Article

Ten years of Swiss National IVF Register FIVNAT-CH. Are we making progress?

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Abstract

In 2001, analysis of Swiss data collected since 1993 included 1001 treatment cycles with IVF, 2217 treatment cycles with intracytoplasmic sperm injection and 2160 treatment cycles with frozen–thawed embryos or zygotes. IVF cycle number has remained constant over the past 10 years, now representing only 18% of the total. ICSI treatment cycles have plateaued since 2001. Altogether, patients receive 1.56 treatment cycles per year, nearly constant since 1995. Mean maternal age has increased from 33.9 to 35.7 years, while mean number of recovered oocytes has increased by 1.3. Considerable improvement was seen in clinical pregnancy rate after 'fresh' treatment cycles since 2000. Mean number of replaced embryos in 'fresh' treatment cycles has fallen to below 2.5 since 1996, long before the legal imposition of the three-embryo transfer limit in 2001, and is still decreasing without affecting the consistent twin pregnancy rate of 19%. The frequency of ovarian hyperstimulation syndrome has increased three-fold. External audits have reduced the mean number of errors per data file by half, and increased the number of correct files by 20%. Data collected over this 10-year period show that despite the introduction of a restrictive law and increasing mean maternal age, the overall clinical pregnancy rate has continued to improve.

Keywords: *data collection, FIVNAT-CH, National IVF Register*

Introduction

The first baby born after IVF in Switzerland will have reached the age of 20 years in 2006. From the beginning, data on assisted reproductive technologies have been collected by the Swiss Academy for Medical Sciences, but prior to 1991 the collected information was limited and quite general. The impulse to start a National Swiss IVF Register came from the former president of the Swiss Society for Fertility-Sterility and Family Planning (SGFSF), Dr M Germond, who in 1992 initiated a special interest group based on the French model FIVNAT (Fécondation In Vitro National). The major aim was to provide quality data about assisted reproductive technologies for scientists, politicians, the media, and last but not least patients, and this aim has so far been achieved. Even more, FIVNAT-CH has imposed since 1997 audits of all participating centres on a regular basis to validate the quality and the consistency of the collected data. The 19 IVF centres in Switzerland all participate on a voluntary basis and fund the register by means of a fee based on the number of cycles they initiate every year. In 2004, SGFSF received a new impulse as it was decided to review the bylaws and to rename the society the Swiss Society for Reproductive Medicine, Schweizerische Gesellschaft für Reproduktionsmedizin. SGRM (www.sgrm.org) and the FIVNAT-CH Register became a separate defined commission of the Swiss Society for Reproductive Medicine. SGRM aims to cover all aspects of Reproductive Medicine, Reproductive Biology and Family Planning, and importance is given to multidisciplinary collaboration. The society organizes meetings and courses. SGRM is responsible for the national IVF data collection and for the publication of a yearly report on assisted reproductive medicine in Switzerland as requested by the law on assisted reproductive medicine. The society is obliged to fulfil quality norms and is open to all residents who are involved in reproductive medicine in Switzerland. This FIVNAT commission defined as one of its primary goals to make public and report in a critical way the evolution of assisted reproductive

technologies in Switzerland between 1993 and 2002, based on data collected by the National Register FIVNAT-CH. This paper not only reports the evolution observed over this 10-year period, but also analyses whether similar improvements in assisted reproductive technologies have occurred in Switzerland to those reported in other countries.

Data collection

For data reporting, four different forms were adopted, containing the following data: (i) details concerning the medical indications for treatment in both the male and female partner; (ii) details of the protocol for ovarian stimulation, oocyte collection, details from the laboratory, embryo transfer and luteal support; (iii) thawing and replacement of frozen–thawed zygotes and embryos; (iv) all details concerning the pregnancy, delivery and neonates.

All forms were anonymous, but were identified by a registration number given to each participating centre and an identification number given by each clinic to each individual couple. The couple's identification number remained the same for repeated treatments in each participating centre. For each started treatment cycle, the centre reported the required data in the corresponding forms. The data were mailed twice a year to a central office (treatment data and delivery data were reported separately), which entered all data in a computer. The central office verified the incoming data and informed the centres if data were missing or inconsistent. An annual report was presented during annual meetings of all participating centres. The data were presented anonymously and an overall mean for Switzerland was calculated. All participating centres received an individual report summarizing their data in comparison with the overall Swiss data. The Swiss results were communicated annually to the European IVF Monitoring special interest group (EIM).

In 2005, SGRM updated the forms and more data concerning embryo cleavage and embryo morphology will be collected in the future. The updated forms also take into account the demands of the Ministries of Justice and the Federal Statistical Office, and will provide data about the number of zygotes/embryos destroyed and the reasons for destruction, including end of the maximum storage period, personal reasons, cleavage arrest, or personal wish of the couple.

