

# Possible Reasons for Discontinuation of Therapy: an Analysis of 571 071 Treatment Cycles From the German IVF Registry

## Mögliche Gründe für einen Therapieabbruch: eine Analyse von 571 071 Behandlungszyklen aus dem Deutschen IVF-Register



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discontinuation of therapy, IVF, ICSI, German IVF Registry

### Schlüsselwörter

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### ABSTRACT

**Introduction** Numerous couples discontinue fertility treatment before achieving the objective, the birth of a child. The aim of this retrospective data analysis is to identify the reasons for early discontinuation of therapy (drop-out).

**Materials and Methods** Retrospective data analysis. With the aid of the German IVF Registry (D-I-R<sup>®</sup>), a total of 122 560 “last cycles” in Germany in the period 2012–2015 were identified and the courses were analysed.

**Results** From the named cohort of “last cycles”, 37.3% of the female patients (45 699) gave birth to a child and ended the therapy. The remaining 76 861 discontinued the treatment before having a child. The fertility treatment was conducted due to a purely male indication in 46.27% of cases and in 17.96% the cause lay exclusively with the woman. 4.53% of the drop-outs suffered a miscarriage in the last cycle. 73.56% of the drop-out patients ended the therapy after the lack of a positive pregnancy test. After the third therapy cycle, 67% of the couples ended their treatment.

**Conclusion** The results make it possible to provide couples with individual counselling. They offer an option for preparing for the emotional and physical hurdles.

### ZUSAMMENFASSUNG

**Einleitung** Zahlreiche Paare brechen die Sterilitätsbehandlung vor Erreichen des Ziels, der Geburt eines Kindes, ab. Ziel dieser retrospektiven Datenanalyse ist es, die Gründe für den vorzeitigen Therapieabbruch (Drop-out) zu erkennen.

**Material und Methoden** Retrospektive Datenanalyse. Mit Hilfe des Deutschen IVF-Registers (D-I-R<sup>®</sup>) wurden im Zeitraum 2012–2015 insgesamt 122 560 „letzte Zyklen“ in Deutschland herausgearbeitet und die Verläufe analysiert.

**Ergebnisse** Aus der genannten Kohorte der „letzten Zyklen“ gebaren 37,3% der Patientinnen (45 699) ein Kind und beendeten die Therapie. Die verbliebenen 76 861 brachen die Behandlung vor Erfüllung des Kinderwunschs ab. Die Fertilitäts-

behandlung wurde in 46,27% der Fälle aufgrund einer rein männlichen Indikation durchgeführt und in 17,96% fand sich eine Ursache ausschließlich bei der Frau. 4,53% der Drop-outs erlitten im letzten Zyklus eine Fehlgeburt. 73,56% der Drop-out-Patientinnen beendeten die Therapie nach dem Ausblei-

ben eines positiven Schwangerschaftstests. Nach dem 3. Therapiezyklus beendeten 67% der Paare ihre Behandlung.

**Schlussfolgerung** Die Ergebnisse lassen eine individuelle Beratung der Paare zu. Sie bieten eine Möglichkeit, auf emotionale und körperliche Hürden vorzubereiten.

## Introduction

The outcome of a reproductive medical treatment cycle can vary:

- Therapy can be discontinued during the hormonal stimulation treatment because the patient does not react adequately to the hormone treatment.
- During retrieval of egg cells it is possible that either no egg cell can be obtained or that all egg cells obtained do not have the corresponding degree of maturity (metaphase II) for further treatment.
- After in-vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) is performed, it is possible that none of the treated egg cells is normally fertilised (2-pronuclei stage).
- During the in-vitro culture, there can be developmental arrest of all cultivated embryos or the patient develops signs of ovarian hyperstimulation syndrome (OHSS) such that no embryo transfer can take place.
- After the transfer of the embryo(s), there either is a pregnancy or no pregnancy.
- After a pregnancy occurs, there is either a miscarriage or the birth of a child.

