

ESHRE PGD Consortium data collection XIV–XV: cycles from January 2011 to December 2012 with pregnancy follow-up to October 2013[†]

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STUDY QUESTION: How does the data collection XIV–XV of the European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium compare with the cumulative data for data collections I–XIII?

SUMMARY ANSWER: The 14th and 15th retrospective collection represents valuable data on PGD/PGS cycles, pregnancies and children: the main trend observed is the increased application of array technology at the cost of FISH testing in PGS cycles and in PGD cycles for chromosomal abnormalities.

WHAT IS KNOWN ALREADY: Since 1999, the PGD Consortium has collected, analysed and published 13 previous data sets and an overview of the first 10 years of data collections.

STUDY DESIGN, SIZE, DURATION: Data were collected from each participating centre using a FileMaker Pro database (versions 5–12). Separate predesigned FileMaker Pro files were used for the cycles, pregnancies and baby records. The study documented cycles performed during the calendar years 2011 and 2012 and follow-up of the pregnancies and babies born which resulted from these cycles (until October 2013).

PARTICIPANTS/MATERIALS, SETTINGS, METHOD: Data were submitted by 71 centres (full PGD Consortium members). Records with incomplete or inconsistent data were excluded from the calculations. Corrections, calculations and tables were made by expert co-authors.

MAIN RESULTS AND THE ROLE OF CHANCE: For data collection XIV–XV, 71 centres reported data for 11 637 cycles with oocyte retrieval (OR), along with details of the follow-up on 2147 pregnancies and 1755 babies born. A total of 1953 cycles to OR were reported for chromosomal abnormalities, 144 cycles to OR for sexing for X-linked diseases, 3445 cycles to OR for monogenic diseases, 6095 cycles to OR for PGS and 38 cycles to OR for social sexing. From 2010 until 2012, the use of arrays for genetic testing increased from 4% to 20% in PGS and from 6% to 13% in PGD cycles for chromosomal abnormalities; the uptake of biopsy at the blastocyst stage (from <1% up to 7%) was only observed in cycles for structural chromosomal abnormalities, alongside the application of array comparative genomic hybridization.

LIMITATIONS, REASONS FOR CAUTION: The findings apply to the 71 participating centres and may not represent worldwide trends in PGD.

WIDER IMPLICATIONS OF THE FINDINGS: The annual data collections provide an important resource for data mining and for following trends in PGD/PGS practice.

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Introduction

The European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium was established in 1997. Its major objectives are to establish guidelines, to promote best practice and to collect data on PGD cycles, pregnancies, deliveries and children. Four guidelines on different aspects of PGD (organization of a PGD centre, FISH-based testing, amplification-based testing and biopsy) have been written (Harton *et al.*, 2011a,b,c,d). To date, 13 extensive data collections have been published, covering all applications of PGD, including monogenic diseases, HLA typing and chromosome abnormalities, PGS and social sex selection (Geraedts *et al.*, 1999, 2000; ESHRE PGD Consortium Steering Committee, 2002; Sermon *et al.*, 2005, 2007; Harper *et al.*, 2006, 2008b, 2010b; Goossens *et al.*, 2008, 2009, 2012; Moutou *et al.*, 2014; De Rycke *et al.*, 2015). An overview has been presented after 10 years of data collection (Harper *et al.*, 2012). In this 14th report, data were exceptionally collected from two consecutive calendar years instead of a single year. Data were collected from cycles carried out in 2011–2012 with follow-up of pregnancies and babies born until October 2013.

Materials and Methods

Participating centres anonymously reported data on PGD/PGS cycles, pregnancies and babies in separate files using a FileMaker Pro database (versions 5–12). The blank FileMaker Pro files were distributed to each PGD Consortium member centre. A preliminary analysis of the submitted data allowed the identification of omissions and any ambivalent data entries. Records with incomplete or inconsistent data were excluded from the calculations. The different files were then assigned to expert co-authors for an in-depth analysis, followed by calculations and presentation of results in tables.

Clinical pregnancies were defined as the presence of one or more foetal hearts at 6 weeks of gestation. Implantation rate was defined as the number of foetal hearts per 100 embryos transferred. Delivery rate was defined as the percentage of pregnancies with delivery per oocyte retrieval procedure (OR) and per embryo transfer procedure.

Results

Only data from centres with a full PGD Consortium membership were taken into account, as only these members can provide full information on all aspects of PGD. This report includes data from 71 centres. The results are represented in tables according to an established lay out. Accompanying text is deliberately concise and four tables are available in an electronic version only: Supplementary Tables SVIIIa (data I–XIII) and SVIIIb (data XIV–XV) list the complications of pregnancy and Supplementary Tables SXIIa (data I–XIII) and SXIIb (data XIV–XV) list the congenital malformations and the neonatal complications. Cumulative data of all cycles collected previously in data collections I–XIII can be

found in Table Ia, while an overview of the current data collection can be found in Table Ib. The data for social sexing (38 cycles) have not been reported in this last table and tables with detailed data (Tables VIa and VIb) have been omitted as well, see below. For all PGD/PGS cycles (11 637 cycles to OR), ICSI was the method most often used for fertilization (10 530/11 637, 90%). For all cycles to biopsy (11 481), zona pellucida drilling was more commonly performed using a laser (9136/11 481, 80%) and cleavage-stage aspiration was the preferential stage/method for biopsy (8735/11 481, 76%) (Table Ib). Overall, blastocyst biopsy was reported in a minority of cases (471/11 481, 4%).

PGD cycles for structural chromosomal abnormalities

Table IIb summarizes the 1953 cycles with OR for data collection XIV–XV. In 169 (9%) cycles, PGD for a structural chromosome abnormality was performed simultaneously with aneuploidy screening, a slight increase as compared with data XIII in which 6% of cycles had PGS as second indication. In 17 cycles, PGD was performed simultaneously for an additional structural chromosomal abnormality (16 cycles) or a monogenic indication (1 cycle).

As for all years (cumulative data shown in Table IIa), data XIV–XV showed that PGD for reciprocal translocations was performed more often than for any other type of structural chromosome abnormality (62%). For reciprocal translocations, the number of cycles performed for female carriers was very similar as that for male carriers, whereas for Robertsonian translocations (27%), the number of cycles performed for male carriers was about 1.6-fold that of female carriers.

Mean female age was 35 years, a figure that shows little variation over the years. In 80% of all cycles to OR, ICSI was used for fertilization, similar to data XIII. Nearly all cycles to OR (96%) reached the biopsy stage. The use of laser drilling for zona breaching covered 76% of all cycles. Aspiration of blastomeres from cleavage-stage embryos remained the preferred biopsy method (83% versus 89% in data collection XIII). Biopsy at the blastocyst stage was implemented for the first time (from less than 1% in data XIII up to 7% of cycles in data XIV–XV). The use of FISH as method of analysis decreased from 93% in data XIII to 85% in the current data collection, in favour of the use of array technology, which increased from 6% to 13% between 2010 and 2012.

For data XIV–XV, 24 578 oocytes were collected, a mean of 12.6 per cycle. Of these, 61% (15 056/24 578) were fertilized (2 pronuclei) and 76% (11 404/15 056) of the resulting embryos were biopsied. Of the embryos successfully biopsied, 94% (10 475/11 103) gave a diagnostic result, of which only 24% (2481/10 475) were transferable. This was in line with previous years (data I–XIII) where a mean of 13.3 oocytes per cycle were collected and 26% of diagnosed embryos were genetically transferable. As expected, the lowest percentage of transferable embryos was found in the reciprocal translocation group (19% for male or female carriers). Of all transferable embryos, 72% were actually transferred and 17% were frozen.

Table Ia Overall cycles, data collection I–XIII.

