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Trends in the use of intracytoplasmatic sperm injection marked variability between countries

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BACKGROUND: ICSI is used increasingly often compared with standard IVF. The aim of the present study was to analyse the changes in the use of ICSI, and discuss possible causes and consequences. METHODS: Data from National and Regional registers were analysed for trends in the use of ICSI and indications for assisted reproductive technology (ART). RESULTS: The use of ICSI increased from 39.6% of ART cycles in 1997 to 58.9% in 2004 (USA 57.5%, Australia/New Zealand 58.6%, Europe 59.3%). The Nordic countries, the Netherlands and the UK used ICSI to a low extent (40.0–44.3%), whereas Austria, Belgium and Germany (68.5–72.9%) and the southern European countries like Greece, Italy and Spain used ICSI frequently (66.0–81.2%). The marked increase in the proportion of ICSI cycles seems primarily due to an increased use in couples classified as having mixed causes of infertility, unexplained infertility and advanced age together with a relative decline in tubal factor infertility. An absolute increase in the prevalence of couples with impairment in semen quality remains a possibility. CONCLUSIONS: ICSI is used increasingly, but huge differences exist between countries within Europe. It is not possible to determine specific factors that explain the differences. As ICSI does not give higher pregnancy rates than IVF in couples without male factors, and as it adds additional costs, infertile couples and society may benefit from a less frequent use of ICSI in some countries.

Keywords: ICSI; trends over time; indications; national registers

Introduction

After the introduction of ICSI (Palermo *et al*., 1992), this technique was rapidly integrated into the routine clinical use of fertility clinics offering assisted reproductive technology (ART) throughout the world. During recent years, ICSI has become the most frequently used method for fertilization, and in 2004 ICSI was used in nearly 60% of all reported ART cycles in Australia and New Zealand, Europe and the USA (Wang *et al*., 2006; Wright *et al*., 2007; ESHRE, 2008). In a recent publication of trends in the use of ICSI in the USA, it was shown that from 1995 to 2004 the proportion of cycles where ICSI was used increased from 11 to 57.5%. From 1999 to 2004, the percentage of ICSI cycles increased from 40 to 57.3%, while the percentage of infertility attributed to a male factor remained stable in same period. Additionally, it was shown that non-medically related factors were related to the use of ICSI, as states with insurance coverage had a higher ratio of ICSI use to diagnosis of male-factor infertility than did states without insurance coverage (Jain and Gupta, 2007). Supporting that the use of ICSI may be related to non-medically related causes is the finding that within Europe the use of ICSI in 2004 ranged more that two-fold between countries (ESHRE, 2008).

In the early years of ICSI during the 1990's, the increase in the use of ICSI is likely to be mainly explained by the fact that fertility clinics had to establish the technique in their laboratories, and incorporate it in the clinical management. Additionally, in some countries ICSI was not initially allowed, as in Norway where it was not legally accepted before January 1996. However, data from Germany shows that already from 1997 all 70 clinics that reported to the national ART register also offered ICSI (Felberbaum *et al*., 2007). It is therefore unlikely that the shift towards ICSI during recent years is related to implementation of the technique or legislation.

As practized presently the pregnancy rates per oocyte retrieval or embryo transfer using ICSI versus IVF are comparable as documented by data from national ART registers both in Europe (ESHRE, 2008), the US (Wright *et al*., 2007) and Australia and New Zealand (Wang *et al*., 2007). It could therefore be argued that the way ICSI is practized today represents an appropriate medical adaptation and development to the benefit of the infertile couples. However, the continuous rise in the use of ICSI as well as the huge differences in the utilization of ICSI between countries in the same region could suggest, that ICSI may be too extensively used for reasons that are not determined by good medical evidence.

The purpose of the present review is to analyse the trends in the use of ICSI in different regions and countries and to discuss possible reasons for the differences and appropriateness of this development.

Materials and Methods

We compiled data from the following Western national registers, either published in journals, reports or available on the web site of the registers:

The European IVF-monitoring programme (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Data from 1997–2004 for most European Countries are published in *Human Reproduction* (ESHRE 2001a, b, 2002, 2004, 2005, 2006, 2007, 2008).

The Centers for Disease Control and Prevention (CDC). Reports from 1995 to 2004 are available from www.cdc.gov/ART/ARTReports.htm. Trends in ICSI data have been analysed by Jain and Gupta and published in *New England Journal of Medicine* (Jain and Gupta, 2007).

Australian and New Zealand Assisted Reproduction Database (ANZARD). Data from 1997–2004 are available from www.npsu.unsw.edu.au. The latest annual reports are by Wang *et al*. (2006) and Wang *et al*. (2007).

The International Committee for Monitoring Assisted Reproductive Technology (ICMART). A world collaborative report on *in vitro* fertilization with data from 2000, is published in *Fertility Sterility*, by Adamson *et al*. (2006).

The Canadian ART Register. Results from 2001-2004 published in *Fertility Sterility* (Gunby and Daya, 2005, 2006, 2007; Gunby *et al*., 2007).

Results

Trends in the use of ICSI and IVF

Table I shows National Register data on the number of ART cycles and the proportion of these cycles that has been reported as ICSI cycles from Europe, selected European countries, selected regions within Europe as well as from Canada, the USA and Australia and New Zealand. Data from other regions like the Middle East, Latin America, Japan and Korea are from the latest available 'World Report'.

It appears from Table I that the percentages of fresh ART cycles where ICSI was performed were almost identical within the three major regions of Europe, North America and Australia and New Zealand in 2004, which is the most recent year where comparable data are available. European clinics made 281 864 fresh non-donor cycles and 59.3% of these were ICSI. In the USA, the corresponding figures were 89 533 cycles and 57.5% were ICSI and in Australia and New Zealand the figures were 19 943 cycles and 58.6% were ICSI. Summarizing the data (391 340 cycles) from these three regions, where the far majority of ART cycles in the World were recorded, ICSI was used in 58.9% of the cycles. The corresponding figures in 1997 were 239 155 ART cycles and 39.6% of these were ICSI. Using year as a linear variable the annual odds ratio for ICSI versus IVF treatment was 1.113 (95% CI: 1.112–1.115) and the odds ratio was 0.457 (95% CI: 0.453–0.462) for ICSI in 1997 versus 2004. During the 8 years of observations, the percentage of ICSI cycles increased by an absolute 19.3%.