The German IVF registry (D-I-R)<sup>®</sup> was founded in 1982 – nine years after the birth of the first person born following in-vitro fertilisation and six years after the birth of the first IVF child in Germany – from the reproductive medicine working groups which then existed and which were all still academic institutions at that time. The fact that these working groups, at a time when there were still no legal regulations, saw the need for central data collection and evaluation and undertook this work of their own accord cannot be appreciated enough. Since this time, the D-I-R has not been only a voluntary, intrinsically motivated instrument of medical quality insurance and improvement but, with more than 1.9 million documented treatment cycles (status as of mid 2018), it is also the largest data collection of treatments performed in the field of assisted reproduction in Germany. In 2016 alone, 103 981 treatment cycles in Germany were documented in the D-I-R. Nearly all of the 135 D-I-R member centres who in turn represent nearly all infertility centres in Germany contribute to data collection by reporting their treatment cycles [1].

The success of reproductive medical treatment can also be defined in different ways: for the attending reproductive medicine physicians and biologists, it is often a success if morphologically ideal embryos are available for embryo transfer, and only the birth of a child is a success for the couple wanting a child.

In Germany, the average probability of leaving the hospital with a child following reproductive medical treatment (baby-take-home rate) in 2015 was 24% following the transfer of a fresh embryo and 17% following the transfer of an embryo which was

thawed after intermediate cryopreservation in the pronuclear stage or division stage and transferred [1]. These probabilities have fortunately increased nationally as well as internationally in recent years [1, 2]. In Great Britain, for example, the live birth rate in 1991 was 14%; in 2000 it was 22% [3]. After a total of three complete IVF (and ICSI) cycles, an analysis of the Human Fertilisation and Embryology Authority registry (HFEA) demonstrated a cumulative live birth rate of 30.8% (for the years 1992–1998) to 42.3% (for the years 1999–2007) [4].

In western industrialised nations, the prevalence of infertility is 17–26%, and only about half of the affected couples utilise reproductive medical treatment [5]. The use of reproductive medical treatment depends on many factors. The change in section 27a of the Social Security Statute Book V (SGB V) in 2004 within the scope of the Health System Modernisation Act (GMG) led, for example, to a decrease in the treatment cycles by more than 50%, since for couples covered by the statutory insurance scheme, only 50% of the treatment costs are paid by the health insurance funds. As a result of this, approximately 10 000 fewer children were born in the following year in Germany after reproductive medicine treatment than before the GMG. Nonetheless the treatment figures have continually increased since then, also because of the continued high psychological strain on couples.

It appears that the likelihood of pregnancy – independent of the woman's age – is the highest in the first IVF or ICSI treatment cycle [6]. Further treatments of course increase the chance of pregnancy [6, 7]. The cumulative likelihood of pregnancy after four treatment cycles is indicated as being between 54 and 75% [3, 4, 8, 9]. For this reason, couples should be encouraged to undergo at least four treatment cycles to fully utilise their reproductive potential. This argument is supported by the prediction models of McLernon and Leijdekkers which predict the individual probabilities for the live birth rate in the case of IVF/ICSI treatments using past history parameters on the basis of registry data from HFEA [4, 10]. However, the international data show that this is often not the case: in England, 30% of couples ended treatment after only one treatment cycle [7]. In Sweden, 65% of couples ended reproductive medical treatment without a child even before utilising the three treatment cycles covered by the health system there at the time of the investigation [11]. The reasons for these (excessively) early therapy discontinuations were discussed in detail and financial aspects appear to be primarily responsible for this [12]. Other authors cited the disappointment over an unsuccessful treatment and the psychological pressure following an unsuccessful therapy cycle as reasons for the discontinuation of treatment [13]. This assumption is supported by data from Australia where an average of three treatment cycles are utilised, although up to six cycles are supported by the state [14].

► **Table 1** Treatment result after the “last therapy cycle”. This includes, for information, the number of patients who do not meet the drop-out criteria in the analysis period (still pregnant or still in treatment at the time of analysis).

