Article

Spontaneous pregnancy after successful ICSI treatment: evaluation of risk factors in 899 families in Germany

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Abstract

There are only scarce data on the incidence of spontaneous pregnancy in infertility patients. Contraception after infertility treatment is another topic that has been neglected so far. Therefore, a questionnaire was sent to 1614 couples with a child conceived by intracytoplasmic sperm injection (ICSI) aged 4–6 years. A total of 899 couples responded (response rate 55.7%). A total of 10.9% of couples had used contraception. Of the couples that had actively tried to conceive, 20.0% had conceived spontaneously, resulting in a live-birth rate of 16.4%. 74.5% of these pregnancies were conceived within 2 years after delivery. A further 26.6% of couples conceived again by ICSI, with a live-birth rate of 20.9%. Maternal age was the only prognostic factor for spontaneous conception. Parents of multiples after ICSI did not have a higher chance of spontaneous conception than parents of singletons. Couples can be counselled that one out of five couples conceive spontaneously after successful ICSI. Even when assuming that none of the families that were lost to follow-up had conceived spontaneously, one out of eight couples would have conceived spontaneously. Therefore, it is important to counsel patients about the possibility of natural conception and necessity to use contraception despite their history of subfertility.

Keywords: *contraception, ICSI, infertility, natural conception, spontaneous conception, spontaneous pregnancy*

Introduction

Little is known about the incidence of spontaneous pregnancies in subfertile patients. Subfertile patients who conceive spontaneously after successful or unsuccessful fertility treatment are known anecdotally to most fertility practitioners. However, data estimating the risk of conceiving are rare. Such information is an important part of counselling of such patients. The unplanned, spontaneous conception of additional children can have unforeseen social, economic and psychological implications, especially for families with multiple births after intracytoplasmic sperm injection (ICSI) treatment.

Reports on treatment-independent pregnancy rates vary from 5–22%, depending on the cohort assessed (Olivennes *et al*., 1997; Shimizu *et al*., 1999; Hennelly *et al*., 2000). However, it is not known whether all couples intended to conceive again or whether they used contraceptives after the IVF birth. There are no data about contraceptive behaviour of infertility patients. Studies that assume that all infertility patients try to conceive again, and therefore do not use contraceptives, underestimate the true treatment-independent pregnancy rate.

This study followed a cohort of 899 families who had a child conceived by ICSI in order to assess data on the use of contraceptives and on further pregnancies.

Materials and methods

Study design

The aim of the study was to assess the chance of a spontaneous pregnancy in patients who had had a liveborn infant(s) after ICSI treatment. The data were collected as part of an ongoing cohort study. The primary outcome of this study was spontaneous pregnancy rate 5 years after successful ICSI treatment, and the outcome of these pregnancies.

Families

The families were recruited from a cohort of children that took part in a previous prospective cohort study (German ICSI follow-up study I) (Ludwig and Katalinic, 2002, 2003; Katalinic *et al.*, 2004). In the previous study, 2688 pregnancies with 3373 fetuses/children after ICSI treatment were followed prospectively and the children were examined at the age of 6–8 weeks. Of the parents of this study, 1947 had agreed to be contacted again. From this cohort of ICSI children, 323 singletons born at term were recruited for a prospective, controlled study about the health of the children at the age of 5–6 years (ICSI follow-up study II).

For the present study, 1614 families who had not been contacted for the ICSI follow-up study II were contacted via postal enquiry and asked to answer a questionnaire.

Questionnaire

The questionnaire was sent out by mail. Those families who had not answered the questionnaire within 4 weeks were reminded by mail. If they did not answer within 4 additional weeks, they were contacted by phone and asked to complete the questionnaire. If they did not return the questionnaire within 4 weeks, they were contacted by phone for a second time and were offered to answer the questionnaire by phone instead of returning it by mail. If the mail could not be delivered, because the family had moved, attempts were made to get the new address by contacting the residents' registration offices.

The questionnaire contained questions on the use of contraceptives, further pregnancies, the mode of conception of further pregnancies and the outcome of further pregnancies.

The parents were also asked to report on the child's medical history and about their attitude towards disclosure. These results are reported elsewhere (Ludwig *et al.*, 2007).

Statistics

The data were evaluated with the program Statistics Package for Social Sciences (SPSS) 15.0 (SPSS, Chicago, IL, USA). The association between factors and outcomes were tested using the chi-squared test. The means of continuous variables were compared using the *t*-test. Logistic regression analysis was performed in order to analyse factors influencing the chance of spontaneous conception. *P*-values less than 5% were considered to be significant.

