

Assisted reproductive medicine in Switzerland

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Summary

Since the first introduction of hormonal contraception, family planning and procreation have become increasingly medicalised. The rapid spread of assisted reproductive technology (ART) is part of this natural development of modern society. However, in Switzerland it has caused severe controversy and its use has been framed by a restrictive legislation since 2001. Despite this, the yearly number of reported treatments with in-vitro fertilisation (IVF), with intracytoplasmic sperm injection (ICSI) and with transfer of frozen/thawed oocytes in the pronucleate stage has risen to more than 10,000 in 2011. As over time the protocols for ovarian stimulation have reached higher levels of efficacy and as the composition of the culture media used for embryo development in the laboratory has become more elaborate, the implantation rate of the transferred embryos has steadily improved leading to higher pregnancy rates, but also resulting in a higher risk of multiple delivery. Deliveries of multiples, including those with twins, often occur prematurely causing significant maternal and neonatal morbidity and mortality. Improved assessment of the developmental potential of embryos together with better freezing protocols have lead to the selection and transfer of one single embryo per treatment cycle in an increasing number of countries but not in Switzerland. This strategy has been shown to be very effective in preventing multiple deliveries without compromising the overall pregnancy rates. In addition, well accepted treatment mod-

alities in assisted reproduction, such as embryo cryopreservation, oocyte donation and preimplantation genetic diagnosis have not been implemented in Switzerland due to the current restrictive legislation. The still present ban on cryopreservation of embryos in Switzerland now leads to a higher incidence of complications and neonatal death than necessary in the presence of an adapted legal environment. There is an urgent need for a public debate about the future role of modern reproductive medicine in Swiss society. This discussion should focus not only on the risks of ART but also on its opportunities.

Key words: infertility; population decline; multiple delivery; embryo; assisted reproduction

Introduction

The term “infertility” is defined by the inability of couples to achieve pregnancy within 12 months despite regular and unprotected intercourse. Individuals suffering from infertility may decide to undergo a set of diagnostic tests aiming at identifying the underlying cause of their problem. In many cases, one or more medical conditions may causing infertility be identified and treated allowing the establishment of pregnancy naturally. However, in a significant proportion of infertile couples the underlying problem cannot be

List of abbreviations

ART	assisted reproductive technology
BFS	Bundesamt für Statistik
EIM	European IVF-Monitoring, a working group of ESHRE
eSET	elective single embryo transfer
ESHRE	European Society of Human Reproduction and Embryology
ICMART	International Committee Monitoring Assisted Reproductive Technologies
FIVNAT	fécondation in vitro nationale
FSH	follicle-stimulating hormone
GnRH	gonadotropin releasing hormone
HCG	human chorionic gonadotropin
ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilisation
PGD	preimplantation genetic diagnostics
SGRM	Swiss Society of Reproductive Medicine

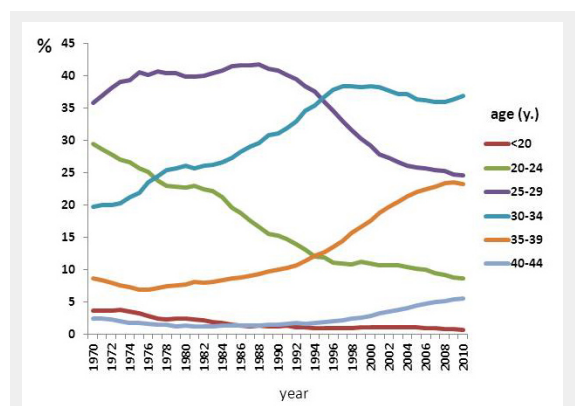


Figure 1

The age at delivery of women delivered in Switzerland since 1970 (Source: BFS; www.bfs.admin.ch). Whereas the number of women giving birth at the age of 30 y or less is on the decline since 1990, the number of older women giving birth is on the rise, in particular those above the age of 35 years.

cured effectively. In these cases, ART may be offered. ART creates an environment in which all events from fertilisation to the development of an embryo may take place in the laboratory. If these events occur successfully, an embryo may be transferred into the uterine cavity, where it may become implanted resulting in a viable pregnancy. Due to the access to human embryos and given its potential for many other applications not directly related to infertility, such as gene therapy, embryo selection, cloning and stem cell research, ART has received considerable interest both in the medical literature and in the lay press and has remained the object of controversial debate since its early beginnings.

Currently, two major methods of ART are in frequent use: conventional IVF, in which the oocyte is inseminated with a number of washed spermatozoa allowing fertilisation under conditions similar to those in the ampulla of the Fallopian tubes. This form of ART may help to overcome blockage of the Fallopian tubes, which cannot be repaired by tubal surgery. The other frequent method in ART consists of ICSI, in which with the help of a micropipette one single, viable spermatozoon is inserted through piercing all the investments of an oocyte directly into the cytoplasm. This form of ART is most often used to overcome severe male infertility, in which to few or no spermatozoa are able to achieve fertilisation naturally. In order to increase the likelihood of successful fertilization and pregnancy, ART is usually accompanied by hormonal enhancement of ovarian function, in which the growth of a suprphysiological number of follicles is stimulated with the help of pharmaceutical products containing gonadotropins and by luteal support with progesterone. One oocyte can be retrieved from each follicle, so that several oocytes can be fertilised allowing the transfer of more than one embryo into the uterine cavity. As current legislation in Switzerland (Fortpflanzungsmedizingesetz, FMedG) limits the maximum number of embryos to be transferred to three, all supernumerary oocytes may be stored frozen [1]. In Switzerland the cryopreservation of embryos is prohibited and because cryopreservation of unseminated oocytes has long been considered technically unfeasible, oocytes at their pronucleate stage are stored frozen. In the absence of successful pregnancy in the first treatment or when the couple wishes a second child, those cryopreserved pronucleate oocytes may be thawed and transferred into the uterine cavity without the need for further hormonal stimulation of ovarian function.

