ORIGINAL ARTICLE

The Risk of Malformation Following Assisted Reproduction

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SUMMARY

Introduction: Intracytoplasmic sperm injection (ICSI) is currently the most frequently used human reproductive technology in Germany. ICSI was introduced as routine, insurance-funded medical care in 2002 by the Federal Joint Committee. A re-evaluation of published literature on malformation rates in children born of ICSI pregnancies within a period of three years formed part of the committee's decision. The analysis investigated whether ICSI increases the risk of malformation in the offspring, compared to in vitro fertilization (IVF) and natural conception.

Methods: Systematic literature review.

Results: 929 studies were identified. Three meta-analyses, 15 studies investigating malformations, and 12 studies analyzing imprinting disorders were included. The risk of malformation was not significantly different in nine studies comparing ICSI versus IVF. Two meta-analyses and three of eight cohort studies and retrospective analysis showed significantly more severe malformations after assisted reproduction than after natural conception. The remaining five studies displayed no significant results. Current evidence does not show a higher risk of major malformations in the offspring resulting from the use of ICSI compared to IVF. However, there is evidence that both techniques increase the risk for major malformations considerably, compared to natural conception, and further research is needed. The validity of the results is low since the studies were heterogeneous and the cohorts used in the studies had limited comparability.

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It is estimated that 10% to 15% of all couples in Europe are childless despite a desire to have children (1). Some of these couples can achieve pregnancy only with the aid of artificial fertilization. Intracytoplasmic sperm injection (ICSI) has been performed in Germany since the early 1990's: this technique increases the chance that a couple will be able to have a child, particularly if it is the male partner that is infertile. It involves the injection of a single spermatozoon through a needle into the oocyte.

Artificial fertilization techniques have been included in the catalog of procedures covered by statutory health insurance in Germany (gesetzliche Krankenversicherung, GKV) since 1990. The German Joint Federal Committee (JFC) has been given the task of writing guidelines regarding the medical details of these techniques in reproductive medicine, including the preconditions for their use and the manner and extent of the interventions to be performed. ICSI was incorporated into the GKV procedures catalog in 2002 (*diagram 1*).

ICSI became the most common method of artificial fertilization shortly after it was introduced; other methods include artificial insemination and in vitro fertilization (IVF). From 2004 onward, couples have been required to pay half of the cost of artificial fertilization themselves. *Diagram 2* shows the falloff in case numbers after the 50% co-payment rule was introduced. The introduction of ICSI gave rise to concern that this procedure might cause a higher rate of congenital malformations than in vitro fertilization or spontaneous (natural) conception. There are essentially three factors associated with assisted reproductive methods that might influence the malformation rate:

- chromosomal anomalies in the gametes used,
- medications used to stimulate fertility,
- and the injection of the sperm cell into the egg cell in ICSI.

Injection of a sperm cell into an egg cell circumvents natural selection at the egg cell membrane, damages the egg cell itself, and introduces foreign material (e.g. culture medium) into the cell.

There are only a few reports in the literature about the potentially damaging effects of stimulation on mature egg cells; the connection between spermogram parameters and the occurrence of chromosomal anomalies is better documented (2). In recent years, a number of so-called imprinting defects have been diagnosed in a small

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DIAGRAM 1

Treatment options for infertility covered by statutory health insurance in Germany

number of children conceived by ICSI. Imprinting defects arise through a disturbance of epigenetic processes during gametogenesis and/or the preimplantation phase of the fertilized egg (3).

Congenital malformations are inborn structural or functional abnormalities. They can be of mono- or polygenic origin or they may be due to external influences such as teratogenic medications or ionizing radiation. They may also be of multifactorial (genetic and external) origin. In most cases, the cause remains unknown. International classifications distinguish major from minor malformations. There is a problem, however, in that the definitions currently in use are not uniformly applied. A possible solution is provided by the classi-

fication system of the European Register of Congenital Anomalies (EUROCAT), in which major malformations are defined as physical abnormalities that are incompatible with life, require surgical correction, and/or cause functional impairment. Such malformations can place major burdens on the affected children and their parents. One-quarter of all deaths in childhood are associated with major congenital malformations (6).