Treatment result	Treatment phase	Number of patients	Percentage
Birth	Drop-out	45 699	37.3%
No birth	Drop-out	76 861	62.7%
Sum of drop-outs		122 560	100%
Ongoing pregnancy	Still in treatment	583	
No birth	Still in treatment	44 721	

It is clear that infertility as well as the reproductive medical treatment have an influence on the psychosocial circumstances of the couple. The couples describe a loss of control, tension to the point of depression and often feel stigmatised; furthermore the couple's relationship may suffer. All of this affects women as well as men [5, 15–21]. The symptoms described worsen with the frequency of unsuccessful treatment cycles.

In this study, we analysed 122 560 last therapy cycles documented in the German IVF Registry from four treatment years for possible events which could explain the discontinuation of the therapy in order to identify these and develop possible strategies to be able to counteract a discontinuation of therapy which is premature from a medical standpoint. The population of 122 560 patients is composed of those who were undergoing treatment as of 2010 and who were on the one hand treated in 2012–2015 and who had the last treatment in 2012–2015, thus who were no longer being treated in 2016.

## Materials and Methods

In this study, we conducted a retrospective data analysis on a patient cohort from the German IVF Registry.

### Data collection by the D-I-R

In the German IVF Registry, all treatment courses and results of reproductive medical treatments performed in Germany were compiled. It serves as information and transparency on the scope and success of reproductive medical measures. The primary objective is to ensure the quality of treatment of IVF patients in Germany. 96% (128 out of 134) of the fertility clinics in Germany, independent of whether they are privately or publicly operated, report their data voluntarily to the registry. The patient data are pseudonymised and the information is transmitted via software after each cycle. By selecting a pseudonym, double documentation is excluded even if the patient switches clinics. It is ensured that patients are followed up in this way until the calculated delivery date of the child.

### Definition of the patient cohort

The cohort analysed here contains 122 560 patients with a “last therapy cycle”. These were identified as follows: all cycles in the period 2010–2016 were considered, independent of whether it is

the first or the x-th cycle. A drop-out patient was defined as follows:

Patients who were in treatment between 2010 and 2016 (thus all analysed patients): 215 720

- minus patients who had their last treatment in 2010 and 2011/ no longer appeared as of 2012: 85 856
- minus patients who reappeared in 2016, thus in 2012–2015 did not have the last treatment: 45 304

This yields the number of patients in treatment as of 2010 who had the last treatment in 2012–2015: 122 560.

In doing so, we took fresh IVF and ICSI cycles as well as cryocycles into account. The observation period covers 2010–2016. The first drop-outs were seen in 2012, and thus the evaluation period was begun in 2012 and continued until the end of 2015. Patients who started treatment in 2016 were excluded from further analysis since they were not able to meet the preconditions for definition as a drop-out. In a period of six years (between 2010 and 2016), a total number of 571 071 cycles of 215 720 patients were documented in the German IVF registry. The number of patients with “last therapy cycles” between 2012 and the end of 2015 was 122 560.

The patients ranged in age from 18 to 49 years. The average age was 35.57 years. The median age is 36 years.

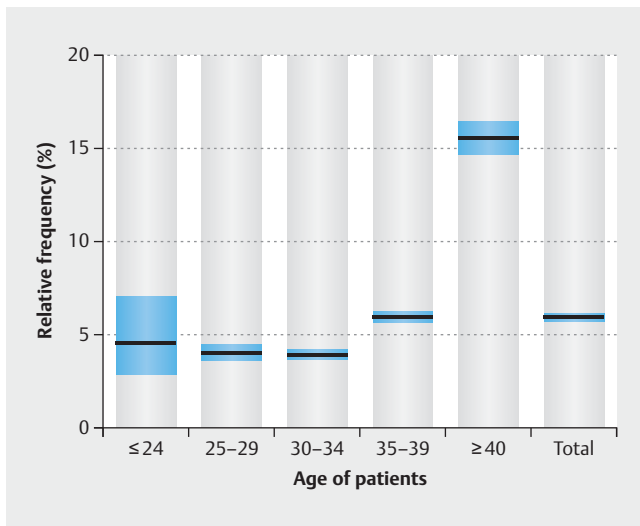
The data collection and the statistical analysis were performed using R. The results were recorded as raw data and also as percentages. 95% confidence intervals (CGI) were used.