Indication	PGD ^a	PGS	Total ^b
Cycles to OR	17 721	26 737	45 163
Number infertile	6102	21 420	27 633
Cancelled before IVF/ICSI	53	3	56
ART method			
IVF	1672	2843	4684
ICSI	15 730	23 348	39 584
IVF + ICSI	89	404	499
Frozen + ICSI + IVF + unknown	189	89	302
Unknown	24	51	75
Cancelled after IVF/ICSI	759	481	1257
Cycles to PGS/PGD	16 945	26 254	43 887
Analysis method			
FISH	7840	26 093	34 439
PCR	8712	10	8904
FISH + PCR	93	0	93
PCR + WGA	196	0	196
FISH + PCR + WGA	2	0	2
Arrays	63	127	190
FISH + arrays	0	4	4
WGA + arrays	2	15	17
Zona breaching			
AT drilling	5332	6493	11 851
Laser drilling	10 643	17 370	28 248
Mechanical	956	2326	3709
Unknown	14	65	79
Biopsy method			
PB biopsy	329	5239	5568
Cleavage aspiration	15726	19821	35728
Cleavage extrusion	576	1005	2087
Cleavage flow displacement	16	22	38
Blastocyst	142	54	197
PB and cleavage	82	26	108
Unknown	16	52	68
Embryology			
COCs	234 850	300 194	544 803
Inseminated	197 272	248 433	453 851
Fertilized	139 790	173 325	318 828
Biopsied	108 478	141 722	254 725
Successfully biopsied	106 980	140 523	251 885
Diagnosed	97 497	131 267	232 691
Transferable	36 107	45 090	82 730
Transferred	22 121	33 335	56 491
Frozen	6191	6090	12 650
Clinical outcome			
Cycles to ET	12 785	19 117	32 420

*Continued***Table Ia Continued**

Indication	PGD ^a	PGS	Total ^b
hCG positive	4742	6768	11 713
Positive heartbeat	3755	5350	9253
Clinical pregnancy rate (% per OR/% per ET)	21/29	20/28	20/29

OR, oocyte retrieval; AT, acid Tyrode's; COC, cumulus oocyte complexes; SS, social sexing; WGA, whole genome amplification; ET, embryo transfer; PB, polar body.
^aPGD column includes PGD for chromosome abnormalities, sexing for X-linked disease and PGD for single gene disorders.

^bTotal includes PGD and PGS for data I–XIII, as well as social sexing cycles for data I–XII (705 cycles). From data XIII onwards, details of social sexing cycles were no longer reported.

From 1953 cycles to OR, only 61% resulted in an embryo transfer procedure. This is in agreement with previous data (embryo transfer in 64% of cycles to OR; data I–XIII 4450/6968) showing that a high level of chromosomally abnormal embryos is found in patients carrying chromosomal abnormalities.

A positive hCG was obtained in 478 cycles, with a positive heartbeat in 372 cycles (19% per OR and 31% per embryo transfer). The poorest outcome, 12% positive heartbeat per OR, was found in the group of deletion carriers. This is linked with the lowest percentage of transferable embryos available for this group. Overall, the implantation rate was 24% (419/1776) and the delivery rate was 15% per OR (287/1953) and 24% per embryo transfer procedure (287/1196). There were 57 miscarriages and 28 clinical pregnancies were lost to follow-up. Implantation and delivery rates have remained stable over the last years: the clinical pregnancy rate for data I–XIII is 18% per OR and 28% per embryo transfer procedure.

PGD cycles for sexing for X-linked diseases

Tables IIIa and IIIb summarize the 1484 and 144 cycles to OR collected for data collections I–XIII and XIV–XV, respectively. As holds true for the PGD cycles for a chromosomal abnormality, the majority of cycles for X-linked diseases was performed with ICSI (66%), laser drilling (86%) and biopsy by cleavage-stage aspiration (91%). FISH was still the most frequently used method (78% of cycles); PCR was applied in 15% and whole genome amplification/arrays in 6% of cycles.

For data XIV–XV, 1616 oocytes were collected (a mean of 11.2 per OR), 70% (990/1424) of inseminated oocytes were fertilized and 79% (785/990) of the resulting embryos were biopsied. Of the embryos successfully biopsied, 96% (728/759) gave a diagnostic result, of which only 35% (255/728) were transferable. From 255 transferable embryos, 148 were actually transferred in 107 cycles (74% of cycles to OR). A positive hCG was obtained in 50 cycles, with a positive heartbeat in 40 cycles. This yielded a clinical pregnancy rate of 28% per OR and 37% per embryo transfer, which was a better result in comparison to the cumulative data I–XIII (20% per OR and 26% per ET). This gave an implantation rate of 27% (40/148). Finally, the delivery rate was 20% per OR (29/144) and 27% per embryo transfer (29/107). There were two miscarriages and nine clinical pregnancies were lost to follow-up.

Table 1b Overall cycle data collection XIV–XV.

Indication	PGD	PGS	Total
Cycles to OR	5542	6095	11 637 ^a
Number infertile	1753	3420	5173
Female age (years)	34	39	36
Cancelled before IVF/ICSI	0	0	0
ART method			
IVF	388	545	933
ICSI	5054	5476	10 530
IVF + ICSI	8	45	53
Frozen + ICSI/IVF	84	15	99
Unknown	2	14	16
Cancelled after IVF/ICSI	123	27	150
Cycles to PGS/PGD	5413	6068	11 481
Analysis method			
FISH	1628	4157	5785
PCR	3470	3	3473
WGA	267	640	907
Arrays	246	1225	1471
Zona breaching			
AT drilling	552	547	1099
laser drilling	4290	4846	9136
Mechanical	571	675	1246
Biopsy method			
PB biopsy	166	1730	1896
Cleavage aspiration	4867	3868	8735
Cleavage extrusion	123	174	297
Cleavage low displacement		21	21
Blastocyst	206	265	471
PB and embryo	51	10	61
Embryology			
COCs	70 965	61 794	132 754
Inseminated	58 763	52 494	111 257
Fertilized	44 047	38 510	82 557
Biopsied	34 229	30 166	64 395
Successfully biopsied	33 344	30 044	63 388
Diagnosed	30 811	28 745	59 556
Transferred	6277	5718	11 995
Frozen	2888	1371	4259
Clinical outcome			
Cycles to ET	4025	3763	7788
hCG positive	1610	1488	3098
Positive heartbeat	1246	1261	2507
Clinical pregnancy rate (% per OR/% per ET)	22/31	21/34	22/32
Number foetal heartbeats	1464	1446	2910
Implantation rate (foetal hearts/embryos transferred)	23	25	24
Deliveries	1019	816	1835

*Continued***Table 1b Continued**

Indication	PGD	PGS	Total
Delivery rate (% per OR/per ET)	18/25	13/22	16/24
Miscarriages	145	214	359
Miscarriage rate (% per clinical pregn – pregn lost to FU)	12	20	16
Clinical pregnancies lost to FU	82	231	313

PGS, preimplantation genetic screening; FISH, fluorescence *in situ* hybridization; PCR, polymerase chain reaction; ART assisted reproduction technology; FU, follow-up.

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

^a38 cycles for social sexing have not been included in this table.