Results

Number and type of initiated cycles

Figure 1 represents the development of the number of initiated treatments with IVF, intracytoplasmic sperm injection (ICSI) and replacement of frozen zygotes/embryos (CRYO). The total number of started cycles (IVF + ICSI + CRYO) in 1993 was 1263, increasing by a factor of 2.7 to reach a total of 3372 in 1997; by 2002, this factor had increased by 4.3 to a total of 5378 initiated cycles. This total number of all initiated cycles, fresh and frozen (IVF + ICSI + CRYO), appears to have reached a plateau and the small increase of 4.8% from 5133 to 5378 (245 cycles) is mainly attributable to the number of initiated CRYO cycles (173 more in 2002). The number of initiated IVF cycles remained nearly constant over the 10-year period, 1036 cycles in 1993 compared with 1001 cycles in 2001. While IVF represented 82.0% (1036/1263) of all initiated cycles in 1993, it only corresponded to 18.6% (10001/5378) by 2002. No remarkable increase in the number of initiated CRYO cycles was observed before 1996; from then on, a parallel increase with the total number of all started cycles (IVF + ICSI + CRYO) was observed, with an exception between 1998 and 1999. In 1993, the number of initiated cryopreservation cycles represented only 13.1% (165/1263), and by 2002 they contributed to 40.2% (2160/5378) of all started cycles.

Number of yearly treatments per patient

Since 1993, there has been very little change in the number of treatments that a patient receives per year, including treatments with oocyte retrieval and cycles with replacement of thawed zygotes/embryos. In 1993, the mean number of fresh treatments (IVF + ICSI) per patient per year was 1.22, and 1.18 in 2002. Treatments with frozen zygotes/embryos (cryopreservation) were respectively 1.48 in 1993 and 1.41 in 2002. The total number of treatments, fresh and frozen together, that a patient received per year has increased continuously since 1993, with a drop of 6.6% in 1999, 4.2% in 2000 and 6.0% in 2002 compared with 2001 (**Table 1**).

Age of female patients

Figure 2 represents the age distribution of female patients for IVF and ICSI between 1993 and 2002. The mean age for ICSI in 1993 was not reported for the 62 ICSI cycles initiated during that year. The mean age of the female patients (IVF and ICSI) remained constant over the first 3 years; however, from 1996, a continuous increase in age was observed and the female patients treated in 2002 were almost 2 years older compared with 1993 (33.9 versus 35.7). The increase in age occurred in parallel for females treated with IVF and ICSI, but from 1995 a constant difference of about 1.5 years was detected between the younger ICSI female patient and the older IVF female patient.

Oocyte retrieval–fertilization rates

Figure 3 represents the mean number of oocytes recovered for the ICSI and IVF cycles with follicle puncture. In 1993, a total of 8493 oocytes were recovered during 1016 oocyte retrievals, corresponding to a mean number of 8.4 oocytes per follicle puncture; by 2002, the number of retrieved oocytes was 29,295 for 3019 oocyte retrievals (IVF + ICSI), with a mean of 9.7 oocytes per retrieval. During this 10-year period, a slow increase of 1.3 oocytes per oocyte retrieval was observed. The fertilization rate after IVF increased by 12% between 1993 and 1996; thereafter, decreases of respectively 4.4% in 1997, 5.7% in 1998, 6.2% in 1998 and 2.8% in 2000 were noted, but by 2002 the fertilization rate was back to the 60% observed in 1996 (**Figure 4**). The initial low fertilization rate after ICSI of 14.8% in 1993 and 29.6% in 1994 increased dramatically from 1995 on to reach 65.7% by 2002, after a small stagnation at 59% between 1998 and 1999.

Developments in zygote and embryo freezing

The number of zygotes frozen increased from 1138 in 1993 to 9320 in 2002 (**Figure 5**). The number of frozen embryos (about

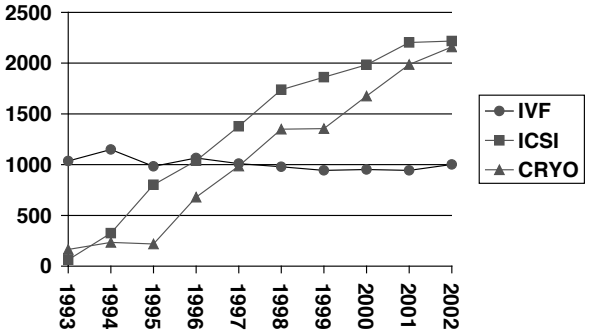

Figure 1. Evolution in the number and type of initiated cycles between 1993 and 2003 as reported by the Swiss National IVF Register FIVNAT-CH. ICSI = intracytoplasmic sperm injection; CRYO = replacement of frozen zygotes/embryos.

Table 1. Mean number of treatments given per patient for each year, with respect to oocyte collection 'Fresh', transfer of thawed zygotes/embryos 'Frozen', and both 'Total', reported by the Swiss National Register FIVNAT-CH.

