3	16
Embryology												
COCs	4558	2690	1470	438	2973	2847	231	849	670	384	3764	20 874
Inseminated	3981	2269	1162	347	2590	2395	164	701	572	331	3160	17 672
Fertilized	2795	1507	816	231	1874	1692	119	498	404	234	2362	12 532
Biopsied	2145	1036	642	173	1241	1263	94	403	278	156	1747	9178
Successfully biopsied	2125	1010	639	171	1228	1240	93	386	277	155	1721	9045
Diagnosed	1812	841	549	149	1031	1048	85	340	233	117	1446	7651
Transferable	1086	449	346	92	454	469	43	237	96	65	683	4020
Transferred	603	335	221	61	322	286	31	128	63	55	438	2543
Frozen	208	58	24	38	34	64	4	50	12	6	110	608
Clinical outcome												
Cycles to ET	289	149	98	28	171	168	14	50	40	25	212	1244
hCG positive	94	58	29	7	51	49	4	16	13	10	74	405
Positive heartbeat	75	44	22	4	40	39	2	15	11	8	60	320
Clinical pregnancy rate % per OR/% per ET	21/26	24/30	20/22	13/14	17/23	18/23	11/14	25/30	15/28	27/32	22/28	20/26

CF, cystic fibrosis (various mutations); β-thal, β-thalassaemia; SC, sickle-cell anaemia; EB, epidermolysis bullosa; DM1, myotonic dystrophy type 1; HD, Huntington's disease; HD exclus, Huntington's disease by exclusion; AP, amyloid polyneuropathy; MS, Marfan's syndrome; CMT, Charcot–Marie–Tooth disease; ACH, achondroplasia; FRAXA, fragile-X syndrome; DMD, Duchenne muscular dystrophy (specific); Haem, haemophilia.

<sup>a</sup>Two cycles for two indications: cystic fibrosis and fragile X syndrome; cystic fibrosis and social sexing. <sup>b</sup>Includes two cycles for sickle cell and β-thalassaemia. <sup>c</sup>Includes two cycles for FRAXA testing and aneuploidy screening. <sup>d</sup>Includes two cycles with frozen-thawed embryos only so they were not counted as cycles with an OR, but were counted as cycles going to PGD. <sup>e</sup>Three cycles had both polar body biopsy and cleavage stage biopsy.

fertilized, 74% (478/644) embryos were biopsied and 96% (461/478) were successfully biopsied. Of the embryos successfully biopsied, 97% (445/461) gave a diagnostic result, of which only 25% (113/445) were transferable (of the desired sex). From 79 OR procedures, only 62% (49/79) resulted in an embryo transfer procedure. A positive hCG was obtained in 20 cycles, with a positive heartbeat in 15 cycles (19% per OR (15/79) and 31% per ET (15/49)). This gave an implantation rate of 23% (21/92). These pregnancy rates were similar to the previous data collections.

For the first time in data collections, the number of cycles undertaken for each gender is reported, and discussed. The majority of cycles were for couples who requested a male embryo (60 cycles) rather than a female embryo (19 cycles). The vast majority of the cycles in this category are from one

centre in the USA where MicroSort® sperm separation is available. Although the initial requests for males and females is reported to be 50:50, those requesting a female may opt for MicroSort® sperm selection only as the average sort purity is >90% for X-bearing sperm, compared with an average sort purity of just over 70% for Y-bearing sperm (Schulman and Karabinus, 2005). This disparity in sort percentage is the most likely cause for the uneven distribution of social sexing PGD cycles.

Social sex selection remains controversial and the debate about its application continues. Many PGS cycles include probes for the sex chromosomes and so the embryonic gender is known. Certainly in some countries, patients are requesting embryos of a particular sex after PGS (Baruch *et al.*, 2006). In other jurisdictions, patients having PGS are