Medicalisation of family planning and its consequences

The rise of ART must be seen in the context of the rapid medicalisation of procreation that has taken place in recent decades. The introduction of the first oral contraceptive Anovular in 1962 has revolutionised family planning in Switzerland, as in most developed countries. Together with other factors, such as economic wealth and the high level of education, unrestricted access to modern contraceptives has resulted in a considerable reduction of the number children born per family. Another, more recent trend is characterised by a steady postponement of child-bearing towards the later years of the reproductive life span

of women (fig. 1). These changes in couples' attitudes have not remained without risk, as the likelihood of infertility rises with advancing age both in the male and in the female. In addition, the higher incidence of infertility is accompanied by a rising incidence of both obstetric and neonatal complications. In order to cope with an increased demand caused by these trends, foetomaternal medicine including prenatal diagnostics has become ever more sophisticated. In this context the rising demand for medical support in couples suffering from infertility must be seen as a logical consequence of these ongoing demographic developments. Modern reproductive care is often epitomized by IVF and was successfully performed for the first time in the United Kingdom leading to the birth of Louise Brown on July 25th in 1978 [2] and in Switzerland resulting in the birth of Jelena in Breitenbach on April 26th in 1985. My own personal early experience with IVF dates back to the birth of Sascha on July 19th 1985 in Oldenburg/Oldbg. in Germany. Much later, the treatment of male infertility was revolutionised by the development of ICSI resulting in the first successful birth in 1992 [3]. However, many other technologies have paved the way for ART long before 1978 and even more benefited from rapidly evolving ART after 1978. The former included cryopreservation of semen [4], the use of human menopausal gonadotropins for ovarian hyperstimulation and ovulation induction [5], radioimmunoassays for the swift measurement of steroid hormone levels in urine and serum [6], complex media for the culture of embryos [7] and methods for the selection of motile spermatozoa from semen [8]. In addition, the rapid spread of conventional IVF since the early eighties has had a deep impact on our understanding of female infertility and has much contributed to present day diagnostic and therapeutic management of both male and female infertility.

Similar to the fast adoption of contraception in present day family planning, modern reproductive medical care became widely used not only in developed countries but also

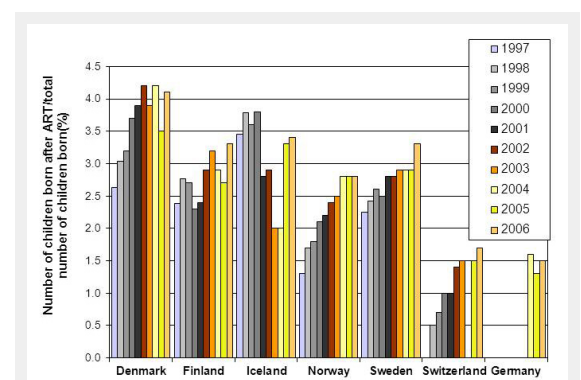


Figure 2

In those countries with a complete coverage of all deliveries after ART, its impact on the total number of neonates can be assessed. In most countries, the impact of ART as given by the number of neonates born after assisted reproduction is on the rise (Source: European IVF-monitoring Group (EIM) of ESHRE, [10]). The relative number of neonates after ART (in %) is the highest in Scandinavian countries, where the treatment costs are covered by the health insurance. In Switzerland the 2004 data were not mentioned by EIM in their annual report, as were the data before 2004 in Germany due to incomplete coverage of deliveries after ART.

on a worldwide scale. The number of children conceived and born after ART is now thought to exceed three million. More than 1.5% of all neonates born in Switzerland now result from treatments with assisted reproduction [9] (fig. 2). In some countries, such as Denmark, in which assisted reproduction has until now been reimbursed by the national health care systems, close to 4.5% of all newborn children arise from ART [10]. Nowadays, ART helps to mitigate the population decline in many European countries including Switzerland. A number of studies have demonstrated that despite the high costs invested in each treatment including those that failed to result in viable pregnancies, ART produces a measurable and long-lasting benefit to the socioeconomic wealth of society [11].

Current protocols in assisted reproduction

Whereas the first pregnancies arose from IVF in otherwise untreated menstrual cycles, since 1981 ovarian hyperstimulation with gonadotropins has been used to optimise the likelihood of achieving pregnancy [12]. The introduction of GnRH-agonists in 1985 has further contributed to the present day efficacy of ART as they prevent premature ovulation. Vaginal sonography, along with rapid assay systems for the measurement of serum concentrations of estradiol and progesterone, have substantially improved the monitoring of ovarian follicular growth. The transvaginal approach for oocyte retrieval, first introduced in 1986 [13], has virtually abolished surgical laparoscopy for oocyte retrieval and has been decisive in turning ART into an outpatient procedure. Embryo transfer may similarly lead to higher pregnancy rates when carried out under transabdominal ultrasound guidance [14].

The worldwide rapid increase in treatment numbers with ART and the need to increase the purity of the gonadotropin preparations spurred the demand for urine of healthy postmenopausal women, from which the human menopausal gonadotropin preparations are extracted. From 1992 onward, recombinant FSH was successfully introduced in-

to ART [15, 16], as these were manufactured from non-human mammalian cells transfected with the genes of the α - and β -chain of the hormone. However, at present, the gonadotropin market in Switzerland is still largely dominated by the urinary gonadotropin preparations, chiefly due to higher price of the recombinant gonadotropins.

A more recent development is the steady shift from the use of long-acting GnRH-agonists towards GnRH-antagonists. In contrast to GnRH-agonists, which need several days to become suppressive and are therefore usually administered during the preceding menstrual cycle, due to their immediate inhibitory action on endogenous gonadotropin secretion GnRH-antagonist can be used at short term during ongoing follicular development. Although GnRH-antagonists result in somewhat lower numbers of oocytes, lesser amounts of gonadotropins are needed and the risk of the ovarian hyperstimulation syndrome has been shown to be significantly reduced, and the pregnancy outcome has now been demonstrated to be equivalent to those achieved with GnRH-agonists [17]. In recent years, GnRH-antagonists have found broader usage in Switzerland and the number of treatment cycles with GnRH-antagonists now exceeds those with GnRH-agonists.

