Ethical Aspects of Soft Tissue Engineering for Congenital Birth Defects in Children—What Do Experts in the Field Say?

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This article is part of the EuroSTEC project, which aims at developing tissue engineering-based treatments for structural disorders present at birth. EuroSTEC is positioned at the intersection of three areas with their own ethical issues: (1) regenerative medicine, (2) research with pregnant women and fetuses, and (3) research with neonates. Because of the overlap of these three areas in this project, we can expect to be confronted with new ethical challenges. To be able to respond adequately and timely to current and possible future ethical issues, a prospective and anticipatory ethical analysis is essential. To obtain a first survey of ethical issues that might arise during the different phases of the project, the Delphi method was used. The professionals directly involved in the EuroSTEC project were questioned about their views on possible ethical issues. The first round yielded 27 ethical issues, which the respondents were asked to prioritize in the second round. For the fundamental research phase, issues deemed most important were privacy and informed consent of the tissue donor. For the animal experimentation phase, three issues were mentioned (in order of decreasing priority): the suffering of animals, the use of animals as means to an end, and the limited adequacy of the animal models. Issues that were deemed most important during the clinical (trial) phase pertained to the problem of weighing risks and benefits for the fetus/child and the pregnant woman.

Introduction

EuroSTEC is an Integrated Project on “soft tissue engineering for congenital birth defects in children.” Funded by the European Commission under the Sixth Framework Program, it commenced on January 1, 2007. The project unites 15 partner organizations (10 research institutes and 5 companies) from nine European countries.1

Modern tissue engineering approaches will be used to treat children with congenital structural disorders, such as spina bifida, urogenital defects, gastrochisis, diaphragmatic hernia, and esophageal atresia. Usually, these closure defects are first diagnosed during routine prenatal ultrasound screening. In case of, for example, spina bifida and diaphragmatic hernia, many pregnant women (parents) may decide to terminate the pregnancy. In other cases, the child will be operated on some time after birth and—depending on the kind and severity of the defect—will require surgery and/or other treatments throughout childhood and even into adulthood. Closure defects are associated with a varying range of morbidity and decreased quality of life.2 In the last two decades, in utero fetal therapy has been performed to reduce long-term morbidity of the child. At present, a multicenter randomized clinical trial (RCT) is being performed in the United States to study maternal–fetal surgery for spina bifida.3 In short, modest advances have been made in the field of maternal–fetal surgery for certain structural defects, although these interventions remain experimental.4-6

The EuroSTEC project focuses on both maternal–fetal (or in utero) as well as neonatal interventions using tissue-engineered products. Part of the EuroSTEC project design is an extensive ethical analysis, which will focus on all three phases of the project—fundamental or in vitro research (which, for the purposes of this article, will be referred to as “fundamental research”), animal experiments, and clinical trials—and will also look ahead to the application of soft tissue engineering in clinical practice.


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The ethics of the clinical applicability of tissue engineering has so far received little attention. Issues that receive a relatively large amount of attention within the broader context of tissue engineering are the use of human embryonic stem cells and therapeutic cloning. The EuroSTEC project is positioned at the intersection of three fields: (1) regenerative medicine, (2) research with pregnant women and fetuses, and (3) research with neonates. All three areas have their own ethical issues, but because of their overlap in this project, the combination of these issues may lead us to be confronted with new ethical challenges. To be able to respond adequately and timely to possible future moral issues, a prospective and anticipatory ethical analysis is paramount.

In this article, we survey experts' views on ethical issues raised by the development of a clinical application of tissue engineering. From the perspective of an empirically based ethics, the views of these professionals—all involved in the EuroSTEC project—are expressly relevant because they have practical experience of the day-to-day (research on the) clinical application of tissue engineering. This unique feature may lead them to identify ethical issues that are difficult to recognize for those who are not directly involved in the process. The central objective of this empirical study was to identify what ethical issues that the experts involved in research on soft tissue engineering for closure defects expect to occur during the different phases of the EuroSTEC project.

**Methods**

*Data collection and analysis*

A modified Delphi study was deemed the most suitable method to survey the ethical issues that the EuroSTEC professionals expect to occur during the course of the project. The Delphi method is a standardized research method. However, it is common to modify a Delphi study and restrict the number of rounds to ensure a high response rate throughout the multiple rounds. The Delphi method is a systematic, iterative forecasting method used to collect and distill knowledge from a group of experts. Characteristic of this qualitative research method is that it takes place over several rounds, with the answers of one round being used to formulate questions for the next rounds.

