"Ethical issues in therapeutic use and research in pregnant and breastfeeding women".

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Abstract

Pregnant, or potentially pregnant women have historically been excluded from clinical trials of new medications. However, it is increasingly recognised that it is imperative to generate evidence from the population in whom the drugs are likely to be used in order to inform safe, evidence-based shared clinical decision making. Reluctance by researchers and regulators to perform such studies often relates to concerns about risk, particularly to the fetus. However, this must be offset against the risk of untreated disease or using a drug in pregnancy where safety, efficacy and dosing information are not known. This review summarises the historical perspective, the ethical and legal frameworks which inform the conduct of such research, then highlights examples of innovative practice which have enabled high quality, ethical research to proceed to inform the evidence-based use of medication in pregnancy.

Introduction

The risks to pregnant women of having no information upon which to make choices about their own treatment with medication have begun to outstrip concerns about the risks to them of participating in research. In this paper, we review the historical context and the ethical and legal frameworks for decisions relating to the inclusion of pregnant or potentially pregnant women in clinical trials, then illustrate examples of best practice drawn from a range of disciplines.

The thalidomide catastrophe of the 1950s clearly demonstrated that potential harms of medications in pregnancy are genuine [1]. However, this was a lesson badly learned, as it arose precisely in the wake of enormous harms arising from ill-advised research exclusion: widespread rollout and clinical use of thalidomide in pregnancy without ever having included pregnant women in the initial clinical trials [2]. The incidence of thalidomide-associated phocomelia is high (20-30%, and likely much higher if the exposure occurs during the critical window of 20-36 days post-conception), which means by the "Rule of Threes" that an early-phase study would only need to have included 10 to 15 pregnant individuals to have detected this harm [3]. Contrasting this to the 10,000 infants born with thalidomide syndrome between 1957 and 1962, the possibility of staggering harms averted by research becomes clear. At the policy level, the global response to the thalidomide crisis, in addition to withdrawing the drug from the market, was to exclude all women of "reproductive potential" from pharmaceutical research; this has cast a long shadow and resulted in a lack of information about the safety, pharmacokinetics, and effects of drugs in women more broadly, including inadequate information about instances where sex-specific differences exist (a recent effort to inventory sex-specific safety, efficacy, or pharmacokinetic differences among drugs available in Sweden found that 15% of drugs have sex-specific differences in at least some populations, and 30% of drugs have inadequate data to determine whether sex-specific differences exist. [4]) Thoughtful advocacy over the past three decades has shifted the global focus somewhat from a paternalistic framework of 'protecting women *from* research' to a perspective of 'protecting women *through* research'. This approach maps to the established bioethical domains of Justice, Autonomy, Beneficence and Non-maleficence (Figure 1).

Extent of Knowledge Deficit on Drugs in Pregnancy and Lactation

A recent study including almost 10,000 pregnant women demonstrated that the majority of women in Europe, North America, South America and Australia used at least one medication during pregnancy [5]. In the US, despite the fact that about 7 in 10 women take at least one prescription drug in pregnancy [6], only 12 drugs have Food and Drug Administration (FDA) approval for use in pregnancy-specific indications (most related to labour and delivery); in the U.K. there are five

prescription medicines specifically indicated for use in pregnancy for non-obstetric indications. Reviewing drugs licensed between 2010 and 2019, Byrne and colleagues noted that animal pregnancy data were available in 90% of cases, but human pregnancy data in only 10% [7]. Notwithstanding the widespread use of prescribed or over the counter medication in pregnancy and breastfeeding, there is rarely evidence-based information to fully describe the dosing and safety of the medication to either mother or infant. The FDA guidance calls for such studies to be done around the time of licensing, when it is anticipated that the drug will be used by women of childbearing age [8-10], but in reality this is rarely done. It is important to physicians and to patients to know whether the dose, efficacy and safety profile of a drug required in pregnancy are the same as in non-pregnant adults. Substantial physiological changes occur in pregnancy, impacting the absorption, distribution, metabolism and elimination of the drug. These processes, summarised as pharmacokinetics, may result in a lower exposure of drug in pregnancy and risk of therapeutic failure [11].

Lessons From HIV

The HIV research community has led the way in many aspects of pharmacological research in pregnant and breastfeeding women, from trial design, advocating for the earlier and routine inclusion of pregnant or potentially pregnant women in such studies [12], providing guiding principles for the design and analysis of high quality pharmacokinetic studies [13, 14] and providing an ethical framework on which to underpin this [15]. A 2016 systematic review of all pharmacokinetic studies in pregnancy identified 198 studies exploring 121 different medications. More than a quarter of these were on antiretrovirals [16]. This may relate to the fact that antiretroviral drugs given to the mother initially had the primary objective of protecting the infant from HIV infection, rather than to improve the mothers' health. Therefore the considerations of risk and benefit were different, as the risks to the fetus of not treating the mother, a 30% chance of acquiring HIV with 50% mortality by two years of age without treatment, were substantial. Furthermore, there has been a strong voice from affected communities and strong partnerships and stakeholder relationships prioritising the generation of evidence to inform the public health approach to management of this slow-burning epidemic which has had devastating consequences for the countries most affected. These factors are not present for most other conditions which may necessitate medication use during pregnancy or breastfeeding, and the evidence gaps, and gaps in the quality of the existing evidence are even greater [16, 17]. Many of the examples of innovation and best practice can therefore be drawn from the realm of HIV pharmacology.