Year	*Fresh cycles, mean ± SD*	*Frozen cycles, mean ± SD*	*Total cycles, mean ± SD*
1993	1.22 ± 0.45	1.48 ± 0.74	1.36 ± 0.42
1994	1.28 ± 0.55	1.33 ± 0.66	1.43 ± 0.42
1995	1.31 ± 0.54	1.34 ± 0.68	1.48 ± 0.40
1996	1.28 ± 0.55	1.30 ± 0.64	1.50 ± 0.36
1997	1.24 ± 0.52	1.40 ± 0.68	1.54 ± 0 34
1998	1.26 ± 0.53	1.42 ± 0.68	1.62 ± 0.36
1999	1.28 ± 0.57	1.36 ± 0.70	1.55 ± 0.30
2000	1.27 ± 0.55	1.40 ± 0.73	1.59 ± 0.30
2001	1.26 ± 0.61	1.43 ± 0.76	1.66 ± 0.34
2002	1.18 ± 0.43	1.41 ± 0.72	1.56 ± 0.28

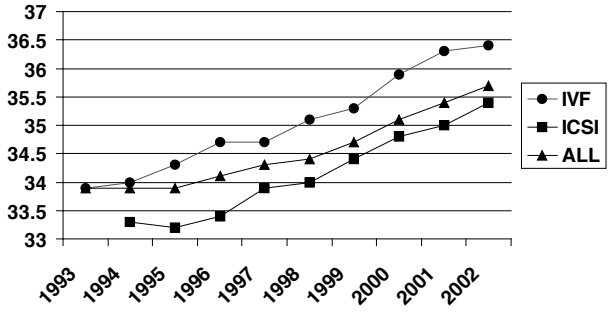

Figure 2. Evolution in the mean age (years) of the female patients for initiated cycles as reported between 1993 and 2002 by the Swiss National Register FIVNAT-CH. ICSI = intracytoplasmic sperm injection.

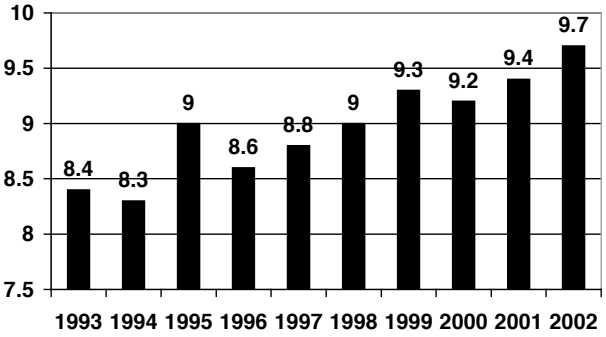

Figure 3. Mean number of oocytes recovered per oocyte retrieval between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH.

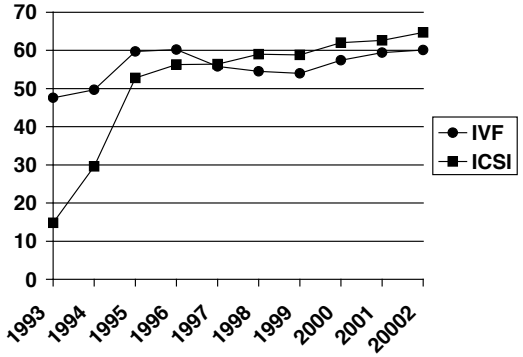

Figure 4. Fertilization rates expressed as percentage of inseminated/injected oocytes for IVF and ICSI between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH. ICSI = intracytoplasmic sperm injection.

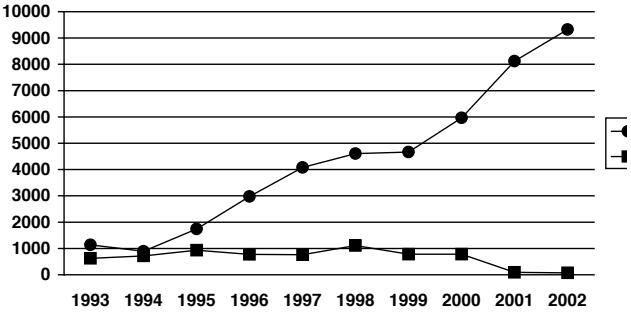

Figure 5. Total number of frozen zygotes and embryos between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH.

780) per year remained quite stable between 1993 and 2000, despite an increasing number of started cycles. Freezing of oocytes in the pronucleate (zygote) stage was adopted early on by many Swiss treatment units and had become standard in 2001, the year in which freezing of embryos was banned legally. Freezing at the zygote stage already accounted for 64.8%. in 1993, for 65.1% (1741/2676) in 1995, for 80.5% (4604/5717) in 1998 and 88.4% (5969/6754) in 2000. The largest numbers of embryos were frozen in 1995 (935) and in 1998 (1113).