As can also bee seen from Table I, major differences are present between countries outside the three regions. Data from year 2000 showed the following percentages of ICSI cycles: Middle East 89.2%, Latin America 70.0%, Japan 48.4% and Korea 30.0%.

Within Europe major differences also exist. In 2004, The Netherlands (40.0%), the Nordic countries (44.3%) and the UK (43.8%) could all be considered to have a rather low utilization of ICSI. In contrast other countries had a high use of ICSI: Austria (72.9%), Belgium (70.6%), Germany (68.5%), Hungary (73.5%), Poland (84.3%), and the Southern European region with an average of 73.9% (Greece 66.0%, Italy 69.2%, Portugal 66.0% and Spain 81.2%).

One of the quality aspects of registers is whether the register includes data from all clinics in the country as in Australia and New Zealand and the USA. In 1997 and 2004, the following European countries had National Registers that covered all ART cycles (Denmark, Finland, France, Iceland, The Netherlands, Norway, Sweden, Switzerland and the UK). Using data only from these countries a total of 103.677 cycles of which 34.6% were ICSI were done in 1997. The corresponding figures for 2004 were 133.356 cycles with 49.7% ICSI.

Data on the most recent trends are available from a few countries from the period 2005 to 2007. In the UK, the percentage of ICSI was 42.8% (41.334 ART cycles) in 2005 and this increased to 47.2% (42.334 ART cycles) in 2006 (HFEA, 2006). In Denmark, the percentage increased to 44.2% (9.541 ART cycles) in 2005, 44.6% (9.936 ART cycles) in 2006 and to 46.0% (10.771 ART cycles) in 2007 (Danish Fertility Society at www.fertilitetsselskab.dk). In Australia and New Zealand, the percentage of ICSI remained unchanged and was 58.5% in 2005 (Wang *et al*. 2007). In Germany, the percentage of ICSI was 68.7% (38.382 ART cycles) in 2005 and increased to 70.4% (39.942 ART cycles) in 2006 (Felberbaum *et al*., 2007). In the USA, the proportion of ICSI cycles increased to 59.6% (97.442 cycles) in 2005 (CDC, 2007).

Based on the European data, the percentage of IVF oocyte collections that resulted in embryo transfer increased by 3.9% from 84.3% in 1997, to 86.7% in 2001 and to 88.2% in 2004. The corresponding figures for ICSI remained unchanged during the years (91.7% in 1997; 92.6% in 2001 and 91.2% in 2004). The pregnancy rates per embryo transfer increased during the period (1997: IVF 26.1%, ICSI 26.4%; 2001: IVF 29.0%, ICSI 28.3%; 2004: IVF 30.1%, ICSI 29.8%).

In Australia and New Zealand, the 'viable pregnancy rate' per oocyte collection in 1997 was 13.3% after IVF and 14.7% after ICSI. In 2004, the delivery rate per cycle was 21.0% after IVF and 20.4% after ICSI.

Trends in the indications for ART

Table II presents data on the indications for ART (IVF and ICSI) in the period from 1997 to 2004 as recorded in five countries, where data on indications over time have been found. It has to be noted that different classification systems are used in different countries regarding the indications for ART treatments. Comparisons between countries should therefore be done cautiously, but all registers where data have been published, seem to record the subgroup with male factor alone, whereas mixed factors/combined factors may also include couples with multiple female factors.

Comparing the 1997 and the 2004 data the percentage of diagnosis that included a male factor or 'mixed factor' increased from 43 to 47% in Australia and New Zealand, from 28 to 37% in Denmark and from 41 to 47% in Finland. In the UK and the US

Table I. Development in the use of ICSI versus IVF in different countries and regions.

Region	Country	1997	*n* (%)	1998	*n* (%)	1999	*n* (%)	2000	*n* (%)	2001	*n* (%)	2002	*n* (%)	2003	*n* (%)	2004	*n* (%)
	Austria													4841	(73.0)	4504	(72.9)
	Belgium	5956	(50.5)	7915	(60.4)	8187	63.2	8983	63.1	9372	67.1	8892	65.0	10 278	(66.5)	13 794	(70.6)
Eastern Europe	Bulgaria									351	(14.8)	838	(36.4)	814	(37.5)	928	(47.4)
	Hungary	1733	(45.6)	2044	(55.1)	1998	(48.4)	2127	(63.7)	6121	(64.4)	6518	(64.6)	2615	(70.9)	2593	(73.5)
	Poland					2035	(69.3)	2877	(63.0)	3174	(71.7)	3349	(73.7)	3032	(83.9)	3675	(84.3)
	Russia	2953	(9.4)	4426	(18.9)	4309	(22.1)	5595	(25.7)	6602	(24.4)	7365	(26.0)	8937	(36.2)	12 052	(28.7)
	Eastern Europe, all	4686	(24.3)	6470	(30.4)	8342	(35.5)	10 599	(43.5)	16 248	(48.5)	18 070	(50.3)	15 398	(59.0)	19 248	(46.2)
	France	38 752	(35.3)	39 414	(44.6)	42 819	(47.2)	46 575	(49.9)	44 923	(50.8)	46 759	(53.9)	48 007	(54.8)	55 217	(56.7)
	Germany	25 267	(60.6)	40 039	(60.8)	51 572	(46.3)	52 276	(32.5)	59 402	(46.7)	68 984	(57.3)	87 185	(60.3)	38 824	(68.5)
	Netherlands	12 572	(24.4)	12 742	(27.6)	13 221	(29.1)	13 725	(30.3)	13 975	(32.9)	14 767	(35.3)	15 769	(38.1)	15 297	(40.0)
Nordic countries	Denmark	6768	(26.7)	7281	(28.9)	7624	(35.2)	8282	(36.3)	8805	(35.6)	9630	(37.0)	9292	(39.3)	9598	(41.9)
	Finland	5090	(36.6)	4886	(41.4)	4577	(39.9)	4323	(38.7)	4550	(39.8)	4369	(39.1)	4438	(39.9)	4761	(38.5)
	Norway	3173	(24.5)	3320	(30.6)	3736	(33.1)	4029	(34.9)	4045	(38.6)	3911	(40.0)	4800	(41.6)	5136	(45.5)
	Sweden	6872	(44.5)	7117	(49.0)	7507	(50.0)	7797	(48.0)	8297	(49.1)	8958	(46.0)	9314	(47.1)	9592	(49.1)
	Nordic countries, all	21 502	(35.2)	22 604	(36.5)	23 444	(40.5)	24 431	(40.2)	25 697	(41.1)	26 868	(40.8)	27 844	(42.4)	29 087	(44.3)
Southern Europe	Greece	6410	(45.7)	6819	(47.2)	6215	(50.9)	5385	(57.1)	3393	(59.6)	5075	(58.4)	8474	(62.2)	8218	(66.0)
	Italy	7827	(46.6)	11 743	(50.9)	13 008	(53.0)	16 295	(57.8)	15 366	(60.6)	15 358	(58.5)	22 517	(63.2)	23 711	(69.2)
	Portugal	1135	(52.7)	1158	(55.8)	1621	(54.7)	1959	(54.3)	1995	(55.2)	2541	(60.0)	2712	(61.1)	2491	(66.0)
	Spain	9384	(54.4)	6607	(64.5)	8389	(61.4)	10 619	(62.6)	9879	(65.2)	10 736	(75.5)	11 734	(73.8)	27 481	(81.2)
	Southern Europe, all	24 756	(45.6)	26 327	(53.6)	29 233	(55.1)	34 258	(59.0)	30 633	(61.8)	33 710	(64.0)	45 437	(65.6)	61 901	(73.9)
	Switzerland	2365	(57.5)	2690	(63.6)	2835	(67.0)	2964	(67.8)	2946	(68.0)	3107	(71.3)	3168	(70.5)	3145	(78.9)
	UK	27 781	(30.7)	27 795	(36.5)	30 215	(24.3)	26 339	(40.4)	26 856	(42.2)	27 673	(41.6)	28 255	(42.4)	30 375	(43.8)
Europe, all		171 337	(40.6)	193 090	(46.2)	220 591	(43.2)	226 937	(44.1)	235 324	(48.6)	257 682	(52.4)	295 081	(55.0)	281 864	(59.3)
Australia+NZ		12 816	(48.0)	14 270	(49.7)	15 196	(52.8)	NA		17 736	(54.7)	16 228	(57.6)	17 431	(57.8)	19 943	(58.6)
	Canada									4767	(55.8)	5770	(54.4)	6313	(55.8)	7874	(58.0)
	USA	55 002	(34.7)	61 650	(39.7)	63 123	(42.4)	71 556	(46.4)	77 102	(50.0)	81 888	(53.2)	86 753	(56.0)	89 533	(57.5)
Latin America								12 284	(70.0)								
Middle East								13 555	(89.2)								
	Japan							16 794	(48.4)								
	Korea							13 053	(30.0)								
All of Europe, Australia/NZ and USA		239 155	(39.6)	269 010	(45.2)	298 910	(43.5)	–		330 162	(49.3)	355 798	(52.8)	399 265	(56.5)	391 340	(58.9)