Another potential advantage of GnRH-antagonists is now under development. Until now, final maturation of the oocytes has conventionally been induced by the administration of high dose of human chorionic gonadotropin (HCG), which also sets the time to schedule the retrieval of the oocytes. Protocols involving GnRH-antagonists, substituting HCG by one bolus injection of a short acting GnRH-agonist and thus enabling an endogenous LH surge may hold promise. This approach may be more physiological but final proof of its superiority to the conventional ovulation induction with HCG still remains to be delivered [18].

Evolution of the laboratory requirements in ART

In ART the gametes and the embryos are cultured in a finely balanced fluid, which must sustain the metabolism of the biological material with the appropriate substrates during the subsequent stages of their development in a constant environment set with the appropriate pH, osmolarity and temperature. The culture media used in conventional IVF in the early eighties were chiefly composed of a mixture of electrolyte buffers, taken from earlier experience with mouse embryo cultures, with the addition of glutamine, pyruvate, penicillin and streptomycin, all making up the so-called Biggers, Whitten & Wittingham medium [7]. With time, the various chemical components of the culture media became increasingly numerous, including amino acids, vitamins and other compounds aiming at mimicking the natural environment of the oocytes and the embryos in the Fallopian tube and in the uterine cavity. Instead of bovine albumin or human albumin from stock solutions, both carrying the risk of xenogenic contamination including viruses and prions, recombinant human albumin has become part of the culture medium. Oocyte and embryo culture are now systematically carried out under paraffin oil, which adds to the stability of the culture conditions, and in incubators allowing a constant temperature

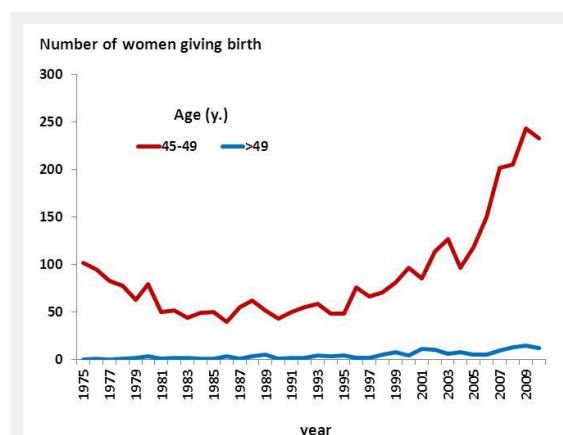


Figure 3

Since 1995 the number of women aged 45 years and older giving birth is on the rise (Source: BFS; www.bfs.admin.ch). This steep increase can only be explained by women receiving oocyte donation in foreign institutions and must be considered as a striking example of reproductive tourism.

and an atmosphere mimicking the physiological conditions in the tissues (5% oxygen, 5% carbon dioxide and 90% nitrogen). Given their current level of complexity culture media are now being manufactured in specialised institutions providing a maximal level of scrutiny and quality assurance. The current efficacy of ART largely stems from a steady improvement of the purity and the composition of the complex culture media used for embryo culture and has enabled the embryologists to prolong the culture of embryo beyond the early cleavage stage up to the blastocyst stage, which most embryos achieve five to six days after fertilisation.

Early embryonic development is inherently a highly selective process, during which the observation of growth rate and a number of morphological aspects of embryonic development allow the embryologists to distinguish between those embryos with significant implantation potential and those without. When an embryo reaches the blastocyst stage, its potential for further development can be assessed with a much higher level of accuracy as compared to the earlier stages. Although the prolonged culture of embryos is still thought by some to expose the embryos to a higher risk of epigenetic abnormalities, the superior pregnancy rates achieved with the transfer of blastocyst embryos will certainly add to the future efficacy of ART [19].

Over time, the improved laboratory conditions improved the implantation rate of the transferred embryos, which resulted in exceeding numbers of multiple gestations and deliveries among women treated with ART. Although current legislation limits the number of embryos that may be placed in one treatment to three, the Swiss medical com-

munity has voluntarily reduced the number of replaced embryos to two [20]. In some other countries, most notably in Sweden and Belgium, a policy of replacing only one embryo has virtually eliminated multiple gestations, including twin pregnancies [21, 22]. Such a single embryo transfer policy requires the selection of one single embryo based on morphological criteria and the cryopreservation of the remaining embryos. As cryopreservation of embryos is prohibited in Switzerland, a policy of single embryo transfer is not feasible without severely compromising the outcome of ART.

Meanwhile, the cryopreservation of embryos and oocytes is being significantly improved by moving from the conventional slow freezing protocols to ultrarapid freezing. Slow freezing protocols have long been used to cryopreserve pronucleate oocytes, but the implantation rates achieved with the thawing of these have always been lower than those achieved with freshly collected oocytes, suggesting that the slow freezing protocols are suboptimal. In addition, cryostorage of unseminated oocytes using the well established slow freezing protocols has met with low success rates [23]. Vitrification involves ultrarapid freezing of biological material but requires much higher concentrations of the ambient cryoprotectants. In specialised institutions the results of vitrification of human oocytes have been demonstrated to be highly superior to conventional freezing protocols [24]. Although vitrification of pronucleate oocytes has not yet found wide acceptance, the much higher success rates achieved with vitrification of oocytes and embryos will inevitably demand a change in policy towards cryopreservation in Switzerland.

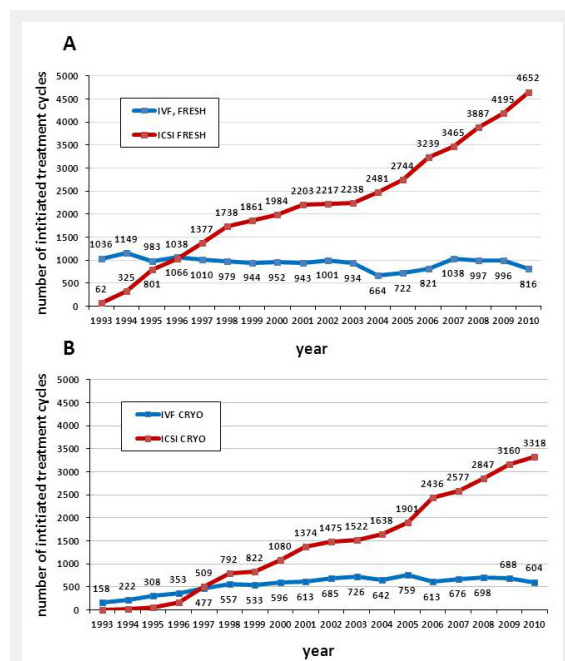


Figure 4
The number of treatment cycles with IVF and ICSI during freshly stimulated treatment cycles (A) and after cryopreservation and thawing (B) have been collected systematically by FIVNAT-CH since 1992 (Source: www.sgrm.org). Whereas the number of treatments with ICSI is continuously rising, those with IVF have remained stable. As the incidental total failure of fertilisation cannot be predicted reliably, many institutions offer ICSI to all couples irrespective of the semen quality.

