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## How Should the Precautionary Principle Apply to Pregnant Women in Clinical Research?

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*The precautionary principle is often invoked in relation to pregnant women and may be one of the underlying reasons for their continuous underrepresentation in clinical research. The principle is appealing, because potential fetal harm as a result of research participation is considered to be serious and irreversible. In our paper, we explore through conceptual analysis whether and if so how the precautionary principle should apply to pregnant women. We argue that the principle is a decision-making strategy underlying risk-benefit decisions in clinical research, which can be applied to pregnant women. However, the current application is a strong one, leading to the promotion of absolute exclusion or, less often, absolute inclusion of pregnant women. In order to change this paralyzing situation, a shift toward weak precautionary thinking is necessary. Instead of automatic extreme precaution, a balance will be found between harms and potential benefits of including pregnant women in clinical research.*

**Keywords:** *exclusion, pregnant women, precautionary principle, research ethics*

## I. BACKGROUND

There has been a longstanding call for fair inclusion of pregnant women in clinical research, motivated by the need to develop effective treatments for women during pregnancy and prevent suboptimal care of pregnant women with acute or chronic obstetric or non-obstetric illnesses (Lyerly, Little, and Faden, 2008; Baylis and Ballantyne, 2016). Not including pregnant women in clinical research leads to two problems. On the one hand, there is a problem of a high percentage of 84%–99% women who take, often off-label prescribed, medications for which there is no substantial data on safety, efficacy, and fetal risk evaluation, leaving pregnant women and clinicians in a difficult position (Chambers, Polifka, and Friedman, 2008; Haas et al., 2011; Lupattelli et al., 2014). For example, the drug ondansetron is currently prescribed off-label to treat extreme nausea and vomiting, while evidence is contradictory: some evidence is indicating no significant birth defects, while other evidence is pointing to birth defects (Baylis and MacQuarrie, 2016). On the other hand, there is a problem of under-treatment of illnesses, which can also have negative effects. For example, poorly treated asthma and untreated depression is problematic for pregnant women and fetuses, associated with premature birth, low birth weight and fetal growth restriction, and, in case of asthma, a higher risk of hypertension and preeclampsia (Lyerly, Little, and Faden, 2008; Little, Lyerly, and Faden, 2009). However, despite the longstanding call for fair inclusion of pregnant women in research projects, they remain underrepresented (Baylis, 2010; Shields and Lyerly, 2013).

The precautionary principle may be one of the underlying reasons for the continuous underrepresentation of pregnant women, as it is often invoked in relation to pregnant women (Lyerly, Little, and Faden, 2008; Baylis and Ballantyne, 2016; Langston, 2016). To illustrate, the 2011 National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) workshop report noted: "Pregnancy may be the last remaining condition for the application of the precautionary principle even when a clinical practice or policy could be updated" (Foulkes et al., 2011). And more recently, Angela Ballantyne stated: "Pregnancy continues to be dominated by the precautionary principle, advocating for the routine exclusion of pregnant women from medical research, particularly intervention studies, on the grounds of foetal vulnerability" (Ballantyne, 2016). The precautionary principle has a specific appeal relative to clinical research in pregnant women, because potential fetal harm as a result of research participation is considered to be serious and irreversible, one of the prerequisites to invoke the precautionary principle. Additionally, there may be secondary reasons for the particular appeal of the precautionary principle to pregnant women. An example is socio-cultural reasoning about risk in pregnancy in general, advocating a "better safe than sorry" approach in relation to issues such as consumables

or the use of technical devices that pregnant women are advised to avoid just to be sure, which might extrapolate to reasoning about risk in clinical research (Lyerly, Little, and Faden, 2008; Baylis and Ballantyne, 2016). Moreover, there is a historical reason in the collective memory of tragedies such as thalidomide and diethylstilboestrol (DES), which may have resulted in a reluctance to include pregnant women in clinical research (Little, Lyerly, and Faden, 2009; Langston, 2016). Furthermore, there may also be financial reasons that advocate precaution in the face of liability fears, especially present among manufacturers (Blehar et al., 2013).