In this case, the first round consisted of a questionnaire with two sections: (1) six short questions asked for certain personal information, such as sex, nationality, and role in the project (respondents were not asked to include their name), and (2) four open-ended questions. Each of these questions invited the respondents to list the ethical issues that they expect to occur during a specific phase of the project (fundamental research, animal experimentation, clinical trials, and clinical practice). For the latter two phases, respondents were asked to answer for maternal–fetal and neonatal interventions separately.

The research population consisted of all persons involved in one or more research areas of the EuroSTEC project (which includes, among others, pediatric urologists, fetal and neonatal surgery specialists, obstetricians/gynecologists, animal research experts, and researchers in the fields of biochemistry, biopolymer synthesis, molecular biology, and bioengineering). All professionals involved in the project were invited to participate in the first round. The questionnaire was sent to the research population by email several days before a central research meeting in November 2007. Respondents had the opportunity to return it by email or in hard copy at the meeting itself.

The results of the first round were initially analyzed by the primary analyst (A.J.M.O.) and subsequently reviewed by the second analyst (W.J.M.D.). Respondents’ answers referring to the same issue were given the same code label. Subsequently, similar ethical issues were grouped in a category. In June 2008, the results were presented to the participants. As is customary in a Delphi study, the results of the first round were used to develop the questionnaire for the second round.

This second questionnaire consisted of (1) the same six short questions as in the first questionnaire and (2) a list of ethical issues distilled from the first round, grouped by research phase. For each ethical issue in the list, respondents were asked to indicate on a 5-point Likert scale how important they thought this issue would be during the project (1 labeled “not important,” 5 labeled “very important”). Again, the entire group of professionals was invited to participate, regardless of whether they had responded to the first-round questionnaire. The second Delphi round was conducted during a central research meeting in November 2008; the questionnaire was sent to the research population several days in advance, and respondents had the opportunity to return it by email or in hard copy at the meeting itself. The results were described and analyzed in the final months of 2008 by calculating the average score per item (on a scale of 1 to 5) using SPSS 16.0 software. Product of round 2 was a list of ethical issues, ranked in order of importance.

**Results**

*Response*

The first round saw a response of 29 out of a total of 48 (60.4%). The response rate of the second round was 67.9% (or 38 of 56). There is a discrepancy in total number of addressees between these rounds, because eight people were added to the EuroSTEC project between rounds 1 and 2 (for respondent characteristics, see Table 1).

The first round yielded a total of 27 ethical issues. During this first round, the questions were divided into four phases: the fundamental research phase, the animal experimentation phase, the clinical trial phase, and the clinical practice phase. However, answers pertaining to the last two phases appeared to be very similar. With exception of certain issues in the field of research ethics, all pertain to both clinical trials as well as eventual implementation of tissue engineering in clinical practice. Therefore, these phases were combined in the second-round questionnaire (and renamed the “clinical [trial] phase”).

The scores given to the 27 issues in round 2 (on a scale of 1 to 5) ranged from 2.54 to 4.59 (see also Table 5).

**Results by research phase**

*Fundamental research.* For the fundamental research phase, the first round yielded two main categories, named “source” and “donation,” with a total of 10 issues mentioned (Table 2).
Table 1. Respondent Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Round 1 (n = 29)</th>
<th>Round 2 (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% male)</td>
<td>20 (69.0)</td>
<td>28 (73.7)</td>
</tr>
<tr>
<td>Nationality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austrian</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Dutch</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>French</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>German</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Swedish</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Swiss</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Educational background (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sciences</td>
<td>16 (55.2)</td>
<td>24 (63.2)</td>
</tr>
<tr>
<td>Medicine</td>
<td>8 (27.6)</td>
<td>13 (34.2)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (17.2)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Involved in (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fundamental research</td>
<td>22 (75.9)</td>
<td>27 (71.1)</td>
</tr>
<tr>
<td>Animal experimentation</td>
<td>6 (20.7)</td>
<td>14 (36.8)</td>
</tr>
<tr>
<td>Clinical (trial) phase</td>
<td>4 (13.8)</td>
<td>5 (13.2)</td>
</tr>
<tr>
<td>Place of work (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University/hospital</td>
<td>25 (86.2)</td>
<td>33 (86.8)</td>
</tr>
<tr>
<td>Industry</td>
<td>4 (13.8)</td>
<td>5 (13.2)</td>
</tr>
</tbody>
</table>

*Some respondents are involved in multiple research phases.

Source: Six different issues all refer to the source of cells used in the fundamental research phase. The origin of these cells appears to be morally problematic or at least morally relevant to the respondents.