Complications and pitfalls

From its early beginnings, the potentially higher risk of foetal or neonatal malformations has aroused much debate, in particular since the advent of ICSI in ART. At present,

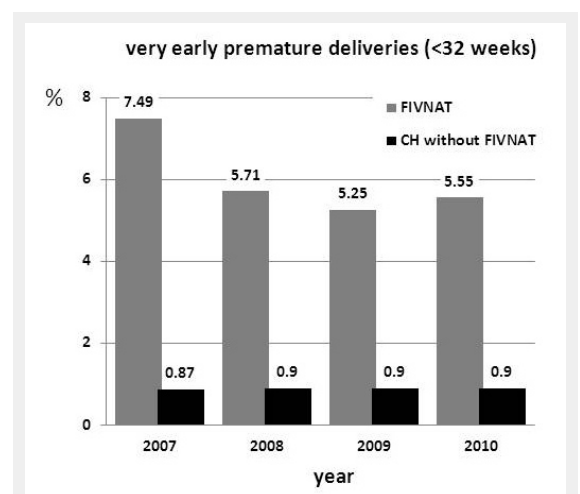


Figure 5
The incidence of very early premature delivery (before week 32 of gestation) is much higher in assisted reproduction than in natural conception (Source: BfS and FIVNAT; www.bfs.admin.ch and www.sgrm.org). Although many cases of very early prematurity are caused by multiple delivery including twins, the risk is also higher in singleton pregnancies among previously infertile women.

long term follow up of several cohorts of children conceived with this technique has failed to demonstrate any major effect of ICSI on the children's malformation rates and the voluntary delay of the age of childbearing is certainly contributing more to the current malformation rate. The controversy surrounding the potential impact of ICSI on the incidence of malformations has had a significant impact as the search for genetic conditions underlying abnormal spermatogenesis has substantially added to our current understanding of male infertility. Mutations in the Cystic Fibrosis Conductance Regulator gene (CFTR) causing azoospermia due to the congenital bilateral aplasia of the vas deferens (CBAVD) have been identified. In addition, numerical and structural chromosomal abnormalities and microdeletions of the Y chromosome were demonstrated to be involved in some cases of severe male infertility. All these findings were implemented into the routine diagnostic evaluation of a couples' infertility, resulting in close collaborations between virtually all ART units and institutions dealing with human genetics. Currently, the potential involvement of epigenetic changes during defective spermatogenesis and of the excessive fragmentation of the spermatozoon's DNA in some infertile men is being discussed controversially and may soon find their way into routine ART.

The high numbers of multiple gestations are of major concern as the long term health hazard to the neonates caused by prematurity has been well established [25]. Although many infertile couples consider a twin pregnancy as desirable after the prolonged suffering of infertility, the risks of a twin gestation and the obstetric and neonatal care of premature delivery by far outweigh the financial benefit caused by the avoidance of a second treatment with ART [26]. The experience with elective single embryo transfer (eSET) in Sweden and Belgium has demonstrated the feasibility of avoiding multiple pregnancies [21, 22].

Legislation and ethics

ART has gone through difficult times in Switzerland and was even prohibited in the Cantons Basel City and St. Gallen between 1990 and 1994. Later, in March 2000, an impressive 71.8% majority of all Swiss voted against a ban on ART. The current legislation in Switzerland regulating the activities of ART has been very helpful in putting an end to the harsh controversy over ART. The Swiss professional community involved in ART has been proactive in voluntarily setting up an organisation, which collects all data on ART, thereby adding to the much needed transparency [20]. Unfortunately, the restrictive legislation has also prevented the introduction of preimplantation genetic diagnostics (PGD) and of eSET and has considerably hampered embryonic stem cell research in Switzerland. In addition, although semen donation has been legally accepted, donation of oocytes is not allowed. The latter is circumvented by many couples through "reproductive tourism", as evidenced by the rapidly rising number of women aged above 45 years of age giving birth in Switzerland (fig. 3).

A major impulse to change the current legislation stems from the decision of the parliament to implement PGD in Switzerland. Convinced by the growing need to adopt

PGD in Switzerland, the Swiss Parliament voted in 2004 in favour of lifting the ban on PGD. The Swiss Office of Health (BAG) then formulated a law proposal to introduce PGD in Switzerland within the existing framework given by the FMedG and by the Article 119 in the Federal Constitution, which stipulates that not more than three embryos can be generated at the any one time in ART. This proposal was immediately rejected by virtually all professional societies, as the technical conditions for PGD were considered impractical. In Mai 2011 the Swiss Government then proceeded to propose a broader modification of current legislation including a change of Article 119 of the Federal Constitution aiming at finally introducing PGD in Switzerland. The new proposition stipulates that the number of embryos that can be cultured will be extended to eight, but only in case of PGD. PGD would be limited to monogenic diseases only, specifically excluding chromosomal abnormalities (such as trisomy 21 causing Down Syndrome) and immunohistocompatibility cases (the so-called "saviour baby" technology). The ban on the cryopreservation of embryos is to be lifted together with an extension of the duration of cryostorage of embryos to more than five years. These adaptations now widen the opportunity to introduce PGD in a number of couples who are carriers of a severe genetic condition. However, this proposal

