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Final ART success rates: a 10 years survey

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BACKGROUND: Cumulative pregnancy rates (CPRs) and live birth rates (CLBRs) are much better indicators of success in IVF programmes than cross-sectional figures per cycle or embryo transfer. They allow a better estimation of patient's chances of having a child and enable comparisons between centres and treatment strategies.

METHODS: A 10 year cohort study of patients undergoing their first assisted reproductive technique cycle was conducted. Patients were followed until live birth or discontinuation of treatment. All IVF and ICSI cycles and cryo-cycles with embryos derived from frozen pronuclear stage oocytes were included. The CPR and CLBR were estimated using the Kaplan–Meier method for both the number of treatment cycles and transferred embryos. The analysis assumed that couples who did not return for subsequent treatment cycles would have had the same chance of success as those who had continued treatment.

RESULTS: A total of 3011 women treated between 1998 and 2007 were included, and 2068 children were born; women already with a live birth re-entered the analysis as a 'new patient'. For 3394 'patients under observation' with 8048 cycles, the CLBR was 52% after 3 cycles (the median number of cycles per patient), 72% after 6 cycles and 85% after 12 cycles. A CLBR of ~50% was achieved for patients aged under 40 years, after the cumulative transfer of six embryos. The mean live birth rate from one fresh cycle and its subsequent cryo-cycle(s) was 33%. Our analysis also shows that ART can reach natural fertility rates but not exceed them.

CONCLUSIONS: Most couples with infertility problems can be treated successfully if they continue treatment. Thereby ART can reach natural fertility rates. Even with the restrictions in place as a result of the German Embryo Protection Law, CLBR reach internationally comparable levels.

Key words: cumulative pregnancy rate / cumulative live birth rate / natural fertility rate / German Embryo Protection Act

Introduction

All IVF patients want to know their chances of success. Generally, the success rates of assisted reproductive techniques (ARTs) are given as clinical pregnancy rates (PRs) per started cycle, oocyte retrieval or embryo transfer and often determined relative to maternal age. At first glance, these rates seem to be disappointingly low, but it is the final ART success rate that is most pertinent to a patient's decision on whether to undertake treatment (Hull, 1994). Furthermore, final ART success rates [cumulative pregnancy rate (CPR) and live birth rate (CLBR)] appear to be a much better indicator of quality and success in IVF programmes and probably allow better comparisons between different centres (Lintsen *et al.*, 2010). This is of particular importance for cross-comparison of IVF results between different countries, especially as an increasing number of patients are looking for cross-border treatment. CPR and CLBR should reflect possible advantages or disadvantages of national IVF policies (restrictions and liberations) and individual treatment strategies of different IVF clinics. Moreover, CPR and CLBR are the most important figures for basing economic and political considerations of ART efficacy and reimbursement costs.

The German national index and most of the international indexes have not published CLBR so far (www.deutsches-ivf-register.de). Several previous studies have calculated cumulative success rates but have some limitations because of inconsistent inclusion criteria, inconsistent treatment procedures or no reporting CLBR (Tan *et al.*, 1992; Hull, 1994; Bergh *et al.*, 1995; Dor *et al.*, 1996; Osmanagaoglu *et al.*, 1999; Kovacs *et al.*, 2001; Olivius *et al.*, 2002; Ubaldi *et al.*, 2004; Lundin and Bergh, 2007; Pelinck *et al.*, 2008; Sundstrom and Saldeen, 2009). More recent studies have published CPR comparing single versus double embryo transfer and discussed the impact on

treatment policy (Sundstrom and Saldeen, 2009; Gelbaya *et al.*, 2010), and one German study has reported on CPR with respect to national restrictions and dropout reasons (Schroder *et al.*, 2004). However, only one centre has published their CLBR, including cryo-cycles with transfers of previously frozen embryos, as well as their treatment policy in detail (Klipstein *et al.*, 2005; Malizia *et al.*, 2009; Moragianni and Penzias, 2010). Furthermore, in most previous studies on CLBR and CPR, the methodological management of women with live birth coming for another child remains completely unclear.

In Germany, the performance of an ART is bound by very strict regulations by law (German Embryo Protection Law of 13th December 1990 http://www.bmj.bund.de/files/-/1148/ESchG.pdf) and also influenced by general health insurances (Gemeinsamer Bundesausschuss der Ärzte und Krankenkassen, http://www.g-ba.de). Until 2004, up to four fresh IVF- and IVF/ICSI cycles were fully covered by insurance. Since then, half the cost of IVF- and IVF/ICSI cycles is covered by the couple with the remainder paid by insurance and only for a maximum of three cycles. Cryo-cycles are entirely privately funded. The change in the reimbursement regulation in 2004 caused a significant drop in the number of treatment cycles in Germany. All numbers and other statistical data are published yearly by the national IVF register and can be seen at www.deutsches-ivf-register.de.