The Table indicates number of started cycles or oocyte retrievals followed by ART (*n*=all ART using non-donor oocytes) and the percentage where ICSI was used. Europe: data are from ESHRE's EIM reports. Latest report: ESHRE (2008). Cycles are started cycles or aspirations. For the years 1997 and 1998 the distribution of ICSI cycles are based on those cycles where follow-up of pregnancies are available. For Europe no data are available regarding 'split fertilization with IVF/ICSI. Data on 'Europe, all' include some countries that are not listed in the table. Canada: data from Canada. Latest report from Gunby *et al*. (2007). Data based on oocyte retrievals. For 2002, ICSI includes 'split IVF/ICSI fertilizations. USA: data adapted from Jain and Gupta (2007). Australia and New Zealand: data available from: www.npsu.unsw.edu.au. Latest report from Wang *et al*. (2007). Middle East: data from Adamson *et al*. (2006). Data exclude Israel,and include Bahrain, Egypt, Jordan Lebanon, Saudi Arabia, Tunesia, United Arab Emirates. Latin America: data from Adamson *et al*. (2006). Include Argentina, Bolivia, Brasil, Chile, Colombia, Ecuador, Mexico, Peru, Uruguay, Venezuela. Japan and Korea: data from Adamson *et al*. (2006).

Table II. The percentage of ART treated couples diagnoses where ICSI may be indicated: (a) male-factor alone or (b) male factor combined with other causes or (c) multiple causes, which may or may not include male factors.

	Diagnosis	1997	1998	1999	2000	2001	2002	2003	2004
Australia/NZ	Male factor alone	33	31	32	31	30	25	24	17
	Multiple causes	20	24	20	21	24	33	31	30
	All	43	45	52	52	53	58	55	47
Denmark	Male factor alone	20	21	24	26	–	27	29	30
	Male and female	8	7	6	7	–	7	9	7
	All 'male related'	28	28	30	33	–	34	39	37
Finland	Male factor alone	26			26				28
	Multiple causes	15			18				19
	All	41			44				47
UK	Male factor alone				28	30	32	32	32
	Male and female				19	16	15	13	12
	All 'male related'				47	46	47	45	44
USA	Male factor alone				23	24	24	25	24
	Male and female				17	18	18	17	18
	All 'male related'				40	42	42	42	42

Data from different countries and regions are shown during the period 1997–2004. Australia and New Zealand: data from www.npsu.unsw.edu.au. Data on multiple causes include: male factor and tubal disease, male factor and endometriosis, tubal factor and endometriosis and other multiple causes. For 2005, the 'multiple causes are only male + combined male-female factors. Denmark: data from the National Board of Health. Available at www.sst.dk. Finland: data from Terava *et al*. (2008). Data only from 3 years 1995 (listed under 1997) 2000 and 2004. UK: data from the HFEA. A long-term analysis of the HFEA Register data, 1991–2006. HFEA (2006). www.hfea.gov.uk. USA: data from www.cdc.gov. The percentages are based on the largest age cohort <35 years.

data could be followed for a 5 years period from 2000 to 2004. It is seen in Table II that the percentage of male-related diagnosis declined from 47% in 2000 to 44% in 2004 in the UK, whereas an increase from 40 to 42% was observed in the USA. As also seen in Table II, there was no consistent trend in the development of couples with a male factor alone diagnosis as an indication for ART.

Data on trends in indications for ART treatment from those countries/regions where ICSI is extensively used like the Middle East, Latin America and some European countries like Spain are to our knowledge not published.

