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Ethical considerations on placebo-controlled vaccine trials in pregnant women

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Abstract

Placebo use in clinical trials, whenever a proven effective treatment exists, is one of the most debated topics in contemporary research ethics. This article addresses the ethical framework for placebo use in clinical trials assessing vaccine efficacy in pregnant women. Vaccine trial participants are healthy at the outset and some must be infected during the study to demonstrate the product's efficacy, meaning that placebo-treated participants are under risk of serious and irreversible harm. If effective vaccines exist, such risk precludes placebo use. This interdiction should be extended to any clinical trial of vaccine efficacy in pregnant women, because a demonstration of clinical efficacy in nonpregnant individuals and comparable immunogenic responses in pregnant women are predictors of efficacy in pregnancy as well. Moreover, product effectiveness in real-world use scenarios can be ascertained by observational studies conducted after its inclusion in vaccination campaigns.

Keywords: Vaccines. Placebos. Clinical study. Bioethics. Therapeutic equipoise. COVID-19. Influenza, human.

Resumo

Considerações éticas sobre ensaios de vacina controlados por placebo em gestantes

O uso de placebo em ensaios clínicos, quando um tratamento comprovadamente eficaz existe, é um dos principais tópicos debatidos na ética em pesquisa contemporânea. Este artigo aborda o quadro ético para o uso de placebo em ensaios clínicos que avaliam a eficácia de vacina em gestantes. Participantes em ensaios de vacina são saudáveis no início e alguns devem ser inoculados durante o estudo para demonstrar a eficácia do produto. Ou seja, participantes tratados com placebo estão sob risco de danos graves e irreversíveis. Se existirem vacinas eficazes, esse risco impede o uso de placebo. Essa interdição deve ser estendida a qualquer ensaio clínico de eficácia de vacina em gestantes, pois a demonstração de eficácia clínica em não gestantes e as respostas imunogênicas comparáveis em gestantes também são preditoras de eficácia na gravidez. Ademais, a eficácia do produto em cenários reais de uso pode ser verificada por estudos observacionais realizados após sua inclusão em campanhas de vacinação.

Palavras-chave: Vacinas. Placebos. Estudo clínico. Bioética. Equipolência terapêutica. Covid-19. Influenza humana.

Resumen

Consideraciones éticas sobre los ensayos de vacunas controlados con placebo en mujeres embarazadas

El uso de placebo en ensayos clínicos es uno de los principales temas debatidos sobre la ética en investigación contemporánea cuando existe un tratamiento eficaz probado. Este artículo aborda la ética en el uso de placebo en ensayos clínicos sobre la eficacia de vacuna en mujeres embarazadas. Las participantes en los ensayos de vacunas estaban sanas al inicio del estudio, y algunas fueron vacunadas durante el estudio para demostrar la eficacia del producto. Las participantes tratadas con placebo corren el riesgo de sufrir daños graves e irreversibles. Si existen vacunas efectivas, este riesgo impide el uso de placebo. Este impedimento debe extenderse a cualquier ensayo clínico de eficacia de vacuna en embarazadas, pues la eficacia clínica demostrada en mujeres no embarazadas y las respuestas inmunogénicas comparables con las embarazadas son predictores de eficacia en el embarazo. Además, la efectividad del producto se constata en estudios observacionales realizados tras las campañas de vacunación.

Palabras clave: Vacunas. Placebos. Estudio clínico. Bioética. Equipoise Terapéutico. Covid-19. Gripe humana.

The authors declare no conflict of interest.

Unethically legitimate inequalities in medical research contribute to unfair disparities in health and health care [1,2]. The gender disparity among participants of clinical trials serves as an example [1,3]. A recent analysis of study participant's sex by burden of disease in clinical trials conducted between 2000-2020 in the United States revealed that women's inclusion advanced over the last decades. Notwithstanding the progress towards sex parity, the analysis showed that gender imbalance persisted with underrepresentation depending on the field of medical research [3].

