Article

# Previous miscarriages influence IVF and intracytoplasmatic sperm injection pregnancy outcome

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## Abstract

Previous conceptions are one predictor for the outcome of assisted reproductive technology procedures. Approximately 18–34% of clinical pregnancies following assisted reproduction procedures result in spontaneous abortion. The risk of such pregnancy loss is believed to increase with women's age, previous miscarriages and use of frozen–thawed embryos. This study analyses German IVF Registry data to examine the impact of previous miscarriages on the outcome of assisted reproduction procedures. The dataset consists of a total of 174,909 assisted reproduction procedures performed between January 1998 and December 2000. Multiple logistic regression is used to assess the correlation between women's age, spousal/partner change, and infertility diagnosis. It is demonstrated that any previous miscarriage will increase the treatment-dependant miscarriage rate in assisted reproduction procedures. A significantly higher impact is shown for one previous miscarriage achieved by assisted reproduction procedures compared with spontaneous conception. Partner change is shown to have no specific impact on the treatment dependant miscarriage rate, whereas a statistically significant increase in miscarriages in all assisted reproduction procedures was found among women older than 34 years of age. Overall, the highest rate of treatment-dependant miscarriages was seen in assisted reproduction procedures with cryopreserved embryo transfer.

***Keywords:*** *IVF outcome, IVF registry, miscarriages, previous conception, reproductive history*

## Introduction

Infertile women who have experience spontaneous single or recurrent abortion will sustain emotional stress (Engelhard *et al.*, 2001). Counselling of subfertile couples should therefore include accurate information about the risk of miscarriage adapted to an individual's reproductive history.

The frequency of loss of clinically recognized pregnancies is reported to be 10% (Gilmore and McNay, 1985). The rate of early pregnancy loss following assisted reproduction procedures is thought to be in the range of 18–34% (Bulletti *et al.*, 1996). Using population-based data of 65,751 assisted reproduction treatments (fresh, non-donor eggs or embryos) performed in the United States in 2000, a miscarriage rate of 14.9% per clinical pregnancy and 5.3% per retrieval was reported (Assisted Reproductive Technology Success Rates, 2002).

Numerous studies have investigated the wide range of aetiology in miscarriages. Women's age (Abdalla *et al.*, 1993), morphological abnormalities of the uterus (Homer *et al.*, 2000), infection of the reproductive tract (Byrn and Gibson, 1986), maternal endocrine disorders such as luteal phase

insufficiency, polycystic ovary syndrome (PCOS), thyroid dysfunction, diabetes mellitus or hyperprolactinaemia (Roberts and Murphy, 2000), ovarian hyperstimulation (Raziel *et al.*, 2002), and genetic disorders (Zheng *et al.*, 2000) have been investigated extensively.

It has been demonstrated that in patients with elevated basal FSH concentrations >10 IU/l, half of the pregnancies achieved by IVF treatment ended in a miscarriage (Cédrin-Durnerin *et al.*, 2003). In addition, a high follicular LH concentration was related to high miscarriage rates in IVF cycles involving clomiphene citrate/gonadotrophin/cetrorelix stimulation (Tavaniotou *et al.*, 2003).

Immunologically mediated abortions (IMA) represent a distinct entity in research. Relations to antiphospholipid antibodies, antinuclear antibodies, antithyroid antibodies, natural killer cells and histocompatibility complex have been described (Kaider *et al.*, 1999; Ghazeeri and Kutteh, 2001). Some studies have also explored the effect of obesity (Fedorcsak *et al.*, 2000), endometriosis (Matorras *et al.*, 1998) and psychological factors (Bergant *et al.*, 1997) in spontaneous abortion. Corresponding to aetiology diversity, various treatment strategies have been developed. The efficacy of heparin and low-dose aspirin in women with antiphospholipid syndrome could be shown in different controlled investigations (Lee and Silver, 2000). The successful use of metformin to reduce miscarriage rate in PCOS has been demonstrated by Jakubowicz (Jakubowicz *et al.*, 2002). The possible connection between miscarriage and ovarian stimulation has been demonstrated in a mouse model by Ertzeid (Ertzeid and Storeng 2001). A prominent area of current research concerns preimplantation genetic diagnosis (PGD) during assisted reproduction procedures (Pellicer *et al.*, 1999).

The aim of the present study was to analyse the impact of previous miscarriages on the outcome of different assisted reproduction procedures including IVF, intracytoplasmatic sperm injection (ICSI), a combination of both treatments (IVF/ICSI) and cryopreserved embryo transfer (CPE) using population-based data of the German IVF Registry (DIR).

