

# Pregnancy course and health of children born after assisted reproductive technologies

*Dr. Michael Ludwig*

*Centre for gynaecologic endocrinology and reproductive medicine*

*Endokrinologikum Hamburg/Germany*

The uses of more or less invasive techniques for the treatment of involuntary childlessness have been more and more expanded worldwide. Meanwhile, one can assume, that about each 100th child, which is born in Germany, e.g., will be conceived by in vitro fertilization (IVF). When one also counts those children, who have been conceived following ovarian stimulation procedures with or without intrauterine insemination – the number will increase to about 2-3 children of 100 born.

This illustrates the enormous impact, which these techniques have on all related fields in medicine – especially in obstetrical and perinatal care.

## **Multiple pregnancies – a burden to get rid off!**

Mainly, this question is influenced by the problem of multiple pregnancies. They make up to 25% of all achieved pregnancies – therefore the risk to have a multiple pregnancy is about 20 times higher for twins and more than 10,000 times higher for triplets after assisted reproduction techniques (ART). This, of course, is a self-made-problem and risks, which arise from multiple pregnancies, are not directly related to ART itself. On the other hand, these problems have to be avoided as much as possible. Approaches, especially from Scandinavian countries, include radical reduction in the number of embryos replaced in IVF cycles, i.e. the elective

single embryo transfer. IVF groups from Finland, e.g., have implemented this strategy in their daily clinical practice and do not see less pregnancies as compared to a couple of years ago. Of course, the success of this approach depends mainly on good laboratory work and the possibility to select embryos according to pronuclear morphology, blastomere morphology, cleavage stage and other markers like absence of multinucleation, speed of cleavage etc. In the future, this may be the golden standard in each IVF clinic worldwide.

## **The risk of major malformation in children born**

Besides this apparent problem, the question is, however, whether there are risks,

which can be attributed directly to infertility or to the techniques used to overcome it.

This question has been addressed in several studies in the last years. In fact, already in the beginning of IVF – in 1978 – it was asked, whether there might be a problem with pregnancies. However, initial studies in the 80's and early 90's were either too small or did not have enough statistical power, or had a bad design and therefore could not show any difference as compared to pregnancies achieved after spontaneous conception. In the late 90's, however, larger studies, which – in part – have also been done prospectively, could show surprising results. Data from Australia, Belgium and Germany demonstrated that there was in fact a slightly increased risk of major malformation following IVF as compared to spontaneous conception. This was also true for intracytoplasmic sperm injection (ICSI) – there was, how

increased malformation risk after ICSI. The surprise therefore lay in the point, that the risk of both techniques was increased towards the basic risk of women, who are fertile.

More data was gathered and it was claimed, that severe condition – like Angelman Syndrome or Beckwith-Wiedemann-Syndrome – also may be more often observed following ART. This, however, is still a matter of debate due to the low number of cases of these very rare conditions.

### **Infertility related risks – the „background risk“**

But what about the increased risk of major malformation following ICSI and IVF? Is it the culture technique? The unnatural conditions, under which the oocytes, sperms and embryos were handled? Or is it the underlying infertility, which contributes to this risk – i.e. „infertility“ as a risk factor by itself?

Data from pregnancies after IVF have shown for a long time, that there might be more problems like pregnancy induced hypertension, pre-eclampsia, placental insufficiency, small for gestational age children and premature birth – excluding multiples and analysing only singleton pregnancies. Already with this information it is absolutely unclear, why those complications occur – since the embryo is replaced, but the placenta grows under natural conditions and is never under an artificial situation. There are, however, several points, which have to be considered in infertile couples. Why are they infertile? There may be factors in the prospective mother, which can contribute to these risks. E.g. there is a higher prevalence of infectious diseases in these women, which may higher the risk of endometrial abnormalities, and consequently lead to implantation problems (e.g. microscars). Beside that, genetic factors may be present, which lead to subfertility on the one hand, but also have an impact on placental morphology and the development of the child.

Interesting data from the USA has

recently shown, that the risk is nearly twice as high for mothers after IVF to bear a child with low or very low birth weight, i.e. < 2.500 or < 1.500 g, respec

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tively. In the same study, however, this risk was not present in mothers after IVF, who are generally fertile – i.e. mothers in surrogate pregnancies.

This also underlines the fact, that there may be problems in the infertile couple themselves, which contribute to the risk of pregnancy – besides the technique used for treatment.

Other data dealt with couples suffering from idiopathic infertility – i.e. infertility with no apparent cause even after extensive diagnostic procedures. In this cohort of women again higher pregnancy related risks have been observed. However, these risks occurred independently whether the women became pregnant following spontaneous conception or IVF.

### **Post partum development of children from ART procedures**

Several studies in the past 20 years have also addressed the question, whether the postpartal development of children is normal or different from naturally conceived children. Altogether the data demonstrated no abnormalities up to the age of 10 years. In future, studies we will also address older children and will help to evaluate this question further.

## **More data was gathered and it was claimed, that severe condition – like Angelman Syndrome or Beckwith-Wiedemann-Syndrome – also may be more often observed following ART**

ever, no difference between conventional IVF and ICSI. The latter has been introduced in 1992 for the treatment of severe male factor infertility. That event had led to a never-ending discussion on the safety of this technique, since sperms, which otherwise would not have had the possibility to fertilize, were used for treatment. Therefore, it was somewhat re-assuring, that as compared to conventional IVF, there was no

### Conclusion – consequences for counselling in daily clinical care

Overall, one has to take into account that there is a higher risk in pregnancies and in children born after ART. However, these risks seem to be related mainly to inherent factors of infertility itself. There seems to be no risk, which directly depends on the techniques. On the other hand, however, the occurrence of conditions like Beckwith-Wiedeman syndrome or Angelman syndrome may show in the direction, that finally a technique related risk cannot totally be ruled out. Futures, well-designed studies, have to address these questions. For the daily clinical practice, the following guidelines should help to counsel couples, who ask for an infertility treatment:

- ◆ there seems to be a slightly elevated risk of major malformations in children born after IVF and ICSI
- ◆ this risk affects 1 out of 12 pregnancies after IVF or ICSI, and is slightly increased as compared to 1 out of 15 pregnancies after natural conception
- ◆ whether this is high or not has to be discussed with the infertile couple on an individual basis
- ◆ the couples can be counselled, that this risk seems to be related mainly to well known risk factors as different ages of couples who undergo an infertility treatment as compared to those, who conceive naturally (age difference: 4-5 years); other risk factors, which can be evaluated from the anamnesis of these couples might explain some more percentages
- ◆ the pregnancy course after ART may seem to be more complicated as compared to naturally conceived pregnancies
- ◆ These risks, again, may be age related, or may be related to certain endocrinological conditions (e.g. increased risk of gestational diabetes in PCO-patients) or related to certain genetic abnormalities (e.g. increased abortion risk in carriers of reciprocal chromosomal translocations) or related to abnormalities in the female reproductive tract (e.g. increased abortion risk, increased risk of premature delivery in the presence of uterine abnormalities) etc.
- ◆ the post partum development of children born after ART do not seem to be affected or different from that after natural conception
- ◆ multiple pregnancies is a major problem after ART and should be avoided as far as possible
- ◆ finally, however, a technique related risk cannot be totally ruled out