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Thirty Years Now – But Can We Say IVF is Safe?

On the Clinical Significance and Durability of Current Knowledge

K.-G. Nygren

We know quite a bit about safety risks for IVF children and their mothers. But we certainly do not yet know the full story. There is documentation on modestly but significantly increased risks for obstetrical complications, birth defects and prematurity after treatments with established technologies like standard IVF, ICSI and slow freezing. This is possibly not due to the technologies *per se*, but to parental characteristics and (with large risks) to iatrogenic multiple pregnancy of high order. Obviously much less is known for experimental procedures. Adult life health consequences are largely unknown. Theoretical risks, not yet clearly documented but currently in focus include epigenetic modifications in vitro and in vivo and intrauterine deviations of growth. How does our current knowledge of safety risks, and our current lack of knowledge of theoretical risks, impact current clinical policies? **J Reproduktsmed Endokrinol 2010; 7 (4): 225–8.**

Key words: IVF, safety

■ Introduction

The first heading of this text is, maybe, a bit presumptuous. IVF is not a well defined entity: it includes a number of different technologies with different characteristics.

To pronounce it to be safe or not seems like an oversimplification. Nothing is totally safe. A certain length of time, like 30 years, would not solve the problem. Different stakeholders may well have a different interpretation or evaluation of current safety data.

Everybody would agree that knowledge of the safety of IVF is crucial. IVF services need to be managed, inter alia, by outcome feedback data on safety. Yet our current knowledge is quite limited. IVF includes a variety of technologies, some of which have been in use for a number of years now, where data on safety is available. In contrast, some others have been introduced only recently, which are “experimental” as long as there is insufficient data to validate their safety.

Data on safety is time-sensitive depending upon changing patient characteristics, changing ovarian stimulation strategies, new laboratory technologies being developed and upon different quality of available maternal and obstetrical care. Safety also varies greatly by geography.

■ Safety Levels

Medical and psycho-social safety is equally important, but this survey will focus on medical risks for women and children.

Basic Risk

There is, of course, no such thing as a zero risk-level for pregnancy and childbirth.

A background or basic risk exists everywhere and at all times, but there are very dramatic risk differences between countries and time periods. Just compare Sudan to Sweden, or Sweden now to Sweden 100 years ago.

Additional Risk from Subfertility

Sub-fertile people have an increased risk, just because they are sub-fertile.

Additional Iatrogenic Risk

IVF patients have yet another, extra, increase of risk because of the IVF treatment or rather of the way this technique is utilized in clinical practice, an iatrogenic extra risk.

These distinctions of risk levels are important when it comes to the protection of safety: what risks are preventable and what risk levels are “acceptable”? It has been argued that, ideally, the safety for IVF children and mothers should not be

worse than for any other child or mother in that setting. It is now clear that this is not achievable, not totally. It is true that iatrogenic risk increase, like multiple births, have been identified and can, and should, be removed. But safety risks dependent on patient characteristics, like birth defects, are much more difficult to eliminate. It seems, at least at present, that a certain risk increase for birth defects has to be accepted. If at all these treatments should continue.

■ Safety Data Collection

Some 4 million children have now been born, following IVF treatments worldwide [1]. The International Committee Monitoring Assisted Reproductive Technologies, ICMART, is continuously collecting data, currently estimated to cover some 75 % of the total, global activity. Most of these data concerns treatment access and treatment efficacy. One very important aspect of safety is also covered, namely iatrogenic, multiple birth.

In contrast, national outcome data covering obstetrical risk, neonatal risk and long-term safety data is available only from a few countries. With a number of country specific factors operating (e.g. patient selection, treatment policies, maternal health care) the question arises on the possibility, feasibility and justification to generalize safety data from one country to another.

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Future data collection needs to cover all nations where IVF is performed, and specific safety data should, as much as possible, be collected. The first of these challenges is clearly within reach, whereas the second is much more difficult to meet. Global data collection needs common terminology and recently a ICMART-WHO Glossary on ART Terminology has been published [2, 3]. A Nordic countries project, MART (Monitoring the safety of Assisted Reproduction Technologies), is in a planning phase and aims at collecting safety data from the Nordic countries, which all have national data from their IVF populations and also from their general populations. This would be the largest data base on IVF safety, so far.

■ Currently Available Data, Clinically Established Procedures

Early Pregnancy Loss

A large number of available data, national and experimental, indicate that spontaneous abortion rates are not increased with established IVF methodology [4].

Obstetrical Risk Increase

IVF pregnancies are risk pregnancies, with disturbances in placental function (OR around 2) including preeclampsia, certainly for multiple pregnancy (iatrogenic), but also, though less so, for singletons (due to sub-fertility) [5].