National registries in reproductive medicine help reveal trends and correlations (de Mouzon *et al.*, 1993). However, analytical studies have to be estimated as representations of special environments of each country, such as legislative restrictions, attitude of insurers and quality of data collection (Lancaster, 1996).

The German Embryo Protection Act (EschG, 1990) and guidelines of the German Medical Association, for example, prohibit any kind of donor programmes in IVF procedures, restrict the maximum number of transferred embryos to three, and effectively prevent embryo selection through only allowing the freezing of fertilized oocytes in the pronuclear stage.

These factors have to be considered when comparing results with those derived from other national data collections. The German registry was founded in 1982 and has expanded at various times to include the implementation of new therapeutic strategies such as micromanipulation, assisted hatching, and pharmaceutical agents for controlled ovarian hyperstimulation (Felberbaum and Dahncke, 2000). Starting with paper questionnaires, data collection was computerized in 1990 and all IVF units use a nearly uniform software solution. This tool is undergoing further development and will be adapted to the guidelines recommended by the International Working Group for Registers on Assisted Reproduction (IWGRAR) under the umbrella of the International Federation of Fertility Societies (IFFS) once clearance will be given by WHO (Adamson *et al.*, 2001). Prospectivity of entered records (with a maximum of 8 days after beginning of ovarian stimulation) was established in 1997. Participation became compulsory in 1999.

Compared with the IVF registries of other countries, the German registry data contains more information on reproductive history (Kupka *et al.*, 2003). The dataset of the American Society for Assisted Reproductive Technology (SART), operational since 1985, documents the number of previous pregnancies, full-term births (≥37 weeks), preterm births (<37 weeks), spontaneous abortions, and surgical sterilizations (Assisted Reproductive Technology Success Rates, 2001). The British Human Fertilization and Embryology Authority, established in 1991, collects data about patient's previous obstetric history including the total number of previous pregnancies (natural and assisted conceptions), the total number of IVF pregnancies, the total number of live births, and the year of the last pregnancy (HFEA, 2000). The annual reports of the French national IVF registry (established in 1986) also provide only limited information about reproductive history (FIVNAT, 2000). The records of the German IVF Registry include data of all previous pregnancies with information about the year, live births, miscarriages, induced abortions, ectopic pregnancies, change of partnership and use of assisted medical procreation (DIR, 2000). Information on whether the male partner has ever made a woman pregnant is not reported to the registry. Protection of privacy in health related registries is required by public authorities. Therefore, multiple cycles for a single patient are not linked and identification of single patients can only be integrated with technical expense using unique algorithms. Similar to other IVF data collections this should be realized soon as well as using modern techniques like the Internet (Cohen, 2001). Annual reports of the four registries are already available on the World-Wide Web.

## Materials and methods

The records of 174,909 assisted reproduction treatment procedures including IVF, ICSI, a combination of IVF and ICSI in one cycle (IVF/ICSI), and CPE were analysed. Gamete intra-Fallopian transfer (GIFT) was performed in 93 cycles only and therefore excluded from the analysis. In addition, intrauterine insemination (IUI) could not be incorporated because data on this procedure are not collected by the German IVF Registry. A total of 103,939 previous pregnancies (including live births, miscarriages, induced abortions and ectopic pregnancies) were reported. Previous assisted reproduction procedures could include IUI, IVF, ICSI, IVF/ICSI, GIFT and CPE without exact specification. Treatments were performed during January 1998 to December 2000. The present analysis was approved by the Board of the Registry. Identifiable information on patient and IVF centre was removed.

A maximum of 103 reproductive centres reported their data, most working as private sector units. Thirty-six are tertiary care centres or university hospitals. To evaluate the impact of previous miscarriages on the outcome of assisted reproduction procedures, the present study assessed correlations of women's age, previous infertility treatments, change of partnership in previous conceptions and infertility diagnoses. The primary outcome measure was the miscarriage rate per clinical pregnancy.

According to the registry guidelines, a miscarriage is defined as the loss of a clinically recognized pregnancy during the first 24 weeks of gestation. Stillbirths are included in this definition, but induced abortions are reported separately. A multiple pregnancy ending in a miscarriage is listed as one miscarriage. According to the registry definition a clinical pregnancy is fixed as the occurrence of at least one ultrasonography confirmed gestational sac (which excludes biochemical pregnancies) with or without confirmation of positive heartbeats, as well as ectopic pregnancies and a pregnancy loss up to a gestational age of 24 weeks. A live birth is described as a treatment cycle that results in at least one live born neonate with a minimum gestational age of 25 weeks. Multiple live births followed the same definition.

