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The German IVF-Registry – D-I-R

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The German IVF-Registry – D-I-R

K. Bühler

Systematic data collection in the field of assisted reproductive techniques is performed in Germany since 30 years. Since 1997, data collection is performed electronically and in a prospective way. In 1998, by a code of the German Medical Association participation at the registry has become mandatory for all IVF centres in Germany. Different software solutions can be used in the centres for data collection. All of them have to cooperate with a special “DIRmod-DLL”, controlling online plausibility and prospectivity of the collected data. More than one million treatment cycles have been reported in the annuals published since 1996 up to 2010. All in all > 1.2 millions cycles are included in the registry. Clinical pregnancy rate increased continuously and miscarriage rate decreased. By reduction of the mean number of transferred embryos of about 20% the percentage of born triplets in relationship to all children born after ART decreased of about 80%. It can be shown with the huge number of documented cycles that political decisions exert a dominating influence on treatment and drug choice. The German IVF registry has been established over the last 30 years as an instrument of quality assurance and has experienced highest regard by colleagues and by the international scientific world. **J Reproduktionsmed Endokrinol 2013; 10 (Special Issue 1): 29–32.**

Key words: IVF, ICSI, IVF registry, pregnancy rate, data collection in IVF

■ Introduction

Systematic data collection in the field of assisted reproductive techniques is performed in Germany since 30 years. In 1982, the year when the first IVF-baby was born in Germany, all 5 centres, performing IVF treatment at this time, decided to put their results together and to publish it. At this time this new treatment to overcome infertility especially when it was due to tubal dysfunction was in a centre of public dispute. The idea behind these statistical reports has been all the time to deliver insight to an interested public into this medical field. Since the very beginning, all physicians participating at this data collection wanted to lend transparency at this treatment modality.

When the register started, participation has been organised on a voluntary base. In 1998, by a code of the German Medical Association, participation became mandatory for the IVF centres. In 2010, 124 centres have sent data to the registry. At the beginning, the centres reported their activities by a written annual summary; starting in 1990 some centres collected their data by using a dBase software solution. With the implementation of the RecDate software, a Filemaker®-based and industry sponsored computer programme for collecting data in the field of ART the electronic data collec-

tion has become mandatory for all participating centres. With the electronic data collection the reporting has to be done cycle by cycle. So it has become reality that data can be checked instantly for plausibility and prospectivity. Prospectivity in this context means that the cycle has to be announced into the system at least within the first 8 days of stimulation before the outcome of the treatment cycle is known.

When in the beginning the registry represented only a loose association of interested centres in 2008 a structural reorganisation has been performed. The “Deutsches IVF-Register e. V.” has become an incorporated association with charitable status.

Since 1996 up to 2010, 1.066.266 cycles have been reported in the yearbooks; when the yearbook 2011 will be published in December this year, more than one million electronically collected cycles will be documented. Concerning IVF and ICSI cycles more than 90% are collected in the prospective way. All in all, since 1982, 1.203.302 datasheets are included in German registry.

In 1996 too, we started to publish an annual report and since the Annual 2009 it is also published in English in the Journal of Reproductive Medicine and Endocrinology [1]. All yearbooks can be seen

on the homepage of the D-I-R; even some of the loose-leaf collections from the former years [2].

■ Method

In 2003, the registry developed and introduced its own data collection software DIRpro, based on a SQL database, which was placed as an industry-independent alternative solution and as an electronic questionnaire including all the registry relevant items and which is at the free disposal to all centres. Also, a special interface for IVF-registry data, “DIRmod-DLL”, was created and implemented in order to react to the widening scope of software solutions for IVF data collection. So, the centres are enabled to use individual software solutions. The only conditions are that these solutions have to fulfil certain rules defined by the registry in the interaction with the DIRmod-DLL in the right way.

The statistical instruments used for the evaluation of all the data collected as well as for presenting these large sets of data and tables in a clear way in the annual reports have been described previously [3].