**Table IVb.** Cycles performed for monogenic disorders using PCR, data collection VII.

Indication	Autosomal recessive			Autosomal dominant				Specific sex-linked			Others	Total	
	CF	β-thal (β-thal + HLA) <sup>a</sup>	SMA <sup>b</sup> (SMA + retinitis pigmentosa) <sup>a</sup>	SC or SCthal (SC + HLA) <sup>a</sup>	HD (HD exclus.) <sup>a</sup>	DM1	APC	NF1	DMD <sup>b</sup>	Haem			FRAX A <sup>b</sup>
Cycles to OR	51	38 (5)	36 (4)	19 (4)	47 (9)	80	12	18	19	8	37	133	520
Number infertile	11	17 (0)	1(0)	3 (0)	11 (0)	8	1	1	1	3	3	18	78
Female age	33	33 (33)	34 (34)	34 (38)	30 (34)	32	30	34	35	31	33	33	33
ART method													
IVF	1	0	1 (0)	0 (0)	0 (0)	0	0	0	0	0	0	1	3
ICSI	50	38 (5)	35 (4)	19 (4)	47 (9)	80	12	18	18	8	37	131	515
ICSI + frozen	0	0 (0)	0 (0)	0 (0)	0 (0)	0	0	0	1	0	0	1	2
Cancelled after IVF/ICSI	1	0 (0)	1(0)	0 (1)	2 (0)	3	3	2	4	1	1	3	22
Cycles to PGD	50	38 (5)	35 (4)	19 (3)	45 (9)	77	9	16	15	7	36	130	498
Zona breaching													
AT drilling	14	24 (2)	9 (0)	7 (0)	13 (0)	15	3	0	2	1	5	29	124
Laser drilling	31	14 (3)	23 (4)	11 (3)	32 (9)	61	6	15	13	5	30	93	353
Mechanical	5	0 (0)	3 (0)	1 (0)	0 (0)	1	0	1	0	1	1	8	21
Biopsy method													
Polar body	0	0 (0)	0 (0)	0 (0)	0 (0)	0	0	0	0	0	0	1	1
Cleavage aspiration	47	34 (5)	32 (4)	19 (3)	45 (9)	76	9	16	15	6	35	124	479
Cleavage extrusion	3	0 (0)	3 (0)	0 (0)	0 (0)	0	0	0	0	0	0	0	6
Blastocyst	0	4 (0)	0 (0)	0 (0)	0 (0)	0	0	0	0	0	0	0	4
Polar body + embryo biopsy	0	0 (0)	0 (0)	0 (0)	0 (0)	1	0	0	0	1	1	5	8
Embryology													
COC's	653	592 (50)	474 (76)	268 (32)	797 (183)	962	199	238	249	120	479	1756	7128
Inseminated	561	482 (47)	396 (33)	231 (25)	666 (158)	805	146	194	209	112	403	1507	5975
Fertilized	386	392 (27)	255 (33)	176 (19)	420 (103)	566	93	148	175	73	288	1077	4231
Biopsied	303	313 (24)	191 (30)	125 (6)	253 (72)	372	47	94	126	57	187	821	3021
Successfully biopsied	303	313 (24)	191 (30)	125 (6)	252 (72)	372	44	94	125	57	186	817	3011
Diagnosed	281	269 (23)	158 (27)	96 (6)	221 (66)	331	38	89	122	49	170	718	2664
Transferable	181	147 (2)	110 (10)	57 (0)	98 (24)	140	13	36	77	28	75	385	1383
Transferred	84	103 (2)	57 (7)	37 (0)	63 (9)	91	10	23	31	14	41	209	781
Frozen	43	12 (0)	7 (0)	0 (0)	16 (6)	16	0	4	20	4	9	67	204
Clinical outcome													
Cycles to ET	44	36 (2)	30 (3)	17 (0)	34 (6)	60	6	13	11	7	25	108	402
hCG positive	16	21 (0)	9 (0)	5 (0)	11 (1)	15	2	6	7	1	8	32	134
Positive heartbeat	12	15 (0)	9 (0)	5 (0)	6 (1)	13	2	3	5	1	6	25	103
Clinical pregnancy rate % per OR/% per ET	24/27	39 (0)/42 (0)	25 (0)/30 (0)	26 (0)/29 (0)	13(11)/18 (17)	16/22	17/33	17/23	26/45	13/14	16/24	19/23	20/26
Number fetal heartbeats % implantation rate (fetal hearts/embryos transferred)	16 > 15 [1 aborted spontaneously]	18 > 17 [1 ectopic] (0)	12 (0)	7 (0)	6 > 5 [1 arrested] (1)	14	2	4	9 > 8 [1 lost]	2 > 1 [1 lost]	7	30 > 29 [1 lost]	128 > 122 [6 lost]
% implantation rate (fetal hearts/embryos transferred)	19	17 (0)	21 (0)	19 (0)	10 (11)	15	20	17	29	14	17	14	16

HD exclus, Huntington's disease by exclusion, DM1, myotonic dystrophy, APC, Adenomatous Polyposis Coli (or FAP Familial adenomatous polyposis), NF1, Neurofibromatosis type 1.

<sup>a</sup>Numbers between brackets are not included in the numbers before the brackets. <sup>b</sup>Includes 1 cycle for specific disease and PGS.

