

The history of Belgian assisted reproduction technology cycle registration and control: a case study in reducing the incidence of multiple pregnancy

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STUDY QUESTION: What is the effect of a legal limitation of the number of embryos that can be transferred in an assisted reproductive technology (ART) cycle on the multiple delivery rate?

SUMMARY ANSWER: The Belgian national register shows that the introduction of reimbursement of ART laboratory costs in July 2003, and the imposition of a legal limitation of the number of embryos transferred in the same year, were associated with a >50% reduction of the multiple pregnancy rate from 27 to 11% between 2003 and the last assessment in 2010, without any reduction of the pregnancy rate per cycle.

WHAT IS KNOWN ALREADY: Individual Belgian IVF centres have published their results since the implementation of the law, and these show a decrease in the multiple pregnancy rate on a centre by centre basis. However, the overall national picture remains unpublished.

STUDY DESIGN, SIZE, DURATION: Cohort study from 1990 to 2010 of all ART cycles in Belgium (2685 cycles in 1990 evolving to 19 110 cycles in 2010), with a retrospective analysis from 1990 to 2000 and prospective online data collection since 2001.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Registration evolved from paper written reports per centre to a compulsory online registration of all ART cycles. From 2001 up to mid-2009, data were collected from Excel spread sheets or MS Access files into an MS Access database. Since mid-2009, data collection is done via a remote and secured web-based system (www.belrap.be) where centres can upload their data and get immediate feedback about missing data, errors and inconsistencies.

MAIN RESULTS AND THE ROLE OF CHANCE: National Belgian registration data show that reimbursement of IVF laboratory costs in July 2003, coupled to a legal limitation in the number of embryos transferred *in utero*, were associated with a 50% reduction of the multiple pregnancy rate from 27 to 11% without reduction of the pregnancy rate per cycle, and with an increase in the number of fresh and frozen ART cycles due to improved access to treatment.

LIMITATIONS, REASONS FOR CAUTION: There is potential underreporting of complications of ART treatment, pregnancy outcome and neonatal health.

WIDER IMPLICATIONS OF THE FINDINGS: Over the 20 years of registration, the pregnancy rate has remained constant, despite the reduction in the number of embryos transferred, optimization of laboratory procedures and stimulation protocols, introduction of quality systems and implementation of the EU Tissue Directive over the period 2004–2010.

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Key words: registration / IVF / assisted reproductive technology / Belgium / multiple pregnancies

Introduction

In Belgium, the first assisted reproduction technology (ART) treatments were performed in 1983. The earliest registration of ART was carried out by an organization called the 'Belgian Register for Assisted Procreation (Belrap)' for ART activities performed during the year 1989. The Belrap was established as a legally registered non-profit organization (Tables I). Seventeen centres registered their activities on a voluntary basis. A number of items of information were reported but these changed over the years. Seventeen items were recorded as key indicators and covered the most important aspects of IVF treatment such as age of the patient, causes of infertility, results, ovarian stimulation, number of embryos transferred and outcome of pregnancies. Results

were reported in English and were accompanied by comments and interpretation in French and Dutch, the two major national languages in Belgium.

The first report covered the years 1989–1991. The number of fresh ART cycles reported per year varied between 2685 and 3750. Interestingly, the general conclusions formulated in that first report 20 years ago are still valid today!

- (i) The pregnancy rates after ET of cryopreserved embryos were about half the pregnancy rates after ET of fresh embryos.
- (ii) The amount of patients ≥ 40 years treated with IVF was low but expected to increase.
- (iii) The pregnancy rates in women ≥ 40 years were less favourable.

Table I Overview of Belgian legislation relevant for MAR.

Publication in Het Belgisch Staatsblad–Le Moniteur Belge	Content	Impact on MAR
25/03/1993: 2283	Belrap statutes	Belrap is the official organ created for reporting ART in Belgium
25/03/1999: 9556	Royal decree on the standards of recognition for centres for reproductive medicine	Criteria for conducting MAR and ART are set. One of the criteria is the obligation for online registration
25/03/1999: 9552	Royal decree on quality check of medical activity in hospitals	Introduction of care programmes in medicine such as the 'Programme for MAR'
15/09/1999: 34415	Ministerial decree on the appointment of the members of the College of physicians for the care programme 'MAR'	Physicians appointed by the government are made responsible for surveillance of quality of treatment in MAR
16/06/2003: 32127	Royal decree on the determination and settlement of the financial budget for hospitals	For the first time, there is a reimbursement of the laboratory costs for ART, but this is coupled to a restriction in the number of embryos for transfer (Table II)
17/07/2007: 38575	Law of 6/7/2007 on medically assisted procreation and the destination of supernumerary embryos and gametes	Describes the frame wherein MAR can be conducted in Belgium. One aspect is that patients can only start a fresh ART cycle when there are no more frozen embryos available
14/10/2008: 5501 I	Royal decree on the introduction of a reimbursement for the treatment of infertility disorders in women	Fixed budgets are set for reimbursement of gonadotrophins in ART and non-ART. Registration of non-ART cycles is obligatory when gonadotrophins are used
30-12-2008: 68774	Law regarding the acquisition and use of human tissue for application in the human or for scientific research	Translation of the EU directive into Belgian legislation

ART, assisted reproduction technology; MAR, medically assisted reproduction.

Table II Embryo transfer policy coupled to the reimbursement of ART.

Maximal number of embryos for transfer In fresh cycles	First cycle	Second cycle	Third-sixth cycle
<36 years	1	1 (2) ^a	2
≥36 and <40 years	2	2	3
≥40 and <43 years	No limit	No limit	No limit

ART, assisted reproduction technology.

^aDepending on embryo quality.

- (iv) The high frequency of multiple pregnancies (especially triplets and higher orders) was a major concern and required consideration of preventive measures.

The year 1992 saw the introduction of micromanipulation techniques like partial zona dissection (PZD), subzonal injection and ICSI. However, the 1992 report, like the 1989–1991 report was based on data collected per centre.

The year 1993 was a year of transition for Belrap as hospitals were asked to provide data on a 'per cycle basis', which increased the validity of the data but also the administrative workload of the centres and of Belrap.

