

## REVIEW

# Extracorporeal Fertilization in the World and in Croatia

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**Aim:** To point out the dangers, side effects and risks of medical assisted fertilization, in vitro fertilization, embryo transfer and injection on sperm in ovum for mother and the child. **Results:** On the one hand the negative side effects for women of an abrupt rising risk for the development of neoplasm under pharmaceutical therapy are mentioned. Especially under a therapy which has the purpose to stimulate the ovulation of the ovary it lies around 100%. An increased level of certain hormones, as for example HCG, which influences the ovulation, is closely related with the risk of developing ovarian cancer. Clinical studies at more than 12000 infertile women (primary and secondary acyesis), with an average age of 30 years, show an elevated risk for the development of a malignant tumor of 98%. Also the application of Gonadotrophin is connected with a risk of 146% for the occurrence of cancer after a period of 15 years. FDT involves a risk of about 12% for the occurrence of breast cancer and shows also an aggravation for the risk of cancer of the endometrium from 79% up to 1152%. On the other hand the risk of spontaneous miscarriages under MAE, which is near 20%, and serious illness of the children, including 47% with need of intensive care unit support after birth, need to be realized. Furthermore the investigation of naturally obtained twins and through ART obtained twins shows in the arrangement a slower and poorer development of the children in the ART group with also great differences in physical development. In total the number of inherent malformation of newborns under the use of ART rises from 47 to 177 %. With an installment of 9% we notice that children who came into being by IVF and ICS also fall more frequently ill. (Teething troubles, more hospitalizations and operations, higher frequency of major inherent malformations). **Conclusion:** All women who want to undergo a medical assisted fertilization should be informed about the side effects and risks for mother and child. **KEY WORDS:** MEDICAL ASSISTED FERTILIZATION, IN VITRO FERTILIZATION, EMBRYO TRANSFER, INJECTION OF SPERM IN OVUM

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## 1. INTRODUCTION

The European Society for Human Reproduction and Embryology (ESHRE) arose through the idea of professor R.G. Edwards, of the Cambridge university, and Dr. J. Cohen, from Paris. In 1985 this Soci-

ety found the first annual meeting in Bonn, Germany. One of the most important tasks of the ESHRE is the promotion and explanation of Reproductive Biology and Medicine. Among other things, they report about the safety and the quality of assisted reproduc-

tive techniques (ART), its morbidity risks, complications and mortality within women and children. Furthermore the ESHRE informs regularly on consequences of ART, concerning hyper stimulation of the ovary (OHSS), oncogenetics, genetics, inherent malformations on newborns and options of the parents. These reports are published in all sides known journals as for example Human Reproduction. Facts on ART are presented to the public in almost every European country; however, they are hardly mentioned in Croatia (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22).

This means that in this matter Croatia is isolated from the rest of Europe and that up to the contemporary day a great number of Croatian physicians and also the general population do not know anything about these procedures. They remain in darkness, because of a view physicians who draw their benefit from the state of general ignorance.

All aspects should become aware to physicians and patients before they consider a medical supported fertilization, in vitro fertilization (IVF) or embryo transfer (ET).

### 1.1. Womens' risks

The general risk for the development of adenocarcinomas in infertile women and its correlation with an increased ovarian activity under a specific therapy Women in the fertilization-capable age and a continuous infertility, have an increased risk for the development of an adenocarcinoma. Here of a variety of organs is affected, as for example the ovaries, the fallopian tubes, the breasts, the uterus, the lungs, the thyroid gland and the colon (10, 35, 68). This increased risk exists independently of a therapy against the sterility. Nevertheless, under a therapy it is soaring up from 30% to above 1000% for the

development of an adenocarcinoma. (32, 11, 28, 14, 15, 16, 30, 31, 27, 46, 20, 47, 38, 12, 33, 1, 5, 8, 39, 44, 42, 133, 134, 135, 136). In literature three essential causes which are confirmed by various studies are made responsible for the occurrence of an adenocarcinoma in infertile women: (98, 94, 99, 94, 57, 17, 43, 96). Repeated ovulations and ruptures of the ovarian surface, which can lead to the development of malignancy. A continuous ovarian stimulation through the hormones LH and FSH, which have a direct carcinogenic effect and also support, through the increased estrogen level, the processing and the growth of tumors. The exposure of the ovaries to chemical carcinogenic agents. In this context the meaning of a positive family history for the development of cancer needs to be mentioned particularly.

