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Review article

In Vitro Fertilization Technology and Child Health

Risks, mechanisms and possible consequences

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Background: Just under 3% of children in Germany, and approximately 6% of children in some other countries, such as Denmark, are now being conceived with the aid of in vitro fertilization (IVF) technology. Alongside the increased risk of organ malformation, there is now evidence for functional abnormalities due to epigenetic modifications.

Methods: This review is based on pertinent publications retrieved by a literature search on currently known associations of IVF therapy with malformations and functional abnormalities. The potential implications for the treatment of infertility are discussed.

Results: The risk of congenital malformations is approximately one-third higher in children conceived with the aid of IVF technology than in other children; specifically, there is an odds ratio (OR) of 1.29 (95% confidence interval, [1.03; 1.60]) for cardiac malformations, and there is a relative risk (RR) of 1.35 ([1.12; 1.64]) for musculoskeletal malformations and 1.58 ([1.28; 1.94]) for genitourinary malformations. The risks of preterm birth and low birth weight are, respectively, 1.7 and 1.5 times higher in IVF singleton pregnancies than in non-IVF pregnancies. Cardiovascular changes are the main type of functional disturbance. Some of the risks associated with IVF have decreased in recent years. An association has been revealed between cardiovascular abnormalities and epigenetic modifications; the causes are thought to include not only maternal and paternal factors, but also the IVF techniques that are used. A modification of IVF therapies might lower the risks, but might also lower the success rate.

Conclusion: For the well-being of the children to be conceived, IVF therapy should only be carried out in cases of infertility that cannot be treated by any other means, as the precise causes of the risks of IVF to child health are unclear.

Today, almost 3% of all children in Germany—and in countries with a very liberal reimbursement policy, such as Denmark, as much as 6% of all children—are conceived by in vitro fertilization (IVF). In other words: In every class at school there is one IVF child.

Given the large number of IVF children, any potential IVF-induced health problem of the offspring would be relevant, both from a medical and social perspective. New studies by a Swiss working group (1, 2) on functional cardiovascular changes attracted international media coverage and triggered a public discussion on the health risks of IVF therapies which left many couples unsettled. Epigenetic modifications have been proposed as one mechanism underlying the reported cardiovascular changes, which appear to be of maternal and paternal nature, but may also be triggered by IVF treatment.

Thus, in addition to the probabilities of congenital malformations and functional abnormalities in IVF children, this article will describe the mechanisms and the relevance of epigenetic modification and finally discuss the possible consequence for sterility treatment.

Methods

The risk associated with IVF technologies were analyzed. The definition of IVF covered all in vitro fertilizations, irrespective of the technology used (insemination or intracytoplasmic sperm injection [ICSI]) and irrespective of whether the embryos were used fresh or after cryopreservation.

The risks of congenital malformations and obstetric adverse events after IVF treatment have already been assessed in numerous meta-analyses and are supported by scientific evidence. Thus, we searched only the PubMed database and restricted the search to meta-analyses published between January 2015 and May 2019. The search terms “in vitro fertilisation” AND “meta-analysis” AND “malformation” were used.

IVF-induced functional health impairments have been discussed for years, but meta-analyses on the subject are scarce. Therefore, the literature search was extended to include systematic reviews. The following search terms were used: “in vitro fertilisation” AND “meta-analysis” OR “systematic review” AND “offspring” OR “babies” AND “blood pressure” OR “obesity” OR “glucose” OR “lipid” OR “cognitive development” OR “bone age” OR “depression” OR “attention deficit disorder” OR “thyroid” OR “autism” OR “cerebral palsy” OR “neurodevelopmental delay”.

New evidence of epigenetic modifications induced by the process of IVF has so far only been found in individual references; therefore, a selective search of the literature was conducted for this topic.

Results

Malformations in children conceived by in vitro fertilization

General malformation risk

Qin et al (3) included 57 cohort studies with mostly IVF children and children after spontaneous conception in a meta-analysis (Table 1). In IVF children, the relative risk (RR) for congenital malformation was 1.33 (95% confidence interval [1.24; 1.43]).