In 1994, a computerized registration system was set up with the ambition to create a national database. However, this turned out to be too ambitious since most centres had already developed their own (computerized) registration system. A limited amount of data was transferred by the individual centres and the data confirmed previously described trends. For this reason, a more simplified central registration system was installed.

The 1995–1996 report showed an increase in the number of centres that participated in the national ART registration (from 14 to 27). However, crosschecks showed that a number of databases contained either incomplete or inconsistent information. The suggestion was made to provide regular feedback to the centres through a formal secretariat in the Belrap office. In 2000, a 10-year overview (1990–1999) was presented (Table III; www.belrap.be; De Sutter *et al.*, 2004).

Since 1999, reproductive medicine and medically assisted reproduction (MAR) have been regulated by many different laws in Belgium (the most important laws are listed in Tables I and II). The Royal Decree of 15/2/1999 defined the standards of recognition of centres for reproductive medicine and the quality control requirements of reproductive medicine in hospitals (Royal Decree, 1999a,b). This Royal Decree also described the terms and conditions for centres to perform activities in reproductive medicine as well as the obligation to register all ART cycles online. For this purpose, doctors were appointed by the government (Ministry of Public Health) to participate in the 'College of Physicians for Reproductive Medicine' (Ministerial Decree, 1999). This College consists of a board whose the members are equally divided between French and Dutch speaking centres, genders and university and non-university hospitals. From this time onwards, the Belgian registration of ART cycles has been done as a public health measure under the authority of the College of Physicians in close collaboration with the established Belrap registry. The challenge for the College was to

provide a system that allowed mandatory registration system, to be implemented in all centres. Sufficient data had to be collected to allow not only descriptive analysis on activities and outcome, but also to address new research questions and assess quality aspects.

In the transition period 2000–2001, the existing registration method continued to be used. In the meantime, a new database was developed that included information about all aspects of ART treatment and outcome such as administrative data, indication for treatment, cycle-specific data (fresh and thawed cycles), data on transfer, complications, early pregnancy, evolution of pregnancy and birth (a total of 118 items). A separate database for the collection of neonatal data comprised 14 items on birthweight, gestational age, stillbirth, early and late neonatal death, admission in the neonatal intensive care unit and the presence of congenital malformations. The separation of these two files allowed a faster data extraction. The first report extracted from this database was based on the ART activities performed in 2002.

In July 2003, a new law enabled reimbursement of ART laboratory costs balanced by a restriction on the number of embryos that could be transferred (Royal Decree, 2003). Patients were allowed to receive reimbursement for six fresh IVF/ICSI cycles per lifetime until the age of 43. The number of embryos that could be transferred was restricted to a number related to the age of the patient, the rank of the cycle and embryo quality (Tables I and II). The goal was to reduce the multiple pregnancy rate by 50% (Ombelet *et al.*, 2005). For 2002–2004, the Belrap report compared data from 1-year prior to the introduction of the reimbursement (1/7/2002–30/6/2003) to 1 year after (1/7/2003–30/6/2004). Therefore no separate data were reported for 2003.

The first individual reports on ART activities per centre including individual feedback were implemented in 2007. Since 2008, data collection and analysis of the items concerning reproductive medicine have been further improved (see the 'Data collection' section in 'Materials and methods'). The Belrap and the College of Physicians have provided data to European IVF Monitoring (EIM) (EIM, 2008) and the International Committee for Monitoring Assisted Reproductive Technology (ICMART) (ICMART, 2009) since 2002.

For non-ART treatments (cycles with intrauterine insemination (IUI) or cycles with controlled ovarian stimulation or ovulation induction), there is an obligation to register all cycles in which gonadotrophins are used (Royal Decree, 2008). Centres are invited to register IUI cycles in natural cycle or with clomiphene citrate on a voluntary basis. This registration is not further discussed in this paper.

Materials and Methods

Data collection

Data are sent anonymously on a per cycle basis by the participating centres. From 2003 up to mid-2009, data were collected from Excel spread sheets or Access files and stored into an Access database with increasing data quality checks from 2007 onwards. From mid-2009, the data collection occurs via a web-based system (www.belrap.be) in which centres can upload or fill in their data and get immediate feedback about missing data, errors and inconsistencies. Finally, data are extracted and processed statistically using SAS[®]. Since 2008, the terminology used is based on the ART Glossary published by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) (Zegers-Hochschild *et al.*, 2009a,b). Since 2009, the national register number of each patient is recorded. All data mentioned in this

Table III Number of ART treatment cycles 1990–2002.

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Number of centres	17	17	17	17	17	17	35	35	35	24	25	25	25
Number of participating centres (%)	11 (65)	13 (76)	17 (100)	14 (82)	14 (82)	14 (82)	27 (77)	26 (74)	23 (66)	23 (96)	24 (96)	22 (88)	NA
Number of oocyte retrievals estimated	4000	4000	5051	5500	7000	8200	8600	8400	9000	9650	9700	10 000	NA
Number of oocyte retrievals reported (%)	2685 (67)	3447 (86)	5051 (100)	4822 (87)	6487 (93)	7723 (94)	7889 (92)	5956 (71)	7868 (88)	9250 (97)	8984 (93)	9462 (95)	11 245 (NA)
No cancelled cycles	NA	NA	NA	NA	NA	NA	NA	NA	NA	1063	848	569	930
IVF (%)	2685 (100)	3151 (91)	4319 (85)	3265 (68)	3681 (57)	3767 (49)	3488 (44)	2924 (49)	3105 (39)	2803 (36)	2837 (35)	2837 (32)	3041 (29)
ICSI ejaculated sperm	NA	296 ^a	732 ^a	1557 ^a	2806 ^a	3956	3870	2775	4345	4345	4983	5769	6811
ICSI MESA/TESE	NA	NA	NA	NA	NA	NA	531	257	418	546	316	292	558
All ICSI cycles (%)	0 (0)	296 (9)	732 (15)	1557 (32)	2806 (43)	3956 (51)	4401 (56)	3032 (51)	4763 (61)	4891 (64)	5299 (65)	6061 (68)	7369 (71)
All fresh cycles	2685	3447	5051	4822	6487	7723	7889	5956	7868	7694	8136	8898	10 410
Cryotransfers	498	670	1110	1347	1533	1610	1709	1296	1091	2115	2340	2410	3006
Maternal age (years, mean \pm SD)	NA	NA	NA	NA	NA	32.9 (\pm 4.9)	32.5 (\pm 4.8)	32.6 (\pm 4.8)	33.1 (\pm 4.9)	33.2 (\pm 4.9)	33.3 (\pm 4.9)	33.4 (\pm 5.1)	33.4 (\pm 5.1)