PGD cycles for monogenic diseases

Tables *IVa* and *IVb* summarize the 9267 and 3445 cycles to OR collected for data collection I–XIII and XIV–XV, respectively. For data XIV–XV, ICSI was used in the majority of cycles (99% of cycles to OR) and PCR was still the most widely used first-line method of DNA amplification (93%). The use of laser was the preferred method for biopsy (81% of cycles to PGD); acidic Tyrode's or mechanical action was applied in 8% and 11% of cycles to PGD, respectively (versus 15% and 10% respectively in data XIII). These results indicate that the application of mechanical biopsy remained constant whereas the use of acidic Tyrode's has decreased in favour of laser. Day 3 cleavage-stage embryo biopsy was most frequently used (93% of cycles to PGD) while the use of blastocyst biopsy remained low (2%). These results were very similar to the previous data collection. Genetic testing was carried out on either one blastomere (58% of cycles to PGD with Day 3 biopsy) or two blastomeres per embryo (28% of cycles to PGD with Day 3 biopsy). This is an improvement compared to the previous data collection, with 43% of 1-cell biopsy cycles and 37% of 2-cell biopsy cycles. A total number of 44 771 cumulus oocyte complexes (COC) were collected and 76% of mature oocytes that were injected actually fertilized. A total of 79% of fertilized embryos were biopsied with a 97% success rate. Of the embryos successfully biopsied, 91% gave a diagnostic result. From 3402 PGD procedures, 80% resulted in an embryo transfer. Per cycle to OR on average 13.0 COCs were collected with 10.7 mature oocytes for injection. This yielded on average 8.1 fertilized embryos. Per PGD cycle on average 6.5 embryos were suitable for biopsy. Diagnosis was achieved for 5.8 embryos. On average 1.3 embryos were transferred while 0.7 embryos were used for cryopreservation, which was very similar to data XIII. A positive hCG was obtained in 1082 cycles, with a positive heartbeat in 834 cycles (25% per OR and 31% per embryo transfer) and this corresponded well with the results from the cumulative data I–XIII (24% per OR and 30% per embryo transfer). There were 1005 foetal hearts, giving an overall implantation rate of 23% (1005/4353). Finally, the delivery rate was 20% per OR and 26% per embryo transfer. There were 86 (11%) miscarriages and 45 clinical pregnancies were lost to follow-up, which is in line with previous data as well.

Table 11a PGD for chromosomal abnormalities, data collection I–XIII.

Indication	Robertsonian translocation male carrier	Robertsonian translocation female carrier	Reciprocal translocation male carrier	Reciprocal translocation female carrier	Other	Total
Cycles to OR	1262	731	1939	2101	935	6968
Number infertile	938	333	1033	879	608	3791
Female age (years)	35	33	34	33	34	34
Cancelled before IVF/ICSI	0	0	5	2	9	16
ART method						
IVF	54	126	332	563	123	1198
ICSI	1185	583	1549	1484	787	5588
IVF + ICSI	6	12	17	20	8	63
Frozen + ICSI + IVF + unknown	17	10	36	32	8	103
Cancelled after IVF/ICSI	61	28	102	117	52	360
Cycles to PGD	1201	703	1832	1982	874	6592
Zona breaching						
AT drilling	415	292	764	842	301	2614
Laser drilling	756	389	1007	1064	501	3717
Mechanical	30	22	61	76	72	261
Biopsy method						
PB biopsy	3	23	2	56	8	92
Cleavage aspiration	1130	627	1710	1786	817	6070
Cleavage extrusion	60	52	104	125	44	385
Cleavage flow displacement	2	0	2	4	3	11
Blastocyst	5	1	14	10	2	32
PB + embryo	1	0	0	1	0	2
Embryology						
COCs	17 328	10 100	26 020	27 946	11 567	92 961
Inseminated	14 424	8595	22 183	24 186	9700	79 088
Fertilized	9815	6262	15 856	17 663	6950	56 546
Biopsied	7005	4780	12 126	13 816	5239	42 966
Successfully biopsied	6922	4723	11 972	13 640	5186	42 443
Diagnosed	6367	4376	11 172	12 788	4810	39 513
Transferable	2440	1289	2254	2427	1776	10 186
Transferred	1584	902	1779	1920	1194	7379
Frozen	363	158	219	194	223	1157
Clinical outcome						
Cycles to ET	926	523	1133	1194	674	4450
hCG positive	363	189	412	412	220	1596
Positive heartbeat	305	151	310	323	174	1263
Clinical pregnancy rate (% per OR, % per ET)	24/33	21/29	16/27	15/27	19/26	18/28

Preimplantation genetic screening

Overall, 6095 PGS cycles were reported in data collection XIV–XV (Table Vb). The mean age of women undergoing PGS was 39 years, which is the same as in data collection XIII but slightly higher than the mean age of 37 years observed in the cumulative data of previous collections I–XIII (Table Va). The most common indications for PGS were advanced maternal age (40%), repeated implantation failure (12%) as a

single indication or in combination either with advanced maternal age (12%) or with recurrent miscarriage (10%) and severe male factor (9%). Other indications were previous abnormal pregnancies, individuals with abnormal karyotypes, including mosaicism for numerical chromosomal abnormalities and couples with more than one indication. A small number of couples underwent PGS following oocyte donation or without a reported medical indication.

Table Iib PGD for chromosomal abnormalities, data collection XIV–XV.

Indication	Robertsonian translocation male carrier ^a	Robertsonian translocation female carrier ^b	Reciprocal translocation male carrier ^c	Reciprocal translocation female carrier ^d	Deletion ^e	Inversion ^f	Other chromosomal abnormalities	Other ^g	Total									
Cycles to OR	326	198	603	604	42	85	77	18	1953									
Number infertile (%)	204 (63)	65 (35)	292 (48)	243 (40)	26 (62)	42 (49)	41 (53)	11	923 (47)									
Female age (years)	37.3	34.6	34.3	34.6	32.9	35.3	35.1	35.7	35.0									
Cancelled after OR before IVF/ICSI	1	0	5	0	0	0	0	0	6									
ART method																		
IVF	13	32	78	157	13	7	9	0	309									
ICSI	303	157	488	419	29	78	67	17	1558									
IVF + ICSI	1	0	5	1	0	0	1	0	8									
IVF + frozen	1	1	3	4	0	0	0	0	9									
ICSI + frozen	7	8	22	23	0	0	0	1	61									
Unknown	0	0	2	0	0	0	0	0	2									
Cancelled after IVF/ICSI	18	6	26	21	3	5	1	0	80									
Cycles to PGD	307	192	572	583	39	80	76	18	1867									
Zona breaching																		
AT drilling	39	36	76	107	3	15	7	1	284									
Laser drilling	247	141	437	419	35	65	65	16	1425									
Mechanical	21	15	59	57	1	0	4	1	158									
Biopsy method																		
PB	1	34	0	19	0	1	1	0	56									
Cleavage aspiration	274	139	489	486	36	69	58	7	1558									
Cleavage extrusion	11	8	35	44	3	0	10	1	112									
Blastocyst	20	10	48	31	0	10	7	10	136									
PB + embryo	1	1	0	3	0	0	0	0	5									
Analysis technique																		
FISH	259	138	498	514	38	68	71	3	1589									
PCR	5	9	13	6	0	0	3	4	40									
WGA/array	43	45	61	63	1	12	2	11	238									
Embryology																		
COCs (mean/OR)	4027	12.4	2453	12.4	7828	13.0	7569	12.5	336	8.0	1239	14.6	920	11.9	206	11.4	24 578	12.6
Inseminated (mean/OR)	3312	10.2	2041	10.3	6554	10.9	6490	10.7	279	6.6	1033	12.1	778	10.1	150	8.3	20 637	10.6
Fertilized (mean/OR)	2225	6.8	1541	7.8	4787	7.9	4835	8.0	199	4.7	772	9.1	575	7.5	122	6.8	15 056	7.7
Biopsied (mean/biopsy)	1641	5.3	1299	6.8	3584	6.3	3667	6.3	147	3.8	557	6.9	421	5.5	88	4.9	11 404	5.8
Successfully biopsied (mean/biopsy)	1588	5.2	1212	6.3	3519	6.1	3597	6.2	143	3.7	552	6.9	404	5.3	88	4.9	11 103	5.7
Diagnosed (mean/biopsy)	1487	4.8	1138	5.9	3309	5.8	3397	5.8	138	3.5	530	6.6	392	5.2	84	4.7	10 475	5.6

Continued

Table IIb Continued

Indication	Robertsonian translocation male carrier ^a		Robertsonian translocation female carrier ^b		Reciprocal translocation male carrier ^c		Reciprocal translocation female carrier ^d		Deletion ^e		Inversion ^f		Other chromosomal abnormalities		Other ^g		Total		
Transferable (%/diagnosed)	560	38%	300	26%	624	19%	636	19%	38	27%	169	32%	133	34%	21	25%	2481	24%	
Transferred	362		212		474		502		25		96		90		15		1776		
Frozen	93		50		120		92		4		34		24		6		423		
Clinical outcome																			
Cycles to ET (%/OPU)	225	69	129	65	340	56	349	58	23	55	62	73	58	75	10	56	1196	61	
hCG positive	83		54		146		137		8		20		25		5		478		
Positive heartbeat	64		46		117		107		5		13		16		4		372		
Clinical pregnancy rate (% per OR/% per ET)	20	28	23	36	19	34	18	31	12	22	15	21	21	28	22	40	19	31	
Number of foetal hearts	80		49		130		119		5		14		17		5		419		
Implantation rate (% foetal hearts/100 embryos transferred)	22		23		27		24		20		15		19		33		24		
Deliveries	41		36		92		89		2		9		14		4		287		
Miscarriages	13		6		20		11		3		2		2		0		57		
Lost to FU	10		4		5		7		0		2		0		0		28		

^aSecond indication PGS ($n = 30$), reciprocal male carrier ($n = 1$).