A relatively high percentage of pregnancies were lost of follow-up (14.2%). From a total of 178,608 records in the dataset, 3699 incomplete records (2.1%) had to be removed before starting the analysis. Information about luteal phase support, body weight, the quality and number of embryos or previous specific treatments in cases of recurrent miscarriages was not available.

Logistic regression was used to model success (defined as a clinical pregnancy) as a binomial dependent variable (McCullagh *et al.*, 1989). Independent variables in the regression models include number of previous miscarriages, duration of infertility, woman's age, clinical pregnancy rate per retrieval and type of assisted reproduction-procedure, all defined as categorical. In models evaluating the impact of the number of previous miscarriages, the reference group was represented by patients without previous miscarriages. In models evaluating the impact of different kinds of assisted reproduction procedure, the reference group was represented by patients undergoing IVF procedures. Odds ratio (OR) comparing each category of the independent variables to the reference group, and their 95% confidence interval (CI) were obtained from the regression coefficient estimates and their standard errors. Wald's Chi-Square ($\chi^2$) test was used to test the null hypothesis of no association (i.e. OR = 1), whereas the precision of the estimates was evaluated using the 95% confidence interval. For categorical data, e.g. age, the Cochran–Mantel–Haenszel statistics with 1 degree of freedom was used. Goodness of fit was indicated by scaled deviance and Pearson $\chi^2$ values (**Table 1**). The Statistical Analysis System (SAS) version 8.02 (SAS Institute Inc.®, Cary, NC, USA) was used in all analyses.

## Results

Most of the assisted reproduction procedures were planned as IVF (*n* = 75,024, 43%) or ICSI cycles (*n* = 70,335, 40%). A combination (IVF/ICSI) was performed in 2529 procedures (1.6%). Cycles involving cryopreserved embryo transfer (CPE, *n* = 27,021, 15.4%) are reported as a separate category (**Table 2**).

The average age of the women was 34 years (SD 4.5, range 17–46). The average duration of infertility was 5 years (SD 3.4, range 0–17). Primary infertility was reported in 65% of the cycles and ranged from 58% of the IVF group to 73% in the ICSI treatment group. Infertility diagnoses were classified in five groups: tubal disease, male factor, ovulatory disorder, unexplained infertility and other reasons. The latter category included multiple diagnoses as well as severe endometriosis, fibroids and other rarer diagnoses.

Of 174,909 started cycles, a total of 161,430 (92%) resulted in oocyte retrieval respectively in vital thawed embryos in CPE cycles. Cycles with follicular puncture where no oocytes could be found and cycles with thawing cryopreserved fertilized oocytes where no vital embryos were found were observed in 8%. A total of 145,807 (83%) cycles resulted in embryo transfer. The overall cancellation rate was 8%. Cycles with no regular fertilization were seen in 11%. A total of 35,648 clinical pregnancies were reported, with an overall clinical pregnancy rate per transfer of 25%. IVF and ICSI yielded similar pregnancy rates (26%), while combination of both methods yielded a slightly lower rate (25%). Transfer of cryopreserved embryos result in a 16% clinical pregnancy rate. Multiple pregnancy was observed in 7930 cycles (22%). A total of 21,335 live births were reported, for an overall rate per transfer of 15%. Due to a relatively high miscarriage rate, the live birth rate in cycles with cryopreserved embryo transfer only amounted to 9%. Ectopic pregnancies were observed in 3% of all procedures.

Compared with other registries, the overall miscarriage-rate was relatively high (23%). The reported 8311 miscarriages include 233 stillbirths. Overall, the highest miscarriage rate was observed in the group of procedures with transfer of cryopreserved embryos (27%), and was similar in both ICSI cycles and IVF cycles (23%). Overall, the miscarriage rates per retrieval ranged from 4.0% in the group of CPE to 5.7% in the group of IVF/ICSI procedures.

A total of 103,939 previous pregnancies were reported. On average, 0.59 (range 0–12, SD 0.98) previous pregnancies per procedure were listed. The largest group represented 41,082 live births (40%). A total of 34,281 miscarriages were registered (33%); ectopic pregnancies were seen in 17,725 cases (17%) and induced abortions in 10,851 cases (10%). The number of previous miscarriages ranged from 1 to 12 (mean 0.19, SD 0.52). In 18,808 cycles, one previous miscarriage was reported, in 3689 cycles two previous miscarriages were notified and three previous miscarriages were seen in 939 cycles. A total number of 107 cycles (0.4% of all cycles with history of pregnancy loss) reported more than three previous miscarriages and were not considered in further analyses to concentrate on the main findings.