In view of these facts, the JFC stipulated, when ICSI was introduced, that the rate of congenital malformations among children conceived by this method should be assessed three years after its introduction. Thus, the question whether children conceived by ICSI have more congenital malformations than those conceived naturally or by IVF was investigated by a systematic evaluation of current data.

Methods

Scientific publications in the PubMed, Cancerlit, and Embase databases were systematically searched in October 2005, and the search was updated in May 2006. The search strategy consisted of search terms related to intracytoplasmic sperm injection, in vitro fertilization, and major malformations. A particular difficulty complicating the task of assessing the risks of these types of treatment is the impossibility of performing randomized, controlled studies. The search was therefore restricted to cohort and case-control studies.

The relevant publications were identified by a two-step search by two assessors working independently – all of the authors of this article participated in the evaluation – and then filtered according to previously determined inclusion and exclusion criteria. Studies were included that compared the rate of malformations in a cohort of ICSI children with that in a cohort of IVF or naturally conceived children. As a further requirement for inclusion the odds ratio (OR) for major malformations had to be either directly stated in the study or else calculable from the reported study data. Independently of these criteria, studies reporting imprinting defects were also included.

Data were systematically extracted from the sources selected in this way (for the manner of data extraction, see www.g-ba.de/informationen/abschlussberichte). To identify systematic distortions in these publications, we looked in each publication for information about the use of prenatal diagnosis and about selective and spontaneous abortions and stillbirths, and we assessed the degree of comparability of the cohorts in each study (diagram 3).

Findings of the systematic literature review

The literature search yielded three meta-analyses (5–7) and 15 primary studies (8–22) from which the OR and the 95% confidence interval (CI) (box 1) could be determined for the comparison of ICSI versus IVF and/or ICSI versus natural conception. These figures were either directly stated in the publications or could be calculated from the reported data. All of

DIAGRAM 2

The number of treatments paid for by statutory health insurance in Germany from 2002 to 2005 including insemination techniques, in vitro fertilization, and intracytoplasmic sperm injection. From 2004 onward, couples were required to pay 50% of the cost of treatment.

these studies were cohort studies. 12 further primary studies (e1–e12) dealt with the subject of diseases traceable to imprinting defects.

Meta-analyses

Among the three meta-analyses that were found, only the one by Lie et al. (5) compared the rate of malformations among children conceived by ICSI with that among children conceived by IVF, while the meta-analyses by Rimm et al. (6) (including 7 studies) and by Hansen et al. (7) (including 25 studies) compared the rates of malformations in IVF- and ICSI-children with the rates in naturally conceived children. In both of the latter two studies, the malformation rates in IVF- and ICSI-children were significantly higher than that among naturally conceived children, with odds ratios of 1.4 (95% CI: 1.28 to 1.53) (7) and 1.29 (95% CI: 1.01 to 1.67), respectively. The meta-analysis by Lie et al. (5) involved four systematically selected clinical studies comparing ICSI cohorts with IVF cohorts with respect to the rate of major malformations, including a total of 5 395 children conceived by ICSI and 13 085 children conceived by IVF. There was no significant elevation of risk for ICSI as compared to IVF, with a relative risk of 1.12 (95% CI: 0.97 to 1.28).

A common weakness of all three meta-analyses is the lack of information about the classification of malformations used in the studies that they included, or about the method of clinical examination of the children. The individual studies included in the analyses of Hansen et al. (7) and Rimm et al. (6) were quite heterogeneous with respect to study design and results. Nor can it be excluded that various sources of error in the individual studies led to distorted results in the meta-analyses.

Having found that the meta-analyses failed to answer the question adequately, we also examined the relevant primary studies directly. Six of the primary studies that we selected had been included in at least one of the meta-analyses.