Dramatic inequalities in clinical research participation also happen among women, and it is well-documented that pregnant women and those at risk of becoming pregnant are severely underrepresented in randomized controlled trials (RCT) of drugs needed to treat disorders that commonly affect them [4-6]. Therefore, many drugs that could benefit this population are not used in pregnancy, or are used regardless of lacking high-quality clinical evidence on effectiveness, most appropriate dose regimens and safety profile for this specific population [4-8].

The aftermath of the thalidomide tragedy in the 1960s raised strong concerns about testing and using drugs during pregnancy [8], given the fear that drugs—even those that apparently do not harm the mother—might seriously impair fetal development and health. At the time, the striking and poorly-understood interspecies difference in the susceptibility to the teratogenic effects of thalidomide added to a great hesitancy in including pregnant women in RCT [9]. The enigmatic mode by which thalidomide caused birth defects and the failure to predict its teratogenicity strengthened the uncertainty about whether previous laboratory tests in animals could reliably anticipate developmental toxicity to humans [9].

As the confidence on the preclinical assessment of safety in pregnancy declined, doubts grew as to whether a pregnant woman's participation in drug trials might harm the fetus, even if the nonclinical studies had predicted the unlikeliness of developmental toxicity to humans.

Bioethical complexity

Clinical research in pregnant women

Clinical research and drug testing in pregnant women is an inherently complex ethical issue for several reasons, including the fact the mother and the conceptus are highly interdependent and so is their health status and the risks and benefits of interventions [10]. However, the potential benefits and the foreseeable risks involved in clinically testing drugs are often unbalanced between mother and unborn child.

Maternal diseases in pregnancy may disrupt placental function and impair embryo-fetal growth and development, and may also result in mother-to-child transmission of infections, birth defects and/or poor health and viability of the unborn child [11-13]. Some infections with light-to-mild symptoms in most infected pregnant women—such as rubella, zika, toxoplasmosis and others—can have devasting effects on their fetuses [11,12].

Conversely, during pregnancy malaria and some viral infections often progress rapidly into a serious clinical condition, endangering maternal life and the fetal viability [14,15]. The occurrence of pre-eclampsia, a serious late pregnancy-related hypertensive condition, may require the C-section delivery of a pre-term baby to save the mother's life.

Maternal diseases during pregnancy may also insidiously affect the unborn child's postnatal development and health, that is, a prenatal-induced health harm may appear during infancy, the adolescence or even much later as deficiencies in postnatal growth and cognitive development and as a greater risk of developing cardiovascular and psychiatric disorders during adulthood [16-18]. The David Barker's developmental origins of disease and health theory is an instigating hypothesis that is supported by the findings from various epidemiological studies [16-18].

Fetal protectionism in clinical research

Considering the mother-conceptus interdependence, an ethical dilemma emerges whenever the interests of a pregnant woman come into conflict with the unborn child's regarding a therapeutic or prophylactic intervention, or a decision to deliberately terminate pregnancy.

The radical fetal protectionist view would offer simplistic solutions to this dilemma, particularly if associated with the notion that human life begins at conception and so does the human right to life. In this framework, the presumed

unborn child's interests—made legitimate by a so-called "fetal right to life"—could eventually take precedence over those of a pregnant woman in a variety of medical situations [19,20].

On the other hand, women's right activists defend that the human right to life does not begin before birth [19], or at least not until the developing fetus becomes viable outside of the maternal body—depending on the quality of the medical care given to preterm infants, this may occur around the 24th week of gestational age [21].

Regardless, the developmental age at which the life of a human being starts is a metaphysical rather than a scientific question, meaning the embryo developmental stage when the conceptus would acquire the human right to life is arbitrarily established depending on social and moral judgements.

Delving deep into this controversial moral issue of fetal rights and into the many faces and origins of fetal protectionism in modern societies goes beyond the scope of this essay, so, fetal protectionism is understood here as a tendency towards prioritizing fetal protection over scientific needs and maternal health interests in clinical research.

Strong fetal protectionism views in clinical practice and research overlook the fact that, as previously mentioned, the very untreated maternal infections and other morbid conditions may be severely detrimental to the unborn child. That is, refraining from treating a sick pregnant woman from clinically testing drugs with potential benefits for this group may negatively impact the reproductive and fetal health.

