

Impact of reproductive history on in vitro fertilization and intracytoplasmic sperm injection outcome: evidence from the German IVF Registry

Markus S. Kupka, M.D.,^{a,b} Christoph Dorn, M.D.,^b Oliver Richter, M.D.,^b
Ricardo Felberbaum, M.D.,^c and Hans van der Ven, M.D.^b

School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama

Objective: To evaluate the effect of reproductive history on the outcome of different procedures in assisted reproductive technologies (ART) comparing IVF, ICSI, and cryopreserved embryo transfer (CPE).

Design: Prospective registration of ART cycles and their outcomes.

Setting: One hundred three reproductive programs in Germany.

Patient(s): Women undergoing 174,909 ART procedures from January 1998 through December 2000.

Intervention(s): Data analysis of reproductive history collected by the German IVF Registry; multiple logistic regression modeling of success rates.

Main Outcome Measure(s): Effect of type of conception and outcome of previous pregnancies, duration of infertility, female's age, and type of ART on clinical pregnancy rate per retrieval. Odds ratios with 95% CIs are reported.

Result(s): More than one previous pregnancy was negatively correlated with outcome of IVF, ICSI, or CPE. This association disappeared when female age was restricted to a maximum of 35 years. A previous pregnancy achieved by spontaneous conception had less impact on outcome of IVF, ICSI or CPE outcome than did a previous assisted conception. Previous live births and miscarriages demonstrated a statistically significant increase compared with ectopic pregnancies and induced abortions.

Conclusion(s): Reproductive history must be considered when counseling subfertile couples. Female age, method of conception, and previous pregnancy outcome have a significant effect on IVF, ICSI, and CPE outcome. (*Fertil Steril*® 2003;80:508–16. ©2003 by American Society for Reproductive Medicine.)

Key Words: Reproductive history, previous conception, IVF, ICSI, age, miscarriage, registry

Numerous prognostic factors must be addressed in counseling subfertile couples who consider ART. Important factors include the woman's age (1–6), the number of previous treatment cycles (7, 8), the number of former successful cycles (9, 10), and cycle cancellations (4). Ovarian response and uterine receptivity are also important determinants of success, as demonstrated by the significant association between pregnancy outcome and the number of aspirated oocytes (10), the proportion of fertilized oocytes (11, 12), the number and quality of embryos (16), the time between oocyte aspiration and embryo transfer (17), and cause of infertility (18). Semen quality is another prognostic factor that includes

sperm concentration, percent motility, quality of motility, and sperm morphology (13–15).

The effect of reproductive history has been mostly evaluated through the association of success rates with primary or secondary infertility (4, 19), as measured by no previous pregnancy or having had at least one previous pregnancy. Some studies have evaluated separately previous treatment-related and spontaneous conceptions (9). Miscarriages as outcomes of previous pregnancies have been extensively evaluated because of the potential risk of recurrent spontaneous abortion (20, 21).

Both the introduction of new technologies and changes in social, ethical and legislative conditions (such as cost-effectiveness consid-

Received August 12, 2002;
revised and accepted
February 3, 2003.

Supported by the German
Research Society, Bonn,
Germany (Deutsche
Forschungsgemeinschaft
DFG, KU 1425/1-1).

Reprint requests: Markus
S. Kupka, M.D., University
Medical Center of
Obstetrics and
Gynecology, University of
Muenchen, Maistrasse 11,
D-80337 Muenchen,
Germany (FAX: 49-089-
5160-4918; E-mail:
mail@kupka.info).

^a Department of
Epidemiology and
International Health, School
of Public Health, University
of Alabama at Birmingham.

^b University Medical Center
of Obstetrics and
Gynecology, University of
Bonn, Bonn, Germany.

^c University Medical Center
of Obstetrics and
Gynecology, University of
Luebeck, Luebeck,
Germany.

0015-0282/03/\$30.00
doi:10.1016/S0015-0282(03)
00760-X

erations and the effort to reduce higher rates of multiple births necessitate careful review of the impact of prognostic factors (22, 23). National registries in reproductive medicine aid in revealing trends and correlations in this rapidly changing technology (24). Country-specific trends, however, reflect legislative restrictions, the attitude of insurers, and the quality of data collection (25, 26). For example, the German Embryo Protection Act (27) and guidelines of the German Medical Association (28) prohibit any kind of donor programs in IVF procedures; restrict the maximum number of transferred embryos to three; and mandate freezing at the pronuclear stage of fertilized oocytes, consequently preventing embryo selection.

These circumstances must be considered when comparing German registry data with those of other national data collection systems, such as that published by the European IVF-monitoring program. Initiated by the European Society of Human Reproduction and Embryology, the program published its second report on assisted reproductive technology (29). Eighteen countries with 521 clinics reported on more than 232,000 treatment cycles in 1998. The last world collaborative report on IVF-ET and GIFT was published in 1992 and covered results from 1989 onward (30). The International Federation of Fertility Societies published its second world report including information on medical, legal, and ethical aspects of ART. Thirty-nine countries presented results from 2000 (31). The World Health Organization published a report covering similar aspects also focusing on ART in developing countries (32).

The German data collection agency was founded in 1982 and modified its data collection requirements several times (33). All IVF units are currently using a nearly uniform computer-based data entry software. This tool is undergoing further development and will be adapted to the guidelines recommended by the International Working Group for Registers on Assisted Reproduction under the auspices of IFFS (34). Since 1997, ART cycles reported to the system are entered prospectively (within 8 days from the beginning of controlled ovarian hyperstimulation). Participation in the registry became mandatory in 1999.