The present study focused on 29,003 reported previous miscarriages, where an embryo transfer in the subsequent assisted reproduction procedure had been performed. In some correlations, only consecutive previous miscarriages were analysed.

**Table 1.** Goodness of fit.

| | *DF* | *Scaled deviance* | *Pearson* $\chi^2$ |
|---|---|---|---|
| Influence of the number of previous miscarriages | 19 | 0.3421 | 0.9963 |
| Influence of women's age | 16 | 0.2431 | 1.1131 |
| Influence of the means of conception (spontaneous/ assisted reproduction) | 16 0.2452 | 1.0392 | |
| Influence of change in partnership | 12 | 0.2675 | 0.9872 |

**Table 2.** Infertility diagnosis, pregnancy rate and clinical outcome.

| | *IVF* | *ICSI* | *IVF/ICSI* | *CPE* |
|---|---|---|---|---|
| *n* | 75,024 | 70,335 | 2529 | 27,021 |
| Woman's age (years)[a] | 33.6 (4.6) | 33.4 (4.6) | 32.8 (4.4) | 33.2 (4.2) |
| Duration of infertility (years)[a] | 5.4 (3.4) | 5.2 (3.6) | 4.9 (3.2) | 5.5 (3.2) |
| Primary infertility (%) | 57.6 | 72.8 | 64.7 | 62.3 |
| Secondary infertility (%) | 42.4 | 27.3 | 35.3 | 37.7 |
| Tubal disease (%) | 30.1 | 3.8 | 13.1 | 16.3 |
| Male factor (%) | 30.6 | 74.6 | 46.6 | 50.2 |
| Ovulatory disorder (%) | 13.6 | 5.0 | 18.0 | 14.7 |
| Unexplained (%) | 8.7 | 2.3 | 4.9 | 5.1 |
| Others (%) | 17.0 | 14.3 | 17.4 | 13.8 |
| No. of retrievals | 68,926 | 64,355 | 2411 | 25,738[b] |
| No. of transfers | 58,393 | 61,010 | 2223 | 24,181 |
| No. of clinical pregnancies | 15,298 | 16,004 | 554 | 3792 |
| Clinical pregnancy rate per transfer (%) | 26.2 | 26.2 | 24.9 | 15.7 |
| Clinical pregnancy rate per retrieval (%) | 22.2 | 24.9 | 23.0 | 14.7 |
| Multiple-fetus-pregnancies | 3676 | 3.534 | 126 | 594 |
| Multiples per clinical pregnancy (%) | 24.0 | 22.1 | 22.7 | 15.7 |
| No. of live births | 8994 | 9836 | 352 | 2.153 |
| Live birth per transfer (%) | 15.4 | 16.1 | 15.8 | 8.9 |
| No. of ectopic pregnancies[c] | 456 | 330 | 22 | 152 |
| Rate of ectopic pregnancy per retrieval (%) | 3.0 | 2.1 | 4.0 | 4.0 |
| No. of miscarriages | 3467 | 3688 | 117 | 1039 |
| Miscarriage rate per clinical pregnancy (%) | 22.7 | 23.0 | 21.1 | 27.4 |
| Miscarriage rate per retrieval (%) | 5.0 | 5.7 | 4.9 | 4.0 |
| Clinical pregnancies with loss of follow-up | 2381 | 2150 | 63 | 448 |
| Rate of loss of follow-up (%) | 15.6 | 13.4 | 11.4 | 11.8 |

[a]Values are means with standard deviation in parentheses.
[b]Vital thawed fertilized oocytes in pronuclear stage.
[c]0.3% heterotopic pregnancies were reported (118/35.673) in 0,2% of assisted reproduction procedures a live birth and additional extrauterine gravidity was reported (39/21,349).
CPE = cryopreserved embryo transfer.

To answer the question how the number of previous miscarriages could influence assisted reproduction outcome, a logistic regression model including assisted reproduction procedures, miscarriage rates per retrieval and number of previous miscarriages was established (**Table 3**). The reference group comprised patients without previous miscarriages. A highly significant impact could be seen for one, two and three previous miscarriages on all four evaluated kinds of assisted reproduction procedures (IVF, ICSI, IVF/ICSI, CPE). In ICSI treatments, the miscarriages rates increased from 22% among patients without previous miscarriages to 39% for patients with three previous miscarriages. The combination of IVF and ICSI showed an even higher increase. In general, a positive impact on the miscarriage rate could be observed comparing women with primary (no previous pregnancy) and secondary infertility.