Donation: The second category within this research phase (entitled “donation”) contains four issues that all refer to some part of the donating process; material received from a person and used for research or development of a tissue-engineered product. Often mentioned in this respect were the protection of the privacy and the need for informed consent of the tissue donor. Also mentioned, although much less often, was the possible invasiveness of the procedure through which tissue is obtained. An example of this, mentioned by a respondent, is the possible risks involved in collecting amniotic fluid from a pregnant woman for the purposes of research.

Table 2. Results—Fundamental Research Phase

<table>
<thead>
<tr>
<th>Category</th>
<th>Issue</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>• The use of fetal cells</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>• The use of cells from neonates</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>• The use of fetal stem cells</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>• The use of excess tissue obtained</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>through abortion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The use of embryonic stem cells</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>• The use of umbilical cord stem cells</td>
<td>26</td>
</tr>
<tr>
<td>Donation</td>
<td>• Privacy of the donor of tissue</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>• Informed consent of the donor of tissue</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>• The possible invasiveness of the procedure through which tissue is obtained</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>• Unclarity about the ownership of donated tissue</td>
<td>20</td>
</tr>
</tbody>
</table>

*Out of a total of 27 ethical issues.

In terms of ranking by importance, issues directly related to the tissue donor (privacy and informed consent of the donor and the invasiveness of the procedure) ranked highly, taking the 4th, 5th, and 11th place in the overall ranking (of 27 issues in total). The use of excess tissue obtained through abortion and the use of embryonic and umbilical cord stem cells were among the lowest ranked (at places 24, 25, and 26, respectively). The other five issues ranked between places 14 and 20 (see also Table 5).

Animal experimentation. For the animal experimentation phase the answers given could be brought back to three issues, grouped under the category of “use of animals” (Table 3). First, as mentioned by almost all respondents, is the suffering of the animals during experiments, which ranked highest among the three (and ranked 7th overall). Second, the instrumental use of animals—as means to an end—to improve the health of human beings was mentioned. Last, the limited adequacy of the animal models was pointed out, although this was mentioned far less frequently than the first two. The latter two ranked at numbers 18 and 21, respectively.

Clinical (trial) phase. The clinical (trial) phase yielded the largest amount of issues (14), more than the fundamental and animal experimentation phase combined. The list of issues could be clustered into five different categories, namely risk–benefit ratio, parents, material, intervention, and miscellaneous (Table 4).

Risk–benefit ratio: A category of issues mentioned by virtually all respondents was difficulties surrounding the risk–benefit ratio. In the EuroSTEC project, the “risk” can be divided into different types of risk. In the case of a maternal–fetal (or in utero) intervention, there are risks for both pregnant woman and fetus. As explained by respondents, for the pregnant woman, this means the negative consequences of a surgical intervention, without actually experiencing any physical benefits herself. These risks include miscarriage and preterm delivery after the procedure, and the risk of bodily injury associated with any surgical intervention. The risks for the fetus include, again, spontaneous abortion or preterm delivery, with associated consequences of severe morbidity or death of the fetus, and the risk of bodily injury.

In addition to risks associated with the surgical intervention, respondents indicated that the materials used carry certain risks with them. The collagen used, derived from bovine tendon, may lead to infection with certain viruses. In addition, there appear to be some questions as to whether

Table 3. Results—Animal Experimentation Phase

<table>
<thead>
<tr>
<th>Category</th>
<th>Issue</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of animals</td>
<td>• The suffering of animals</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>• The use of animals as means to an end</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>• The limited adequacy/ extrapolation of the animal models</td>
<td>21</td>
</tr>
</tbody>
</table>

*Out of a total of 27 ethical issues.*
the use of certain cells could give rise to the development of tumors later in life.

However, the maternal–fetal intervention has numerous possible benefits, both for the future child and the pregnant woman. As pointed out by several respondents, the future child may need fewer or no more surgical procedures later in life, or may even survive where it would have died with conventional treatment. Benefits for the pregnant woman include, for example, an improved psychological well-being due to having a healthier child. As pointed out by the respondents, the ethical question is how we balance the risks against the benefits, especially because so little is known about some of the risks.

Parents: The category we called “parents” comprises three different issues all somewhat related to the parents’ involvement in decision making regarding participation of their fetus or child in clinical research or consenting to treatment of this child. Respondents indicated that parents may experience discomfort or feel pressured by the researcher and/or physician (ranked 9th). Also mentioned was the impossibility of fully informing the parents of the risks involved in procedures using tissue-engineered products (number 13 on the ranking list), because the technology is complex and difficult to understand, especially for lay people, and particularly at a time of intense pressure. Mentioned only once was the matter of respecting parents’ religious beliefs when dealing with their views about the use of certain materials (from animal sources) in their (unborn) child (ranked 23rd).