The increase in the proportion of cycles that use ICSI could be caused by a reduction in the proportion of treatments due to other causes of infertility. Recent data from the UK (HFEA, 2006) show that the tubal factor infertility alone decline from 19.1% in 2000 to 15.3% in 2006. Data from Denmark show that the tubal factor was the indication for 43.3% of treatments in 1997 and this decreased to only 21.0% in 2004 (Danish National Board of Health at www.sst.dk). In Finland, the proportion of couples treated for tubal infertility decreased from 22% in 1995 to 16% in 2000, and down to 9% in 2004 (Terava *et al*., 2008). In Australia and New Zealand, tubal infertility accounted for 17.7% of all ART treatments in 1996, and this declined to 12.4% in 2001 and to 7.3% in 2005 (Dean and Sullivan, 2003; Wang *et al*., 2006).

In contrast to the decline in tubal factor infertility there has been an increase in couples with unexplained infertility. In the UK, unexplained infertility accounted for 17.5% in 2000 and this increased to 23.1% in 2006 (HFEA, 2006). In Finland, unexplained infertility increased from 13% in 1995 to 22% in 2004 (Terava *et al*., 2008). In Denmark, unexplained infertility accounted for 14% of the diagnosis in 1997 and 15% in 2004. In Australia and New Zealand, unexplained infertility accounted for around 15% in 1997 (Hurst *et al*., 1999) and 17.3% in 2005 (Wang *et al*., 2007).

Trends in indications for ICSI

Combining the data from Table I and II, it is seen that the proportion of male-related diagnosis in couples treated with ART (37–47% in 2004) is less than the percentage of couples treated with ICSI (58.9% in 2004). It is thus clear that ICSI is also used to a large extent on other indications than those that are related to male infertility. Unfortunately, very limited National Register data are available on the indications for the subpopulation treated with ICSI. However, the comprehensive register from Australia and New Zealand provide detailed information on causes of infertility in relation to use of IVF versus ICSI (Table III). These data from 2004 show that among ICSI-treated couples only 27.6% were treated due to a male factor alone, whereas 38.4% had multiple causes and 11.7% had unexplained infertility as indication for the ICSI treatment. In the US data from 2005 showed that among the 58.079 ICSI cycles 50.4% involved male-factor infertility, whereas 49.6% did not include any male-factor diagnosis as an indication (CDC, 2007).

Use of ICSI in relation to age

Data from Australia and New Zealand show that in 2005, ICSI was used increasingly often with increasing female age. In all 30–34 years old couples the percentage of ICSI cycles was 54.5%, but this increased to 68.5% in all couples with female age ≥40 years (Wang *et al*., 2007). Supporting a link between advanced female age and use of ICSI are also found in data from the USA in 2004 where 29.2% of couples without a male-factor diagnosis received ICSI when the female age was <35 years, whereas this increased to 37.9% in the age group 41–42 years and to 39.8% in the age group >42 years (Wright *et al*., 2007).

Similar data are not available from Europe, but the mean proportion of women ≥40 years among the IVF-treated couples was 14.7% in 2004, whereas the corresponding figure for

Table III. ART treatment cycles recorded by cause of infertility, IVF and ICSI in Australia and New Zealand, 2004.

Causes of infertility	IVF	*n* (%)	ICSI	*n* (%)
Male factor only	379	(4.1)	3427	(27.6)
Female factor	2287	(24.5)	737	(5.9)
Tubal disease	1259	(13.5)	389	(3.1)
Endometriosis	822	(8.8)	284	(2.3)
Combined tubal and endometriosis	206	(2.2)	64	(0.5)
Multiple causes	1956	(20.9)	4766	(38.4)
Unexplained[a]	2044	(21.9)	1446	(11.7)
Other	1348	(14.4)	625	(5.0)
No cause or not stated	1326	(14.2)	1409	(11.4)
All causes	9340	(100.0)	12410	(100.0)

Table adapted from Wang *et al*. (2006). [a]Includes combined male factor, tubal disease, endometriosis, unexplained and/or other causes.

ICSI-treated women was 12.5% (ESHRE, 2008). The highest proportion of both IVF and ICSI-treated women that were $\geq$40 years of age was found in the Southern European countries of Greece (IVF 21.0% and ICSI 21.8% $\geq$40 years) and Italy (IVF 21.0% and ICSI 22.4% $\geq$40 years).

Discussion

Trends in the use of ICSI

The results extend those obtained from the USA by Jain and Gupta (2007) by showing that the trend observed in the USA has also occurred in Europe and in Australia/New Zealand. Interestingly, ICSI is used in a similar proportion of couples in the three regions of Australia and New Zealand, Europe and the USA as around 60% of all ART cycles now use this technology for fertilization. The trend observed in the period from 1997 to 2004 seems to continue from 2005 onwards, even though with a lower rate. Very high ICSI rates were found in other regions like Latin America (70.0%) and the Middle East (89.2%) and within Europe 2-fold differences were found in the rates of ICSI, being below 40% in Finland and Russia and $>$80% in Spain. Even neighbouring countries like Belgium (ICSI 70.6%) and the Netherlands (ICSI 40.0%) use ICSI very differently. The overall trend is that the use of ICSI is rather low in the Northern and high in the Southern European countries. In general, each country has its own consistent profile, as those countries that have a high utilization of ICSI have had this throughout the entire period of recording.

The registers from Australia and New Zealand and the USA include all clinics. For the period studied (1997–2004) only nine European countries reported register data that covered all treatments (ESHRE, 2001a, b; ESHRE, 2008). If the results are analysed separately from these nine countries the use of ICSI has increased from 34.6 to 49.7%. These countries include the Nordic countries, the Netherlands, France and the UK that all use ICSI to a low, moderate degree. The European data should therefore be interpreted with caution, as the available National data from some of the countries where ICSI is most frequently used, only covers a proportion of the treatments.

The rise in the use of ICSI has been temporarily associated with an increase in overall pregnancy rates for ART. Only the European data can be analysed separately for IVF versus ICSI during the selected period from 1997 to 2004, where the pregnancy rates per transfer increased from 26 to 30% after both IVF and ICSI (ESHRE, 2001a; ESHRE 2008). This increase occurred despite a decrease in the number of embryos transferred during a time period, but the increase can evidently be explained by several factors. Another potentially beneficial effect of the increased use of ICSI could be that the number of oocyte retrievals with IVF that resulted in embryo transfer in Europe increased from 84.3% in 1997, to 86.7% in 2001 and to 88.2% in 2004.