Concerns about fetal well-being are valid, and it seems logical to start from a precautionary standpoint in light of the uncertainties and potential serious and irreversible harm surrounding clinical research in pregnant women. At the same time, assuming that risks are present and excluding pregnant women without looking at the costs and potential benefits of exclusion or inclusion may have the opposite effect, causing pregnant women to be both unsafe and sorry. The aim of our paper is to explore through conceptual analysis whether and, if so, how the precautionary principle should apply to pregnant women. First, we provide a brief overview of the literature on the origins and basic characteristics of the precautionary principle itself. Second, we analyze the current application of the precautionary principle to pregnant women. Third and finally, we discuss how a shift toward weak precautionary thinking is necessary. A weak interpretation applied to pregnant women in clinical research may shift the attention away from automatic extreme precaution to a focus on balancing harms and potential benefits of inclusion of pregnant women in clinical research.

## II. ANALYSIS OF THE PRECAUTIONARY PRINCIPLE

The precautionary principle was initially introduced in the early 1970's in light of environmental policy-making, by people favoring proof of safety to human health and environment before adapting new technologies (Kopelman, 2004). The precautionary principle thus involves a reversal of the burden of proof, demanding a reasonable demonstration of the absence of risk and proof of safety by the proponents of a new technology (Sandin, 1999; Petrenko and McArthur, 2010). In essence, the precautionary principle is a concept about plausibility and reasonableness, which applies to decisions under ignorance where there are threats that have not yet materialized into harm (Cranor, 2004; Manson, 2008). The precautionary principle involves a judgment and a normative choice relative to substantial values we attach to a certain state of affairs that is threatened (Cranor, 2004; Ahteensuu, 2007). The widespread endorsement of the precautionary principle was motivated by the idea that traditional risk-benefit analyses were flawed and not apt to deal with large-scale uncertainty and global threats (Gardiner, 2006).

Ever since, many interpretations of the principle have developed and are currently applied in the broader field of public health.

In common language, the precautionary principle is best translated as “*in dubio abstine*,” which is known as the Hippocratic adage, or “*better safe than sorry*.” The *in dubio abstine* version can only be interpreted as a requirement for inaction in the face of uncertainty and is, in the context of healthcare, often based on the interest of the individual. The *better safe than sorry* version can theoretically result in a requirement for inaction, as well as action. An example of the requirement for action is the commonly quoted formulation of the precautionary principle that was drafted during a 3-day conference dedicated to defining the precautionary principle in 1998. The scholars attending the conference came from diverse backgrounds but all shared a concern for activities that would pose threats to the human and natural environment. The result of the conference was formulated in the Wingspread Declaration, which comprises the following sentence: “When an activity raises threats of harm to human health or the environment, precautionary measures should be taken, even if some cause-and-effect relationships are not established scientifically” (Wingspread Declaration, 1998). Here, the Wingspread Declaration is mandating decision-makers to take precautionary action in the face of uncertainty, in light of a global threat. Consequently, the precautionary principle can result in precautionary inaction (e.g., bans on certain potentially harmful activities in order to be on the safe side) as well as precautionary action (e.g., promotion of certain precautionary measures) aiming to prevent a threat.

The basic characteristic of any interpretation of the precautionary principle is the dual trigger: (i) if there is a potential for serious and irreversible harm (ia) and scientific uncertainty about the magnitude (ib), then some kind of (ii) precautionary action or inaction *before* there is strong proof of the harm is required (Sandin’s *if-clause*). Schematically portrayed, the precautionary principle necessitates (Sandin, 1999; Gardiner, 2006; Manson, 2008; Steele, 2006):

- ia) *a damage condition: some kind of adverse event, a threat of harm to an issue that is deemed to be valuable;*
- ib) *a knowledge condition: an extent of scientific plausibility that this event could occur, but uncertainty about the impact and causality; and*
- ii) *a remedy: the precautionary response (action or inaction) that should be taken if the previous two conditions are present.*

It is with regard to the remedy that the interpretations of the precautionary principle differ. Roughly, a distinction between strong and weak interpretations can be made. Strong interpretations prioritize one goal over all others and require that precautionary action or inaction should be taken whenever there is any possibility, no matter how small, that harm may occur, without any consideration of potential benefits or economic costs. On the contrary,

weak interpretations, also referred to as comprehensive or weak interpretations (Soule, 2000) aim to strike a balance between different factors and allow, but do not require, precautionary action or inaction in the face of uncertainty. Additionally, there must be some evidence about the likelihood and severity of consequences. As Garnett and Parsons illustrated: strong interpretations of the precautionary principle tend to lean toward risk prevention, whereas weak interpretations are concerned with risk management and emphasize gathering information about the potential harms (Garnett and Parsons, 2017). A common criticism is that strong interpretations are too extreme and narrow-mindedly paralyze progress, whereas weak interpretations are less controversial but too vague to be useful (Holm and Harris, 1999; Sunstein, 2003). Notwithstanding the critiques, we propose that the precautionary principle, when viewed as a strategy for decision-making, can be useful.