Justice and Risk-Urgency Calibration in the Inclusion of Pregnant Women in Drug Development Trials

Justice is fairness in the distribution of benefits and burdens [18]. It is a fundamental normative standard of bioethics and as such it applies not only to health care and to public health as domains of action *directly* affecting individual and community health, but also and fully to the large supporting institutional structures and activities of biomedical research including drug development research [19, 20]. Justice applies to biomedical research generally and drug development in particular because of the highly consequential impact they have on the distribution of health among different populations. The point of drug development research is not only to *understand* the world better but to understand the world better in ways that *make* the world better by improving the health of human lives. The distribution of drug development research – different allocations of research activity among different problems, products, and populations – stands to significantly affect the

downstream distribution of medical and public health benefits among diverse populations, and this brings it squarely under the norm of justice.

Justice applied to drug development research requires comprehensively identifying and evaluating disparities in the ways that different groups of people, such as pregnant women, are systematically treated and impacted by particular policies, programs, and practices of drug development (such as particular research agendas and trial designs). Justice is a comparative assessment of these differences as they arise among alternative approaches or actions [21], such as between the inclusion vs exclusion of pregnant women in drug development trial designs. An assessment of the justice of a particular drug development agenda or trial design must, for instance, take stock of the differential risks for study-related harm that pregnant women or their fetuses stand to face from participation as opposed to the risks they face from non-participation. Equal inclusion of pregnant women in drug development trials may pose unequal risks of study-related harm to them of their fetuses compared to other groups or to the general population. This well-recognized point of assessment, important though it is, is not in itself dispositive of the justice of including or excluding pregnant women in a drug development trials as there are other countervailing domains of trial design-attributable benefits and burdens relevant to the *comprehensive* assessment of justice in drug development research.

Another justice-relevant domain of disparities in benefits and burdens from drug development trial design is the *differential time to evidence* for given levels of safety and efficacy data for a drug in the general adult population as compared to in pregnant women. Exclusion of pregnant women from drug development trials – and not simply sporadic exclusion from a particular drug development trial but systemically consistent exclusion from a wide array of drug development trials in multiple areas of biomedical research – risks causing significant delays in achieving particular levels of safety and efficacy data on which to base optimal use of drugs in the medical care of pregnant women as compared to general adult population [22]. The burden of these delays for pregnant women is a function of the magnitude of the delays as well as the *urgency* of the medical problems addressed by the particular drug development trials. This urgency in turn is a function of the severity of the medical problems, their frequency in pregnant women, the availability, safety, and efficacy of existing alternatives for managing those problems during pregnancy, and the level of evidence supporting the safety and efficacy of those putative alternatives in pregnancy. Significant trial design attributable delays in time of evidence for high urgency medical problems is a burden of substantial ethical concern as a matter of justice. They represent high impact shortfalls in achieving equality of evidence and comparably evidence-based medical care for pregnant women as compared to the general adult population.

Whilst some delays in time to evidence may be inevitable irrespective of trial design, exclusionary trial designs can significantly prolong that delay. Trial design attributable delays is a disparity of great ethical relevance under the bioethical principle of justice. Evidence based medicine is rightly predicated on the benefit that greater rather than lesser.

An easily overlooked point must first be made about the precise *relevance to justice* of comparatively differential study-related risks between pregnant women and their fetuses and the general population. This requires logically distinguishing between two contrasting ideas (Figure 2): *1*) the idea of including pregnant women in a drug development trial to study a question that would be otherwise well answered by simply including members of the general population: the

general safety and efficacy of the drug in the general human population and *2*) the very different idea of including pregnant women in a drug development trial to study something that cannot justifiably be assumed to be otherwise well studied simply by the inclusion of members of the general population: the precise safety, efficacy, and optimal dosing in pregnant women themselves. In fact, the later idea can and should be stated more strongly in many instances: it is not simply that we cannot justifiably assume that the safety, efficacy, or optimal dosing of a drug are all equally well studied with or without the inclusion of pregnant women and their fetuses in a drug trial, but rather that we often have compelling scientific reasons to believe they will *not* be equally well studied without the inclusion of pregnant women and their fetuses. The two ideas are points along a continuum of thought between viewing pregnant women as *commensurable* with the general population and as *incommensurable* with the general population.

If the relevance to justice of differential study-related risk is framed within Idea 1, then the inclusion of pregnant women in a drug development trial would appear to be a gratuitously higher-risk approach to the very same research objective as a trial that excludes pregnant women. The latter design will then appear to offer an ethically superior approach to the common research objective of studying drug safety and efficacy in the general human population, as it avoids the distribution of needlessly excessive risk. This is a misleading frame. Idea 1 is archaic and harkens to an earlier period in human subject research in which there existed an implicit idea that clinical trials were able to produce evidence and data about human beings *as such*, with a corresponding expectation of broad generalizability of safety and efficacy data to all human populations. Within such a frame and its corresponding research paradigm there was no positive value to ensuring inclusion of different genders, ethnicities, ages, or concurrent heath conditions such as pregnancy; human beings were generally *commensurable* with one another and as such appropriate research *proxies* for one another. Not only would it be *permissible* to omit particular populations without justification from a trial under a commensurability paradigm, but if there were any amount of surplus risk attached to a particular population, it would appear ethically obligatory to omit them as a matter of justice. A very different framework prevails now.