^aAll types of micromanipulations (partial zona dissection, subzonal insemination, ICSI)
 NA, Not available; MESA, microsurgical sperm aspiration; TESE, testicular extraction of sperm.

manuscript and also those data that are not shown can be found at www.belrap.be in the section 'Reports' as annual reports.

Results

Number of treatment cycles

Over the past two decades, the number of reported ART cycles increased from 5051 in 1992 (the first year with complete data) to

19 110 in 2010, with a sharp increase in IVF activity until 1995 followed by a slower increase up to 2003 when a second sharp increase occurred following the introduction of the reimbursement of laboratory costs (Fig. 1). Table III shows the number of participating centres and the number and types of cycles from 1990 to 2002 and Table IV shows the number and types of cycles from 2004 to 2010. Micromanipulation techniques were introduced in 1992 and by 1995 ICSI was used as the fertilization technique in >50% of cycles. ICSI is now the preferred method of insemination and has been used in more than 70% of all

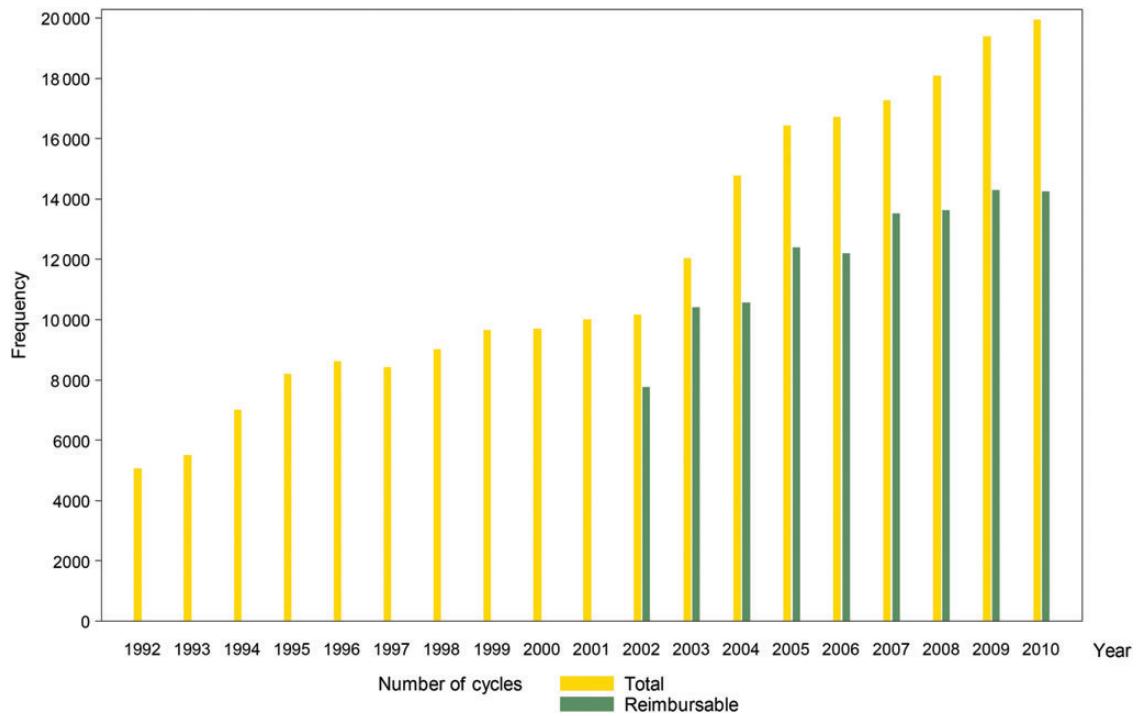


Figure 1 Evolution of total number of fresh cycles (own and recipient cycles).

Table IV General overview and type of cycles 2004–2010.

	2004	2005	2006	2007	2008	2009	2010
Initiated fresh cycles ART	15 208	17 080	17 504	18 025	19 061	20 436	21 201
Cancelled fresh cycles ART (%)	971 (6.4)	1241 (7.3)	1409 (8.0)	1437 (8.0)	1715 (9.0)	1880 (9.2)	2091 (9.9)
Aspiration cycles ART	14 237	15 839	16 095	16 588	17 346	18 556	19 110
Aspiration cycles IVF (% IVF)	4084 (28.7)	3851 (24.3)	3619 (22.5)	3852 (23.2)	4128 (23.8)	4377 (23.6)	4579 (23.6)
Aspiration cycles ICSI (% ICSI)	9803 (68.9)	11 563 (73)	11 928 (74.1)	12 357 (74.5)	12 712 (73.3)	13 425 (72.3)	13 707 (71.7)
Initiated cryocycles	5165	5933	6020	7197	8576	8878	9342
Cryocycles with transfer (% transfer cryocycles)	3767 (72.9)	4422 (74.5)	4321 (71.8)	5087 (70.7)	6352 (74.1)	6536 (73.6)	7142 (76.5)
Fresh PGD cycles	654	707	839	716	658	474	614
Oocyte donation cycles	454	452	507	506	578	682	653
Oocyte reception cycles	607	663	697	751	820	930	911
Cross border treatment overall (%)	20.8	20.0	20.1	20.8	25.4	21.6	19.1
Maternal age (years, mean \pm SD)	33.4	33.4	33.6	33.6	33.9	34.0	34.1

ART, assisted reproduction technology; PGD, preimplantation genetic diagnosis.

fresh ART cycles in Belgium since 2005, this is higher than the mean proportion of 60% for Europe in 2004 (Nyboe et al., 2008).