According to the German Embryo Protection Law of 1990, the cell-culture of more than three pronuclears (PNs) is prohibited because only as many oocytes at the PN stage as are planned to be transferred in one cycle are allowed to be cultured. PNs that are not intended for implantation within one cycle have to be discarded or cryopreserved. As a consequence, prolonged embryo culture with the selection of the best embryos or blastocysts and embryo cryopreservation is prohibited. Embryo cryopreservation is allowed only in cases of emergency. There is an ongoing and viable discussion on the interpretation of the German Embryo Protection Law. Therefore, the question arises of whether the strategy of one IVF or ICSI-cycle and its subsequent cryo-cycle(s) yields a lower cumulative CPR and CLBR than one IVF or ICSI-cycle with prolonged embryo culture and embryo selection before transfer.

In this cohort study, we calculated CPR and CLBR by the Kaplan–Meier-method (Kaplan and Meier, 1958), which allows for the estimation of CPR and CLBR without under- or overestimation, which is of particular importance if patients are censored for reasons other than pregnancy or live birth. The Kaplan–Meier method assumes inherently that those who exit treatment for reasons other than pregnancy or live birth have the same probability of future success as those who continued.

We performed this 10-year survey from 1998 to 2007 in a single IVF centre in Germany in order to provide estimates of the final success that a couple would have if continuing treatment and to allow comparisons with international success figures. We included all IVF, IVF/ICSI and cryo-cycles involving the transfer of embryos derived from frozen PN stage oocytes.

Materials and Methods

Data collection and analysis

All ART cycles included IVF, IVF/ICSI and cryo-cycles with embryos from cryopreserved PN stage oocytes but no oocyte donations as it is prohibited in Germany. Cycles between January 1998 and December 2007 were observed in a cohort study, including all women undergoing their first fresh cycle in our centre. These women were followed as 'patients under observation' until either discontinuation of their treatment or live birth as the primary outcome. All patients without a live birth who returned for further treatment underwent a further attempt. Cycles without oocyte 6 retrieval were not included. Only cryo-cycles with embryo transfer were considered. For the Kaplan–Meier estimations, women already with a live birth re-entered the analysis as a 'new patient under observation' if they underwent further ART. Patients who did not return (perhaps because they changed the IVF centre or stopped treatment for any other reason) were censored after the last treatment.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Medical and laboratory data were recorded using the clinic management program MEDISTAR, the IVF laboratory managing program RECDATE and Microsoft EXCEL. Data collected included the length of time trying to conceive, information of previous treatments for infertility and, if available, the reason of discontinuation, relevant information about ovarian stimulation and procedures in the IVF laboratory and outcomes of the treatment cycles. All couples had to sign an informed consent about data storage and anonymous results reporting and transfer to the national register.

Data were analysed using the SAS package, version 9 (SAS Institute Inc., Cary/USA). Kaplan–Meier survival rates were estimated over all treatment cycles or number of transferred embryos. The usual survival rates with means and 2 standard errors approximating the 95% confidence interval (CI) were computed and the cumulative probability curves (non-parametric distribution functions) were derived for the CLBR or CPR. Since age is the major factor of importance for the success rates (Lass *et al.*, 1998; Bar-Hava *et al.*, 1999), Kaplan–Meier curves were additionally calculated separately for different age groups. Additionally, we also calculated non-estimated live birth rates (LBRs) and PRs for one treatment sequence, which is one fresh cycle followed by its subsequent cryo-cycle(s), to allow comparisons with cross-sectional statistics. Statistical significance was derived by the Log-rank-test for Kaplan–Meier survival rates and the *t*-test for other continuous data.

Fresh cycles

The fresh IVF- or IVF/ICSI-cycle treatment strategies have previously been described in detail (Gnoth *et al.*, 2008). The main indications for ART were male subfertility (65%), tubal pathology (12%), endometriosis (12%), idiopathic infertility (9%) and repeated polyfollicular development in gonadotrophin stimulation cycles for IUI (2%). The majority of patients began treatment with a monophasic oral contraceptive pill on Days 3–5 of the cycle. The long agonist protocol was used preferentially. In about 20% of all fresh cycles, stimulation was according to the antagonist protocol especially in cases of expected low ovarian response. Controlled ovarian hyperstimulation (COH) was performed with either recombinant follitropin α or β (rec FSH) or urinary HMG. The starting dosage was adjusted according to the patient's age, Anti-Müllerian hormone and antral follicle count. Most of our patients under 35 years of age were started with 150 mIU/ml. In patients with expected or proved low ovarian response ($\leq$4 oocytes in a previous cycle), we started with 300 mIU/ml. After 5 days of stimulation, the follicular development was assessed by ultrasound and hormonal measurements. If necessary, the dose of gonadotrophins was adjusted. Transvaginal oocyte retrieval was performed 35 h after ovulation induction. The luteal phase was supported with vaginal application of progesterone and in the case of low ovarian response, vaginal estradiol (E_2) was used additionally. In accordance with the regulations, two PN stage oocytes were cultured if a transfer of two embryos was planned

or three PN stage oocytes if three embryos should be transferred in one cycle. In all cases, a PN scoring was performed. All supernumerous PN stage oocytes were frozen. Approximately 30% of all fresh cycles were conducted as IVF and 70% were conducted as IVF/ICSI. The number of embryos transferred depended on maternal age, parity, number of previous attempts and the couple's wish, and was 2.06 per transfer on average. The ongoing clinical PR was considered to be the secondary outcome measure defined as a gestational sac and heart beat assessed by vaginal ultrasound 2–3 weeks after a positive pregnancy test.