Equity of Access to Research

Moving from a Commensurability paradigm to an Incommensurability paradigm, similarity or difference between non-pregnant and pregnant individuals is a matter to be proven, on a drug-by-drug basis, and not assumed. Therefore, it is imperative that drugs are studied in the populations in whom they are to be used. Examples abound of harms resulting from inadequate study of drugs in certain populations, including inappropriate withholding of drugs. At a time when efavirenz was the most virologically effective available HIV drug, it was systematically withheld from women in the first trimester of pregnancy because of concerns about a preclinical toxicity signal in monkeys. Clinical research that followed in non-pregnant people found no toxicity but it was assumed that they were incommensurable with pregnant women; therefore the drug was withheld in pregnancy. Only a decade later, when registry data had accumulated and the studies were eventually done in pregnant women, did it become clear that there was a species difference in the observed toxicity; no embryotoxicity was observed among pregnant humans [12, 23]. The potential benefits of research participation include later access to the fruits of a particular research endeavour: a safe, tolerable and effective drug. Systematic exclusion from research is unjust partly because it results in systematic exclusion from these benefits.

Autonomy & Considerations of Informed Choice

Autonomy requires both the removal of barriers to an individual's decision-making, and providing the necessary support for that individual to make informed decisions. Movement away from paternalistic "top-down" models has led to an increasing emphasis on clinical shared decision-making with patients after providing them with relevant information that they need in order to decide. This type of inclusive shared decision-making is not possible in the absence of relevant evidence-based information on which to base shared decisions. Per recent guidance from the General Medical Council in the UK, needed information includes "the potential benefits, risks of harm, uncertainties about, and likelihood of success for each option." [24] When deciding about drugs for pregnant and lactating women, however, generally the most guidance physicians can provide their patients is to highlight the many unknowns at hand, caused by a dearth of research involving pregnant women, and a resulting information vacuum.

Autonomy is the opportunity and capability of individuals to make informed decisions for themselves including informed health care decisions and decisions regarding participation in clinical research. Along with justice, autonomy is one of the four fundamental principles of bioethics and a key principle in biomedical research ethics[18]. The principle of autonomy is founded on the recognition of self-determination as a fundamental aspect of well-being in human life. Under the principle of autonomy, medical and research institutions should actively promote the exercise of self-determination in matters of healthcare and research participation.

Autonomy is not supported or secured simply through a passive non-interference in the decisions of individuals by health care providers or research coordinators – a form of medical *Caveat Emptor* - but rather also requires the positive and robust provision of supporting conditions that enable individuals to effectively expresses and act upon their relevant preferences in making health care choices and choices about research opportunities. Active discussion of risks, benefits, and alternatives by treating providers or research coordinators, institutionalized mechanisms for advanced directives and for establishing preferred surrogate decision makers such as health care power of attorney are among the diverse supports of autonomy in health care and research settings. A basic implication of the bioethical principle of autonomy is the unqualified right of individuals to refuse unwanted interventions or unwanted participation in research. There is also a corresponding right to be informed of relevant risks, benefits, and alternatives on which the individual may base their decision to refuse or accept a given treatment or study. Absent such information, their decision may be distorted and fail to represent the way the particular intervention or study truly aligns or fails to align with their real preferences; in a meaningful sense, their autonomy would be compromised.

Drug development research and clinical trials play an important role in the autonomy of health care consumers including pregnant women. Such research produces the evidence and data on which providers base discussions of relevant risks and benefits and on which health care consumers may then rely in assessing the alignment of potential treatments with their personal preferences. Drug development trials are among the positive conditions that support patient autonomy. It is for this reason that the widespread exclusion of pregnant women from drug development trials is an ethical concern under the principle of autonomy: doing so selectively compromises the evidence base on which pregnant women can rely, as others do, in assessing the alignment of possible medical interventions with their personal preferences. Under the principle of justice, we noted the ethically significant role that evidence (and evidence gaps or disparities in time to evidence) may play in the distribution of health care relate benefits and harms. Here, under the principle of autonomy,

evidence plays a second, distinct ethically significant role in underwriting the informed self-determination of pregnant women. If pregnant women are selectively excluded as a group from drug development trials, they are also thereby denied an essential set resources and preconditions for their exercise of autonomy in making comparably informed health care decisions.

The autonomy of pregnant women is compromised by the systematic selective exclusion from drug development trials in another ethically significant respect: exclusion directly curtails their autonomy to voluntarily participate on an informed basis in biomedical research opportunities that would otherwise be available and of personal interest to them. To design drug trials with pregnancy as an exclusion criterion is to make the decision about non-participation *for* pregnant women generally rather than allow the decision to be made *by* individual pregnant women for themselves in light of their own individual informed appraisal of the risks and benefits of participation and in light of their own individual values and preferences. The bioethical principle of autonomy is unquestionably compromised by study designs substituting *judgments for pregnant women* in place of *judgments by pregnant women*. A general call for such autonomy is expressed in the phrase "Nothing about us without us" or *Nihil de nobis, sine nobis*.