Primary studies

Study characteristics and assessment of the evidence

We identified a total of 15 studies that allowed a comparison of the rates of major malformations in a cohort of children conceived by ICSI and in another cohort of children conceived either by IVF (9 studies) or naturally (8 studies) (comparisons were made with both types of cohort in two of these studies). Kuwata et al.'s small study (14) was performed exclusively on twins and is therefore not shown in the diagrams together with the other studies (see *table*).

There was a notable degree of variation across studies in the rate of malformations in each type of cohort – ICSI, IVF, and naturally conceived children. The malformation rate for the ICSI cohorts ranged from 1% to 13%, for the IVF cohorts from 2% to 9%, and for naturally conceived children from 2% to 13%. The mean baseline risk in the naturally conceived cohorts was

DIAGRAM 3

Methods used for the literature search

4.9% (standard deviation $\pm 2.9\%$). The malformation rates in the individual studies can be found in the *table*. Because of this wide heterogeneity in both study design and study results, we refrained from performing a meta-analysis for this article, instead choosing to compare the odds ratios with each other descriptively.

The risk of malformations in children conceived by ICSI versus IVF

Nine of the 15 primary studies addressed this question. In four of them, the ICSI and IVF cohorts were both observed prospectively; in two of them, a prospective ICSI cohort was compared with a retrospective IVF control cohort. Six of the 15 primary studies were purely retrospective cohort studies, and the remaining three exclusively involved registry data and were therefore classified as retrospective studies with secondary data.

BOX 1

Statistical definitions

- Relative risk (RR): The risk of malformations in the ICSI cohort divided by that in another cohort to which it is compared
- Odds (chance): The risk of malformations in a cohort divided by the probability of no malformation in the same cohort
- Odds ratio (OR): The ratio of the odds favoring a malformation in the ICSI cohort divided by the odds in another cohort to which it is compared
 - OR = 1: the odds in the ICSI cohort and the other cohort are the same
 - OR < 1: the odds are lower in the ICSI cohort
 - OR > 1: the odds are higher in the ICSI cohort
- Confidence interval (CI): The range in which the "true value" for the population sampled in the study lies with 95% probability

The informational value of these primary studies was limited because of their mostly small size, imperfect comparability of the cohorts, and multiple testing. *Diagram 4* shows the OR and CI as a function of the size of the cohorts (depicted on a logarithmic scale); the studies were numbered in decreasing order of size.

As seen in *diagram 4*, the confidence interval for the odds ratio includes 1.0 in all studies, i.e., no significant difference was found in any study. Six studies showed an odds ratio less than 1.0, i.e., a lower risk of malformations for children conceived by ICSI compared with those conceived by IVF. In three studies, however, the odds ratio was greater than 1.0, corresponding to a higher risk of malformations after ICSI than after IVF. Two studies that were larger by far than the remaining 13 studies, each involving more than 1000 children conceived by ICSI, both belonged to the first group and yielded very similar results: the odds

ratios in these two studies were 0.84 and 0.89, i.e., values very near 1.0 indicating no significant differences between the two groups. There is thus no evidence for a higher rate of malformations among children conceived by ICSI compared to children conceived by IVF.

The risk of malformations in children conceived by ICSI versus naturally conceived children

Eight of the 15 primary studies addressed this question. *Diagram 5* shows the maximally adjusted odds ratios with their 95% confidence intervals as a function of the size of the ICSI cohort (depicted on a logarithmic scale). While the ICSI cohort of most studies was observed prospectively, the cohorts of naturally conceived children were often obtained retrospectively and sometimes drawn from secondary data sources. Thus, it is highly likely that the cohorts differed from each other not just in the mode of conception, but also in other relevant risk factors for major congenital malformations. Only a few of the studies provided adequate data to control for known risk factors such as maternal age, malformations in siblings, or maternal alcohol use during gestation (see *table*) and the validity of the results is therefore questionable (*diagram 5*). The results with regard to the question of ICSI versus natural conception are much more heterogeneous than those for the comparison of ICSI with IVF; this is presumably due to a large degree of distortion of the results by other risk factors for malformations that are differently distributed in normally fertile couples and in infertile couples trying to have children.