Ethics

The study was approved by the ethics committee of the University of Lübeck, Germany. Written informed consent was obtained from the parents.

Results

Response rate

Out of the 1614 families that were contacted by mail, 899 families answered the questionnaire, resulting in a response rate of 55.7%. The responses are summarised in **Tables 1** and **2** and detailed below.

Contraceptive behaviour

Of the 899 families, 77.3% (695) had actively tried to conceive, 10.9% (98) had used contraceptive methods, 1.8% (16) had undergone prior sterilization or hysterectomy and 1.2% (11) of couples had separated meanwhile or one of the partners had died. Thus, 13.9% (125/899) of couples had not actively tried to conceive again. No information about use of contraceptives was available for 8.8% (79) of couples.

The parental age at birth of the ICSI child did not influence the contraceptive behaviour. Couples who had used contraceptive methods were more likely to have had other children born before the birth of the ICSI child compared with couples without preceding live births (mean number of live births before the birth of the ICSI child: 0.36 versus 0.20, $P < 0.001$). Parents with twins or triplets were more likely to use contraceptives than parents with a singleton ICSI child ($P < 0.001$). Of the 98 couples who had used contraception, 48.0% (47) had given birth to multiples after ICSI compared with 21.0% (146) of the couples who had actively tried to conceive. However, 30.6% (30) of the couples who were using contraceptives did so even though the ICSI child was their only child.

Pregnancies

Of the 695 couples that had actively tried to conceive, 44.9% (312) conceived again within 6 years after the birth of the ICSI-conceived child, regardless of the mode of conception, and 37.6% (261) had given birth to at least one further child. 20.0% (139) of couples had conceived spontaneously at least once resulting in a treatment-independent delivery rate of 16.4% (114) (**Table 1**). 26.6% (185) had conceived at least once again by ICSI and 20.9% (145) had given birth to at least one more ICSI-conceived child. 14 couples had conceived spontaneously even after two ICSI pregnancies resulting in 10 live births (**Figure 1**). Pregnancy outcome is summarized in **Table 2**. Among the 125 couples who had not actively tried to conceive again, one couple had conceived spontaneously in spite of the use of contraceptives.

Factors influencing the chance of spontaneous conception

Maternal age was an independent prognostic factor for the chance of spontaneous conception after an ICSI pregnancy (**Table 3**). Mothers who conceived spontaneously were significantly younger than those who did not conceive spontaneously (32.06 ± 4.08 versus 33.01 ± 3.80 years, $P = 0.013$). Also, fathers were significantly younger in couples that conceived spontaneously (34.89 ± 5.07 versus 36.20 ± 4.95 years, $P = 0.008$). Reproductive history did not influence the chance of spontaneous conception. A previous pregnancy or a previous live birth before the birth of the ICSI-conceived child did

Table 1. Reproductive behaviour and further pregnancies and births following successful intracytoplasmic sperm injection (ICSI) treatment.

	Per cent (n)
Reproductive behaviour[a]	
Trying to conceive again	77.3 (695)
Use of contraceptive methods	10.9 (98)
Partners separated or one of the partners died	1.2 (11)
Prior sterilization or hysterectomy	1.8 (16)
No information on use of contraceptives	8.8 (79)
Further pregnancies and births[b]	
≥1 pregnancy after ICSI-conceived child	44.9 (312)
≥1 birth after ICSI-conceived child	37.6 (261)
≥2 births after ICSI-conceived child	2.7 (19)
≥1 spontaneously conceived pregnancy after ICSI-conceived child	20.0 (139)
≥1 birth after spontaneous conception after ICSI-conceived child	16.4 (114)
2 births after spontaneous conception after ICSI-conceived child	2.0 (14)

[a]$n = 899$ (all respondents); [b]$n = 695$ (respondents who tried to conceive again).

Table 2. Pregnancy outcome of all further pregnancies conceived after the birth of a child conceived by intracytoplasmic sperm injection (ICSI).