Day of transfer and number of replaced embryos

Transfer of fresh embryos on day 2 represented about 90% of all transfers up to 1998. Since 1998, day 3 transfers have accounted for 20.6% (469/2273), with a maximum of 33.4% (889/2662) in 2001, falling back to 23.3% in 2002. Transfers after day 3, mainly transfers at the blastocyst stage, never represented more than 10% of the total number of fresh transfers, with a peak of 9.1% (213/2341). Transfer at the blastocyst stage continued to be practised after 2000, but represented not more then 4.5% (**Figure 6**). The mean number of replaced fresh embryos obtained after IVF or ICSI never exceeded three and has remained consistently less than 2.5 since 1996, with a further drop close to 2 after 1998 for all types of treatments (**Figure 7**).

Implantation and pregnancy rate

The clinical pregnancy rate per transfer of fresh embryos for IVF did not fluctuate much between 1993 and 2001, with the exception of a considerable drop of 5.2% between 1996 (23.4%) and 1997 (18.2%). This drop occurred in parallel for the ICSI treatments. Since 1998, there has been a slow but marked increase of 4% (23.6–27.6%) in the clinical pregnancy rate obtained after ICSI and an increase of 9.6% (20.7–30.3%) in the clinical pregnancy rate after IVF (**Figure 8**). The clinical pregnancy rate per transfer after replacement of thawed zygotes/embryos evolved similarly between 1993 and 2002. After 1995, the clinical pregnancy rate after replacement of thawed zygote/embryos obtained with ICSI has nearly always been higher than with IVF, with the exception of the year 1998 (10.2 versus 12.9%) and the year 2001 (13.3 versus 18.2%).

The clinical pregnancy rates of ICSI and IVF after transfer of fresh embryos on day 3 were lower than after transfer on day 2, but transfer on day 5 appeared to be better, with a clinical pregnancy rate of 42.4% in 2001 (**Figure 9**).

The increase in clinical pregnancy rate after transfer of fresh embryos (IVF + ICSI) observed since 1997 corresponds to a concurrent increase in the implantation rate (**Figure 10**). Between 1997 and 2002, the implantation rate after transfer of fresh embryos increased from 9.2 to 18.1% with IVF and from 10.9 to 15.5% with ICSI.

The implantation rates after replacement of thawed zygotes/embryos obtained after ICSI has been subject to very large fluctuations even after the first 3 years following introduction of the ICSI technique. The lowest implantation rate of 6.4% occurred in 1998 but nearly doubled 1 year later to reach 11.4%. The implantation rate after transfer of thawed zygotes/embryos obtained after IVF remained much more constant compared with ICSI, and increased from 7.5% in 1993 to 9.8% in 2002. By 2002, similar implantation rates were observed after transfer of thawed zygotes/embryos for IVF (9.8%) and ICSI (10.5%).

Multiple pregnancy rate

The highest triplet rates after replacement of fresh embryos (IVF + ICSI) were observed between 1993 and 1995; 3.1, 4.5 and 5% respectively. After 1996, triplet pregnancies represented less than 2%, with the exception in 2000 of 3.2%. Twin pregnancies remained nearly constant at around 19% between 1993 and 2002. The twin pregnancy rate after replacement of thawed zygote/embryos has remained continuously above 10% since 1998, and the triplet pregnancy rate is comparable to that observed after replacement of fresh embryos (**Figures 11** and **12**).

Cumulative pregnancy rate

As all collected data on pregnancies obtained after replacement of thawed zygotes/embryos are linked in the Swiss National Register to the initial cycle in which the oocytes were collected, it is possible to calculate the cumulative pregnancy per year of oocyte collection. Those calculations have been possible for the years 1997 (24%) to 2000 (32.3%). As the results may still continue to rise, the data reported here represent the situation as observed in 2004 (**Figure 13**).

Ovarian hyperstimulation syndrome

Among the possible complications of assisted reproduction, ovarian hyperstimulation syndrome (OHSS) ranks among the most frequent. The Swiss Register requires reporting of the occurrence of this complication and differentiation between those cases treated ambulatory and those needing hospitalization. The data are summarized in **Figure 14**. There has been a continuous increase in the incidence of OHSS with and without hospitalization from 1.2% in 1993 to 3.5% in 2002. However, there has also been a general tendency for fewer hospitalizations from 33% in 1993 to 25.7% in 2002.

Neonatal status

Since 1993, not less that 93% of the data on child status has been collected, with the exception of 13.1% of loss in follow-up in 1994. Between 1997 and 2000 nearly all data were collected, but since then there seems to have been an increase in the loss of data of about 6% for the last 2 years. Intrauterine or neonatal deaths were observed in less than 1% of all cases. The percentage of children with a disability at birth ranged between 0.5 and 2.7% (**Table 2**). The incidence of neonatal malformations ranged between 0.6 and 4.7% during the observation period from 1993 to 2002.