The knowledge of a positive family history on cancer diseases or melanomas of the breasts, the ovaries, the fallopian tubes, the peritoneum, the endometrium, the stomach, the bile system, the pancreas, the oropharynx or the esophagus is from great relevance. Obviously in this group of patients a special attention and caution must prevail referring to the question of planning and realizing a therapy against the infertility by extracorporeal fertilization. (2, 49, 51, 50). Infertile women in the fertilization-capable age show an especially high risk for the development of ovarian cancer. In the year 2000 the United States National Cancer Institute draw the conclusion from several investigations, that a repeated and continuous ovulation during lifetime courses a rising probability for the development of ovarian cancer in general. With regard to this, there is a saved evidence that an increased activity of the ovaries caused by an increased level of certain hormones, as for example under the influence of HCG stimulating the ovulation, is closely related to an aggravated risk for the occurrence of ovarian carcinoma.. The analysis of patients with existing ovarian cancer show, that the risk for the development of this kind of neoplasia is hardly influenced by the use of specific pharmaceuticals for the stimulation of the ovulation (65). Women with use of these pharmaceuticals show a risk of 3-4% for developing ovarian cancer, in contrast to the risk of women without specific ovulation stimulating therapy which is about 1-2%. Accordingly, the risk for women for the development of ovarian cancer under an increased

ovarian activity caused by ovulation stimulating pharmaceutical therapy rises about 100% compared with the risk of women without such a medication. (181, 4, 19, 67) Following conclusion can be derived from that: The commitment of pharmaceuticals in the therapy of infertility, which increases the number of ovulations can lead directly to an increased risk for ovarian cancer. The hazard for the development of a malignant tumor with a low malignant potential lies at 143% (18).

Clinical studies at more than 12.000 infertile women (primary and secondary acycosis), with an average age of 30 years, show an increased risk for the development of a malignant tumor of 98%. Pharmaceuticals for the therapy of infertility, as for example Clomiphen-citrate, make the risk go up onto 48% after 15 years of application (23). Also the application of Gonadotrophin is connected with an increasing risk of about 146% for the development of cancer after a period of 15 years. (6, 63, 9, 36, 37).

### **1.2. Possible risks of harm for mother and child referring to the different medical procedures**

In vitro fertilization and the occurrence of ovarian cancer. The utilization of the in vitro fertilization led to the occurrence of aneuploidy in the granulosa lutein cells in 50 to 73 %, that means in the vast majority of cases. Further investigations showed aneuploidy at 17% of the oocytes and it needs to be mentioned that this aneuploidy normally represents the starting point for the development of cancer (40, 77). In scientific literature, there are many discussions about the benefit, the risks and the dangers of IVF (137, 172). In spite of those ones, who claim that there are no dangers or risks in artificial insemination (45, 13, 138) reliable physicians should clear up their patients about possible complications and make these sign a written consent declaration before they carry out the intervention (41).

Some findings in scientific literature emphasize, that already the first attempt to stimulate the ovulation in the ovary can end in the occurrence of ovarian cancer. The starting point for the development of cancer was probably already available and was overlooked through a lacking anamnesis and preliminary investigation. Others report that more than 10 attempts are necessary until it results in the occurrence of ovarian cancer, so that 10 artificial attempts for the stimulation of the ovulation might serve as a boundary. This can not be accept-

able even to the most liberal attitude.

### **1.3. The effects of the pharmaceutical stimulated ovulation and the rising risk for development of cancer**

The utilization of pharmaceuticals for the stimulation of the ovulation in the ovary accelerates the development of clinically unapparent and undiscovered tumors (30, 3, 8). CIS has to be mentioned particularly and also new occurring breast cancer (30, 48, 55, 59, 61, 131). Unkila-Kalio et al. (34) refer in their study, that 15% of the study participants with breast cancer and 85% with ovarian cancer had a preceding stimulation of the ovulation. The higher risk for the development of genetically changed cells and following the occurrence of cancer, increases with every "stamped" ovulation (94, 97, 98, 99, 173). Furthermore the stimulated ovulation intensifies the status of a systemic inflammation, rise of the CRP for example, and of the implantation (87). Besides the stimulations with Gonadotrophin can increase the risk for the development of cancer in the ovaries, the breasts and the endometrium and therefore lead to malignancy (88, 12, 25, 52, 72).

