

Gender-specific medicine and the ethics of women's involvement in research

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Summary. The awareness of the need of studying the influence of sex and gender on diseases started to spread in the '90s but, almost 30 years later, progress in this area is not sufficient to rule out concerns about a possible inequality in medicine. In order to understand the difficulties behind the persisting gap in knowledge, it is important to be aware of the reasons that led to the regular exclusion of women from clinical research. This paper presents a historical reconstruction of the ethical debate about the involvement of women in research: from the protectionist approach of the '70s to the demands for inclusion of the '80s and the '90s. Such reconstruction shows that the main ethical arguments in favour of inclusion, i.e. the principles of beneficence and justice, also justify the need for a gender-specific medicine. The paper discusses some elements that could have hampered the efforts to reduce the male bias, such as the emphasis on the issue of women inclusion in research, instead of the focus on women's health needs. Moreover, it is argued that a participatory approach to research – i.e. an approach that considers women as partners who can offer a contribution at all levels of biomedical research – is the most effective in order to achieve the goal of including attention to women's health into the research agenda.

Key words. Research ethics, women's participation in research, beneficence, justice, participation.

Medicina genere-specifica e etica del coinvolgimento delle donne nella ricerca

Riassunto. La consapevolezza della necessità di studiare l'influenza di sesso e genere sulle malattie si diffuse negli anni Novanta, ma, quasi trent'anni dopo, il progresso compiuto in questo campo non è sufficiente a eliminare la preoccupazione di una mancanza di uguaglianza in medicina. Per capire le difficoltà all'origine di questo persistente scarto nelle conoscenze, è importante essere consapevoli delle ragioni che hanno condotto alla sistematica esclusione delle donne dalla ricerca clinica. Nel saggio viene presentata una ricostruzione storica del dibattito etico sul coinvolgimento delle donne nella sperimentazione: dall'approccio protezionista degli anni Settanta alle richieste di inclusione degli anni Ottanta e Novanta. Questa ricostruzione mette in luce che i principali argomenti etici a favore dell'inclusione, vale a dire i principi di beneficenza e giustizia, giustificano anche la necessità di una medicina genere-specifica. Il saggio discute alcuni elementi che potrebbero aver ostacolato gli sforzi di ridurre il

bias 'maschile', in particolare l'enfasi sulla questione dell'inclusione delle donne nella ricerca invece che sui loro bisogni di salute. Inoltre, si sostiene che un approccio partecipativo alla ricerca, che consideri le donne come partner che possono offrire un contributo a tutti i livelli della ricerca biomedica, è la via più efficace per realizzare l'obiettivo di includere l'attenzione per la salute delle donne nell'agenda della ricerca.

Parole chiave. Etica della ricerca, ricerca sulle donne, beneficenza, giustizia, partecipazione.

Introduction

At a time when we aim at personalized medicine – i.e. a medicine capable of tailoring treatments to the genetic features of each individual patient – realizing that we still lack crucial information about the influence of sex and gender on the prevalence, symptoms, severity and treatment of very common diseases is astonishing. And even more so if we think that the awareness about the need of filling this knowledge gap started to spread in the early '90s, and that almost 30 years later – notwithstanding some significant progress at many levels, including the regulatory one¹ – we are still calling for scientific research to take gender more systematically into account.²

Even if gender-specific medicine applies equally to both sexes, it is undeniable that the female population has suffered the most from the risks related to a lack of unbiased information. This lack of information, in turn, depends on the exclusion or the underrepresentation of women in clinical trials, a phenomenon that lasted for decades, and is unfortunately not over. In order to understand where the need to make explicit the gender-specific nature of medicine stems from, it is illuminating to focus on the ethical debate on the participation of women in research. I maintain that the awareness of the historical roots and the ethical preconditions of a gender-specific approach to medicine is crucial in order to effectively implement it. In the following pages, I will shortly present the evolution of the ethical debate on the participation of women in research, I will point out some elements that might explain the difficulties in changing exclusive practices, and I will underline the importance of adopting a participatory approach.

The ethics of research involving women: a historical overview

Until recently, the exclusion or underrepresentation of the female population from/in biomedical research – starting from preclinical animal tests – was a so established and common phenomenon that it is difficult to ascribe it to a limited set of causes. Feminist authors underline the role played by the acceptance of the male world view as the norm,³ an androcentrism that had (and still has) a powerful impact both on the choice and definition of the health issues that are being investigated and on the way the research agenda priorities are set. This resulted in the almost systematic exclusion of women from research: very often, women were not allowed to be part of a trial because of its exclusion criteria; sometimes, even if they were allowed to be involved, investigators failed to enroll them; finally, even when women were included, in many cases the resulting data were not analyzed by sex. This kind of practices – feminists point out – is related to a general lack of attention to women's health needs and to a lack of appreciation of their relevance: it is indeed one of the multiple forms in which the female population is being oppressed in our society.⁴⁻⁶ Even if partially arguable, these analyses highlight the deep influence of cultural elements on a practice – scientific research – that we are used to depict as the epitome of objectivity and neutrality. In fact, one of the lessons we can learn from the history of clinical research involving women is the importance of being aware of the limits of the evidence on which clinical practice is based, and of monitoring the possible flaws in the way biomedical research is carried out.