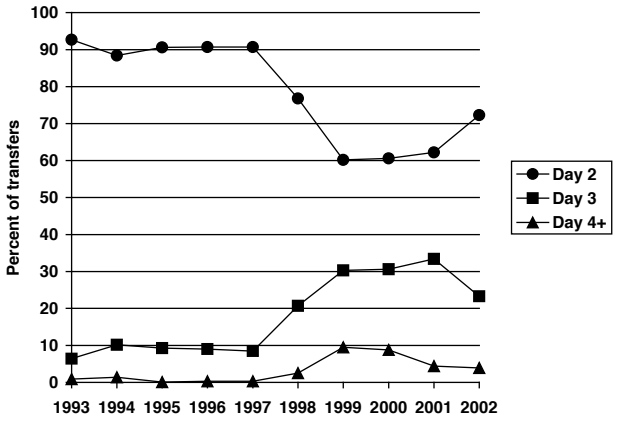

Figure 6. Percentage of the total number of transfers according to the day of transfer between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH.

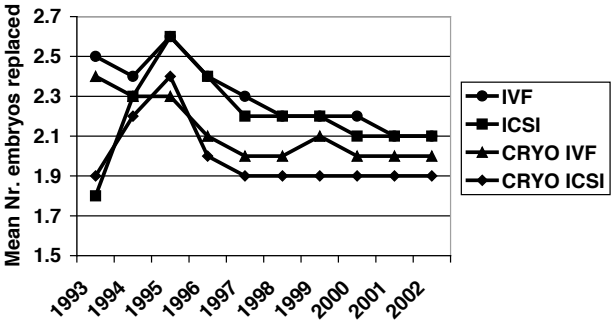

Figure 7. Mean number of embryos replaced after IVF and intracytoplasmic sperm injection (ICSI) between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH. CRYO = replacement of frozen embryos.

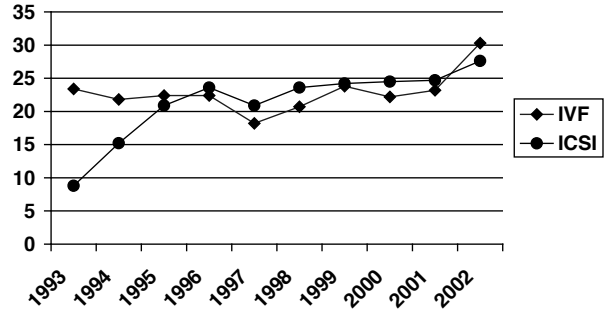

Figure 8. Clinical pregnancy rate (%) per transfer after IVF and intracytoplasmic sperm injection (ICSI) with fresh embryos between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH.

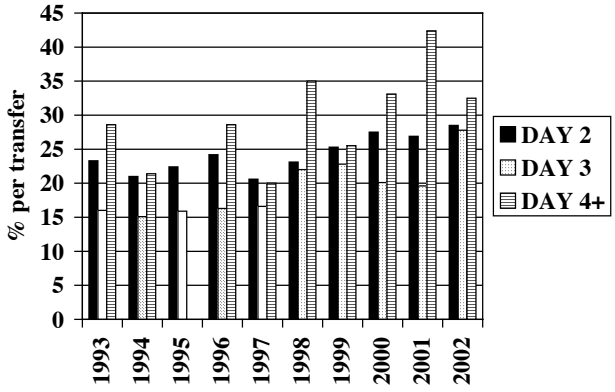

Figure 9. Clinical pregnancy rate related to the day of transfer between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH.

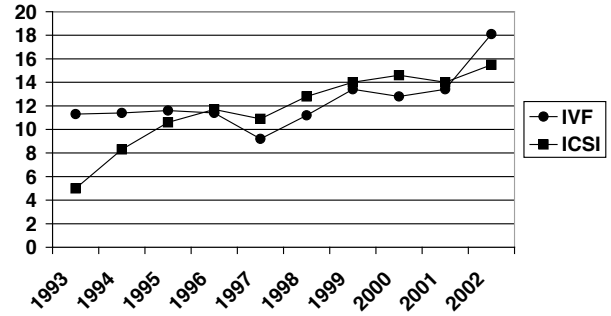

Figure 10. Implantation rates (%) after replacement of fresh embryos between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH. ICSI = intracytoplasmic sperm injection.

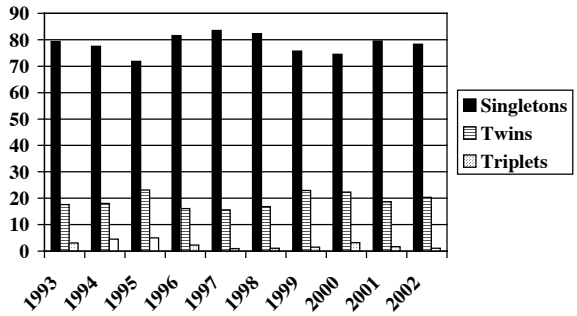

Figure 11. Multiple pregnancy rates (%) after replacement of fresh embryos between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH.