Perhaps even more challenging than the question of a woman's autonomy to make her own decisions relates to who *else* should have autonomy to make decisions on behalf of the unborn child. Ongoing debate surrounds this question and epitomises the challenge of producing harmonised guidance applicable across the varying societal, community and family structures encountered worldwide. Paternal consent requirements for research involving pregnant women are seen by proponents to recognise and respect the parental rights of fathers and protect the welfare of the fetus, whereas its opponents argue that it fails to respect the autonomy of the pregnant woman, fails to recognise the diversity of family structures, is difficult to apply and may interfere with access to research which may be beneficial to the child. The US regulation on research with pregnant women requires paternal consent should the research be of potential benefit to the fetus alone and not to the mother. It carries the caveat that paternal consent is not required if there is prospect of benefit to the mother or if the father 'is unable to consent because of unavailability, incompetency, or temporary incapacity or the pregnancy resulted from rape or incest' [25], and is similar to guidance from other countries such as Uganda [26]. An additional complexity in the context of HIV is that a woman may not have disclosed her HIV status to her partner and that to do so during pregnancy may carry a real threat of gender-based violence and abandonment; some studies have proceeded with 'paternal objection' as an exclusion criterion rather than insisting on a requirement for paternal consent (NCT02245022 and NCT03249181) [27, 28].

These considerations are complex, nuanced, and there will be variation between families and partnerships even within a community with a strong prevailing view on decision making and gender dynamics. The pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) project sought detailed understanding of these considerations with respect to research into the treatment and prevention of HIV in pregnancy, seeking views on paternal consent requirements from arguably the most important stakeholders – the women themselves. Analysis of views of 140 women in the U.S. and Malawi revealed that the majority of women in both settings supported the requirement for paternal consent, stemming from views surrounding parental rights, protecting the interests of the fetus and aspects of relationship and gender dynamics. Most concerns and objections related to fear of conflict or violence, to fathers who are absent, and in the case of HIV where this work was

performed, issues of disclosure of HIV status; interestingly, the concerns could be mapped to the same themes as the supportive statements.

PHASES also considered the perspectives of researchers. Sixty two HIV researchers described the challenges including ethical concerns such as how to weigh risks and benefits in pregnancy, and legal concerns relating to interpretation of current regulations, concluding that advancing research in pregnancy will require clearer guidance regarding ethical and legal uncertainties. A requirement for ethically responsible, action-guiding recommendations presented in a user-friendly format was noted [29]. Such guidance relating to HIV-related research in pregnancy, was produced in late 2020 [15]. Although the focus of PHASES was HIV-related research, the insights and considerations the project are of broad relevance to the inclusion of pregnant women and other excluded populations, across *all* sectors of biomedical research.

Both the American College of Obstetricans and Gynecologists (ACOG) and the Council for International Organizations of Medical Sciences (CIOMS) consider a model that enables robust participation by fathers, rather than consent. This has been described as a dyadic framework which encourages shared decision making where the family circumstances allow it, but places final control in the hands of the woman [30]. A difficult balance is found in attempts to craft a rule that respects the autonomy of the pregnant woman, values fathers' interests and engagement whilst also appreciating the diverse nature of families and contexts, and respects the importance of reducing barriers of access to research. Successful case studies of where this has been applied, such as the DolPHIN studies [27, 28], together with continued engagement and dialogue with all relevant stakeholders, may enable advances in this realm.

Considerations of Risk-Benefit Ratio: Beneficence and Non-Maleficence

Concern is often expressed that studying drugs in pregnancy brings risks. However, women with chronic medical conditions requiring medication become pregnant, and new medical conditions (acute or chronic) can present in pregnancy. The risks of therapeutic research in pregnancy must be weighed against the risks in the clinical domain of giving a drug when the pharmacokinetics and safety in pregnancy are unknown or withholding a potentially beneficial treatment because of lack of evidence (Figure 3). Perceptions of risk are complex, and with regard to medical decisions made in pregnancy this complexity increases. Particular biases include the over-interpretation of the risk of making a decision, without recognising that to avoid such a decision or to take no action may itself carry greater risk, a concept known as 'risk distortion'. A good example of this is excluding pregnant women from COVID treatment and vaccine trials because of the perceived risks of their participation, even given the disproportionately higher risk they face of severe disease from COVID [31]. Furthermore, concerns of any perceived theoretical risk to the fetus may be given greater weight than actual threats to the health of the mother [32]. In lactation, this risk perception may be even more distorted: in high-income countries, a default option has been to advise a lactating woman that there are no data to support the safety of a drug in pregnancy and therefore switching to artificial feeding might be preferable. However, this assumes that prevention or premature discontinuation of breastfeeding carries no risks, whereas the body of evidence supporting the myriad of benefits of breastfeeding to both mother and infant continues to grow [33-35]. To not perform research on drugs which are likely to be used in pregnant or lactating women does not remove risk; rather it shifts the risk into the clinical domain where potentially greater harms might occur (Figure 4). Rather than presumptive exclusion of such populations, there should be a move to fair inclusion. [36]