In order to explain the observed trends, the inadequacy of the majority of National ART Registers becomes evident as the causes of infertility of the ART-treated couples are often not published at all and when published, the classifications do not follow an international consensus. Additionally, biases regarding classification of indications may occur. One example is that re-imbursement of ICSI was only possible in Germany if the sperm quality assessment revealed a marked impairment (personal communication). Similar, but unrecognized factors may be operating in other countries. With these reservations, the following sections discuss possible explanations for the trend over time and the differences between countries.

Possible reasons why the use of ICSI has increased—declining sperm quality

Based on the National Register data there is an increase, although minor, in the percentage of couples with male infertility that are treated with ART, and it is a possibility that an increased number of couples seek treatment due to a real decline in male fertility. Although the issue is still controversial (Jouannet *et al*., 2001), several studies have indicated that there has been a global decrease in sperm concentration during the past five to six decades (Carlsen *et al*., 1992; Irvine *et al*., 1996; Swan *et al*., 2000; Lackner *et al*., 2005; Sripada *et al*., 2007) with wide regional differences (Swan *et al*., 2000; Jørgensen *et al*., 2006) although other studies found no time trend in sperm concentration (Paulsen *et al*., 1996; Andoltz *et al*.,1999; Seo *et al*., 2000). Currently, the World Health Organisation defined lower limit of normal sperm concentration as 20 million/ml (WHO, 1999). However, studies have indicated that this value may be too low to consider as a normal sperm concentration, since men with sperm counts $<$40 million/ml have prolonged waiting time to pregnancy (Bonde *et al*., 1998a; Slama *et al*., 2002). The decline in semen quality appear to be birth cohort related with the birth cohorts born before 1960 having the highest sperm concentrations and the younger cohorts born around 1980 having the lowest sperm counts with mean sperm concentrations around 40 million/ml (Bonde *et al*., 1998b; Zorn *et al*., 1999; Andersen *et al*., 2000). It is estimated, that as many as 30% of young Danish men may have semen quality in a subfertile range (Skakkebæk *et al*., 2006). Indeed, the adverse trends in male reproductive health may have reached a 'tipping point', where the rising proportion of subfertile men is becoming significant (Andersson *et al*., 2008). The increasing use of ICSI may thus to some extend be caused by declining semen quality with more men in the subfertile range.

Another contributing factor to a possible decrease in male fertility is the postponed childbearing in most Western countries.

As women tend to postpone conception, the mean age of fathers has also increased with a significantly larger proportion of men fathering a child in their 50's (Plas *et al*., 2000; Kidd *et al*., 2001; Kühnert and Nieschlag, 2004; Lackner *et al*., 2005; ESHRE Capri Workshop Group, 2005). Age-related changes in spermatogenesis have been well described with decreasing semen volume, sperm motility and sperm morphology, whereas no consistent data have confirmed that sperm concentration also declines with advancing age (Kidd *et al*., 2001; Kühnert and Nieschlag, 2004; ESHRE Capri Workshop Group, 2005) even though declining trends in sperm concentration and total sperm counts have been described in some studies (Auger *et al*., 1995; Eskenazi *et al*., 2003). In a review of the literature, Kidd *et al*. (2001) found a decrease in semen volume of 3–22%, a decrease in sperm motility of 3–37% and a decrease in percent morphologically normal sperm of 4–18% when 50-year-old men were compared with 30-year-old men. These changes in semen quality were associated with relative decreases in pregnancy rates between 23 and 38% when controlling for female age. Furthermore, it has been shown that older men have increased sperm DNA damage, which may be a cause of infertility (Singh *et al*., 2003; Wyrobek *et al*., 2006; Schmid *et al*., 2007).

Another explanation for the increased use of ICSI could be a shift towards an increased use for mild and borderline male-factor infertility, although the data to support the use of ICSI for this indication are limited. Randomized controlled trials using parallel group comparison of ICSI versus IVF in couples with light to moderate male infertility are not available. However, studies have compared fertilization rates and embryo development after IVF and ICSI in sibling oocytes. These studies have found no significant differences in pregnancy rates using IVF versus ICSI fertilized oocytes in couples with mild / borderline sperm quality impairment defined as at least one abnormal semen parameter according to the WHO classification, even though there were significantly fewer complete fertilization failures of the oocytes exposed to ICSI (Plachot *et al*., 2002; van der Westerlaken *et al*., 2006). Tournaye (2002) compared the results of ICSI and two different IVF regimes with standard (0.2 million/ml spermatozoa) or high concentration (0.8 million/ml spermatozoa) in couple with moderate male infertility using sibling oocytes and found that fertilization rates were significantly lower with standard IVF compared with ICSI (37.4 versus 64.3%), but similar when high concentration IVF was used (59.6 versus 67.6%). Overall there were no significant differences in pregnancy rates. These data were included in a meta-analysis of eight RCTs comparing IVF and ICSI in sibling oocytes confirming higher fertilization rates with ICSI compared with conventional IVF but not in comparison to high concentration IVF (Tournaye *et al*., 2002).

One issue of concern is the lack of a general scientific consensus on how to define those couples with a mild to moderate impairment in semen quality that should be offered ICSI and not IVF.

Evaluation of sperm morphology by strict criteria have been used by some to predict the outcome after IVF (Kruger *et al*., 1988; Ombelet *et al*., 1995) and it has been shown that increased fertilization failure by IVF occurred when less than 5% of the sperm in the ejaculate had normal forms (review by Coetzee *et al*., 1998; Söderlund and Lundin, 2006). On the other hand Keegan *et al*. (2007) found that isolated teratozoospermia did not reduce fertilization in IVF compared with ICSI. The total number of motile sperm after sperm preparation has also been shown to predict the outcome after IVF (Rhemrev *et al*., 2001) and a count of 500,000 has been suggested as a cut-off value for IVF (Devroey *et al*., 1998) although others recommend a number of >1 million progressive motile sperm (Rhemrev *et al*., 2001).

In conclusion, a real decline in semen quality and a higher proportion of subfertile men, as well as increased paternal age could be a contributing factor to the rise in the use of ICSI. It could also be speculated that an increase in subtle changes in semen quality, which may not always be recorded as male infertility, has occurred. Lack of a general consensus on the degree of sperm quality impairment that would require ICSI versus IVF, could be a factor explaining some of the variability seen within countries.