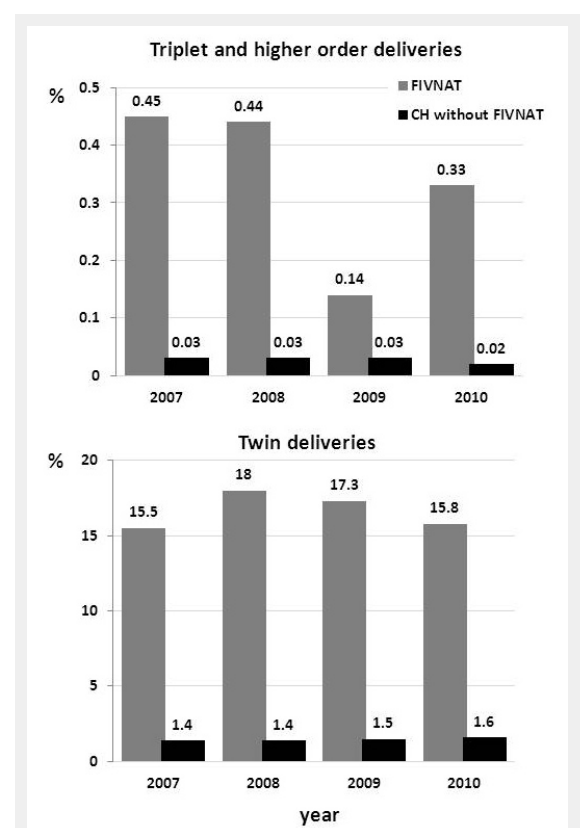


Figure 6

Both the incidence of twin deliveries (B) and of higher order deliveries (A) after assisted reproduction as recorded by FIVNAT (Source: www.sgrm.org) far outnumber those among women conceiving naturally. A significant proportion of multiple pregnancies in Switzerland not registered by FIVNAT may be attributed to treatments with clomiphene citrate and ovulation induction followed by IUI or to treatment that was carried out in ART institutions outside Switzerland.

has again been rejected by most experts and professional and scientific societies due to a multitude of inconsistencies and lack of practicability.

In addition to the introduction of PGD, the urgent need to prevent multiple deliveries is driving the medical community involved in ART to convince the lawmakers in Switzerland to allow eSET through legalisation of embryo cryopreservation.

The organisation of ART in Switzerland

In 2010 twenty six institutions in Switzerland were involved in offering ART to infertile couples. All except one are members of the central data collection organisation, FIVNAT, which is a working group of the Swiss Society of Reproductive Medicine (SGRM). The number of treatment cycles with IVF and ICSI as collected by FIVNAT since 1993 are recorded (fig. 4). The FIVNAT has an office with an administrator and a statistician. The data collected and processed by FIVNAT are transmitted to the Federal Office of Statistics (BfS), located in Neuchâtel, to the European IVF-Monitoring Group (EIM) of the European Society of Human Reproduction and Embryology (ESHRE) and to the International Committee Monitoring Assisted Reproductive Technologies (ICMART). The quality assurance of the FIVNAT-CH data collection is continuously monitored by two external, non-Swiss auditors, who visit each participating institution every second year. The numbers of treatments performed either with IVF or with ICSI have been compiled since 1993 (fig. 4). In 2009 all institutions in Switzerland performed 10,374 treatments in 6,281 infertile women, thereby achieving a total of 1,628 deliveries and 1,891 newborns (data taken from the website of the Federal Office of Statistics in Neuchâtel, BfS). The monitoring of the ongoing treatments and of the outcome, including the deliveries and the health status of the newborn children, is of utmost importance, as the incidence of obstetric complications is known to be increased after ART, as exemplified by the incidence of very early prematurity (born before week 32 of gestation, fig. 5). In 2011 FIVNAT launched a newly designed and innovative software allowing the participating institutions to report data online. In addition, starting in 2012 an instant statistical analysis of the incoming data will be implemented. This tool will enable the participating centres a continuous analysis of their performance in comparison to the combined results of all other institutions in Switzerland. This network will assist each participating centre in attaining an online benchmark aimed at improving the treatment outcome through rapid detection of systematic or temporal flaws in single institutions.

Conclusion and future developments

Modern reproductive medicine including ART fulfils an important function in our society by antagonising or compensating some of the unfavourable effects of ongoing demographic trends in family planning. The activities in ART are framed by a legislation which was designed to prevent fraud and unethical conduct in the handling of embryos. Unfortunately, many of the restrictions of the cur-

rent legislation are now outdated and have become counterproductive, as they are contributing to complications, most notably multiple pregnancies (fig. 6), that can now be avoided with modern technology. Even the statements concerning child welfare, one of the main goals of the current law, now appear paternalistic and seem unfitting to the requirements of present day society [27]. The original intention of the lawmakers to prevent all embryo selection in ART stands in contrast to the more recent law on legal abortion, which was instituted in October 2002, giving the right to all women to choose to have a legal abortion before the twelfth week of pregnancy.

The current trend to delay the age of childbearing is considerably adding to the incidence of complications during pregnancy and childbirth. These complications include gestational diabetes, hypertension, myocardial infarction and neonatal malformations, all bearing the potential for long-lasting morbidity both to the mother and her offspring. Reproductive tourism, considered by some to be the result of an excessively restrictive legislation, is adding to the obstetrical and neonatal complication rate of ART, as the potential risks are often disregarded both by the frustrated couples and some foreign institutions. There is a growing need to define criteria for in depth counselling of couples to the potential of pregnancy-related complications. In addition, guidelines for preventive treatment prior to ART in a subset of women suffering from infertility should be established. These criteria should be formulated by the specialists involved in ART in close collaboration with obstetricians and neonatologists. In addition, the public should be informed about the multiple risks of delaying the age of childbearing and its consequences. Finally, a debate should be initiated on preventive measures, either by accepting the option of cryopreservation of oocytes in women at an earlier age or by the development of a predictive screening system, in which women at risk of losing their fertility prematurely are identified at a younger age.