Compared with IVF registries of other countries, the German registry contains more information about reproductive history. The American Society for Assisted Reproductive Technology, whose results have been published since 1985, documents the number of previous pregnancies, full-term births (≥ 37 weeks), preterm births (< 37 weeks), spontaneous abortions, and surgical sterilizations (35). The British Human Fertilization and Embryology Authority, established in 1991, collects data about patients' obstetric and gynecologic history, including the total number of previous pregnancies (by natural and assisted conception), the total number of IVF pregnancies; the total number of live birth, and the year of the last pregnancy (36). The annual reports of the French IVF-Registry (Registre national de la

FIV en France), established in 1986, also provides only limited information about reproductive history (37).

The records of the German IVF Registry include data of previous pregnancies with information about the year of conception, the outcome, change of partnership, and use of ART (38). Further development of the registries should include the use of modern communication techniques (24, 26). Annual reports of the four registries are already available on the Internet (35–37).

MATERIALS AND METHODS

The database comprises records of 174,909 treatment procedures, including IVF, ICSI, IVF and ICSI in one cycle (IVF/ICSI), and cryopreserved embryo transfer (CPE), performed in Germany between January 1998 and December 2000. Gamete intrafallopian transfer treatments were performed in only 93 cycles, and these data were therefore disregarded.

A maximum of 103 reproductive centers reported data each year; most of these are private assisted reproductive technology units, whereas 36 were tertiary care centers or university hospitals. These data cover 98% of all treatments in Germany. A total of 102,119 previous pregnancies, including live births, miscarriages, induced abortions, and ectopic pregnancies, were reported in the reproductive history section of the records. Data for each pregnancy include the year of conception, whether the sexual partner was the same as the current partner, and whether any kind of ART was used for procreation. The data set includes information only if an ART treatment was used that lacks an exact classification. Such a treatment could include IUI, IVF, ICSI, IVF/ICSI, GIFT and CPE.

Our analysis was approved and supported by all board members of the German IVF Registry. We performed no therapeutic intervention on patients; thus, institutional review board approval therefore was not needed. Identifiable information on patient and IVF center was removed from the database before release to the authors.

Our analysis also included variables affecting the outcome of ART procedures other than number of previous pregnancies, including the woman's age, duration of infertility, and type of infertility treatment. The outcome was defined as the proportion of cycles continuing with retrieval that led to a clinical pregnancy. Live birth rates were also evaluated in one analysis but were not chosen as the primary outcome because follow-up on a relatively high percentage (14.2%) of clinical pregnancies was not reported to the system.

A clinical pregnancy was defined as the occurrence of at least one ultrasonographically confirmed gestational sac with or without confirmation of heart beat. This definition includes ectopic pregnancies and pregnancy losses but ex-

TABLE 1

Characteristics of the sample.

Characteristic	IVF (n = 75,024)	ICSI (n = 70,335)	IVF/ICSI (n = 2,529)	CPE transfer (n = 27,021)
Female age (y) ^a	33.6 ± 4.6	33.4 ± 4.6	32.8 ± 4.4	33.2 ± 4.2
Duration of infertility (y) ^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	5.11
Others (%)	17.0	14.3	17.4	13.8
No. of retrievals	68,926	64,355	2,411	25,738 ^b
No. of transfers	58,393	61,010	2,223	24,181
No. of clinical pregnancies	15,298	16,004	554	3,792
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
No. of multiple fetus pregnancies	3,676	3,534	126	594
Multiples per clinical pregnancy (%)	24.0	22.1	22.7	15.7
No. of live births	8,994	9,836	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 pregnancies (%)	3.0	2.1	4.0	4.0
No. of miscarriages ^d	3,467	3,688	117	1,039
Rate of miscarriages per clinical pregnancy (%)	22.7	23.0	21.1	27.4
Pregnancies with loss of follow up	2,381	2,150	63	448
Rate of pregnancy loss (%)	15.6	13.4	11.4	11.8

Note. CPE = cryopreserved embryo.

^a Data are the mean (±SD).

^b Thawed fertilized oocytes in pronuclear stage.

^c A total of 0.3% heterotopic pregnancies were reported (118 of 35,673). In 0.2% of ART procedures, a live birth and additional extrauterine pregnancy were reported (39 of 21,349).

^d Including stillbirths and induced abortions.

Kupka. Reproductive history and IVF/ICSI outcome. *Fertil Steril* 2003.

cludes biochemical pregnancies. A live birth was defined as a treatment cycle that resulted in at least one live-born neonate at a gestational age of at least 25 weeks. Multiple live births follow the same definition. Miscarriages (gestational age < 25 weeks) and stillbirths were grouped as pregnancy losses. The data set structure of the registry does not allow merging of different cycles from one couple.

Logistic regression was used to model success (defined as a clinical pregnancy or a live birth) as a binomial dependent variable (39). Independent variables in the regression models include number and outcome of previous pregnancies, duration of infertility, female age, clinical pregnancy rate per retrieval, and kind of ART procedure, all of which are categorical.

In models evaluating the effect of the number or outcome of previous pregnancies, the reference group was represented by patients without former conceptions. In models evaluating the impact of different kinds of ART procedures, the reference group was represented by patients undergoing IVF procedures.

Odds ratios (with 95% CIs) comparing each category of the independent variables to the reference group were obtained from the regression coefficient estimates and their standard variables. The Wald χ^2 test was used to establish the null hypothesis of no association (odds ratio, 1.0), whereas the precision of the estimates was evaluated by using the 95% confidence interval. SAS software, version 8.02 (SAS Institute, Inc., Cary, NC) was used to perform all analyses.

