Belgian Advisory Committee on Bioethics

Opinion No. 31 of 5 July 2004 regarding experiments on pregnant and breastfeeding women

Introduction

In Consultation Document No. 13, which deals with the ethical aspects of experimenting on human beings, the issue of clinical trials carried out amongst vulnerable groups was referred for further opinions.

Experiments on a pregnant or breastfeeding woman present a particular problem in that there are three parties involved: the woman, the unborn or newly-born child and the father.

Preliminary remarks

- Before discussing the issue of experiments involving pregnant or breastfeeding women, it is worth pointing out that, when experimenting on a woman who is not pregnant, the presence of a pregnancy has to be ruled out before she can be included in the study. Furthermore, the measures to be taken to ensure that the woman does not become pregnant during the course of the study need to be discussed.
- In the case of experiments relating to contraception, due attention should be paid to the problem of the possible failure of the contraceptive method and, amongst other things, the issue of an insurance policy in this context.
- When evaluating an appropriate protocol for experiments on pregnant women, the local ethical review committee should bear in mind that various stages of the pregnancy carry with them a totally different set of risks: possible effects on germ cells or the implantation of the fertilized egg cell, potential teratogenic effects, possible embryotoxic effects and the impact on the physiological changes caused by pregnancy as well as on the functioning of the maternal-foetal unit. Therefore, when analysing this problem, it is customary to differentiate between a number of different stages: before conception; the first week of the pregnancy; the second week up to and including the eighth week, the second and third trimesters and the delivery.
- Experiments involving a pregnant or breastfeeding woman may be carried out for a number of different reasons, each with their own ethical concerns.
    1. Research into problems specific to pregnancy (e.g. pregnancy-related pathological complications such as repeated miscarriages, foetal hypotrophy, etc.), but also physiological or physiopathological research (e.g. in relation to circulatory changes during pregnancy). In this case, both the mother and the child are relevant to the objectives of the research and both can benefit from the study and its results.
    2. Research into pathological conditions that are not linked to pregnancy, but that occur in pregnant women and, consequently, present particular diagnostic or therapeutic problems, such as the diagnosis or treatment of hyperthyroidosis or comedocarcinoma. In this case, the concern is mostly for any adverse effects on the foetus that might be caused by the medication used. Conversely, the benefits to the foetus are, for the most part, less important.
    3. Research into pathological complications that mostly affect the foetus (e.g. deformities, toxoplasmosis, cytomegalovirus). Here, it is mostly the foetus or the child that benefits. The mother, on the other hand, may be exposed to a variety of unwanted side effects during treatment, such as major risks in the event of in-utero surgery, for example. This category also includes research into the extent to which treatment can protect mother-to-child (foetus) transmission of the HIV virus.
- Promoters, researchers and local ethical review committees should pay particular attention to the insurance issues facing such trials where there is a risk not only of

adversely affecting the course of a pregnancy (foetal death in utero, abortion), but also of causing abnormalities in children which can have lifelong consequences (e.g. phocomelia caused by the administration of thalidomide).

- The question arises as to whether or not the child or, later, the adult has the right to know if his or her mother has taken part in a clinical trial during pregnancy and if so, what compensation is available to him/her for any harm which may be suffered. The question of the extent to which the informed consent of the mother involves her unborn child is a subject of controversy.
- A number of guidelines relating to experiments involving pregnant and breastfeeding women already exist:
    1. In November 2002, the 'Council for International Organizations of Medical Sciences' (CIOMS) issued the "*International Ethical Guidelines for Biomedical Research Involving Human Subjects*". Guideline No. 16 discusses women as research subjects and in particular, those who become pregnant whilst participating in a study. Guideline 17 deals more specifically with pregnant woman as research subjects. The guidelines are also accompanied by individual commentaries.
    These guidelines are as follows:

CIOMS Guideline 16: Women as research subjects

Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research. The potential for becoming pregnant during a study should not, in itself, be used as a reason for precluding or limiting participation. However, a thorough discussion of risks to the pregnant woman and to her foetus is a prerequisite for the woman's ability to make a rational decision to enrol in a clinical study. In this discussion, if participation in the research might be hazardous to a foetus or a woman if she becomes pregnant, the sponsors/ investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences. Where such access is not possible, for legal or religious reasons, investigators should not recruit for such possibly hazardous research women who might become pregnant.

CIOMS Guideline 17: Pregnant women as research participants

Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the foetus and their subsequent offspring, and to their fertility.

Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her foetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity.