We argue that the precautionary principle is a decision-making strategy that may underlie traditional risk-benefit analyses that depend on a combination of, for example, statistical evidence and scientific understanding of causal relationships in order to make some sort of quantitative risk assessment. The precautionary principle assumes that, in some cases, such probabilistic assessments of risk are inadequate, because it is impossible to precisely predict and calculate the potential threats. In those cases, risk assessments can be supplemented or replaced by other criteria, such as moral judgments that go beyond cost-effectiveness reasoning (Morris, 2002). The precautionary principle assumes that risks do not have to be neutral but may be weighed differently, based on moral importance (Munthe, 2011). Applying the precautionary principle therefore necessitates a value judgment.

While the precautionary principle is often related to environmental reasoning, the principle may also be used as a decision-making strategy underlying risk-benefit decisions in clinical research. To illustrate, Research Ethics Committees (RECs) may at times use the precautionary principle when they are confronted with large-scale scientific uncertainty and conflicts between the risks for the individual and the potential benefits for the group. RECs may handle this uncertainty by adopting a version of the precautionary principle which implicates a willingness to take action (or inaction) in advance of full scientific proof of evidence or of the need of the proposed action (Barke, 2009). RECs are advised to take all possible harms into account, including unquantifiable harms such as ethical risks to science and society, and then focus their discussion on what would constitute a reasonable response (Resnik, 2004; Council for International Organizations of Medical Sciences & World Health Organization, 2015). As such, the reasoning that underlies the protection of research subjects may at times be viewed as precautionary (McGuinness, 2008).

As an underlying strategy for decision-making, there are certain normative choices and commitments that have to be established before further

specification of the principle (Ahteensuu, 2007). One choice relates to the determination of the generally accepted level of risk which ultimately determines the threshold of the damage condition. In this case, where the precautionary principle is introduced to the regulatory context of the traditional risk-benefit analyses in clinical research, the generally acceptable level of risk for pregnant women will be minimal risk or a minor increase over minimal risk (Council for International Organizations of Medical Sciences & World Health Organization, 2002; Secretariat on Responsible Conduct of Research, 2018). If we interpret the absolute minimal risk standard, it appears that minimal risk implies that risks are not more than healthy pregnant women and fetuses ordinarily encounter in daily life or during the performance of routine clinical care. If we interpret what a minor increase over minimal risk is, this would constitute a minor increase over that threshold of what healthy pregnant women and fetuses ordinarily encounter. Another commitment regards the norm to take pre-emptive actions in order to protect the thing we deem valuable. In the concrete, pre-emptive actions could include phase-outs or bans or a request for extra scientific information or extra pre-marketing testing (Ahteensuu, 2007).

Keeping the dual trigger, i.e., the idea that if there is potential for serious harm (ia) and scientific uncertainty about the magnitude (ib), it follows that precautionary action or inaction should be taken (ii) and with the notion of the precautionary principle as a strategy for decision-making in mind, we can analyze how the precautionary principle is currently applied to pregnant women in clinical research.

### III. ANALYSIS OF THE PRECAUTIONARY PRINCIPLE APPLIED TO PREGNANT WOMEN

As mentioned earlier, the precautionary principle has an intuitive appeal in relation to clinical research in pregnant women and the accompanying safety concerns it poses. Erring on the side of caution seems logical for pregnant women, healthcare professionals, REC members, and everyone else concerned with fetal and maternal well-being (Baylis and Ballantyne, 2016; Langston, 2016). Upon further reflection, it becomes apparent that the basic characteristics of the aforementioned dual trigger are met when the precautionary principle is applied to pregnant women in clinical research. First, (ia) there is potential for serious and irreversible harm in the form of potential adverse effects (e.g., congenital malformations or long-term health consequences) which threaten something valuable, namely, fetal well-being. Fetal well-being is considered to be a value of paramount importance, something we find worth protecting against the threat of possible harm of including pregnant women in clinical research. Even though we might disagree concerning the specific moral status of the fetus, we can reasonably

agree that actions that would unjustifiably harm a future child should be avoided, and protecting fetal well-being is therefore valuable (Strong, 2011). Second, (ib) there is scientific uncertainty about the magnitude and plausibility that this harm will occur. Paradoxically, because pregnant women are underrepresented in clinical research, scientific information on the actual harms that inclusion may cause is lacking. Following (ii), since the damage condition and the knowledge condition are present, a precautionary remedy is needed.