^bSecond indication PGS ($n = 31$).

^cSecond indication PGS ($n = 45$), robertsonian male carrier ($n = 3$), inversion ($n = 5$), monogenic disease ($n = 1$).

^dSecond indication PGS ($n = 31$), robertsonian male carrier ($n = 3$), inversion ($n = 3$).

^eSecond indication PGS ($n = 3$).

^fSecond indication PGS ($n = 29$), reciprocal female carrier ($n = 1$).

^g18 cycles for translocations of unknown carrier gender.

Table IIIa Sexing only for X-linked disease, data collection I–XIII.

	Total
Cycles to OR	1484
Number infertile	336
Female age	32
Cancelled before IVF/ICSI	2
ART method	
IVF	423
ICSI	1038
IVF + ICSI	14
ICSI + Frozen	5
IVF + Frozen	2
Cancelled after IVF/ICSI	74
Cycles to PGD	1408
Zona breaching	
AT drilling	644
Laser drilling	686
Mechanical	78
Biopsy method	0
PB	2
Cleavage aspiration	1328
Cleavage extrusion	69
Flow displacement	5
Blastocyst	4
Embryology	
COCs	19 163
Inseminated	16 765
Fertilized	11 911
Biopsied	9100
Successfully biopsied	8893
Diagnosed	8191
Transferable	2849
Transferred	1934
Frozen	545
Clinical outcome	
Cycles to ET	1112
hCG positive	372
Positive heartbeat	290
Clinical pregnancy rate (% per OR/% per ET)	20/26

The majority of biopsies (67%) were performed at cleavage stage; blastocyst biopsy was carried out in only 4% of cycles. Laser biopsy was the preferred method (80%); acidic Tyrode's or mechanical zona breaching was applied in 9% and 11% of cycles to PGS, respectively. For the genetic analysis FISH was used in 68% of cases while arrays were used in 20% of cases (Table 1b); in data collection XIII only 4% of PGS cycles were carried out with arrays. This indicates the onset of a more

Table IIIb Sexing only for X-linked disease, data collection XIV–XV.

	Total
Cycles to OR	144
Number infertile (% OR)	49 (34%)
Female age (years)	33
ART method	
IVF	48
ICSI	95
IVF + frozen	1
Cancelled after IVF/ICSI	-
Cycles to PGD	144
Zona breaching	
AT drilling	7
Laser drilling	124
Mechanical	13
Biopsy method	
Cleavage aspiration	131
Cleavage extrusion	10
Blastocyst	3
Analysis method	
FISH	113
PCR	22
WGA/array	9
Embryology	
COCs (mean/OR)	1616 (11,2)
Inseminated (mean/OR)	1424 (9,9)
Fertilized (mean/OR)	990 (6,9)
Biopsied (mean/biopsy)	785 (5,5)
Successfully biopsied (mean/biopsy)	759 (5,3)
Diagnosed (mean/biopsy)	728 (5,1)
Transferable	255
Transferred	148
Frozen	80
Clinical outcome	
Cycles to ET (%/OR)	107 (74)
hCG positive	50
Positive heartbeat	40
Clinical pregnancy rate (% per OR/% per ET)	28/37
Number foetal hearts	40
% Implantation rate (foetal heartbeats/100 embryos transferred)	27
Deliveries	29
Delivery rate (% per OR/% per ET)	20/27
Miscarriages	2
Miscarriage rate (% per clinical pregn – pregn lost to FU)	6
Clinical pregnancies lost to FU	9

Table IVa Cycles performed for single gene disorders, data collection I–XIII.

Indication	X-linked	Autosomal recessive	Autosomal dominant	HLA		Other	Total
				HLA only	HLA + monogenic disease		
Cycles to OR	1330	2838	3114	174	469	1342	9267
Number infertile	258	901	554	2	21	239	1975
Female age (years)	32	34	32	35	34	31	33
Cancelled before IVF/ICSI	0	0	3	0	0	1	4
Art method							
IVF	17	21	2	0	0	12	52
ICSI	1298	2773	3084	169	458	1317	9099
IVF + ICSI	3	2	4	2	1	0	12
IVF + frozen	0	0	1	0	0	0	1
ICSI + frozen	4	14	8	0	4	0	30
IVF+ICSI + Frozen	6	21	6	1	6	9	49
Unknown	2	7	6	2	0	5	22
Cancelled after IVF/ICSI	47	97	106	6	12	54	322
Cycles to PGD	1283	2741	3005	168	457	1289	8943
Zona breaching							
AT drilling	266	773	679	4	38	318	2078
Laser drilling	888	1770	2142	161	404	868	6233
Mechanical	127	194	179	3	15	100	618
Unknown	2	4	5	0	0	3	14
Biopsy method							
PB biopsy	51	50	71	0	0	63	235
Cleavage aspiration	1185	2552	2866	145	421	1155	8324
Cleavage extrusion	9	87	45	10	8	32	191
Blastocyst	7	39	8	13	29	11	107
PB + embryo	30	10	11	0	0	25	76
Unknown	3	7	5	0	0	6	21
Embryology							
COCs	15 712	38 582	40 703	2423	6697	18 603	122 720
Inseminated	13 142	31 716	33 751	1940	5487	15 382	101 418
Fertilized	9924	23 410	2201	1571	4471	11 315	75 892
Biopsied	7120	17 960	18 313	1200	3615	8203	56 411
Successfully biopsied	6997	17 674	18 073	1196	3590	8113	55 643
Diagnosed	6312	15 596	16 286	1099	3282	7217	49 792
Transferable	3160	8832	6876	213	508	3487	23 076
Transferred	1765	4695	3807	155	396	1990	12 808
Frozen	545	1685	1190	84	378	609	4491
Clinical outcome							
Cycles to ET	1002	2396	2402	105	259	1058	7222
hCG positive	364	977	878	39	115	401	2774
Positive heartbeat	294	776	684	30	100	318	2202
Clinical pregnancy rate (% per OR/% per ET)	22/29	27/32	22/28	17/29	21/39	24/30	24/30

widespread implementation of array comparative genomic hybridization (CGH), but is not yet linked with an uptake of blastocyst biopsy. From a total of 52 494 oocytes that were inseminated, 38 510 (73%) were fertilized. Of 30 044 embryos that were successfully biopsied, 28 745 resulted in a diagnosis (55% of all oocytes inseminated and 96% of all embryos successfully biopsied). Of these 28% were genetically

Table IVb Cycles performed for single gene disorders using PCR, data collection XIV–XV.