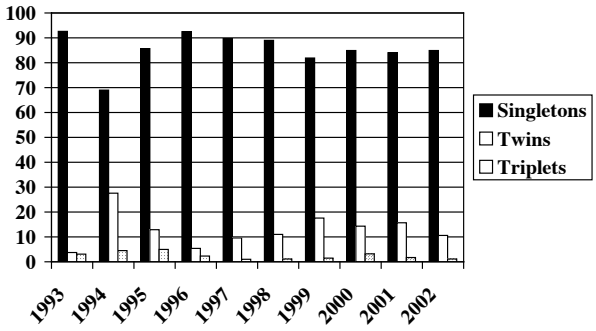

Figure 12. Multiple pregnancy rates (%) after replacement of thawed zygotes/embryos between 1993 and 2002 as reported by the Swiss National Register FIVNAT-CH.

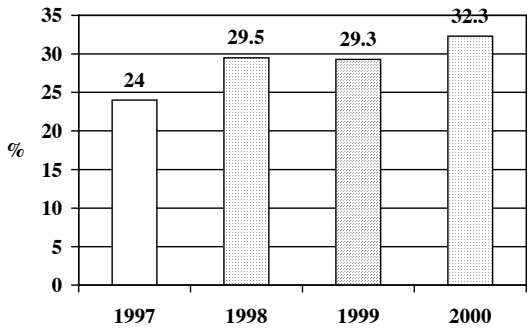

Figure 13. Cumulative pregnancy rates (%) expressed per year of the original year of oocyte collection, situation in 2003, Swiss National Register FIVNAT-CH.

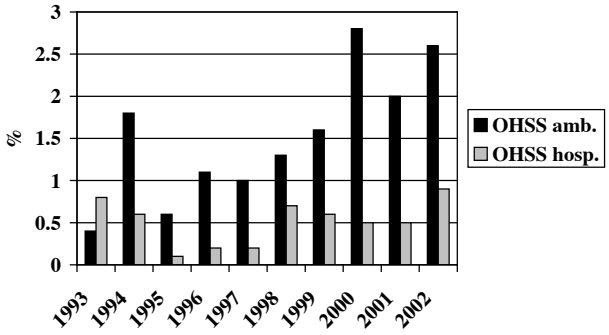

Figure 14. Occurrence of ovarian hyperstimulation syndrome with hospitalization (hosp) and without hospitalization (amb.) between 1993 and 2002 as reported by Swiss National Register FIVNAT-CH.

Table 2. Child status for all births obtained from fresh and frozen embryo replacements between 1993 and 2003 as reported by the Swiss National Register FIVNAT-CH.

Year	*Death in utero, %*	*Neonatal death <day 7, %*	*Neonatal death <day 28, %*	*Disabled, %*	*Unknown, %*
1993	0.6	0.6	0.6	1.9	3.8
1994	0.5	0.5	0	0.5	13.1
1995	0.5	0.8	0.3	1.8	4.4
1996	0.6	0.9	0.3	2.5	4.1
1997	0.7	0.3	0	1.7	2.3
1998	0.4	0.2	0	1.0	2.7
1999	0.4	0.5	0.2	0.7	2.9
2000	0.3	0.4	0	2.7	2.4
2001	0.6	0.4	0.5	2.5	6.1
2002	0.5	0.3	0.2	1.6	6.4

Table 3. Data validity and quality as reported by external auditors.

Year	*Planned audits*	*Achieved audits*	*Centres with logbook*	*Checked files*	*Files with at least 1 error (%)*	*Errors in mandatory field*	*Errors per checked file*
1998	15	15	3	246	200 (81)	472	1.90
1999	8	6	<6	116	102 (88)	247	2.10
2000	6	4	2	?	?	?	?
2001	6	5	4	?	?	?	?
2002	8	8	8	157	92 (58)	181	1.15
2003	10	10	8	161	97 (60)	193	1.20

Discussion

Before entering the discussion, it is necessary to consider that if the above data represent the entire data for the whole of Switzerland collected over 10 years by 23 different centres (from which 20 were still active in 2004), there is an enormous difference among the various centres concerning the input by the different centres. The two largest centres represent respectively 23.3 and 19% of the 34,754 cycles reported here, and 17 centres account each for less than 5%. From those 17, 11 each represent less that 2% of the total number of reported cycles.

The more than four-fold increase in the number of assisted reproduction treatments provided in Switzerland between 1993 and 2002 may appear enormous at first sight. However, this apparent rise must be related to the number of inhabitants in Switzerland. If those data are expressed as treatment per million inhabitants, then it becomes quite clear that Switzerland provides the lowest number of treatments per million inhabitants, respectively 472 for 1997, 586 for 1998, 563 for 1999 and the second lowest number of treatments in 2000, with 644 per million inhabitants as reported by the EIM consortium data. Expressed as number of treatments a patients receives per year (**Table 1**), this figure has remained around 1.5 since 1993. These results can be compared with results from Denmark, a country with 5 million inhabitants, 2 million less than Switzerland, and with the highest number of treatments per million inhabitants, respectively 1448, 1659, 1608 and 1830 (Nygren and Andersen, 2001a,b, 2002; Nygren *et al.*, 2004). A similar comparison can be made with Finland, a country also with 5 million inhabitants and 1538 treatments per million in 1997, or with Iceland with only 0.27 million inhabitants but 1442 treatments per million in 1997. The EIM report estimated for Switzerland the mean number at 2.3 treatments per year (Nygren and Andersen, 2001b). This figure places Switzerland first in line and the United Kingdom second, with 2.5 treatments for a population of 59 million in 1998. The FIVNAT-CH data reveal that this figure was overestimated for Switzerland. The real treatment rate per patient fluctuates around 1.5 treatments per year and per patient (**Table 1**), and is five times lower than the 7.3 reported for Denmark. This comparison points to the large differences in the mean number of treatments between countries, and illustrates the impaired accessibility to the treatments due to absence of reimbursement in Switzerland. This absence of reimbursement, in combination with the fear of fertilization failure with IVF, explains why the majority of treatments are performed with ICSI.