Notwithstanding the importance of the influence of sociocultural elements in shaping research-related attitudes towards women, my analysis will focus on the ethical debate about the acceptability of including them in clinical trials. In fact, ethical concerns were behind the 1977 FDA guideline *General considerations for the clinical evaluation of drugs*, that forbade the involvement of women of reproductive age in the early phases clinical research – unless it was related to life-threatening conditions – and that is generally considered one of the main regulatory measures that impeded the involvement of the female population. But what was the ethical reasoning that led to such a consequential decision?

First of all, it should be noted that the '70s were dominated by what has been defined as a "protectionist approach" to research ethics:⁷ after many scandals related to deeply unethical experiments that involved human beings, there was a huge emphasis on the need of protecting trial subjects from the harm and abuses that had proven to be far more than simple hypotheses. As Carol Levine famously put it, "our basic approach to the ethical conduct of research and approval of investiga-

tional drugs was born in scandal and reared in protectionism".⁸ The emphasis on research-related risks and the need of protection was particularly vivid with regard to the so-called vulnerable subjects, a label that often included women. This is not surprising, if we think that some of the scandals that had a great impact on the ethical thinking of that period involved women.

At least two of such events are worth mentioning, because of the impact they had: the first one on the inclusion of women among the vulnerable subjects, the second on linking women vulnerability to their child-bearing potential. In San Antonio, Texas, 398 women attending the Research Clinic of the Southwest Foundation for contraceptive assistance were enrolled in a placebo-controlled, double-blind, crossover investigation on the side effects attributed to oral contraceptives.⁹ Most of them were Mexican-American and poor; 76 of them unknowingly received the placebo and 6 out of these got pregnant during the study. The results were published in 1971, and the criticism was immediate: Robert Veatch significantly ends his paper for the *Hastings Center Report* by asking "what steps are now being taken to prepare the scientific community and the society at large to [...] protect themselves against potential future ethical abuses?".¹⁰ The second scandal is that of thalidomide: as it is well known, thalidomide was a drug used against nausea and to alleviate morning sickness in pregnant women; it was taken off the market between 1961 and 1962 because it had led to serious birth defects (in particular phocomelia) in about 10,000 newborns. Even if it did not occur in the research context, the thalidomide disaster made a strong case for implementing special protections for women because of their child-bearing potential and the possible harm to the fetus.

These and other scandals explain both the precautionary approach the FDA took in 1977 towards women of reproductive age, and the attention *The Belmont Report* devotes to the need of protecting vulnerable subjects – such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized – "against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate".¹¹ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research linked this idea to the principle of justice, defined as fair participant selection: fairness should be granted in the overall distribution of the risks and benefits of research, both at the individual and at the social level, i.e. at the level of group or population. The National Commission seems to echo Hans Jonas's proposal of a "descending order of permissibility" as a principle for subjects enrolment: we should first try to involve "the most highly motivated, the most highly educated, and the least 'captive' members of the community", and to include the most vulnerable members of

the society only as a last resort.¹² It is clear that this “protectionist approach” is based on fundamental ethical principles: in order to be sure that scientific research respects the participants and the principles of beneficence and justice, it is important to be aware that there are some actual conditions that make it particularly difficult to give a free consent to participate and that increase the likelihood of harm and exploitation. What is open to debate is not so much the abstract validity of these principles, but the way we interpret them, with regard to specific studies involving populations that raise peculiar concerns. The strategy of protecting special populations by excluding them from research started to be criticized in the '80s, because it was perceived as discriminatory and paternalistic.

This view was connected to a particular change in the social perception of clinical research that is commonly ascribed to the HIV/AIDS crisis:^{8,13} in a situation where no cure was available, people facing the disease considered participating in a trial as their only chance of getting a treatment, albeit only an experimental one. The emphasis shifted from the risks of harm and abuse to the possible benefits related to medical research, and from the need to protect potential participants to that of securing access to clinical trials. In this new cultural climate, there was also an increasing awareness of the risks related to the exclusion from research of entire groups: not having the chance to participate in research may harm them individually – denying them the possible direct benefits that some trials offer – and as a group – denying them the benefits of the knowledge gained through research.