A balanced consideration of risks and benefits for each proposed clinical trial must be conducted. Figure 5 considers two examples at opposite extremes of both risk and benefit. In ebola virus disease, without treatment there has been a maternal case fatality rate of over 80% accompanied by pregnancy outcomes which were universally grim with spontaneous abortion, stillbirth or neonatal death in all documented cases [37]. These risks, and potential lifesaving benefits, would justify use of a drug with an unknown safety profile in either the short or long term, or indeed a drug which was known to carry substantial risk. Despite this, women were initially excluded from the trials– a stance that has been described as being 'protected to death' [38]. An opposite example is the evaluation of a drug where there exists an effective treatment with proven safety and favourable pharmacokinetics in pregnancy. An example of this is the comparison of different formulations of the antiretroviral tenofovir, tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF) as part of combination antiretroviral treatment [39]. Whilst important to consider the incremental benefits of novel formulations which may bring improved toxicity profiles [40] as well as programmatic improvements through harmonisation of first-line regimens, the potential benefits to the individual participant and her fetus over the existing standard of care are small. Potential risks of the novel drug or combination must be considered in the light of this.

Another historical example, vaccination against rubella, provides a 'cautionary tale about caution'. An abundance of caution led to a campaign that vaccinated 'around the pregnant woman' rather than vaccinating in pregnancy itself. This shifted the median age of infection, and many more children were born with congenital rubella syndrome because their mothers were not candidates for vaccination prior to or during pregnancy. Where vaccination did occur, hundreds of pregnancies were electively terminated because of theoretical risks (which have not been borne out through exposure registries) and absence of data on vaccine safety in pregnancy. This is a clear example of the paradox whereby efforts to prevent harm can put in harm's way the very population cautious policies are meant to protect [41], and further illustrates the danger of transferring uncertain risk from the research to the clinical domain.

Novel formulations of antiretroviral drugs illustrate this further. The FDA approval in January of 2021 of Cabenuva®, combining two nanoformulated long-acting antiretrovirals, cabotegravir and rilpivirine, for the once-monthly injectable treatment of HIV, ushers in a new treatment era. This dosing approach may circumvent some adherence and stigma challenges and stand to particularly benefit women in both pregnancy and the postpartum period, a demanding time when loss to follow-up is common and adherence to daily oral pills is challenging [42, 43]. Long-acting strategies have never been studied in pregnancy or lactation, so their pharmacokinetics, safety, and efficacy in this period are unknown. A strong call to study these agents among pregnant and postpartum women has been supported in part by the high acceptance among women of long-acting injectable depot forms of contraceptives [44].

Women of 'Childbearing Potential'

Concerns about potential risk mean that many studies, particularly those involving novel agents, require women to be using a form of contraception that the investigators consider 'adequate'. This requirement may result in reluctance of women to participate. However, in the clinical realm, there are few drugs where contraception is insisted upon, primarily the known teratogens such as isotretinoin [45]. Once more, 'risk shifting' occurs, due to not undertaking research as to the actual risks and benefits in pregnancy [32].

If long-acting ART is rolled out among women of reproductive age, some will become pregnant while on the drugs (as 50% of pregnancies are unplanned [46]). Accepting this as a potential risk from the

outset, a clinical trial enables evaluation in a controlled context: women who become pregnant in the context of a study should be allowed to continue on the trial and on study drug, with all evaluations and appropriate monitoring of both the fetus and the mother—otherwise nothing will be learned to benefit others who follow [12, 13]. As discussed by Fairlie and colleagues, rather than immediate withdrawal from a clinical trial, follow-up for safety endpoints should be standard irrespective of whether the participant remains on the investigational drug or is switched to standard of care. If she is in the second or third trimester, she could be invited for pharmacokinetic analysis to provide data on the drug disposition in pregnancy [12].

Should pregnant women be considered 'special' or 'vulnerable': Non-Maleficence

Different terms are used to described pregnant and lactating women in the context of research, including 'special' and 'vulnerable'. 'Special populations' is a broad term referring to individuals who are often excluded from clinical trials; but is it right to consider 50% of a population who are undergoing a normal and natural physiological process to be 'special'? 'Vulnerable' is a term which is less frequently used in recent years. It could be argued that it is rather the lack of evidence to inform safe treatment that renders a pregnant or lactating woman to be vulnerable! Increasingly, populations that have been deemed vulnerable have advocated for themselves, calling for quite different policy of inclusion in research and access to research products, rather than the status quo: discriminatory systematic exclusion supposedly on their behalf [47-50].

This situation was seen with the antiretroviral dolutegravir. Licensed in 2013, it was shown to reduce viral load far more rapidly than comparator regimens [51], to have a more favourable drug-drug interaction profile[52, 53], to be suitable for co-formulation with other antiretrovirals and potentially to incur fewer adverse effects [54]. Botswana made an early decision to transition national policy to use dolutegravir-based regimens as first-line, knowing that pregnancies would occur. During this period, the Tsepamo birth surveillance study was active in the country, exploring the association between the current standard of care efavirenz-based regimen and birth defects; the protocol adapted to explore birth outcomes with dolutegravir. Other countries began to introduce dolutegravir among specific populations with a view to scale up. To inform international guidance, in 2018 the WHO requested an interim analysis of the Tsepamo data which revealed the surprising finding of a significantly higher incidence of neural tube defects among the babies of mothers who had conceived whilst taking dolutegravir (4/426 exposed pregnancies, 0.9%) [55]. This led to immediate international alerts, and many countries withdrew dolutegravir as an option for women considered to be of childbearing potential (often taken to be women with a uterus who had not been surgically sterilised, aged between 15 and 49 years). However, by this point, an appreciable proportion of women who had tolerated disabling adverse effects from the efavirenz-based regimens [56], knowing that there was no alternative first-line option, had been switched to dolutegravir and experienced a substantially improved quality of life.