Possible reasons why the use of ICSI has increased—declining tubal infertility

Tubal infertility is the classical indication for IVF rather than ICSI, and the data show that the proportion of couples with tubal infertility has been declining. The decline in tubal infertility has been quite pronounced with a reduction of more that 50% in less than a decade in Australia/New Zealand, Denmark and Finland. The reasons why tubal infertility may decrease as an indication for ART is beyond the scope of the present review, but it is fair to conclude that this may be another contributing factor explaining the changes seen in the distribution between IVF and ICSI during recent years.

Possible reasons why the use of ICSI is increased—non-male-factor infertility

As mentioned, National Register data on the indications for ART in general are very inadequately documented, and specific data on indications for those couples treated with ICSI are only published from Australia and New Zealand and the USA. However, as seen from Table II, the proportion of male-related diagnosis in couples treated with ART in the five countries ranged from 37–47% in 2004, and as the percentage of couples treated with ICSI was 58.9%, it is evident that ICSI is now used to a large extent for other indications than those related to male infertility. Data on specific indications for ICSI from Australia and New Zealand (Table III) confirmed that the main indications for ICSI in 2004 were mixed causes of infertility (38.4%) and unexplained infertility (11.7%), whereas 27.6% were due to male factors alone. In the USA, only 50.4% of all ICSI cycles in 2005 involved couples with a male factor (CDC, 2007).

Possible reasons why the use of ICSI is increased—advanced age

As found in the present analysis, data from Australia and New Zealand as well as from the USA show that ICSI is used increasingly often with increasing female age. Data from Australia and New Zealand show that in 2005, the use of ICSI was increased to 68.5% in all couples with female age ≥40 years (Wang *et al*., 2007). The data from the USA support the link between advanced female age and use of ICSI as the proportion of couples without a male-factor diagnosis that received ICSI increased from 29.2% when the female age was below 35 years, to 39.8% in the age group >42 years (Wright *et al*., 2007). In Europe, the overall

use of IVF and ICSI has a similar age distribution (ESHRE, 2008), but detailed data linking both age, diagnosis and use of IVF versus ICSI are not available, so age and diagnosis can not be linked.

As documented in the UK (HFEA, 2006) more females of advanced reproductive age are presently being treated with ART, as a mirror of the changes in natural conception, where more and more women in the 'Western World' delay childbearing (Lampic *et al*., 2006). Female age has an effect on the diagnostic categories of infertility as shown by Maheshwari *et al*. (2008) who studied 7172 couples referred to the Aberdeen Fertility Centre. They found that among women with primary infertility twice as many women ≥35 years had unexplained infertility and less presented with ovulatory disturbances, compared with women aged <35 years. Indeed, unexplained infertility and advanced age may to some extent cover the same diagnosis, and in the USA the category diminished ovarian reserve is recorded as a separate diagnosis in the register during recent years (Wright *et al*., 2007). As shown in the present study, ICSI is often used in unexplained infertility, so the trend towards treatment of older women with ART (HFEA, 2006) could be another explanation for the shift towards more frequent use of ICSI, even though the available data do not allow solid conclusions to be drawn.

Possible reasons why the use of ICSI has increased—conclusions

It seems clear that the predominant indications for ICSI are now not severe impairment of semen quality, but rather mixed causes of infertility and unexplained infertility, and these account for most of the increased use of ICSI. Additionally, it is possible, although still not adequately documented, that age-related decline in oocyte quantity and quality may be an increasingly important non-male factor that contributes to the rising use of ICSI.

Differences in the use of ICSI between regions and countries—medical causes

Data that directly explains the huge differences between the utilization of ICSI between different countries is not available, but there could be a number of possible explanations. One of the reasons could be that intrauterine inseminations (IUI) are used to a varying degree. The indications for IUI are mainly unexplained subfertility, light to moderate male subfertility and mixed male and female causes, which are now also among the frequently used indications for ICSI. Miskry and Chapman (2002) analysed the use of IUI among fertility centres in Australia and New Zealand, and showed that instead of IUI almost one third of centres recommended ART as first line therapy in unexplained infertility. Whenever semen parameters were reduced, IUI was rarely considered.

In the recent update of the National Institute for Clinical Excellence (NICE) guidelines on fertility treatment in the UK couples with both unexplained infertility as well as patients with minor abnormalities in semen characteristics were recommended 6 cycles of IUI before entering ART (www.nice.org.uk). It should be noted, that in countries where national evidence based guidelines on treatment of infertility recommend 3 to 6 IUI cycles before ART, like Denmark (www.fertilitetsselskab.dk), The Netherlands (Hagen *et al*. 2005) and the UK (www.nice.org.uk), the use of ICSI is rather low. Unfortunately, the number of IUI cycles using husband semen is only reported from a number of countries, and the data available are likely to represent only part of the national activity (ESHRE, 2008). We can therefore only hypothesize that in those countries where the National guidelines recommend 3–6 cycles of IUI, more couples may be treated with IUI and around 25% will achieve a live birth (Khalil *et al*., 2001), and may thus not need treatment with ICSI.

Medical reasons for the differences between countries cannot be analysed as data on the specific indications are neither available for ART in general nor ICSI separately from the majority of European countries. It should be noted that the southern European countries of Greece and Italy have the largest proportion (21–22%) of women ≥40 years of age and this may contribute to their frequent use of ICSI. On the other hand the proportion in Spain is only 11%, but 80% of cycles are ICSI.

The conclusion is that medical reasons explaining differences in ICSI versus IVF in different countries are not apparent, but an extensive use of IUI as first line therapy may reduce the proportion of couples that proceed to an ICSI cycle.

Differences in the use of ICSI between countries—non-medical causes

Non-medical reasons for the differences observed between countries and regions could be different degrees of public funding or insurance coverage of ART. Data from the USA indicated that differences between states in the re-imbursement of the ART treatment influenced the extent that ICSI was used. It was shown that states with a mandated insurance coverage had a higher ratio of ICSI use to diagnosis of male-factor infertility than did states without insurance coverage (Jain and Gupta, 2007). However, the overall use of ICSI was almost similar in states with or without insurance coverage. This is in contrast to the differences between countries in Europe where two-fold differences exist. Data from Europe do not support that public funding of ART is a major factor determining the rate of ICSI versus IVF (Jones and Cohen, 2004). In the 4 Nordic countries where infertile couples are offered 3 fresh ART transfer cycles free of charge, the utilization of ICSI was low (44.3%). The situation is similar in the Netherlands where ICSI accounted for 40% of cycles. However, in Belgium and Spain where ART was also offered free of charge for 3 to 4 cycles through the National Health Programme, the rate of ICSI was high at 70.6–81.2%. In Switzerland with no National Health Programme funding of ART, the rate of ICSI was also high at 78.9%. Danish data from 2007 shows that the percentage of ICSI was 45.9% (4.628 cycles of ART) at private fertility clinics, where patients covered 100% of the costs of treatment, compared with 46.0% (6.143 cycles of ART) at public fertility clinics providing free of charge treatment (www.fertilitetsselskab.dk). It is thus evident that no direct relationship exists between presence or absence of state funding of ART and the percentage of ICSI cycles.