**Table Va.** Cycles performed for PGS, data collection I–VI.

Indication	AMA	AMA + spontaneous abortion <sup>a</sup>	AMA + RIF1	Recurrent spontaneous abortion	RIF	Severe male factor <sup>b</sup>	No indication	Other	Total
Cycles to OR	1518	105	326	723	1366	352	104	297	4791
Number infertile	1371	93	296	612	1343	310	104	238	4367
Female age	40	41	40	36	35	33	33	35	36
<b>ART method</b>									
IVF	224	20	41	79	165	2	40	64	635
ICSI	1278	83	277	630	1160	349	64	218	4059
IVF + ICSI	7	0	2	10	8	0	0	1	28
Frozen + ICSI	3	2	1	3	9	1	0	0	19
Unknown	6	0	5	1	24	0	0	14	50 <sup>c</sup>
Cancelled after IVF/ICSI	64	12	2	15	57	11	4	8	173
Cycles to PGS	1454	93	324	708	1309	341	100	289	4618
Zona breaching									
AT drilling	751	48	189	480	688	134	46	188	2524
Laser drilling	643	43	130	212	522	200	49	71	1870
Mechanical	47	2	5	15	62	7	5	16	159
Unknown	13	0	0	1	37	0	0	14	65 <sup>c</sup>
Biopsy method									
Polar body biopsy	116 <sup>d</sup>	33	108	17	78	0	3	8	363 <sup>d</sup>
Cleavage aspiration	1186 <sup>d</sup>	59	216	655	1108	297	95	274	3890 <sup>d</sup>
Cleavage extrusion	133	1	0	34	79	43	2	6	298
Cleavage flow displacement	7	0	0	1	6	1	0	1	16
Unknown	13	0	0	1	38	0	0	0	52 <sup>c</sup>
Embryology									
COC's	15 614	930	3291	9874	19 140	5228	1273	3877	59 227
Inseminated	13 303	770	2739	8193	16 145	4178	1148	3230	49 706
Fertilized	9380	494	1917	5869	11 513	2822	832	2311	35 138
Biopsied	7534	489	1802	4453	8292	2051	631	1793	27 045
Successfully biopsied	7434	488	1778	4352	8197	2031	607	1758	26 645
Diagnosed	6503 <sup>e</sup>	464	1698	3776 <sup>e</sup>	7624 <sup>e</sup>	1794	452 <sup>e</sup>	1520 <sup>e</sup>	23 831 <sup>e</sup>
Transferable	1750 <sup>e</sup>	129	543	1413 <sup>e</sup>	2944 <sup>e</sup>	788	316 <sup>e</sup>	663 <sup>e</sup>	8546 <sup>e</sup>
Transferred	1838 <sup>e</sup>	103	417	1077 <sup>e</sup>	2023 <sup>e</sup>	578	187 <sup>e</sup>	514 <sup>e</sup>	6737 <sup>e</sup>
Frozen	206	16	71	172	451	85	32	108	1141
Clinical outcome									
Cycles to ET	974	63	251	549	1023	297	91	223	3471
HCG positive	275	13	58	198	312	129	33	93	1111
Positive heartbeat	207	11	45	154	228	104	30	66	845
Clinical pregnancy rate % per OR/% per ET	14/21	10/17	14/18	21/28	17/22	30/35	29/33	22/30	18/24

RIF, recurrent implantation failure. Other—includes data with two indications.

<sup>a</sup>These data were not extracted from I–IV. <sup>b</sup>These data were not extracted from I–III. <sup>c</sup>Several cycles had incomplete results. <sup>d</sup>One cycle had cleavage stage biopsy and polar body biopsy. <sup>e</sup>Several cycles from one centre had no information on the number of embryos diagnosed, number embryos diagnosed as transferable, but patients did have embryos transferred. In these cases, undiagnosed or abnormal embryos were transferred.

not permitted to choose embryos on the basis of gender. Sex selection for non-medical reasons is still prohibited in Europe and Australia.

### **Pregnancies and babies**

Tables VIIa, VIIb, IXa, IXb, Xa, Xb, XIa, XIb, (VIIIa, VIIIb, XIIa and XIIb) summarize the pregnancy and baby data. Data VII was comparable with previous data collections. Thirty-three of the 45 participating centres sent in data on the follow-up of their pregnancies and babies born. It is clear from these figures that not all PGD centres invest in long-term follow-up of the pregnancies they initiate. This shortcoming was also identified by a survey conducted jointly by IPTS (Institute for Prospective Technological Studies of the EU's Joint Research Centre), Eurogentest and ESHRE (Corveleyn *et al.*, 2007). The PGD Consortium strongly recommends that all PGD centres follow-up their pregnancies.

Six hundred and seventy nine pregnancies were reported for data VII representing 665 fetal sacs (Table VIIb). Of the 603 cycles ending in a pregnancy with a positive heartbeat, follow-up on 526 clinical pregnancies was reported. Of the 456 pregnancies reported to have ended in the birth of at least one baby (total number of babies=557), neonatal data on 528 babies born from 431 deliveries were submitted, i.e. 431 baby records were submitted from the 456 pregnancy records. The majority of deliveries were by Caesarean section (234/456) (Table IXb). The live birth rate per cycle to OR could only be calculated based on the data from centres that send in pregnancy data, as only in these instances could the cycles ( $n = 2965$ ) be followed through to their final outcome. Cycles ending in a pregnancy that was reported by the centre to be lost to follow-up were excluded from the calculation ( $n = 18$ ). Of the 456 reported deliveries, 455 ended in the birth of at least one live born baby. This leads to a live