The percentage of cancelled cycles was ~11% in 1999, and decreased to 6.4–9.9% of initiated cycles in the period 2004–2010. ART cycles using microsurgical epididymal sperm aspiration (MESA)/testicular sperm extraction (TESE) have been officially registered since 1996. The proportion of cycles performed in Belgian patients (~80%) and foreign patients coming to Belgium for cross border reproductive care (~20%) has been registered since 2004 and has remained stable.

As expected, the amount of frozen–thawed embryo transfer (ET) cycles has also increased annually since the registration in 1990, and nearly doubled during the period 2004–2010. Overall, preimplantation genetic diagnosis (PGD) cycles remains a marginal activity, only 474–839 fresh cycles and 4–15 frozen–thawed embryo transfer cycles being done per year. Similarly, oocyte donation and reception is not frequently performed in Belgium.

Age of the patients

The mean age of the female partner gradually increased each year from 32.9 years in 1995 to 34.1 years in 2010 (Tables III and IV). The proportion of patients ≥40 years also increased from 6% (1990) over 13% (2004) to 18% (2010).

Number of embryos transferred

Figure 2 shows an overview (1992–2010) of the number of embryos transferred during fresh ART cycles.

In 1992, 32% of transfers were of two embryos, 47% of three embryos and 10% of four or more embryos. At that time, this embryo transfer (ET) policy was interpreted as a 'voluntary reduction in the number of embryos for transfer', in comparison to 1992 FIVNAT data from France (Roalier et al., 1993) where 22.9% of transfers consisted of four or more embryos.

After a gradual increase of double embryo transfer at the expense of triple ET in the mid-nineties, the legal restriction of the number of embryos allowed for ET since 2003 resulted in an increase in the number of single ETs at the expense of the number of double embryo transfers. Overall, since 2004, single and double embryo transfers account for ~50 and 40% of all ETs, respectively, and three or more embryos are only transferred in 10% of the ET cycles.

There has been a gradual tendency towards single ET in frozen–thawed embryo transfer cycles (FET) reaching 50% during the period 2004–2010. Even though ET of more than two embryos is legally forbidden in FET cycles since 2003, there still is a small percentage of FET cycles of three or more embryos, which can be explained in part by a lack of logic in the legislation. For instance, it is allowed to transfer an unlimited number of embryos in fresh ART cycles in women aged 40 years and older, whereas only two embryos can be transferred during frozen–thawed cycles in the same age group (Tables I and II).

In oocyte recipient cycles, there is a trend towards single ET but the majority (50–60%) of cycles are still associated with the transfer of two embryos. This can be explained by the fact that the Belgian legislation is made for homologous reproduction, and restrictions regarding the number of embryos allowed for ET are related to the age of the recipient irrespective of the age of the donor.

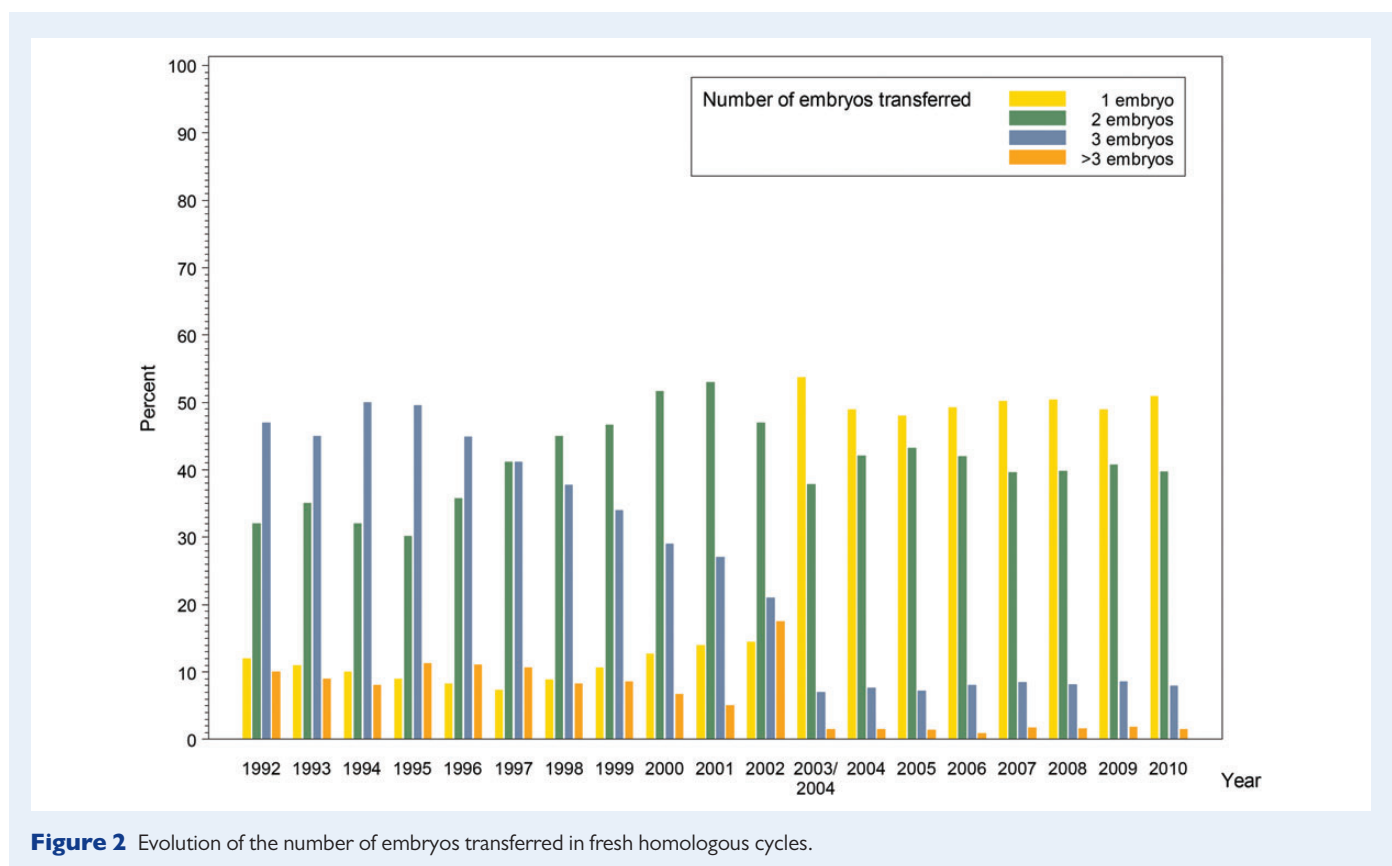


Figure 2 Evolution of the number of embryos transferred in fresh homologous cycles.