For a better understanding of all the data the definition of the basic set, e.g. “all cycles”, “plausible cycles”, and “prospectively collected cycles”, is given in

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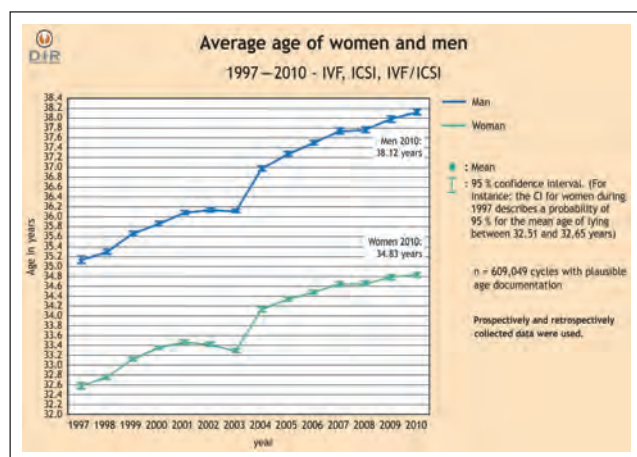


Figure 1. Mean age of the couples since 1997 [3].

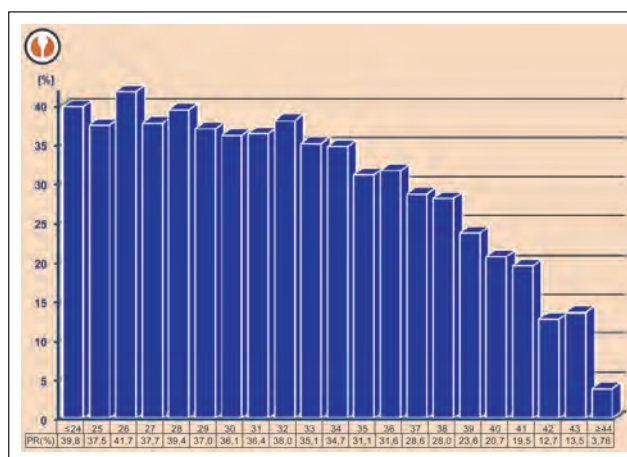


Figure 2. IVF therapy: clinical pregnancy rates by age, 2008–2010, 26.663 cycles with embryo transfer.

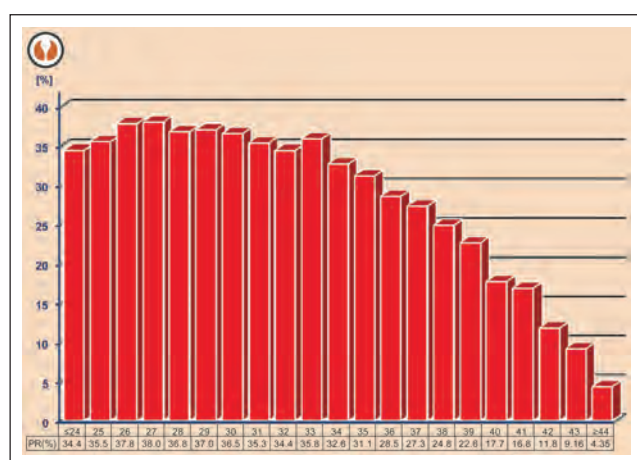


Figure 3. ICSI therapy: clinical pregnancy rates by age, 2008–2010, 87.702 cycles with embryo transfer.

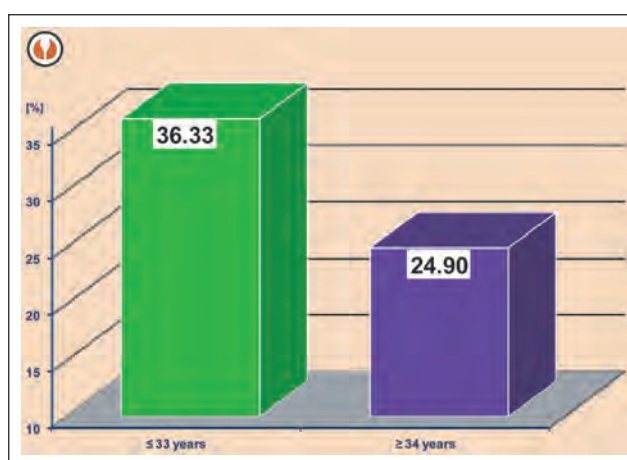


Figure 4. Clinical pregnancy rates in IVF and ICSI treatment in age classes; 2008–2010: ≤ 24 years to 33 years, n = 44.712; 34 years – ≥ 44 years, n = 69.653.

every graph and table shown in the yearbooks.

