Original Papers

Polish Psychological Bulletin
2009, vol. 40 (3), 145-155
DOI - 10.2478/s10059-009-0027-x

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In vitro fertilization (IVF) and the risk of birth and developmental defects – facts and fictions

Poland is being swept by a wave of discussions on various aspects of IVF application. Scientists of various disciplines are getting involved in these discussions as opponents to this form of procreation. Referring to research carried out all over the world, they demonstrate that children born thanks to the in vitro procedure are significantly more susceptible to all sorts of disease. The author, surveying available research data, shows that, in reality, the worse health of in vitro-conceived children deals with a narrow number of well-identified disorders and in most cases is of correlative, not causative nature. The main reason for the weaker health of these children is often connected with the advanced age of the parents who choose IVF and their health condition (mothers' in particular), as compared to those who become parents in a natural way.

Keywords: *Birth, developmental defects, IVF*

Introduction

Social discussion around the **in vitro** fertilization has become quite turbulent in Poland. It is addionally being incited by the fact that, having formerly signed the European Bioethic Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine, Poland eventually refused to ratify (Biesaga, 2006) this settlement. In Poland, legal regulations for principles of assisted reproduction are also being currently worked on. The clash of opposite attitudes in the pro- and anti-**in vitro** camps is influenced by the broad impact of the Roman Catholic Church on social life in Poland, as well as by the fact that advanced infertility treatment is not reimbursed by the Polish National Health Fund. The discussion on the moral aspects of medical intervention into human fertility is not likely to change people's attitudes and thus is not the subject of this article. Public opinion seems to accept the procedure of **in vitro** fertilization (Budzyńska, Dudziak, 2003; Jawień, Matusik, 2004, after Pelwecka, 2007) and information about the child's conception does not seem to affect the social evaluation of people who undergo artificial fertilization (Kuchmister, 2009). One of the points against the legality of technologically advanced methods of assisted reproduction (extracorporeal fertilization) is concern over health the of children conceived by using this method. The opponents of artificial fertilization methods among Polish scientific authorities refer to data of alleged high mortality, a high occurrence of birth defects, higher morbidity rates than average, and abnormal development of children conceived **in vitro**. Their scientific titles become the premise of credibility, confirmed by references in expert literature. Warnings addressed to the broader circle of popular periodical readers most probably evoke the latter's anxiety, particularly when these warnings are supposedly authenticated by current scientific research.

State of health and threats for children conceived in vitro in light of information published in the mass media as presented by expert literature

Periodicals convey information that evokes justified concern of a growing group of people who consider resorting to the procedure of assisted fertilization or have already done it (according to estimated data, infertility concerns around 20% of couples of reproductive age). Anxiety and doubts are shared also by those who are interested in this problem for other reasons, for instance those responsible for any potential reimbursement system for assisted fertilization treatment. The question is currently

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subject to public debate, and with the assumption of the worse health conditions and deviant development of the growing group of children conceived in vitro, the costs of treatment and rehabilitation of these children would be an extra expenses to the taxpayer. Therefore a critical and objective verification of data concerning the state of health of in vitro children seems indispensable.

"After 30 years of in vitro procedure application, which generated two million births, half of the children are now less than 5 years old – the scientists are warning. The mortality of these children is terrifying" – this statement keeps reappearing in the Google search engine. Ascribed to professor Bogdan Chazan (www.kosciol.pl), it has been quoted on catholic websites as well as – in the literal or paraphrased versions – in forum discussions on extracorporeal conception problems. The author's real intention was to point out that even though the method has been applied since 1978, it has become widespread only in recent years (Babuchowski, 2008). In industrialized countries, the percentage of children born as a result of this method reaches 1-2% of the population and it is forecasted to reach 4 - 5% in the near future.

Unfortunately, the statement can be easily misinterpreted (particularly in the context of terrifying mortality and alarming scientists) and understood that half of the children conceived *in vitro* die before reaching the age of 5.

Other pieces of information found on the Internet sound equally – and this time, unambiguously – threatening. Let us take this example:

According to research conducted by Dr. Andrew Feinberg of John Hopkins Medical Institutions in Baltimore and Dr. Michael DeBaun of Washington University in St Louis, the Beckwith-Wiedemann syndrome develops in 5% of children conceived by the in vitro method. The probability of the disorder is directly proportional to the time of storing the embryos in artificial conditions before transferring them to human body

which is quoted on at least two websites frequently visited by people suffering from infertility: (www.nasz-bocian.pl/modules.php?name=News&file=article&sid=302 ; www.dlapolski.pl)

The reader will also learn that the above conclusion originates from serious research, published in a prestigious scientific periodical: Newsday.com – *26.08.2003. Source: M.P. Lee, M. DeBaun, G. Randhawa, B.A. Reichard, S.J. Elledge, A.P. Feinberg, "Low Frequency of p57KIP2 Mutation in Beckwith-Wiedemann Syndrome" in: "American Journal of Human Genetics", No. 61, pp. 304-309."* (www.nasz-bocian.pl/modules.php?name=News&file=article&sid=302; www.dlapolski.pl ; www.naszdziennik.pl)