As is evident from Table I, both the number of ART treatment cycles and the distribution between IVF and ICSI showed major fluctuations during short time periods in Germany. The main reasons seem to be changes in the re-imbursement policy of governmental coverage for ART in general and for ICSI in particular (personal communication, Markus Kupka). In 1997 to 1998 ICSI accounted for 60.6 and 60.8% of all treatments, whereas this

declined to a nadir of 32.5% in 2000. Subsequently the number of ART cycles increased to 87.185 and the rate of ICSI returned to a level of 60.3% in 2003. In the following years the number of ART cycles declined by almost 50% but the percentage of ICSI remained rather stable. The German data have been linked with changes in the re-imbursement policy in Germany. After the initial rise in the use of ICSI the public funding of 4 cycles of ICSI was removed after 1998 in order to await the results of the large German database on safety of ICSI (Katalinic *et al*., 2004). At that time only IVF was reimbursed. Later, from 2001 onwards the public funding was given again also for ICSI cycles, and this resulted in a marked rise. From 2004 onwards the re-imbursement for all ART was reduced to 50% and the number of treatment cycles from 4 to 3. This resulted in a dramatic drop in total number of ART cycles, but no major change in the proportion of ICSI. The conclusion that can be drawn from the German data is, as one could expect, that selective withdrawal of re-imbursement of ICSI cycles had a major impact on the distribution of ICSI versus IVF.

The conclusion is that there is no clear link between the re-imbursement system of the country and the percentage of ICSI, but as illustrated from Germany selective withdrawal of governmental reimbursement for ICSI caused a dramatic decline in the number of treatments.

Is the rising use of ICSI in non-male-factor infertility an appropriate technological adaptation?

The main explanation for the rising use of ICSI is related to its expanding use on non-male factor indications. The concern is that on these indications, the available studies show that ICSI offers no advantage over IVF in relation to pregnancy rates. A few randomized controlled studies have compared the efficacy of IVF versus ICSI in couples with unexplained infertility (Foong *et al*., 2006), tubal factor infertility (Aboulghar *et al*., 1996; Bukulmez *et al*., 2000) or non-male-factor infertility (Bhattacharya *et al*., 2001; Poehl *el al*., 2001) in terms of pregnancy rates or live birth rates. None of these studies have indicated that there are any benefits of ICSI compared with IVF. In the largest study, Bhattachaya *et al*. (2001) randomly assigned 415 consecutive couples with non-male-factor infertility including tubal and unexplained infertility and found that per retrieved oocyte there was a significantly higher fertilization rates in the IVF group (58%) compared with the ICSI group (47%) and the pregnancy rate per cycle was also significantly higher in the IVF group (33 versus 26%). In the study by Aboulghar *et al*. (1996) the fertilization rates per retrieved oocyte were also found to be significantly higher in the IVF group compared with the ICSI group (64.8 versus 53.5%). However, in the review by van Rumste *et al*. (2004) only the above-mentioned study by Bhattachaya *et al*. (2001) met the criteria of optimal study designs. The lack of any increase in pregnancy rates using ICSI on non-male indications was thus based on limited data, but the results have been confirmed in an appropriately done, although rather small, Canadian study by Foong *et al*. (2006).

Previously published studies have found that 2–15% of all cases of IVF with normospermia resulted in total fertilization failure and about 20% in low fertilization rate (<25%) together with a recurrence risk of 30–50% (Ola *et al*., 2001, van der Westerlaken *et al*., 2005). Fertilizations failure under such conditions may be explained by a defect in the oocyte, lack of penetration of the zona pellucida by the spermatozoon, oocyte activation failure or sub-optimal culture conditions.

In the randomized controlled trial between IVF and ICSI Bhattacharya *et al*. (2001) found that failed fertilization after IVF took place in 5% (11/206) compared with 2% (4/209) after ICSI. The study included only women below the age of 37 years with non-male indication and couples with a fertilization rate below 20% in a previous IVF cycle were excluded. According to this study, it would require 33 ICSI cycles to prevent one unexpected total fertilization failure (primary prevention).

The fear of recurrence of total fertilization failure or low fertilization rate (<20–25%) after conventional IVF performed on non-male indication has in many clinics resulted in doing ICSI in a subsequent cycle (secondary prevention). However, Kinzer *et al*. (2007) found in a retrospective analysis of patient treatment cycles, that fertilization successfully occurred in 94% of subsequent cycles after total IVF fertilization failure. In total, 22% delivered which was comparable to other second IVF cycles in the clinic at the same time period. Nevertheless, most of their patients (67%) changed to ISCI in a subsequent cycle after failed IVF fertilization.

Another approach to avoid recurrence of total fertilization failure implies that sibling oocytes are divided in two groups, using standard IVF and ICSI on each half. Register data does not provide published information on this type of cycles, so the quantity remains unknown. In a prospective cohort study, Van der Westerlaken *et al*., (2005) randomized sibling oocytes to either IVF or ICSI from 24 couples with primary total fertilization failure and 14 couples with low fertilization rate (<25%). Oocytes treated with ICSI showed a significantly higher fertilization rate than oocytes treated with IVF. The recurrence rate of total fertilization failure in the oocytes exposed to IVF was 67% after primary total fertilization failure and 50% after low fertilization. Even though the semen quality by routine standards in the laboratory in all cases was regarded within the normal range, a comparison of semen characteristics, suggested some kind of male factor, since the total motile sperm count after preparation was higher in the IVF group with fertilization than without. The authors concluded that performing ICSI on at least a part of the oocytes can avoid unnecessary recurrent fertilization failure and since the contribution of IVF was small one might even perform ICSI on all oocytes. However, whether the higher fertilization rate implies more live born children was not investigated and a study with live birth as the primary outcome measure and the couple as the unit to randomize instead of fertilization rate and oocytes has not been conducted.