Cryo-cycles

Cycles with the transfer of embryos derived from cryopreserved PN stage oocytes were performed after priming the endometrium with a vaginal application of 2–4 mg micronized E_2 per day. Luteal phase was initiated with additional vaginal application of progesterone after ultrasound assessment of the endometrium ideally showing a trilaminar pattern and a thickness of at least 7 mm. The PN stage oocytes were thawed on Day 3 of vaginal progesterone and transferred after 2 days of embryo culture (Day 5 of vaginal progesterone). Clinical pregnancy was confirmed as before.

Results

Overall 3011 individual women were eligible for inclusion. Women already with a live birth re-entered the analysis as a 'new patient'. Therefore, 3394 'patients under observation' contributed 8048 cycles, which are summarized in Table I. The mean duration of involuntary infertility was 3.4 years before ART indicating serious subfertility (Gnoth *et al.*, 2005). The overall mean number of treatment cycles was 2.7 (median: 3) per patient (range 1–22). This resulted in 2193 clinical pregnancies and 1718 deliveries, producing a total of 2068 children (1373 singletons, 680 twins and 15 triplets). The transfer of embryos in cryo-cycles accounted for 20% of live births. The miscarriage rate was 19.5%, and the ectopic PR was 2.2%. The clinical PR was 27.2% per oocyte retrieval. The transfer of three embryos in a cryo-cycle was as effective for PR per embryo transfer as the transfer of two embryos in a fresh cycle.

Cumulative live birth rates

Figure 1 shows the overall CLBR for all treatment cycles with oocyte retrieval and all age groups. The CLBR were 52% after 3 cycles (approximate 95% CI: 50–54%), 72% after 6 cycles (approximate 95% CI: 69–74%), 85% after 12 cycles (approximate 95% CI: 80–89%) and 94% after 18 treatment cycles (approximate 95% CI: 85–100%). The maximum number of treatment cycles that resulted in a successful pregnancy was 18 with the birth of healthy twins. Because of the re-entry of women after a live birth as 'new patients', we included 3394 'patients under observation' in the estimations of CLBRs and CPRs (Fig. 1). The proportion of re-entry in 'patients under observation' is 11.3%. The maximum of re-entry is three times with four children born to one woman after treatment for infertility in our centre. CLBR and CPR did not differ according to whether re-entry was allowed or not.

Figure 2 shows the CLBR, for all treatment cycles with oocyte retrieval, stratified for the different age groups. The Log-rank test revealed a significantly lower LBR for women over 40 years of age. Although the CLBR also seemed to be lower in age group over 35 up to 40 years of age, it failed to reach statistical significance when compared with the younger age groups.

Table I Basic characteristics of patients and treatment cycles.

Time	1998–2007
Total number of individual women	3011
Patients under observation	3394 (with 383 re-entries after live birth)
Total cycle number observed	8048
Patient's age (entire study, before and after the change of reimbursement policy in Germany in 2004)	33.7 ± 4.4 years; minimum 20 years, maximum 46 years of age (all patients. entire study) 34.33 ± 4.74 years (before 2004, not pregnant in study time)[a] 35.75 ± 4.4 years (2004 and beyond, not pregnant in study time)[a] 32.73 ± 8.8 years (before 2004, finally pregnant)[a] 33.71 ± 3.9 years (2004 and beyond, finally pregnant)[a]
Duration of infertility	3.4 years
Cycles/patient (entire study, before and after the change of reimbursement policy in Germany in 2004)	2.7 ± 1.3 (mean, entire study) 2.4 ± 1.7 (before 2004, not pregnant in study time)[a] 2.7 ± 1.9 (2004 and beyond, not pregnant in study time)[a] 1.9 ± 1.4 (2004 and beyond, finally pregnant) 1.9 ± 1.4 (2004 and beyond, finally pregnant)
Maximum cycles/patient	22
Oocytes/retrieval	10.35 (mean)
Embryos transferred/cycle	2.06 (mean)
IVF-cycles	30% of all fresh cycles
IVF/ICSI-cycles	70% of all fresh cycles
Cryo-cycles	34% of all cycles
Mean pregnancy rate	27.3%/cycle
Miscarriage rate	19.5%/cycle
Stillbirth rate	0.4%/birth
Ectopic pregnancy rate	2.2%/cycle

[a]Significant difference between the subgroups.

Figure 3 shows the CLBR according to the number of transferred embryos. Except for women over 40 years of age, an overall CLBR of ~50% was reached after the cumulative transfer of six embryos, in two or up to six cycles.

There was no statistical significant difference in the overall CLBR between the IVF and ICSI groups, when all ages were considered. However, when women over 35 and up to 40 were examined separately, ICSI was the more favourable option ($P = 0.002$ for CPR and $P = 0.0040$ for CLBR).

Cumulative pregnancy rates

The overall ongoing CPRs were 79% after 6 cycles (approximate 95% CI: 77–82%), 91% after 12 cycles (approximate 95% CI: 88–95%) and 100% after 18 treatment cycles.