Results

In the yearbook 1997, the first one in which all data were only collected electronically, the clinical pregnancy rate in IVF treatment was of 24,4% per embryo transfer and of 23,3% for ICSI treatment respectively. In 2009, the clinical pregnancy rate in IVF treatment was at 30,2% per embryo transfer and at 29,3% in ICSI treatment. The amelioration in this medical field becomes even more obvious when only such cases are compared in which only 2 embryos of good quality have been transferred. 1997, the pregnancy rate correspond to 24,5% and in 2010 to 35,9% independent from the patients age. This increase reflects the progress in medical treatment, the development of the used stimulation drugs and regimens, the growing experience with such treatments, as well as ad-

vances in the IVF laboratory regarding the treatment of germ cells, the identification of embryos with high development potential, the culture media and culture techniques in total. So, the registry is able to document the progress in this field of medicine in a large scale. This increase in quality is even more important considering the fact that within the last 14 years the average age of the treated couples has increased significantly (Fig. 1). Meanwhile, more than 60% of treated women are at the age of 35 years and more. The mean age of treated women increased since 1997 from 32.51 years up to 34.83 years in 2010 and in men from 35.16 years to 38.12 years respectively. Due to the social change an increasing number of couples want to realise their family planning at a later stage of life. But as well shown in Figure 2 and Figure 3 in more than 114.000 IVF and ICSI transfer cycles in the years 2008–2010 the women's age is of a crucial importance

on pregnancy rate. At the age of more than 33 years pregnancy rates decrease obviously (Fig. 4).

Women younger than 35 years showed a mean pregnancy rate of 39.8% by IVF or ICSI treatment during the past 5 years if 2 good quality embryos could be transferred and there was an adequate ovarian response to stimulation, meaning that at least there were two more oocytes in the correct pro-nuclear stage in surplus. These results are comparable to the international standard in spite of the legal restrictions in Germany in the field of ART compared to other European countries, e. g. Spain, Great Britain, Poland, Belgium or the Netherlands.

Another sign for the increased quality since 1997 can be seen in the reduction of the mean number of transferred embryos. In so-called fresh cycles the reduction was between 18.5% and 19.5% compared with the numbers from 2010.

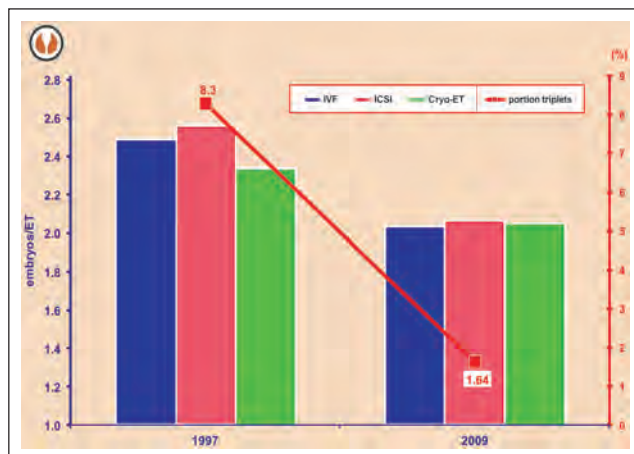


Figure 5. Mean number of embryos transferred in IVF and ICSI treatment and after cryopreservation of oocytes in the 2-PN stage, 1997–2009 (blue ordinate); percentage of born triplets in relationship to all children born after ART procedure, 1997–2009 (red ordinate).

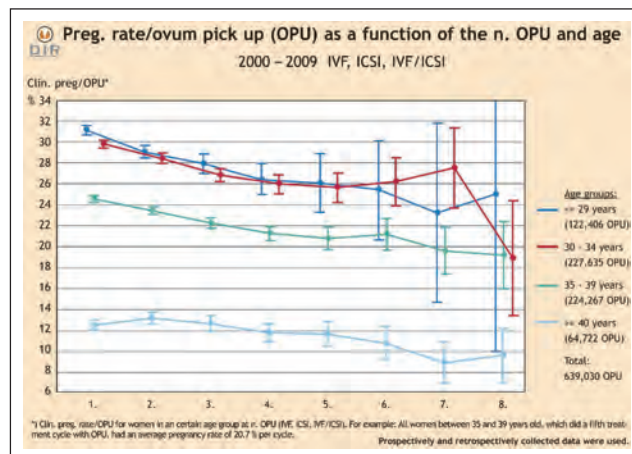


Figure 6. Clinical pregnancy rate per OPU as a function of the number of the executed cycle in 4 different age classes (≤ 29 years, 30 years–34 years, 35 years–39 years, ≥ 40 years) [1].