There broadly seem to be two different ways in which the precautionary principle is currently applied to clinical research in pregnant women. On the one hand, the precautionary principle appears to promote the *exclusion* of pregnant women from clinical research. This is the most common application of the precautionary principle applied to pregnant women. The primary motivation is concern about fetal well-being and potential irreversible adverse birth defects of the individual fetus in clinical research. The argument is that if there is a possibility that research participation can result in serious adverse effects for the fetus, the precautionary action should be to exclude pregnant women from clinical research. This stance seems to be taken in some regulations as well as in practice, where pregnant women are mostly excluded from participation in clinical research (Shields and Lyerly, 2013; Scaffidi, Mol, and Keelan, 2016). Advocates of this application of the precautionary principle seem to adhere to the *in dubio abstinence* formulation of the principle: there is an uncertain threat (adverse fetal effects that may be caused by including pregnant women in clinical research); therefore, a remedy is needed, which, in this case, is inaction, in the form of exclusion.

On the other hand, the precautionary principle sometimes seems to promote the *inclusion* of pregnant women in clinical research. The primary motivation is the lack of evidence about how to safely and effectively treat pregnant women with a pre-existing condition or when they become ill during pregnancy. Advocates of this interpretation argue that exclusion of pregnant women simply shifts the risks to the community as a whole, resulting in more people at risk and in unsafe and less-controlled situations. "The danger to pregnant women and their foetuses arises primarily from the lack of evidence about medical treatment during pregnancy, not from research itself" (Ballantyne, 2016). The argument is that if there is a possibility that exclusion from research results in serious harm, the precautionary action should be to include pregnant women in clinical research. Including pregnant women may allow assessment of effectiveness and safety of treatments during pregnancy in a well-controlled fashion, with adequate long-term follow-up of the offspring. Standard exclusion of pregnant women leaves the physicians with less or no information on effectiveness and safety of necessary treatments. Follow-up is less organized, and it may take much more time to obtain clinical information on the effect on offspring. These scholars argue that the exact opposite lesson should have been learned



from, for example, the thalidomide and DES tragedies. As such, they argue that inclusion should be the rule rather than the exception, and pregnant women should not only be included in clinical trials specifically targeting pregnant women, they should also be included in clinical trials targeting the general population, as long as certain trial design matters and ethical issues are respected (Baylis and Halperin, 2012; Ballantyne, 2016; Baylis and MacQuarrie, 2016; Kaposky, 2016). Although this view may seem moderate at first sight, in practice it comprises a particular type of routine inclusion in a large variety of clinical studies. Advocates of this application of the precautionary principle seem to adhere to the “better safe than sorry” formulation of the principle that demands precautionary action: there is an uncertain threat (*adverse fetal effects may be caused by exclusion of pregnant women from clinical research*); therefore, a remedy is needed, which, in this case, is action in the form of the promotion of inclusion of pregnant women in clinical research.

Both applications of the precautionary principle to pregnant women in clinical research have a similar starting point: wanting to prevent uncertain damage to fetuses. Yet the remedies range at the opposite ends of the spectrum: exclusion or inclusion of pregnant women. Further analysis demonstrates that both applications are problematic for three reasons. First, both of them follow a strict interpretation of the precautionary principle, which results in inaction (exclusion of pregnant women) or action (inclusion of pregnant women). This strict interpretation paralyses the situation because the all-or-nothing stance that both sides follow results in a reluctance to look for compromises, and therefore nothing changes, which is ultimately harming pregnant women and fetuses. Especially the application which results in action demonstrates how precaution and inaction have become conflated relative to clinical research in pregnant women (Langston, 2016). Second, the precautionary principle requires that potential threats are clearly defined. Threats should comprise plausible harms relating to specific cases: “for the precautionary principle to be coherent, the threat must be clearly identified, while the alleged causal relation between action and the exercise of the threat must be scientifically plausible” (Petrenko and McArthur, 2010, PAGE). Contrarily, the precautionary principle is currently invoked about harms concerning the very broad scope of inclusion or exclusion in clinical research as a whole, not relative to specific instances. Third, the remedy offered by the precautionary principle should not be counter-productive (Kramer and Zaaijer, 2017). Avoidance of counter-productivity requires that safety measures should not cause more harm than they prevent. The precautionary remedies that are provided can both be counter-productive. To illustrate: exclusion of pregnant women from clinical research, which follows from inaction as a remedy, may be counter-productive because the consequence of exclusion is that research for pregnant women and fetuses is paralyzed while there are no alternative ways to perform this research. Consequently,

the risks are shifted to the population of pregnant women as a whole and actually put all pregnant women at increased risk rather than preventing harm. Routinely including or including pregnant women without careful design and planning could be counter-productive because fetuses may be included in potentially hazardous research.