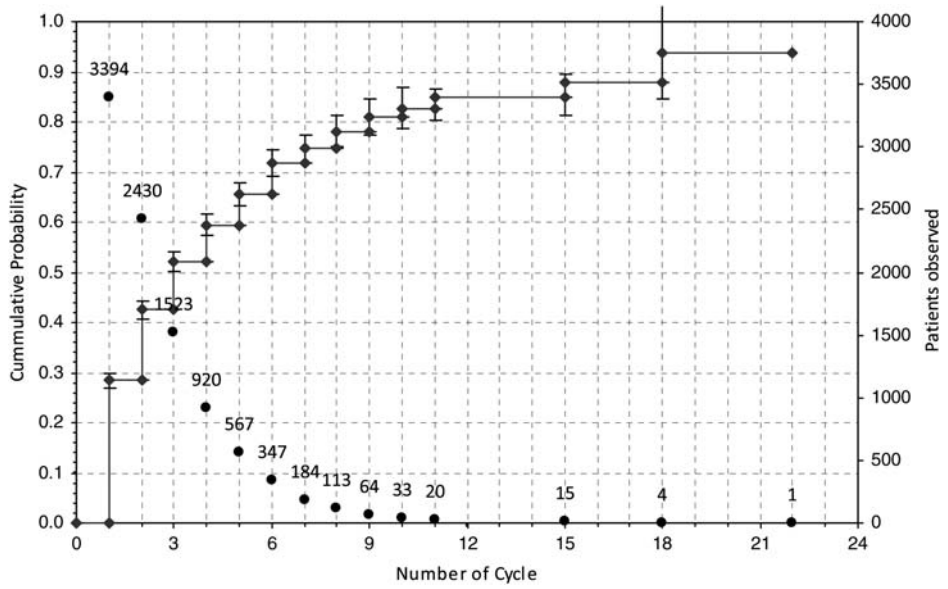

Figure 1 Overall CLBR (means ± 2 standard errors to give the 95% region) for all patients and age classes over the number of treatment cycles. For each cycle, the number of 'patients observed' up to this time is given.

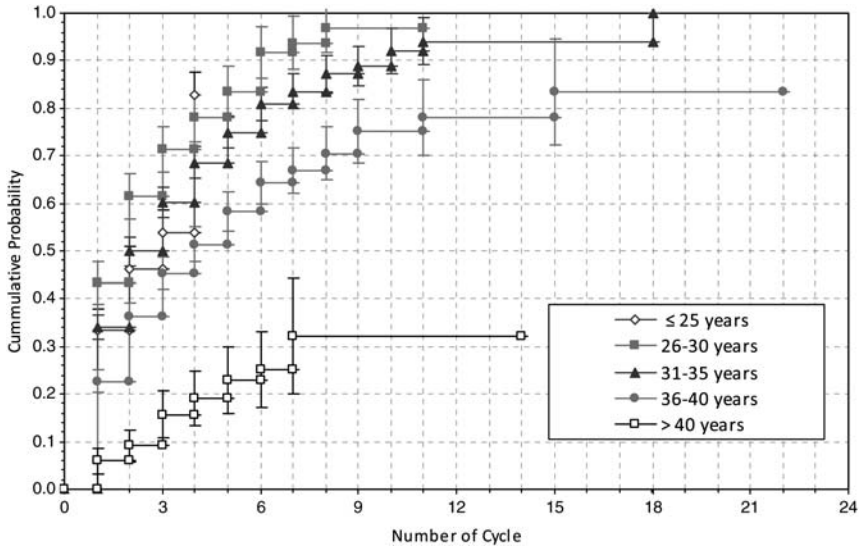

Figure 2 CLBRs (means ± 2 standard errors to give the 95% region) for all patients stratified for the different age groups.

Pregnancy and LBRs out of one fresh cycle and its cryo-cycles

The mean ongoing PR (not estimated) from one fresh cycle and its subsequent cryo-cycle(s) (therapy sequence) was 41%, 39% in the IVF group and 42% in the IVF/ICSI group. Women in their 30s were the biggest group seeking ART (74% of all women), and for this group the PR from one fresh cycles and its cryo-cycles was 43%. There was no difference in outcome between IVF and ICSI per therapy sequence.

The mean LBR (not estimated) out of one fresh cycle and its subsequent cryo-cycle(s) was 33%, 31% in the IVF group and 34% in the ICSI group. For women in their 30s, the mean LBR from one fresh cycle and its cryo-cycles was 34%. Again there was no statistically significant difference between IVF and ICSI per therapy sequence.

A maximum of four pregnancies and maximum of three live births occurred from one therapy sequence of one fresh cycle and its subsequent cryo-cycles.