RESULTS

Most of the ART procedures were planned as IVF (43%) or ICSI cycles (40%). Combination IVF/ICSI was performed in 2,529 procedures. Cycles involving cryopreserved embryo transfer (CPE, 27,021) are reported as a separate category (Table 1).

The average age of the women was 34 ± 4.5 years (range, 17–46 years); no significant difference was observed among the four ART procedure groups. The average duration of

TABLE 2

Previous pregnancies and clinical pregnancy rates per retrieval in all ART procedures.

	No. of cycles	IVF (%)	ICSI (%)	IVF/ICSI (%)	CPE transfer (%)	Odds ratio (95% CI)	P value
Previous pregnancies							
Total	161,430	22.2	24.9	23.0	14.7		
0	104,147	21.9	24.7	23.7	14.7	1.000	
1	36,033	23.0	26.3	22.8	15.1	1.070 (1.040–1.102)	<.0001
2	12,552	22.0	24.2	21.0	15.7	1.006 (0.961–1.053)	.796
3	5,328	22.8	19.7	12.9	12.1	0.943 (0.880–1.010)	.093
>3	3,370	21.6	19.5	22.2	11.8	0.906 (0.831–0.988)	.055
Previous pregnancies any women ≤35 years of age							
Total	111,895	24.5	27.4	24.2	15.7		
0	78,739	23.6	26.7	24.7	15.4	1.000	
1	20,186	26.3	31.0	23.5	16.5	1.178 (1.137–1.222)	<.0001
2	8,142	25.2	29.2	23.2	16.4	1.104 (1.046–1.164)	.0003
3	2,868	26.1	25.1	18.8	15.8	1.081 (0.990–1.180)	.0825
>3	1,960	26.3	32.7	27.8	13.5	1.154 (1.040–1.281)	.0067

Note: CPE = cryopreserved embryo.

Kupka. Reproductive history and IVF/ICSI outcome. *Fertil Steril* 2003.

infertility was 5 ± 3.4 years (range 0–17 years); again, the four groups did not differ. Primary infertility was reported in 65% of the cycles and ranged from 58% in the IVF group to 73% in the ICSI group. Infertility diagnoses were classified as tubal disease (24%), male factor (22%), ovulatory disorder (22%), unexplained infertility (23%), and other reasons (22%). The latter category included multiple diagnoses as well as severe endometriosis, fibroids, and other, rarer diagnoses. All variables listed above were significantly associated with pregnancy outcome in ART procedures, as seen in the regression model with all five determinants included.

Of 174,909 started cycles, 161,430 (92%) resulted in oocyte retrieval and 145,807 (83%) resulted in embryo transfer. The overall cancellation rate was 8%. Cycles with no regular fertilization were seen in 11% of cases. A total of 35,648 clinical pregnancies were reported, with an overall clinical pregnancy rate per transfer of 25%. In vitro fertilization and ICSI each yielded similar pregnancy rates (26%), whereas IVF/ICSI yielded a slightly lower rate (25%). Transfer of cryopreserved embryos result in a 16% clinical pregnancy rate. A multiple pregnancy was observed in 7,930 cycles (22%). A total of 21,335 live births were reported, for an overall rate per transfer of 15%. Because the miscarriage rate is relatively high, the live birth rate in cycles with cryopreserved embryo transfer was only 9%.

Ectopic pregnancies occurred in 3% of all procedures. The overall miscarriage rate per clinical pregnancy averaged 23%. The reported 8,311 miscarriages include 233 stillbirths. The highest miscarriage rate per clinical pregnancy was observed in patients undergoing CPE transfer (27%) and was similar in ICSI cycles (23%) and IVF cycles (22.7%).

A total of 102,119 previous pregnancies had been reported. In 31,750 cycles, 1 previous pregnancy was reported;

in 14,785 cycles 2 previous conceptions were listed. More than 2 pregnancies were seen in 10,748 cycles. The range spanned 0–13 previous pregnancies (SD, 0.98). Of all 102,119 previous pregnancies, 41,082 (40%) culminated in a live birth, 34,281 (34%) ended in miscarriage, 16,044 (16%) were ectopic pregnancies, and 10,712 (11%) ended in induced abortion.

The percentage of previous pregnancies ending in a live birth decreased from 44% in women with one previous pregnancy to 27% in women with at least four previous pregnancies. The opposite trend was seen for miscarriages (32% vs. 38%). No trend was seen in ectopic pregnancies and induced abortions. Only half of the previous pregnancies (49%) occurred in the current partnership, decreasing from 50% in women with one previous pregnancy to 43% in the group with at least four previous pregnancies. On average, 19% of the previous pregnancies had been achieved by using ART.

The influence of the number of previous pregnancies on ART outcome was evaluated in a logistic regression model that included ART procedure and the number of previous pregnancies as the independent variables and clinical pregnancy as the dependent variable. The reference group was patients without previous conceptions for the category of number of previous pregnancies and by patients undergoing IVF treatment for the category of ART treatment. Having at least one previous pregnancy was associated with a small but significant increase in clinical pregnancy rate per retrieval in all ART treatment groups (Table 2). More than one former conception showed an inverse association to ART success rate; this was largely due to the confounding effect of age. When the analysis of pregnancy rates was restricted to women younger than 36 years of age, woman with one, two,

TABLE 3

Age and clinical pregnancy rates per retrieval in ART procedures.