The strong fetal protectionism in research involving pregnant women was questioned by the 1990s and, to some extent, softened. Not only have various RCT in pregnant women been judged ethically justifiable, but the default exclusion of this specific subpopulation from RCT of potentially beneficial drugs for them is increasingly viewed as discriminatory, unfair and unethical [4-7,22].

From a modern perspective in bioethics, pregnant women are no longer considered a "vulnerable" population that requires special protection in research. Pregnant women are fully capable of protecting their own interests and those of their unborn children for whom they are responsible as any mentally competent adult. If a pregnant woman is not underage, has no significant intellectual disability, and fully understood the risks and benefits of the research for herself and her fetus, one should assume that she can provide valid informed consent (IC) to participate in RCT [4,23].

The complexity of the scientific and ethical framework behind conducting RCT in pregnancy is further illustrated by the fact that, depending on who is expected to be the main beneficiary of the tested intervention, the unborn child's father may also be required to consent for a pregnant woman's participation.

In a recent draft guidance to the industry, the Food and Drug Administration of the US shed light on this sensitive ethical matter stating that the consent for participation in the RCT should be given by both the pregnant woman and the child's father *if the research holds out the prospect of direct benefit solely for the fetus*, and only if that is the case, except *if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest* [24].

Notwithstanding the paradigm shift towards inclusivity in clinical research, RCT involving pregnant women still face complex scientific and ethical issues. The use of placebo-controlled arms in RCT to test the efficacy of vaccines or prophylactic methods is a pivotal ethical issue in clinical research during pregnancy.

Ethical issues

Use of inactive (placebo) comparators in randomized controlled trials

The use of placebo controls in RCT, if effective and safe treatments for the disease or condition under investigation exist, is one of the most debated topics in contemporary clinical research ethics.

One of the cornerstones of medical professional ethics is that physicians are morally obliged to offer their patients the treatment(s) they believe to best meet their individual clinical needs. Physicians are bound to the combined beneficence-nonmaleficence bioethical principle

by the *Hippocratic Oath*—"to help (to do good) or at least to do no harm"—, a professional commitment that holds true for both a physicians' clinical practice and their involvement in clinical research [25,26].

As clinical researchers, physicians face a moral dilemma whenever they are involved in placebo-controlled RCT if treatments proven effective and safe exist for the disease/condition under investigation.

This medical research ethical issue was brought into evidence by a still unresolved debate on the validity and applicability of the equipoise/clinical equipoise principle [27,28]. The term equipoise means an equilibrium state or situation in which things are perfectly balanced. Thus, according to the principle, clinical researchers must be in a state of genuine uncertainty about the relative efficacy (and/or safety) of the therapeutic interventions under comparison to render a RCT ethical.

The concept of equipoise was considered unworkable in research practice, so, a proposition to replace it with that of "clinical equipoise" was made, referring to a situation in which a collective professional uncertainty about the treatment alternatives would exist or, in Freedman's words, *when there is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested* [27].

Obviously, if physicians/researchers are aware proven and safe treatments for the disease/condition under investigation exist and believe that the new treatment under testing could also be effective, the use of placebo or no treatment arms in RCT violates the equipoise, or clinical equipoise, principle [28].

Whether or not—and the extent to which—placebo use in RCT is scientifically justifiable if treatments of demonstrated efficacy and safety exist, is a largely unsettled issue. RCT using active comparators indicate whether an experimental drug (or vaccine) is more effective and safer, noninferior (noninferiority trials), or worse than an existing one of proven efficacy and safety [28]. In contrast, placebo control trials show whether the drug/vaccine is efficacious and safe in absolute terms.

Although RCT using active comparators can also yield compelling evidence of drug (or vaccine) efficacy and safety, under specific circumstances, placebo-controlled trials offer methodological advantages, some of which were presented and discussed elsewhere [28].