Indication	X-linked	Autosomal		HLA		Other	Total							
		recessive	dominant	Only	+ monogenic disease									
Cycles to OR	573	997	1698	26	136	15	3445							
Number infertile	121	311	339	0	1	9	781							
Female age (years)	32.5	33.7	32.6	35.2	33.2	33.2	32.9							
Cancelled before IVF/ICSI	0	0	0	0	0	0	0							
ART method														
IVF	1	4	4	5	14	3	31							
ICSI	570	986	1691	20	122	12	3401							
ICSI + frozen	2	7	3	1			13							
Cancelled after IVF/ICSI	5	10	27	0	1	0	43							
Cycles to PGD	568	987	1671	26	135	15	3402							
Zona breaching														
AT drilling	39	92	121		9		261							
Laser drilling	424	742	1410	26	124	15	2741							
Mechanical	105	153	140		2		400							
Biopsy method														
PB	53	19	38				110							
Cleavage aspiration	501	899	1607	26	130	15	3178							
Cleavage extrusion			1				1							
Blastocyst	7	40	15		5		67							
PB + embryo	7	29	10				46							
Biopsy policy														
1 cell biopsy	264	663	9939	22	86	7	1981							
2 cell biopsy	193	215	520	2	33	6	969							
1 or 2 cell biopsy	81	55	178	2	9	2	327							
> 2 cells (including TE)	5	3	2		1		11							
1 and 2 polar bodies	18	13	20		0		51							
Unknown	7	38	12		6		63							
Analysis method ^a														
FISH	13	14	23		6		56							
PCR	571	977	1686	26	134	15	3409							
WGA	23	85	50		2		160							
arrayCGH	3	18	9				30							
Embryology														
COCs (mean/OR)	7225	12.6	13 327	13.4	21 845	12.9	369	14.2	1852	13.6	153	10.2	44 771	13.0
Inseminated (mean/OR)	5983	10.4	10 904	11.0	17 953	10.6	281	10.8	1451	10.7	130	8.7	36 702	10.7
Fertilized (mean/OR)	4506	7.9	8342	8.4	13 639	8.1	239	9.2	1174	8.6	101	6.7	28 001	8.1
Biopsied (mean/biopsy)	3494	6.2	6332	6.4	10 989	6.6	166	6.4	968	7.2	91	6.1	22 040	6.5
Successfully biopsied (mean/biopsy)	3336	5.9	6169	6.3	10 758	6.4	166	6.4	964	7.1	89	5.9	21 482	6.3
Diagnosed (mean/biopsy)	3035	5.3	5506	5.6	9949	6.0	154	5.9	879	6.5	85	5.7	19 608	5.8
Failed (mean/biopsy)	202	0.4	416	0.4	642	0.4	10	0.4	50	0.4	4	0.3	1324	0.4
Abnormal (mean/biopsy)	227	0.4	449	0.5	1063	0.6	24	0.9	118	0.9	15	1.0	1896	0.6
Transferred (mean/biopsy)	762	1.3	1519	1.5	1944	1.1	20	0.8	88	0.7	20	1.3	4353	1.3
Frozen	233		968		1007		10		148		19		2385	0.7

Continued

Table IVb *Continued*

Indication	X-linked		Autosomal recessive		Autosomal dominant		HLA Only			+ monogenic disease		Other		Total	
Clinical outcome															
Cycles to ET (%/OR)	469	82	851	86	1305	77	15	58	68	50	14	93	2722	(79%)	
hCG Positive	163		376		516		6		24		6		1082		
Positive heartbeat	123		300		383		6		16		6		834		
Clinical pregnancy rate (% per OR)	22		30		23		23		12		40		25		
Clinical pregnancy rate (% per ET)	26		35		29		40		24		43		31		
Number foetal heartbeats	141		370		459		7		23		5		1005		
Implantation rate (% foetal hearts/embryos transferred)	19		24		24		35		26		25		23		
Deliveries	104		238		337		6		14		4		703		
Delivery rate (% per OR)	18		24		20		23		10		27		20		
Delivery rate (% per ET)	22		28		26		40		20		29		26		
Miscarriages	12		38		33		0		2		1		86		
Miscarriage rate (% per clinical pregn – pregn lost to FU)	10		14		9		0		12		20		11		
Clinical pregnancies lost to FU	7		24		13		0		0		1		45		

TE, trophoctoderm.

^aSometimes more than one method of analysis per cycle was reported, making the total sum of the section analysis method exceed the number of cycles to PGD.

transferrable, 72% were actually transferred and 17% were frozen. This was in accordance with the cumulative data (Table Va) where 34% (45 090/131 267) of diagnosed embryos were transferable and 74% (33 332/45 090) were used for transfer while 14% were cryopreserved.

Overall, of 6095 cycles that reached OR, 3763 (62%) had an embryo transfer and a positive hCG was obtained in 1488 cycles, with a positive heartbeat in 1261 cycles, yielding a clinical pregnancy rate of 21% per OR or 34% per embryo transfer procedure. This was slightly better than the overall clinical pregnancy rates from data I–XIII (20% per OR and 28% per embryo transfer). There were 816 reported deliveries, and 231 clinical pregnancies were lost to follow-up. The overall delivery rate was 13% per cycle to OR and 22% per cycle to embryo transfer. The overall miscarriage rate per clinical pregnancy was 21% for all indications, ranging from 8% for advanced maternal age combined with severe male factor or oocyte donation and severe male factor to 35% for advanced maternal age in combination with repeated IVF failure.

PGD cycles for social sexing

The number of reported cycles for social sexing in data XIV–XV was similar to previous data collections, accounting for less than 1% (38/11 675) of all cycles submitted. Details on 705 cycles for social sexing were reported in data I–XII. Because social sexing as an indication for PGD is debatable, from data XIII onwards, only cycle numbers were included in the reports.

Pregnancies and babies

Tables VIIa, VIIb, IXa, IXb, Xa, Xb, XIa, XIb and the Supplementary Tables SVIIIa, SVIIIb, SXIIa and SXIIb summarize the pregnancy and baby

data. Data XIV–XV included 2147 clinical pregnancies (Table VIIb) with 1755 deliveries of 19 stillborns and 2066 liveborns. The number of multiple pregnancies remained high (427/2147, 20%—Table VIIb); which is in accordance with previously published data collections. Of the 2147 clinical pregnancies presenting with a positive heartbeat, follow-up data on 1231 pregnancies were reported. There were 91/1231 complications in pregnancy reported (Supplementary Table SVIIIb). The delivery rates per indication were reported in Tables IIb, IIIb, IVb, Vb and VIb. Caesarean section was performed for 44% of the deliveries (765/1755) (Table IXb). In 315 cases, the method of delivery was not known. Confirmation of the diagnosis was performed prenatally in 506 cases, and/or post-natally in 590 cases (Table Xb). In 10 cases, a chromosomal abnormality was found, not related to the indication for PGD. Table Xb and Supplementary Table SXIIb describe the data on congenital malformations, neonatal complications and perinatal deaths. In 1585 out of 2066 cases (77%) the information on malformations found during pregnancy was lacking, and in 1674 out of 2066 liveborns (81%) the information on neonatal malformations was lacking. In 26 out of 481 cases (5%), a minor- and/or major-malformation(s) was reported. Of these cases, 11 resulted in termination of pregnancy (TOP). In 6% of the reported cases a neonatal complication occurred (Supplementary Table SXIIb).

Unfortunately, the organization of adequate children follow-up is even more difficult than the follow-up of the clinical pregnancies. However, follow-up of the children born after PGD remains of great importance.

Misdiagnoses

Table XIIIa summarizes the misdiagnoses reported for data I–XIII, with no misdiagnoses reported in data X, data XI and the current dataset.