The ongoing increase in the mean age is a very important factor for proper interpretation of the global outcome of assisted reproduction. Switzerland ranks among the three countries with the highest proportion of female patients aged between 35 and 39 years, 36.5% in 1997, 36.1% in 1998, 40% in 1999 and 36% in 2000 (Nygren and Andersen, 2001a,b, 2002; Nygren *et al.*, 2004). Despite the increasing maternal age, there was an increase in the mean number of oocytes collected. It is unlikely that this increase is associated with the introduction of recombinant FSH, as reported in a recent Cochrane review (Daya and Gunby, 2004), as it was concluded that recombinant FSH did not increase the mean number of retrieved oocytes compared with urinary FSH and might provide a smaller number of oocytes at the metaphase II stage (Huang *et al.*, 2004). On the other hand, the mean number of recovered oocytes seems to lie in the range associated with the best outcome in terms of pregnancies (Melie *et al.*, 2003). The most plausible explanation for the increase in the mean number of retrieved oocytes is the acquired experience in ovarian stimulation, and probably the more intensive stimulation as seen by the increase in the total number of cases of OHSS. The quality and consistency of recombinant FSH has been reported in detail, and its possible advantages commented on (Bassett and Driebergen, 2005). Recombinant FSH has been used in approximately 50% of all ovarian stimulation cycles since 2000. During the same observation period urinary gonadotrophins were used in 22–33% of all treatment cycles. Data about the mean number of gonadotrophin units used per stimulation are not available from FIVNAT-CH. It was not possible to examine whether the centres applied higher daily dose stimulated regimens in order to obtain more oocytes after the ban of embryo freezing in January 2001. The increase in the percentage of treatments with OHSS started from 1998 on (**Figure 14**). This is a matter of concern for the future, as the observed frequency in 2002 of 3.5% is far above 0.9% in 1999 and 1.1% reported by EIM or the 0.6% (336/52276) reported in 2000 in Germany a country with a similar legislation as in Switzerland (Nygren and Andersen, 2001b, 2002).

From the beginning of the FIVNAT records, it was common in Switzerland to see zygotes and embryos frozen within the same treatment cycle, leaving a limited number of zygotes in culture for embryo transfer. One of the large centres in Switzerland

reported in 2000, based on a study held between 1993 and 1995, that keeping a maximum of three zygotes in culture for embryo transfer and freezing all the remaining ones was not only a safe technique, but led in the end to a higher cumulative pregnancy rate (Senn *et al*., 2000). Their conclusion is confirmed by the true cumulative pregnancy rates reported here. The FIVNAT-CH cumulative pregnancies rates described in **Figure 13** are related to the original year of oocyte collection and are comparable with the cumulative live birth rate of 26.7% reported after four cycles with replacement of thawed embryos (Osmanagaoglu *et al*., 2004). This might also explain why blastocyst transfer did not really gain acceptance in Switzerland, and the real benefit of blastocyst transfer has been questioned (Plachot *et al*., 2000). A recent randomized study has reported similar implantation and pregnancy rates for cleavage stage embryos and blastocyts (Hreinsson *et al*., 2004) as confirmed by the Cochrane review (Blake *et al*., 2002). In 2001, the new law limited the number of zygotes kept in culture to three and prohibited embryo freezing and embryo selection became impossible. Day 3 embryo transfer remained quite a common practice, despite this new situation and despite some randomized studies showing that the results between day 2 and day 3 replacement were similar (Laverge *et al*., 2001). The FIVNAT-CH data never showed better results with day 3 transfer compared with day 2 (**Figure 10**).

Cycles with replacement of frozen–thawed zygotes/embryos represented 13.1% of all treatments in 1993, 32.8% (1312/4002) in 1998 and 40% in 2002. This is a considerable increase compared with countries with a similar total number of treatment cycles in 1998, such as in Russia 1.9% (88/4692) and in Norway 27.9% (1017/3643). Therefore, it can be stated that long before the change in the law forbidding the freezing of embryos in Switzerland, the majority of cryopreservation was performed with zygotes. As the debates leading to the new law on reproductive medicine took time Swiss IVF centres obviously invested more in zygote freezing. The estimation of the cumulative pregnancy rate after six cycles of 59.6% and of 84% after 12 cycles reported very early (Guzick *et al*., 1986) seem relatively overestimated in relation to the true cumulative pregnancy rate as reported by FIVNAT-CH, and the supplementary benefit of cryopreservation is probably limited, as reported by others (de Jong *et al*., 2002). However, the most limiting factor to obtain the maximal cumulative pregnancy rate per IVF treatment might be the limitation of the cryopreservation period to 5 years, especially if it is taken into consideration that the mean number of treatments per year and per patient is low in Switzerland.