Age (y)	No. of cycles	IVF (%)	ICSI (%)	IVF/ICSI (%)	CPE transfer (%)	Odds ratio (95% CI)	P value
All	161,430	22.2	24.9	23.0	14.7		
≤26	11,211	23.7	27.4	19.9	14.0	1.000	
27–28	12,945	25.6	28.0	21.7	15.6	1.106 (1.042–1.173)	.0008
29–30	20,757	25.0	28.4	28.9	16.7	1.121 (1.062–1.182)	<.0001
31–32	26,864	24.6	27.8	23.9	16.3	1.088 (1.033–1.145)	.0015
33–34	27,413	24.3	26.8	23.0	15.4	1.050 (0.997–1.105)	.0657
35–36	23,801	22.3	24.9	26.3	14.4	0.949 (0.900–1.001)	.0551
37–38	17,535	20.1	21.6	22.3	13.5	0.814 (0.769–0.862)	<.0001
39–40	12,382	16.8	17.1	13.1	10.6	0.629 (0.589–0.671)	<.0001
41–42	5,620	11.4	12.1	12.5	8.9	0.418 (0.380–0.458)	<.0001
>42	2,902	5.8	4.9	—	3.9	0.175 (0.148–0.208)	<.0001

Note: CPE = cryopreserved embryo.

Kupka. Reproductive history and IVF/ICSI outcome. *Fertil Steril* 2003.

three, or more than three previous pregnancies had higher pregnancy rates than did the women with no previous conceptions (reference group).

The effect of age was evaluated by including terms for 10 age groups in the logistic model, using the youngest group as the reference (Table 3). For IVF treatments, the best results were observed in women 27 or 28 years old, who had a clinical pregnancy rate per retrieval of 26%. For ICSI procedures, the best results were seen in women 29 or 30 years of age (clinical pregnancy rate per retrieval, 28%). The combination of IVF/ICSI and transfer of CPE were also most successful in this age category (29% and 17%, respectively). The success rates of all ART procedures decreased in higher age categories. All procedures in women older than 36 years of age showed highly significant negative correlations (P

<.0001). Women 27 to 30 years of age had statistically significant associations with success rate and kind of treatment. Among women 33 to 36 years of age, the threshold of significance was not reached (P = .0657 and .0551).

To evaluate the influence of the outcome of a previous pregnancy on a planned IVF, ICSI, or CPE treatment, another regression model was established to correlate the outcome (live birth, miscarriage, induced abortion or ectopic pregnancy), method of conception (with or without any former ART treatment), and the four evaluated ART procedures (IVF, ICSI, IVF/ICSI, and CPE). To reduce further bias, only the results of previous pregnancies in the same partnership as ART procedures were analyzed (Table 4). A former successful ART procedure resulting in a live birth or miscarriage was detected as the most important prognostic

TABLE 4

Outcome of previous pregnancies and clinical pregnancy rates per retrieval in ART procedures in the same partnership as the previous conception.

Previous pregnancies	No. of cycles	IVF (%)	ICSI (%)	IVF/ICSI (%)	CPE transfer (%)	Odds ratio (95% CI)	P value
None	104,147	21.9	24.7	23.7	14.7	1.000	
≥1 live birth ^a	4,987	24.1	24.9	27.9	14.8	0.955 (0.905–1.008)	.7162
≥1 live birth ^b	6,134	27.3	33.3	20.6	19.1	1.069 (0.996–1.147)	<.0001
≥1 miscarriage ^a	6,815	21.4	24.0	26.6	14.6	0.907 (0.856–0.962)	.3416
≥1 miscarriage ^b	5,425	26.2	29.2	29.8	16.3	0.973 (0.914–1.035)	<.0001
≥1 induced abortion ^a	1,063	22.6	22.9	20.0	15.0	0.906 (0.850–0.964)	.8342
≥1 induced abortion ^b	125	26.4	27.5	—	25.8	0.972 (0.837–1.126)	.1392
≥1 ectopic pregnancy ^a	6,018	23.7	22.7	16.0	13.0	0.927 (0.857–1.004)	.3144
≥1 ectopic pregnancy ^b	1,215	22.6	22.8	14.3	13.8	1.028 (0.964–1.096)	.7162

Note: CPE = cryopreserved embryo.

^a Spontaneous conception.

^b Conception after ART procedure, including IUI, IVF, ICSI, IVF/ICSI, GIFT, or CPE.

Kupka. Reproductive history and IVF/ICSI outcome. *Fertil Steril* 2003.

TABLE 5

Duration of infertility and clinical pregnancy rates per retrieval in ART-procedures.

Duration of infertility (y)	No. of cycles	IVF (%)	ICSI (%)	IVF/ICSI (%)	CPE transfer ^a (%)	Odds ratio (95% CI)	<i>P</i> value
Total	124,602	26.6	26.4	25.1	15.9		
0–2	19,005	27.4	27.7	26.0	16.6	1.000	
3–4	48,786	26.9	26.3	25.6	16.2	0.952 (0.916–0.989)	.0122
5–6	32,003	26.6	26.5	24.3	15.8	0.949 (0.911–0.989)	.0144
7–8	17,482	25.8	26.0	25.4	15.2	0.917 (0.875–0.962)	.0004
>8	7,326	25.1	24.9	19.3	15.0	0.873 (0.818–0.930)	<.0001

Note: CPE = cryopreserved embryo transfer.