In three of the eight studies, the risk of major malformations was found to be significantly higher in children conceived by ICSI than in naturally conceived children. The study with by far the largest prospective cohort, compared to a retrospective control group, was among the three studies showing a significant elevation of risk (13). In this largest study, the malformation rate was 8.7% in the ICSI cohort and 6.1% in the control group. After adjustment for other factors, the odds ratio was found to be 1.24 with a 95% confidence interval of 1.02 to 1.5. Among the five studies in which statistically insignificant differences were found, the rate of malformations in the ICSI cohort was higher than that in the control group in three, and lower in two. All in all, these results point toward a possibly higher risk among children conceived by ICSI, but no firm conclusions can be drawn because of the heterogeneity of the findings and the high likelihood that they have been distorted by selection and confounding variables.

Imprinting defects

Imprinting is the process of activation and deactivation of parental genes during the development and fusion of germ cells. In recent years, a number of reports have been published with initial evidence of a possible association between artificial fertilization and an increased frequency of certain rare diseases

BOX 2

Brief description of some syndromes and diseases associated with imprinting errors

- Beckwith-Wiedemann syndrome: Abnormality on chromosome 11: gigantism, macroglossia, abdominal wall malformations, tumors (e.g. Wilms tumor)
- Angelman syndrome: Abnormality on chromosome 15: neurological and cognitive impairment (also called "happy puppet syndrome")
- Prader-Willi Syndrome: Abnormality on chromosome 15: cognitive and motor developmental retardation and handicap; later on, often polyphagia and obesity
- Retinoblastoma: Abnormality on chromosome 13: malignant retinal tumor, often before age 5

TABLE

Studies yielding data from which the odds ratio for malformations (ICSI versus IVF or ICSI versus natural fertilization) can be calculated