### Ethical aspects

The collected data were saved in compliance with the applicable data processing regulations. The retrospective analysis was supported by Merck Pharmaceuticals with an unrestricted educational grant.

## Results

Of the 122 560 patients included, 45 699 patients had a successful treatment: They not only achieved a pregnancy but had a living child after the 24th week of pregnancy. This cohort is not incorporated in the data analysis of the study. The remaining 76 861 patients discontinued IVF treatment without reaching their initial objective – the birth of a living child (► **Table 1**). We identified



► **Fig. 1** Age-adjusted drop-out rate (percentage) after suffering a miscarriage. The mean values (black line) are shown with the confidence interval (blue box).

the reasons for the premature end by analysing the last treatment cycle in each case of these drop-out patients.

The fertility treatment was conducted in 46.27% of cases due to a male indication and in 17.96% of cases, the cause lay with the woman. In 21.23%, both partners had an indication for fertility treatment and in 8.6% of cases, the cause of the infertility could not be clarified. The main reason for men to start fertility treatment was reduced male fertility in terms of an abnormal spermogram according to WHO criteria (77.13%). The causes on the part of women were either unknown (47.56%), tubal pathology (21.76%), irregular cycles (15.98%; without PCOS and/or hyperandrogenemia), endometriosis (15.97%), PCOS and hyperandrogenemia (10.32%), uterine and cervical pathology (5.17%) and psychological disorders (0.36%).

A statistical analysis of the stimulation result in the group of unsuccessful drop-outs with consideration of a possible result of pregnancy was performed (► **Table 2**):

The majority of the drop-out patients ended the therapy in the course of the IVF treatment after failure to achieve pregnancy

(73.56%). In another 10.39% of the drop-out patients, no embryo transfer could take place and 4.53% suffered a miscarriage. In the age-adjusted group of women over 40 years of age, the percentage of patients who ended treatment after a miscarriage increased to 15% (► **Fig. 1**).

### Duration of treatment until discontinuation of the therapy

The majority of the drop-out patients (68.5%) discontinued the therapy within the first year after the start of treatment. 13.5% of all drop-outs ended the therapy after one to two years of unsuccessful treatment and 18% of all drop-outs were treated for 2–6 years.

### Number of completed treatment cycles until discontinuation of therapy

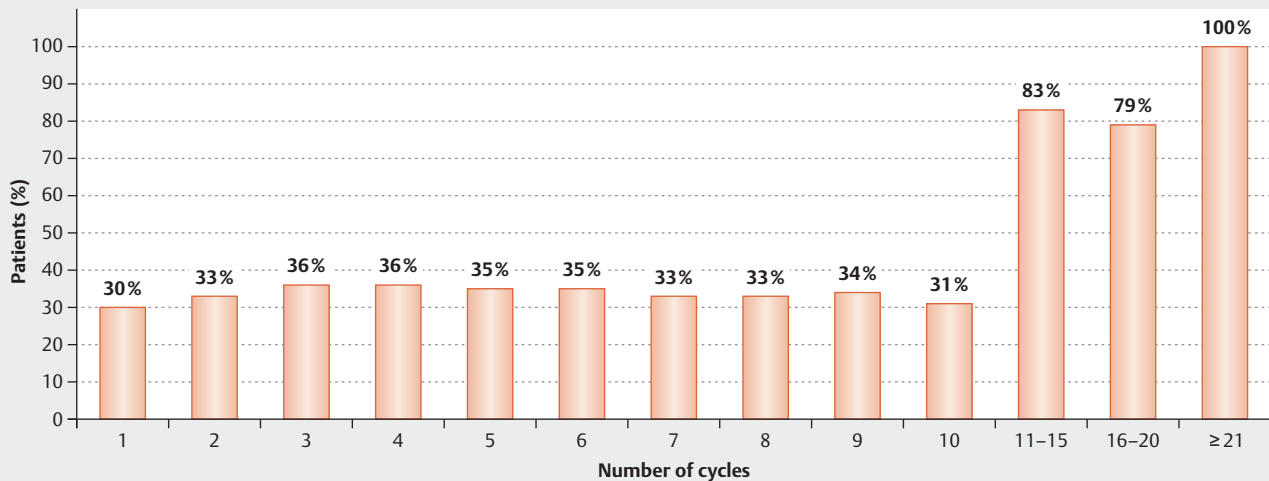
The percentage of patients who end treatment independent of the result (thus with and without a live birth) after each cycle varies between the treatment cycles. It varies between 30% after the first cycle, 36% after the fourth cycle and 31% in the tenth cycle (► **Fig. 2**).