By the '90s, it was clear that this was precisely the case of women: they were taking drugs that had not been tested on female participants, and were therefore exposed to unknown risks, and what is more in an uncontrolled setting and in a larger number than that which would have been required to detect the same risks in the first phases of a research. As Rebecca Dresser pointed out,¹⁴ the exclusion of women was “a glaring moral mistake”, one that violated both the principle of beneficence (maximizing any possible benefits and minimizing any possible harm) and justice (fair distribution of the benefits and burdens of research). At that point, many studies had shown that data obtained through research carried out only on male subjects could not be applied to women without risks – and that this was the case also for children and other social minorities. This resulted in a form of discrimination against female patients:¹⁵ medical doctors did not have the evidence to treat them appropriately. Of course, it was – and still is – also a matter of good science: for a medical research that aims at minimizing biases through sophisticated study designs, letting such a bias pass unnoticed seems inexcusable. The new awareness of the need to involve also vulner-

able populations in research led to changes at the level of research policies and regulations, and left to bioethics the task of balancing two crucial elements: the ‘protection’, but at the same time the ‘inclusion’ of participants, vulnerable ones in particular. The need of inclusion was justified by a different interpretation of the principle of justice: an equitable participant selection¹⁶ should not only avoid excessive burdens on subjects that could be particularly vulnerable, but also guarantee a fair distribution of research benefits, and therefore equal opportunities of participation in research. Moreover, the principle of justice requires research to be representative of the full range of people affected by the studied disease, or likely to receive the investigational product once approved and marketed.

The acknowledgment of the importance of including women in research for their own good – both as individuals and as a group, on the basis of the principles of beneficence and justice – demands that, in order to exclude them, one should have a good reason. It is therefore important to briefly examine some of the main arguments that are used to justify the general exclusion of women.^{14,17} The first refers to the idea that the inclusion of women would complicate a study and its data analysis, in particular because of the hormonal changes related to the menstrual cycle, thus making the research more expensive. It is evident that this alleged increased complexity is not a good reason to exclude over half of the population from clinical research: there is no scientific rationale behind the choice of men as the standard model for trials.

A second argument justifies the exclusion of women of childbearing potential because of the risks for the (potential) fetus. This argument expresses a valid ethical concern: the need to put in place some protection for the women that could become pregnant while taking part in a clinical trial whose effects on newborns are unknown. However, the systematic exclusion of women of reproductive age from research seems an excessive measure to accomplish this goal.¹⁸ We could argue that it is possible to minimize the risk in other ways, eg. adequate preclinical research on the teratogenicity of the investigational drug, appropriate information of potential participants, mandatory use of contraceptives during the trial, etc. In addition, the same argument could justify the exclusion of men of reproductive age, when a research could pose reproductive risks by damaging their semen; but in the case of men the measures just mentioned are usually deemed to be a sufficient safeguard. Therefore, we would need other reasons to justify why things should be different for women.

A third group of arguments is centered on some specificities of the female population that make women both more vulnerable and more difficult to enroll. These specificities relate to the fact that women have historically been oppressed, and even nowadays it could be

that they have difficulties in protecting their own interests, they have the tendency to defer to powerful groups, such as physicians, and they have an inferior social status: all features that could increase the likelihood of exploitation and of unduly induction to participation. At the same time, some of these characteristics could make the enrolment of women more difficult, for example because of the women's role as caregivers, that often leaves them with no time to spare. The main limitation of this argument is related to the broad use of the concept of vulnerability: even if it is important to be aware of specificities that could raise ethical concerns, it is quite problematic to attribute them to a category of individuals as a whole, with the risk of defending or creating stereotypes,¹⁹ and of neglecting individual variability. It is true, however, that these specificities are relevant: in order to involve more women in research, the strategy of removing prohibitions has proved insufficient, and I will argue that this is related also to the failure of taking into account some needs that are common among the female population.

Towards a participatory approach

After this historical overview, it is clear that an ethically sensitive approach to the participation of women in research should balance the need of protecting them from abuses – keeping in mind that at least some women could be more vulnerable than the 'standard' man – with the importance of including them in biomedical research. However, even if it is undeniable that ensuring access to research to the female population is a matter of justice, it seems that the campaigns for inclusion did not obtain the success hoped for: in fact, as previously mentioned, they started in the '90s, and we are still condemning a persisting "inequality in medicine".²⁰ I would like to suggest possible explanations by pointing out some elements whose underestimation could have played a role in hampering progress in this area.

A first point is that including women should be a true commitment by the whole research community. On the one hand, it is not enough to remove barriers (like the 1977 FDA guideline or exclusion criteria based on childbearing potential), but we need an active effort to make sure that women are actually represented in clinical trials. This means acknowledging the scientific value of their participation, and then having the dedication to understand the factors that obstruct their involvement, and finally do something to remove them. For example, this could mean to provide for diverse recruitment strategies, if need be. On the other hand, the issue of inclusion should not concern only funding agencies and Research Ethics Committees (RECs) or Institutional Review Boards (IRBs), but scientific journals, medical

schools and individual physicians as well: they all have a role to play in order to promote a greater gender equality in medicine.