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

Indication	AMA	AMA + miscarriage	AMA + RIFI	Recurrent miscarriage	Recurrent IVF failure	Severe male factor	Oocyte donation	Prev abn preg	No indication	Other	Total
Cycles to OR	9054	1213	2602	3352	5621	2387	341	164	675	1328	26 737
Number infertile	6974	804	2427	1718	5286	2124	271	54	634	1128	21 420
Female age (years)	41	40	41	34	34	35	39	37	35	36	37
Cancelled before IVF/ICSI	0	0	0	0	1	0	0	0	0	1	2
ART method											
IVF	1175	235	390	323	426	12	4	14	148	116	2843
ICSI	7748	953	2184	2936	5084	2322	334	150	469	1169	23 349
IVF + ICSI	102	17	17	73	67	41	3	0	57	26	403
IVF + frozen	0	2	1	1	1	1	0	0	0	0	6
ICSI + Frozen	22	6	5	18	18	11	0	0	1	2	83
Unknown	7	0	5	1	24	0	0	0	0	14	51
Cancelled after IVF/ICSI	186	26	10	44	128	35	0	0	27	24	480
Cycles to PGS	8868	1187	2592	3308	5492	2352	341	164	648	1303	26 255
Zona breaching											
AT drilling	1746	217	633	953	1366	827	38	36	278	399	6493
Laser drilling	6690	841	1490	2214	3418	1227	191	128	321	851	17 371
Mechanical	419	129	469	140	671	298	112	0	49	39	2326
Unknown	13	0	0	1	37	0	0	0	0	14	65
Biopsy method											
PB	1616	470	1516	236	942	39	0	1	151	268	5239
Cleavage aspiration	6854	674	994	2931	4253	2227	247	154	488	1000	19 822
Cleavage extrusion	367	34	77	114	239	80	94	3	3	30	1041
Cleavage flow displacement	7	0	0	3	7	1	0	0	0	4	22
Blastocyst	3	6	2	22	10	3	0	6	1	1	54
PB + embryo	9	3	3	1	3	2	0	0	5	0	26
Unknown	13	0	0	1	38	0	0	0	0	0	52
Embryology											
COC's	86 910	11 378	23 778	41 713	71 867	34 040	4356	1846	7570	16 746	300 204
Inseminated	73 526	9409	18 767	34 528	58 732	27 621	3758	1551	6506	14 035	248 433
Fertilized	51 686	6691	13 018	25 494	42 376	19 445	2849	1160	4533	9994	177 246
Biopsied	40 124	6003	13 306	19 343	33 823	14 637	2144	867	3691	7879	141 817
Successfully biopsied	39 725	5968	13 206	19 174	33 396	14 575	2137	858	3640	7814	140 493
Diagnosed	37 064	5601	12 227	17 928	31 442	13 776	2 084	811	3269	7065	131 267
Transferable	10 208	1519	3930	6532	11 777	5529	992	323	1435	2845	45 090
Transferred	8777	1283	3316	4550	8120	3603	559	205	930	1989	33 332
Frozen	1089	147	397	1008	1646	736	269	87	180	531	6090
Clinical outcome											
Cycles to ET	5416	792	1916	2567	4431	1977	302	126	527	1063	19 117
HCG positive	1625	229	459	1092	1617	859	166	58	216	447	6768
Positive heartbeat	1250	177	366	868	1262	724	138	50	180	345	5360
Clinical pregnancy rate (% per OR/% per ET)	14/23	15/22	14/19	26/34	22/28	30/37	40/46	30/40	27/34	26/32	20/28

AMA, advanced maternal age; RIFI, repeated implantation failure; SMF, severe male factor; Prev abn preg, previous abnormal pregnancy.

Table Vb Cycles performed for PGS, data collection XIV–XV.

Indication	AMA ^a	AMA + Rec misc ^b	AMA + RIF ^c	Rec. Misc ^d	RIF ^e	RIF + Rec	SMF ^f	Prev abn preg ^f	RIF + SMF	AMA + SMF	NumAbno ^f	NO indic	Ovum donat	Ovum donat + SMF	Total
Cycles to OR	2471	312	727	592	754	32	531	56	49	91	168	181	76	55	6095
Number infertile	1125	96	440	158	598	9	471	25	46	64	160	113	71	44	3420
Female age (years)	41.2	41.1	39.9	36.3	35.9	36.9	35.4	37.6	35.5	40.8	39.5	40.5	40.9	41.6	39.2
ART method															
IVF	279	41	113	25	40	2	2	3	2	1	5	32	0	0	545
ICSI	2164	266	608	553	708	30	521	53	45	90	160	147	76	55	5476
IVF + ICSI	21	1	0	7	4	0	7	0	0	0	3	2	0	0	45
ICSI + frozen	2	4	3	6	0	0	0	0	0	0	0	0	0	0	15
IVF + frozen	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	5	0	3	1	2	0	1	0	1	0	0	0	0	0	13
Unknown + frozen	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Cancelled post OR	13	0	0	0	0	0	3	0	0	0	0	11	0	0	27
Cycles to PGD	2458	312	727	592	754	32	528	56	49	91	168	170	76	55	6068
Zona breaching															
AT drilling	107	26	154	48	64	1	71	1	6	17	38	6	5	3	547
Laser drilling	2197	278	552	495	540	28	354	51	32	66	28	140	33	52	4846
Mechanical	154	8	21	49	150	3	103	4	11	8	102	24	38	0	675
Biopsy method															
PB	750	99	456	89	209	7	15	2	15	3	6	79	0	0	1730
Cleavage aspiration	1559	184	238	462	456	20	483	48	27	86	158	51	41	55	3868
Cleavage extrusion	41	2	18	15	36	0	21	1	3	1	1	0	35	0	174
Cleavage low displacement	17	0	4	0	0	0	0	0	0	0	0	0	0	0	21
Blastocyst	88	27	11	25	50	5	9	4	3	1	3	39	0	0	265
PB + embryo	3	0	0	1	3	0	0	1	1	0	0	1	0	0	10
Embryology															
COCs	21 911	2927	6227	6903	8786	399	7083	586	543	1007	1815	2112	745	750	61 794
Inseminated	18 770	2539	5477	5728	7384	322	5775	498	451	822	1524	1809	687	708	52 494
Fertilized	13 604	1858	3804	4345	5558	259	4225	387	327	576	1149	1326	556	536	38 510
Biopsied	10 599	1508	3489	3316	4265	196	3186	288	250	448	849	897	442	433	30 166
Successfully biopsied	10 552	1503	3477	3306	4252	196	3171	287	249	448	849	884	441	429	30 044
Diagnosed	10 177	1417	3270	3165	4034	183	3046	281	243	432	841	835	416	405	28 745
Transferable	2111	323	701	1064	1366	64	1137	82	76	91	304	306	208	137	7970
Transferred	1739	257	640	685	896	35	666	56	48	79	219	211	109	78	5718

Frozen	249	77	103	206	264	16	214	15	15	5	39	89	48	31	1371	
Clinical outcome																
Cycles to ET	1236	171	428	432	572	23	406	37	33	55	131	132	62	45	3763	
hCG positive	403	65	106	215	243	14	208	22	13	21	69	61	22	26	1488	
Positive heartbeat	335	54	101	176	203	10	188	19	12	14	52	53	18	26	1261	
Clinical pregnancy rate (% per OR/% per ET)	14/27	17/32	14/24	30/41	27/35	31/43	35/46	34/51	24/36	15/25	31/40	29/40	24/29	47/58	21/34	
Number of foetal hearts	369	64	112	212	236	11	206	21	13	14	67	65	19	37	1446	
Implantation rate (% foetal hearts/100 embryos transferred)	21	25	18	31	26	31	31	38	27	18	31	31	17	47	25	
Deliveries	213	29	53	115	125	9	119	16	8	9	45	41	11	23	816	
Delivery rate (% per OR/% per ET)	9/17	9/17	7/12	19/27	17/22	28/39	22/29	29/43	16/24	10/16	27/35	23/32	14.5/18	42/51	13/22	
Miscarriages	69	15	28	30	26	1	24	3	3	1	5	5	2	2	214	
Miscarriage rate (% per clinical pregn – pregn lost to FU)	24	34	35	21	17	11	17	10	27	8	10	12	15	8	21	
Clinical pregnancies lost to FU	53	10	20	31	52	0	45	0	1	4	2	7	5	1	231	

Cycles with a second indication:
^a23 cycles.
^b11 cycles.
^c36 cycles.
^d43 cycles.
^e8 cycles.
^f2 cycles.

Table VIIa Evolution of pregnancy, data collection I–XIII.