Modern reproductive medicine including ART has now become part of our society. All parties involved acknowledge that ART requires a legal framework aimed at protecting both the embryos and the infertile couples from abuse. However, this legal framework should be sufficiently flexible to enable adaption to the evolving needs of society and to the possibilities and limitations inherent in the technology itself.

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Figures (large format)

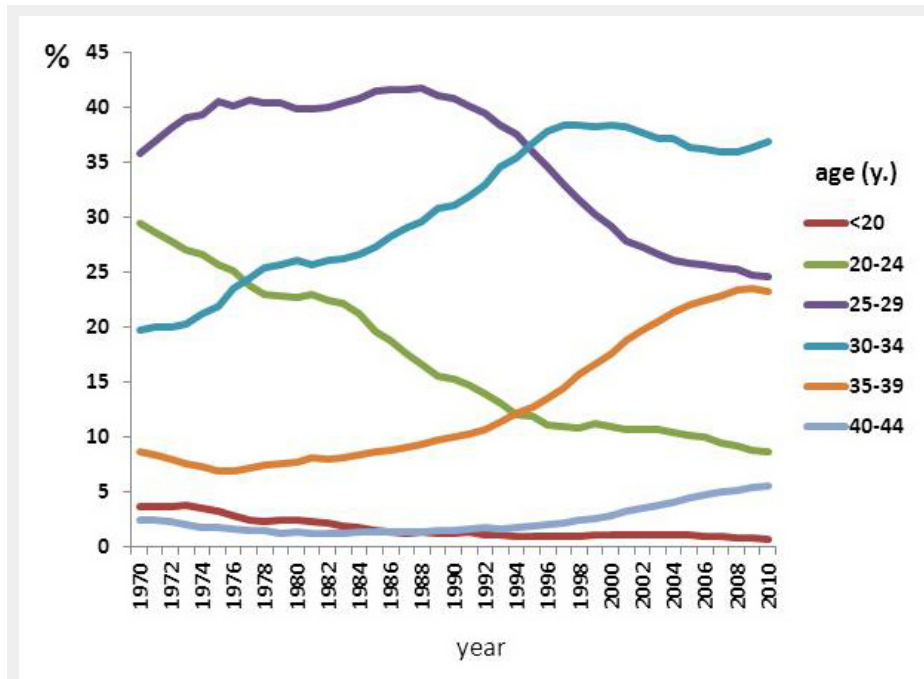


Figure 1

The age at delivery of women delivered in Switzerland since 1970 (Source: BfS ■■■). Whereas the number of women giving birth at the age of 30 y or less is on the decline since 1990, the number of older women giving birth is on the rise, in particular those above the age of 35 years.

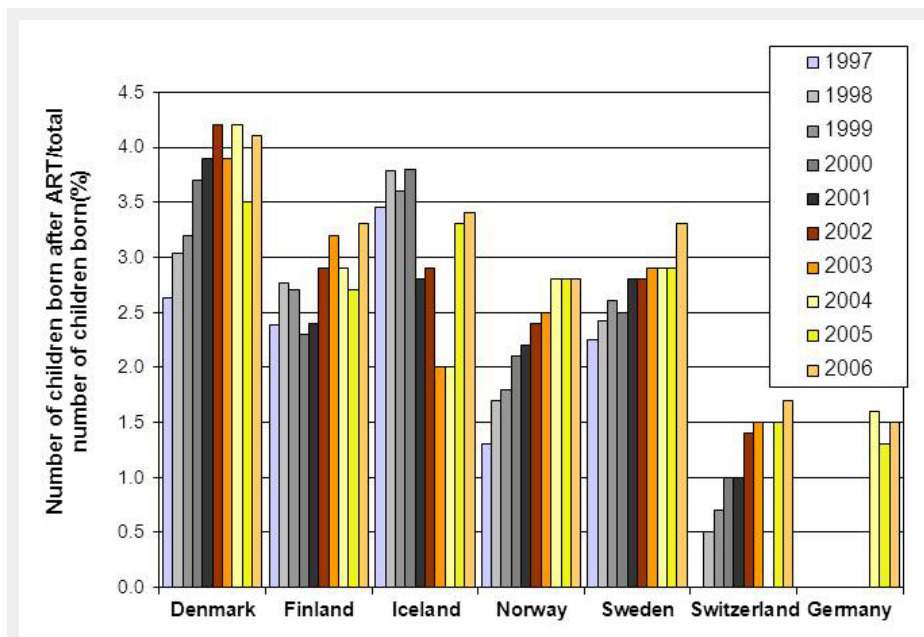


Figure 2

In those countries with a complete coverage of all deliveries after ART, its impact on the total number of neonates can be assessed. In most countries, the impact of ART as given by the number of neonates born after assisted reproduction is on the rise (Source: European IVF-monitoring Group (EIM) of ESHRE, ■■■). The relative number of neonates after ART (in %) is the highest in Scandinavian countries, where the treatment costs are covered by the health insurance. In Switzerland the 2004 data were not mentioned by EIM in their annual report, as were the data before 2004 in Germany due to incomplete coverage of deliveries after ART.