A second point is that the emphasis on inclusion could be misleading, in the sense that inclusion is actually only the means to realize a broader goal: taking care of women's health needs. When one brings the attention back to the final purpose, it is easier to see that, in order to realize it, we need to operate at all the different levels of research: from study design to RECs evaluation, from data analysis to the dissemination of results; and, probably the most important one, at the level of setting priorities and defining the research agenda. It is only at this level that it is possible to make sure that the real health needs of a population are given the attention they deserve and, in the case of women, that the need of filling in a knowledge gap is taken into due account.

Finally, we could argue that, in order to overcome unfair inclusion or exclusion practices, we should reflect on their causes. Here, I focused on some ethical views that influenced them but, as already mentioned, also socio-cultural elements played – and still play – a crucial role.^{6,21} An analysis of these elements is outside the scope of this paper. Suffice it to say that, at the very least, it is crucial to put an effort into raising the awareness of the medical community (physicians and future doctors alike) about gender inequity in research and healthcare.

Many of these observations, at least in my view, point to the need of a different focus: what matters the most is not so much inclusion, but women participation. The concept of participation conveys not only the idea that women should participate in clinical trials (just like inclusion does, but with a more active nuance), but also the idea of a broader involvement in all the different phases of the research process as 'partners'. A participatory approach is probably the most effective to make sure that women's health needs receive appropriate attention in the research agenda; that funding agencies require that both sexes are represented in the trial (unless there are good scientific reasons to exclude one or to limit its representation); that studies are designed in such a way as to facilitate female participation; that possible vulnerabilities are taken into account when relevant; that RECs evaluations devote attention to gender equality; that data are analyzed by sex; that research results are adequately disseminated; and so on. The inclusion of representatives of communities and of different social groups in the many steps of the research process seems a good answer to the ethical concerns related to their potential vulnerability: on the one hand, it is a way of giving voice and decisional powers to groups that historically did not have them; on the other, ensuring diversity among decision-makers at the different levels should help making sure that the needs of all people receive the attention they deserve.

Conclusions

The awareness of the evolution of the ethical reflection relating to women participation in clinical research is relevant for the present efforts to promote gender specific medicine at least for two kinds of reasons. Firstly, I argued that ethical concerns played a crucial role in the '70s in determining the exclusion of women, and that in order to change exclusive practices it is necessary to know where they stemmed from. Secondly, the historical overview shed light on the justification of the importance of defending a gender-specific approach to medicine. As we have seen, it is first of all a matter of good science, of scientific objectivity;^{2,22} medicine has unconsciously incorporated a male bias that has produced a huge gap in knowledge which, in turn, has negative effects on the quality of the healthcare that we can offer to more than half of the population. This situation raises serious ethical concerns relating both to the appropriateness of the treatments that are offered to women, and to the persistent presence of unconscious discriminatory practices. As discussed above, the need of taking gender into account is based on fundamental ethical principles, like beneficence and justice. These are strong arguments to defend a research effort to investigate the gender differences of diseases as the essential first step towards a truly personalized medicine.

At the same time, I think we can learn two lessons from the changes underwent by the inclusion of women in research. On the one hand, it reminds us of the ever-present risk of bias and of the limitations of scientific objectivity: physicians can only benefit from keeping in

mind that the evidence at their disposal is not tailored on the individual patients they treat. Moreover, scientific knowledge is constantly evolving and, from what we have discussed so far, it is clear that the same arguments that support the study of female specificities could also support the study of the impact on health of other differences, for instance those related to belonging to ethnic or social minorities. Also, the complex issue of involving pregnant women in clinical research is still being debated, and very much related to the new ethical sensibility towards the involvement of women. On the other hand, the analysis of the evolution of the inclusion of women in research emphasizes the importance of focusing on the bigger picture: we should not aim just at improving the enrolment of female participants, the actual goal is including a concern for women's health into the research agenda. I argued that the most effective way to do that is adopting a participatory approach that considers trial participants as partners who can offer a contribution at all the levels of the research enterprise.

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Key messages

- In the '70s, in order to avoid excessive research-related burdens, women were treated as a vulnerable population who needed special protection.
- The exclusion of women from research was "a glaring moral mistake" that violated both the principle of beneficence (maximizing possible benefits and minimizing possible harm) and justice (fair distribution of the benefits and burdens of research).
- The emphasis on the participation of women in research could be misleading, since such inclusion is just the means to achieve a broader goal: taking care of women's health needs.
- The need of taking gender into account is based on two fundamental ethical principles: beneficence and justice.
- A participatory approach to clinical research is probably the most effective way to ensure that women's health needs receive appropriate attention within the research agenda.

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