

Vulnerability, therapeutic misconception and informed consent: is there a need for special treatment of pregnant women in fetus-regarding clinical trials?

Abstract

Historically, women have been considered vulnerable research subjects and have rarely been enrolled in clinical trials. The concept of vulnerability in clinical research is mentioned in a number of international regulations but has never been clearly defined. Generally vulnerability is seen as linked with lack of or limited decision-making capacity, and in terms of clinical trials relates to children and adults unable to give informed consent due to their physical or mental incapacity. This lack of or limited decision-making capacity is regarded as putting these groups at risk of exploitation where others can take unfair advantage of them. With regard to pregnant women, the notion of vulnerability has, however, been criticised since they are generally seen as able to make autonomous decisions and are not particularly susceptible to exploitation. This paper suggests, that all the same an argument can be presented for the vulnerability of a specific group of pregnant women, namely those newly diagnosed with a fetal condition for which there is no effective treatment and the only option is enrolment in a clinical trial. Where such vulnerability exists special measures are necessary to ensure their consent to become part of a scientific investigation is free, informed and voluntary. The requirements of English law and professional ethical guidance regarding the provision of information *and* the need for understanding the information are currently not stringent enough. Because of the emotional stress these pregnant women are under the ethical question as to the nature of their autonomy and decision-making capacity remains.

Introduction

Historically, women have been considered vulnerable research subjects and so women of child-bearing age have rarely been enrolled in clinical trials. The arguments against the inclusion of women have been that the different physiology of women to that of men added a further variable to the study,[1, 2] and that harm might ensue to the fetus with the risk of ethical and legal problems for the clinical investigators and sponsors.[2]

The concept of vulnerability in clinical research is mentioned in a number of international and national regulations but it has never been clearly defined. The Declaration of Helsinki 2013 speaks of some groups and individuals as being particularly vulnerable with an increased likelihood of being wronged or of incurring additional harm. The US Federal Research Guidelines refer to the need for minimal risks regarding the participation of vulnerable people in clinical trials. In England, the Medicine for Human Use (Clinical Trials) Regulations 2004 (henceforth the current CTRs) simply mention vulnerable groups without giving any further details.[3] The proposed new EU Regulation 536/2014 on Clinical trials on medicinal products for human use (henceforth the proposed CTR), which has been

adopted by the EU Member States but will not apply in England before 28 May 2016, also does not define the criteria for vulnerability. However, it includes pregnant women amongst the groups of vulnerable research subjects and restricts the conduct of clinical trials on pregnant women unless certain conditions are met.[4]

Vulnerability is often seen as linked with lack of or limited decision-making capacity, and in terms of clinical trials relates to children and adults who are unable to give informed consent due to their physical or mental incapacity. This lack of or limited decision-making capacity is regarded as putting these groups at risk of exploitation where others can take unfair advantage of them to the subject's detriment.[5] With regard to pregnant women, the notion of vulnerability has, however, been criticised since pregnant women are generally seen as able to make autonomous decisions and are not considered particularly susceptible to exploitation.[5] This is the case whether or not the woman and her fetus are considered a double unit, consisting of two parts, or a single unit, since the woman is the only person who can and should make a decision in the case of an invitation to participate in a clinical trial.[5] This article suggests, however, that even if pregnant women as research subjects are not inherently vulnerable,[2, 5, 6] an argument can be presented for the vulnerability of a specific group of pregnant women, namely those newly diagnosed with a fetal condition for which the only option apart from watchful waiting is enrolment in a clinical trial. Where such vulnerability exists special measures are necessary to ensure their consent to become part of a scientific investigation is free, informed and voluntary.

Special circumstances of vulnerability

In his critique of the inherent vulnerability of specific groups or sub-groups, Kipnis formulates six different forms of vulnerability for clinical research: cognitive, juridic, deferential, medical, allocational and infrastructural.[7] He sees them as 'a checklist of circumstances or contexts that, along with other conditions, can invalidate the permissibility of research' because they 'call into question the efficacy of consent'. According to him, one or more of these vulnerabilities would justify the implementation of supplementary measures in the design of the trial protocol as a condition for proceeding. While research candidates may display several or all of these vulnerabilities, as will be demonstrated, it is Kipnis' concepts of cognitive and medical vulnerabilities most likely to be exhibited by pregnant women newly diagnosed with a fetal condition.