Anger was expressed by community advocacy groups that women were not engaged in the dialogue surrounding dolutegravir and the potential risks. A well-publicised protest took place at the International AIDS Society conference in Amsterdam in July 2018, and the Kigali Stakeholder Meeting, convened in April 2019 concluded that 'it is critical to not just view a pregnant mother, or any woman of childbearing potential, as a vessel for a baby, but as an individual in her own right, who deserves access to the very best, evidence-based treatment available and the right to be adequately informed to make a choice that she feels is best for her.' [57]. Women wished acknowledgement of their ability to manage their reproductive health, including the choice to delay or not to undergo a pregnancy and stated that 'blanket exclusions that deny women equitable

access to this optimal HIV treatment are not warranted or justified' [57]. Qualitative research revealed the tension between the desires of women for information and autonomous choice [58] with the significant concerns of the stakeholders to protect their populations from potential harm [59]. Detailed modelling of potential risks and benefits of widespread dolutegravir use in South Africa, should the increased risk be genuine, suggested that even despite such an increased risk, there would be significantly improved population health and the intervention would be cost-effective [60]. As further Botswanan women who had conceived on dolutegravir reached delivery, the signal for embryotoxicity diminished, and by July 2019, dolutegravir-based regimens were adopted by the WHO as preferred first-line antiretroviral therapy, including for women of childbearing potential. Many lessons can be learned from this unfolding of events, particularly with relation to communication and the complexity of risk-benefit considerations as recently discussed by Mofenson and colleagues [61]. Pertinent to our current paper are the considerations that the affected community and other key stakeholders be involved throughout, and that information be provided to engage all levels of knowledge.

Vulnerable may have meant originally to refer more to the fetus than the pregnant woman. The vulnerability, however defined, should be understood to apply to the same demographic both inside *and* outside the clinical trial setting; only some of a vulnerable population may stand to participate in a given study but the other members of that vulnerable population may nevertheless stand to be affected in ethically relevant ways by the design and conduct of that study. Accounting for the impact of trial design on a vulnerable population is not just this looking beyond the borders of the studies themselves, although this is a first step towards their full ethical assessment, but also accounting for the cumulative magnitude of impacts within and beyond the trials- this means not just comparing the harms and benefits to representative member(s) of the vulnerable population inside and outside the trial, but also accounting for the numbers of individuals in the vulnerable population who stand to be affected by the study design, for how long they stand to be affected, and to what degree. If the vulnerable group beyond the confines of a trial is large, faces a significantly prolonged delay in therapeutics or preventives for a high morbidity or mortality illness from trial design that excludes that group then, the adverse impact of the trial design on that vulnerable group may be great indeed due to a design-attributable period of de facto clinical or public health neglect of the vulnerable population compared to other populations.

Legislation & Legal Aspects

In the U.S, the 21st Century Cures Act of 2016 (Section 2041) established the PRGLAC Task Force on research specific to pregnant and lactating women, which has issued guidance to the Secretary of Health and Human Services (HHS) on how to improve the inclusion of pregnant and lactating women in research [62]. Specifically, the PRGLAC mandate was to develop "a plan to identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women, including the development of such therapies." [63] A key recommendation was a call for reducing liability around the study of therapeutics in pregnancy and lactation.

An important consideration in the design and conduct of clinical studies that include pregnant women are the various national regulatory requirements that such studies must satisfy in order to secure state sponsored funding, obtain IRB approvals, and move forward to approval for market entry in particular countries. FDA regulations, although originating in the US federal government, have influenced research in many parts of the world beyond the US borders, serving at times and in places as *de facto* research regulations in many nations. This reflects *inter alia* both the outsized importance of the US market for medical technology as well as the outsized importance of US

government research funding in global research endeavors. An appraisal of US regulations on human subjects' research inclusive of pregnant women is key to understanding the opportunities that exist to expand the early inclusion of people who are pregnant in clinical research. Such appraisal is not a once and for all exercise; US FDA regulations pertaining to the inclusion of pregnant women in clinical research are, like all administrative regulations, subject to legislative and Agency review and revision over time.

The US regulatory requirements were originally codifed in 1975 in 45 CFR Subpart B: "Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research" [64]. This set forth selectively restrictive conditions for inclusion of pregnant women in clinical trials. Specifically, it stipulated that pregnant women could be included in clinical trials only if trial-related risks to the fetus were caused solely by interventions that offered prospect of direct benefit to the woman or the fetus or else, if there is no prospect of direct benefit, only if the risk to the fetus is minimal and the trial's purpose is to provide important scientific information that cannot be otherwise obtained. It also requires that trials including pregnant women should be preceded, "where scientifically appropriate," by preclinical studies as well by clinical studies including studies in nonpregnant women.