	Per cent (n)
First pregnancy after ICSI-conceived child	44.9 (312/695)
Mode of conception	
Spontaneous	40.1 (125/312)
ICSI	57.1 (178/312)
Infertility treatment other than ICSI	2.8 (9/312)
Pregnancy outcome	
Birth	78.4 (243/310)
Miscarriage	17.7 (55/310)
Induced abortion	2.6 (8/310)
Ongoing pregnancy	1.3 (4/310)
Delivery	
Vaginal delivery	66.7 (156/234)
Caesarean section	33.3 (78/234)
Second pregnancy after ICSI-conceived child	7.5 (52/695)
Mode of conception	
Spontaneous	50.0 (26/52)
ICSI	48.1 (25/52)
Infertility treatment other then ICSI	1.9 (1/52)
Pregnancy outcome	
Birth	57.7 (30/52)
Miscarriage	26.9 (14/52)
Induced abortion	5.8 (3/52)
Ongoing pregnancy	9.6 (5/52)
Delivery	
Vaginal delivery	66.7 (20/30)
Caesarean section	30.0 (9/30)
Mode of delivery unknown	3.3 (1/30)

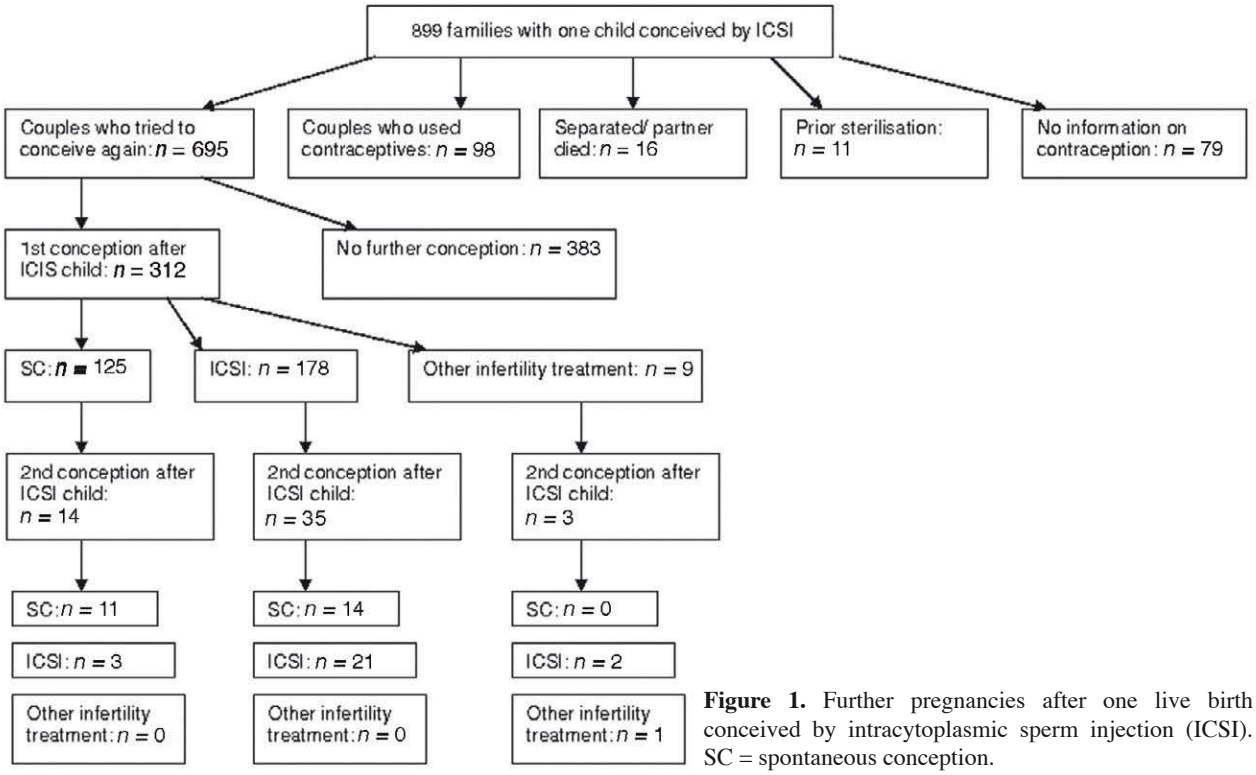

Figure 1. Further pregnancies after one live birth conceived by intracytoplasmic sperm injection (ICSI). SC = spontaneous conception.

Table 3. Factors influencing the chance of spontaneous conception assessed by logistic regression after previous birth of a child conceived by intracytoplasmic sperm injection (ICSI).