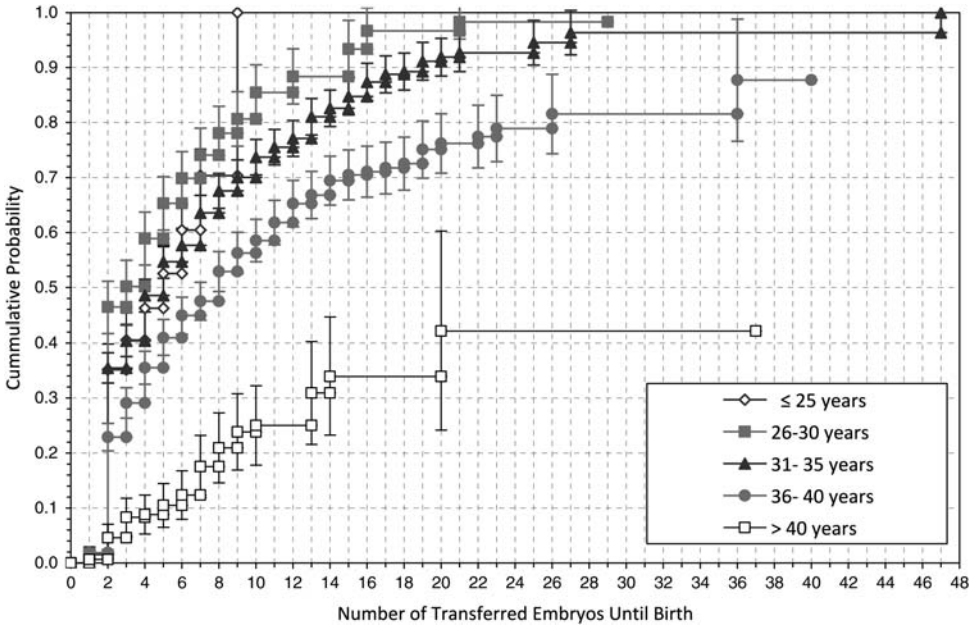

Figure 3 CLBRs (means ± 2 standard errors to give the 95% region) for all patients stratified for the different age groups over the number of transferred embryos.

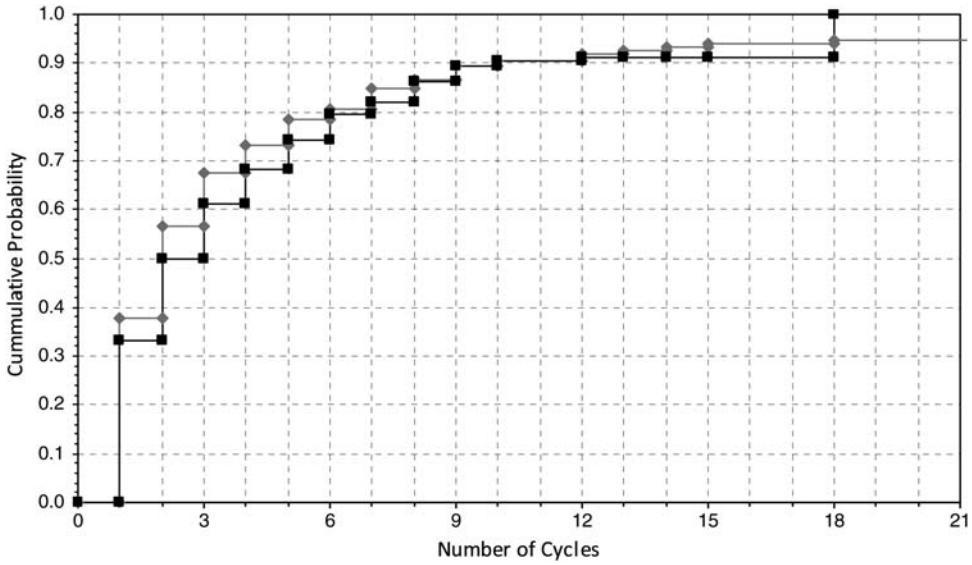

Figure 4 CPRs after ART (squares, 3394 patients) and CPRs in natural cycles [(Gnoth *et al.*, 2003), diamonds, 340 patients].

CPRs after ART and in natural cycles after spontaneous conception

When plotting our data of CPR after ART into the graph of CPR in natural cycles from our 'Time to pregnancy-study' (Gnoth *et al.*, 2003), the curve shapes were found to be nearly congruent (Fig. 4).

Discussion

A total of 3011 individual women who had treatment between 1998 and 2007 were included in our survey and 2068 children were born. Women already with a live birth re-entered the analysis as new 'patients under observation'. Our overall CLBR in 3394 'patients under observation' with 8048 cycles were 52% after 3 cycles

(median number of cycles per patient), 72% after 6 cycles, 85% after 12 and 94% after 18 treatment cycles. The mean, not estimated, LBR from one fresh cycle and its subsequent cryo-cycle(s) was 33%. Therefore, as previously noted (Damario *et al.*, 2000), cryopreservation of PN stage oocytes is an effective treatment strategy that optimizes the final results from one oocyte retrieval. Provided patients continue with treatment, the likelihood of success is high as shown by Kaplan–Meier figures. Obviously, during infertility treatment, many women re-evaluate their situation, and our figures are useful to aid their decisions on whether to continue with treatment, on the number of future cycles and on the number of embryos to be transferred the next time. This is important in cases in which only one embryo is intended or probably only available for the next transfer.

In this study, we did not classify patients or cycles according to the different causes of infertility because even recent studies have shown that CLBR do not vary substantially with the indication for ART (Dor *et al.*, 1996; Lintsen *et al.*, 2007, 2010).