In summary, an analysis of the precautionary principle as currently applied to pregnant women demonstrates that both applications follow strong versions of the precautionary principle, which lead to both the promotion of exclusion and inclusion of pregnant women in clinical research.

#### IV. DISCUSSION

Our analysis shows that the precautionary principle as an underlying strategy for risk-benefit decision-making is currently applied to pregnant women in clinical research. At present, the applications of the precautionary principle to pregnant women follow a strong version of the principle. In clinical research, the strong applications lead to either the promotion of precautionary measures that result in absolute inaction (routine exclusion of pregnant women from clinical research) or, less often, the promotion of precautionary measures that result in absolute action (including pregnant women whenever ethically and scientifically possible). An example of the latter is the call for a particular type of routine inclusion of pregnant women in any trial on drug safety and effectiveness, unless the scientific or ethical reasons to exclude them are compelling (Baylis, 2010; Baylis and Halperin, 2012). Although we sympathize with the proposal for routine inclusion as a call for fair treatment of pregnant women, at the same time we realize that such a proposal is far removed from sentiments of, for example, regulators with a preference for zero-risk for the fetus in research (van der Zande et al., 2017) or RECs and pharmaceutical companies' fear of liability (Allesee and Gallagher, 2011; van der Zande et al., 2017). The strong versions of the precautionary principle that are applied to clinical research seem to reflect the situation that pregnant women encounter in daily life. There appears to be an "*in dubio abstine*" paradigm of strong precaution that results in absolute inaction when it comes to pregnant women. Many stakeholders, such as RECs, funders, researchers, and pregnant women themselves, seem to act in a manner where the word 'pregnant' is automatically linked to extreme precaution and a reluctance to face any risk. This attitude is in line with the earlier established tendency to notice the risks of taking any sort of action versus those of not doing anything and a distorted perception of risk when it comes to pregnant women (Lyerly et al., 2010; van der Zande et al., 2017). As Lucy Langston has aptly phrased, it seems as if the stakeholders themselves have become affected by the norm of inaction as precaution when it concerns pregnant women (Langston, 2016).

However, the precautionary attitude in which risks are avoided at all costs is especially challenging in relation to clinical research, because while a reluctance to include pregnant women may prevent them from being exposed to some new risks, it also prevents them from reducing their exposure to existing risks (Morris, 2002). As such, both strong applications of the precautionary principle that are currently applied to pregnant women in clinical research are morally problematic because they are unspecified and counter-productive and, moreover, they result in a paralyzing situation. This paralyzing status-quo is undesirable, because in order to improve the evidence-base underlying the adequate treatment of pregnant women and fetuses requires the inclusion of pregnant women in clinical research and a mind shift that moves from the “all or nothing approach” to asking the questions how and when can we include pregnant women in a responsible way. We propose that, as a strong application of the precautionary principle applied to pregnant women in clinical research is not advancing the situation, a shift toward weak precaution may, instead, be worthwhile and effective as precautionary thinking in itself is still appropriate with regard to pregnant women in clinical research. Decisions about inclusion or exclusion are often decisions under ignorance, where potential large-scale irreversible threats have not yet materialized into harm and it is reasonable to expect some demonstration of the absence of risk for either option (the reversal of the burden of proof). Acting on weak evidence may be acceptable when so much is at stake. As the current applications function at two extremes, there is room for reasonable in-between, or, as they are referred to in the precautionary discourse and as described above, weak, solutions. Similar to the starting point of strong interpretations of the precautionary principle a weak interpretation sustains the ethical consideration that fetal well-being is an important value to protect. However, a weak interpretation also takes other alternatives into account. A weak interpretation requires a balance between costs and benefits of inclusion and exclusion, taking a broad scope of harms and possible alternatives into account, and a clear definition of the threat. Moreover, a weak version necessitates that the harms of the precautionary measure itself are taken into account, in order to prevent counter-productivity (Kramer, Zaaier, and Verweij, 2017; Wilson and Atkinson, 2017). Finally, a weak interpretation allows, but does not require, precautionary action, which leaves room for contextualization.