	OR	*95% CI*	P-*value*
Maternal age	0.93	0.88–0.98	0.004
Previous pregnancies	1.59	0.93–2.73	NS
Previous live births	0.75	0.39–1.45	NS
ICSI pregnancy: singletons versus multiple births	1.21	0.75–1.95	NS
Origin of spermatozoa: ejaculate versus TESE/MESA	0.08	0.01–0.61	0.014
Indication for ICSI: severe OAT versus other[a]	0.96	0.55–1.68	NS

[a]Obstructive azoospermia, non-obstructive azoospermia or failed fertilization in IVF.
CI = confidence interval; MESA = micro-epididymal sperm aspiration; NS = not statistically significant; OAT = oligoasthenotheratozoospermia; OR = odds ratio; TESE = testicular sperm extraction.

Table 4. Characteristics of the initial successful intracytoplasmic sperm injection (ICSI) cycle.

	Spontaneous conception after ICSI child (% [n])	*No spontaneous conception after ICSI child (% [n])*	P-*value*
Indication for ICSI (%)			
Severe OAT	84.2 (117/139)	78.8 (436/553)	NS
Obstructive azoospermia	1.4 (2/139)	2.5 (14/553)	
Non-obstructive azoospermia	0.7 (1/139)	4.2 (23/553)	
Failed fertilization in IVF	8.6 (12/139)	7.8 (43/553)	
Other	5.0 (7/139)	6.7 (37/553)	
Number of spermatozoa in ejaculate ($\times 10^6$/ml)[a]	18.25 ± 21.65	15.53 ± 33.37	NS
Origin of spermatozoa (%)			
Ejaculated spermatozoa	97.8 (136/139)	91.3 (505/553)	0.013
TESE	2.2 (3/139)	7.8 (43/553)	
MESA	0 (0/139)	0.9 (5/553)	

[a]Data were available for 124 couples with spontaneous pregnancy and 472 couples without spontaneous pregnancy.
MESA = micro-epididymal sperm aspiration; NS = not statistically significant; OAT = oligoasthenotheratozoospermia; TESE = testicular sperm extraction.

not influence the chance of spontaneous conception. Parents of multiple births conceived by ICSI did not have a higher chance of spontaneous conception than parents of ICSI-conceived singletons (22.8% versus 19.3%, not statistically significant).

The indication for ICSI did not influence the chance of spontaneous conception. However, in the majority of cases the indication was severe oligoasthenoteratozoospermia; only 20.4% of patients had undergone ICSI for other indications (**Table 4**). The origin of the spermatozoa significantly influenced the chance of spontaneous conception (**Table 3**). Couples who had undergone ICSI with ejaculated spermatozoa were more likely to have conceived spontaneously than those who had undergone ICSI with testicular sperm extraction (TESE) or micro-epididymal sperm extraction (MESA). However, three out of 46 couples had conceived spontaneously after having conceived the ICSI child with ICSI/TESE. The number of spermatozoa in the ejaculate used for the ICSI cycle in which the ICSI child was conceived did not influence the chance of spontaneous conception.

Time to pregnancy

Couples who had conceived spontaneously had conceived after a mean duration of 18.8 ± 12.7 months after the birth of the ICSI-conceived child, while couples who had conceived again by ICSI did so after 25.5 ± 11.6 months ($P < 0.001$).

Of the spontaneous pregnancies, 74.5% were conceived within 24 months. Only 16% of the spontaneous pregnancies were conceived after more than 3 years (**Figure 2**). Of the further ICSI pregnancies, 53.9% were conceived within 24 months (**Figure 2**).