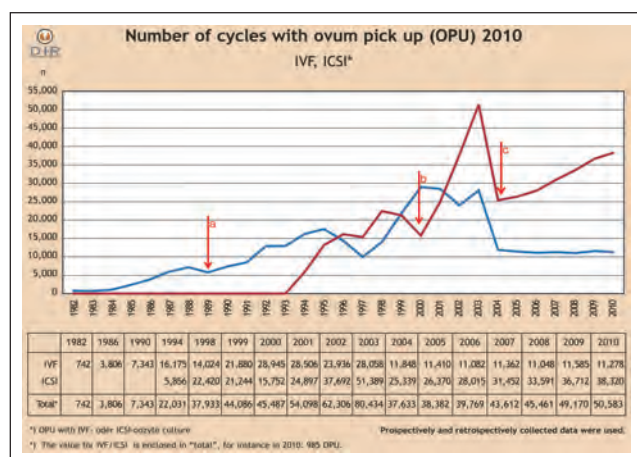


Figure 7. Number of treatment cycles with oocyte retrieval, 1997–2010; a, b, c see text. [3].

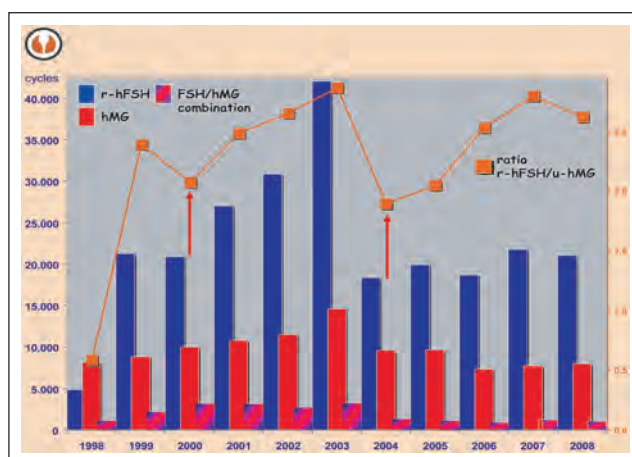


Figure 8. Gonadotropins applied 1998–2008, expressed in cycles (blue ordinate) and ratio between recombinant FSH and u-hMG (orange ordinate).

Even if this seems not to be much, we recorded a very pleasing development as clinical consequence: When in 1997 8.3% of all children born after ART were triplets, in 2009 this rate decreased to 1.64%, that means a reduction of 80% (Fig. 5).

As shown in Figure 6 in more than 600.000 treatment cycles with ovarian puncture (OPU) the number of performed treatment cycles per patient seems not to be of such a great importance in regard to the pregnancy rate. The most important factor is once more the age of the women. Patients younger than 35 years show even in the sixth treatment cycle a pregnancy rate of more than 26% per OPU.

Figure 7 shows how the numbers of oocyte retrievals have been developed since 1982. It is easy to see political in-

fluences. So, in 1989 IVF treatment was not reimbursed by the health insurance system (Fig. 7a). In 2000, ICSI was not reimbursed (Fig. 7b) and since 2004 (Fig. 6c) the health insurance system has been changed completely. Exceptionally, only 3 cycles are reimbursed instead of generally 4 and this, starting from 2004, only to 50% of all the cycle costs, medical treatment and drugs, and new nonsensical age limits have been installed. So, in 2004 there was a dramatic drop of more than 50% in the number of OPU compared with 2003 and of about 40% compared to 2002 respectively. In the following years a re-increase of nearly 35% can be seen, but only due to the rising in the ICSI procedure. Political influences induce also consequences in the prescription habit of the physicians. Briefly after introduction on the market, recombinant FSH has become the most applied gonadotropin also in Germany.

But regarding the ratio between recombinant FSH and u-hMG it is obvious that in the years 2000 and 2004 relatively more u-hMG was prescribed (Fig. 8). Also, when women have passed the age of 40 years more u-hMG than recombinant FSH is used (Fig. 9). It seems that German physicians have a trend to prescribe the assumed less expensive drug in situations when the patients are not or less reimbursed.