A case in which a weak precautionary approach is applied to decisions about clinical research may be illustrative. For example, a REC may be presented with a protocol in which researchers aim to establish the effects of using selective serotonin reuptake inhibitors (SSRIs) in pregnancy. SSRI use poses more than minimal risk of serious and irreversible adverse effects for fetuses due to the risk of congenital malformations, preterm birth and developmental issues (ia) damage condition) (Brown et al., 2016; Eke, Saccone, and Berghella, 2016; Bérard et al., 2017). There are some studies that indicate

that there is a plausibility of these risks, but the magnitude of the exposure is uncertain (ib) knowledge condition). Consequently, precautionary measures are called for (ii) remedy). In order to determine the precautionary measure required, the REC could look at the traditional risk assessment of the risks that are quantifiable; the broader risks for society (the whole population of pregnant women versus a controlled group in a research setting); the costs of exclusion (i.e., lack of knowledge), costs of inclusion (is it no more than a [minor increase over] minimal risk); societal risks and other potentially relevant considerations. Based on this information, the REC could decide on a precautionary measure consisting of a rejection of the research proposal. However, RECs also need to assess the harms of the precautionary measure itself. In this case, it may turn out that rejecting the research proposal will cause more than minimal harm, for example because a larger group of pregnant women will be exposed. To illustrate, SSRI use during pregnancy is increasing and an estimated 4%–10% of pregnant women currently use SSRIs, while no scientific evidence on the effects of SSRIs will be gathered (Cooper et al., 2007; Wichman et al., 2008; Brown et al., 2016; Bérard et al., 2017). Because the precautionary measure leads to more than minimal harm, a weak application of the precautionary principle may suggest a balanced approach: for example, careful inclusion of pregnant women who use SSRIs, with extra fetal monitoring and interim analyses as a safeguard. When new evidence about SSRI use becomes available, a new assessment is needed. In addition, long-term follow-up of the offspring should be routinely performed in order to assess the effects of SSRIs on child development.

The case illustrates that a weak interpretation of the precautionary principle applied to pregnant women in clinical research may promote further inclusion of pregnant women. Instead of halting a study the moment there are any risks for the pregnant woman or her fetus, weak precaution requires that we take different elements into account, even when these elements may in themselves be inconclusive. It is expected that shifting toward a weak interpretation of the precautionary principle will change the current paralyzing situation by shifting the attention away from automatic extreme precaution to a focus on balancing harms and potential benefits of inclusion of pregnant women in clinical research.

## V. CONCLUSIONS

As a decision-making strategy underlying risk-benefit decisions, the precautionary principle can be applied to pregnant women in clinical research. However, the current application of the precautionary principle is a strong one, leading to the promotion of two extremes: absolute exclusion or, less often, absolute inclusion of pregnant women. As such, the two applications are paralyzing the current situation in which pregnant women are not

included in clinical research, which is undesirable with regard to the already lacking evidence-base for pregnant women and fetuses. A shift toward a weak interpretation of the precautionary principle is necessary. A weak interpretation leaves room for contextualization of a situation instead of automatically linking the word “pregnant” to extreme precaution. Moreover, a weak interpretation means careful weighing of all harms, including harms resulting from the precautionary measure itself. By taking the harms of the precautionary measure into account, we expect that shifting toward a weak interpretation of the precautionary principle will in most instances lead to less overprotection or counter-productive inaction (i.e., exclusion) of pregnant women in clinical research.