If investigators do believe that placebos can be advantageous or necessary for scientific reasons when effective and safe treatments exist, a conflict may emerge opposing their perceived research needs to the ethical constraints generally imposed on clinical trials. The World Medical Association (WMA) [29] provides the *Declaration of Helsinki* (DoH), an ethics guidance document that makes an exception allowing placebo use when effective therapies exist, that is, if the placebo use is scientifically necessary and results in no serious or irreversible harm to trial participants.

If RCT participants allocated to placebo arms take health risks and no prospects of health benefits exist, their personal consent to participate is essentially altruistic, meaning the trial's social value must be such that offsets the individual risks taken. The social value of a study depends on the foreseeable contribution of the data that it collects—typically in conjunction with data from other studies—to improve health care, public health and, sometimes, attenuate unfair inequalities in medicine. Social value is a key requirement to render RCT ethically acceptable and is endorsed by the DoH, Brazilian regulations and most authors [30].

The social value of a research project and the risks and prospects of benefits for participants—be them those allocated to the experimental or placebo control arm— must be clearly explained in IC form. Whatever might be the alleged social value of a RCT, if a proven effective and safe treatment option exists, any risk of serious and irreversible health harm is unacceptable.

A unique ethical problem of RCT in pregnancy is that a pregnant woman implicitly consents for herself and the unborn child for whom she is responsible. The validity of consent based on altruism, and not on prospects of direct health benefits, that was given by a legal representative (mother) on behalf of someone else (unborn child) who is incompetent (or unable to do it), is a delicate ethical issue that needs further clarification.

The general assumption is that in the absence of reasonable prospects of direct health benefits

for the woman or fetus, anticipated fetal risks greater than minimal is an obstacle to conduct RCT in pregnancy.

According to the FDA guidance draft, one of the key conditions to be met by a RCT in pregnancy is that (...) *if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means* [31].

"Minimal risk" is defined by the FDA guidance draft as *the probability and magnitude of harm or discomfort anticipated in the research* [that] *are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests* [32].

Ethical concerns about the use of inactive comparators in RCT were strengthened in 1994 by a placebo-controlled clinical study performed in low-middle income countries to evaluate whether a specific AZT dose regimen (known as 076 Regimen) would decrease mother-to-child HIV-1 transmission [33]. Treating HIV-infected pregnant women with an inert substance (placebo) was considered a morally outrageous practice because, at the time, sufficient clinical evidence showing that AZT was an effective antiretroviral agent existed [33]. Another ethical question raised by this unfortunate clinical trial was an unacceptable double standard adopted by the pharmaceutical industry for studies in developed and in developing countries, where research ethics restrictions are generally looser [33].

Placebos in clinical research

Declaration of Helsinki *guidance for physicians*

On the use of placebo in clinical trials, the DoH statement of ethical principles for medical research, throughout its successive revisions undertaken by the WMA—which were systematized and compared by Paumgartten [28]—evolved from the interdiction of any use of placebos, if there are proven effective treatments available—which prevailed in the 1990s and early 2000s—, to a prohibition by default with an exception that opens a door for their use under special circumstances, introduced in 2008 and in effect since then.

The first revision of the DoH, in 1975, implicitly forbade the use of inactive comparators or untreated groups in any RCT when an effective treatment for the disease or condition under investigation exists: *In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method* [34].

The first explicit reference to the prohibition of placebo controls appeared in the DoH's fourth revision, made in 1996: *In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists* [34].

The fifth revision, made in 2000, clearly informed that the prohibition of placebo use in RCT applies not only to therapeutic and diagnostic interventions, but also to prophylactic methods: *The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists* [34].

As of 2008, the seventh DoH revision, the strict interdiction was loosened, and the use of placebo control arms in RCT, when proven effective interventions exist, was allowed *where for compelling and scientifically sound methodological reasons, the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo, or no treatment will not be subject to any risk of serious or irreversible harm* [34].

Along the same line, the Brazilian *Code of Medical Ethics* also prohibits physicians of maintaining (...) *any type of connection with clinical studies in humans using a placebo as the sole medical intervention, whenever there is an effective prophylactic or therapeutic method available* [35].