**Table Vb.** Cycles performed for PGS, data collection VII.

Indication	AMA	AMA + spontaneous abortion	AMA + RIF	Recurrent spontaneous abortion	RIF	SMF	Prev abn preg	RIF + SMF	AMA + SMF	No indication	Other	Total
Cycles to OR	541	85	188	267	670	195	18	9	13	79	22	2087
Number infertile	477	73	173	251	669	193	13	9	11	73	21	1963
Female age	41	41	41	36	35	34	35	31	40	34	34	37
ART method												
IVF	41	8	3	27	25	0	1	0	0	38	7	150
ICSI	485	73	182	228	639	185	14	9	13	35	15	1878
IVF + ICSI	13	4	3	12	6	6	2	0	0	5	0	51
Frozen + IVF/ICSI	2	0	0	0	0	4	1	0	0	0	0	8
Cancelled after IVF/ICSI	25	3	1	4	27	10	2	0	0	4	0	76
Cycles to PGD	516	82	187	263	643	185	16	9	13	75	22	2011
Zona breaching												
AT drilling	118	27	19	81	103	47	4	0	5	7	3	414
Laser drilling	358	36	86	173	395	124	11	9	8	52	19	1271
Mechanical	40	19	82	9	145	14	1	0	0	16	0	326
Biopsy method												
PB biopsy	45	18	119	11	135	0	0	0	0	16	0	344
Cleavage aspiration	435	57	66	235	490	185	16	9	13	59	22	1587
Cleavage extrusion	36	7	2	17	18	0	0	0	0	0	0	80
Cleavage flow displacement	0	0	0	0	0	0	0	0	0	0	0	0
Embryology												
COC's	5296	798	1586	3504	8400	2630	245	159	146	914	351	24 029
Inseminated	4366	641	1049	2869	6711	2169	206	121	113	750	322	19 317
Fertilized	3045	469	702	2105	4844	1465	149	99	78	525	230	13 711
Biopsied	2454	443	1037	1592	4228	1132	117	70	65	441	172	11 751
Successfully biopsied	2428	441	1024	1585	4146	1130	117	70	65	427	172	11 605
Diagnosed	2309	423	968	1498	3880	1062	111	54	59	408	166	10 938
Transferable	703	131	339	559	1436	473	55	25	36	190	55	4002
Transferred	504	91	235	373	941	316	23	25	21	86	26	2641
Frozen	72	14	15	102	158	63	25	0	8	40	18	515
Clinical outcome												
Cycles to ET	322	55	140	205	520	155	11	9	11	57	15	1500
hCG positive	100	12	21	90	169	73	4	4	1	21	6	501
Positive heartbeat	74	6	14	72	129	56	2	3	1	15	4	376
Clinical pregnancy rate (% per OR/% per ET)	14/23	7/11	7/10	27/35	19/25	29/36	11/18	33/33	8/9	19/26	22/27	18/25
Number of fetal hearts	87	6	14	91	160	81	4	3	1	13	5	465
% implantation rate (fetal hearts/embryos transferred)	17	7	6	24	17	26	17	12	5	15	19	18

SMF, severe male factor.

**Table VIa.** PGD for social sexing, data collection I–VI.

Method for sexing	FISH	PCR	Unknown	Total
Cycles to OR	218	110	5 <sup>a</sup>	333 <sup>a</sup>
Number infertile	25	16	1	42
Female age	36	36	35	36
ART method				
IVF	110	5	3	118
ICSI	103	94	2	199
Frozen + IVF/ICSI/unknown	5	11	0	16
Cancelled after IVF/ICSI	4	6	5	15
Cycles to PGD	214	104	0	318
Zona breaching				
AT drilling	9	10	0	19
Laser drilling	113	0	0	113
Mechanical	92	94	0	186
Biopsy method				
Cleavage aspiration	121	10	0	131
Cleavage extrusion	93	94	0	187
Embryology				
COC's	2830	1658	23	4511
Inseminated	2463	1239	19	3721
Fertilized	1716	808	11	2535
Biopsied	1402	665	0	2067
Successfully biopsied	1311	655	0	1966
Diagnosed	1208	604	0	1812
Transferable	405	360	0	765
Transferred	272	269	0	541
Frozen <sup>b</sup>	108	61	0 <sup>c</sup>	169
Clinical outcome				
Cycles to ET	150	89	0	239
hCG positive	60	38	0	98
Positive heartbeat	50	24	0	74
Clinical pregnancy rate % per OR/ % per ET	23/33	22/27	—	22/31

<sup>a</sup>One natural cycle included. <sup>b</sup>Eleven cycles with embryos frozen without biopsy or failed diagnosis included. <sup>c</sup>Three embryos frozen without biopsy were not included.

birth rate per cycle to OR of 455/2965, or 15%. It is hoped that for data VIII a breakdown of the delivery rate per indication will be possible.

Confirmation of the diagnosis was performed either prenatally (316/667) or post-natally (287/581) (Table IXb). (Table XIIIb) shows the abnormalities found during or after the pregnancy. Several abnormalities were found that were not related to the PGD.

This report again indicates that pregnancies and babies born after PGD are very similar to the pregnancies obtained and babies born after ICSI treatment (Bonduelle *et al.*, 2002, Tables XIa and XIb). In our series, the number of multiple pregnancies remains high: 36% (200/557) of the babies born are part of a multiplet at birth. As multiplicity is clearly related to maternal and child morbidity and mortality, the practice of limiting the number of embryos transferred should also be introduced in PGD as it has been introduced in regular IVF.

### Misdiagnoses

An overview of the misdiagnoses reported in the previous reports and additional misdiagnoses that have subsequently been reported are shown in Table XIIIa. The table only contains details of 'adverse' misdiagnoses, i.e. when an affected or aneuploid embryo was transferred. One occurrence of a misdiagnosis without adverse effect was reported previously: the birth of twins where the two children carried cystic fibrosis

**Table VIb.** PGD for social sexing, data collection VII.

	PCR	Total
Cycles to OR	79	79
Number infertile	0	0
Female age	38	38
ART method		
IVF	5	5
ICSI	74	74
Cancelled after IVF/ICSI	1	1
Cycles to PGD	78	78
Zona breaching		
Laser drilling	1	1
Mechanical	77	77
Biopsy method		
Cleavage aspiration	1	1
Cleavage extrusion	77	77
Embryology		
COC's	1220	1220
Inseminated	949	949
Fertilized	644	644
Biopsied	478	478
Successfully biopsied	461	461
Diagnosed	445	445
Transferable	113	113
Transferred	92	92
Frozen	25	25
Clinical outcome		
Cycles to ET	49	49
hCG positive	20	20
Positive heartbeat	15	15
Clinical pregnancy rate (% per OR/% per ET)	19/31	19/31
Number fetal hearts	21	21
% Implantation rate (fetal hearts/embryos transferred)	23	23

Nineteen cycles were performed for sexing female and 60 for sexing male.

whereas at PGD the embryos had been diagnosed as homozygous normal. For most pregnancies data on this situation would not be available. Confirmation of the diagnosis for dominant disorders is not usually performed post-natally.