The piece of information above, multiplied in discussions on the purpose of assisted reproduction methods, is a model example of extremely biased exploitation of the argument of bad health prognoses for children conceived *in vitro*. The text referred to as the source has nothing to do with extrasomatic fertilization. It constitutes a description of 40 Beckwitt – Wiedemann syndrome (BWS) cases. In fact, Feinberg and DeBaun -- the initiators of the American BWS register, on the basis of data indicating a certain over-representation of children conceived via ART (Assisted Reproductive Technology) in these registers -- set forth a hypothesis that the application of assisted reproduction may constitute a BWS risk, but they do so not in the article indicated as the source but in their other works (see: DeBaun at al, 2003). However, like some other researchers, they are also unable to identify the risk conditions of the given ART technique. Neither can they define the dependence between the time of incubation or cryoconservation of human embryos and BWS occurrence (*if* such an interdependence exists). The claim that Beckwitt-Wiedemann syndrome is found in 5% of *in vitro*-conceived children is absurd. In the years 1993-2003, in the BWS registers in the USA, there were merely 341 records of this disease. According to these registers, 19 of those children were born thanks to ART techniques (Chang et al, 2005). This would mean that amongst the whole group of people suffering from BWS, 5.5% are ART- conceived children, while 3.5% of the latter group are children conceived via the *in vitro* fertilization procedure (of the 19 cases, two were born as a result of ICSI, and 2 by classical IVF). Similar proportions can be observed in equivalent registers in France (Gicquel at al, 2003, after: Lucifero et al. (2004)) and Great Britain (Maher et al., 2003).

Unfortunately, the mistake of overestimating the occurrence rate of rare genetic disorders is made not only by anonymous internet users. Śliwa (2008), considering potential ART dangers for the human population, writes: "Up till now, a higher risk of certain genetic disorders in ART-children has been found. For example, the Beckwitt-Wiedemann syndrome has been found in 4.6% of these children, and the Angelmann syndrome - in 3.5% of the ART-child population" (p. 13).

Were the author right, there should be around 2100 *in vitro*-conceived children born in the years 1996-97 suffering from BWS in the USA alone, and respectively, 1600 children with the symptoms of Angelmann syndrome (compare Schieve et al, 2002).

In reality, however, by the year 2003, on the basis of American BWS registers, 7 cases of BWS in children conceived via ART have been diagnosed, and no cases of Angelmann syndrome (Lucifero et al., 2004, DeBaun et al, 2003). The Angelmann syndrome is generally rare – occurring once in every 15,000 births. Its occurrence among children conceived via ART is mentioned in the relevant literature on the basis of a mere several (!) cases, detected in Europe (Cox at al, 2002, Orstavik at al, 2003, Doornbos et al, 2007).

Even if we assume the data provided by Chang (2005),

which indicate that not 7 but 19 cases of the Beckwith-Wiedemann syndrome among ART-conceived children were detected, this number still does not justify the data presented by Śliwa. At the same time it is worth keeping in mind that the data referred not only to the cases of children conceived *in vitro*, but also to all ART methods, including ovarian stimulation, gamete donation and insemination.

Regrettably, Śliwa ignores the rudimentary difference between the percentage of children suffering from the given disease within the group of *in vitro*-conceived children, and the percentage of children conceived *in vitro* among all children suffering from the disease.

Let us take a closer look at other – scientific, or so it would seem – revelations on artificial fertilization risks.

"Meta-analysis of 15 independent studies, carried out by American scientists, has indicated a two times higher mortality rate of newborns and a 30-40% risk of developmental birth defects in children conceived *in vitro* as compared to children conceived in the natural way. Furthermore, 51.3 per cent of children conceived *in vitro* are born from multiple pregnancies; ectopic pregnancy occurs twice as frequently and placenta previa – 6 times more often. Observation of children born thanks to the *in vitro* procedure indicates a 2.6 times higher risk of low birth weight of the newborn, and a 60% higher risk of brain damage in the form of cerebral palsy – 230% higher for unfrozen embryos. Physical development is also worse in children born thanks to the *in vitro* method, as well as more problems in upbringing," writes Ludwika Sadowska (2008, http://www.naszdziennik.pl/index.php?typ=my&dat=20080123&id=my12.txt). A sensible approach to these theses, so dissonant with what one can find in reliable literature on the subject, is hardly possible. The source of the quoted data is not even given by the author, so there is no chance for any verification.