Kupka. Reproductive history and IVF/ICSI outcome. *Fertil Steril* 2003.

factor for ART outcome in this model ($P < .0001$). One or more previous live births resulting from spontaneous conception also nonsignificantly improved the clinical pregnancy rates of ART procedures. Compared with patients who had no former conception, the success rate in IVF cycles increased from 22% to 27% among patients with at least one live birth achieved by an ART procedure. In ICSI treatments, the difference was even greater (25% vs. 33%). A previous miscarriage as a result of an ART procedure was associated with an increase of the clinical pregnancy rate per retrieval in IVF cycles from 22% to 26% in cycles with no former conception. In ICSI cycles, the difference was similar (25% vs. 29%). When former induced abortions and ectopic pregnancies were analyzed, a statistically significant effect on ART outcome could not be demonstrated, although the clinical pregnancy rate in IVF cycles increased in all categories. No statistically significant impact was observed for previous pregnancies achieved by natural conception.

Duration of infertility was tested in a logistic model including the different ART procedures and success rates (Table 5). Five categories of duration were established. All ART treatments had best results in patients with a maximum of 2 years of infertility. Duration of infertility of 2 years or longer was negatively and significantly correlated with the clinical pregnancy rate per retrieval. The most powerful significance was seen in patients who had been infertile for up to 8 years ($P < .0001$). In IVF treatments, the pregnancy rate per retrieval decreased from 27% in patients with a maximum of 2 years of infertility to 25% in patients with more than 8 years of infertility. In ICSI treatments, the pregnancy rate per retrieval decreased from 28% to 25%.

DISCUSSION

Counseling of subfertile couples should include accurate information about estimated success rates. Various prognostic factors in ART procedures have been described and analyzed, including cause of infertility (18), previous successful treatment cycles (9, 10), cancellation rates (4), the number of aspirated oocytes (10), the proportion of aspirated

to fertilized oocytes (11, 12), semen quality variables (13–15), the number and quality of embryos (16), the time between oocyte aspiration and embryo transfer (17), and basal follicle stimulating hormone levels (3). Spira (40) described the female factors in human fertility as especially related to age but also to lifestyle, environmental factors in general, pathologic events during the cycle, and the functional status of the genital organs.

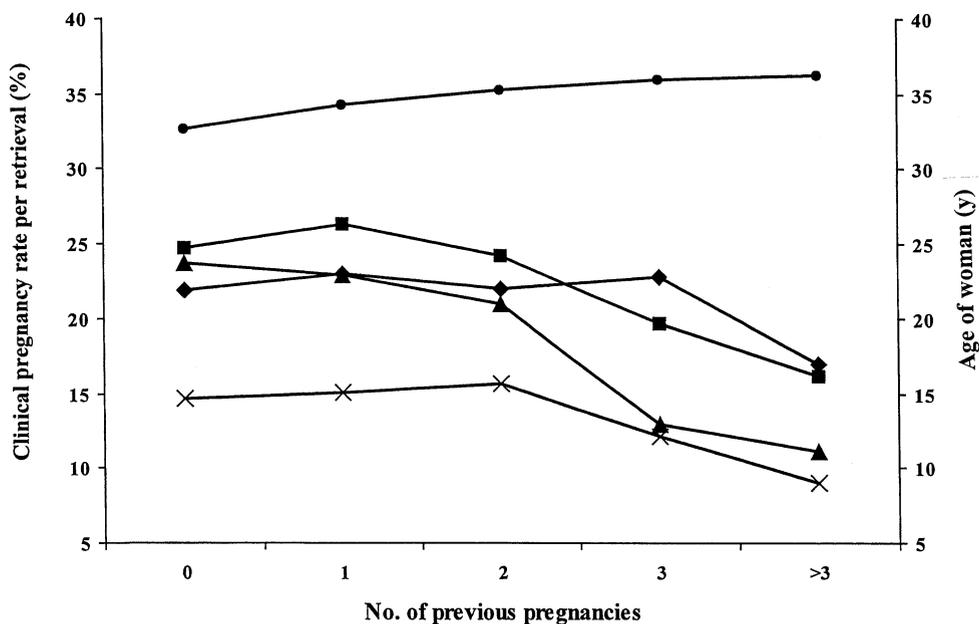
Several attempts have been made to express a likelihood of conception as a mathematical formula (4, 10, 16, 41). Templeton et al. (41) analyzed IVF cycles to establish a mathematical model for prediction of live birth rate. Age, cause of infertility, duration of infertility, and former IVF attempts were integrated and assigned a specific mathematical weight. Eimers et al. developed an infertility score that included such items as female age, duration of infertility, and previous pregnancies to calculate the chances of conception. Primary infertility was assigned 7 points, suggesting only slight influence. In contrast, female age older than 41 years had 20 points (42).

Thonneau et al. created a logistic regression model calculating different risk factors for infertility that also included ectopic pregnancies, which had been regarded as a risk against further conceptions (43). Baeten et al. (4) created a model to identify characteristics correlated to uterine receptivity in IVF treatments. In 281 cycles, a significant effect of primary vs. secondary infertility was not demonstrated. Hughes et al. (10) devised another formula for the probability of obtaining a pregnancy in IVF treatment that included female age and previous failed fertilization. Reproductive history was not considered. Focusing on the effect of the number of transferred embryos, Engmann et al. (44) described a previous IVF live birth with an odds ratio of 1.5, increasing the probability of birth per embryo transfer.

We found that a previous conception had an effect on all ART procedures, including IVF, ICSI, combined IVF/ICSI, and CPE transfer. This result is similar to those of other studies (4, 19). Templeton et al. (41) analyzed 52,507 IVF cycles from the British IVF Registry and demonstrated an

FIGURE 1

Clinical pregnancy rates per retrieval in IVF (◆), ICSI (■), IVF/ICSI (▲) and CPE transfer (×) relative to the number of previous pregnancies and female age (●).



