Reassessing Maternal Bioethics

Pandemic Influenza and Pregnancy: An Opportunity to Reassess Maternal Bioethics

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Large-scale infectious epidemics present the medical community with numerous medical and ethical challenges. Recent attention has focused on the likelihood of an impending influenza pandemic caused by the H5N1 virus. Pregnant women in particular present policymakers with great challenges to planning for such a public health emergency.

By recognizing the specific considerations needed for this population, we can preemptively address the issues presented by infectious disease outbreaks. We reviewed the important ethical challenges presented by pregnant women and highlighted the considerations for all vulnerable groups when planning for a pandemic at both the local and the national level. (*Am J Public Health*. 2009;99:S231–S235. doi:10.2105/AJPH.2008.140780)

THE RECENT WIDESPREAD global attention on pandemic influenza planning comes at a time when society has had recent direct experience with large-scale disasters. Policymakers and health care providers are increasingly recognizing the importance of preemptive disaster preparedness for catastrophic events, whether environmental, infectious, or human made. Such events have produced a heightened awareness of the need for preemptive planning by the medical establishment for public health emergencies. Infectious agents, such as severe acute respiratory syndrome (SARS) or multidrug-resistant tuberculosis, foreshadow the potential for pandemics to result in widespread devastation. The capacity for such an agent to rapidly spread across borders raises challenging and compelling questions about the management of patients and members of the community during times of an unprecedented demand on resources. Recent natural disasters, such as Hurricane Katrina, serve as an example of the consequences of insufficient emergency planning. The potential large-scale devastation produced by an influenza pandemic in the 21st century could be unparalleled, given the nearly universal susceptibility to unique influenza strains and the availability of global travel enabling rapid transmission.

An influenza pandemic has been the focus of recent discussions about public health emergencies. The avian H5N1 influenza strain, also known as the "bird flu," appears to be one of the most likely agents capable of initiating a pandemic. The virus has demonstrated its aggressive course in those infected (approximately 60% mortality) and an endemic nature among avian populations in Southeast Asia.[1] It is projected that another influenza pandemic will happen as evidenced by the natural history and constant evolution of the influenza virus. What is not clear is exactly when this will occur, to what extent the outbreak will produce global morbidity and mortality, and how effectively the medical community will be able to temper the emergency by using the proposed and traditional countermeasures.[2]

This situation provides a timely juncture for further discussion about pandemics and their effect on diverse groups of the population. Previous influenza pandemics suggest that pregnant women represent an important subset of the population that will likely have unique vulnerabilities to H5N1. The well-being of this group can also affect the health of the rest of the community. By recognizing the special risks associated with the management of pregnant women, health care providers and policymakers can be better prepared to recognize and address the needs of diverse populations and, in so doing, gain a better understanding of how such subpopulations play a critical role in outcome for the entire population. These types of considerations are critical when preparing rationing schemes aimed at effectively reducing the number of persons that become ill or die during a pandemic.

THE ROLE OF ETHICS IN PREPAREDNESS PLANNING

Influenza pandemics have the potential for massive devastation for the global population, causing illness, disability, and death. The public health emergency presented by the 1918–1919 "Spanish flu" resulted in more than 500 000 deaths in the United States alone.[3] This enormous human toll lies in stark contrast to the yearly influenza epidemics that typically produce 36 000 US deaths per year.[4] While staggering, these statistics do not reflect the

total number of persons affected, because they exclude those who became ill but survived the infection. Nor do the figures reflect the massive demands that the 1918 pandemic placed on medical supplies and personnel needed to manage the crisis.

A primary element for controlling the extent of pandemic devastation is preparedness planning for all members of the population.[5] At the time of the next influenza pandemic, a finite amount of resources will be available, and the likelihood is great that these resources will be surpassed by demand. Many preparedness efforts are in their infancy, and sufficient stockpiles of necessary medical supplies have not yet been reserved. If an influenza pandemic were to occur tomorrow, critical and difficult decisions would have to be made about the prioritization of medical resources in the midst of the event. An additional consideration is that an incomplete plan may unfold within a context of logistical barriers to health care delivery, such as the interruption of communication and transportation infrastructures, in addition to fear-driven disarray throughout the community and among health care workers.