In conclusion, the use of ICSI as primary prevention of fertilization failures in couples without a clear male factor is not supported by experimental evidence. However, ICSI is likely to be used as secondary prevention, even though there is a good chance of achieving fertilization following repeated IVF.

Advanced age is associated with achievement of less oocytes after controlled ovarian stimulation as the number declines with around 1 oocyte per 2.3 years (Ziebe *et al*., 2001). As advanced age may be used increasing often as an indication for ICSI, it is interesting that Moreno *et al*., (1998) randomized 96 low-responder patients with non-male-factor infertility to either IVF or ICSI, and

showed that ICSI offered no benefits in relation to pregnancy rates in this specific group of patients. Clinically, the risk of a fertilization failure is always more imminent using standard IVF when only few oocytes are retrieved (Rhemrev *et al*., 2001) so physicians may be inclined to choose ICSI in older women.

In summary, ICSI offers no general benefits in patients with unexplained infertility, tubal factors, 'non-male' factors or in women with advanced age that are often 'low-responders', but ICSI generally overcomes total fertilization failure after IVF. Whereas ICSI originally was used for severe male-factor infertility, it is suggested that ICSI may now be used more frequently in some countries compared with what is based on good medical evidence. This needs further assessment so there is a need for good randomized trials of IVF versus ICSI, for all indications except those with severe male reproductive problems.

ICSI and costs

IVF and ICSI are both expensive technologies with the latter being most costly due to more demanding expertise and equipment in the laboratory. In a comprehensive survey of the health economic aspects of IVF/ICSI by Collins (2002), it was estimated that the average cost per IVF/ICSI cycle in 2002 was US$ 9547 (95% CI: US$ 8249–10 846) in USA and US$ 3518 (95% CI: US$ 2924–4111) in 25 other countries. No separate analyses of IVF and ICSI were performed.

Three studies which reported costs for IVF and ICSI separately (Silverberg *et al.*, 2002; Strandell *et al*., 2005; Kjellberg *et al*., 2006) found that an ICSI cycle in average costs 11% more than an IVF cycle, while Kovacs *et al*. (2004) found a difference of more than 30%. However, differences in study design and the health-care setting make comparability between countries difficult.

Ola *et al*. (2001) found a cost difference of about £600 per fresh cycle between IVF and ICSI and estimated that £60 000 (cost needed to treat, CNT) would be needed to gain one additional live birth when ICSI was used for patients requiring IVF. Further, budget impact analysis showed that 29 extra cycles of conventional IVF could be done for the estimated CNT. Taken this into account the authors would not recommend routine use of ICSI to all IVF treatments.

Hollingsworth *et al*. (2007) evaluated the cost effectiveness of ICSI in Australia 2003 and included analyses of the potential costs if the indication for ICSI was expanded from severe to subnormal semen quality. Cost per ICSI cycle was estimated to A$2200–3500 and the crude costs per birth for ICSI with ejaculated sperm to A$8500–35 000 depending on live birth rate per cycle (10–25%). If ICSI was used instead of IVF the additional cost was estimated to A$600 per cycle and each additional live birth would cost an extra A$3636 under the best-case scenario. If there was no benefit, e.g. no child born, the additional incremental cost was A$600 per procedure.

A recent Dutch study (Bouwmans *et al*., 2008), where indications for ICSI were not reported, evaluated the costs of IVF and ICSI per first treatment cycle in four IVF centres and found that the total costs per ICSI cycle was 8.3% higher than for IVF. Hormonal stimulation (down-regulation with GnRH agonist, recombinant FSH and hCG) covered more than half of the total costs per cycle and as expected increased for both procedures with increasing age of the women. Fertilization costs constituted 12% for IVF and 20% for ICSI. Total actual costs per started IVF and ICSI cycle were €2381 and €2578, respectively, but the costs per ongoing pregnancy were €446 less for ICSI compared with IVF. This was explained by a lower cancellation rate and a higher success rate per cycle.

In conclusion, the actual costs of ICSI are higher than for IVF and it is doubtful that expansion of the indications for ICSI is cost-effective. However, more analyses estimating the costs for different indications are needed.

ICSI and safety

With the introduction of ICSI in 1992 concern about the safety of the procedure was raised due to the invasiveness of the procedure. Further, it has been shown that couples undergoing ICSI because of severely impaired ejaculated semen quality or surgically retrieved sperm have an increased prevalence of chromosomal aberrations and Y-microdeletions. Since some of these chromosomal abnormalities can be inherited to the child (Aittomäki *et al*., 2004; Mau Kai *et al*., 2008), a karyotype should be included in the investigations of the male partner before ICSI is performed.

The risk of adverse perinatal outcome seems to be comparable to that of standard IVF (Källén *et al*., 2005). Two meta-analyses have demonstrated the same pattern for congenital malformations (Hansen *et al*., 2005; Lie *et al*., 2005), while a long-term follow-up study and a recent nationwide Danish registry study have found that the risk of chromosomal aberrations, especially inherited and de novo autosomal structural abnormalities and sex chromosome aneuploidy, was increased after ICSI (Bonduelle *et al*., 2002; Gjerris *et al*., 2008) when compared with the general population or IVF, respectively.

Long-term follow-up studies are sparse but reassuring, showing that in the age of 5–10 years cognitive, motor and socio-emotional development and growth were similar to IVF and spontaneously conceived children (Barnes *et al*., 2004; Wennerholm *et al*., 2006; Leunens *et al*., 2008).

The ESHRE Capri Workshop Group (2007) has in the article entitled *Intracytoplasmic sperm injection (ICSI) in 2006: evidence and Evolution* thoroughly discussed this issue and recommended more follow-up studies in order to clarify whether ICSI children differ from IVF children, children born after non-ART treatments or spontaneously conceived children from infertile as well as fertile couples. This is another argument against too liberal use of ICSI.

Conclusions

The trend is that ICSI is used increasingly and it seems that at more than half of all ICSI cycles are now done in couples without a diagnosis of severe male factor. Although the rate of ICSI is almost identical in Australia and New Zealand, Europe and the USA, huge differences exist between countries. The explanations for these differences remain uncertain, partly due to inadequate National Register data and a lack of an international consensus on how to subclassify the indications for ART.

The available medical evidence does not support the liberal use of ICSI in couples with unexplained infertility, light to moderate

impairments of semen quality and in patients with various mixed causes of infertility or few oocytes. ICSI may therefore now in many countries be used excessively compared with IVF, without good medical evidence that it is beneficial neither for the patients or society.

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