

FEATURE

// IVF IN GERMANY //



Germany's first IVF baby was born on 16th April 1982 in the care of the late Professor Siegfried Trotnow (pictured below, right, in 1983) and Safaa Al-Hasani at the University Hospital of Erlangen, still one of Germany's leading centres in reproductive medicine.



One million cycles and still counting

Markus Kupka tells the story of IVF in Germany and how its successful history so far has been recorded cycle by cycle in a non-governmental registry system.



The German IVF Registry (Deutsches IVF Register, D-I-R) was founded in 1982, the year that (West) Germany's

first IVF birth was announced, a baby boy born in April at the University Hospital of Erlangen. Two years later the Lübeck group reported that between July 1982 and March 1983 they had treated 130 patients with

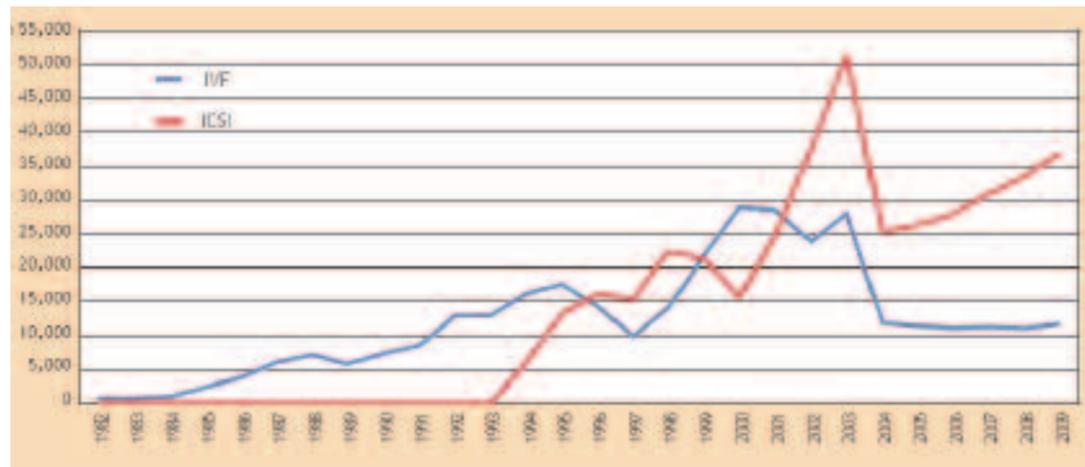
IVF, with 585 follicles punctured and 404 egg cells obtained; embryo transfer was achieved in 95 patients, and pregnancy in 14 cases. Since then, in reflection of the remarkable advance of ART in Germany, data submitted to the D-I-R for 2010 are likely to reach a cumulative total of 1 million cycles reported.

And just as Germany's IVF programmes moved so rapidly forward, so did the country's data

collection requirements. By 2009, when the registry adopted a new legal form and created articles of incorporation, 120 IVF centres were providing data, reporting a total performance of 49,602 IVF and ICSI cycles that year.

The registry itself remains an initiative based on the involvement all physicians engaged in the field of reproductive medicine in the German healthcare system - that is, it is not

Table 1. The number of IVF and ICSI cycles performed in Germany between 1982 and 2009



	1982	1986	1990	1994	1996	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
IVF	742	3806	7343	16175	14344	14024	21880	28945	28506	23936	28058	11848	11410	11062	11362	11048	11715
ICSI				5856	16108	22420	21244	15752	24897	37692	51389	25339	26370	28015	31452	33591	37006
Total*	742	3806	7343	22031	30452	37933	44086	45487	54098	62306	80434	37633	38382	39769	43612	45461	49602

* The value of IVF/ICSI cycles is conyained in the toal - eg, 881 cycles in 2009

supported by the government. So, financial support is provided by the IVF units themselves and is not part of any government funding scheme.

As can be seen in the table above, the percentage of ICSI cycles increased rapidly in Germany from 1993 onwards - as it did throughout Europe - and today ICSI accounts for almost three times the ART activity of IVF. The other major trend, clearly evident in the table, is that until 2004 government reimbursement covered 100% of the cost of four treatment cycles. But that year the reimbursement system was changed to provide only 50% payment for three cycles. This change prompted a dramatic

decrease in cycle numbers, which is only now creeping back towards former levels.

D-I-R participates in data collection for the European IVF Monitoring consortium (EIM) of ESHRE, and also sends data to the International Committee Monitoring Assisted Reproductive Technologies (ICMART), which operates on a worldwide scale. Germany now ranks as Europe's second most active ART country (after France) according to data submitted to the EIM.

In comparison to other international and European registries, D-I-R employs a large dataset which also collects follow-up information on

the babies born.