Outcome of treatment cycles

The clinical pregnancy rate per aspiration cycle varied between 21 and 28% in the period 1990–2002, with a live birth rate of 17–21%. The highest pregnancy rate was obtained after the transfer of three embryos. However, the high incidence of multiple (twin and triplet) pregnancies (range 30–40%) during the early nineties forced clinicians to reduce the number of embryos they transferred. This change in

embryo transfer policy was not associated with any changes in pregnancy and live birth rates, nor any significant change in the incidence of multiple (twin and triplet) pregnancies until 1999, when the multiple pregnancy rate dropped to 25% (Fig. 3).

Table V shows that clinical pregnancy, delivery and implantation rates per oocyte aspiration cycle for fresh homologous ART between 2004 and 2010 remained stable in the range of 26–32%, 17–21 and 20–23%,

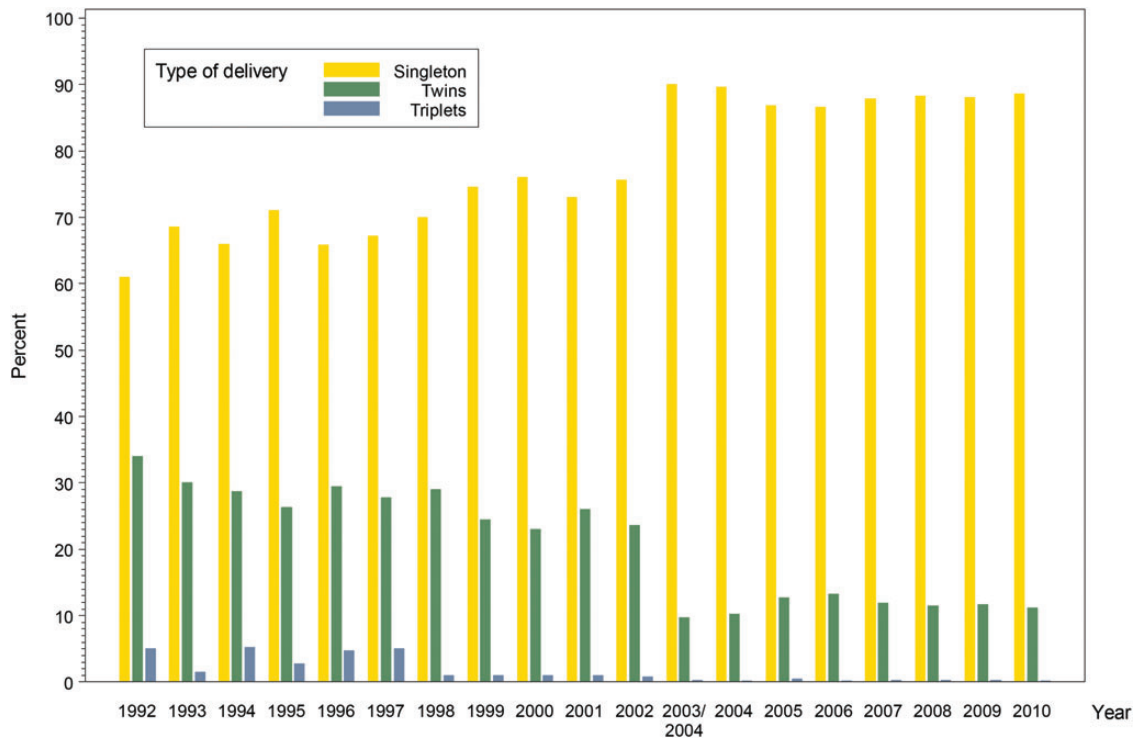


Figure 3 Evolution of the number of single and multiple deliveries in fresh homologous cycles.

Table V Cycle outcomes 2004–2010.

Results	2004	2005	2006	2007	2008	2009	2010
Fresh IVF aspiration cycles							
Clinical pregnancy rate (%)	31.9	29.2	28.3	29.8	28.9	27.1	26.8
Delivery rate (%)	18.6	19.7	21.4	22.6	20.7	19.9	19.8
Implantation rate ^a (%)	23.1	22.4	21.4	23.3	22.8	21.1	20.8
Fresh ICSI aspiration cycles							
Clinical pregnancy rate (%)	30.0	26.7	27.2	27.6	26.8	25.8	26.4
Delivery rate (%)	17.3	18.5	18.8	20.9	19.3	18.4	18.8
Implantation rate ^a (%)	20.7	19.9	20.4	21.0	20.75	19.8	20.3
Thawed cycles							
Clinical pregnancy rate(%)	17.9	15.1	15.2	16.3	18.1	17.1	18.5
Delivery rate (%)	9.5	10.0	9.8	12.1	12.7	12.3	12.6
Implantation rate ^a (%)	14.8	13.2	13.8	15.5	17.5	16.6	17.0

^aImplantation rate = sacs (ICMART).

respectively, over the last 7 years. In 2010, the median live birth rate per centre was 18.0% (P10 = 10.1% and P90 = 24.8%).

During the same period, clinical pregnancy, delivery and implantation rates per thawed cycle varied between 15.1–18.5, 9.5–12.7 and 13.2–17.5%, respectively.

It is difficult to compare these results with those obtained before the introduction of reimbursement (i.e. before 2003) since registration of pregnancy rates has become increasingly reliable over the years, especially since 2008. Nevertheless, it appears that the introduction of a legally enforced restriction in the number of embryos for transfer has not been associated with any change in the overall clinical pregnancy rates per cycle.