Peri-Natal Data

Still birth and neonatal death have been reported elevated. Prematurity of all levels of severity are sharply elevated due to multiple births and there is again a small increase also for singletons. Recent reporting shows that lowering multiple birth rates will actually decrease this additional risk [6].

Birth Defects

Risk is elevated with an OR around 1.5, possibly due to parental characteristics of sub-fertility and not significantly affected by multiple birth [7].

■ Data not Currently Sufficiently Available, Experimental Procedures

Experimental Technologies

The efficacy and safety of “experimental” technologies are not, yet, sufficiently

validated. There is no international agreement on when to pronounce a method to be “still experimental” although there are examples of such efforts e.g. from the ASRM (American Society for Reproductive Medicine). The ideal would be that clinics embarking on new technologies should do so only in the framework of a clinical trial with proper comparison groups, thereby contributing to speed up the process of validation. To just start using (and advertising) a new un-validated method without properly collecting efficacy and safety data is not good clinical practice. Also, patients should be informed about the experimental nature of the method. Vitricification [8] and blasto-cyst culture [9] would be current examples.

Another aspect is that, in most settings, the introduction and use of new methods or new laboratory or clinical equipments are not scrutinized and regulated formally, the ways drugs are. Such mechanism needs to be installed.

Epigenetic Risks

The recently opened research field of epigenetics and the theoretical risk of introduction of epigenetic risks in IVF is very interesting, with a potentially great impact on the understanding of risk mechanisms [10]. Imprinting problems are part of this phenomenon where there seems to be a risk increase with IVF. Different clinical severe syndromes of birth defects, like the Angelman-Syndrome or the Beckwith-Wiedemann-Syndrome have a varying likelihood of being caused by imprinting. In a recent report on 32.000 IVF children 7 such cases were found when three were expected [7]. So far the risk seems small but there is the possibility that epigenetic effects could be responsible, as mediators, for other disturbances as well.

Health Risks Later in Life

Only a small proportion of individuals born after IVF have yet reached adult life. A theoretical risk for health consequences later in life of disturbances in intrauterine growth has been suggested. Also, reproductive problems need to be investigated when the population gets older.

■ Causes of Risk Increase

When, at first, evidence of an increase risk for birth defects after IVF was

presented by Lancaster [11] the question was raised whether such a risk-increase was caused by the techniques *per se*, by clinical policies on ovarian stimulation and embryo transfer or by characteristics of the couples treated. Current data indicates that all three mechanisms are operating, but with different outcomes.

Patient's Characteristics

They seem to be largely responsible for the increased risk of birth defects. An statistically significant increased OR of 1.4 was found for 16.000 children born after IVF, compared to controls, but “disappeared” to not significant levels when years of infertility was controlled for [5].

Drugs

Used for ovarian stimulation, they do not seem to cause health problems for the children, whereas strong stimulation (which still is the norm in most settings) may cause the dangerous and potentially lethal ovarian hyperstimulation syndrome (OHSS) in women. For women who actually get pregnant and give birth after IVF, long term elevated risks on e.g. cancer later in life does not seem to occur [5]. For women receiving repeated but unsuccessful treatments the situation is less clear.

Methodologies

The safety of drugs are supervised by regulations from national and international drug agencies (e.g. the Food and Drug Administration, FDA, in the USA) whereas methodology and equipments used in the laboratory or the clinic usually are not. Examples include culture media, culture timing, new technology for freezing and thawing of gametes and embryos. This situation urgently needs to be rectified. A recent study from the Netherlands [10] showed significant differences in the birth weight of children coming from the culture of embryos in different media, the composition of which is not openly declared.

Clinical Policies

Clinical policies on the number of embryos transferred has been demonstrated to be responsible for a much increased risk of prematurity and of sequels thereof, whereas clinical policy revision to use SET as the norm has been demonstrated to decrease prematurity and its sequels

for women (e.g. preeclampsia) and children (e.g. perinatal mortality and morbidity, like CP) [6, 12].

Maternal Health Care

Maternal health care and obstetrical care may well influence risk. If IVF pregnancies are not recognized as risk pregnancies neglects may follow. Drug use during pregnancy has been shown to differ substantially between pregnancies after IVF and other pregnancies [5].

■ Interpretation of Data

The interpretation of risk data needs to consider the distinction between a statistically significant finding and its clinical significance and between relative risk and absolute risk. The risk for a birth defect to occur after IVF is statistically significantly elevated but the absolute risk is low and may not be clinically significant for some couples but may again be highly relevant for other, who may be in a different situation. The risk for cancer for individuals born after IVF has been known to be increased, although not significantly so among 16,000 individuals [5]. The interpretation of this situation may again be different for different persons. If the risk increase remains when the observation groups will be expanded it may actually reach statistical significance. So the message is not so clear for the individual. A statistically increased risk may well be important “on a population level”, whereas the absolute risk for the individual may be perceived as “low” and acceptable. Correct information to the patients is crucial.