Regarding the pregnancy rates since 1997 we could observe a continuous increase. In the same period we could state a decrease in the frequencies of miscarriage: from about 22% in IVF and ICSI cycles to 18%. This fact can be explained by the increased capability in detecting the embryos with best development potential. But we have to notice that pregnancies induced with oocytes cryopreserved in the 2-PN stage show

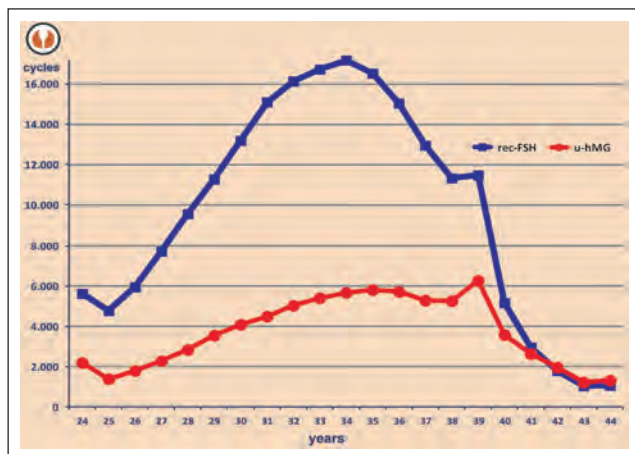


Figure 9. Gonadotropins applied in relationship to patient's age, 2000–2008.

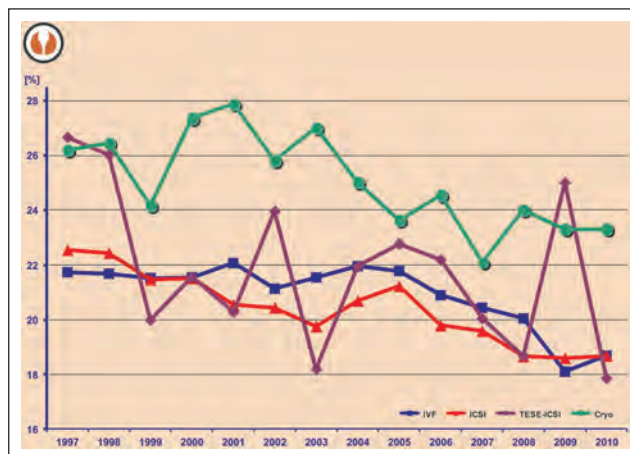


Figure 10. Miscarriage rates in different treatment modalities, 1997–2010.

over the entire period a miscarriage rate four to five percentage points higher than with “fresh” oocytes (Fig. 10). The question arises: Is this due to the freezing procedure or because the cryopreserved oocytes mostly represent only a “second choice”?

Discussion

Such large databases are not in competition with randomized controlled trials (RCT) and meta-analysis. Both represent completely different objectives and apply not comparable methodologies. With RCT, particular questions are investigated, usually in a well-defined group of patients with strict inclusion and exclusion criteria and with a previously well-defined study protocol. Due to the great effort linked with such cost-intensive investigations the number of observations is mostly limited. In order to enlarge the number of cases for statistical evaluation meta-analyses pool the results of several studies with similar objectives and methods.

Databases, such as the German IVF registry, first document only the daily practice without any special hypothesis. Daily practice is characterized by a large heterogeneity of the observed patients. There are no patient selection, nor inclusion or exclusion criteria. Nevertheless, a good, ongoing and prospective data

collection and the huge number of cases – in the German registry more than one million cycles are documented – allow to draw reliable conclusions to a certain extent, and with the possibility to extract more or less homogenous subgroups also treatment strategies can be compared [4]. However, conclusions from such large observations are sometimes critical due to the possible distorting bias influence. On the other side, RCTs and meta-analyses are not “bias-free” as it was recently shown in a large Cochrane analysis regarding simply the question of sponsorship [5]. It is also questionable whether all results of RCT and meta-analyses can be transferred into daily practice and are relevant for all patients?

The German IVF registry has been established over the past 30 years as an instrument of quality assurance, both nationwide as well as in every participating centre itself. During all these years this instrument has experienced highest regard by all colleagues, politicians, journalists, the international scientific world and even the highest, constitutional court in Germany relies decisions on results of this data collection.

Acknowledgement

Everybody in all the IVF centres is gratefully acknowledged. Only with

their continuous and sometimes exhausting collation of all relevant data such a register can exist. We also thank the staff of the Schleswig-Holstein Medical Association, where in the last 15 years, organisation and data analysis of the D-I-R were performed. The register also pays his thanks to the former chairmen, Prof. F. Lehmann, who has launched the registry 1982, Prof. H. Rjosk and Prof. R. Felberbaum, and all the members of the Directorial Board, Advisory Board and the Board of Trustees who have sacrificed innumerable time to make this registry to what it is today.

Conflict of Interest

No potential conflict of interest to this article was reported.

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