Assessments of the efficacy of prophylactic and therapeutic interventions

A basic methodological distinction between RCT on the efficacy of pharmacotherapies and those on the efficacy of vaccines—or any other prophylactic intervention—is that, whereas in the first case all participants suffer from the disease or condition to be treated, in the second case all participants are healthy volunteers at the trial outset.

If a prophylactic approach is indeed efficacious, participants allocated at random to the experimental arm are protected, and thus the proportion who becomes sick is lower than the proportion of control-arm participants who become sick after receiving no intervention or inactive comparators (placebos).

Therefore, to test the hypothesis that a vaccine is effective, so the null hypothesis can be rejected or not by a robust statistical analysis, it is needed to estimate in advance a target (minimum) number of individuals, among those selected for the study, that must be diagnosed with the contagious disease to be prevented before the blinding code is broken for a preliminary (or final) evaluation of the study results. This is detailed in the World Health Organization's recommendations for clinical studies of vaccine efficacy [36,37].

Regarding research ethics, an almost unsurmountable obstacle to using placebos in RCT of prophylactic interventions when proven effective vaccines exist, is that, depending on the disease/condition to be prevented, no intervention or administering an inactive comparator (placebo) to control arm participants implies in subjecting them to *risk of serious or irreversible harm* [34] that could be minimized or averted using an active comparator (for example, another vaccine of proven efficacy).

Therefore, the DoH's exception that would render the use of placebo controls in some RCT acceptable when comparators of proven efficacy exist is not readily applicable for prophylactic interventions. For instance, in RCT of vaccines against potentially severe and life-threatening respiratory viral infections, such as COVID-19 and some influenza viruses, not to vaccinate control arms participants means taking risks of serious and irreversible harm that could be prevented.

If a previous RCT demonstrated the efficacy of other vaccines for the infection under investigation, further studies on immunizing products for the same contagious disease must always use active comparators instead of inactive ones [37]. This holds true for any vaccine efficacy trial involving men and/or women, be them pregnant or not.

Trials of vaccines and other prophylactic interventions in pregnant women

Drug therapies and prophylactic interventions intended for treating both nonpregnant and pregnant women are usually first tested in adult men and nonpregnant women and, if proven to be efficacious and safe for this population, an additional RCT is conducted with pregnant women [38].

The pregnant population being last in a stepwise approach is a precautionary measure since not only a complete dataset from nonclinical safety studies—developmental and reproductive toxicity animal tests (DART)—will be available, but also clinical data on the efficacy and safety for adults, for a thorough assessment of risks for the mother and unborn child [38]. Conversely, if a previous RCT fails to demonstrate efficacy in nonpregnant women, mothers and fetuses are spared from being unnecessarily exposed to interventions likely to be ineffective for them as well.

As far as a vaccine or another prophylactic method is concerned, the inclusion of placebo or no treatment groups in studies designed to primarily assess the safety—not the clinical efficacy—of the intervention for pregnant women does not necessarily expose placebo-recipient mothers and their fetuses to a significant risk of serious and irreversible harm, if the trial duration is sufficiently short, concomitant non-pharmacological measures of protection are taken, and the unprotected participants receive a proven effective vaccine as soon as possible after the trial blinding code is broken and the obtained data can be analyzed.

In other words, if safety and not clinical efficacy is the primary goal of the study, a somewhat higher risk for placebo control group participants remains but the excess can be minimized so the risks taken by control and experimental trial arm participants tend to be similarly low.

The inclusion of no treatment or placebo controls in studies testing the clinical efficacy of vaccine/prophylactic methods unavoidably subject healthy participants to a risk of serious and irreversible harm. If the vaccine (or prophylactic intervention) is indeed effective, said risk should be higher than that taken by participants allocated to the experimental arm. In fact, some of the unprotected subjects must get sick during the trial to reach the target number of infected participants required to eventually prove or refute the hypothesis that the immunizing product (vaccine) is effective [36].

Nonetheless, when a vaccine or another prophylactic product efficacy is ready to be tested by a phase 3 trial in pregnancy, clinical investigators are aware that the prophylactic intervention was already proven to be effective and safe for adult men and nonpregnant women. Moreover, as far as vaccines are concerned, clinical researchers are aware that, in previous phase 1-2 trials in pregnant women, the tested product elicited clinically-relevant immunogenic responses (such as increase in blood levels of neutralizing antibodies) [39-41].