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### REFERENCES

- Ahteensuu, M. 2007. Rationale for taking precautions: Normative choices and commitments in the implementation of the precautionary principle. *TRAMES* 11(61/56):366–81.
- Allesee, L. and C. M. Gallagher. 2011. Pregnancy and protection: The ethics of limiting a pregnant woman’s participation in clinical trials. *Journal of Clinical Research & Bioethics* 2(108):1000108.
- Ballantyne, A. 2016. New Zealand needs guidelines for the safe and responsible inclusion of pregnant women in medical research. *The New Zealand Medical Journal* 129(1437):64–70.
- Barke, R. 2009. Balancing uncertain risks and benefits in human subjects research. *Science, Technology, & Human Values* 34(3):337–364.
- Baylis, F. and S. A. Halperin. 2012. Research involving pregnant women: Trials and tribulations. *Clinical Investigation* 2(2):139–46.
- Baylis, F. 2010. Pregnant women deserve better. *Nature* 465(7299):689–90.
- Baylis, F. and A. Ballantyne. 2016. Missed trials, future opportunities. In *Clinical Research Involving Pregnant Women, Research Ethics Forum*, eds. F. Baylis, and A. Ballantyne, 1–8. Cham, Switzerland: Springer International Publishing.
- Baylis, F. and R. MacQuarrie. 2016. Why physicians and women should want pregnant women included in clinical trials. In *Clinical Research Involving Pregnant Women, Research Ethics Forum*, eds. F. Baylis and A. Ballantyne, 17–32. Cham, Switzerland: Springer International Publishing.
- Bérard, A., J. P. Zhao, and O. Sheehy. 2017. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: An updated analysis of the Quebec Pregnancy Cohort. *BMJ Open* 7(1):544.e1–e5.
- Blehar, M. C., C. Spong, C. Grady, S. F. Goldkind, L. Sahin, and J. A. Clayton. 2013. Enrolling pregnant women: Issues in clinical research. *Women’s Health Issues* 23(1):e39–45.
- Brown, A. S., D. Gyllenberg, H. Malm, I. W. McKeague, S. Hinkka-Yli-Salomaki, M. Artama, M. Gissler, et al. 2016. Association of selective serotonin reuptake inhibitor exposure

- during pregnancy with speech, scholastic, and motor disorders in offspring. *JAMA Psychiatry* 73(11):1163–70.
- Chambers, C. D., J. E. Polifka, and J. M. Friedman. 2008. Drug safety in pregnant women and their babies: Ignorance not bliss. *Clinical Pharmacology and Therapeutics* 83(1):181–3.
- Council for International Organizations of Medical Sciences & World Health Organization. 2015. *CIOMS Draft Guidelines* [On-line]. Available: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf> (accessed April 22, 2021).
- . 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects* [On-line]. Available: [https://cioms.ch/wp-content/uploads/2021/03/International\\_Ethical\\_Guidelines\\_for\\_Biomedical\\_Research\\_Involving\\_Human\\_Subjects\\_2002.pdf](https://cioms.ch/wp-content/uploads/2021/03/International_Ethical_Guidelines_for_Biomedical_Research_Involving_Human_Subjects_2002.pdf) (accessed April 22, 2021).
- Cooper, W. O., M. E. Willy, S. J. Pont, and W. A. Ray. 2007. Increasing use of antidepressants in pregnancy. *American Journal of Obstetrics and Gynecology* 196(6):e1–e5.
- Cranor, C. F. 2004. Toward understanding aspects of the precautionary principle. *Journal of Medicine and Philosophy* 29(3):259–79.
- Eke, A.C., V. Saccone, and V. Berghella. 2016. Selective Serotonin Reuptake Inhibitor (SSRI) use during pregnancy and risk of preterm birth: A systematic review and metaanalysis. *American Journal of Obstetrics and Gynecology* 214(1 SUPPL. 1):S443.
- Foulkes, M. A., C. Grady, C. Y. Spong, A. Bates, and J. A. Clayton. 2011. Clinical research enrolling pregnant women: A workshop summary. *Journal of Women's Health* 20(10):1429–32.
- Gardiner, S. M. 2006. A core precautionary principle. *Journal of Political Philosophy* 14(1):33–60.
- Garnett, K. and D. J. Parsons. 2017. Multi-case review of the application of the precautionary principle in European Union law and case law. *Risk Analysis* 37(3):502–16.
- Haas, D. M., B. Gallaresi, K. Shields, D. Zeitlin, M. F. Hebert, Z. Ren, S. C. Nallani, et al. 2011. Pharmacotherapy and pregnancy: Highlights from the Third International Conference for Individualized Pharmacotherapy in Pregnancy. *Clinical and Translational Science* 4(3):204–9.
- Holm, S. and J. Harris. 1999. Precautionary principle stifles discovery. *Nature* 400(6743): 398.
- Kaposky, C. 2016. Presumptive inclusion and legitimate exclusion criteria. In *Clinical Research Involving Pregnant Women*, eds. F. Baylis and A. Ballantyne, 51–62. Cham, Switzerland: Springer International Publishing.
- Kramer, K., H. L. Zaaijer, and M. F. Verweij. 2017. The precautionary principle and the social institution of blood donation. *The American Journal of Bioethics* 17(3):52–4.
- Kopelman, L. M. 2004. Minimal risk as an international ethical standard in research. *The Journal of Medicine and Philosophy* 29(3):351–78.
- Langston, L. 2016. Better safe than sorry: Risk, stigma and research during pregnancy. In *Clinical Research Involving Pregnant Women, Research Ethics Forum*, eds. F. Baylis and A. Ballantyne, 33–50. Cham, Switzerland: Springer International Publishing.
- Little, M. O., A. Lyerly, and R. Faden. 2009. Pregnant women and medical research: A moral imperative. *Bioethics Forum* 2(2):60–5.
- Lupattelli, A., O. Spigset, M. J. Twigg, K. Zagorodnikova, A. C. Mardby, M. E. Moretti, M. Drozd, et al. 2014. Medication use in pregnancy: A cross-sectional, multinational web-based study. *BMJ Open* 4(2):e004365.
- Lyerly, A. D., L. M. Mitchell, E. M. Armstrong, L. H. Harris, R. Kukla, M. Kuppermann, M. O. Little. 2010. Risks, values, and decision making surrounding pregnancy. *Obstetrics & Gynecology* 109(4):979–84.