Kipnis describes cognitive vulnerability as the lack of or limited decision-making capacity of research subjects with some intellectual or developmental barrier to participating in the informed consent process. However, cognitive vulnerability in pregnant women generally has been disputed as pregnant women are unlikely to lack decision-making capacity because of their pregnancy, except possibly in active labour.[2,5] All the same, the cognitive functioning of a pregnant woman may be affected because of her unfamiliarity with the language in complex clinical trials and because of the available time frame for decision-making. Cognitive functioning and thus decision-making capacity may also be affected by the highly emotional state of the pregnant woman at the time of invitation to the trial where such an invitation precedes the diagnosis of a fetal condition for which there is no effective treatment option.[8] In such circumstances they may feel very afraid and develop 'in the midst of crisis'[7] catastrophic thinking blocking their ability to deliberate and derailing decision-making capacity.[8]

Medical vulnerability exists for Kipnis in the situation where a proposed research participant suffers a serious health-related condition for which there is no satisfactory remedy.[7] Medically vulnerable patients are often recruited because there is no treatment for their disease so that the patient who has few or no other options is liable to consent to participate in the trial whatever the risks involved. Although 'forced choice alone does not annul consent', a research subject in this position clearly has 'a poor bargaining position'. [7] Of course, pregnant women who are invited to participate in a trial because of their condition are not necessarily medically vulnerable to the extent that they would take unreasonable risks.[2] Rather, the vulnerability of pregnant women may more often be as a result of their lack of inclusion in clinical trials when drugs never tested in pregnancy are prescribed to them.[2, 5] However, the description of a pregnant woman's medical vulnerability generally ought to be viewed as dependent on the context. In a wanted pregnancy where her fetus is diagnosed with a condition for which there is no satisfactory remedy and the woman is invited to participate in a trial with the fetus as the sole object of the research, she may well be in a situation of medical vulnerability. She may be faced with the prospect of doing nothing and possibly losing her unborn child. Where the trial potentially has benefits for the fetus, however minor, the woman may ignore any possible

risks to herself, and may feel morally obliged to do the best for her 'unborn child' and focus solely on the glimmer of hope for its survival.

Findings from British and German interview studies with pregnant women who were either enrolled or asked their opinion about enrolling in clinical trials in critical situations or [9, 10] support the view that in situations where the pregnant woman feels moral pressure to do what is best for her 'unborn child', she is likely to be at higher risk of exploitation. In the German interview study,[10] which tested hypothetical scenarios, almost all women would participate in a trial if it was for the benefit of the fetus. Even if there was a risk to themselves, as long as there was great potential benefit to the fetus some women would ignore or downplay it. In the British interview study [9] where women were asked about their experience of participating in an actual trial during their pregnancy, the findings were similar. The main motivation for taking part was the hope of a delay in pre-term labour and therefore an improved outcome of their pregnancy. Although they were informed of the risks of the trial, most women believed at the time of the interview that there had been no risk associated with taking part. Therefore, medical vulnerability is not only linked with the risk of exploitation but also with the problem of therapeutic misconception.

Therapeutic misconception

Medical vulnerability due to restricted treatment choices can give rise to therapeutic misconception by the research participant. Therapeutic misconception describes the situation where research subjects who have legal capacity do not understand the distinction between clinical care and clinical research, and misinterpret the nature of clinical research and the intentions of the researchers.[7, 11] This problem is acute in patients who know that there is no treatment or no satisfactory treatment for their condition. Although they have been informed that they are being invited to participate in a *trial*, they tend to enter the trial in the hope that the *treatment* works and that they will benefit from it.[7] This problem can also be identified in pregnant women with a wanted pregnancy who have been informed that their fetus has a developmental abnormality and where the only options – apart from trial participation – are the termination of pregnancy or watchful waiting.