Study	Country	Size of ICSI cohort	Source of data	Malformation rate	Raw odds ratio (95% CI)	Adjusted odds ratio (95% CI) as reported in the study
(8) Bonduelle et al. (2002)	Belgium	ICSI: 2840 IVF: 2955	Prospective cohort	ICSI: 0.034 IVF: 0.038	ICSI/IVF: 0.89 (0.67–1.17)	
(9) Bonduelle et al. (2004)	Belgium Sweden USA	ICSI: 300 Ctrl: 266	ICSI: prospective cohorts Ctrl: retrospective comparison group	ICSI: 0.063 Ctrl: 0.03	ICSI/Ctrl: 2.18 (0.9–5.1) *1, *4, *5	ICSI/Ctrl: 2.53 (1.07–5.98) *10
(10) Bonduelle et al. (2005)	Belgium UK Sweden Denmark Greece	ICSI: 504 IVF: 437 Ctrl: 538	Prospective cohorts and (partially) registry data	At birth: ICSI: 0.03 IVF: 0.02 Ctrl: 0.02 At 5 years: ICSI: 0.061 IVF: 0.041 Ctrl: 0.022	At birth: ICSI/IVF: 1.64 (0.73–3.69) ICSI/Ctrl: 1.82 (0.83–3.98) At 5 years: ICSI/IVF: 1.52 (0.84–2.73) ICSI/Ctrl: 3.44 (1.68–7.05) *1, *4, *5	ICSI/Ctrl: 2.54 (1.13–5.71) *1, *4, *6, *7, *8, *11
(11) Bowen (1998)	Australia	ICSI: 89 IVF: 84 Ctrl: 80	Prospective cohorts	ICSI: 0.045 IVF: 0.036 Ctrl: 0.05	ICSI/IVF: 1.27 (0.28–5.85) ICSI/Ctrl: 0.89 (0.22–3.7) *1, *2, *3	
(12) Hansen (2002)	Australia	ICSI: 301 IVF: 837 Ctrl: 4000	Registry data	ICSI: 0.086 IVF: 0.09 Ctrl: 0.042	ICSI/IVF: 0.94 (0.59–1.50) ICSI/Ctrl: 2.2 (1.3–3.3)	ICSI/Ctrl: 2.0 (1.0–3.2) *1, *3, *5, *9
(13) Katalinic et al. (2004)	Germany	ICSI: 3372 Ctrl: 8016	ICSI: prospective cohorts Ctrl: registry data	ICSI: 0.088 Ctrl: 0.061	ICSI/Ctrl: 1.48 (1.27–1.72)	ICSI/Ctrl: 1.24 (1.02–1.5) *1, *13, *14
(14) Kuwata (2004)	Japan	ICSI: 84 IVF: 148 Ctrl: 188	Prospective cohorts, twins only	ICSI: 0.13 IVF: 0.074 Ctrl: 0.021	ICSI/IVF: 1.88 (0.78–4.54) ICSI/Ctrl: 6.93 (2.1–22.5)	ICSI/Ctrl: 6.7 (2.1–21.9) *1
(15) Ludwig/Katalinic (2002/2003)	Germany	ICSI: 3372 Ctrl: 30 940	ICSI: prospective cohorts Ctrl: registry data	ICSI: 0.086 Ctrl: 0.069	ICSI/Ctrl: 1.29 (1.13–1.46) *10	
(16) Olson (2005)	USA	ICSI: 476 IVF: 986 Ctrl: 6374	IVF- and ICSI-registry data	IVF + ICSI: 0.062 Ctrl: 0.044		ICSI/IVF: 0.86 (0.54–1.38) *1, *2, *3
(17) Palermo (2000)	USA	ICSI: 2059 IVF: 1796	Prospective cohorts in a single institution	ICSI: 0.011 IVF: 0.017	ICSI/IVF: 0.84 (0.37–1.11)	
(18) Place (2003)	Belgium	ICSI: 66 IVF: 52 Ctrl: 59	For the endpoint "congenital malformations": retrospective cohorts	ICSI: 0.076 IVF: 0.058 Ctrl: 0.051	ICSI/IVF: 1.34 (0.3–5.88) ICSI/Ctrl: 1.53 (0.35–6.7) *1, *2, *3, *4 *5, *7, *8, *12	
(19) Sutcliffe et al. (2001)	UK	ICSI: 208 Ctrl: 221	ICSI and Ctrl: matched retrospective cohorts	ICSI: 0.048 Ctrl: 0.045	ICSI/Ctrl: 1.07 (0.43–2.62)	
(20) Sutcliffe (2003)	Australia	ICSI: 56 Ctrl: 39	Retrospective cohort	ICSI: 0.09 Ctrl: 0.128	ICSI/Ctrl: 0.69 (0.18–2.55) *1, *4, *5, *6, *7, *8	
(21) Van Golde (1999)	Spain (data) / Netherlands (analysis)	ICSI: 120 IVF: 132	Retrospective cohorts	ICSI: 0.017 IVF: 0.03	ICSI/IVF: 0.54 (0.1–3.02)	
(22) Westergaard (1999)	Denmark	ICSI: 177 IVF: 1913 Ctrl: 2 228	Registry data	ICSI: 0.017 IVF: 0.049 Ctrl: 0.046	ICSI/IVF: 0.33 (0.11–1.06) ICSI/Ctrl: 0.36 (0.11–1.14) *1, *2, *3, *4	

Results were controlled for the following variables by logistic regression:

- *1 maternal age; *2 multiple pregnancy; *3 parity; *4 age of child; *5 sex of child;
 - *6 educational status of mother; *7 social class; *8 geographic region; *9 correlation in twins;
 - *10 effect of individual centers; *11 maternal smoking and alcohol consumption;
 - *12 ethnic group; *13 malformations in parents; *14 earlier pregnancy with malformed child.
- ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; Ctrl, control (natural conception)

Comparison
between ICSI and
IVF as a function of
study size

that might be due to imprinting defects.