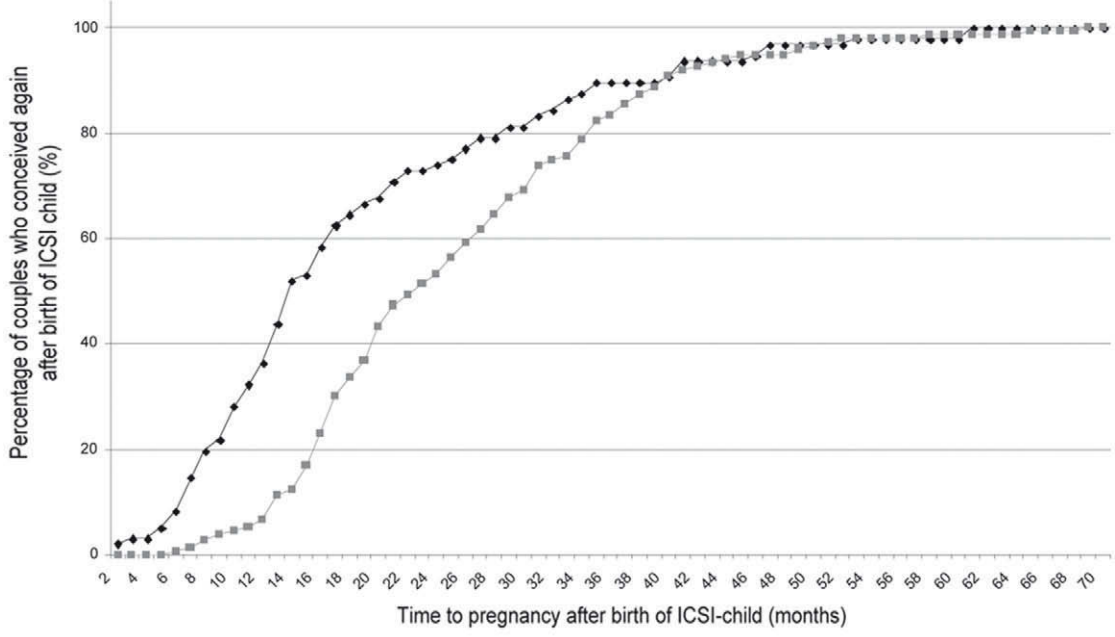

Figure 2: Time to a further pregnancy conceived spontaneously or by intracytoplasmic sperm injection (ICSI) after the birth of an ICSI-child.

Perinatal characteristics

There were no significant differences between spontaneously conceived singletons and those singletons that were again conceived by ICSI in the perinatal outcome in means of the birth weight (3510 g versus 3465 g, respectively), the gestational age and birth (38.8 weeks versus 39.1 weeks), the percentage of singletons born preterm (4.9% versus 4.6%) and the number of term singletons born with a low birthweight of <2500 g (0% versus 0.7%).

Discussion

Future fertility is often neglected when counselling infertility patients, probably because they are assumed to be happy if they conceive spontaneously even if the pregnancy is unplanned. The couples themselves often assume that they cannot conceive and that they therefore do not have to worry about contraception.

However, there are also subfertile patients who do not want to conceive again. In this follow-up of 899 families who had given birth to a child conceived by ICSI, it could be shown that 10.9% of couples had used contraceptives. The fact that 30.6% of those couples had had only one child born after ICSI shows that, even after infertility treatment, not only parents of multiple births or parents of several children use contraceptives. By neglecting the fact that previous infertility patients would not use contraceptives, the treatment-independent spontaneous pregnancy rate is underestimated in most studies.

Of the 695 couples that tried to get pregnant again, 20.0% conceived spontaneously at least once with a delivery rate of 16.4%.

For comparison, the likelihood to conceive within 12 months is 92% for normal fertile couples when optimizing the chances to conceive by correct timing of intercourse (symptothermal) (Gnoth *et al.*, 2003). In another recent study, the cumulative pregnancy rate over 2 cycles was 22.7% for couples using a home fertility monitor and 14.4% for couples not using a fertility monitor ($P = 0.003$) (Robinson *et al.*, 2007).

Although most couples conceive within 12 months, there is still a chance to conceive after a longer period. The cumulative live-birth rate in untreated infertility patients has been shown to be 14.3% over a period of 12 months (Collins *et al.*, 1995). Relevant prognostic factors were the pregnancy history, the female partner's age, the underlying cause of infertility and the duration of infertility.

The pregnancy rate of infertility patients who have already conceived by IVF or ICSI varies from 8.9% (Olivennes *et al.*, 1997) to 18% (Shimizu *et al.*, 1999) and 22.2% (Hennelly *et al.*, 2000).

Shimizu *et al.* (1999) followed 142 women who had conceived by IVF and showed that 18% of these women conceived spontaneously within 60 months after the IVF birth. Most conceptions occurred within 2 years after delivery. Hennelly *et al.* (2000) showed that the spontaneous pregnancy rate after an ICSI birth is much lower than after an IVF birth. They reported a spontaneous pregnancy rate of 22.2% in 469 couples who had given birth to a child after IVF and of only 4.6% in 44 couples with a child born after ICSI (Hennelly *et al.*, 2000). The pregnancy rate in this ICSI cohort in the present study was much higher. However, the ICSI cohort assessed by Hennelly *et al.* was rather small and therefore less representative.