To evaluate the influence of previous miscarriages on the outcome of assisted reproduction procedures in general, 68,703 IVF cycles were analysed (**Table 4**). Clinical pregnancy rates and miscarriage rates were associated with the number of previous miscarriages. The live birth rate decreased from 13% in patients without a previous miscarriage to 10% in patients with three previous miscarriages. The miscarriage rate per clinical pregnancy increased from 21 to 31%. The live birth rate decreased from 13% in patients without any previous miscarriage, to 10% in the group of patients with three previous miscarriages.

Women's age is a well-known prognostic factor in human reproduction. To demonstrate the correlation to previous miscarriages, 10 age categories were used (≤26, 27–28, 29–30, 31–32, 33–34, 35–36, 37–38, 39–40, 41–42, ≥43). The percentages of women with no previous miscarriage declined from 92% among those less than 27 years of age to 72% among women 43 years or older. One previous miscarriage was observed only in 7% in the youngest age category with an increase to 21% in the group of women older than 42 years. The same increase could be shown for two and three previous miscarriages. To analyse the relation of women's age to the miscarriage rate in assisted reproduction procedures in more detail, a logistic regression model including assisted

**Table 3.** Previous pregnancies and miscarriage-rate per clinical pregnancy in assisted reproduction procedures.

| *Previous pregnancies* | n | *IVF (%)*[a] | *ICSI (%)* | *IVF/ICSI (%)* | *CPE (%)* | *OR* | *CI* | P-*value* |
|---|---|---|---|---|---|---|---|---|
| All | 174,909 | 22.7 | 23.0 | 21.1 | 27.4 | | | |
| 0[b] | 128,147 | 20.9 | 21.4 | 19.5 | 26.2 | 1.000 | | |
| 1[c] | 19,553 | 24.9 | 26.5 | 23.9 | 28.9 | 1.253 | 1.190–1.318 | <0.0001 |
| 0[d] | 137,670 | 21.4 | 21.8 | 19.4 | 26.4 | 1.000 | | |
| 1[e] | 18,808 | 27.4 | 29.8 | 27.1 | 30.9 | 1.412 | 1.314–1.519 | <0.0001 |
| 2[f] | 3689 | 26.1 | 36.8 | 50.0 | 31.9 | 1.538 | 1.318–1.793 | <0.0001 |
| 3[g] | 939 | 31.4 | 39.1 | 33.3 | 33.3 | 1.786 | 1.299–2.456 | 0.0004 |

[a]Percentages refer to the clinical pregnancy rate per retrieval.
[b]No previous pregnancy (primary infertility).
[c]At least one previous pregnancy (secondary infertility).
[d]No previous miscarriage but potentially previous pregnancies with different outcome.
[e]One previous miscarriage.
[f]Two previous miscarriages.
[g]Three previous miscarriages.

**Table 4.** Previous miscarriages and assisted reproduction outcome in IVF procedures.

| *Previous miscarriages* | *0*[a] | *0*[b] | *1* | *2* | *3* | P-*value*[c] |
|---|---|---|---|---|---|---|
| *n* | 39,729 | 56,957 | 9156 | 2053 | 537 | |
| Clinical pregnancy rate (%)[d,e] | 21.9 | 22.2 | 22.9 | 21.3 | 19.6 | 0.0192 |
| Live birth rate (%)[d,e] | 13.2 | 13.3 | 12.3 | 11.5 | 10.1 | <0.0001 |
| Miscarriage rate (%)[d,e] | 4.6 | 4.8 | 6.3 | 5.6 | 6.2 | <0.0001 |
| Miscarriage rate (%)[e,f] | 20.9 | 21.4 | 27.4 | 26.1 | 31.4 | <0.0001 |

[a]No previous pregnancy (not included in Cochran–Mantel–Haenszel statistics).
[b]No previous miscarriage but potentially previous pregnancies with different outcome.
[c]Cochran–Mantel–Haenszel statistics.
[d]Per retrieval.
[e]Percentages refer to the sum of each column.
[f]Per clinical pregnancy.

reproduction procedures, miscarriage rates per clinical pregnancy and age categories was established (**Table 5**). The reference group was represented by patients younger than 27 years undergoing IVF procedures. A highly statistically significant correlation was observed for women 35 years or older.