Eighteen misdiagnoses have been reported, 9 after PGD for PCR and 9 after PGD or PGS using FISH. In all cases of misdiagnosis, unprotected sex during the PGD cycle could be responsible as any embryos generated *in vivo* would not be tested. Patients should be advised to avoid unprotected intercourse during PGD/PGS cycles (Thornhill *et al.*, 2005).

The problems that lead to PCR misdiagnoses are well known: contamination or allele drop-out. Furthermore, embryo mosaicism and notably the presence of haploid cells could cause misdiagnoses. Certainly, for the earlier reported misdiagnoses, when the current practice of multiplex PCR or even preimplantation genetic haplotyping was not introduced, these phenomena could lead to erroneous conclusions. The misdiagnoses for DM1 and SMA were probably due to contamination according to the centres. The misdiagnoses for sexing were probably due to non-amplification of the Y-specific sequences. For the other misdiagnoses, the centres could not offer an explanation. After PGD with PCR, it is often difficult to trace back the reason for misdiagnosis. This is mainly due to the fact that the same sample cannot be analysed twice after single cell PCR. Also, because often non-transferred embryos are not systematically checked, there is no internal check to rule out human error eg incorrect labelling of the embryos, transfer of the wrong embryo, etc.

**Table VIIa.** Evolution of pregnancy, data I–VI.

	Number of pregnancies	Number of fetal sacs
Pregnancies	1634	1843
FISH cycles	1282/1634 <sup>a</sup>	
PCR cycles	353/1634 <sup>a</sup>	
Subclinical pregnancies <sup>b</sup>	212/1634	
Extrauterine gestation	7	
Clinical pregnancies	1415	1843
Singletons	1039/1415	1039/1843
Twins	324/1415	648/1843
Triplets	49/1415	147/1843
Quadruplet	2/1415	8/1843
Unknown	1/1415	1/1843 <sup>c</sup>
First trimester loss	143/1415	224/1843
Spontaneous abortion	132/1415 <sup>d</sup>	145/1843
Extrauterine pregnancy	10/1415 <sup>e</sup>	11/1843
Vanishing twins/triplets		67/1843
TOP	1/1415 <sup>f</sup>	1/1843
Ongoing pregnancies >12 weeks	1272	1619
Second trimester loss	30/1272	41/1619
Spontaneous abortion	21/1272 <sup>g</sup>	31/1619 <sup>g</sup>
TOP after misdiagnosis <sup>h</sup>	4/1272	4/1619
TOP after amniocentesis <sup>i</sup>	5/1272	5/1619
Reduction <sup>j</sup>		1/1619
Reduction of multiple pregnancies		31/1619
Quadruplet to twin	2	4/1619
Triplet to twin	11	11/1619
Triplet to singleton	7	14/1619
Twin to singleton	2	2/1619
Normal evolution	1242	1547
Lost to follow-up	65	77
Deliveries	1177	1470
Singletons	897/1177	897/1470
Twins	267/1177	534/1470
Triplets	13/1177	39/1470

<sup>a</sup>One fetal sac was tested by FISH and PCR. <sup>b</sup>Subclinical pregnancy defined as pregnancy without any other clinical signs, but positive serum hCG. <sup>c</sup>Number of fetal heartbeats not known. Counted further as 1 fetal heartbeat. <sup>d</sup>One spontaneous abortion after amniocentesis. <sup>e</sup>One heterotrophic gestation continued as singleton after reduction of extrauterine gestation at 6 weeks. <sup>f</sup>TOP for encephalocele. <sup>g</sup>One triplet: fetal reduction, followed by amniocentesis and loss of remaining twin at 16 weeks (1 fetal sac counted in reduction, 2 in spontaneous abortion, 1 second trimester pregnancy loss after spontaneous abortion counted). <sup>h</sup>TOP, termination of pregnancy. One misdiagnosis for sexing, FISH, female fetus, indication social sexing; one misdiagnosis for beta thalassaemia, PCR; one misdiagnosis for myotonic dystrophy, PCR, one misdiagnosis after PGS, karyotype 45,X. <sup>i</sup>TOP for abnormalities found after amniocentesis, not related to the PGD: trisomy 18, indication for PGD parent carrier of reciprocal translocation not involving chromosome 18; one polymalformation, one cystic hygroma, failed karyotype, one Turner mosaic, one spina bifida. <sup>j</sup>One misdiagnosis for sexing, PCR, indication Duchenne, twin pregnancy, selective termination of male fetus. Cycle done in 1996, Y-specific amplification only.