Kupka. Reproductive history and IVF/ICSI outcome. *Fertil Steril* 2003.

increase of the live birth rate per retrieval from 14.1% in patients without a former pregnancy to 15.4% in couples with at least one former conception and 25.3% in couples with one former live birth achieved by an IVF treatment.

Without adjustment for age, more than one former conception was negatively correlated with ART pregnancy rates. When female age was restricted to a maximum of 35 years, the association disappeared. This confounding effect of female age was also illustrated by several other studies (1–6). Preutthipan et al. (5) demonstrated that female age of 35 years is a significant threshold with regard to the IVF success rate. Results from the U.S. IVF Registry also demonstrate that in age groups older than 35 years, live birth rates for ART cycles using fresh, nondonor eggs or embryos decrease. In the age group 35 years of age or younger, the ART live birth rate among women with primary infertility was 31%; this rate decreased to 9% in the age group of 41 or 42 years (35).

Another age-related factor is the duration of infertility. We found a statistically significant decrease in the clinical pregnancy rate per retrieval that was related to duration of infertility. The findings were similar to those of Eimers et al. (42), who established five categories of infertility duration (1, 2, 3 or 4, 5 or 6, and ≥ 7 years) with specific mathematical factors for each group. Templeton et al. described six such groups (0, 1–3, 4–6, 7–9, 10–12, and > 12 years) and

found a significant reduction in the success rate with increased duration of infertility (41).

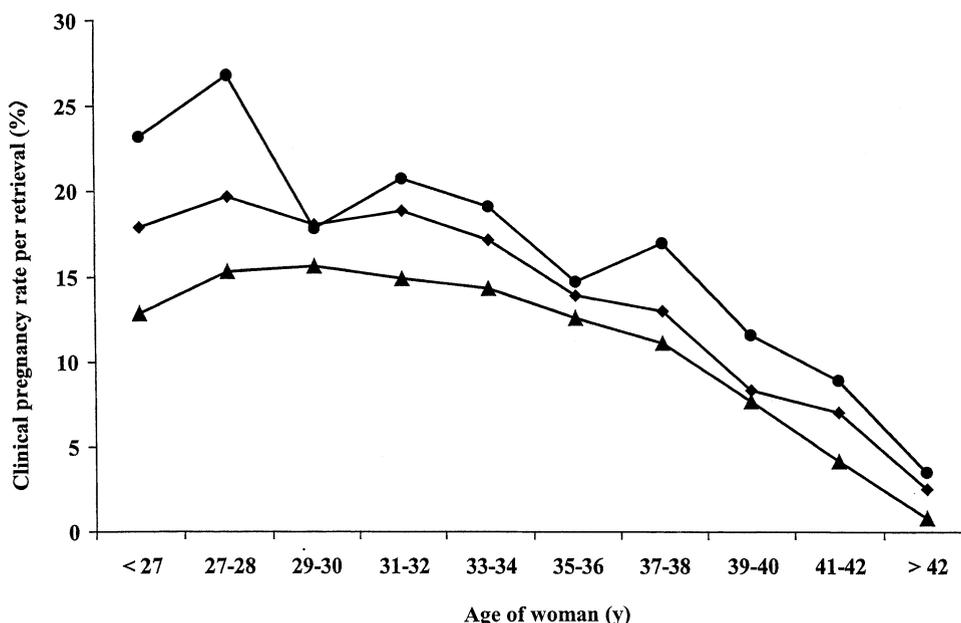
In terms of the effect of a previous pregnancy on the outcome of IVF, ICSI, or CPE transfer, no statistically significant difference was observed for live births, miscarriages, induced abortions, or ectopic pregnancies achieved by natural conception. This is surprising, as most of the former investigations described a positive effect of at least one former live birth (24, 41).

Our results demonstrate increased but nonsignificant success rates. This could be caused by the data set structure of the registry, which does not allow merging different cycles from one couple. In addition, the variety of classified former pregnancies in at least 16 categories (outcome, method of conception, partnership) could have influenced the statistical results. Comparison with results of other registries is not possible because no other registries collect data concerning previous pregnancies in such detail. The United Kingdom data set contains information about the total number of previous pregnancies (natural and assisted conception), IVF pregnancies, and live births. The data set of the U.S. Registry contains items concerning the total number of previous pregnancies, previous full-term and preterm births, and spontaneous abortions.

We found that a former successful ART treatment has the most significant effect on ART outcome. This is similar to

FIGURE 2

Clinical pregnancy rates per retrieval in IVF relative to previous pregnancies achieved by spontaneous conception or ART procedures; *triangles* represent no previous pregnancies; *diamonds* represent one or more live births (no ART); and *circles* represent one or more live births (ART).



Kupka. Reproductive history and IVF/ICSI outcome. *Fertil Steril* 2003.

Templeton et al.'s findings (41), in which a difference in IVF live birth rates per retrieval was observed depending on the method of former conception (by ART, 25.3%; by spontaneous conception, 17.0%). Croucher et al. (46) analyzed 9,316 IVF cycles and concluded that the pregnancy rate increased from 23.6% to 32.5% depending on a previous unsuccessful vs. successful therapy cycle.