2. On 30 June 2004, the Committee of Ministers of the Council of Europe adopted the *"Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*", of which Article 18 deals specifically with research during pregnancy or breastfeeding. The text of this Protocol is accompanied by an explanatory report.

Council of Europe - Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research - Article 18 - Research during pregnancy or breastfeeding

1. Research on a pregnant woman, which does not have the potential to produce results of direct benefit to her health, or to that of her embryo, foetus or child after birth, may only be undertaken if the following additional conditions are met:

i. the research has the aim of contributing to the ultimate attainment of results capable of conferring benefit to other women in relation to reproduction or to other embryos, foetuses or children;
ii. research of comparable effectiveness cannot be carried out on women who are not pregnant;
iii. the research entails only minimal risk and minimal burden.

2. Where research is undertaken on a breastfeeding woman, particular care shall be taken to avoid any adverse impact on the health of the child.

Recommendations

The members of the Advisory Committee on Bioethics uphold Article 18 of the Council of Europe's "*Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research"*, as well as Guidelines 16 and 17 issued by the CIOMS, but nevertheless wish to draw attention to a number of points.

- Experiments on pregnant women present more problems than those on women who are not pregnant, given the possible risk to the unborn child. All the precautions required for any experiment whatsoever will therefore have to be complied even more stringently in such cases. In addition, particular attention should be paid to the need for comprehensive information that is properly understood and for truly informed consent, given only after the individual has had sufficient opportunity to consider whether or not to participate. In this last regard, an opportunity must be provided to consult a person who is not involved in the research (doctor, nurse, member of the local ethical review committee, chaplain, moral consultant, etc.). Researchers and the local ethical review committees should pay particular attention to these aspects.
- Article 18 of the Council of Europe's "*Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research"* sets out the conditions to be fulfilled by experiments which do not provide any direct benefit for the pregnant woman or her child. Such experiments may only be carried out when it may be presumed that there is no risk, or where the risk is negligible. The Bioethics Advisory Committee would like to stress that such clinical trials, where there is no prospect of direct benefit to the mother or child, are not permissible during the first three months of the pregnancy except where the risk of teratogenesis or other problems (e.g. premature birth) can be ruled out. It goes without saying that, where a potential research subject is in the later stages of pregnancy, trials without direct benefits may only be carried out after careful consideration of the relevance of the purpose of this experiment set against the possible risks involved. The local ethical review committees, when evaluating the protocols on such trials, should weigh up the benefits

linked to the expected results against the risks involved in the experiment. If there is no direct benefit to the participant, these risks should be negligible.

- In trials such as these, it is important to avoid over-representation of women belonging to socially disadvantaged or minority groups, as they are often less attentive to the potential risks involved in a study of this nature. They may, moreover, be attracted by the fact that participation in the trial may mean their receiving free medical care. On the other hand, women from these groups should not be systematically excluded either. It is necessary to ascertain whether or not such women, particularly if they are foreign language speakers, have in fact fully understood the consent form presented to them.
- The question arises as to the extent to which the father of the unborn child (or the partner) should be involved in giving informed consent.

  The members of the Advisory Committee are of the opinion that the autonomy and decision of the woman must take precedence in the case of experiments which might be of therapeutic benefit to the woman or the child she is bearing. Nonetheless, they feel that, in the case of a stable relationship, it is highly recommended that the father or partner be consulted. Certain members of the Advisory Committee, some more than others, wish to underline the role of the father here. They feel that, whilst it is the woman who mostly bears the burden of any risks to the pregnancy or the development the unborn child, the pregnancy involves both parents and the responsibility of the father cannot be denied. These members believe that it is problematic to include a woman in such a trial, where there is no agreement on her participation between herself and the father or partner, as this can cause conflicts, for instance should the child display deformities at birth, in view of the resulting affective or financial burden which this may imply for the family as a whole.

  In the case of experiments which are not of any direct benefit to the woman or the foetus, some Committee members feel that the agreement of the father or partner must be obtained before a trial can begin. Other members would contend that the autonomy of the woman takes precedence, even in cases such as these.

The opinion was prepared by select commission 97/8 – 2004, consisting of:

Joint chairmen	Joint reporters	Members	Member of the Bureau
M. Bogaert	M. Bogaert	A. André	
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The working documents of select commission 97/8 – 2004 – questions, personal contributions of the members, minutes of meetings, documents consulted - are stored as Annexes 97/8 – 2004 at the Committee's documentation centre, where they may be consulted and copied.