Olivennes *et al.* (1997) reported a spontaneous pregnancy rate of only 8.9% in a follow-up study of 370 IVF children. However, these children were born during 1981–1988. In those years, when IVF was a new technique and ICSI was still unknown, IVF therapy was probably performed in a highly selected cohort of patients. Over time, the indication for IVF therapy has been extended from tubal infertility to other causes of infertility like endometriosis and idiopathic infertility. This might explain the lower pregnancy rate reported by Oliviennes *et al.* (1997) and by other early studies (Haney *et al.*, 1987; Roh *et al.*, 1987; Fadini *et al.*, 1993; Olivennes *et al.*, 1997) that reported treatment-independent pregnancy rates of 6.6–11.2% in infertility patients who were treated in the 1980s.

The spontaneous pregnancy rate of patients who have discontinued infertility treatment after failed cycles is lower than after successful cycles. After failed IVF cycles, a spontaneous pregnancy rate of 11.2% has been reported by Vardon *et al.* (1995). Osmanagaoglu *et al.* (2002) found a delivery rate after spontaneous conception of 11.5% in 200 ICSI patients younger than 37 years who had discontinued ICSI therapy. The monthly spontaneous fecundity rate was 0.23% (23 pregnancies/8349 months). The mean time for a spontaneous pregnancy was 20.2 months.

Three-quarters of all spontaneous pregnancies were achieved within 2 years after delivery of the ICSI child. This is in accordance with previous studies (Shimizu *et al.*, 1999; Hennelly *et al.*, 2000; Osmanagaoglu *et al.*, 2002).

Maternal age was the only factor in this study that significantly influenced the chance of a spontaneous conception ($P < 0.004$). The correlation between maternal age and the chance of conception is in agreement with the findings of Shimizu *et al.* (1999) and Hennelly *et al.* (2000). This is unsurprising, as age is known as a major prognostic factor for the chance of spontaneous conception as well as conception by infertility treatment (Schroder *et al.*, 2004). However, in the study by Osmanagaoglu *et al.* (2002) the maternal age did not influence the chance of conception. In that study, the duration of infertility significantly influenced the chance of spontaneous conception. Unfortunately, this information cannot be provided for this cohort. The reproductive history did not influence the chance of spontaneous conception. For conception by assisted reproduction treatment, Kupka *et al.* (2003) could show that previous pregnancies were associated with a small but significant increase in the pregnancy rate after treatment.

Having conceived multiple children with ICSI did not increase the chance of spontaneous conception, despite the argument that couples that conceive multiple pregnancies are more fertile than those who conceive a singleton pregnancy after ICSI.

The origin of the spermatozoa significantly influenced the chance of spontaneous conception ($P = 0.014$), because spontaneous pregnancies cannot be expected in azoospermic patients.

However, three patients conceived after having undergone ICSI/TESE. In these patients the TESE might have been performed because of an extremely low sperm count or motility of the ejaculated spermatozoa. Another possibility is that these women underwent a 'natural donor cycle', a possibility that can never be excluded but is beyond evaluation.

It has also been shown here that the perinatal outcome of spontaneously conceived singleton pregnancies in these former ICSI patients did not differ from singleton pregnancies that were conceived again by ICSI. This finding supports the hypothesis that the increased perinatal morbidity observed in assisted pregnancies is not caused by the technique itself but by the parents infertility *per se* (Sutcliffe and Ludwig, 2007) despite the various influences during treatment and especially ICSI (Ludwig *et al*. 2001; Schröder *et al*. 2001; Varghese *et al*. 2007).

The response rate of 56% is within the range of what can be realistically expected 5 years after delivery. If it is assumed that all families who did not respond tried to get pregnant again and failed to conceive, the spontaneous pregnancy rate would be 9.9%. If it is assumed that only 77% of the non-responders tried to conceive again (the same percentage as the responders), but all non-responders failed to conceive again, the spontaneous pregnancy rate would be 12.5%. However, these assumptions are not likely. There are many reasons why families do not respond in follow-up studies. Some families might not have responded to the questionnaire and do not want to be contacted again because they do not want to disclose the ICSI conception to their child, especially if they have conceived spontaneously after ICSI therapy. Other families might not have responded because they have separated and therefore have not tried to conceive again. Although the true likelihood of conceiving spontaneously after having conceived by ICSI is probably lower than 20% due to non-responders, it is not likely to be as low as 12.5%.

There is a perception among patients who conceived through IVF/ICSI that they cannot conceive in another way. It might seem odd to use contraceptives for those couples, even if they have had a multiple birth. These data clearly show that this is not true for as many as one out of five couples and especially for those who are younger. Therefore, information about the probability of spontaneous conception and the choice to use contraceptives has to be included in the counselling of infertility patients.

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