Professor-Emeritus Zofia Bielańska-Osuchowska, formerly the head of the Histology and Embryology Department at Warsaw University of Life Sciences (SGGW), presents in turn her doubts as to the safety of widespread application of extrasomatic fertilization in her open letter entitled: "*In Vitro* – The Threats", published in the popular weekly "Tygodnik Powszechny" (Bielańska-Osuchowska, 2006). The doubts of "a biologist tracing the processes connected with animal reproduction", as the author presents herself, do not deal here with animals, though, which seems a curiosity in itself. As a matter of fact, *in vitro* offsprings of farm animals were produced considerably later than human *in vitro* children – the first *in vitro* sheep were born in 1987, when Louise Brown (the first *in vitro* child) was 11, and the first fouls – only in 2002. Apart from that, there are surprisingly numerous problems connected with artificial fertilization of animals – high mortality rate of embryos and developmental disorders of *in vitro*-born animals (Duszewska i Reklewski, 2007). One could then understand that an expert in these matters, is seriously worried about the fate of people born of *in vitro*.

The real problem is, though, that Bielańska-Osuchowska uses illegitimate argumentation. She writes: "an analysis of the development of children aged up to 5 from 5 European countries was published in 2005, comparing ca.500 of all *in vitro* children and of those conceived naturally. What has been concluded is that the former more often suffer from childhood diseases, are more often subject to surgical operations, and stay longer in hospital (reasons: cerebral palsy, epilepsies, asthma, cancer, infections and birth defects)" (http://tygodnik2003-2007.onet.pl/1580,1355026,dzial.html).

The author does not refer to any sources of this information, but we can assume that most probably the author meant the study by Bonduelle et al. (2005), who estimated the health condition and compared children conceived naturally, born as a result of intracytoplasmic sperm injection (ICSI), and conceived via standard IVF (N=538, N= 540, N=437, respectively), from Great Britain, Belgium, Greece, Sweden, and Denmark. The results obtained by Bonduelle et al. indicate a significantly higher occurrence of birth defects in children conceived by artificial fertilization. When it comes to the so-called minor birth defects, they were found in 20% of children conceived naturally, in 29% of children conceived by intracytoplasmic sperm injection (ICSI), and in 31% of children conceived by the classical *in vitro* method. The question of the increase of major birth defects risk (the assumed classification criterion: ICD-10) turned out to be more complex. Only the differences in the occurrence rate of urogenital system defects – particularly in boys conceived by ICSI – turned out to be statistically significant. A relatively high occurrence rate of defects in this group is explained above all as a consequence of genetic predisposition, which in turn results in the very necessity to use ICSI. However, what has not been demonstrated as a higher defect risk in 5-year-olds born by *in vitro* is the occurrence of neurological defects and diseases (including cerebral palsy and epilepsies, the latter not even appearing as differential category), as well as asthma (both in the sense of positive diagnosis and recommendation of pharmacological treatment typical for asthma). Moreover, none of the data indicated a higher occurrence of cancer diseases in the examined group. What follows is the conclusion that Zofia Bielańska-Osuchowska either knows and refers to some other data, or swerves from the facts.

More frequent hospitalizations and treatment of children from the *in vitro* group are explained by Bonduelle and co-authors (2005) mainly as a consequence of parents' over-protectiveness and constant focus on the child's health. The fact of the more frequent hospitalization of these children that Bielańska-Osuchowska refers to, according to the authors of the study, is not caused by the very diseases

that Bielańska-Osuchowska enumerates – like cerebral palsy, epilepsies, asthma, cancer, or infections, but because of the necessity of surgical correction of birth defects. The question is what causes this necessity, then? Parents of children conceived *in vitro* are older, and mothers are more often chronically ill. Therefore children conceived *in vitro* are from the statistical point of view more endangered by birth or after-birth complication risks than children conceived naturally. That very risk, and not the way of getting pregnant, may be the primary cause of the worse health state of children conceived by artificial fertilization. In other words, the connection between the assisted reproduction procedure and the increase of risks for the children's health can be entirely apparent. (This question shall reappear further in this article.)

Two years later, in the same periodical, Stanisław Cebrat (2008) presented his doubts and argumentation against the application of assisted reproduction technology. One of the many points raised by the author is the lack of profound and statistically well-planned research on the health condition of people born thanks to the methods of assisted reproduction embraced by the common term FIVET (or *in vitro* fertilization followed by embryo transfer). As he concludes: "If systematic research on the health condition of these people were carried out, we would have had by now some excellent data "for" and "against" the application of these techniques. Alas, no such data exists. I suppose, however that if such data were favorable for the laboratories where FIVET is applied, it would have been published". Further he adds: "The laboratories hide themselves behind medical confidentiality and the welfare of the patient, while the data for such statistical research can be gathered anonymously and discreetly" (http://tygodnik2003-2007.onet.pl/1546,1462369,3,559916,dzial.html). It's hard to believe that the author of such a categorically formulated judgement could have failed to notice that in the countries where *in vitro* procedures are reimbursed -- both the *in vitro* treatment cases as well as births resulting from ATR -- the health status of these children undergo full registration, which enables evaluation. The identification of children conceived via ART is possible for example in Scandinavian countries, Holland, Belgium, Great Britain, Ireland, the USA, and Australia, on the basis of local, national registers or clinical reports. On the basis of the French FIVNAT register, in the years 1986-1990 it was already possible to evaluate the course of pregnancy and birth, as well as the health state of 80% of the cases of artificial fertilization in this country (FIVNAT, 1995). It seems that parents of *in vitro* children are more often ready to agree to medical and psychological examination of their children than parents who conceived their children naturally, for example in the research by Ponjaert-Kristofferson and co-workers, carried out in large medical centers, 45 to 96% of the *in vitro* children's parents agreed to participate in the 5-year-old health and development evaluation, as compared to 34 – 78% of the spontaneously conceived children's parents (2005).