The analysis of every cycle showed that 26% of the patients who ended their treatment between 2012–2015 and who did not become pregnant in the first cycle ended their treatment after this first therapy cycle. By contrast, the remaining 72% of all drop-out patients underwent an additional treatment cycle. After the second unsuccessful cycle, another 23% of the drop-out cohort ended the treatment. After three unsuccessful cycles, the cumulative drop-out figure is 67% (► **Table 3**). According to this, the birth rate per cycle was shown to be 14% for the first cycle, 12% for the second cycle and again 12% for the third cycle. The subsequent cycles show a constant birth rate of 9–11% up to the tenth cycle (► **Table 3**).

On the basis of the entire cohort of unsuccessful patients in the years 2010–2016, 25% discontinued their treatment after the first unsuccessful treatment cycle. Another 29% of the entire cohort ended treatment after the second therapy cycle. This means that more than half of all therapy discontinuations occurred before the third treatment. It is also interesting to observe that the drop-out rate fluctuated between 30–36% up to the 10th cycle (► **Table 3**).

► **Table 2** Therapy results of the drop-out patients.

	Number of patients	Percentage
Discontinuation of the stimulation	2400	3.12%
No embryo transfer	7989	10.39%
Negative pregnancy test (following transfer)	56541	73.56%
Miscarriage	3484	4.53%
Extrauterine pregnancy (EUP)	211	0.27%
Lost to follow up	6236	8.11%
Total number of drop-outs without live birth of a child	76861	100%



► **Fig. 2** Patients (with and without live birth) who end the therapy as percentage of all patients treated in this cycle.

► **Table 3** Discontinuation and success rates listed according to cycle number.

Number of cycles	Total	1	2	3	4	5	6	7
Number of patients	122 560	122 560	85 708	57 660	36 978	23 675	15 399	9 972
Number of drop-outs, total	122 560	36 852	28 048	20 682	13 303	8 276	5 427	3 319
Live birth rate (LBR)		14%	12%	12%	11%	11%	11%	10%
Drop-out (as percentage of all patients of this cycle)		30%	33%	36%	36%	35%	35%	33%
Drop-out with birth	45 699	17 242	10 438	6 731	4 229	2 575	1 643	968
▪ drop-out with birth (as percentage of all drop-outs in the respective cycle)		47%	37%	33%	32%	31%	30%	29%
Drop-out without birth	76 861	19 610	17 610	13 951	9 074	5 701	3 784	2 351
▪ drop-out without birth (as percentage of all patients in the respective cycle)		16%	21%	24%	25%	24%	24%	23%
▪ drop-out without birth (as percentage of all drop-outs in the respective cycle)		53%	63%	67%	68%	69%	70%	71%
▪ drop-outs without birth (as percentage of the sum of all drop-outs, over all cycles)	100%	26%	23%	18%	12%	7%	5%	3%

### Switching clinics in the group of patients discontinuing therapy

As a result of the lack of success of the therapy, couples may wish to switch reproductive medicine centres. In the cohort analysed, this occurred in 8.6% of cases. Another 0.7% of the drop-out patients switched to a third clinic for further therapy. 90.7% of the patients remained at the same clinic throughout the entire duration of therapy.