Material: Two issues were grouped under “material,” both initially mentioned by only a few respondents. First, the use of animal material inside the human body or, as one respondent put it, the “mixing of humans and animals” was identified as an ethical issue. Second, one respondent mentioned possible objections against the use of animal material (or rather, material from certain specific types of animals) for religious reasons. Incidentally, these two issues were ranked low compared with the other issues, placing at positions 22 and 27 of the ranking list, respectively.

Intervention: A fourth category of ethical issues refers to difficulties surrounding the determination of the right time of intervention. Although it may seem like a medical–technical question, it does have a moral layer, as discussions about the right timing of an intervention are related to the moral status of the fetus and the idea that it is gradual and dependent on viability. In the discussion we will return to the respondents’ phrasing of the ethical issues.

An issue that came up repeatedly—and was deemed the most important issue during the second round—was the dilemma of choosing between termination of pregnancy and surgical intervention with poor long-term quality-of-life prospects for the child.

Several professionals involved in clinical research and/or clinical practice mentioned the issue of determining the right timing of a maternal–fetal intervention. This in effect is related to weighing risks and benefits of the two options—respondents named the example of spina bifida, in which early intervention (i.e., covering of the defect) diminishes secondary damage to the spinal cord due to prolonged exposure of the neuronal tissue to amniotic fluid, but which in turn might lead to delivery before the fetus is viable. If one were to intervene later in the pregnancy, even when the fetus has a chance of survival if born prematurely, secondary damage to the spinal cord would have already occurred.

Another issue mentioned is the difficulty of determining how severe a defect should be for a surgical intervention to

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**Table 4. Results—Clinical Phase**

<table>
<thead>
<tr>
<th>Category</th>
<th>Ethical issues</th>
<th>Rank&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| Risk–benefit ratio | - Weighing risks for the mother against possible benefits for the unborn child  
                   | - Weighing risks for the fetus/neonate against possible benefits for the fetus/neonate  
                   | - Weighing the possible risks and benefits of a maternal–fetal intervention against those of a neonatal intervention | 2, 3, 6          |
| Parents         | - The possible pressure or discomfort experienced by parents during the decision-making process concerning the participation of their child in a clinical trial  
                   | - The impossibility of fully informing parents of the risks involved in trials/clinical applications of tissue engineering  
                   | - Respecting parents’ religious beliefs  
                   | 9, 13, 23                                                   |
| Material        | - The “mixing” of animals and humans through the introduction of animal material into the human body  
                   | - Religious objections to the use of animal material inside the human body  
                   | 22, 27                                                     |
| Intervention    | - The dilemma of choosing between terminating the pregnancy, on the one hand, and surgical intervention with poor long-term quality-of-life prospects for the child, on the other hand  
                   | - Weighing the possible risks and benefits of early intervention during pregnancy against those of intervention later in pregnancy  
                   | - Difficulty of determining how severe a defect should be for a surgical intervention to be required/unavoidable  
                   | 1, 8, 10                                                   |
| Miscellaneous   | - Determining the right moment to cease clinical research and implement the intervention in clinical practice  
                   | - Rights of the fetus  
                   | - Distributive justice  
                   | 12, 16, 17                                                  |

<sup>a</sup>Out of a total of 27 issues.
be required. In some cases, the defect is nonlethal but comes with considerable morbidity. Respondents questioned whether we should then take the risk of intervening in utero, with a possibly better long-term quality-of-life prospect, but also with the risks of infection and premature delivery associated with a maternal–fetal intervention. In other words, if a neonatal intervention is an option, should we still want to perform a maternal–fetal intervention?

All three issues ranked relatively highly, at numbers 1, 8, and 10, respectively.

Miscellaneous: Several uncategorized issues were grouped under “miscellaneous.” An issue mentioned once was distributive justice or, as the respondent put it, “will this only be available to the richest, or is it for everyone?” (ranked 17th). Mentioned more frequently were the so-called “rights of the fetus” (ranking at number 16).

An issue that pertains specifically to clinical trials is deciding on the right moment to cease clinical research and implement the intervention in clinical practice. As several respondents indicated, this should not be done too early, because enough evidence of the risks and benefits associated with the treatment should be available. On the other hand, it would be a shame to wait too long, because it would delay the potential good that can be done.