TABLE 1

Risk of health effects in the child after in vitro fertilization treatments* according to current meta-analyses

Risk factors	References	Included studies	Number of subjects studied	Statistically significant risk increase	Absolute risk changes (absolute numbers or calculation based on RR and OR)
General risk of malformations	Qin et al. 2015 (4)	57 studies	118 846 IVF children, 1028 children after insemination or hormonal stimulation versus 1 212 320 spontaneously conceived children	RR: 1.33, 95% CI [1.24; 1.43]	Increase from approx. 4.6% (4) to 6.1% (based on RR [× 1.33])
Risk of heart defect	Giorgione et al. 2018 (6)	8 studies	25 856 IVF children versus 287 995 spontaneously conceived children	OR: 1.45 [1.20; 1.76]	Increase from approx. 0.7% (6) to approx. 1.0% (based on OR [× 1.45])
Risk of high blood pressure	Guo et al. 2017 (11)	19 studies	2112 IVF children/adults versus 4096 spontaneously conceived children/adults	Increase in systolic pressure: +1.88 mm Hg [0.27; 3.49] Increase in diastolic pressure: +1.51 mm Hg [0.34; 2.70]	Increase in systolic blood pressure: +1.88 mm Hg (11), diastolic blood pressure: +1.51 mm Hg (11)
Risk of premature birth (<37 weeks of pregnancy) and low birth weight (<2500 g) Risk for malformations of specific organ systems	Hoorsan et al. 2017 (5)	30 studies	297 440 IVF children, 17 962 children after insemination or hormonal stimulation versus 5 154 779 spontaneously conceived children	Preterm birth: OR: 1.79 [1.21; 2.63] Low birth weight: OR: 1.89 [1.36; 2.62] Urogenital tract: OR: 1.58 [1.28; 1.94] Musculoskeletal system: OR: 1.35 [1.12; 1.64] Central nervous system: OR: 1.36 [1.10; 1.70]	Increase from approx. 7% (Switzerland) (12) to approx. 12.5% (based on OR [× 1.79]) from approx. 6.5% (Switzerland) (12) to approx. 12.3% (based on OR [× 1.89]), from approx. 1.7% (13) to approx. 2.7% (based on OR [× 1.58]), from approx. 1.6% (13) to approx. 2.2% (based on OR [× 1.35]), from approx. 0.4% (13) to approx. 0.54% (based on OR [× 1.36]),
Risk of preterm birth and low birth weight after transfer of previously cryopreserved embryos	Maheshwari et al. 2018 (9)	20 studies	Approx. 80 000 IVF singletons after cryopreservation of embryos versus approx. 200 000 singletons without cryopreservation	Preterm birth: RR: 0.90 [0.84; 0.97] Low birth weight: RR: 0.72 [0.67; 0.77] Macrosomia (> 4000 g): RR: 1.85 [1.46; 2.33]	Changes from approx. 9.4% (9) to approx. 8.5% (9) (based on RR [× 0.9]). from approx. 8.8% (9) to approx. 6.3% (9) (based on RR [× 0.72]), from approx. 6.2% (9) to approx. 11.5% (9) (based on RR [× 1.85])
Risk of urogenital malformations with ICSI	Massaro et al. 2015 (10)	22 studies	24 240 IVF children without ICSI versus 12 270 IVF children conceived with ICSI	OR: 1.27 [1.02; 1.59]	Increase from approx. 0.8% (10) to approx. 1.0% (based on OR [× 1.27])

ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; CI, confidence interval; OR, odds ratio; RR, relative risk.
* IVF treatments—unless otherwise described—are defined as all IVF technologies, i.e. in vitro fertilizations, irrespective of the technology used (insemination or intracytoplasmic sperm injection) and irrespective of whether the embryos had been cryopreserved or not.

Table 1 Risk of health effects in the child after in vitro fertilization treatments* according to current meta-analyses

The generally increased risk persisted if only singletons (RR: 1.38 [1.30; 1.47]), major malformations (RR: 1.47 [1.29; 1.68], matched/adjusted studies (RR: 1.37 [1.27; 1.47]), and high-quality studies (RR: 1.40 [1.27; 1.55]) were included. The increased risk was lower, but still significant, if IVF twins (RR: 1.18 [1.06; 1.32]) were compared to spontaneous pregnancies.

The latter result was largely confirmed by the meta-analysis by Zheng et al. (4) which, however, found an increased risk of chromosomal abnormalities in multiple pregnancies (RR: 1.36 [1.04; 1.77]).