For the FISH misdiagnoses the situation is different. Slides with spread blastomeres, trophoctoderm cells or polar bodies should be kept and re-probed if any discordance with a conceptus is identified. For the PGS misdiagnosis, the centres re-analysed the slides and confirmed the normal result. However, there are several ways a misdiagnosis can result during FISH analysis. If cleavage or blastocyst stage biopsy was carried out a possible explanation could be mosaicism of the embryo, with a normal cell being biopsied from an otherwise abnormal embryo. If more than three FISH probes are used the efficiency of the FISH procedure is decreased and the risk of

**Table VIIIb.** Evolution of pregnancy, data VII.

	Number of pregnancies	Number of fetal sacs
Pregnancies	679	665
FISH only cycles	557	548
PCR only cycles	120	115
FISH + PCR	2	2
Subclinical pregnancies <sup>a</sup>	147	
Clinical pregnancies	526	665
Singletons	398	398
Twins	119	238
Triplets	7	21
Quadruplet	2	8
Unknown	6	
Lost to follow-up during first trimester	16	20
First trimester loss	40	61
Spontaneous abortion	35	39
TOP	3 <sup>b</sup>	4
Extrauterine pregnancy	2	3
Vanishing twins/triplets	0	15
Reduction of multiple pregnancies		7
Quadruplet to twin		4
Triplet to twin		2
Twin to singleton		1
Ongoing pregnancies (>12 weeks)	470	577
Second trimester loss	12	18
Spontaneous abortion	7	12
TOP	5 <sup>c</sup>	5
Selective reduction twin to singleton	0	1 <sup>d</sup>
Lost to follow-up during second trimester	2 <sup>e</sup>	2
Deliveries	456	557
Singletons	357	357
Twins	97	194
Triplets	2	6

<sup>a</sup>Subclinical pregnancy defined as pregnancy without any other clinical signs, but positive serum hCG. <sup>b</sup>Anencephaly on ultrasound, TOP for social reasons, twin with misdiagnosis for CMT1A. <sup>c</sup>Misdiagnosis reciprocal translocation 46,XY,der(15)t(13;15)(q25.1;q26.3), enlarged lateral ventricle on ultrasound, two singletons with cardiopathy on ultrasound, one singleton with tetralogy of Fallot. <sup>d</sup>One twin with hydrocephalus was selectively reduced. <sup>e</sup>One misdiagnosis (47,XXX after PGS for RIF) lost to follow-up.

overlapping signals or failure of hybridization is higher (Ruangvutitert *et al.*, 2000). There were two cases of trisomy 16 after PGS of the first polar body; although non disjunction of chromosome 16 typically occurs during maternal meiosis I, these misdiagnoses may still have resulted as a consequence of meiosis II error, fertilization with aneuploid spermatozoa, post-zygotic non-disjunction in the embryos or FISH or human error. Cumulus cell contamination is also possible during FISH

**Table IXa.** Method of delivery and gestational age, data collection I–VI.

	Total	Singletons	Twins	Triples
No. delivered	1177	897	267	13
Method of delivery				
Vaginal	507	450	56	1
Caesarian	562	374	177	11
Vaginal and Caesarian	3	2	1	0
Unknown	105	71	33	1
Term at delivery				
Preterm	292	125	157	10
Term	707	637	68	2
Unknown	178	135	42	1

**Table IXb.** Method of delivery and gestational age, data VII.

	Total	Singleton	Twin	Triplet
No. deliveries	456 <sup>a</sup>	357 <sup>a</sup>	97 <sup>a</sup>	2
Method of delivery				
Vaginal	189	175	14	
Caesarean	234	157	76	1
Vaginal and Caesarean	1		1	
Unknown	32	25	6	1
Term at delivery				
Preterm	142	71	70	1
Term	303	279	24	
Unknown	10	7	2	1

<sup>a</sup>For one twin there was only partial information: pregnancy was reported as a twin, birth and baby as a singleton.

which would result in a normal female nucleus being analysed. This is a possible explanation for the misdiagnosis of sex in the social sexing case and the XO case. When using FISH for sexing it is advisable to include the sex chromosome probes in the first round of FISH and to reduce the number of other probes in this round to ensure an accurate diagnosis of sex. For the misdiagnosis of the 47,XX,+der(22)t(11;22)(q23.3;q11.2) mat it was clearly shown that the choice of probes did not allow identification of this unbalanced product of the translocation

**Table Xa.** Confirmation of diagnosis per fetal sac, data collection I–VI.

Method	Result			
	n	Normal	Abnormal	Unknown
Prenatal diagnosis				
FISH				
CVS	56	56	0	0
Amnio	322	314	6	2
Ultrasound	244	240	4	0
Unknown	3	3	0	0
Total	625	613	10	2
PCR				
CVS	78	77	1	0
Amnio	64	57	7	0
Ultrasound	15	14	1	0
Unknown	2	2	0	0
Total	159	150	9	0
Post-natal diagnosis				
FISH				
Karyo spontaneous abortion	42	20	22	
Karyo post-natal	73	70	3	
Physical examination	446	444	2	
Total	561	534	27	
PCR				
Karyotype spontaneous abortion	4	4	0	
DNA test spontaneous abortion	2	2	0	
DNA test post-natal	30	29	1	
Sweat test	6	6	0	
Physical examination	14	13	1	
Karyotype	6	6	0	
Karyo + DNA	1	1	0	
Algo test	2	2	0	
Unknown	6	6	0	
Total	71	69	2	

FISH fetal sacs tested: 625/1445.

PCR fetal sacs tested: 159/399.