The retrospective and prospective research evaluating birth result and the health status of children conceived *in vitro* (Ericson, Kallen, 2001; Anthony et al., 2002; Pinborg et al., 2003, Boulet et al., 2008); the functioning of babies and small children (Barnes et al., 2004; Papaligoura et al., 2004; Ponjaert-Kristoffersen et al., 2005; Klemetti et al., 2006; Leunens et al.; 2006; Sun et al., 2007; Belva et al., 2007; Knoester et al., 2007a; Knoester et al., 2007b); , of teenagers and adults (Colpin and Bossaert, 2008, Zhu et al., 2009; Wagenaar et al., 2009), as compared to naturally conceived children – is obviously plentiful.

Another group of research compares the health status of children conceived via different ART techniques (Govaerts et al., 1998, Lie et al., 2005; De Sutter et al., 2005). The focus of these studies is for instance the birth result and the health state of children conceived by assisted reproduction methods, including adoption of gametes, as well as the development of children born after pre-implantation diagnosis (PGD/PGS) (Soderstrom-Anttila et al., 1998; Sheffer-Mimouni et al., 2002; Nekkebroeck et al., 2008a; Nekkebroeck et al., 2008b). Subject to extremely detailed analysis are the cases of chromosomal and genetic syndromes -- Beckwith-Wiedemann, Prader-Willie, and Angelmann syndromes in particular, as associated with ART application. (Manning et al., 2000; Cox et al., 2002; Orstavik et al., 2003; De Baun, Niemitz and Feinberg, 2003; Lucifero et al., 2004, Ludwig et al., 2005; Bowdin et al., 2007; Doornbos et al., 2007; Chang et al., 2005) Studies are also available verifying potential connections between the application of ART and the occurrence rates of cancer in artificially conceived children (Sutcliffe et al., 1995, Bergh et al., 1999; Klip et al.,2001). Apart from comparative cohort studies of children born thanks to extracorporeal fertilization, there are also review studies and meta-analyses (Lie et al., 2005; Hansen et al. 2005; Hvidjorn et al., 2009). The accepted custom has become also the researchers' declaration of the lack of conflicting interests, which excludes personal engagement and in turn minimizes any tendencies of research procedure manipulation or result misinterpretation.

The lack of access to the group of ART conceived children, as presented by Cebrat, is far from being a fact. Such research seems widespread. Unfortunately, often these studies are not free from certain methodological defects, as in the examples below.

The credibility of research results in studies of the health condition of ART-born children: conflicting interests

Childless people, doctors who help fighting infertility, researchers of the process of unnatural fertilization and its short- and long-term effects, supporters and opponents of ART - all have quite varied intentions. Doctors who are primarily interested in the treatment of infertility aim to increase therapy effectiveness, and as currently extrasomatic fertilization happens to be the most effective therapy available, it should be expected that they are mostly interested in the improvement of ART-obtained pregnancy parameters. Pediatricians and epidemiologists are interested above all in the state of health of their patients, which is connected with detecting potential dangers for human health and life. The infertile want to stop being childless as soon as possible, at minimum emotional, social, and financial costs. The opponents to the application and popularization of medical intervention into reproduction, usually concentrate on the religious or ethical context of assisted procreation. They are then likely to stress all the negative aspects of ART. While they are fully entitled to do so from the position of a theologian or an ethicist – once they assume the role of a doctor, biologist, sociologist, or psychologist, they should stick to the facts, which in these cases are quite complex.

In the relevant literature, a lot of attention has been focused on the occurrence of rare genetic syndromes in children born thanks to ART. Precise registration of such cases – both in the general population and in the group of ART-born children – has been postulated by all kinds of researchers and certainly would become indispensable for evaluation of the consequences of *in vitro* fertilization. The disputable question, however, is the precision and accuracy of such evaluation, particularly when faced with the problems of precise estimation of the percentage of children conceived thanks to assisted reproduction methods. If we assume that these children make 1% of the population of the USA, then the risk of BWS occurrence in this group is 4.2 times higher than in the group of children conceived naturally. However, if we assume that children conceived *in vitro* constitute 1.9% of the general number of newborn babies, then the risk increase ceases to be statistically significant (Lucifero et al, 2004).