It was seen, that patients who had used pharmaceuticals for the stimulation of the ovulation (Fertilization Drug Therapy-FDT), and have developed breast cancer which continued far, fall sick with a very aggressive kind of neoplasia that shows a low degree of differentiation (56, 58, 60, 62). Within this group of patients a treatment is extremely complicated and it often results in therapy resistance of the tumor so that an extremely bad prognosis for these women results.

As already mentioned, there is a general risk for the development of ovarian cancer in the course of life of approximately 1,8%, which rises up onto 4-5% under the use of a FDT (69, 137, 140, 178, 179). The risk for the occurrence of breast cancer under FDT is among 12%. For cancer of the endometrium the risk under FDT results in a rise from 79% up to 1152% (130). In this context it is needed to say, that not only the risk for the development of a sarcoma of the uterus does increase under a FDT but also the sarcoma itself shows a higher malignancy than other cancer diseases (28, 20, 24, 26, 29). Furthermore statistics show, that women who underwent a FDT and nevertheless not became pregnant, have a significant rise of the cancer risk in comparison to women without fertility problems in the anamne-

sis. (22, 139, 181).

This matter of special importance must be made clear to any women who consider to undergo an IVF. About the effect of the injection of sperm in ovum (ICSI) onto the infantile development and the mothers' risks. The investigation of naturally obtained twins and through ART obtained twins, showed in the arrangement a slower and poorer development of the children in the ART group, especially great differences in physical development were observed. Nevertheless no difference in the intellectual development of all children up to the 24th life month was proved (90). In contrast to this, the study of Bowen (123) demonstrates, that although most of the children received by ICSI ran through a normal physical and sanitary development the MDI (mental development index) shows a slight and significant delay of the intellectual development at more than 85 % of the cases. In comparison to that, the part of delayed intellectual development of children brought to life by natural fertilization is about 2% ( $p < 0.0001$ ). An investigation at the King Chulalongkorn Memorial Hospital in Thailand also showed, that the use of the ICSI technology caused a multiple pregnancy within 27% of the women, while the part of multiple pregnancies at natural conception was about 0.93%. A quarter of these children were premature infants and 85.7% were born by Caesarean section. 1.3% of them appeared with major inherent malformation and at least 49.3% showed one or some slight malformations (125). In total the number of inherent malformation of newborns under the use of ART increases from 47 to 177 %. With an installment of 9% children received by IVF and ICS also fall ill more frequently. Examples for this are teething troubles, higher number of hospitalizations and operations and higher frequency of major inherent malformations. (146, 144, 92, 127, 120, 124, 154, 155, 156).

#### 1.4. The childrens' side

Risks of medical assisted fertilization (MAF) for children in general. During the luteinization phase the influence of a surplus of Progesterin can lead to an endometric luteinisation and to an unripe appearance of the implantation frame, which complicates the nidation of the embryo (164, 165, 166, 167, 168, 169, 170). In the case of IVF and ET the human menopausal gonadotropin (hMG) has the ability to interrupt the endometric tendency towards the implan-

tation (86, 114, 113, 118, 117, 115, 112, 157, 159, 160, 161, 162, 175, 176, 177). Beyond this, an ovarian hyperstimulation (OHSS) during IVF influences the gene expression in the endometrium. In this case up to 200 genes can change their expression around 300%. This means a modification of the gene express around a triple in comparison with a normal menstruation cycle (116, 71, 70, 163, 174). Besides investigations on oocytes and embryos show, that only 6.7% of the embryos have a normal mononuclear blastomer (75, 160, 172).

In this context it needs to be made clear, that the modification of mitochondrial genes of the oocytes and the following associated modifications of the embryo have a dominant influence on the further development of the growing up embryo (94, 93, 73, 74, 171). These variances in the development of the growing up fetus caused by medical assisted fertilization can be named such as variances in the birth weight, fetal malformations, aneuploid chromosomes and syndrome of genetic imprinting (77, 142). The manipulation of the gametes' and the embryos' under the aid of the IVF technology leads as already mentioned to a prenatal phenotypic modifications of the fetus and also represents an activator of cellular stress, which leads to epigenetic modifications of the genetic expression (143, 76, 122, 53).

In the course of development the incidence of newborns that were received by IVF is about 2% compared with the total number of newborns, while the number of Caesarean sections in this group rises up to 54.3% in contrast to 10.8% of Caesarean sections in the control group. Added to this, Schieve (91) points in his study, that children who were received by IVF have a 2,6 times higher risk for a low birth weight.