Total prenatal testing: 784/1844. One fetal sac had PCR and FISH at PGD.

Total PCR sacs/babies tested: 62/399.

Total post-natal testing: 582/1844.

**Table Xb.** Confirmation of diagnosis per foetal sac, data collection VII.

Method	Result		
	n	Normal	Abnormal
Prenatal diagnosis			
FISH			
CVS	12	12	0
Amniocentesis	65 <sup>a,b,c</sup>	63 <sup>a</sup>	2 <sup>b,c</sup>
Ultrasound	180 <sup>a,d</sup>	176	4 <sup>a,b</sup>
Total	254	251	6
PCR			
CVS	19	19	0
Amniocentesis	35 <sup>e,f</sup>	32	3 <sup>e,f</sup>
Ultrasound	11 <sup>f,g</sup>	9	2 <sup>f,g</sup>
Total	63 <sup>f</sup>	59	4
Post-natal diagnosis			
FISH			
Karyo spontaneous abortion	14 <sup>h,i</sup>	7	7 <sup>h,i</sup>
Karyo post-natal	27 <sup>j</sup>	27 <sup>j</sup>	0
Physical examination	214 <sup>i,k</sup>	212 <sup>j</sup>	2 <sup>k</sup>
Unknown	2 <sup>l</sup>	2 <sup>j</sup>	0
Total	253	244	9
PCR			
DNA test spontaneous abortion	0	0	0
Karyo spontaneous abortion	1	0	1 <sup>l</sup>
Physical examination	11	11	0
DNA test post-natal	10 <sup>m</sup>	10 <sup>m</sup>	0
Karyotype	3 <sup>m</sup>	3 <sup>m</sup>	0
Total	24	23	1

FISH foetal sacs tested: 255/550.

PCR foetal sacs tested: 63/117.

Total prenatal testing: 316/667.

FISH fetal sacs/babies tested: 253/482.

PCR fetal sacs/babies tested: 24/99.

Total post-natal testing: 287/581.

<sup>a</sup>Three foetal sacs with abnormalities on US (enlarged lateral ventricle, cardiopathy, hydrocephalus) with normal result on amnio. <sup>b</sup>Misdiagnosis 47,XXX after PGS for RIF. <sup>c</sup>Misdiagnosis 46,XY,der(15)t(13;15)(q25.1;q26.3). <sup>d</sup>Cardiopathy found on ultrasound. <sup>e</sup>Twin pregnancy, both misdiagnosed for CMT1A. <sup>f</sup>Absent ductus arteriosus, mosaic 47,XXY, 46,XY after PGD for DMD. <sup>g</sup>Third acardiacus twin found in normally developing twin pregnancy. <sup>h</sup>Trisomy 9 after PGS RIF; 47,XX,+16 after PGD for reciprocal translocation t(8;12); 48,XY,+7,t(10;16),+22/47,XY,t(10;16),+22 after PGD for reciprocal translocation t(10;16); 47,XX,+14 after PGS for AMA; 47,XY,+20 after PGS for AMA. <sup>i</sup>Mosaic 46,XY/47,XY,+22. <sup>j</sup>Two children had physical examination and a karyotype, two children had unknown check and karyotype. <sup>k</sup>One singleton born with coarctation of the aorta, one twin born with hydrocoele. <sup>l</sup>45,X after PGD for fragile X syndrome. <sup>m</sup>One baby had post-natal karyotype and DNA testing.

**Table XIa.** Data on live-born children, data collection I–VI.

Total children born	1431	
Sex		
Male	610	
Female	773	
Unknown	48	
Mean birthweight (g)		
Singletons	3242	n = 804
Twins	2424	n = 416
Triplets	1655	n = 27
Mean birth length (cm)		
Singletons	50	n = 531
Twins	46	n = 241
Triplets	43	n = 9

**Table XIb.** Data on children born, data collection VII.

Total children born	557	
Sex		
Male	247	
Female	275	
Unknown	35	
Mean birthweight (g)		
Singletons	3199	$n = 316/357^a$
Twins	2347	$n = 172/194^a$
Triplets	2016	$n = 3/6^a$
Mean birth length (cm)		
Singletons	49.8	$n = 217/357^a$
Twins	46.2	$n = 76/194^a$
Triplets	44.3	$n = 3/6^a$
Mean head circumference (cm)		
Singletons	34.1	$n = 130/357^a$
Twins	29.6	$n = 40/194^a$
Triplets		
Apgar scores after 1 min		$n = 247/557^a$
Good <sup>b</sup>	226	
Poor <sup>b</sup>	21	
Apgar scores after 5 min		$n = 229/557^a$
Good <sup>b</sup>	225	
Poor <sup>b</sup>	4	
Apgar scores after 10 min		$n = 122/557^a$
Good <sup>b</sup>	118	
Poor <sup>b</sup>	4	

<sup>a</sup>Numbers indicate the number of newborns for whom information is available out of the total number of newborns. <sup>b</sup>Good is defined  $\geq 7$ , poor is defined  $< 7$ .

(Sermon *et al.*, 2005; Mackie Ogilvie and Scriven, 2004; Kyu Lim *et al.*, 2004).