With the use of the Kaplan–Meier method, which censors data for patients who did not return for further treatment for any reasons, we assume that those women would have had the same chance of a live birth by treatment as those who continued. This approach is a matter of contention as some authors have suggested it as possibly too optimistic (Stolwijk *et al.*, 1996, 2000; Sharma *et al.*, 2002) because of the possible early dropout of women with a poor prognosis and no realistic chance of a pregnancy or a live birth in subsequent treatment cycles (Hendriks *et al.*, 2008). So a rigorous pessimistic approach assumes that women, who did not return for further treatment, have a zero chance for achieving a pregnancy. On the other hand, patients with a poor prognosis might be more inclined to continue treatment if this seems to be the only chance of success (Roest *et al.*, 1998) resulting in an underestimation of real CPR and CLBR.

There are many factors that can result in such over- or underestimation of cumulative success rates if the reasons for dropout are not taken into account (Verberg *et al.*, 2008) although patients' true dropout reasons mostly remain unknown. The 'methodological' bias is mainly influenced by treatment strategy and counselling (Verberg *et al.*, 2008). So, the realistic CLBR lies in between the two extremes but may be closer to the optimistic assumption as natural conceptions do occur in women who have ceased ART. A study by Verhagen *et al.* (2008) found the PR in patients who were advised to stop treatment because of a medical indication (repeated fertilization failure after ICSI or very poor ovarian response), yet continued treatment, to be 14%. So, selective dropout of patients with poor treatment prognosis does not necessarily disadvantage our assumptions as it depends on the centre's treatment strategy and the population studied (Roest *et al.*, 1998; Schroder *et al.*, 2004). In case of a negative pregnancy test, patients with a good prognosis are generally encouraged to continue treatment. However, also in cases of doubtful prognosis, patients may be advised to go for further treatment cycles as the only reasonable way to achieve success (Croucher *et al.*, 1998; Klinkert *et al.*, 2004). Of course, this decision purely depends on the wishes of the couple. Another important aspect is the existence of alternatives for couples with a poor prognosis, e.g. oocyte donation, which is prohibited in Germany. As long as one, at least moderately developed embryo was present on the day of transfer, we encouraged patients to continue treatment in case of a negative test. So in this study, towards the higher number of treatment cycles, we may have an accumulation of patients with limited prognosis reducing the overestimation bias.

Our CPR and CLBR could also be biased because some couples, even with good prognosis, probably did not return for further treatment after unsuccessful cycles because of financial reasons. Before 2004, four cycles were fully reimbursed, but then legislation required couples to privately fund half the cost of ART, resulting in a massive drop in procedures conducted from 2003 to 2004 and beyond (yearbooks of the German IVF Index on www.deutsches-ivf-register.de). The mean maternal age and the mean number of cycles per 'patient under observation' who did not conceive increased significantly after 2003 in our study, reducing overestimation failures. However, the median number of treatment cycles remained unchanged with three cycles per 'patient under observation' before 2004 and beyond. The overall ART success rates were not affected by this policy change, which was proved by usual, continuous cross-sectional statistics and separate calculations of CLBR before and after 2004.

Women with a live birth re-entering the study for a next child were included as 'new patients under observation' in all estimations of CLBRs and CPRs. We are aware of this minimal lack of independence in censoring by re-entering individual women as new patients after a live birth. Re-entry of patients is not a problem in usual survival analysis (e.g. survival of cancer patients) but there is an inherited bias in cumulative ART success rates, which is not discussed in most success studies. In this study, the proportion of re-entries in 'patients under observation' is relatively low. However, this still might result in overestimation of cumulative ART success rates (Molloy *et al.*, 1995), though only with a significant effect on the first two cycles (Stolwijk *et al.*, 2000). Based on our experiences with the calculation of CPR in natural cycles, this bias of re-entry is very small because of the long child spacing in our population (Gnoth *et al.*, 2003). Therefore, CLBR and CPR did not differ whether re-entry was allowed or not. Allowing re-entry in the analysis best reflects the real situation in treatment and counselling of couples.

Some of our couples changed to another IVF centre, a practice also recorded in the national index where our patient's migration is around 7%. Therefore, for ~3–4% of our patients, their 'first cycle' in our centre may already be their cycle two or three, further reducing the overestimation bias just mentioned.

In exactly 4% of all fresh cycles with supernumerous PN stage oocytes, they were not cryopreserved, but discarded, mainly because of financial reasons of the couple. Therefore, the mean PR and LBR out of one fresh cycle are slightly underestimated as well.

An important strength of this survey is consistency in that the centre's treatment policy remained nearly unchanged throughout the entire survey with the same team of reproductive specialists and the same responsible embryologists. Treatment methods did not change substantially either in the entire survey except for a continuous increase in the proportion of ICSI cycles. Over time, antagonists were introduced, laser-assisted hatching was offered and recently polar body biopsy, spindle view and zona imaging has been added to the repertoire of methods. Quarterly, cross-sectional statistics showed a slight increase in clinical PRs per transfer over the years, which was not tested for significance and was not attributed to new methods or drugs yet.

For all the reasons above, we assume that the inherited methodological overestimation bias in our study is relatively small but it cannot

be assessed exactly. Possibly, the slightly optimistic success rates best reflect counselling situations: the couple's future chances of live birth is based on the rates of those who continued in the past.