Studies on the problems of the course of ART pregnancys, birth result, and the health status of the children born with ART effect, including particularly the advanced methods like ICSI, IVM, PGD/PGS, usually end up with the conclusion of the necessity of widespread research on large groups, with either random choice of the research participants or thorough examination of all ART children, followed by providing systematic information to potential ART parents about the risks of having a sick child. The postulate of large-scale and well-planned research on ART children's health condition, although certainly necessary, is very hard to perform, for two main reasons. An ideal research procedure assuming the possibility of legitimate comparison is impossible because it would require, for example, artificial fertilization of an experimental group of fertile couples in the optimum procreation age of 20-25 years, followed by a comparative study of the course and result of pregnancy in a control research group with no infertility treatment or any ART procedures. It would also have to take into account both the successful recruitment of volunteers for the experimental group and the qualms of conscience of the researcher who would invite and encourage healthy couples to participate in an emotionally and medically exhausting procedure. Also systematic examination of all ART-engaged parents and children seems unrealistic because of the necessity to respect the patient's free will to undergo examination. The acceptance of a research procedure assuming, for example, children's health evaluation is largely dependent on the cultural context and is connected with ART availability. In the countries where full databases are available (e.g. Scandinavian countries, Belgium, Holland), the costs of the treatment are refunded, ART procedures availability and application criteria are clear and widespread, social approval for ART application is high, and medical examination of children is largely accepted by the parents. Whereas in the countries where the costs of ART procedures are not refunded (Poland), and also where the procedures are not readily available and the very question of infertility is treated in terms of intimacy violation (Poland, Greece), people's inclination to submit to such examination is lower and the credibility of the obtained data more doubtful.

It is therefore symptomatic that as much as 96% of Swedish *in vitro* parents agreed to their own health evaluation (78% of the control group parents agreed to such evaluation), but in Greece, only 25% of the *in vitro*-children's parents agreed to the evaluation (and all the parents of the control group – of children conceived naturally – agreed to undergo the examination) (Bonduelle et al., 2005).

Health condition and developmental possibilities of ART-born children

It is worth while to have a closer look at what comes out of the above mentioned and other properly conducted studies. There seems to be no other way to fully and objectively approach the argument over potential children's health risks connected with assisted reproduction technology.

According to the ESHERE report (2007), ICSI doubles the risk of neonatal mortality of children, premature birth, and low birth weight of children, and triples the risk of

extremely low birth weight of the newborn. However, no such differences have been found between children conceived by standard IVF and ICSI. Examinations of the condition of health and functioning of children conceived by *in vitro* fertilization seem to show consistently two independent tendencies. Firstly, ART-born children have generally worse prognoses resulting from the circumstances of their coming into the world – shorter pregnancy, higher percentage of multiple pregnancies, more neonatal complications, a greater number of diagnosed major and small birth defects, and more frequent use of medical care and interventions in the first years of life. Research differentiation of ART-children and children conceived naturally is required, as differentiation within the ART group deals above all with the higher occurrence of urogenital system defects of children (particularly boys) conceived by ICSI. The other tendency is the obliteration of differences between ART-children and naturally-conceived children as their age progresses. Comparative studies show consistent elimination of differences during the development process – while in the neonatal phase the prognoses for ART-children is worse than for children conceived naturally, their development at the age of several years is comparable.

Obviously, there are some differences between the results of particular studies, but they are caused by the controlling methods applied or by such demographic factors as the education and economical status of the parents, their health condition, number of siblings, etc. Apart from that, because of the legal differences in particular countries – concerning the legitimacy of the *in vitro* treatment and possibilities of refunding its costs – these factors modify the obtained pattern of dependencies in a varied way. Another source of divergence is also the differences in the assumed research methodology. It is worth noting that in a great number of cases this methodology is far from being ideal (above all because of the selection and homogeneity of the compared couples). (Hansen et al, 2005, Knoester et al, 2007b).

In comparison to children conceived naturally, developmental defects are more frequently diagnosed in IFV/ICSI children. The difference coefficient which defines the risk of the given defect occurrence in comparison to the control group of naturally conceived children, ranges – depending on the source of publication – from 1.04 (confidence interval .78-1.39) (Westergaard et al., 1999) up to 2.27 (confidence interval .12-135.45) (Morin et al., 1989, after Hansen et al., 2005).

The organic localization and the degree of the defect (maintaining the division into major and minor defects), except for the more frequent occurrence of urogenital system defects, particularly in boys born of ICSI, is at the same time varied and dependent on paternal variables and genetic background as the primary causes of infertility and the use of infertility therapy (ESHERE, 2007) rather than on the conditions of conception or particular method of assisted reproduction.

There is no evidence whatsoever that would allow an assumption of any connection between the application of *in vitro* fertilization and the occurrence of cancer in children thus conceived (Lidegaard et al., 2005, Klip et al., 2001)

In three national registers of rare diseases caused by disorders of epigenetic DNA regulation, a certain over-representation has been noted for Beckwith-Wiedemann syndrome (caused by the lack of genes imprinting on chromosome 11p15) and Angelman syndrome (caused by a gene imprinting disorder on chromosome 15) in people conceived by assisted reproduction methods. Out of nine rare syndromes caused by improper gene imprinting which are being associated with ART, currently only three (BWS, Angelmann syndrome, and maternal hypometylation syndrome) are treated as ART-related, although the mechanism, the range and the risk factors are not yet identified and the possible dependencies are construed on the basis of patient registers and case studies (Amor and Halliday, 2008).