	N pregnancies	N foetal sacs
Analysis method	10 639	
FISH	7940	
PCR	2490	
FISH + PCR	18	
WGA/array	71	
WGA + PCR ^a	102	
PCR + Array	16	
FISH + Array	2	
Subclinical pregnancies ^b	1698	
Clinical pregnancies with foetal heartbeat	8810	10 912
Singletons	6642	6642
Twins	1871	3742
Triplets	161	483
Quadruplet	11	44
Unknown	125	1
Lost to FU during first trimester	131	161
First trimester loss	865	1083
Miscarriage	973	1060
TOP	18	19
Vanishing/miscarriage multiples	0	215
Reduction of multiple pregnancies	0	80
Quadruplet to twin	0	14
Triplet to twin	0	24
Triplet to singleton	0	21
Twin to singleton	1144	1403
Unknown	29	37 ^c
Ongoing pregnancies > 12 weeks	6433	7974
Second trimester loss	115	188
Miscarriage	123	162
Miscarriage twin to singleton	0	4
TOP	50	54
Twin to twin transfusion	1	2
Vanishing/miscarriage multiples		
Reduction of multiple pregnancies		39
Quadruplet to twin		4
Triplet to twin		11
Triplet to singleton		14
Twin to singleton		6
Lost to FU during second trimester	1457	333
Deliveries	7134	8765
Singletons	5560	5560
Twins	1517	3037
Triplets	57	171

TOP, termination of pregnancy.

^aData available since data collection XI.

^bSubclinical pregnancy defined as pregnancy without any other clinical signs, but positive serum hCG.

^cNumber of foetal heartbeats not known for data I–VIII, counted further as one foetal heart.

Table VIIb Evolution of pregnancy, data collection XIV–XV.

	N pregnancies	N foetal hearts	
Pregnancies	3097		
FISH only cycles	1359		
PCR only cycles	1014		
Array	407		
PCR + WGA	74		
PCR + Array	10		
FISH + Array	0		
FISH + PCR	8		
Subclinical pregnancies ^a + lost to follow-up	950		
Clinical pregnancies, with foetal heartbeat	2147	2600	
Singletons	1720	1720	
Twins	403	806	
Triplets	22	66	
Quadruplet	2	8	
First trimester loss			
Miscarriage	303	408	
TOP ^b	1	2	
Vanishing/miscarriage multiples			
Twin to singleton	32	32	
Triplet to twin	1	1	
Triplet to singleton	4	8	
Reduction of multiple pregnancies			
Triplet to twin	6		
Twin to singleton	0	0	
Triplet to singleton	3	6	
Quadruplet to twin	2	2	
Ongoing pregnancies (> 12 weeks)	1795	2135	
Second trimester loss			
Miscarriage	33	43	
TOP	7	7	
Deliveries	1755	2085 ^b	2066 ^c
Singletons	1429	1429	1419
Twins	322	644	635
Triplets	4	12	12

^aSubclinical pregnancy (i.e. biochemical and blighted ovum) defined as a pregnancy without any other clinical signs.

^bLiveborns and stillborns.

Discussion

In order that the data are up to date, this 14th data report of the ESHRE PGD Consortium involves data from two consecutive calendar years instead of a single year. The most time-consuming step in data processing involves data 'cleaning': inconsistent data are clarified or

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

	Total	Singletons	Twins	Triplets
Number of deliveries	7075	5514	1505	56
Method of delivery				
Vaginal	2993	2694	297	2
Caesarian	3343	2243	1053	47
Vaginal and Caesarian	11	2	9	0
Unknown	728	575	146	7
Term at delivery				
Preterm (<37 weeks)	1786	777	968	41
Term	4758	4333	420	6
Post term	7	7	0	0
Unknown	523	397	116	9

Table IXb Method of delivery and gestational age, data collection XIV–XV.

	Total	Singleton	Twin	Triplet
Number of deliveries	1755	1429	322	4
Method of delivery				
Vaginal	675	616	59	0
Caesarean	765	545	216	4
Unknown	315	268	47	0
Term at delivery				
Preterm (<37 weeks)	327	140	183	4
Term	1230	1123	107	0
Unknown	198	166	32	0

Table Xa Confirmation of diagnosis per foetal sac, data collection I–XIII.

Method	Result			
	N	Normal	Abnormal	Failed
Prenatal diagnosis				
Array				
CVS	3	3		
Amniocentesis	1	1		
Ultrasound	2	2		
Total	6	6		
FISH				
CVS	158	150	7	1
Amniocentesis	925	898	24	3
Ultrasound	1508	1492	15	1
Unknown	3	3		
Total	2594	2543	46	5

Continued

Table Xa Continued

Method	Result			
	N	Normal	Abnormal	Failed
PCR				
CVS	257	248	9	
Amniocentesis	376	355	20	1
Ultrasound	64	59	5	
Unknown	2	2		
Total	699	664	34	1
PCR + WGA				
CVS	1	1		
Amniocentesis	1	1		
Total	2	2		
Total Prenatal	3301	3215	80	6
Postnatal diagnosis				
Array				
Karyo miscarriage	1			1
Karyo postnatal	1	1		
Karyo + physical examination	4	4		
Total	6	5		1
FISH				
Karyo miscarriage	134	65	67	2
Karyo postnatal	321	314	5	2
FISH microdeletion	2	2		
Physical examination	1951	1944	7	
Karyo postnatal + physical examination	84	84		
Karyo postnatal + DNA	1	1		
Unknown	3	3		
Total	2496	2413	79	4
PCR				
Karyotype miscarriage	16	10	4	2
DNA test miscarriage	2	2		
DNA test postnatal	226	224	2	
Sweat test/IRT	19	19		
Physical examination	179	178	1	
Karyotype	25	24	1	
Karyo + DNA	57	56	1	
Karyo + phys exam	37	37		
Hearing test	3	3		
Algo test	2	2		
Other	3	3		
Unknown	35	35		
Total	604	593	9	2
FISH + Array				
Physical examination	1	1		
PCR + WGA				
DNA test postnatal	26	26		
PCR + Array				
Karyo + DNA	1	1		
Total Postnatal	3134	3039	88	7

CVS, chorionic villus sampling; IRT, immunoreactive trypsinogen test; karyo, karyotype.

Table Xb Confirmation of diagnosis per foetal sac, data collection XIV–XV.

Method	N	Result		
		Normal	Abnormal	Failed
Prenatal diagnosis				
Array				
CVS	4	4	0	0
Amniocentesis	7	7	0	0
Ultrasound	185	185	0	0
Total	196	196	0	0
FISH				
CVS	23	20	3 ^a	0
Amniocentesis	45	43	2 ^b	0
Ultrasound	134	134	0	0
Total	202	197	5	0
PCR				
CVS	20	18	2 ^c	0
Amniocentesis	60	57	3 ^d	0
Ultrasound	25	25	0	0
Total	105	100	5	0
PCR + WGA				
CVS	1	1	0	0
Ultrasound	2	2	0	0
Total	3	3	0	0
Postnatal diagnosis				
Array				
Karyo	2	2	0	0
Physical examination	246	245	1 ^e	0
Total	248	247	1	0
FISH				
Karyo	28	28	0	0
Physical examination	193	193	0	0
Total	221	221	0	0
PCR				
Physical examination	57	57	0	0
DNA test	62	62	0	0
Other	2	2	0	0
Total	121	121	0	0

^aTrisomy 21 (three times).

^bChromosomal abnormality, not specified. And Trisomy 21.

^cTrisomy 21 and Trisomy 13.

^dTrisomy 21 (twice) and Trisomy 18.

^eHydrocephalus.

missing data are added following contact between the relevant centre and the science manager of ESHRE. As data analysis had fallen behind, it was decided to reduce this laborious part and omit inconsistent and incomplete data. This is the main reason for the higher percentages of follow-up losses in cycles, pregnancies and children born. This may also explain why the total number of reported cycles has remained constant compared to data XIII, while it is clear from the European

Table XIa Data on liveborn children, data collection I–XIII.

Total children born	8453	
Sex		
Male	3929	
Female	4166	
Unknown	358	
Mean birthweight (g)		
Singletons	3225	4853
Twins	2489	2856
Triplets	1949	115
Mean birth length (cm)		
Singletons	50	3273
Twins	46	1549
Triplets	45	34

Numbers in the right column indicate the number of newborns for whom information is available.