Hoorsan et al. (5) investigated the risks for specific malformations and found increased risks for central nervous system malformations (odds ratio [OR]: 1.36 [1.10; 1.70]), for urogenital malformations (OR: 1.58 [1.28; 1.94]) and for musculoskeletal malformations (OR: 1.35 [1.12; 1.64]), but not for chromosomal aberrations (OR: 1.14 [0.90; 1.44]).

Risk of congenital heart defects

Giorgione et al. (6) performed a meta-analysis based on 8 cohort studies with children after IVF and children after spontaneous conception (Table 1). Both single and multiple pregnancies were included. Heart defects were observed in 1.3% and 0.68% of IVF children and spontaneously conceived children, respectively (pooled OR: 1.45 [1.20; 1.76]). The increased risk persisted if only singleton pregnancies were included (OR: 1.55 [1.21; 1.99]) and multiple adjustments were made (pooled OR: 1.29 [1.03; 1.60]).

Obstetric risks in children conceived by in vitro fertilization

General obstetric risks

The meta-analysis by Hoorsan et al. (5) included 30 studies with mostly IVF children and spontaneously conceived children (Table 1). The odds ratios for the risks of preterm birth (<37 weeks' gestation) and low birth weight (<2500 g) were 1.79 [1.21; 2.63] and 1.89 [1.36; 2.62], respectively.

Obstetric risks of singleton and multiple pregnancies

A meta-analysis including a total of 4 636 508 spontaneous singleton pregnancies compared 52 cohort studies with 18 741 IVF singletons (7). The prevalence of preterm birth was approximately 1.7 times higher in IVF pregnancies (10.9% [10.0; 11.8]) compared to spontaneous pregnancies (6.4% [5.8; 7.0]). The prevalence of low birth weight was 8.7% [7.4; 10.2] and 5.8% [4.8; 6.9], respectively, i.e. about 1.5 times higher in IVF pregnancies.

Obstetric risks were also increased in multiple pregnancies, but this increase was less pronounced compared to the increase observed with singleton pregnancies. Qin et al (8) included 39 cohort studies on multiple pregnancies with a total of 38 053 children after IVF and 107 955 children after spontaneous conception in a meta-analysis. The increased relative risks for preterm birth and low birth weight after IVF were 1.08 [1.03; 1.14] and 1.04 [1.01; 1.07], respectively.

Risks associated with specific in vitro fertilization technologies

Obstetric risks after transfer of cryopreserved embryos

Maheshwari et al. (9) compared in a meta-analysis of 26 studies almost 80 000 singletons after IVF thawing cycles, i.e. embryo transfers of previously cryopreserved embryos, with approximately 200 000 singletons after IVF fresh cycles. The risks for preterm birth (RR: 0.90 [0.84; 0.97]) and low birth weight (RR: 0.72 [0.67; 0.77]) were lower in thawing cycles (Table 1). By contrast, the risks of "large for gestational age" (LG) newborns, i.e. a birth weight above the 90th percentile (RR: 1.54 [1.48; 1.61]), and for macrosomia (>4000 g) (RR: 1.85 [1.46; 2.33]) increased.

Malformation risk after fertilization by intracytoplasmic sperm injection

In a meta-analysis including 22 studies, Massaro et al. (10) compared children conceived by IVF with ICSI to children conceived by IVF without ICSI (Table 1). ICSI was associated with an increased risk for genitourinary malformations (OR: 1.27 [1.02; 1.59]). However, if only studies with a low risk of bias (IVF with ICSI: n = 7727, IVF without ICSI: n = 14 308) were analyzed, there was still a trend towards an increased risk of genitourinary malformations, but the difference was no longer statistically significant (OR: 1.28 [1.00; 1.64]). A subanalysis indicated increased risks for hypospadias (OR: 1.21 [0.87; 1.69]) and cryptorchidism (OR: 1.39 [0.97; 2.00), but the predefined significance level was not met.