### Age of the drop-out patients

The success of fertility treatment is heavily influenced by the age of the woman [1]. The highest rate of live births is achieved by women aged 25–29 years. This rate is 31.3% (IVF) and 30.4% (ICSI) (D-I-R yearbook). The rates of pregnancy and live births decrease with increasing age, independent of the means of concep-

tion (spontaneous or assisted) and the method used (IVF or ICSI). In the group of patients aged 30–34 years, the rate of live births is 29.9% (IVF) and 28.9% (ICSI). Among patients aged 35–39 years, the live birth rate eventually decreases to 23.3% (IVF) and 22% (ICSI). In women aged 40 and over, the pregnancy rate decreases to 27.5% after IVF and below 26.3% in the case of ICSI and the live birth rate decreases due to the increasing number of miscarriages to below 15.1% (IVF) and 14% (ICSI). In our analysed cohort, the overwhelming majority (69%) of drop-outs was by patients under age 40.

### Course of therapy as reason for the discontinuation

Increasing frustration during an unsuccessful course of therapy likely contributes to premature discontinuation of therapy. The following courses are seen in the analysed cohort as a possible

trigger: lack of or inadequate stimulation response (non- or low-responder), hyperstimulation syndrome, or other medical reasons (e.g. premature ovulation, incorrect use of the hormone injections). Compared with the drop-out rate following an unremarkable course of therapy, the drop-out rate after prematurely ending the stimulation cycle due to one of the above reasons is three times as high.

### **Lack of embryo transfer as reason for discontinuation of therapy**

Another discouraging reason during the course of therapy could be the surprising lack of embryo transfer. The possible reasons for this are varied: premature progesterone increase during the stimulation phase, lack of egg cell retrieval, immature egg cells, lack of fertilisation, embryo arrest during development in the laboratory or for medical reasons involving the patient (infection, intrauterine fluid collections or threatened OHSS). In our analysed cohort, a lack of embryo transfer was seen in 10% of all drop-out patients in the last cycle.

### **Negative pregnancy test as reason for discontinuation of therapy**

55 000 patients in the drop-out cohort analysed here did not achieve pregnancy in their last cycle. The frustration of these patients following comprehensive therapy and a hopeful waiting period is surely enormous and this could therefore be a possible trigger for the decision to discontinue therapy.

## **Discussion**

The psychological stress of infertility and also the stress caused by the reproductive medical treatment itself are among the most common reasons why IVF therapy is not continued [3, 22, 23]. If pregnancy is achieved and the deeply desired child is ultimately born, previous frustrations and disappointments can be compensated. Ending infertility treatment (too) early, by contrast, can lead to resentment and bitterness. The possible reasons for ending infertility treatment were investigated in various publications. They include: financial, physical and psychological stress, frustration, social problems and partner problems [3, 22–24]. However, these investigations related to comparatively small collectives outside of Germany.

In our investigation, we were not able to identify any possible reasons for ending the therapy in 8.4% of the drop-outs. Here specifically, but also in the case of all other drop-out patients, it can be presumed that psychosocial factors represent a possible reason for ending therapy. People who work in reproductive medicine are very familiar with the emotional stress of infertility and consecutive reproductive medical treatments which weigh on the couples. Couples struggling with infertility suffer from anxiety, depression, isolation, anger and frustration more frequently than those not affected by it [15]. Following unsuccessful treatment, these symptoms significantly increase in frequency and intensity in comparison to the situation before treatment [25]. The couples' resilience can greatly decrease due to the inability to become or remain pregnant.