Such regulatory restrictions on inclusion of pregnant women in clinical trials have been criticized [65] and in 2018 the FDA issued new draft guidance "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry", encouraging earlier inclusion of pregnant women in clinical trials [66]. The draft guidance requires adequate nonclinical studies (including studies in pregnant animals) be completed, but this provision does not mirror the Subpart B reference to preceding clinical studies in nonpregnant women. It also requires that the research enrolling pregnant women offer the prospect of direct benefit to the pregnant woman or fetus. The guidance also addresses the most appropriate point for inclusion of pregnant women within the arc of drug development research. The guidance states that generally pregnant women should be excluded from phase 1 and phase 2 trials and leave enrollment to later-phase clinical trials. However, it does state two considerations that may support earlier-stage inclusion of pregnant women: 1) limitations of therapeutic options and 2) prior safety data on the drug in pregnancy. Where limited treatment options are available, the draft guidance states that "risk-benefit considerations may favor enrollment of pregnant women in earlier phase trials". The notion of risk-benefit assessment is a prominent motif in the guidance.

It is essential to remember that all of these guidelines lack an enforcement mechanism, but do express legislative sense that increased inclusion of unrepresented populations is beneficial, rather than harmful, and to be supported. The goal of PRGLAC was to identify opportunities to promote such inclusion through future regulatory and legislative action (e.g., changing liability law or legislative incentives for the inclusion of pregnant people, or requirement to explain and justify their exclusion.)

Specific Examples of Innovation in Research in Pregnancy

Development of Best Practices Guidance for PK Studies in Pregnancy and Lactation

Whilst it is ethically imperative to investigate drugs and vaccines in the population where they are to be used, it is also ethically imperative for the studies to use the most efficient study design and minimal amount of risk and intervention. However, the converse is often true. Perhaps stemming

from the concerns about undertaking research in pregnancy, many pharmacokinetic studies have employed an opportunistic study design whereby a woman who is already enrolled in a clinical trial, or who is requiring a drug for her own health is invited to have additional blood samples taken to measure drug concentrations, often coinciding with an already scheduled clinical or study appointment. Whilst this approach may minimise the number of additional clinic visits and sampling procedures required, difficulties in interpretation of the resulting data relate to lack of ascertainment of dosing history, of dosing time relative to the sampling occasion and to lack of choice of the sampling time point/s relative to dosing. Furthermore, even sparse sampling protocols should ideally have two or more samples taken relative to an individual timed dose, so that the change in drug concentrations within the individual can be measured [13, 67]. Population pharmacokinetic approaches are a powerful tool to explore variability in drug exposure between individuals through analysis of sparse datasets[68] but are unable to correct for incorrect study design or lack of accurate dose and time information. Therefore, such studies represent a missed opportunity and may yield confusing or contradictory results [17, 69]. In any situation where a participant provides consent for their data and samples to be used in research, the investigators have a responsibility to undertake this to the highest possible standards to maximise the understanding of the clinical question. Recognising some of these challenges, the WHO and the IMPAACT study group hosted a two-day consultation in 2019 to define best practice for pharmacokinetic studies in pregnant and breastfeeding women with HIV, and published guidance on these aspects of study design, sample collection and data analysis [13].

Statins for Preeclampsia

Use of innovative study design and multi-disciplinary working between basic and clinical pharmacologists can increase mechanistic understanding, challenge previously unexplored assumptions and pave the way for safe, ethical conduct of clinical trials that transform practice [70]. This can be illustrated by the repurposing of pravastatin to treat pre-eclampsia [71]. Introduced in 1987 for the management of hypercholesterolaemia, the earliest member of the 3-hydroxy-3 methyl-glutaryl coenzyme-A reductase inhibitors (statins) class, lovastatin, was given the 1979 FDA category X for use in pregnancy: ‘studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risks … and the risks involved in use of the drug in pregnancy women clearly outweigh potential benefits’, under the assumption that there would be no benefit from using this class of drug in pregnancy. Additionally, there was a suggestion of congenital malformations with lipophilic statins in rodent models [72] which was never revised to reassess risk with hydrophilic statins and was not borne out through pharmacoepidemiological studies [73] or analysis of pharmacovigilance registries [74]. It was increasingly recognised that the actions of statins are multifaceted rather than restricted to lipid lowering, and the reversal of angiogenic imbalance, endothelial dysfunction and reduction in inflammatory and oxidative stress are all mechanisms implicated in the development of pre-eclampsia which affects 3-5% of pregnancies [75, 76]. Pravastatin, the most polar hydrophilic member of the statin class, was shown in animal models and in vitro studies to reverse some pathophysiological pathways associated with pre-eclampsia, and accumulating evidence [73, 77] refuted the concerns about teratogenicity. Prior to large scale clinical trials, ex vivo placental models were used to further define potential fetal exposure [78], and longer term neurodevelopmental studies were conducted in murine models [79]. Finally, phase I and II safety and pharmacokinetic studies were undertaken in high-risk pregnant women, defined as those with a history of pre-eclampsia resulting in a previous delivery before 34 weeks [76], before moving on to clinical trials such as the StAmP trial [80]. This stepwise process illustrates involvement of multi-disciplinary experts in basic and clinical pharmacology, research

methods and feto-maternal medicine to address the logistical, ethical and regulatory challenges in repurposing a drug for use in pregnancy after a previous prohibitive safety classification.