Functional abnormalities in children conceived by in vitro fertilization

Blood pressure

Guo et al. (11) carried out a meta-analysis of 19 studies in which 2112 IVF children and young adults were compared with 4096 spontaneously conceived individuals

(Table 1). The systolic blood pressure of the IVF offspring was found increased by 1.88 mm Hg [0.27; 3.49] and the diastolic blood pressure by 1.51 mm Hg [0.34; 2.70]. Furthermore, according to five studies which compared 402 IVF children to 382 spontaneously conceived children, the cardiac diastolic function was suboptimal and the blood vessel thickness was higher.

Glucose metabolism

To evaluate the aspect of glucose metabolism, 7 studies including 477 IVF children were compared with 1852 spontaneously conceived children (11). While fasting insulin levels of IVF children were significantly increased (0.38 mIU/L [0.08; 0.68]), no significant difference was found for fasting glucose levels (−0.03 mM [−0.13; 0.06]) and insulin resistance, measured using the homeostasis model assessment (HOMA) index (0.02 [−0.06; 0.12]). Overall, the comparisons revealed only a trend towards abnormal glucose metabolism.

Obesity and lipid metabolism

There is no conclusive evidence of an increase in birth weight or relevant abnormalities of lipid metabolism.

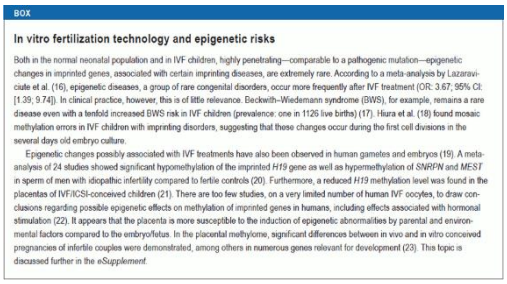
Cognitive development

Rumbold et al. (14) conducted a systematic review including 7 studies on cognitive development of IVF children. Children conceived with IVF treatment without fertilization with ICSI showed no impairment in cognitive development. However, the data for IVF treatments with fertilization with ICSI were less clear. Three studies compared IVF children with IVF/ICSI children. One study showed a significant increase in the risk of cognitive impairment in IVF/ICSI children, one study found that the intelligence quotient was on average 3 points lower in IVF/ICSI children and one study showed no difference.

Catford et al. (15) arrived at a similar conclusion in a systematic review focusing on psychosocial health in IVF children without and with ICSI fertilization. The neurological development of children aged two months to 7.5 years was monitored in 22 studies. Fourteen studies used spontaneously conceived children for comparison. ICSI-conceived offspring appeared to be at an increased risk of cognitive impairment (5/14 studies) and autism (2 studies). The risk of autism was particularly high when sperm after testicular sperm extraction was used (RR: 3.29 [1.58; 6.87]), but also when ICSI was performed in absence of an andrological factor (RR: 1.57 [1.10; 2.09]). However, in both samples this effect was no longer significant when only singletons were included in the analysis.

Epigenetic risks associated with in vitro fertilization technology

Epigenetic risks and the temporal association of IVF processes and epigenetic programming are shown in the *Box* and in the *Fig*ure.



BOX

In vitro fertilization technology and epigenetic risks

Both in the normal neonatal population and in IVF children, highly penetrating—comparable to a pathogenic mutation—epigenetic changes in imprinted genes, associated with certain imprinting diseases, are extremely rare. According to a meta-analysis by Lazaraviciute et al. (16), epigenetic diseases, a group of rare congenital disorders, occur more frequently after IVF treatment (OR: 3.67; 95% CI: [1.39; 9.74]). In clinical practice, however, this is of little relevance. Beckwith–Wiedemann syndrome (BWS), for example, remains a rare disease even with a tenfold increased BWS risk in IVF children (prevalence: one in 1126 live births) (17). Hiura et al. (18) found mosaic methylation errors in IVF children with imprinting disorders, suggesting that these changes occur during the first cell divisions in the several days old embryo culture.

Epigenetic changes possibly associated with IVF treatments have also been observed in human gametes and embryos (19). A meta-analysis of 24 studies showed significant hypomethylation of the imprinted *H19* gene as well as hypermethylation of *SNRPN* and *MEST* in sperm of men with idiopathic infertility compared to fertile controls (20). Furthermore, a reduced *H19* methylation level was found in the placentas of IVF/ICSI-conceived children (21). There are too few studies, on a very limited number of human IVF oocytes, to draw conclusions regarding possible epigenetic effects on methylation of imprinted genes in humans, including effects associated with hormonal stimulation (22). It appears that the placenta is more susceptible to the induction of epigenetic abnormalities by parental and environmental factors compared to the embryo/fetus. In the placental methylome, significant differences between in vivo and in vitro conceived pregnancies of infertile couples were demonstrated, among others in numerous genes relevant for development (23). This topic is discussed further in the *eSupplement*.