In Germany – under certain conditions for persons with statutory health insurance – 50% of the costs of treatment for three IVF or ICSI treatments are covered by the health insurance funds. Assuming that the financial burden on couples is a main reason for ending therapy, we would have expected a significant effect after three treatments. In fact, 67% of the couples ended their treatment after the third cycle of therapy without the birth of a child, however 36 978 couples still underwent a fourth and even more treatment cycles. On the other hand, 26% of couples did not continue treatment after the first unsuccessful therapy cycle. This high percentage cannot, in our view, be explained solely by the financial burden.

These different observations on the influence of finance are also proven in other investigations; in one study, couples indicated financial reasons as the main reason for ending therapy [12], in other studies, the highest rate of therapy terminations could be observed even before the financial support offered in the respective countries was exhausted [13, 14, 26].

To be able to better investigate this question in our cohort, a correlation of the drop-out rate with the insurance status would be helpful, but unfortunately these data are not recorded in the D-I-R. However, it can by all means be speculated that whether the couple falls under the benefit prerequisites of the statutory health insurance fund (maximum of three IVF or ICSI cycles) or a private health insurance (funding in the case of a "sufficient chance of success" for more than three IVF or ICSI cycles) could have an influence.

A reason for ending infertility treatment could also be the adverse events during the therapy cycle: discontinuation of the hormonal stimulation, for example, due to insufficient response to egg cell maturation, few or no egg cells retrieved, no possible embryo transfer due to a lack of fertilisation or development arrest of all embryos, negative pregnancy test after transfer, miscarriage or extrauterine pregnancy. All of these factors also contribute to an increase in the psychological stress on couples. In our cohort, in nearly all of the drop-outs, there was no significant cluster of the incidents described, in comparison to the couples who continued their treatment. Only a miscarriage was observed far more frequently in the last therapy cycle performed in women over age 40: the average number of last therapy cycles in which a miscarriage occurred was 5–7% in the overall collective; this figure was 15% in the age group of women over 40.

These cases appear to be particularly burdensome for the couple. Since achieving pregnancy is already a rare feeling of success in this patient group, the early loss of this pregnancy could limit motivation for further treatment and lead to the end of therapy. In 2010, Harris et al. showed that women who became pregnant during IVF treatment and then suffered a miscarriage did not continue the treatment due to a loss of control, grief and anxiety about repeated setbacks [27].

Further reasons for ending treatment could be the number of cycles and repeated negative events in the therapy cycle and thus unsuccessful treatments. In our patient group, this is reflected by the slight increase in the number of drop-outs without a birth as the treatment cycles continue: 30% of the patients end treatment after the first unsuccessful cycle. In the fourth cycle, this figure increases to 36% and is reflected in 31% after the tenth therapy

cycle. In summary, it is not possible here to establish a number of critical cycles after which most patients end their treatment. The cumulative analysis of therapy discontinuations showed that 79% of the early drop-outs occurred within the first four cycles.

In this regard, it appears important to emphasise once again that the birth rate decreases only moderately with the number of treatment cycles. The birth rate after the first cycle is 14% and decreases to 11% after the sixth cycle and to 9% after the tenth therapy cycle. This shows a moderately decreasing chance of a successful pregnancy.

The reliability of these results is based on the large patient cohort on the basis of which the analysis is conducted. The evaluation was performed independent of a particular site in Germany and also independent of various legal conditions or therapy options and thus a realistic image of the situation at German IVF centres can be shown. At the same time, the reappraisal of retrospective data from a registry is vulnerable to errors: selection or manipulation of data during entry by the participants of the registry and inadequate documentation in the case of patients lost to follow-up are the most common points of criticism. Neither source of error can be estimated in retrospective data cohorts, however they should be critically incorporated in the interpretation of the data.

## Conclusion for Clinical Practice

These figures and connections can enter into the couple's continued individual counselling in order to identify realistic possibilities of the course of therapy and prepare the couples for emotional and physical hurdles. In doing so, the only slightly reduced chance of success within the first ten therapy cycles should be brought up, as motivation. A realistic estimate of its success could help couples better withstand the psychologically and physically demanding IVF therapy.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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