Singleton, twin and triplet deliveries

Legally enforced reduction since 2003 in the number of embryos allowed for uterine transfer has been associated with a major decrease in the multiple pregnancy and delivery rates. Whereas the multiple delivery rate in fresh ART cycles was 24–34% in the period 1990–2002 (Fig. 3), the twin delivery rate has dropped to 8.8–13.2% since 2004 and the triplet rate to <1% in 2004–2008 and 0.2% in 2008–2010 (Supplementary data, Table SI). During the years 2004–2010, the twin delivery rate in frozen–thawed cycles remained stable (11.0–14.2%) and varied between 14.0 and 22.0% in egg recipient cycles (higher proportion of cycles with double embryo transfer; data not shown).

Supplementary data, Table SI shows the data on perinatal outcome of singleton, twin and triplet pregnancies regarding term, preterm and very preterm birth and birthweight, low birthweight and very low birthweight from homologous, heterologous and frozen–thawed cycles.

Complications

Supplementary data, Table SII shows that 0.9–1.6% of all fresh aspiration cycles were associated with complications, including most frequently (43–77%) severe ovarian hyperstimulation syndrome (OHSS) (Grade III and IV), but also bleeding (6–10%), infection (4–10%) and other complications (12–26%). In ~4% of the cycles, the presence of complications was unknown. The incidence of thrombosis per aspiration cycle varied between 0 and 2.3%. Two maternal deaths were reported in this period on a total of 117 748 aspiration cycles performed.

Congenital anomalies

Congenital anomalies have been registered for many years. Since mid-2009, registration is done according to the Eurocat classification system (<http://www.eurocat-network.eu>). The data mentioned in Supplementary data, Table SIII represent congenital anomalies registered in 2010 from own fresh cycles either after birth or abortion.

Reference group for internal and external benchmarking

Since 2009 separate calculations are made for the specific subgroup of women younger than 36 during the first two cycles and this reference group is also used for benchmarking purposes. Each centre gets individual feedback of their performance in this reference group, benchmarked against the performance of all other individual centres that are listed anonymously.

Discussion

Registration

From 1992 until today, registration of ART in Belgium developed from a voluntary, retrospective gynaecologist-based data collection system towards an obligatory, prospective, online, statistically oriented cycle data entry system, a dynamic process aiming at continuous quality improvement. Online registration was legally made obligatory for all ART cycles in 1999 and in 2006 for all non-ART MAR cycles (ovulation induction cycles and IUI cycles) using gonadotrophins.

Quality control of data

Whereas in the early days of registration (1992), acquisition and completeness of the data were the main focus, critical comments on the quality of the data were made by the gynaecologists involved in data collection and in the College. This led to gradual evolution towards computer-based consistency checking of the acquired data and interpretation by the clinicians of the data retrieved.

The current detailed registration and reporting allows the detection of deviations from legal prescriptions, like abnormalities in the embryo transfer policy such as three embryos for FET transfer and a high percentage of double embryo transfers in the second cycle in women <36 years of age. In case of obvious violation of the law, centres are invited to explain the possible reason for violation. Severe and persistent violations will be punished by withholding the payment for the laboratory costs by the government. Over the years, the College of Physicians in Reproductive Medicine, which controls the national Belgian MAR registration, has become more strict in its reimbursement policy, based on the principle that cycles that do not meet the legal criteria will not be reimbursed.

The Belgian model illustrates the reduction of multiple pregnancy rates while maintaining pregnancy rates per cycle at the same level and increasing social access, leading to an increased number of cycles. The impact of the introduction of reimbursement of ART laboratory costs in July 2003, coupled to a limitation in the number of embryos for transfer, has reached the target of decreasing the multiple pregnancy rate by half, without significant reduction in the clinical pregnancy rate per cycle (De Sutter et al., 2003; Debrock et al., 2005; Gordts et al., 2005; Van Landuyt et al., 2006; Salame et al., 2011). A side effect of the reimbursement of the laboratory costs was the increase in the number of IVF/ICSI cycles that followed improved access to the treatment. However, the number of 1500 cycles per 1 million population per annum, which is the number of cycles calculated to provide adequate fertility services (Collins, 2002), is not surpassed in Belgium.

The number of frozen–thawed embryo transfer cycles has doubled over the past 7 years. Since 2008, this evolution can at least partly be explained by a change in legislation (Tables I and II), obliging patients and centres to perform transfers of frozen–thawed embryos (when available), before they are allowed to start a new fresh IVF/ICSI cycle (Law, 2007). The Belgian registration system does not allow the detection of whether more embryos were available for freezing after the marked increase of single embryo transfer (SET).

Oocyte donation and reception is a marginal activity in Belgium, comprising of only 4.4% of the egg retrieval cycles. In oocyte recipient cycles, over the past 7 years there is a trend to a decrease in the number of embryos transferred but this trend lags behind the SET policy strictly applied in homologous ART cycles. Consequently,

embryo transfers in oocyte recipient cycles are done using two embryos in 50–60% of the cycles, resulting in a twin pregnancy rate of 14–20%. This result can be largely explained by the fact that the mean age of recipients is 37–38 years and embryo transfer policy is linked to the age of the recipient and not to the age of the donor; the latter is usually much younger (<37 years in most centres, although no age limit has been imposed by the law for egg donors). In egg recipients, the multiple pregnancy risk needs to be balanced against the fact that egg recipients may have only one cycle in their lifetime to become pregnant after transfer of embryos derived from donor eggs, in view of the major problem they face to find suitable egg donors. The major problem with finding appropriate egg donors is that, due to lack of volunteers, patients are dependent on recruitment among family members and friends. It is interesting to see that when access is restricted (for whatever reason), infertile couples and professionals favour the risk of twins when balanced against the risk of no pregnancy.