To analyse the correlation of infertility diagnoses and miscarriage rate in assisted reproduction procedures, a logistic regression model including miscarriage rates per retrieval, infertility diagnoses and number of previous pregnancies was established. The reference group comprised patients with no previous miscarriage. A statistically significant association to the number of previous miscarriages could be found. The groups of cycles with one (OR 1.375, CI 1.238–1.526, $P<0.001$), two (OR 1.288, CI 1.037–1.600, $P = 0.0221$) and three (OR 1.651, CI 1.093–2.495, $P = 0.0173$) previous miscarriages demonstrated increased rates in all diagnosis categories.

To answer the question of whether the assisted reproduction miscarriage rate would differ between patients with previous miscarriages achieved by assisted reproduction treatments or by spontaneous conception, a regression analysis performed, including assisted reproduction procedures, miscarriage rate per clinical pregnancy, and previous consecutive miscarriages (**Table 6**). The most important finding was that one previous miscarriage resulting from an assisted reproduction treatment (IVF, ICSI, IVF/ICSI, CPE or IUI) increased the miscarriage rate of an ongoing assisted reproduction procedure for all kinds of treatment relative to the rates where a previous miscarriage was achieved by spontaneous conception. In IVF cycles, the rate increased from 26 to 31% and in cycles where a combination of IVF and ICSI was performed, the difference was even larger (27 versus 35%). No statistically significant difference could be shown for two or three previous miscarriages.

**Table 5.** Women's age and miscarriage rate per clinical pregnancy in assisted reproduction procedures.

| *Women's age (years)* | n | *IVF (%)* | *ICSI (%)* | *IVF/ICSI (%)* | *CPE (%)* | *OR* | *CI* | P-*value* |
|---|---|---|---|---|---|---|---|---|
| All | 161,430 | 22.7 | 23.0 | 21.1 | 27.4 | | | |
| ≤26 | 11,211 | 20.1 | 19.5 | 25.6 | 29.4 | 1.000 | | |
| 27–28 | 12,945 | 17.0 | 19.3 | 23.1 | 27.4 | 0.910 | 0.801–1.034 | 0.148 |
| 29–30 | 20,757 | 17.9 | 20.0 | 16.3 | 23.5 | 0.912 | 0.812–1.023 | 0.117 |
| 31–32 | 26,864 | 19.4 | 20.5 | 21.0 | 25.1 | 0.979 | 0.876–1.093 | 0.701 |
| 33–34 | 27,413 | 21.1 | 21.5 | 15.5 | 28.0 | 1.062 | 0.952–1.186 | 0.282 |
| 35–36 | 23,801 | 23.9 | 23.4 | 23.4 | 28.4 | 1.204 | 1.076–1.347 | 0.001 |
| 37–38 | 17,535 | 26.3 | 28.3 | 20.4 | 30.3 | 1.110 | 1.278–1.622 | <0.0001 |
| 39–40 | 12,382 | 36.6 | 33.5 | 35.0 | 30.2 | 2.015 | 1.768–2.296 | <0.0001 |
| 41–42 | 5620 | 43.1 | 48.0 | 50.0 | 28.1 | 2.945 | 2.461–3.524 | <0.0001 |
| >42 | 2902 | 56.1 | 48.3 | – | 56.7 | 3.935 | 2.868–5.399 | <0.0001 |

**Table 6.** Previous consecutive miscarriages achieved by spontaneous conception/assisted reproduction and miscarriage-rate per clinical pregnancy in assisted reproduction procedures.

| *Previous miscarriages* | n | *IVF (%)* | *ICSI (%)* | *IVF/ICSI (%)* | *CPE (%)* | *OR* | *CI* | P-*value* |
|---|---|---|---|---|---|---|---|---|
| 0 | 104,147 | 20.9 | 21.4 | 19.5 | 26.2 | | | |
| 1[a] | 13,488 | 26.4 | 29.4 | 26.7 | 29.3 | 1.000 | | |
| 1[b] | 6006 | 30.5 | 31.1 | 35.3 | 32.6 | 1.162 | 1.011–1.335 | 0.034 |
| 2[a] | 2586 | 23.6 | 37.8 | 50.0 | 30.5 | 1.000 | | |
| 2[b] | 622 | 30.9 | 31.6 | 33.3 | 45.8 | 1.175 | 0.804–1.720 | 0.404 |
| 3[a] | 732 | 35.1 | 45.7 | 33.3 | 27.3 | 1.000 | | |
| 3[b] | 76 | 37.5 | 33.3 | – | 50.0 | 1.179 | 0.385–3.611 | 0.772 |

[a]Miscarriages after spontaneous conception.
[b]Miscarriages after assisted reproduction procedure (IVF, ICSI, IVF/ICSI, CPE, IUI).