Recently, single centre CLBRs were published by Malizia *et al.* from the Waltham-IVF centre, Boston/USA (Malizia *et al.*, 2009). Compared with their optimistic assumptions, our CLBR after six cycles is the same: 72%. This is very interesting, because of completely different treatment strategies in both IVF centres. According to the German Embryo Protection Law, it is not allowed to culture more PN stage oocytes than the embryos which are to be transferred later in that cycle. Therefore, embryo selection as performed by this and many other foreign centres probably with prolonged cell-culture is not possible here. We strictly cryopreserved all supernumerous PN stage oocytes for later cryo-cycles. Embryos were cryopreserved only in very rare cases for emergency reasons. Obviously, completely different treatment strategies may lead to the same results: a CLBR of 72% after six treatment cycles. Just for patients over 40 years of age, we achieved a lower CLBR presumably because of study cohort differences, as there was a high proportion of women over 40 entering the IVF programme but then turning to oocyte donation early in Waltham.

The congruent CPR after ART and CPR in natural cycles (Gnoth *et al.*, 2003) (Fig. 4) are in line with recently published simulation models (Stanford *et al.*, 2010) and provide reliable experimental evidence as support, because of the same methodological approaches in both of our studies. This strongly suggests that ART can reach natural fertility rates but cannot exceed them.

Most of the patients in this study did not undergo many treatment cycles (mean 2.7; median 3 with a CLBR of ~50%)—even those with reasonable good prognosis for final success—because they probably could not afford the emotional or financial cost independent of the reimbursement. However, from the medical point of view, there is no reason for generally restricting the number of cycles e.g. to three, as done in Germany.

It was our intention to calculate final success rates for live birth to facilitate counselling of couples with infertility problems and to highlight the potential of ART even under rigorous restrictions by law. In this respect, it is important to emphasize again that reproductive medicine can be successful for most couples if they continue treatment.

Authors' roles

C.G. played a role in study design, running of the cycles, statistical analysis and writing the manuscript. B.M. took part in raw data collection and quality checking. T.S. was involved in raw data preparation, statistical analysis and proofreading. K.F. and J.T. were involved in study design, running the cycles and proofreading. E.G. took part in statistical mentoring, performing the final statistical analysis and writing the manuscript.

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References

Bar-Hava I, Orvieto R, Ferber A, Ashkenazi J, Dicker D, Ben-Rafael Z. Standard *in vitro* fertilization or intracytoplasmic sperm injection in advanced female age—what may be expected? *Gynecol Endocrinol* 1999;**13**:93–97.

Bergh C, Werner C, Nilsson L, Hamberger L. Cumulative birth rates following cryopreservation of all embryos in stimulated *in vitro* fertilization (IVF) cycles. *J Assist Reprod Genet* 1995;**12**:191–194.

Croucher CA, Lass A, Margara R, Winston RM. Predictive value of the results of a first *in-vitro* fertilization cycle on the outcome of subsequent cycles. *Hum Reprod* 1998;**13**:403–408.

Damario MA, Hammitt DG, Session DR, Dumesic DA. Embryo cryopreservation at the ' stage and efficient embryo use optimizes the chance for a liveborn infant from a single oocyte retrieval. *Fertil Steril* 2000;**73**:767–773.

Dor J, Seidman DS, Ben-Shlomo I, Levran D, Ben-Rafael Z, Mashiach S. Cumulative pregnancy rate following *in-vitro* fertilization: the significance of age and infertility aetiology. *Hum Reprod* 1996; **11**:425–428.

Gelbaya TA, Tsoumpou I, Nardo LG. The likelihood of live birth and multiple birth after single versus double embryo transfer at the cleavage stage: a systematic review and meta-analysis. *Fertil Steril* 2010;**94**:936–945.

Gnoth C, Frank-Herrmann P, Freundl G, Godehardt D, Godehardt E. Time to pregnancy: results of the German prospective study and impact on the management of infertility. *Hum Reprod* 2003; **18**:1959–1966.

Gnoth C, Godehardt E, Frank-Herrmann P, Friol K, Tigges J, Freundl G. Definition and prevalence of subfertility and infertility. *Hum Reprod* 2005;**20**:1144–1147.

Gnoth C, Schuring AN, Friol K, Tigges J, Mallmann P, Godehardt E. Relevance of anti-Mullerian hormone measurement in a routine IVF program. *Hum Reprod* 2008;**23**:1359–1365.

Hendriks DJ, te Velde ER, Looman CW, Bancsi LF, Broekmans FJ. Expected poor ovarian response in predicting cumulative pregnancy rates: a powerful tool. *Reprod Biomed Online* 2008;**17**:727–736.

Hull MG. Effectiveness of infertility treatments: choice and comparative analysis. *Int J Gynaecol Obstet* 1994;**47**:99–108.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958;**53**:457–481.

Klinkert ER, Broekmans FJ, Looman CW, te Velde ER. A poor response in the first *in vitro* fertilization cycle is not necessarily related to a poor prognosis in subsequent cycles. *Fertil Steril* 2004;**81**:1247–1253.

Klipstein S, Regan M, Ryley DA, Goldman MB, Alper MM, Reindollar RH. One last chance for pregnancy: a review of 2705 *in vitro* fertilization cycles initiated in women age 40 years and above. *Fertil Steril* 2005; **84**:435–445.