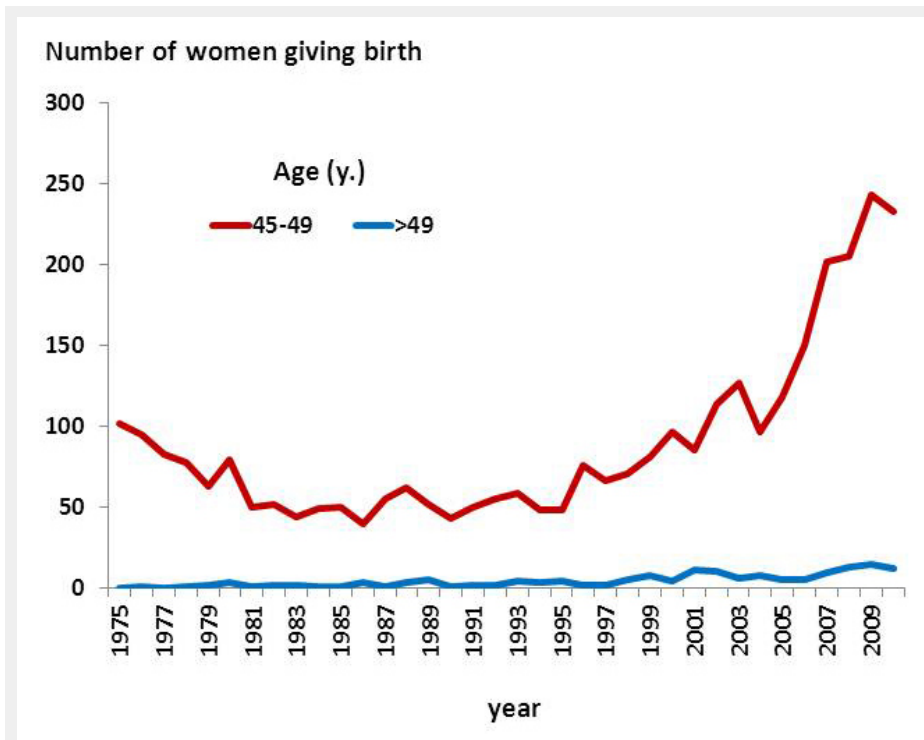


Figure 3

Since 1995 the number of women aged 45 years and older giving birth is on the rise (Source: BFS ■■■). This steep increase can only be explained by women receiving oocyte donation in foreign institutions and must be considered as a striking example of reproductive tourism.

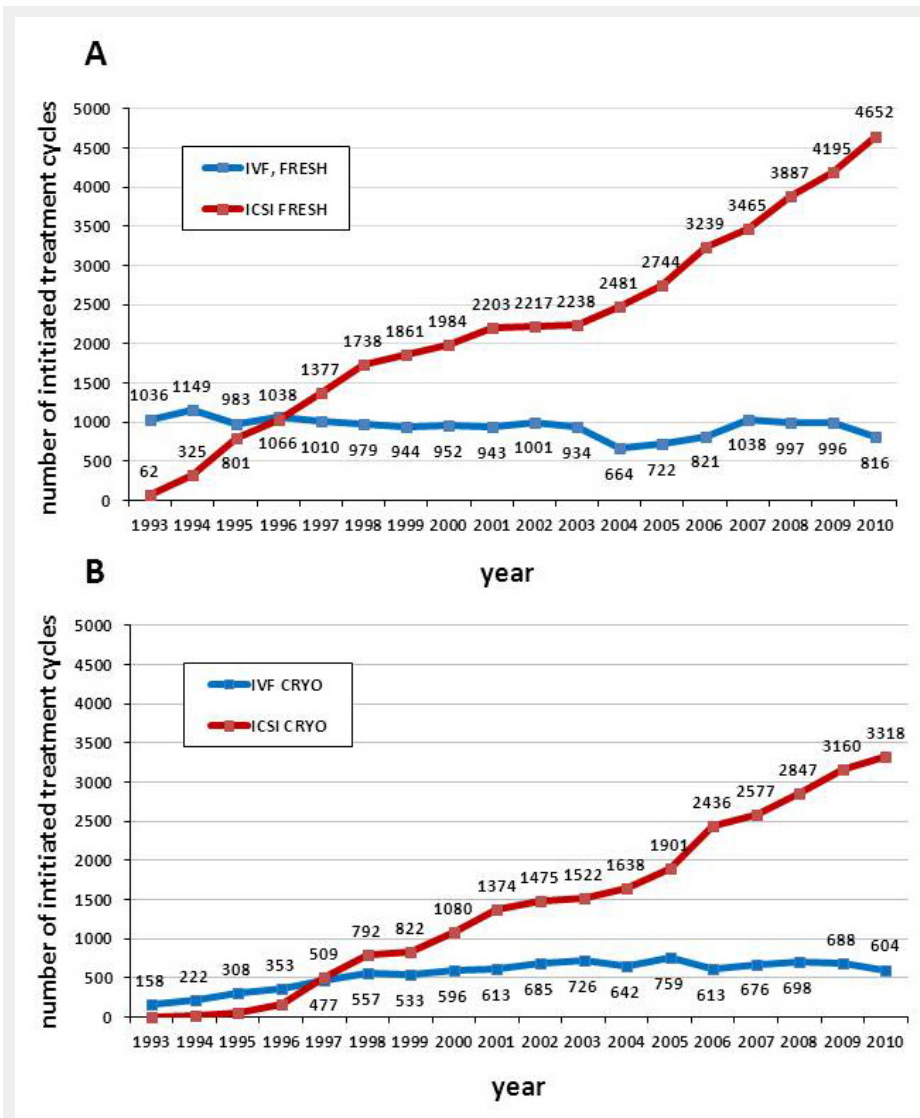


Figure 4

The number of treatment cycles with IVF and ICSI during freshly stimulated treatment cycles (A) and after cryopreservation and thawing (B) have been collected systematically by FIVNAT-CH since 1992 (Source: ■■■?). Whereas the number of treatments with ICSI is continuously rising, those with IVF have remained stable. As the incidental total failure of fertilisation cannot be predicted reliably, many institutions offer ICSI to all couples irrespective of the semen quality.