As already stated above, these cases are extremely rare – and would still be classified as such even if the occurrence rate increased several times.

Increased risk factors of worse prognosis for ART-children – artificial fertilization or parental condition?

The divergence between the compared groups of ART-children and naturally-conceived children can be explained by three independent factors – the application of ART methods, the parents' characteristics (including: the cause of their infertility), and prior infertility treatment (especially stimulation of multiple ovulation), or an interaction of at least two of these factors.

The more technologically advanced the procedure of assisted reproduction, the more controversy it raises. Doubts are being raised by biologists and epidemiologists, comparing the risk connected with natural fertilization to assisted reproduction techniques, particularly to ICSI. The application of ovulation induction, unnatural selection of sperm to fertilize the ovum, the conditions and the very fact of rearing embryos in artificial nutrients simulating the natural oviduct environment, prolonged rearing of embryos to the blastocyst stage, freezing of the surplus embryos in liquid nitrogen, and finally, the application of preimplantation diagnosis – all this extends the list of potential risks for the expected human being.

What is characteristic: the authors of the alarmist study of the higher incidence of health threats for children conceived by *in vitro* fertilization (Hansen et al, 2002), focused on the method of sperm microinjection into the oocyte as the basic risk factor. This study elicited a stormy discussion

(its Pubmed quotation index exceeded 450 items), with clashing arguments of the poor methodological value of the study with those of revealing possible mechanisms damaging gonads and embryos resulting from the ICSI procedure. The outcome of the studies comparing the birth results, health condition and development of children born as a consequence of insemination (IUI), standard IVF and intracytoplasmic sperm injection into the oocyte (ICSI) seems to conclusively show a lack of differences between the groups (Govaerts et al., 1998, Lie et al., 2005; De Sutter et al., 2005, Knoester et al., 2007b).

The last, but by no means least important factor connected with the increased risk for worse health in ART-conceived children is parental characteristics. This factor seems to have a greater impact on the analyzed questions than the demonized effect of the assisted reproduction technological advancement. The age and health condition of the parents is the main explanation of the worse health condition of the children born via ART. The responsibility is on the part of both parents – their age (more advanced as compared to parents conceiving naturally) and health condition (which often underlies their infertility). Similar results (lack of defect risk after introducing parental variables) and conclusions were presented by Westergaard et al. (1999), Ericson and Kallen (2001). Parity as the factor leveling the developmental differences appeared in the study by Knoester et al. 2007b, Sutcliffe et al., 2001; Pinborg et al., 2004; Ponjaert-Kristoffersen et al., 2005; Belva et al., 2007.

The explanation of worse health functioning in the IVF-children, as compared to naturally conceived children, due to the maternal factor was set forth by Anthony et al. (2002). The total odds ratio for various defects and disorders which [initially] equaled 1.20, dropped down to the value of 1.03 after taking into account such factors as mother's age, parity, and nationality.

Women using the *in vitro* method are on average 3 to 6 years older than women not using IVF (Bielak, Wilczyński, 2005). In comparative studies, the age variable significantly differentiates the *in vitro* group from the control group. However, not only the absolute differentiation should be noted here. The risk of all sorts of pregnancy, childbirth, birth results, and child's health complications, the occurrence of developmental defects and genetic and chromosomal abnormalities is not linear, and a marked increase in negative birth results occurs in mothers older than 35. It is then worthwhile to focus on the characteristics of mothers of ART-children with diagnosed major developmental defects. An analysis of the National Birth Defects Prevention Study data (including data of birth defects of children born in 10 American states) indicates that in the 35+ age range group, as many as 4.5% of mothers gave birth to a child with a birth defect. At the same time, 1.1% of mothers of children with birth defects born in the years 1997-2003, reported the application of ART techniques. Comparing the age of mothers who gave birth to children with birth defects and used ART to the age of mothers who also gave birth to children with birth defects, but conceived naturally, it is hard to ignore the basic difference. In the first group, 44.9% of the mothers exceeded the critical age of 35, in the latter – only 12.9% of the mothers were over that dangerous age threshold (com. Reefhuis et al., 2009).

The comparative analysis of the mothers' age and the defects diagnosed in their children (taking into account miscarriages, stillbirths and live births) indicated significantly more frequent occurrences of abnormal karyotype in older mothers, progressive increase in the occurrence of structural defects in children depending on mothers' age, and the additional risk of non-chromosomal malformation increase with mothers' age over 35. The probability of cardiac defects is almost 4 times higher in the group of children born of mothers aged 40 or older, in comparison to children of 20-24-year-old mothers (Hollier et al., 2000). Couples treated because of infertility problems become parents at a more advanced age, and in at least 50% of these couples the parents are over 35 (Society for Assisted Reproductive Technology and Medicine, 2002, after: Lambert, 2003).