These women will generally want to do whatever possible to have as healthy a child as possible. However, even under ideal conditions people may not appreciate the distinction

between clinical care and clinical research.[12, 13] In the case of an affected pregnancy, the conditions are not ideal. Cognitive and medical vulnerability may coincide so that the pregnant woman's decisions about participating in a fetus-regarding clinical trial are likely to be based on unreasonable expectations. These expectations are heightened by the fact that such early phase trials will tend to be hybrid phase I/II trials as phase I trials are not acceptable in this situation for legal and ethical reasons.[12] Phase I/II are designed to investigate the safety, dosage and efficacy of a compound whereas phase I trials only assess the toxicity of a compound and are generally carried out in healthy volunteers or, under certain circumstances, in patients with the condition. If we consider a pregnant woman as a double unit, a pregnant woman whose pregnancy is affected is neither a healthy volunteer nor is she strictly speaking the patient with the condition. However, the fact that a phase I/II trial assesses dosage and efficacy is likely to create the impression of therapeutic intent where in reality there is no or only borderline therapeutic intent.[13] The dosages given to reduce dose-related toxicity would usually be too low, at least for the first patient cohort, for the fetus to derive any benefit.

In addition, the vulnerability of the pregnant woman who is invited to participate in a fetus-regarding trial is amplified by her highly stressed emotional state after she has just been informed that her 'unborn baby' has or is likely to develop serious health problems or disabilities.[14] The pregnant woman's emotions towards her fetus and the wish for a healthy baby are likely to override all her other responses and may even reduce, at least temporarily, her decision-making capacity.[8, 14] In this state, the woman is even more likely to construe a therapeutic intention when such an intention is absent. Adding to the woman's emotional turmoil is the fact that when making her decision she will often deal with researchers who are also doctors and care-givers. She is likely to trust that they will prioritise her health and that of her fetus.[15] The doctor-patient relationship contains considerable emotions [11, 15] and trust is one of these.

When facing such traumatic circumstances during pregnancy it is likely that the woman's emotions temporarily block her capacity for decision-making.[11, 16] Even in the absence of misinformation she is unable to make a free choice. She is vulnerable and her autonomy is compromised in her ability to understand and weigh up the information provided. Where she incorrectly attributes primarily therapeutic intent to a trial she is likely to underestimate

the risks and overestimate the benefits of the trial.[9, 10, 15] It is therefore questionable the extent to which she is legally and ethically temporarily able to provide genuine informed consent unless this incapacity is addressed explicitly and effectively.

Some proposed measures dealing with cognitive and medical vulnerabilities

In these circumstances of medical and cognitive vulnerability, for the decision-making to be truly based on the pregnant woman's own choice she needs to have time to reflect and not be unduly influenced by clinical investigators and researchers. As with other vulnerable research subjects, particular care needs to be taken so that she understands the nature, the objectives, risks and inconveniences of the trial to herself and her fetus. This means that she should be informed that she is invited to take part in an experiment that aims to answer a scientific question. She should be informed that there is no or very little likelihood of any benefit to the fetus but that it may help future pregnant women who have been given the same diagnosis of fetal problems. It needs to be made clear to her that there may be risks to her own health. In particular, she also needs to understand the likely risks for her fetus, such as whether the trial might entail a greater risk of stillbirth. To enable these issues to be understood, comprehension ought to be assessed as part of the informed consent process.[17] Thus, it has been suggested that understanding may be aided by the use of consent forms which use short, simplified sentences with non-technical language.[17] In addition, the use of terms such as trial and experiment rather than treatment, and of researcher and investigator rather than doctor may help minimise the risk of therapeutic misconception.[15, 17] Finally, it has been demonstrated that an extended discussion between the researcher and the research participant is much more likely to improve understanding [17, 18] than any improvements to the consent form, especially where the woman is in a highly stressed emotional state.