Box

In vitro fertilization technology and epigenetic risks

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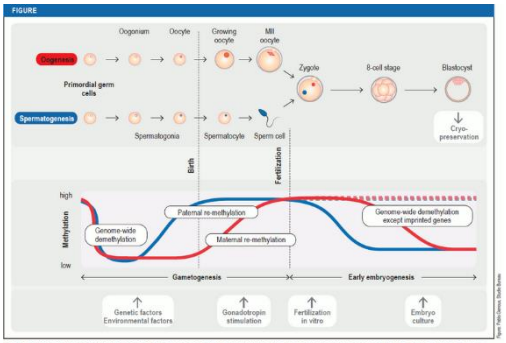

Germ cell development and temporal association of genetic and environmental factors as well as in vitro fertilization processes with de- and re-methylation (gray). During gametogenesis and early embryogenesis, two waves of epigenetic reprogramming occur (37) in which (almost) the entire genome is first demethylated and then remethylated. With the exception of 100 to 200 imprinted genes, the germline methylation patterns are erased in early embryogenesis and replaced by somatic patterns. During these reprograming processes, the epigenome is particularly vulnerable to external factors.

Figure

Germ cell development and temporal association of genetic and environmental factors as well as in vitro fertilization processes with de- and re-methylation (gray

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Discussion

This paper covers a wide range of aspects, from malformations and functional abnormalities in IVF-conceived children to the risk of epigenetic changes to possible implications for treatment. The broad range of the topics covered reduces the level of detail; however, this only plays a minor role in the general discussion of risks in daily practice.

Mechanisms underlying the increased risks

The studies described in this review showed numerous increased health risks in IVF children (Table 1). Does this mean that IVF technology is causal per se? Or are infertility or other risk factors, such as paternal age, responsible for these risk increases (24)?

There are two possible study approaches that can be used in an attempt to answer these questions. One research strategy could be to compare IVF-conceived offspring with spontaneously conceived offspring of subfertile parents. One definition of subfertility is more than 1 year of trying to conceive before pregnancy occurs. The other strategy could be to study siblings of the same biological mother who gave birth to both IVF-conceived and spontaneously conceived children.

For the first approach, 2 of 6 multiply adjusted studies by Pinborg et al. (25) were combined for a meta-analysis. The risk of preterm birth was found increased in IVF

children with an adjusted OR (aOR) of 1.55 [1.30; 1.85] compared to spontaneously conceived children of subfertile couples. Luke et al. (26) compared 10 149 IVF-conceived singletons (8054 singletons of these from a subfertile population) with 441 420 singletons from a fertile population. The risks of preterm birth and low birth weight were increased with an adjusted RR (aRR) of 1.26 [1.14; 1.39] and 1.21 [1.08; 1.36], respectively, compared to the subfertile population. The subfertile population was defined as women taking medication to improve fertility but not undergoing IVF.

For the second approach, the comparison of siblings, Pinborg et al. (25) combined two studies, adjusted, among other factors, for maternal age, parity and year of birth, to perform a meta-analysis. The proportion of spontaneously conceived children in the meta-analysis population was about the same as that of their IVF-concieved siblings born before or after them. The IVF children had an increased risk of preterm birth, with an aOR of 1.27 [1.08; 1.49].

In summary, both study approaches show that the risk of an adverse peripartum outcome is increased in IVF-conceived children, even if almost identical control groups are selected; overall, however, this increase is smaller than the risk increase found when all spontaneously conceived children are used for comparison. This means that both infertility and IVF technology appear to be risk factors.

Risk trends in recent years

In this article, only meta-analyses or, where appropriate, systematic reviews were analyzed in order to be able to find clear answers to the question of potential health risks, based on a large number of studies. However, the disadvantage of relying on these large meta-analyses is that changes over time cannot always be recognized.