Autoimmune Disorders

Some conditions, such as chronic inflammatory systemic diseases, disproportionately affect women with peak incidence during reproductive years. There is growing recognition that uncontrolled disease activity prior to conception and disease flares during pregnancy present the greatest risks to maternal and infant outcomes. Biologics, particularly those targeting the pro-inflammatory cytokine tumour necrosis factor (TNF) are increasingly used, but there has been uncertainty about the risk-benefit ratio of these drugs in pregnancy. A particular challenge in determining risk results from the fact that women with more severe disease, and therefore a higher pre-existing risk of adverse pregnancy outcomes, are more likely to be prescribed biologics. Robust methodology is required to disentangle the potential confounding resulting from disease severity in assessment of risk of adverse birth outcomes resulting from drug therapy. Given the exclusion of pregnant women from trials of these drugs, Tsao and colleagues systematically reviewed 24 observational studies which included pregnant women with exposure to biologics from three months prior to conception or during pregnancy and reported on birth outcomes. Almost sixty thousand mother-infant pairs including over five thousand where biologic exposure occurred, were included, and initial unadjusted analysis suggested higher risk among the exposed group. After stratification for severity of underlying disease, which can itself be associated with adverse pregnancy outcomes and which might skew the clinical decision towards the prescription of a biologic, there was no significant association with congenital anomalies or adverse birth outcomes [81]. This work supports the pro-active study of these agents in women of reproductive potential, and underpins the ethical imperative to use the highest quality methods to correctly interpret available data.

Collaboration, Data Sharing, & Reusability

The ethical imperative to maximise the benefits of data obtained through the study of drugs in pregnancy informs data management. It is increasingly recognised that datasets should be made findable, accessible, interoperable and reusable to others (FAIR) [82], but increasing awareness of these principles have not yet transformed practice [17]. It is recognised that a cultural shift is required to move towards widespread adoption of the recommendations. Whilst the principles apply to all trials and pharmacokinetic studies, there is particular importance in transparency of data arising from populations who are rare or difficult to recruit and where the research is believed to have involved some degree of risk. It would be unethical to need to repeat a study because of lack of availability of prior data. Reusability of data is the ultimate goal of FAIR, and this is a major factor separating traditional data management from FAIR data stewardship. Reusability allows data to be repurposed for new user communities, for new needs and for new applications. Data in this sense can become more valuable to more people across a range of organisations [82]. Furthermore, gaps in reporting can lead to misinterpretation of study findings and lack of generalisability. In recognition that clinical pharmacokinetic studies are not held to structured reporting guidelines such as CONSORT for clinical trials and PRISMA for systematic reviews, tools such as the ClinPK checklist have been developed to support the transparent and complete reporting of such studies. Involving 68 stakeholders from nine countries, four rounds of a modified Delphi survey and a series of small virtual meetings were required to generate consensus for a 24-item checklist considered to be essential to the reporting of clinical pharmacokinetic studies [83]. The use of such tools should be encouraged and promoted. Further information sharing, particularly on safety events, can be facilitated by the creation of national and international registries such as the antiretroviral drugs in

pregnancy registry [84], the FDA pregnancy registries [85] and the UK Medicines and Healthcare Regulatory Authority (MHRA) registry [86]; in low and middle income countries, ground-breaking work in the Western Cape of South Africa has set a strong precedent [87, 88].

Neglected Tropical Diseases—Twice Neglected in Pregnancy?

Lastly, neglected tropical diseases, such as African sleeping sickness, leishmaniasis, Chagas disease, filarial diseases and mycetoma, impact populations where contraception uptake may be low, but evaluation of new treatments is a priority. The Drugs for Neglected Diseases Initiative (DNDi) encompasses the full range of drug development from early research and preclinical though phase I, II and III clinical trials, with the aim of generating robust data in all populations who will require such treatments. Couderc-Petry and colleagues propose a framework for inclusion of women susceptible to pregnancy in such trials, including guidance on the appropriate action should an unintended pregnancy occur [89].

Conclusion

Although research inclusion of pregnant women can be complex, the weighing of risks and benefits for pregnant women in daily, largely off-label treatment and clinical care is fraught with even greater complexity. Principles of bioethics such as Autonomy and Respect for Persons dictate that pregnant people should be able to make their own decisions about participation in clinical research. Justice and Beneficence demand that they have equitable access to new technologies and therapies that emerge from that research and have been studied in people like them, in conditions relevant to their lives. The truly vulnerable group should properly be conceptualised as extending well beyond those individuals who participate in a trial and risk its harms. Finally, the longer pregnancy- and lactation-specific knowledge is delayed, the more urgent it becomes to fill these knowledge gaps.

Conflict of interest statement

None of the authors has a conflict of interest

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Figure legends

Figure 1 Bioethical principles relating to research in pregnancy

Figure 2 Assessment of commensurability

Figure 3 Disease consequence- drug safety calibration of research priority

Figure 4 Risk shifting from clinical to research domain

Figure 5 Balance of risks and benefits to pregnant women of participation in research