Discussion

Our Delphi study yielded a total of 27 ethical issues. Some issues were rather nonspecific, such as “informed consent of tissue donor” for the fundamental research phase or “the suffering of animals” for the animal experimentation phase. Others—like many of the 14 mentioned for the clinical phase—more specifically related to the EuroSTEC project, because they pertained to either tissue engineering research, or research with fetuses or neonates (or a combination of both). As mentioned previously, the project is positioned at the intersection of different fields with their own ethical issues. It is interesting to note that the issues deemed most important are not specific to tissue engineering research, but to research with pregnant women and fetuses and neonates.

Some of the issues mentioned were more in the realm of morally relevant facts and problems than true ethical issues. An example is “the possible invasiveness of the procedure through which tissue is obtained” (ranked 11th).
through which tissue is obtained,” although the implications of risks associated with a procedure do inform the moral judgments about the acceptability of the procedure, the invasiveness itself is not an ethical issue in the strict sense of the word. Our participants were not ethicists and may have had some trouble identifying ethical issues in their practice and phrasing them in the questionnaire. In addition, the fact that we used a questionnaire as method of data collection most likely had some influence: written questionnaire answers are usually somewhat concise (more concise than, e.g., during a face-to-face interview). This may have caused participants to phrase their answers as morally relevant facts and problems, whereas if they were to elaborate further, the underlying ethical issue would become more explicit. Therefore, we did include these morally relevant items in our analysis.

In a previous literature study focusing on ethical aspects of tissue engineering,7 an overwhelming majority of papers was found to focus solely on the use of human embryonic stem cells or therapeutic cloning, while other ethical issues received little attention. It was argued that the most pressing matter at this time were ethical questions related to clinical trials, because of the current stage of development of the field of tissue engineering. Trommelmans et al.13,14 too argued that these issues have so far received relatively little attention.

A recent publication by Trommelmans et al. reported on a survey conducted among participants of a consortium of universities and enterprises focusing on tissue engineering of skin, cartilage, bone, and viscera.15 Participants were asked for their opinion on the need for development of ethical guidance and presented with statements concerning clinical trials. Our study took a more bottom-up approach: we started by asking the participants to name ethical issues, instead of presenting them with a fixed list. Based on their study, Trommelmans et al. argued that clinical trial issues are in need of more profound reflection, a conclusion we endorse based on our own research.

As evidenced by our priority list—issues more or less related to clinical trials were in the top half of this list—tissue engineering professionals too consider these issues to be of great importance. Both previously cited articles and our participants note that the complexity of tissue-engineered products poses challenges to meeting the requirements of informed consent (for donors as well as recipients of tissue/tissue-engineered products) and making an accurate risk-benefit analysis. We believe that the ethical challenges in clinical trials are in most immediate need of attention, both from tissue engineers and ethicists.

It might be objected that knowledge gained from the two Delphi rounds was—by nature of those rounds—more broad than deep. However, this was our explicit objective, to give an initial survey of the full range of ethical issues expected by people with experience in tissue engineering research. The mere wording of some of the respondents’ answers request further explanation in face-to-face conversations. An example of this would be the issue “the rights of the fetus.” Although it may seem a rather straightforward concept, by using the term “right” in combination with “fetus,” a certain interpretation of the entity “fetus” as a subject with rights is implied. Future research—in the form of focus groups—will aim to deepen this knowledge and explore the issues further.

Our research population consisted of a diverse group of tissue engineering professionals: participants were involved in fundamental research, animal experiments, and/or clinical research, and many different countries, nationalities, occupations, and institutions were represented. In future empirical research, we wish to extend the target population to include other groups, such as tissue engineering experts outside of the EuroSTEC project. Additionally, the views of ethicists and of prospective patients and/or their parents are lacking in this study. It is our explicit intention to include them in future research.

Ethics of tissue engineering and regenerative medicine remain a relatively small field. This study was one of the first to feature a survey of tissue engineering professionals’ views on ethical aspects of a clinical application of tissue engineering. Although the participants of this Delphi study were recruited from one specific project, we feel the relevance of our results is not limited to this project. Numerous parallels can be drawn between the project at hand and any other (pre)clinical study in the field of tissue engineering. The full list of ethical issues is unique to the research of EuroSTEC, but, for example, issues pertaining to animal experiments with tissue-engineered products will be of interest to those conducting these types of experiments. Those involved in clinical trials in this field will find the ethical issues that refer to this phase relevant to their own research. Therefore, we feel our study will be of relevance to research on applications of tissue engineering in general.

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