Although not being a straightforward measurement of "efficacy" (meaning, not getting sick is the best primary endpoint for clinical efficacy), the vaccine-induced rise in levels of neutralizing antibodies is an immunogenic response (meaning, a valid surrogate endpoint for efficacy) that predicts its clinical efficacy [41].

Together, a proven clinical efficacy for male and nonpregnant female adults and a powerful immunogenic response in pregnant women, reliably indicate that the vaccine under investigation should protect this specific group of adult women as well. Under these circumstances, it is very unlikely that immunizing products proven to be efficacious and safe for nonpregnant women, would fail to confer a clinically meaningful degree of protection for pregnant ones. Acquired maternal protection extends to the unborn child because the neutralizing antibodies—acquired by natural infection or vaccination—are transferred through the placenta and, after birth, breast milk [42].

In view of these facts, a question arises as to whether exposing a group of "placebo-recipient" (and/or "no treatment") pregnant participants to risks of serious and irreversible harm is ethically justifiable. In this specific case, the control group participants are exposed to risks of serious health harms to confirm the protective efficacy that had been anticipated by previous trials with the same product, that is, that the immunizing agent being tested is clinically effective for pregnant women as well.

Depending on the contagious disease preventable by immunization, the detrimental health consequences of inactive comparators (placebos) for pregnant women may be greater than the detrimental health consequences of inactive comparators for nonpregnant women and men. For instance, it was reported that, compared to their nonpregnant counterparts, pregnant women present higher rates of morbidity and mortality associated with some respiratory viral infections such as influenza (H1N1) and COVID-19 [15,43]. Resulting in pregnant women being generally considered a priority group in vaccination campaigns against these respiratory viral infections.

In summary, even if there is no clinical study on the efficacy of the immunizing product in pregnant women, a proof of its efficacy for nonpregnant women, allied to a nonclinical and clinical demonstration that it is safe in pregnancy, and an immunogenic response of clinically meaningful magnitude in pregnant women, must be considered sufficient to assume that—until proof to the contrary—the product is effective (and safe) in pregnancy as well.

In other words, in RCT that were designed to confirm the efficacy for a pregnant population of a vaccine proven to be effective (and safe) for nonpregnant women, that caused a strong immunogenic response in pregnant women, and that the preclinical studies showed no evidence that it could be developmentally toxic,

there would exist no *compelling and scientifically sound methodological reasons* [to affirm that] *the use of placebo is necessary to determine the efficacy or safety of the intervention* [34].

Anyhow, since a placebo (or no treatment) group in trials of vaccine efficacy implies in taking a significant *risk of serious or irreversible harm* [34] for control participants, be them pregnant or not, the exception opened by DoH guidance for placebo use—whenever a proven effective intervention exists—is not applicable.

Additionally, even if the efficacy of a new vaccine was not directly assessed by placebo-controlled RCT, the degree to which pregnant women are protected by this immunizing product (that is, vaccine effectiveness in real-world scenarios) can be assessed by observational studies. This confirmation of effectiveness and safety by epidemiological studies is feasible if pregnant females are vaccinated with the product in mass immunization campaigns.

For example, an observational longitudinal study involving a large cohort with 10,861 vaccinated pregnant women (COVID-19 mRNA BNT162b2 vaccine) matched to 10,861 unvaccinated pregnant controls, was conducted after a mass vaccination campaign took place in Israel [44]. The estimated vaccine effectiveness—after the second dose—was 96% (95% confidence interval [CI], 89–100%) for any proven symptomatic infection and 97% (91–100%) and 89% (95%CI, 43–100%) for SARS-CoV-2 infection-related hospitalizations, an effectiveness that was comparable to that estimated for the general population [44].

The data yielded by the large observational study in women immunized with a COVID-19 mRNA vaccine during pregnancy are consistent with the standpoint presented here that a strong immunogenic response in a pregnant population, paired with a previously demonstrated efficacy for nonpregnant women, reliably predicts a product's efficacy for pregnant women [44]. The assumption that the same holds true for other COVID-19 vaccines—such as inactivated virus and adenoviral vector-based immunizing agents—is thus plausible.