Law and ethics of informed consent in clinical trials

It is the responsibility of the personnel recruiting trial participants to ensure that their participation in the research is based on an adequate understanding of the nature of the trial and its implications and risks. This is even more important in clinical trials that involve complicated, novel drugs or procedures. However, legally, there is little distinction between the understanding required for the consent a patient gives for day-to-day medical treatment

and for taking part in research. Generally, English law presumes that a patient is autonomous and has the capacity to make decisions about consent to treatment. [19]

The patient's informed consent or lack thereof is governed by the law of negligence in England. The focus in negligence has been on the doctor's behaviour, the doctor's duty to provide the patient with information [20, 21] but there has not been an insistence on the understanding of the patient. This is despite the fact that for a patient to have made an informed decision suggests a process of deliberation based on understanding. Thus, in *Al Hamwi v Johnston*, [22] a case which dealt with the explanation of the amniocentesis test to a pregnant woman, the High Court judge held that although clinicians should take reasonable steps to satisfy themselves that the patient has understood the information provided, the obligation to ensure that the patient has understood would be too onerous an obligation on the clinician [22, 23] Informed consent in negligence therefore elided the distinction between a patient who has been merely notified rather than one who comprehends, the essentially one-way process of imparting information and the kind of dialogue that truly equips the patient to work towards a decision. [21]

However, this may no longer be good law according to the recent decision of the Supreme Court in *Montgomery v Lanarkshire Health Board* [24]. The judgment by the Law Lords placed greater emphasis on the need for the understanding of the patient; they regarded the advisory role of the doctor as involving 'dialogue, the aim of which is to ensure that the patient understands ... so that she is then in a position to make an informed decision.' The information provided must therefore be comprehensible: 'The doctor's duty is not ... fulfilled by bombarding the patient with technical information which she cannot reasonably be expected to grasp.' [24] However, their Lordships did not articulate what steps a doctor needs to take to discharge her duty and ascertain that the patient has understood the information. [25]

The case itself concerned a pregnant diabetic patient who alleged lack of disclosure by the defendant obstetrician of the risk of shoulder dystocia involved in vaginal delivery. The appellant claimed that had she had been warned about this risk she would have opted for a Caesarean section. While the decision by the House of Lords in *Sidaway v Board of Governors of the Bethlem Royal Hospital* [26] in 1985 had led to much academic debate over the standard of the doctor's duty to disclose, namely whether the significance or materiality

of the treatment risks and benefits which need to be disclosed are to be judged by a standard more favourable to the doctor, i.e. the *Bolam* [27] standard, or according to the prudent patient standard, [26] the Supreme Court in *Montgomery* clarified the matter holding that the *Bolam* test had no place regarding information disclosure. Following the decision in the Australian case of *Rogers v Whitaker* [28] their Lordships held that the doctor is under a duty to take reasonable care to ensure the patient is aware of any material risks involved in the treatment and of reasonable alternatives. A risk was defined as material if, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or if the doctor is or should reasonably be aware that the patient, if warned of the risk, would be likely to attach significance to it. The risk disclosure remains, however, subject to therapeutic privilege so that a doctor can withhold information about a risk if she is satisfied that the disclosure would be seriously detrimental to the patient's health. Despite this exception, *Montgomery* promotes the notion of patient autonomy and patient rights in the treatment setting speaking of 'patients as persons holding rights', rather than recipients of the care of the medical profession [24]. In that it not only follows the ideas already conveyed by their Lordships in *Chester v Afshar* [29], a case on information disclosure and causation, but it also comes close to current GMC guidance [30]. Thus the guidance 'Consent: Patients and Doctors Making Decisions Together' refers to the relationship between doctor and patient as a partnership and more specifically, regarding the patient's informed consent, it states that doctors *should* check whether the patient has understood the information she has been given and also that they should check whether the patient needs any additional support to understand the information.[30]

While at least pre-*Montgomery* GMC guidance thus tended to place more stringent conditions on patient consent to treatment than the law [30, 31] GMC guidance does place more demanding conditions on consent to research than consent to treatment. After all the goal of research is to obtain generalizable new knowledge rather than provide the individual with therapeutic benefit so that a higher consent standard ought to be in place. This distinction also holds when comparing the consent requirements for research and for, already approved, new medical technologies such as, for example, in utero repair of spina bifida and shunting for urinary tract obstructions. Thus, in 'Consent to Research' [31] the

GMC guidance states as an overriding duty when conducting research doctors *must* make sure that people are given information in a way that they can understand. The guidance then continues with the lesser obligation that doctors *should* check that people understand the terms used and any explanation given about the proposed research method. If necessary, they *should* support their discussion with simple and accurate written material or visual or other aids.