For data VII, three new misdiagnoses are reported, one for PCR (CMT1A) and two for FISH (47,XXX after PGS for RIF and 46,XY,der(15)t(13;15)(q25.1;q26.3)pat after PGD

for this reciprocal translocation) (Table XIIIb). The centre where the misdiagnosis for CMT1A occurred reported that the haplotype analysis of the family before PGD was incorrect. The family was informative for only one linked marker, for which the interpretation in the family was difficult. This couple had previously had a son after PGD using the same test, and unfortunately it was shown that this child was also affected with CMT1A (Table XIIIa). For the FISH misdiagnoses, further enquiries with the centres are ongoing.

## Discussion

Since the introduction of the filemaker Pro database in 2002, the data collection is continually being simplified. Most notably, the referral and frozen sheets will no longer be used and the data on the cancelled cycles and the re-analysis of embryos will no longer be requested. Re-analysis of untransferred embryos is important and the PGD Consortium have set up a misdiagnosis working group. A survey of centres performing re-analysis of untransferred embryos is underway.

For the first time, the misdiagnoses are reported separately and in detail. The misdiagnosis working group plans to make an in-depth analysis of these misdiagnoses, by going back to the centres and requesting specific information on the circumstances in which the misdiagnosis occurred. These findings will be published in a separate report with the aim of highlighting the pitfalls that may cause misdiagnosis and developing guidelines to minimize the risks.

The Consortium is committed to improvements in communication on issues regarding PGD. As a result, a number of initiatives are underway. There are now two levels of

**Table XIIIa.** Summary of misdiagnosis from data I–VI.

Indication	Method used	PND-post-natal	Outcome	Year of OR	Reported in consortium paper
<b>Monogenics</b>					
Myotonic dystrophy type 1	PCR	PND	TOP	1998	1
$\beta$ -thalassaemia	PCR	PND	TOP	2000	2
Familial amyloid polyneuropathy	PCR	PND	Born	2001	4
Cystic fibrosis	PCR	PND	Born	1998	2
Cystic fibrosis (1 of twins)	PCR	Post	Born	2001	4
CMT1A	PCR	Post	Born	2001	Cycle reported in data V. Misdiagnosis detected later
SMA	PCR	Post	Born	2000	Cycle reported in IV. Misdiagnosis not reported
<b>Sexing for X-linked disease</b>					
46 XY in retinitis pigmentosa	PCR	PND	Born	1998	4
46 XY in Duchenne muscular dystrophy twin	PCR	PND	TOP of one twin	1996	3
45, X Haemophilia A	FISH	PND	TOP	2001	4
<b>Translocations</b>					
46,X?,+13,der(13;14)(q10;q10)pat	FISH	Aborted spontaneously	Aborted spontaneously	2002	6
47,XX,+der(22)t(11.22)(q23.3;q11.2)mat	FISH	PND	TOP	2001	3
<b>PGS</b>					
Trisomy 16 after first PB biopsy only	FISH	Aborted spontaneously	Aborted spontaneously	2003	6
Trisomy 16 after first PB biopsy only	FISH	Aborted spontaneously	Aborted spontaneously	2002	5
Trisomy 16	FISH	Aborted spontaneously	Aborted spontaneously	2003	6
Trisomy 16	FISH	Aborted spontaneously	Aborted spontaneously	2003	6
Trisomy 21	FISH	Post	Born	1998	3
<b>Social sexing</b>					
Requested male but female fetus	FISH	PND	TOP	2000	3

PND, prenatal diagnosis.

The numbers in the last column indicate the PGD Consortium report number.

**Table XIIIb.** Misdiagnosis from data VII.

Indication	Method used	PND-post-natal	Year of OR	Outcome
Monogenic CMT1A (twins)	PCR	PND	2004	TOP of both twins
PGS 47,XXX	FISH	PND	2004	Lost to follow-up
Translocation 46,XY,der(15)t(13;15)(q25.1;q26.3)pat	FISH	PND	2004	TOP

membership of the Consortium; full membership for centres who submit annual data and associate membership for centres who cannot submit data (including new clinics, IVF units who work with a diagnostic lab who is a member of the Consortium or full members who cannot submit data for a particular year). The centres who submit data will have access to the raw data while the associate centres will be allowed to participate in the annual Consortium meetings. A quarterly newsletter for all members of registered centres is also produced.

The Consortium has set up four working groups to deal with important issues in PGD. The first is to investigate laboratory accreditation as this is now a requirement of many diagnostic laboratories. However, different countries have different systems in operation and some do not presently require any accreditation. Nevertheless, the Consortium foresees that ultimately all genetic diagnostic laboratories, including those performing PGD, will have to be accredited and be complying with ISO 15189/2007 (the Consortium are also launching an on line quality assurance scheme for PGS). The task of the second working group is to investigate current practices, appropriate indications and efficiency of aneuploidy screening, including the formulation of a consensus on the terminology. The third working group is preparing a detailed paper on the misdiagnoses and will discuss the possible sources of error that could lead to affected pregnancies. They will also collate data on re-analysis of untransferred embryos. The fourth working group is looking at ways to improve the data collection.

The paediatric follow-up of PGD babies has been launched and all Consortium members will have the opportunity to be involved in this study.

Data VIII (cycles performed in 2005) has been collected and is currently being analysed by the steering committee. It is hoped that the end-point for data VIII will be delivery rather than implantation rates for each indication.

The huge amount of detailed information the Consortium has collected is unique and studies are underway to analyse many aspects of the data in more depth.

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