In summary, using placebos instead of active comparators is ethically unacceptable in any RCT, if effective and safe therapeutic or prophylactic treatments for the disease exist and if "no treatment" or inactive comparators entail risks of serious or irreversible harm to participants. Studies of clinical efficacy of vaccines unavoidably leave participants of untreated control or placebo control groups unprotected, and thus at an increased risk of getting infected. Therefore, if available, an active comparator must be employed in these cases.

We suggest that this reasoning should be extended to encompass any use of placebo in phase-3 RCT of vaccines in pregnancy. We maintain that a clear demonstration of vaccine efficacy for nonpregnant women and men, and a comparable immunogenic response in pregnant women is sufficient to reliably predict the efficacy for this female population, a highly plausible hypothesis to be further confirmed by observational studies of vaccine effectiveness in real world scenarios of use. In addition to entailing risks of serious harm for the unvaccinated participants, no "compelling and scientifically sound methodological reasons" supporting the view that using placebos is necessary in this case exists.

Final considerations

Pregnant women are underrepresented in clinical trials of drugs potentially beneficial for them and such research participation inequality has been increasingly questioned. In general, when a drug or prophylactic method (vaccine) is intended to be used by nonpregnant and pregnant women, it is first clinically tested in the nonpregnant population and, if proven effective and safe for this population, a confirmatory phase-3 trial is performed with pregnant ones. This order of testing is expected to better protect the mother and unborn child.

However, trials involving a pregnant population present an ethical problem if the clinical efficacy is determined by comparing data from a test intervention arm with those

of a placebo control arm. As explicitly stated in the DoH, placebo use is ethically inadmissible if a proven effective and safe intervention for the medical condition under investigation is available. If so, an active comparator should be used to ascertain the clinical efficacy of the test product. The 2008 revision of the DoH presents an exception allowing the use of placebo if effective treatment exists, if there are compelling scientific reasons to use an inactive comparator (or no treatment) in the trial, and only if the placebo use does not imply in exposing trial participants to risks of serious and/or irreversible harm.

When a trial is performed to investigate the clinical efficacy of a vaccine, participants allocated to a placebo control arm, pregnant or not, are unavoidably exposed to the infectious agent—they remain unprotected—and, consequently, to risks of serious and irreversible harm. Therefore, if there are proven effective and safe vaccines, using an active comparator instead of an inactive one is an ethically mandatory procedure.

In this article, we defend that an ethical concern on the use of placebo exists, even if there is no vaccine demonstrated to be clinically effective in pregnant women. As part of a stepwise clinical research, the clinical efficacy of an immunizing product in pregnancy occurs after previous studies confirmed its effectiveness and safety for nonpregnant women. Moreover, by the time tests in pregnant women begin, clinical efficacy and safety for nonpregnant women and men has already been demonstrated, in addition to the availability of nonclinical and clinical data on the safety for pregnant women, and on the magnitude of the immunogenic response induced in this population, a reliable surrogate predictor of overall clinical efficacy.

Under those circumstances, a question comes to light: Would it be ethically acceptable to expose a group of placebo-treated pregnant women to serious/irreversible harm solely to confirm what the previously obtained clinical data had strongly indicated?

The fact that some vaccine-preventable infections pose greater health risks for pregnant women than for their nonpregnant counterparts bolsters the argument that placebo use in trials of vaccine efficacy in pregnancy is unethical.

Finally, we emphasize that the efficacy and safety of a vaccine for pregnant women can be reliably assessed by observational studies conducted after the product is used in mass vaccination campaigns that do not exclude this specific population [45].

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Both authors conceived the article, revised the text, and approved the submitted version of the manuscript. Francisco J. R. Paumgartten wrote a first draft of the manuscript while Ana Cecilia Amado Xavier de Oliveira conducted an extensive literature search on bioethical and scientific topics, revised the text for scientific style, and introduced changes to improve the clarity and readability of the manuscript.

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