Zhu et al., (2006) demonstrate that not only the therapy, but the infertility itself plus time waiting for pregnancy increase the risk of congenital malformations in children – as compared to children of fertile couples (pregnancy waiting time – below 12 months, no therapy), the odds ratio of having a child with a defect equals 1.20 for infertile couples (waiting time over 12 months), and the application of infertility therapy increases the defect occurrence risk to 1.39. The application of infertility therapy increases slightly the risk of congenital malformations (odds ratio = 1.17) only in comparison to infertile people who did not attempt therapy. It is unknown to what degree these results can be explained by heredity and what caused the infertility, but it can be assumed that within the group of people who undergo therapy are also children whose fathers passed to them genetic charges that made them incapable of becoming parents without advanced assisted reproduction (heavy oligospermia). What is known, however, is that the paternal factor was not considered in the data analysis. Mortality of newborn babies conceived via infertility therapy occurs more often than neonatal death of children conceived naturally (odds ratio = 2.7), with premature birth as the most frequent death cause and multiple pregnancy as the significant cause of premature birth. However, the risk of neonatal death in the group of untreated infertility is still higher (odds ratio = 3.3) and not justified by multiple pregnancy (Draper et al, 1999).

The probability of childlessness increases with the mother's age – it is directly proportional to the age of the

ovaries, and which follows, to the number and quality of the produced oocytes. Pregnancy in advanced age (over 40 years old) increases the risk of complications caused by a worse physical condition of the woman and higher occurrence of age-associated diseases e.g. civilization diseases. The comparative studies of the health condition of pregnant women 40+ and 20-29 years of age (Dulitzki et al., 1998; Gilbert et al., 1999 after: ESHERE, 2005) indicated that the minimum fetal growth restriction (2.5 vs. 1.4%), malpresentation (11 vs. 6%), gestational diabetes (7 vs. 1.7%) were more common for older women - nulliparous. Similar, though smaller differences were noted for multiparous, with a similar frequency of gestational diabetes occurrence (7.8 vs 1.6). The comparison of the newborn condition, pre-term births, low births and intensive care admission, born by mothers of advanced age and young ones, leads to the conclusion that advanced mother's age *does* constitute a risk factor for the child (Dulitzki et al. 1998, after: ESHERE, 2005). The hypertension tendency grows with the mother's age and the BMI index (also increasing with the woman's age) makes an additional independent factor increasing that risk. What is also extremely important is the fact that advanced mother's age is a risk factor of aneuploid occurrence (Reefhuis et al, 2009). In conclusion it has to be stated that the parents' age – and mothers' age in particular – has a significant impact on their reproductive abilities, the course of the pregnancy, birth result, and – which follows – on the child's health.

Therefore, it seems that it is not the very *in vitro* fertilization procedure, but rather the passage of time that is the most dangerous enemy, limiting fertility and increasing the risk of possible complications for the child and the mother.

The procedures of assisted reproduction are associated with the increase of complications in children born thanks to these methods. The increase of risk, according to the data presented here, is mainly a derivative of the age and health condition of the parents as well as the cause of infertility. However, the assisted reproduction procedure itself certainly cannot be excluded as a risk factor (Katalinic et al, 2004). The monitoring of pregnancy progression resulting from ART and the health of children born due to these methods is by all means required and justified. Large-scale prospective cohort studies evaluating physical and mental condition based on stable criteria (e.g. on a group of 400,000 as proposed by Kurinczuk, (2003) or 100,000 (Lucifero, 2004) and enabling the control of conscientiously defined variables which could modify potential risks – have become indispensable. The alarming outcome of pregnancies resulting from multiple ART indicates avoiding the iatrogenic mistake of transferring many embryos at once, and the recommendation of a well-planned single embryo-transfer, as multiple pregnancies – not the ART technique – turned out to be the risk factor.

Final remarks

Doubts of a religious, ethical, or legal nature have accompanied the techniques of assisted reproduction from the very moment when extracorporeal fertilization became a real fact. The health of children born due to ART becomes a public question because of the popularization of the technique and the lack of other alternatives. Considerations of whether the procedure is eugenic in nature (bringing to the world disabled children) or dysgenic (enabling the planning of optimum features for children, according to parents wishes) (Cebrat, 2008) is certainly relevant, but if the health condition of *in vitro*-children is an important point in the discussion, it deserves a serious and balanced approach. Reports on the health of those who benefit from ART should be thoroughly discussed and described. Both underestimation and overestimation of data is a mistake. The primary aim of ART results research should be the optimization of the reproduction method, not its discrediting. A good example of such an approach can be the study by Kurinczuk (2003): by consistently presenting data of significantly higher risks of developmental defects in children born thanks to the *in vitro* method (and often interpreting the data in a methodologically illegitimate way), he strives for standards that would minimize the risks. Over 30 years of using of the *in vitro* procedure have made the method safer mainly by the introduction of less aggressive ovary stimulation, which means obtaining a smaller number of better quality oocytes, transferring a lower number of embryos, using the standard *in vitro* procedure when circumstances are favorable, standard cytogenetic examination of the parents, more accurate diagnosis, better ART-resulting pregnancy care and treating every ART pregnancy as high-risk pregnancy (ESHERE, 2007).