Legally, the conditions for informed consent to research are governed by the current CTRs 2004 [3] and will in future be governed by the proposed CTR 2014 [4]. The current CTRs make little attempt at ensuring that the research subject has actually understood the information nor do they go as far as the GMC guidance on research [31]. Thus Schedule 1 (part 1) of the current CTRs states that an adult with capacity gives informed consent if her decision to take part in the trial is given freely after being informed of the nature, significance, implications and risks of the trial. Only Part 3 adds the more onerous condition that the research subject must have had an interview with the clinical investigator in which she has been *given the opportunity* to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. Being given the opportunity to understand the objectives is not the same as requiring that what has been communicated has actually been understood.

In contrast, the proposed CTR requires that information given for the purposes of obtaining informed consent *shall enable* the research to understand the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial (Article 28 (2)(a)). Although not as specific as the GMC guidance 'Consent to Research' it makes some attempt at encouraging the understanding of the research subject when consenting to trial participation. Article 29 (2)(b) refers to the need for the information to the research subject to be kept 'comprehensive, concise, clear, relevant, and understandable to a layperson'. The information is to be provided in an interview with a member of the investigating team (Article 29 (2)(c)) who *shall* pay particular attention to the information needs of the research subject, the methods of imparting the information and verifying the understanding of the research subject (Article 29 (4)).

Despite the fact that the proposed CTR imposes stricter informed consent requirements than the current CTRs it still does not go far enough to prevent the risk of therapeutic misconception of vulnerable research participants such as the group of pregnant women under discussion. Still, doctors and clinical investigators will look to the GMC rather than to the law reports for guidance on professional and ethical standards, but it is questionable whether the obligations imposed by the GMC are sufficient. When dealing with this group of pregnant women affected by cognitive and medical vulnerabilities and additionally under considerable emotional stress [16] there is a need to implement strategies to eliminate the therapeutic misconception and to ensure that they understand the information provided and make the decision to participate freely and voluntarily. To achieve such understanding of a vulnerable person requires not only skill on the part of clinical investigators as they will have to gauge each individual's level of comprehension, it will also require extended, frank discussion in language liable not to mislead. [15, 18]

Conclusion

Pregnant women who have been diagnosed with a severe fetal condition for which there is no treatment other than expectant obstetric management and who are offered the option to participate in an early phase trial must be considered cognitively and medically vulnerable research participants prone to the risk of therapeutic misconception. Although they may legally have the decision-making capacity to sign a consent form and do so voluntarily, as has been argued, the requirements of English law and GMC guidance regarding the provision of information *and* the need for understanding the information are not stringent enough. Thus, the ethical question as to the nature of these pregnant women's autonomy and decision-making capacity remains. Because of the emotional stress these women are under when being informed that there is no satisfactory treatment for the condition of their fetus they are less likely to comprehend the information given to them and more likely to misconstrue a trial as something that offers a lifeline to their fetus. Apart from any perceived social and biological imperative to produce a child, they may feel under psychological pressure to do what is 'best for baby'.

In the context of being invited to participate in fetus-regarding trials, it is only when pregnant women are treated as cognitively and medically vulnerable research participants that they will not be under undue risk of being enrolled in 'exploitative' research. Ensuring

actual comprehension in the informed consent process over and above what the law and GMC guidance currently demand would reduce or even eliminate this risk. Extended dialogue between the researcher and the pregnant woman to improve comprehension is essential and should avoid terms giving the impression that she and/or her fetus will receive treatment. She should be given sufficient time to consider the issues and to discuss them with her partner, family and friends. She should be informed in non-technical language that early phase trials are experiments that aim to answer a scientific question. Further, the message should be clearly conveyed that the experiment is unlikely benefit her unborn child and that there may be risks to her own health and possibly also to her fetus. Such an approach would help safeguard that, despite these women's poor bargaining position, their consent is based on comprehending the information they have been given and that their trial participation is really free, voluntary and informed.

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