Henningsen et al. (27) therefore compared the obstetric outcome of 62 379 IVF singletons and 362 215 spontaneously conceived singletons in Sweden, Denmark, Finland and Norway born from 1988 to 2007 over the course of time. Among singletons, the probability of premature birth and low birth weight compared to spontaneously conceived children in the years 1988 to 1992 (aOR: 2.47 [2.09; 2.92] and 2.94 [2.44; 3.54], respectively) and in the years 2003 to 2007 (aOR: 1.50 [1.43; 1.58] and 1.49 [1.40; 1.58], respectively) was one of the key findings.

A similar approach was taken by Guo et al. (11) to evaluate blood pressure over time. While, as discussed already, overall systolic and diastolic blood pressure levels were found increased in IVF children compared to spontaneously conceived children, separate analyzes of the 1990–1999 and 2000–2009 cohorts showed elevated blood pressure levels in the older cohorts, but no longer in the younger cohorts (2000–2009: systolic blood pressure [BP]: –0.19 [–1.38; 1.00]; diastolic BP: –0.19 [-1.38; 1.00]). This observation was independent of the proportion of ICSI fertilizations and the age of the children studied.

Overall, the risk for some IVF-induced health impairments appeared to decrease over the years. The possible mechanisms underlying these changes can only be speculated upon. Among the possible causes are a change in the patient population and the use of different IVF technologies.

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Active risk minimization

The IVF technique itself also seems to have impact on health risks. However, whether IVF-related epigenetic modifications play a causative role or whether other factors are involved, remains unclear. What is certain, however, is that data are available for every IVF technology—although in some cases only from animal models—supporting the possibility of a causal relationship. For this reason, Table 2 breaks down the individual IVF technologies, but also the genetic and environmental factors. In addition, suggestions for possible modifications to reduce risk are made. However, the currently available data do not allow to draw definite conclusions on intervention options.

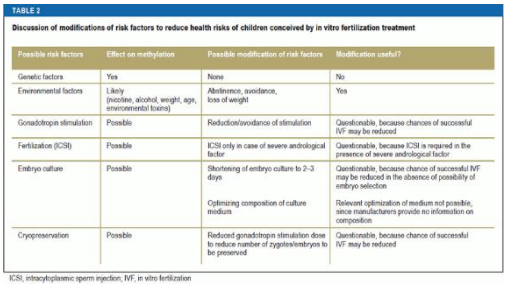

TABLE 2

Discussion of modifications of risk factors to reduce health risks of children conceived by in vitro fertilization treatment

Possible risk factors	Effect on methylation	Possible modification of risk factors	Modification useful?
Genetic factors	Yes	None	No
Environmental factors	Likely (nicotine, alcohol, weight, age, environmental toxins)	Abstinence, avoidance, loss of weight	Yes
Gonadotropin stimulation	Possible	Reduction/avoidance of stimulation	Questionable, because chances of successful IVF may be reduced
Fertilization (ICSI)	Possible	ICSI only in case of severe andrological factor	Questionable, because ICSI is required in the presence of severe andrological factor
Embryo culture	Possible	Shortening of embryo culture to 2–3 days	Questionable, because chance of successful IVF may be reduced in the absence of possibility of embryo selection
		Optimizing composition of culture medium	Relevant optimization of medium not possible, since manufacturers provide no information on composition
Cryopreservation	Possible	Reduced gonadotropin stimulation dose to reduce number of zygotes/embryos to be preserved	Questionable, because chance of successful IVF may be reduced

ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization

Table 2

Discussion of modifications of risk factors to reduce health risks of children conceived by in vitro fertilization treatment

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Conclusion

IVF is associated with an increased health risk for the offspring in the form of malformations, functional disorders, and a poorer peripartum outcome. This is possibly caused by parental factors, but also by factors related to the IVF technology used. Even though some of these risks have decreased over the years, an increased health risk can still be assumed. Consequently, IVF should only be performed if a pregnancy cannot be achieved in another way.

Conflict of interest statement

Prof. von Wolff received consultancy fees from Merck Serono and Ferring. He received reimbursement of congress fees and travel expenses as well as study support (third party funding) from IBSA Institut Biochimique. He received lecture fees from TEVA, Theramex, and Ferring. He heads the IVF-Naturelle Competence Network.

Prof. Haaf declares that no conflict of interest exists.

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►Supplementary material