As evidenced by lively current discussion among patients, professions and regulators in different settings, there often seems to be a “trade off” between safety and other indicators of benefit, like efficacy and cost. Iatrogenic risks, induced by deliberately chosen clinical policies, are possibly less “acceptable” than other risks. In Sweden, some 7–8 years ago, national data on safety clearly showed, and was interpreted by all stakeholders in a similar way, that the generally accepted trade off between safety and efficacy of the time, was actually not longer acceptable. So, a new trade off manifested itself in a change of clinical practice towards single embryo transfer (SET) as the new norm and this was later verified by a change of law [13]. A simi-

lar tendency is visible in many other countries [4].

“Surrogate endpoints”, e.g. survival rates of thawed blastocysts, and biomarkers are not valid as clinical indicators of child safety and may be dangerous [14]. Such endpoints are useful in exploratory research, but cannot be used clinically, until clinically validated by true endpoints [15].

■ Risk Evaluation by Different Stake-Holders

Patients

In some countries or settings, patients seem to accept a higher risk increase after IVF for their children. This may seem surprising, but has to do with efficacy and affordability, reimbursement of cost from public resources an insurance coverage. If a higher efficacy can be achieved at the cost of less safe procedures, this may be the couple's choice. The perception of the level of risk is dependent on the actual (national) availability of valid safety data, and on the presentation to the couple of such data.

In some countries society has regulated clinical safety policies “to protect the best interest of the child”. It has been argued that neither the parents nor their doctor do always regard the safety of the child as their first priority in the trade off with efficacy. Patients autonomy, also when deciding on the acceptance of risk levels, seems to be more emphasized in the USA compared to Europe.

Evaluation of safety is, or certainly should be, one important factor when deciding on Cross Border Fertility Care (CBFC) [16].

Infertility Services

As already mentioned there has been a general tendency, in the past more than at present, to actually accept certain of safety risks for a higher efficacy (often in an alliance and understanding between patients and doctors). We now see changing trends, with less embryos being transferred in many countries [4], following a re-evaluation of the safety-efficacy balance. One reason behind this, apart from an increasing knowledge and insight on safety, is a better efficacy slowly evolving allowing for fewer embryos to be replaced without losing too much on efficacy [13].

A dilemma for clinicians may occur when a decision is needed whether to go for a newly introduced technology: “What to do when we don't know?” A strategy of good clinical practice should first consider if there is a safer alternative. If the decision is that a new promising methodology needs to be tested, this should be done as a proper clinical trial.

Industry

Recent results strongly suggest that methodology actually need to undergo a similar rigorous testing as drugs currently do. Not to declare the composition of culture media is no longer acceptable. A satisfactory battery of testing should be agreed upon, possibly including epigenetic testing.

Society

Society needs to be satisfied that the safety of mother and child are appropriately protected through regulation of the services either by society itself or by the professions. If this is not done, society will eventually lose confidence in IVF and withdraw legal or financial support.

■ Protection of Safety

The iatrogenic risk increase, so clearly demonstrated when it comes to multiple pregnancy, should not be accepted. Outcome research has now demonstrated large and important gains in safety for both mothers and children, is actually achieved if iatrogenic multiple pregnancy is avoided.

A series of clinical strategies should be considered:

- Accept single embryo transfer (SET) as the norm.
- Stimulate ovaries less vigorously.
- Monitor safety continuously.
- Distinguish between established and experimental methods.
- Regulate/scrutinize laboratory methodology and equipments.

■ Conclusion

We know now, after 30 years, quite a bit about medical safety risks for IVF children and their mothers. But we certainly do not yet know the full story. There is documentation on modestly but both statistically and clinically significantly increased risks for obstetrical complications, birth defects and prematurity after

treatment with established technologies like standard IVF, ICSI and slow-freezing of embryos. This is possibly not due to the technologies *per se*, but to parental characteristics of sub-fertility and, importantly, to iatrogenic high proportions of multiple pregnancies, which can be and needs to be prevented. Obviously, much less is yet known for experimental procedures, like vitrification or blastocyst culture. Either such technologies should be avoided until declared “established” or should be performed in the framework of research, including documentation of safety. Adult life risks for health consequences are largely unknown until a sufficient number of individuals born after IVF have reached adult life. We will have to wait a few decades more to know. Theoretical risk much discussed today includes consequences of epigenetic changes.

■ So, is IVF Safe?

No, not totally safe, but safe enough, as we know IVF so far, to continue using it, but only if we make efforts to actually reduce currently increased risk levels and handle new experimental methodologies in a responsible way. Some of

this risk increase is iatrogenic, and therefore can be and should be prevented already. Some risks, like the increased risk for birth defects cannot be avoided, at present. Future research on epigenetics may shed light on this. As the field keeps evolving we need to keep watching.

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