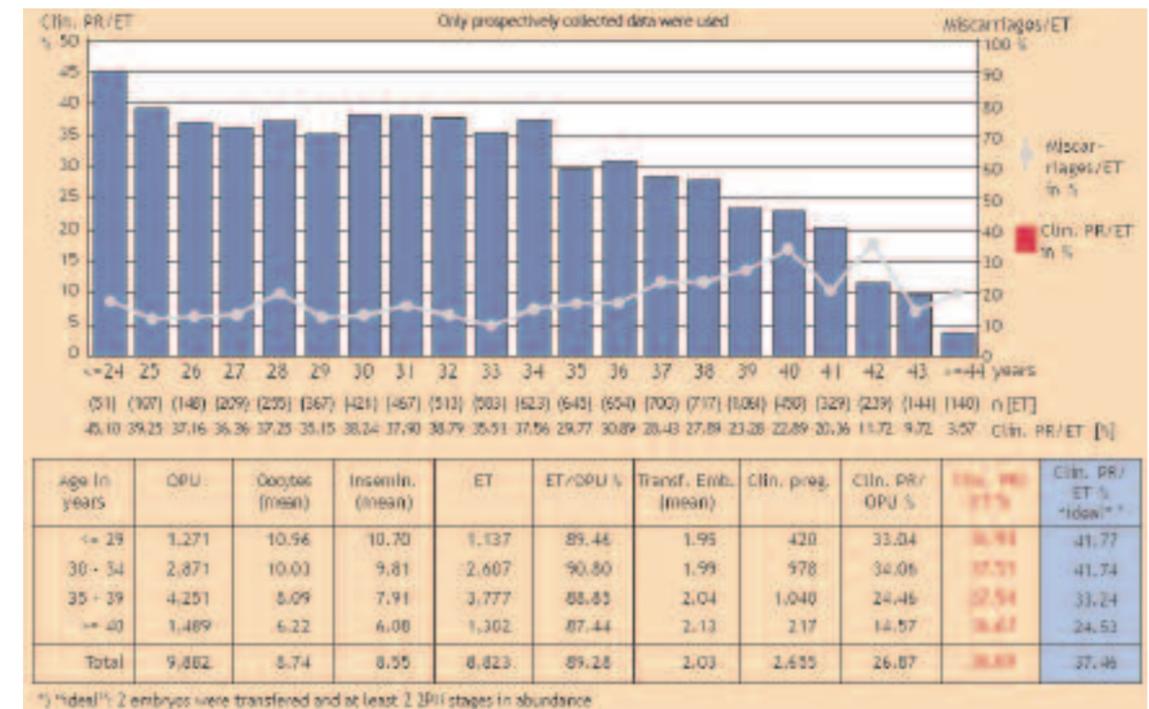
However, the German healthcare system, unlike that of Denmark or the UK, has no social security number or other unique registration system for each individual. Thus, D-I-R is now preparing a dedicated ID based on the so-called 'DDR code', which creates a unique case number out of the family name, first name, date of birth and sex. This code can only be read in one direction, which means that individual identity cannot be decoded from the eight-digit number, but case, treatment and outcome can be tracked, as well as couples changing their treatment centre.

Unfortunately, the code is not sufficient to analyse cross-border activities, which appear to play an important role throughout Germany but especially in the southern regions, where overseas clinics with more liberal laws are highly promoted.

Legal restrictions in Germany - the principal reason for cross-border treatment - are currently among the most restrictive in Europe. The Embryo Protection Law, passed 20 years ago in 1991, allows the freezing of fertilised oocytes only at the pronuclear stage, outlaws embryo



MARKUS KUPKA: 'THE FRAMEWORK FOR ART IN GERMANY IS MUCH DIFFERENT FROM THAT OF MOST OTHER EUROPEAN COUNTRIES.'



* "ideal": 2 embryos were transferred and at least 2 ZPN stages in abundance

Table 2. Clinical pregnancy and miscarriage rates by age group from IVF treatments in 2009. The right-hand column below provides estimated results for 'ideal' patients.

selection, and requires that no more than three embryos can be transferred. The legislation is unequivocal: 'Anyone will be punished with up to three years imprisonment or fine who attempts, within one treatment cycle, to transfer more than three embryos into an woman and attempts to fertilise more egg cells from a woman than may be transferred to her within one treatment cycle.' Egg donation and research on embryos or PGD are also illegal.

The framework for ART in Germany, therefore, is much different from that of most other European countries. Nevertheless, over the years our success rates have been comparable, as demonstrated in the annual reports of D-I-R, which were first made available in 1991. Average pregnancy rate for IVF cycles reported for 2009 was 30%, and 28.9% for ICSI. As explained in Table 1, a single cycle combination of IVF and ICSI was performed in 881 instances in 2009, while frozen transfers (embryos derived from oocytes cryopreserved at the 2PN stage) were performed in 17,646 cases and achieved a pregnancy rate

of 18.2%. A twin rate of 20.8% (and higher multiple births of 0.8%) was documented from pregnancies.

Since 1996, the annual report has been published as a single booklet (www.deutsches-ivf-register.de/Jahresberichte). But now, starting in 2010, the report is also published in English in the *Journal of Reproductive Medicine and Endocrinology* (www.kup.at/journals/reproduktionsmedizin).