In general, the comparatively low clinical pregnancy rate and live birth rate in the German data set is related to the German Embryo Protection Act of 1991 and the consequences of limiting the maximum number of embryos to be transferred, forbidding a donor program, and preventing embryo selection by limiting the period of freezing to the pronuclear stage. In 1999, the average clinical pregnancy rate per retrieval in IVF cycles was 35.4% in the United States and 24.2% in Germany. The U.S. report demonstrates that in 36% of ART cycles using fresh, nondonor eggs or embryos, more than three embryos had been transferred (35). The percentage of twins among all ART live births was reported to be 32% in the United States and 22% in Germany. Higher multiples (triplets or more) were reported in 4.9% of cases in the United States and in 3.1% of cases in Germany (35, 38). Nevertheless, in the interest of avoiding higher multiple pregnancies, the number of embryos transferred can be reduced from three to two without affecting the overall pregnancy rate, even under the German legislative

conditions (47). The relatively high miscarriage rate in the German data set (22.3% in IVF cycles in 1999) also includes stillbirths and induced abortions. Furthermore, the high rate of loss of follow-up (11.4% in IVF/ICSI cycles and 15.6% in IVF cycles) biases the results. The U.S. registry only reported a rate of 1.1% (35). To improve data quality and ensure sufficient data, a new data set description and software with integrated plausibility checks have been initiated.

In conclusion, we found that a previously successful ART procedure ending in a live birth (or even a miscarriage) had a statistically significant positive effect on outcome of IVF, ICSI, or CPE transfer. Previous natural conceptions had a positive but insignificant effect. More than one previous pregnancy was negatively correlated. This association disappeared when female age was restricted to a maximum of 35 years. Female age and the duration of infertility had a statistically significant inverse association with ART success. Thus, the individual reproductive history and female's age must be taken into account when counseling subfertile couples.

Acknowledgments: The scientific adviser of the project for data analysis was Maurizio Macaluso, M.D., Dr.P.H., Senior Research Scientist, Chief of the Women's Health and Fertility Branch, Division of Reproductive Health,

National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, United States Department of Health and Human Services, Chamblee, Georgia. He assisted with the logistic regression model and contributed to data analysis.