The FIVNAT-CH data show a continuous improvement in the clinical pregnancy and implantation rates over the 10-year period, an observation made in the reports of 20 years use of assisted reproduction in the USA and Australia (Toner, 2002; Quinn, 2004). Both communications report an increase in the clinical pregnancy rate by a factor of 2, a figure slightly higher than that observed by FIVNAT, 1.7 for IVF and 1.3 for ICSI between 1997 and 2002. The effect of maternal age plays an important role, and the clinical pregnancy rate per cycle after replacement of fresh embryos (IVF + ICSI) in women over 40 does not exceed 8.9 and 10.8% according to the FIVNAT-CH 2003 and 2000 annual reports, a figure slightly lower than the 12% reported in the USA in 2000 (Toner, 2002). For patients aged between 30 and 35 years, the FIVNAT annual reports give 32.8% in 2003 and 28.7% in 2000, and again those figures are lower than those reported in the USA. The differences must be attributed to the rapidly increasing mean age of the female patient in Switzerland, in combination with the restrictive legislation banning all embryo selection. However, despite these two limitations, the clinical pregnancy rate continues to rise.

The observation that multiple pregnancies observed by FIVNAT-CH are certainly lower than those reported in the USA (Toner, 2002), and overall slightly lower than the 26.4% published in the 2000 EIM report (Nygren *et al*., 2004), is encouraging. Data on multiple pregnancy rates should, however, always be related to the mean number of embryos replaced. It is generally assumed that replacement of three or more embryos is still common practice in the USA; however, there has been a considerable fall in triplets from 6.5 to 4.5% after IVF in 1999 (Toner, 2002). On the contrary there has been very little fluctuation in the twin pregnancy rate after replacement of fresh (IVF + ICSI) embryos in Switzerland. The restrictions imposed by Swiss law render it impossible to benefit from embryo selection, a key factor in establishing single embryo transfer, or to use blastocyst culture with single embryo transfer as true target (De Neubourg and Gerris, 2003). Despite restrictive laws, multiple pregnancies still occur and Swiss laws have had very little influence on the twin pregnancy rate, 22.3% in 2000, 18.6% in 2001 and 20.3% in 2002. Multiple pregnancies in the overall Swiss population represented in 2004, 1.6% of all live births (1170/73082) according to the Swiss Federal Statistical Office (www.bfs.admin.ch). Laws, especially those made in Switzerland by direct public votes, are rigid instruments. Policy makers must themselves abide by certain general principles, first and foremost to avoid placing the specialist in the position of 'bad medical practice' (Benagiano and Farris, 2003). The observation that even after the new law there are still about 100 embryos frozen a year, shows that some Swiss centres consider the high risk for triplets and twins, in young patients with two or three excellent embryos (De Neubourg and Gerris, 2003), as an emergency situation in which embryos must be frozen. This observation reinforces the statement that legislators should produce texts that truly protect the 'public good' and make it possible to help at the same time as many individual cases as possible. The creation of an authority and providing a legislative act with clear principles should make it possible to resolve the myriad of individual problems that are and will continue to arise from the application of assisted reproductive techniques (Benagiano and Farris, 2003).

The data collected on intrauterine death and death before 7 and 28 days are very similar to the data reported in Denmark, where 13.1/1000 stillbirths were reported for twin pregnancy and 6/1000 for singletons and the same remark can be made concerning the observed malformations (Pingborg *et al*., 2004). Stillbirths represented in 2004, 0.4% of all live births as reported by the Swiss Federal Statistical Office; this figure is not different from the data reported in this paper (**Table 2**).

From 1998, FIVNAT-CH organized external audits to evaluate the data validity and quality. The results of these audits are reported in **Table 3**. By 2003, 80% of the visited laboratories had a cycle registration logbook, the percentage of files with errors was reduced by 20%, and the number of errors per file was nearly reduced by half between 1998 and 2003.

In conclusion, data collection organized by the FIVNAT-CH National Register has been quite effective. The quality of the collected data increased once external audits were introduced. It was possible to analyse and compare the results of 10 years of assisted reproductive technologies and analyse for possible effects of the introduction of a restrictive law. The pregnancy rate after replacement of fresh embryos (IVF + ICSI) continued to increase after the introduction of the new law, but this increase was lower compared with other countries without restrictions. The new law did not reduce the twin pregnancy rate. The number of cases of OHSS syndrome has increased by a factor of 3.

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