Introduction of quality systems and implementation of the EU tissue directive

The multiple pregnancy rate, which is still the most important complication of ART, not only in terms of incidence but also in terms of medical, financial, social, economical and psychological impact, has been decreased successfully in Belgium since 2004. However, the pregnancy rate has not significantly increased over the last 20 years despite optimization of laboratory procedures and stimulation protocols, introduction of quality systems and implementation of the EU tissue directive (Directive, 2004; Commission directive 2006/17/EC, 2006; Commission directive 2006/86/EC, 2006). The Belgian pregnancy (28.9%) and delivery (20.7%) rates for IVF/ICSI per aspiration cycle are comparable to the Swedish pregnancy (29.2%) and delivery (22.5%) rates in 2008, and SETs accounted for 50.4 and 69.5% of the transfers in Belgium and in Sweden, respectively (Ferraretti *et al.*, 2012). This lack of increase in pregnancy rates is disappointing given that daily practice of ART has become much more laborious in terms of laboratory practice, administration and management. We speculate that the increasing age of the ART patients, and especially the legal limitation in the number of embryos allowed for transfer could be in part responsible for the lack of improvement in reproductive outcome. As efficacy on a per cycle basis has not significantly improved, quality systems and regulation/legislation could be responsible for a higher safety for patients and personnel (Willemen *et al.*, 2012). From a clinical point of view, the incidence of complications and the type of complication do not seem to have evolved significantly towards more safety.

Complications in ART are rare in Belgium at an incidence of 0.9 to 1.6% per aspiration cycle, with OHSS being the most frequent complication (0.3–1.0%). This compares with the data from EIM that vary between 0.7 and 1.2% (De Mouzon *et al.*, 2012). However, one should take into account that ART complications are potentially underreported. The same remark can be made for maternal deaths with only two registered between 2004 and 2010 on a total of 117 748 cycles. Underreporting of maternal deaths after ART could be present, not necessarily deliberately since maternal death may occur in another hospital or because of the delay between the ART treatment and the time of death, e.g. due to an thromboembolic disease (Braat *et al.*, 2010).

Future focus

From the patients' perspective, results provided as cumulative data per patient from fresh and frozen–thawed embryo transfer cycles, which take into account the time frame and the patient's age, would give a much clearer picture to the patient of what to expect from ART treatment. To our knowledge, cumulative data have been delivered by individual centres but not by national registries (De Neubourg *et al.*, 2010). Our registration method has made the necessary adaptations to allow patient registration and future calculation of cumulative reproductive outcome per patient, taking into account the patient's privacy aspects.

So far, the Belgian register has collected data on the effectiveness and safety of MAR. Although this focus is also found in global ART monitoring (Nygren *et al.*, 2011) and in quality monitoring in other fields of medicine (Copnell *et al.*, 2009), these are only two of the six dimensions of quality of healthcare according to the Institute of Medicine (Corrigan *et al.*, 2001). The other quality dimensions are timeliness, equity, efficiency and patient-centeredness. Three recent studies indicated that, besides effectiveness and safety, patient-centeredness is very important to both fertility healthcare providers and patients (van Empel *et al.*, 2011; Dancet *et al.*, 2012, 2013). In the future, quality monitoring needs to be extended to all quality dimensions. Therefore, more work is needed to develop and validate instruments to assess the four remaining quality dimensions, with special attention for patient-centeredness as its value has been demonstrated.

Conclusion

Registration of Belgian ART activity has a longstanding tradition and has evolved from a voluntary retrospective gynaecologist-based system towards an obligatory prospective online cycle-based statistically oriented data entry process. The data collected are now reliable, have become progressively exhaustive and complete, and can therefore be used for investigation of quality issues as well as compliance with the Belgian and European legislation. Furthermore, they can be used for research purposes.

Supplementary data

Supplementary data are available at <http://humrep.oxfordjournals.org/>.

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Authors' roles

D.D.N. was involved in conception and design of the study, acquisition and interpretation of data. K.B. and N.G. were involved in the acquisition of data, the statistical analysis, interpretation of data and critical revising. A.A. and E.L. contributed to the critical revision of the manuscript. C.W., M.Cam., M.Can., M.De., A.Db., A.De., P.D.S., M.Dh., M.Du., Y.E., S.G., B.L., W.H., F.L., W.O., S.P.H., F.V., J.V.D.E. were involved in acquisition and interpretation of data and in the critical revising. T.D. was involved in