References

- Dicker D, Goldman JA, Ashkenazi J, Feldberg D, Shelef M, Levy T. Age and pregnancy rates in in vitro fertilization. *J In Vitro Fert Embryo Transf* 1991;8:141-4.
- Age and in vitro fertilization. French National Register on In Vitro Fertilization. *Contracept Fertil Sex* 1997;25:503-6.
- Bassil S, Godin PA, Gillerot S, Verougstraete JC, Donnez J. In vitro fertilization outcome according to age and follicle-stimulating hormone levels on cycle day 3. *J Assist Reprod Genet* 1999;16:236-41.
- Baeten S, Bouckaert A, Loumaye E, Thomas K. A regression model for the rate of success of in vitro fertilization. *Stat Med* 1993;12:1543-53.
- Preuthippan S, Amso N, Curtis P, Shaw RW. Effect of maternal age on clinical outcome in women undergoing in vitro fertilization and embryo transfer (IVF-ET). *J Med Assoc Thai* 1996;79:347-52.
- Ashkenazi J, Orvieto R, Gold-Deutch R, Feldberg D, Dicker D, Voliovitch I, et al. The impact of woman's age and sperm parameters on fertilization rates in IVF cycles. *Eur J Obstet Gynecol Reprod Biol* 1996;66:155-9.
- de Mouzon J, Rossin-Amar B, Bachelot A, Renon C, Devecchi A. FIVNAT. Influence of attempt rank in in vitro fertilization. *Contracept Fertil Sex* 1998;26:466-72.
- Tan SL, Royston P, Campbell S, Jacobs HS, Betts J, Mason B, et al. Cumulative conception and live birth rates after in-vitro fertilisation. *Lancet* 1992;339:1390-4.
- Simon A, Ronit C, Lewin A, Mordel N, Zajicek G, Laufer N. Conception rate after in vitro fertilization in patients who conceived in a previous cycle. *Fertil Steril* 1993;59:343-7.
- Hughes EG, King C, Wood EC. A prospective study of prognostic factors in in vitro fertilization and embryo transfer. *Fertil Steril* 1989;51:838-4.
- Tan SL, Doyle P, Maconochie N, Edwards RG, Balen A, Bekir J, et al. Pregnancy and birth rates of live infants after in vitro fertilization in women with and without previous in vitro fertilization pregnancies: a study of eight thousand cycles at one center. *Am J Obstet Gynecol* 1994;170(1 Pt 1):34-40.
- De Vries MJ, De Sutter P, Dhont M. Prognostic factors in patients continuing in vitro fertilization or intracytoplasmic sperm injection treatment and dropouts. *Fertil Steril* 1999;72:674-8.
- Bouckaert A, Psalti I, Loumaye E, De Cooman S, Thomas K. The probability of a successful treatment of infertility by in-vitro fertilization. *Hum Reprod* 1994;9:448-55.
- Sukcharoen N, Keith J, Irvine DS, Aitken RJ. Prediction of the in-vitro fertilization (IVF) potential of human spermatozoa using sperm function tests: the effect of the delay between testing and IVF. *Hum Reprod* 1996;11:1030-4.
- Van Voorhis BJ, Barnett M, Sparks AE, Syrop CH, Rosenthal G, Dawson J. Effect of the total motile sperm count on the efficacy and cost-effectiveness of intrauterine insemination and in vitro fertilization. *Fertil Steril* 2001;75:661-8.
- Minaretzis D, Harris D, Alper MM, Mortola JF, Berger MJ, Power D. Multivariate analysis of factors predictive of successful live births in in vitro fertilization (IVF) suggests strategies to improve IVF outcome. *J Assist Reprod Genet* 1998;15:365-71.
- Laverge H, De Sutter P, Van der Elst J, Dhont M. A prospective, randomized study comparing day 2 and day 3 embryo transfer in human IVF. *Hum Reprod* 2001;16:476-80.
- Yovich JL, Matson PL. The influence of infertility etiology on the outcome of IVF-ET and GIFT treatments. *Int J Fertil* 1990;35:26-33.
- 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 diagnosis and primary or secondary subfertility. *Hum Reprod* 2000;15:203-9.
- Bates GW, Ginsburg ES. Early pregnancy loss in in vitro fertilization (IVF) is a positive predictor of subsequent IVF success. *Fertil Steril* 2002;77:337-41.
- Bulletti C, Flarnigni C, Giacomucci E. Reproductive failure due to spontaneous abortion and recurrent miscarriage. *Hum Reprod Update* 1996;2:118-36.
- Collins J, Graves G. The economic consequences of multiple gestation pregnancy in assisted conception cycles. *Hum Fertil (Camb)* 2000;3:275-83.
- Steinberg EP, Holtz PM, Sullivan EM, Villar CP. Profiling assisted reproductive technology: outcomes and quality of infertility management. *Fertil Steril* 1998;69:617-23.
- Lancaster PA. Registers of in-vitro fertilization and assisted conception. *Hum Reprod* 1996;11(Suppl 4):89-104.
- de Mouzon J, Bachelot A, Spira A. Establishing a national in vitro fertilization registry: methodological problems and analysis of success rates. *Stat Med* 1993;12:39-50.
- Cohen J. The future of international registries for assisted reproductive technologies. *Fertil Steril* 2001;76:871-3.
- Gesetz zum Schutz von Embryonen (Embryonenschutzgesetz-EschG) BGB1 (1990). 1:2746. Available at <http://www.bmgesundheit.de/rechts/genfpm/embryo/embryo.htm>.
- Richtlinien der Bundesärztekammer zur Durchführung der assistierten Reproduktion. *Deutsches Ärzteblatt* 1998;49:A-3166.
- Nygren KG, Andersen AN. The European IVF-monitoring programme (EIM). Assisted reproductive technology in Europe, 1998. Results generated from European registers by ESHRE. *European Society of Human Reproduction and Embryology. Hum Reprod* 2001;16:2459-471.
- Testart J, Plachot M, Mandelbaum J, Salat-Baroux J, Frydman R, Cohen J. World collaborative report on IVF-ET and GIFT: 1989 results. *Hum Reprod* 1992;7:362-9.
- Jones HW Jr, Cohen J. IFFS surveillance 01. *Fertil Steril* 2001;76(5 Suppl 2):5-36.
- Vayena E, Rowe PJ, Griffin PD. Current practices and controversies in assisted reproduction—Report of a meeting on "Medical, Ethical and Social Aspects of Assisted Reproduction." Available at <http://www.who.int/reproductive-health/infertility/>.
- Felberbaum R, Dahncke W. The German IVF Registry as a quality assurance tool and for use in patient counseling. *Gynäkologe* 2000;33:800-11.
- Adamson GD, Lancaster P, de Mouzon J, Nygren KG, Zegers-Hochschild F. A simple headstone or just eliminate the chads? *Fertil Steril* 2001;76:1284-5.
- Centers for Disease Control and Prevention, American Society for Reproductive Medicine, Society of Assisted Reproductive Technology, RESOLVE. 1999 Assisted Reproductive Technology Success Rates. Atlanta: Centers for Disease Control and Prevention; 2002. Available at <http://www.cdc.gov/nccdphp/drh/ART99/index99.htm>; data set, <http://www.sartcors.com/#DataCollect>.
- HFEA Human Fertilisation and Embryology Authority Annual Report 2000. Available at <http://www.hfea.gov.uk/frame3.htm>.
- FIVNAT 2000 report. French National Register on In Vitro Fertilization. Available at <http://perso.wanadoo.fr/fivnat.fr/bilan2000.htm>.
- Deutsches IVF-Register DIR, Jahrbuch 2000. Ärztekammer Schleswig-Holstein, Bad-Segeberg, Germany. Available at <http://www.deutsches-ivf-register.de>.
- McCullagh P, Nelder JA. Generalized linear models. 2nd ed. London: Chapman and Hall; 1989.
- Spira A. Epidemiology of human reproduction. *Hum Reprod* 1986;1:111-5.
- Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 1996;348:1402-6.
- Eimers JM, te Velde ER, Gerritse R, Vogelzang ET, Looman CW, Habbema JD. The prediction of the chance to conceive in subfertile couples. *Fertil Steril* 1994;61:44-52.
- Thonneau P, Quesnot S, Ducot B, Marchand S, Fignon A, Lansac J, et al. Risk factors for female and male infertility: results of a case-control study. *Hum Reprod* 1992;7:55-8.
- Engmann L, Maconochie N, Tan SL, Bekir J. Trends in the incidence of births and multiple births and the factors that determine the probability of multiple birth after IVF treatment. *Hum Reprod* 2001;16:2598-605.
- Assisted reproductive technology in the United States: 1999 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil Steril* 2002;78:918-31.
- 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;13:403-8.
- Ludwig M, Schopper B, Katalinic A, Sturm R, Al-Hasani S, Diedrich K. Experience with the elective transfer of two embryos under the conditions of the German embryo protection law: results of a retrospective data analysis of 2573 transfer cycles. *Hum Reprod* 2000;15:319-24.