Kovacs GT, Maclachlan V, Brehny S. What is the probability of conception for couples entering an IVF program? *Aust N Z J Obstet Gynaecol* 2001; **41**:207–209.

Lass A, Croucher C, Duffy S, Dawson K, Margara R, Winston RM. One thousand initiated cycles of *in vitro* fertilization in women ≥ 40 years of age. *Fertil Steril* 1998;**70**:1030–1034.

Lintsen AM, Braat DD, Habbema JD, Kremer JA, Eijkemans MJ. Can differences in IVF success rates between centres be explained by patient characteristics and sample size? *Hum Reprod* 2010; **25**:110–117.

Lintsen AM, Eijkemans MJ, Hunault CC, Bouwmans CA, Hakkaart L, Habbema JD, Braat DD. Predicting ongoing pregnancy chances after IVF and ICSI: a national prospective study. *Hum Reprod* 2007; **22**:2455–2462.

Lundin K, Bergh C. Cumulative impact of adding frozen-thawed cycles to single versus double fresh embryo transfers. *Reprod Biomed Online* 2007; **15**:76–82.

Malizia BA, Hacker MR, Penzias AS. Cumulative live birth rates after *in vitro* fertilization. *N Engl J Med* 2009;**360**:236–243.

Molloy D, Doody ML, Breen T. Second time around: a study of patients seeking second assisted reproduction pregnancies. *Fertil Steril* 1995; **64**:546–551.

Moragianni VA, Penzias AS. Cumulative live birth rates after assisted reproductive technology. *Curr Opin Obstet Gynecol* 2010;**22**:189–192.

Olivius K, Friden B, Lundin K, Bergh C. Cumulative probability of live birth after three *in vitro* fertilization/intracytoplasmic sperm injection cycles. *Fertil Steril* 2002;**77**:505–510.

Osmanagaoglu K, Tournaye H, Camus M, Vandervorst M, Van SA, Devroey P. Cumulative delivery rates after intracytoplasmic sperm injection: 5 year follow-up of 498 patients. *Hum Reprod* 1999; **14**:2651–2655.

Pelinck MJ, Knol HM, Vogel NE, Arts EG, Simons AH, Heineman MJ, Hoek A. Cumulative pregnancy rates after sequential treatment with modified natural cycle IVF followed by IVF with controlled ovarian stimulation. *Hum Reprod* 2008;**23**:1808–1814.

Roest J, van Heusden AM, Zeilmaker GH, Verhoeff A. Cumulative pregnancy rates and selective drop-out of patients in *in-vitro* fertilization treatment. *Hum Reprod* 1998;**13**:339–341.

Schroder AK, Katalinic A, Diedrich K, Ludwig M. Cumulative pregnancy rates and drop-out rates in a German IVF programme: 4102 cycles in 2130 patients. *Reprod Biomed Online* 2004;**8**:600–606.

Sharma V, Allgar V, Rajkhowa M. Factors influencing the cumulative conception rate and discontinuation of *in vitro* fertilization treatment for infertility. *Fertil Steril* 2002;**78**:40–46.

Stanford JB, Mikolajczyk RT, Lynch CD, Simonsen SE. Cumulative pregnancy probabilities among couples with subfertility: effects of varying treatments. *Fertil Steril* 2010;**93**:2175–2181.

Stolwijk AM, Hamilton CJ, Hollanders JM, Bastiaans LA, Zielhuis GA. A more realistic approach to the cumulative pregnancy rate after *in-vitro* fertilization. *Hum Reprod* 1996;**11**:660–663.

Stolwijk AM, Wetzels AM, Braat DD. Cumulative probability of achieving an ongoing pregnancy after *in-vitro* fertilization and intracytoplasmic sperm injection according to a woman's age, subfertility diag-nosis and primary or secondary subfertility. *Hum Reprod* 2000;**15**:203–209.

Sundstrom P, Saldeen P. Cumulative delivery rate in an *in vitro* fertilization program with a single embryo transfer policy. *Acta Obstet Gynecol Scand* 2009;**88**:700–706.

Tan SL, Royston P, Campbell S, Jacobs HS, Betts J, Mason B, Edwards RG. Cumulative conception and livebirth rates after *in-vitro* fertilisation. *Lancet* 1992;**339**:1390–1394.

Ubaldi F, Rienzi L, Baroni E, Ferrero S, Iacobelli M, Minasi MG, Sapienza F, Martinez F, Anniballo R, Cobellis L *et al.* Cumulative pregnancy rates after transfer of fresh and thawed embryos. *Eur J Obstet Gynecol Reprod Biol* 2004;**115**(Suppl 1):S106–S109.

Verberg MF, Eijkemans MJ, Heijnen EM, Broekmans FJ, de KC, Fauser BC, Macklon NS. Why do couples drop-out from IVF treatment? A prospective cohort study. *Hum Reprod* 2008;**23**:2050–2055.

Verhagen TE, Dumoulin JC, Evers JL, Land JA. What is the most accurate estimate of pregnancy rates in IVF dropouts? *Hum Reprod* 2008; **23**:1793–1799.