To evaluate the impact of a change in partnership on previous consecutive miscarriages, a similar regression model was performed (**Table 7**). The reference group was the group of patients with previous miscarriages in the same partnership. No statistically significant difference could be shown for one, two or three previous consecutive miscarriages.

## Discussion

Various prognostic factors in assisted reproduction procedures have been described, such as women's age (Templeton *et al.*, 1996), infertility aetiology (Tan *et al.*, 1992), previous successful treatment cycles (Simon, 1993), semen quality parameters (Sukcharoen *et al.*, 1996), embryo quality and number of embryos (Scott *et al.*, 1991). It could be demonstrated that in poor responder cycles, the miscarriage rate was 17% (Ulug *et al.*, 2003). Unfortunately, the quality and number of embryos was not available in this dataset.

The present study has examined the relationship between previous miscarriages and the loss of clinically recognized pregnancies in assisted reproduction procedures. Previous research has indicated that miscarriage rates are higher in pregnancies achieved by assisted reproduction, although the reasons for that observation are not yet completely understood (Ezra and Schenker, 1995). The overall miscarriage rate in the present study (23%) was relatively high compared with other data. This rate is influenced in part by the relatively high rate of cycles lost to follow-up. The Danish IVF Registry reported for the years 1994 and 1995 a miscarriage rate per clinical pregnancy of 17% in IVF cycles and in 25% of ICSI cycles (Westergaard *et al.*, 2000). Coulam described a miscarriage rate in IVF cycles of 17% (Coulam *et al.*, 1998). The Israeli Registry reported an overall miscarriage rate of 24% for the period 1995 and 1996 (Insler *et al.*, 2000). The British registry reported a miscarriage rate per clinical pregnancy in IVF and CPE cycles of 13% in the period of April 1998 to March 1999 (HFEA, 2000).

In this study, the overall miscarriage rate ranged from 21 to 27%, with the highest range in patients undergoing frozen–thawed embryo transfer. This could be affected by the procedure of freezing and thawing itself, but also by the selection process on day 1 after follicular puncture. According to the German embryo protection law, freezing is only allowed until this day. Fertilized oocytes in the pronuclear stage of lower quality will be selected for freezing. This could also affect the pregnancy rate and consequently the abortion rate.

It was found that having a previous miscarriage increases the treatment dependant miscarriage rate in all analysed assisted reproduction procedures. Similar findings have also been described by other researchers (Tatham *et al.* 2001).

A significantly higher impact was shown for one previous miscarriage resulting from assisted reproduction procedures compared with a previous miscarriage resulting from spontaneous conception. Bates described a positive effect of one previous early pregnancy loss in IVF cycles (Bates *et al.*, 2002). This finding could not be seen in the present study, since it was not possible to differentiate between previous assisted reproduction procedures because cycles of individual couples are not linked. A new software solution for data collection will help to solve this problem in the future.

Stolwijk described a significant difference in the cumulative probability to achieve an ongoing pregnancy in IVF/ICSI cycles in the first attempt comparing women with primary and secondary infertility (16 versus 23%) (Stolwijk *et al.*, 2000). This also could be seen in the present study. The clinical pregnancy rate in IVF cycles increased from 22% in patients with primary infertility to 23% in patients with one previous miscarriage ($P$ = 0.0192). Nevertheless, in cycles with more than one miscarriage, the pregnancy rate decreased to 20%.

A previous successful IVF cycle was described as a positive prognostic factor for a following attempt (Simon *et al.*, 1993; Templeton *et al.*, 1996). Unfortunately, this seemed to be associated with a higher miscarriage rate, as seen in the current investigation.

The impact of women's age in assisted reproduction procedures has been evaluated in several studies. Hughes found women's age to be a more important factor than semen quality, embryo quality and previous response to stimulation in IVF treatments (Hughes *et al.*, 1989). Similar to the present findings, Dicker described an increase in miscarriages in IVF treatments from 28% in women aged 25 years or younger to 50% in women 40 years or older (Dicker *et al.*, 1991). The present study demonstrated a statistically significant increase in miscarriages in all assisted reproduction procedures in women older than 34 years.

To evaluate the impact of age concerning uterine and ovarian factors, Abdalla demonstrated that in cycles with oocyte donation, women aged 40 years or older will benefit significantly (Abdalla *et al.*, 1993). He described a miscarriage rate of 58% in non-donor treatments among women older than 40 years. This was similar to the present findings (**Figure 1**).