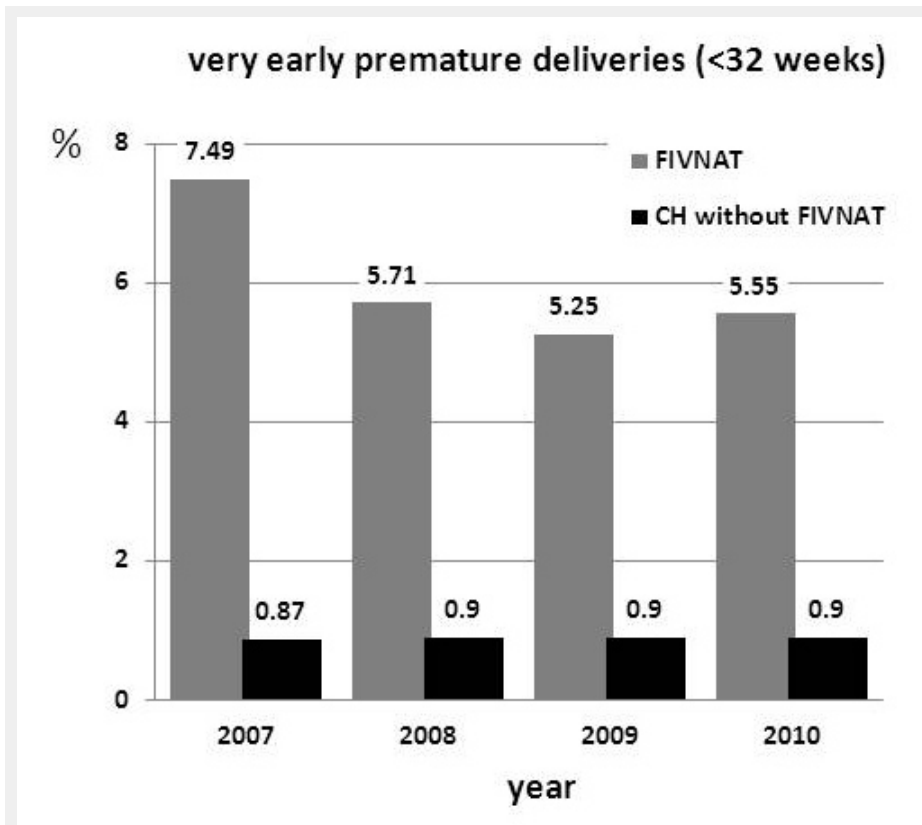


Figure 5

The incidence of very early premature delivery (before week 32 of gestation) is much higher in assisted reproduction than in natural conception (Source: BfS and FIVNAT ■■■). Although many cases of very early prematurity are caused by multiple delivery including twins, the risk is also higher in singleton pregnancies among previously infertile women.

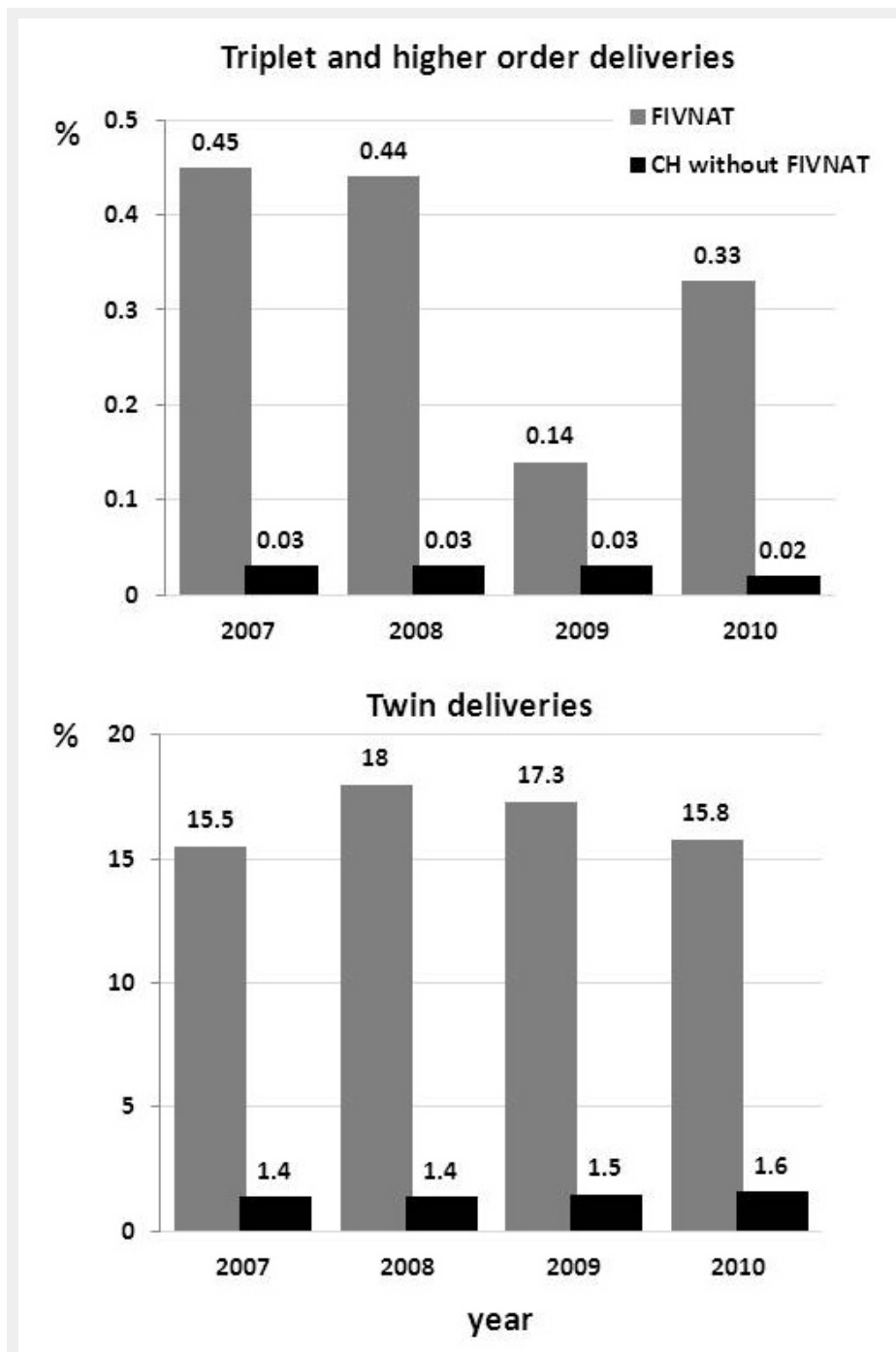


Figure 6

Both the incidence of twin deliveries (B) and of higher order deliveries (A) after assisted reproduction as recorded by FIVNAT (Source: ■■■?) far outnumber those among women conceiving naturally. A significant proportion of multiple pregnancies in Switzerland not registered by FIVNAT may be attributed to treatments with clomiphene citrate and ovulation induction followed by IUI or to treatment that was carried out in ART institutions outside Switzerland.