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Conflict of interest

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References

- Belrap statutes. *Het Belgisch Staatsblad—Le Moniteur Belge* 25/03/1993:2283.
- Braat DD, Schutte JM, Bernardus RE, Mooij TM, van Leeuwen FE. Maternal death related to IVF in the Netherlands 1984–2008. *Hum Reprod* 2010; **25**:1782–1786.
- Collins J. An international survey of the health economics of IVF and ICSI. *Hum Reprod Update* 2002;**8**:265–277.
- Commission directive 2006/17/EC. Implementing directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. *Official J Eur Union* 2006;**38**:40–52.
- Commission directive 2006/86/EC. Implementing directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. *Official J Eur Union* 2006;**294**:32–50.
- Copnell B, Hagger V, Wilson SG, Evans SM, Sprivilis PC, Cameron PA. Measuring the quality of hospital care: an inventory of indicators. *Intern Med J* 2009;**39**:352–360.
- Corrigan JM, Donaldson MS, Kohn LT, Maguire SK, Pike KC. *Crossing the Quality Chasm. A New Health System for the 21st Century*. Washington, DC: Institute of Medicine, National Academy of Sciences, National Academy Press, 2001.
- Dancet EA, D'Hooghe TM, Sermeus W, van Empel I, Strohmer H, Wyns C, Santa-Cruz D, Nardo LG, Kovatchki D, Vanlangenakker L et al. Patients from across Europe have similar views on patient-centered care: an international multilingual qualitative study in infertility care. *Hum Reprod* 2012;**27**:1702–1711.
- Dancet EA, D'Hooghe TM, Spiessens C, Sermeus W, De Neubourg D, Karel N, Kremer J, Nelen WLD. Quality indicators for all dimensions of infertility care quality: consensus between professionals and patients. *Hum Reprod* 2013;**28**:1584–1597.
- Debrock S, Spiessens C, Meuleman C, Segal L, De Loecker P, Meeuwis L, D'Hooghe TM. New Belgian legislation regarding the limitation of transferable embryos in in vitro fertilization cycles does not significantly influence the pregnancy rate but reduces the multiple pregnancy rate in a threefold way in the Leuven University Fertility Center. *Fertil Steril* 2005;**83**:1572–1574.
- de Mouzon J, Goossens V, Bhattacharya S, Castilla JA, Ferraretti AP, Korsak V, Kupka M, Nygren KG, Andersen AN, European IVF-Monitoring (EIM), Consortium for the European Society on Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2007: results generated from European registers by ESHRE. *Hum Reprod* 2012;**27**:954–966.
- De Neubourg D, Daels C, Elseviers M, Mangelschots K, Vercruyssen M, Van Royen E. Cumulative live-birth delivery after IVF/ICSI since the progressive introduction of single-embryo transfer. *Reprod Biomed Online* 2010; **20**:836–842.
- De Sutter P, Van der Elst J, Coetsier T, Dhont M. Single embryo transfer and multiple pregnancy rate reduction in IVF/ICSI: a 5 year appraisal. *Reprod Biomed Online* 2003;**6**:464–469.
- De Sutter P, Lejeune B, Dhont M, Leroy F, Englert Y, Van Steirteghem A. Tien jaar registratie van medisch begeleide voortplanting (MBV) in België. *Tijdsch Geneesk* 2004;**60**:905–914.
- Directive. 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Official J Eur Union* 2004;**102**:48–58.
- European IVF-Monitoring Consortium, European Society of Human Reproduction and Embryology. Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE. *Hum Reprod* 2008;**23**:756–771.
- Ferraretti AP, Goossens V, de Mouzon J, Bhattacharya S, Castilla JA, Korsak V, Kupka M, Nygren KG, Nyboe Andersen A, The European IVF-monitoring (EIM), Consortium for the European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2008: results generated from European registers by ESHRE. *Hum Reprod* 2012; **27**:2571–2584.
- Gordts A, Campo R, Puttemans P, Brosens I, Valkenburg M, Norre J, Renier M, Coeman D, Gordts S. Belgian legislation and the effect of elective single embryo transfer on IVF outcome. *Reprod Biomed Online* 2005;**10**:436–441.
- International Committee for Monitoring Assisted Reproductive Technology, de Mouzon J, Lancaster P, Nygren KG, Sullivan E, Zegers-Hochschild F, Mansour R, Ishihara O, Adamson D. World collaborative report on Assisted Reproductive Technology, 2002. *Hum Reprod* 2009; **24**:2310–2320.
- Law of 6/7/2007 on medically assisted procreation and the destination of supernumerary embryos and gametes. *Het Belgisch Staatsblad—Le Moniteur Belge* 17/07/2007:38575.
- Ministerial decree of 10/6/1999 on the appointment of the members of the College of physicians for the care programme 'reproductive medicine'. *Het Belgisch Staatsblad—Le Moniteur Belge* 15/09/1999:34415.
- Nyboe Andersen A, Carlsen E, Loft A. Trends in the use of intracytoplasmic sperm injection marked variability between countries. *Hum Reprod Update* 2008;**14**:593–604.
- Nygren KG, Sullivan E, Zegers-Hochschild F, Mansour R, Ishihara O, Adamson GD, de Mouzon J. International Committee for Monitoring Assisted Reproductive Technology (ICMART) world report: assisted reproductive technology 2003. *Fertil Steril* 2011;**95**:2209–2222.
- Omelet W, De Sutter P, Van der Elst J, Martens G. Multiple gestation and infertility treatment: registration, reflection and reaction—the Belgian project. *Hum Reprod Update* 2005;**11**:3–14.
- Roalier A, Bachelot A, de Mouzon J, Rufat P, Logerot H. Evaluation of FIVNAT 1992. *Contracept Fertil Sex* 1993;**21**:354–357.
- Royal Decree of 15/2/1999a on the standards of recognition for centres for reproductive medicine. *Het Belgisch Staatsblad—Le Moniteur Belge* 25/03/1999:9556.
- Royal Decree of 15/2/1999b on quality check of medical activity in hospitals. *Het Belgisch Staatsblad—Le Moniteur Belge* 25/03/1999:9552.
- Royal Decree of 4/6/2003 on the determination and settlement of the financial budget for hospitals. *Het Belgisch Staatsblad—Le Moniteur Belge* 16/06/2003:32127.
- Royal Decree of 6/10/2008 on the introduction of a forfaitary reimbursement for the treatment of infertility disorders in women. *Het Belgisch Staatsblad—Le Moniteur Belge* 14/10/2008:55011.
- Salame Y, Devreker F, Imbert R, Delbaere A, Fontenelle N, Englert Y. Contribution of cryopreservation in a mandatory SET policy: analysis of

- 5 years of application of law in an academic IVF center. *J Assist Reprod Genet* 2011;**28**:1059–1066.
- van Empel IW, Dancet EAF, Koolman XH, Nelen WL, Stolk EA, Sermeus W, D'Hooghe TM, Kremer JA. Physicians underestimate the importance of patient-centredness to patients: a discrete choice experiment in fertility care. *Hum Reprod* 2011;**26**:584–593.
- Van Landuyt L, Verheven G, Tournaye H, Camus M, Devroey P, Van Steirteghem A. New Belgian embryo transfer policy leads to sharp decrease in multiple pregnancy rate. *Reprod Biomed Online* 2006;**13**:765–771.
- Willemsen D, D'Hooghe T, Knoop I, De Neubourg D, Spiessens C. Does the European union tissues and cells directive improve quality in the *in vitro* fertilization laboratory? A case study in a tertiary referral center. *Semin Reprod Med* 2012;**30**:191–198.
- Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S. International Committee for Monitoring Assisted Reproductive Technology; World Health Organization. *Hum Reprod* 2009a;**24**:2683–2687. <http://www.ncbi.nlm.nih.gov/pubmed/19801627>.
- Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, Vanderpoel S. International Committee for Monitoring Assisted Reproductive Technology; World Health Organization. *Fertil Steril* 2009b;**92**:1520–1524. <http://www.ncbi.nlm.nih.gov/pubmed/19828144>.