- Lyerly, A. D., M. O. Little, and R. Faden. 2008. The second wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches to Bioethics* 1(2):5–22.
- Manson, N. A. 2008. Formulating the precautionary principle. *Environmental Ethics* 24(3): 263–74.
- McGuinness, S. 2008. Research ethics committees: The role of ethics in a regulatory authority. *Journal of Medical Ethics* 34(9):695–700.
- Morris, J. 2002. The relationship between risk analysis and the precautionary principle. *Toxicology* 181–182:127–30.
- Munthe, C. 2011. *The Price of Precaution and the Ethics of Risk*. New York: Springer.
- Petrenko, A. and D. McArthur. 2010. Between same-sex marriages and the large hadron collider : Making sense of the precautionary principle. *Science and Engineering Ethics* 16(3):591–610.
- Resnik, D. B. 2004. The precautionary principle and medical decision making. *Journal of Medicine and Philosophy* 29(3):281–99.
- Sandin, P. 1999. Dimensions of the precautionary principle. *Human and Ecological Risk Assessment: An International Journal* 5(5):889–907.
- Scaffidi, J., B. W. Mol, and J. A. Keelan. 2016. The pregnant women as a drug orphan: A global survey of registered clinical trials of pharmacological interventions in pregnancy. *BJOG* 124(1):132–40.
- Secretariat on Responsible Conduct of Research. 2018. Tri-Council Policy Statement (TCPS-2): Ethical conduct for research involving humans.
- Shields, K. E. and A. D. Lyerly. 2013. Exclusion of pregnant women from industry-sponsored clinical trials. *Obstetrics and Gynecology* 122(5):1077–81.
- Soule, E. 2000. Assessing the precautionary principle. *Public Affairs Quarterly* 14(4):309–28.
- Steele, K. S. 2006. The precautionary principle: A new approach to public decision-making? *Law, Probability and Risk* 5(1):19–31.
- Strong, C. 2011. Minimal risk in research involving pregnant women and fetuses. *The Journal of Law, Medicine, and Ethics* 39(3):529–38.
- Sunstein, C. R. 2003. Beyond the precautionary principle. *University of Pennsylvania Law Review* 153(3):1003–10058.
- Wichman, C. L., A. Fothergill, K. M. Moore, T. R. Lang, R. H. Heise Jr., and W. J. Watson 2008. Recent trends in selective serotonin reuptake inhibitor use in pregnancy. *Journal of Clinical Psychopharmacology* 28(6):714–6.
- Wilson, K. and K. Atkinson. 2017. Toward neo-precaution: A new approach to applying the precautionary principle to public health. *The American Journal of Bioethics* 17(3):44–6.
- van der Zande, I. S. E., R. van der Graaf, J. L. Browne, J. J. M. van Delden. 2017. Fair inclusion of pregnant women in clinical research: A systematic review of reported reasons for exclusion. In *Clinical Research Involving Pregnant Women, Research Ethics Forum*, eds. F. Baylis and A. Ballantyne, 65–94. Cham, Switzerland: Springer International Publishing.
- van der Zande, I. S. E., R. van der Graaf, M. A. Oudijk, J. J. M. van Delden. 2017. A qualitative study on acceptable levels of risk for pregnant women in clinical research. *BMC Medical Ethics* 18:35.