	IVF-Group	control-group
Birth weight less 2500g	57.5%	8.2%
Premature born children	49.9%	8.2%

Special risks for Children received through medical assisted fertilization (MAF). The special risk for children that were received under the use of MAF to come down with some rare teething troubles lies at 270 to 570% (143, 145, 106, 104). The in vitro technology, the artificial stimulation of the ovaries or the infertility itself are made responsible as possible reasons for this enormous increase. (81, 78, 82, 80, 79,

121). As already mentioned the use of medical assisted fertilization, IVF and ICSI technology, causes an increased risk for the fetus to have a low birth weight, cerebral paralysis, injuries of the newborn and inherent malformations (148, 146, 147, 85, 83, 54, 64, 119, 152). It should also be noticed that the masculine infertility is potentially hereditary and that in 6.4% of the cases hypospadias occurs in children who were received by ICSI.

#### 1.5. Higher frequency of spontaneous abortions, early births and postnatal complications

The risk of spontaneous miscarriages under MAF is near 20% while the normally risk for a spontaneous miscarriage within healthy women is up to 21% (105). Only a few fertile women show a risk of 70% for an early spontaneous miscarriage. Besides, 47% of the children who were received by MAF are in need of immediately intensive care unit support after birth (103, 66).

Studies at 53928 women prove that the incidence of fetal damages is close to 30% in contrast to a number of 19% for fetal damages according to natural conception. Also single-embryo pregnancies achieved through medical assisted fertilization show a lower success as a natural twin pregnancy. Furthermore in 5.2% of the cases deliveries before the 32nd week appear at women who have been treated with MAF, IVF or ICSI (107, 110, 109, 108, 64, 100, 101, 102).

Helmerhorst even points out, that an early delivery can lie with 227% before the 32nd pregnancy week and with 104% in the 37th pregnancy week. In this case the birth weight lies in average with a risk of 200% under 2500 g and with a risk of 40% under 1500g. In his study 54% of the children needed to be born by Caesarean section and 27% of these newborns needed to be passed over onto the intensive care unit. The perinatal mortality was near 68% (84).

What it all amounts to is, that IVF and ICSI show a 10-times higher risk for a delivery before the 37th pregnancy week and a 7.4-times higher risk for a delivery before the 32<sup>nd</sup> pregnancy week. The danger for a birth weight of lesser than 2500 g is at 1080% and for a birth weight under 1500 g at 440% and 80% of the newborns have an increased risk for cerebral paralysis (RR=1.8). Furthermore there is a rise of the risk for sleep troubles around 100% and a risk for the origin of a malignant hemic disease around 130%. (144, 1, 7, 9, 21, 111,



119, 126, 128, 129, 150, 153).

## 1.6. Recommendations for the utilization of the ART

Members of the ESHRE recommend the highest transfer to be two embryos or what would be the best thing, to transfer only one embryo (141, 154, 147, 100, 101, 102, 149). A controlled hyper stimulation of the ovaries or an intrauterine insemination should be carried out at most three times (89, 173). It is urgently necessary to create a list in the Croatian Republic in which the morbidity, the complications and the mortality of MFO, IVF and ET are performed.

## 2. DISCUSSION AND CONCLUSION

More than 200 articles and 150 publications were examined for the circumstances of the case, which emphasize the negative effects of the medical assisted fertilization, IVF and ET on mother and child.

It is necessary to review the method of in vitro fertilization onto the right to live and the dignity of the human being. As an ethical criterion, the human being should not be considered as an object. It should not be allowed to use embryos for experimental purposes, to freeze or to sell them. This was also the conclusion of the supreme court of Costa Rica on 11 October 2000, which led to the prohibition of IVF and ET. The reasons for these decisions lay in the violation of the section four of the Constitution of American Human Rights Convention.

We approve and support all forms of the medical assisted fertilization within the framework of the natural cycle. In spite of this, we would like to come forward with the proposal that IVF and ET within the uterus should not be applied. This stands in unison with the opinion of his holiness Pope Benedict XVI. and the doctrine of the Holy Catholic Church. Through this the love in marriage in family and the responsibility to the upbringing of our children should be preserved. We kindly ask the readers of these pages to follow us and to contribute on this discussion, by expressing their opinion and arguments freely. This is from special relevance, because it is about an extremely complex, than also ethical, genetic, medical, biologically sensitive topic. Only by the way of conversation a responsible dealing with this subject and the formation of adequate conclusions and an adequate attitude will be achieved.

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