The diseases that are most commonly mentioned in this context are Beckwith-Wiedemann syndrome (BWS) and Angelman syndrome (AS); others are Prader-Willi syndrome, retinoblastoma, and further rare syndromes such as Silver-Russell syndrome (*box 2*).

The 12 publications that we found on imprinting defects (e1–e12) mostly dealt with uncontrolled, retrospective studies and single case reports or case series. Because of their small size and their liability to distortions of many different kinds, these types of study are not suitable for a demonstration of causation, yet they may provide clues toward possible associations and thus enable the formulation of hypotheses to be tested. These 12 publications provided no evidence of

a difference between ICSI and IVF with regard to malformation rates, but they do arouse suspicion of a possible connection between artificial fertilization and BWS, AS, and retinoblastoma. This question will need to be addressed in future studies.

Discussion

The variability of the reported malformation rates was notably high. Reported malformation rates depend on the system of classification used as well as on the time at which the children are examined, the examination method (clinical alone or with ancillary testing), and the qualifications of the examiner. The reported study results seem to depend largely on the degree of care with which procedures susceptible to selection bias were reported, the application of definitions, and the methods of calculating the malformation rate from the data that were obtained. The sources differ considerably from one another in all of these respects. The malformation rate can be heavily influenced, e.g., by selection before embryo transfer, as well as by the induction of abortion after pathological findings are made in prenatal diagnosis.

The rate of malformations after assisted fertilization is low in any case in all of the studies that were analyzed. It follows that differing designations of various types of malformation as major or minor can bring about vast differences in the final results. Furthermore, most studies reported the malformation rates as a fraction of live births only, while failing to consider malformations among stillbirths and induced abortions as recommended by EUROCAT. No final conclusion about malformation rates after artificial fertilization can be drawn until large prospective cohort studies are performed whose procedures and definitions are transparently reported.

Conclusion

After our review of the relevant literature, it seems unlikely that conception by ICSI significantly increases the risk of malformations compared to conception by IVF. This, in turn, should lessen concern about the possible induction of congenital malformations by manipulation of the oocyte, which is a risk inherent to the technique of ICSI. We cannot rule out a possible elevation of the risk of major malformations by ICSI as compared to natural conception, but this concern applies equally to IVF. Our review of the meta-analyses on this question yielded fairly consistent findings of an elevation of the risk by about 30%, with odds ratios of 1.4 (95% CI, 1.28 to 1.53) (7) and 1.29 (95% CI, 1.01 to 1.67) (6). These figures should be interpreted with caution, however, because biases of various types in the primary studies cannot be excluded. These results might reflect a real, technique-dependent risk due to gamete manipulation, but they might also reflect differences in the primary risks of the parents. More research is needed in this area. These findings imply that, when prospective parents are counseled about assisted reproductive techniques, they should be

Comparison
between ICSI and
natural conception
as a function of
study size

informed that a possible elevation of the rate of congenital malformations as compared to natural conception is of some concern not just for ICSI, but for IVF as well.

No firm conclusion can be drawn from the sparse publications in recent years that have addressed the question of possible associations between ICSI and/or IVF and certain rare diseases that are thought to be due to so-called imprinting defects. A possible elevation of risk by artificial fertilization cannot be excluded at present. Therefore, the occurrence of these imprinting defects should be observed further. The Health Technology Assessment report "Fehlbildungsrisiko der mit der Methode der ICSI gezeugten Kinder in Vergleich zu IVF- beziehungsweise natürlich konzipierten Kindern" (The risk of malformations in children conceived by ICSI compared to those conceived naturally or by IVF) will be released by the Joint Federal Committee and will be available at www.g-ba.de/informationen/abschlussberichte.

Conflict of interest statement

The authors state that no conflict of interest exists as defined by the guidelines of the International Committee of Medical Journal Editors.

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