The higher rates of illness among *in vitro* children are often used as an argument against the application of IVF, even if for the interested couple it remains as the only chance of having offspring. Nobody denies women suffering from diabetes the right to have a child – which is obviously right.

The general percentage of defect occurrence in children of women suffering from diabetes equals 6-10% and is three times higher than per general population. These are mostly defects of one organ or the whole system, most often the central nervous system, alimentary system, blood circulation system, urogenital system and the skeleton. Birth defects of children from a diabetes-complicated pregnancy often result in intra-uterine death of the fetus, extremely bad condition of the newborn, the newborn's death or considerable invalidism. The most characteristic child defect among mothers with diabetes is caudal regression syndrome, which occurs 200 times more frequently than in the general population and results in impaired development

of legs, intestines, and urinary bladder palsy (Bomba, Wielgoś, 1999).

Even the most alarmist data on the ART-children's health condition do not estimate such high defect risks as in the case of children born from diabetes-complicated pregnancies. Despite the identification of the cause of these defects – a metabolical disorder affecting the organogenetic process, the task for the diabetologists and obstetricians is to balance glycemia during the conception and early pregnancy phase (Bomba, Wielgoś, op.cit.) – not the prevention of pregnancy in diabetic women. Both diabetes and infertility are civilization diseases, but according to the artificial fecundation opponents, only the latter of these diseases raises stipulations and only when treated by the *in vitro* method.

The same refers to the age of people who decide on the *in vitro* procedure. Bearing in mind that the advanced age of the mother (and also father) increases the probability of developmental defects and illness occurrence for the child, it is worth noting that the increased percentage of birth defects depending on the mother's age is not restricted to the advanced age range. Reefhuis and Honein (2004), analyzing non-chromosomal birth defects in children born in the years 1968-2000 in Atlanta and attributing them to the age of mothers, concluded that both age-advanced (35-40 years) and adolescent (14-19 years) maternity is connected with higher risk of defects, and adolescent mothers' children seem particularly vulnerable. The odds ratio for having a baby with a particular defect (OR) ranges from 1.12 (heart defects) up to 1.85 (hypospadias second degree or higher) for mothers 35-40 years old while the odds ratio for an adolescent mother's baby defect ranges from 1.28 (all ear defects) up to 7.18 (gastroschisis).

The negative atmosphere around the *in vitro* fertilization is the reason why a number of women do not really reject this method but rather think of it as "the last chance method", trying other ways of getting pregnant for many years. In many cases this results in childlessness of couples who would have had chances to become parents had they decided on *in vitro* earlier. "Unfortunately, even ART cannot compensate for >30-50% of the fecundity that it lost by delaying attempts at conceiving" (ESHERE, 2005, p. 273). The impact of parental age on the ART result is demonstrated by a prospective study of 221 IVF and GIFT couples. The risk of getting pregnant and not giving birth to a live baby is, respectively, over 4 and over 20 times higher for 40-year-old mothers and older, as compared with 35-year-old mothers and younger. Every additional year of a man's life results in 11% odds increase of not achieving pregnancy and 12% odds of not giving birth to a live child, in the conditions of extracorporeal fertilization (Klonoff-Cohen, Natarajan, 2004).

Advanced age of the parents is on the one hand a childlessness risk factor, and on the other, the possible reason of worse health prognosis for their children. Unfortunately, infertile people rarely reach out for research results; to learn about the potential dangers of ART, they much more often choose everyday press, which does not differentiate between artificial fertilization (not bothering about the terminology) and the increased risk for worse health in ART-children, which overwhelms them with revelations of considerably exaggerated proportions of defects, and treats the *in vitro* – child's risk connection as causative instead of correlative. The conclusions of the researchers that more research is required and that at present one cannot exclude the impact of the extracorporeal fertilization procedure on the child's health are interpreted in alarmist terms.

In the meantime, the opponents of assisted reproduction technology use most often randomly interpreted data to illustrate not so much some ethical doubts, as their own protest against the abnormality of this form of procreation. The poor health of children born due to the *in vitro* method is one of their main points against ART. All this is done in an unscientific manner. They pre-select some of the data purposely, ignoring other inconvenient data, confuse correlative and causative dependencies, and quote data numbers without source references, making it impossible to verify their theses by the reader. This manner unfortunately leads to social disorientation and extending the tragedy of people who do not have restraints of a religious or ethical nature about using the *in vitro* procedure, but are anxious that the child they could have thanks to this method will (almost) certainly be ill.

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