Table XIb Data on liveborn children, data collection XIV–XV.

Total liveborn children	2066		
Sex			
Male	963		
Female	1032		
Unknown	71		
Mean birthweight (g)			
Singletons	3112	3440 (1272/1419) ^a	
Twins		2389 (568/635) ^a	
Triplets		2006 (9/12) ^a	
Mean birth length (cm)			
Singletons	96.2	102.8 (930/1419) ^a	
Twins		76.7 (306/635) ^a	
Triplets		45.2 (6/12) ^a	
Mean head circumference (cm)			
Singletons	63.4	62.2 (254/1419) ^a	
Twins		69.7 (65/635) ^a	
Triplets		29.7 (3/12) ^a	
Apgar scores after 1 min			
Good ^b	Singletons	Twin	Triplet
	354	108	3
Poor ^b	26	13	0
Apgar scores after 5 min			
Good ^b	368	115	3
Poor ^b	8	4	0
Apgar scores after 10 min			
Good ^b	185	60	3
Poor ^b	5	3	0

^aNumbers between brackets indicate the number of newborns for whom information is available out of the total number of newborns.

^bGood is defined ≥ 7 , poor is defined < 7 .

Table XIIIa Summary of misdiagnosis from data I–XIII (no misdiagnosis reported for data X and XI).

Indication	Method used	PND-postnatal	Outcome	Reported in
Monogenics				
Myotonic Dystrophy	PCR	PND	TOP	I
β-thalassaemia	PCR	PND	TOP	II
β-thalassaemia	PCR	PND	TOP	VIII
Familial amyloid polyneuropathy	PCR	PND	Born	IV
Cystic fibrosis	PCR	PND	Born	II
Cystic fibrosis (one of twins)	PCR	Post	Born	IV
Charcot-Marie-Tooth IA	PCR	PND	Born	Cycle reported in V but misdiagnosis in VII
Spinal Muscular Atrophy	PCR	Post	Born	Cycle reported IV but misdiagnosis in VII
Charcot-Marie-Tooth IA (twins)	PCR	PND	TOP of both twins	VII
Fragile X	PCR	PND	Born	XIII
Fragile X	PCR	PND	TOP	VIII
Sexing for X-linked disease				
46,XY in Retinitis pigmentosa	PCR	PND	Born	IV
46,XY in Duchenne Muscular Dystrophy twin	PCR	PND	TOP of one twin	III
45,X, Haemophilia A	FISH	PND	TOP	IV
46,XY, Haemophilia A	FISH	Post	Born	VIII
Translocations				
Trisomy 13 after 45,XY,der(13;14)(q10;q10)	FISH	Miscarried	Miscarried	VI
47,XX,+der(22)t(11;22)(q23.3;q11.2)mat	FISH	PND	TOP	III
46,XY,der(15)t(3;15)(q25.1;q26.3)pat	FISH	PND	TOP	VII
46,XY,der(17)t(5;17)(p13;p13)mat	FISH	PND	TOP	XII
PGS				
47,XXX	FISH	PND	Lost to follow-up	VII
45,X	FISH	PND	Miscarriage	VIII, reported in IX
Trisomy 16 after first PB biopsy only	FISH	Miscarried	Miscarried	VI
Trisomy 16 after first PB biopsy only	FISH	Miscarried	Miscarried	V
Trisomy 16	FISH	Miscarried	Miscarried	VI
Trisomy 16	FISH	Miscarried	Miscarried	VI
Trisomy 21	FISH	Post	Born	III
Trisomy 21	FISH	PND	TOP	IX
Trisomy 21	FISH	PND	TOP	IX
Trisomy 21	FISH	PND	TOP	XIII
Trisomy 21	FISH	Postnatal	Born	XIII
46,XY/47,XY+18	FISH	PND	TOP	IX
46,XY	FISH	PND	Born	XII
Trisomy 21	FISH	PND	Miscarried	XII
Social Sexing				
Requested male but female foetus	FISH	PND	TOP	III

PND, prenatal diagnosis.

IVF-Monitoring ESHRE Consortium data that the number of reported PGD/PGS cycles increased from 6399 (2010) to 6824 (2011) and to 8433 (2012) (Kupka *et al.*, 2014, 2016; Calhaz-Jorge *et al.*, 2016). Another reason, especially true for missing pregnancy and baby data, is that adequate follow-up of these aspects was not in place in many centres. Nevertheless, the number of participating centres (71) was higher than for the previous data collection XIII (62). Data submission is a

time-consuming activity and the steering committee acknowledges the effort of all contributing centres.

Up to data XIII, the number of PGS cycles had increased annually but by 2010 a number of RCTs had clearly demonstrated that routine PGS using FISH at cleavage stage was not beneficial. The number of PGS cycles had decreased from 58% in data XII to 52% in data XIII and it has remained constant for the 2 years of the current data collection.

A consensus was published by the ESHRE PGD Consortium stating that future studies with alternative biopsy timing and genetic testing were necessary to evaluate the clinical benefit of PGS (Harper et al., 2010a). Data XIV–XV showed that genetic testing with genome-wide arrayCGH instead of FISH was applied in 20% of PGS cycles, but this was not yet linked with blastocyst biopsies. The uptake of arrayCGH was also observed in PGD cycles for chromosomal abnormalities, although less prominent than for PGS, and it was associated with the implementation of Day 5–6 biopsies. Techniques such as arrayCGH provide a generic platform, avoiding the need to develop locus- and family-specific tests, but consumables and equipment are expensive. It may take some time before workflows and instruments have been adapted and the personnel have been adequately trained. Turning from Day 3 to Day 5–6 biopsy requires an optimal embryo culture system and may lead to problems of limited time for analysis in case of fresh embryo transfer. This can be overcome by cryopreservation and embryo transfer in a deferred cycle. Again, such strategies require adaptations in laboratory organization and personnel training, explaining why the switch towards genome-wide genetic testing and blastocyst biopsy is not more advanced yet.

No further misdiagnosis cases were reported in this data collection. Although data reporting is anonymous, it may be that centres do not wish to reveal this information. Another explanation may be further improvement of laboratory quality management systems. The preceding years have seen an increased implementation of accreditation together with the first PGD external quality assessment schemes carried out from 2009 onwards (Deans et al., 2013). To date, including all cycles up to data XIV–XV, misdiagnosis has been reported for only 13/12 790 PCR-based cycles, 21/40 640 FISH-based PGD cycles and no data yet on the new genome-wide technologies. As many embryo transfers have no follow-up (no pregnancy or birth), and only a minority of centres perform audit through re-analysis of untransferred/non-cryopreserved supernumerary embryos, the numbers reported in the data collections may not reflect the true misdiagnosis in PGD.

The evaluation and publication of data collections have been lagging. PGD and PGS cycles have become more complex and the FileMaker Pro database system, created before 2000, is no longer adequate to further monitor data and trends in PGD services. Therefore this data collection is the last to be published relying on FileMaker Pro files. The retrospective data from 2013 to 2015 will be published as summary data, while a new platform for prospective data collection has been launched in June 2017 to handle data from 2016 onwards. This on-line platform is analysis-based instead of cycle-based and collects data over the various segments of OR, biopsy, analysis, transfer, pregnancy and babies, taking into account that PGD cycles are no longer carried out within the timeframe of a single procedure.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

V.G. was responsible for raw data curation and editing of the tables and manuscript; G.K. was responsible for preparing the tables and text of the PGS section; E.C. prepared the tables and text of the section about structural chromosomal abnormalities and sexing for X-linked diseases; M.H.-H. contributed to the tables and text about the pregnancies and babies. C.M. prepared the cumulative tables and made adaptations to the FileMakerPro database; M.D.R. contributed to the tables and text for the section about monogenic disorders, prepared overall data analysis and the discussion section and was responsible for final editing of the main text and tables. All authors revised the final manuscript.

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Conflict of interest

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