The impact of infertility diagnosis on miscarriage rate was analysed by Tan, using a collective of 700 pregnancies achieved by IVF therapy (Tan *et al.*, 1992). He described the highest miscarriage rate in women with unexplained cause of infertility (36%) followed by tubal damage (34%) and male factor (32%). Miscarriage rates in the present investigation were lower in general, with the highest percentage seen in women suffering from tubal damage and unexplained causes of infertility. Infertility diagnosis showed a specific relation to the number of previous miscarriages in the present study. Kiefer reported a 40% increase in spontaneous abortions in ICSI cycles with severe oligoasthenozoospermia, but this finding was based on a relatively small group of patients (6/15) (Kiefer *et al.*, 1997). In the current investigation, the overall miscarriage rates in ICSI cycles amounted only 23.0% and only a small increase was seen compared with IVF cycles (22.7%).

IVF as a therapeutic approach in women experiencing recurrent miscarriages is a controversial topic. Balasch found that in a group of 12 couples suffering from recurrent pregnancy loss, all achieved pregnancies after IVF treatment ended in a live birth (Balasch *et al.*, 1996). Raziel reported no decrease of miscarriage rates after IVF treatment in 14 couples (Raziel *et al.*, 1997). In the present investigation, a higher clinical pregnancy rate in IVF treatments was observed in women experiencing one previous miscarriage. No benefit was observed in reproductive histories with more than one previous

**Table 7.** Previous consecutive miscarriages in the same/different partnership and miscarriage rate in assisted reproduction.

| *Previous miscarriages* | n | *IVF (%)* | *ICSI (%)* | *IVF/ICSI (%)* | *CPE (%)* | *OR* | *CI* | P-*value* |
|---|---|---|---|---|---|---|---|---|
| 1[a] | 7408 | 5.7 | 8.1 | 4.4 | 4.6 | 1.000 | | |
| 1[b] | 4798 | 6.5 | 6.8 | 6.5 | 3.9 | 0.977 | 0.841–1.351 | 0.7618 |
| 2[a] | 1077 | 5.9 | 11.7 | 23.1 | 4.5 | 1.000 | | |
| 2[b] | 749 | 4.1 | 7.4 | 5.6 | 5.2 | 0.685 | 0.463–1.012 | 0.0576 |
| 3[a] | 259 | 6.9 | 4.7 | – | 3.2 | 1.000 | | |
| 3[b] | 185 | 4.6 | 5.8 | – | – | 0.724 | 0.296–1.776 | 0.4815 |

[a]Same partnership.
[b]Different partnership.

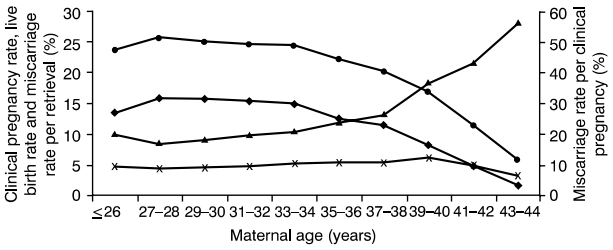


**Figure 1.** Women's age correlated to clinical pregnancy rate (•) live birth rate (♦) miscarriage rate per retrieval (×) and miscarriage rate per clinical pregnancy (s ) in IVF procedures.

miscarriage. The live birth rate was negative correlated and the miscarriage rate positively related to the amount of previous miscarriages.

Only limited information is available about the impact of change in partnership and miscarriage rates in assisted reproduction procedures. Although this investigation could not demonstrate any specific correlation, it would have been expected that the treatment dependant miscarriage rate in women with previous miscarriages in a different partnership would be affected (Carp *et al.*, 1994; Stricker *et al.*, 2000).

Counselling of subfertile couples should include information about both the age dependant likelihood of treatment dependant miscarriages and the relation to previous pregnancy loss.

The major findings of this study are that any previous miscarriage will increase the treatment dependant miscarriage rate in assisted reproduction procedures. A significantly higher impact is shown for one previous miscarriage achieved by assisted reproduction procedures compared with spontaneous conception. Partner change is shown to have no specific impact on the treatment dependant miscarriage rate, whereas a statistically significant increase in miscarriages in all assisted reproduction procedures was found among women older than 34 years of age. Overall, the highest rate of treatment dependant miscarriages was seen in assisted reproduction procedures with cryopreserved embryo transfer.

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