Nearly all German IVF units are currently using a standard, computer-based dataset description, but employ different software tools to submit their data to the registry. These tools have undergone numerous developments, but, from its inception, the registry has been collecting data on a cycle-by-cycle basis. The report thus represents a summary of all reported cycles, but, because of German legal requirements and internal procedural rules, no data related to specific centres can be released.

The report is broken down into three sections. The first is a patient-based section comprising responses to common questions or offering comments on different therapeutic

options. The second section is a uniform analysis of all reported cycles and contains detailed charts and tables. The third section focuses on those special statistics which vary from year to year and consider lifestyle aspects or regional differences. An epilogue, a comment on aspects related to the statistics and data processing together with a list of all participating centres, is also included.

Since 1997, more than 80% of all ART cycles reported to the system have been entered prospectively (within seven days of the start of ovarian stimulation). This is intended to prevent cycle selection, and is one of the most powerful quality tools in the system. A dynamic link library (DLL) maintained by the registry allows data plausibility to be monitored either online or shortly after data input. Participation in the registry became mandatory in 1999.

In 2009, a total of 75,662 cycles were reported, 84% prospectively. In contrast to the IVF registries of other countries, the D-I-R contains information about reproductive history and pre-existing conditions for both partners.

Quality		<= 29 years		30 - 34 years		35 - 39 years		>= 40 years		Total	
ideal	non-ideal	ET	Clin. PR/ET %	ET	Clin. PR/ET %	ET	Clin. PR/ET %	ET	Clin. PR/ET %	ET	Clin. PR/ET %
0	1	67	8.96	193	6.74	381	8.40	207	5.31	848	7.31
0	2	287	22.30	655	21.83	679	15.46	179	9.50	1,800	18.28
0	3	24	25.00	79	15.19	177	13.56	102	11.76	382	14.14
1	0	425	22.88	964	28.41	1,813	15.88	1,026	4.51	4,228	15.59
1	1	560	34.46	1,141	26.56	1,369	21.91	364	12.64	3,434	24.52
1	2	32	21.88	93	31.18	264	18.56	150	12.67	539	19.29
0	0	3,919	46.84	7,729	36.43	7,814	32.48	1,629	17.68	21,151	35.84
2	1	76	36.84	240	30.00	593	27.15	323	17.65	1,232	25.81
3	0	346	37.38	904	38.55	2,346	31.45	1,313	23.34	4,909	38.39
Total		5,736	38.37	12,058	34.86	15,436	27.36	5,293	15.36	38,523	29.70

Only prospectively collected data were used.

Table 3. 2009 results for IVF, ICSI and IVF/ICSI as a function embryo quality and number transferred.'

Each centre provides information twice a year (on average) and the published data not only report a clinic's own results but also a comparison with all other participating centres.

Since the registry requests data for both the current year as well as past years, our loss to follow-up - 13% after a year - is generally low. However, as in other European countries, many foreign couples are also treated in Germany, making it somewhat difficult to obtain complete information on the outcome of pregnancy.

The pale blue column in Table 2 describes the 'ideal' couple. To overcome geographical differences in reimbursement or availability of services the registry has generated a model pregnancy rate when two embryos are transferred with at least two more at the 2PN stage (cryopreserved or destroyed). Overall, this 'ideal' pregnancy rate was calculated to be 37.5% per embryo transfer.

Our data have also confirmed that the age of female partner represents the most confounding factor for outcome, and the D-I-R provides detailed statistics on this. Table 3, for example, shows success rates as a function of the number and quality of embryos transferred in each of four age groups. This table is frequently

used during patient counselling to explain the effect of age. As can be seen, treatment of women over the age of 34 shows a significant decrease in the likelihood of pregnancy - especially with 'non-ideal' embryos.

Each year the annual report also includes 'special' statistics which vary from year to year. In 2009 we included data on pregnancy rates in patients with an ideal prognosis (and other patients too) as a function of centre size over ten years (2000-2009). We defined ideal prognosis as age under 35 years and having a first stimulation cycle for ART. We demonstrated that for both ideal patients and others the larger centres (more than 500 cycles per year) offered a trend of higher pregnancy rates than the smaller centres.

Consumer demands for information and clarity in this highly sensitive area of human reproductive medicine are more than justified. The success of these treatments will only be socially acceptable and misunderstandings can only be prevented once a reliable assessment and an open discussion of the attainable results have been carried out. And this is why national registries in nearly every European country have collected and are analysing their data. In Germany, this has been our aim since 1982. Over the years, the number of participating

centres and registered treatments has greatly increased, but further improvement is still required. Our introduction of 'ideal' patient modelling has gone some way to removing variations in reimbursement or availability, and our registry data cannot be combined with prenatal medical data or cancer registries. The creation of follow-up ID statistics on infant births is extremely difficult.

And now, as its cumulative total heads towards 1 million cycles, our DIR report will for the first time be published in English and we are now able to research specific angles such as lifestyle factors (smoking, weight) or reproductive history (former pregnancies, miscarriages). However, from our perspective the greatest advance of the German registry lies in the decision of nearly every IVF unit to support its work through prospective data collection and payments made to maintain such comprehensive files.

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