The keystone to any such plan is an ethically sound rationing scheme that distributes limited resources in ways that minimize the resulting injury. Various ethically justifiable rationing schemes exist for the allocation of limited medical resources.[6,7] One accepted strategy prioritizes the needs of populations who are particularly vulnerable to both infection and transmission and thus play a critical role in the resulting morbidity and mortality.[8] Under this scheme, scarce resources are initially triaged to at-risk populations despite the fact that all members of the population could benefit. By doing so, health policy is enacted in a way to mitigate illness, injury, and death while limiting infection transmission to the larger community.

It is equally important to construct rationing schemes in a way that preserves the ethical values of the society. During public health emergencies, the interests and rights of individuals may be temporarily compromised for the purpose of helping the greater community. This trade-off should take place only when the threat to public health is real and imminent. When individual liberties are conceded, the respect and human dignity granted to individuals must be preserved to the greatest extent possible. Individual rights and autonomy should be restored as soon as the emergency has passed.

When weighing the interests and needs of various at-risk groups, the concept of vulnerability should be considered. Vulnerability can take on many different forms. One important group to consider is the medically vulnerable. In the case of an infectious pandemic, medically vulnerable members of the population will be at increased risk of illness and death because of biological factors and existing social systems. This subset of the population includes individuals who are highly susceptible to infection and rapid decompensation. As a result, medically vulnerable persons can rapidly become very ill and require a larger amount of medical supplies and personnel for management than other infected individuals in the community. This can result in a disproportionate level of injury across that population in addition to the consumption of a significant share of resources by a small segment of the population. Furthermore, because of their health status, the medically vulnerable have a pivotal role in the morbidity and mortality of the entire population; they can serve as the catalyst for logarithmic spread of the infectious agent among the community.[5]

Another critical aspect to pandemic planning is to recognize how an infectious agent will manifest differently among subsets of the population, and to use this information to guide difficult decisions of resource allocation. In terms of vulnerable populations, this is a two-step process. The first step is to identify subpopulations within the community that are at increased risk of infection and illness. The second step is to gain a better understanding of the challenges specific to these populations to avoid exacerbation of existing vulnerabilities.

PREGNANT WOMEN AS A CRITICALLY IMPORTANT POPULATION

Pregnant women are an important medically vulnerable subset of the population. Evidence from two of the most recent 20th century influenza pandemics in addition to recent data from seasonal influenza epidemics indicates that pregnant women are uniquely at risk for complications resulting from influenza infection. Their vulnerable status leads to disproportionate morbidity and mortality compared with that of the general population. This heightened risk includes the pregnant woman and the unborn fetus.

Reports from the 1918–1919 pandemic demonstrate the medical vulnerability of this population. Harris reported on a series of more than 1300 cases of pandemic influenza in pregnancy. Roughly 50% developed pneumonia, and of these, 50% died.[9] Among the critically ill, high preterm delivery and fetal loss rates were noted, demonstrating the potential dual impact of critically ill gravidas and their affected fetuses and newborns on hospitals providing maternity care.[9] Woolston[10] documented that of 2154 patients admitted to Chicago's Cook County Hospital during the pandemic, 101 were pregnant. Of these pregnant women, 51.4% died (52), a high rate compared with the 33% mortality experienced among nonpregnant admissions with pneumonia.[10] Data on the influenza pandemic of 1957 in New York City and Minnesota show that mortality rates among pregnant women were two to three times higher than were those of nonpregnant women. In addition, pregnant women accounted disproportionately for 50% of the total mortality among the entire cohort of young healthy women (aged 19–35 years)[11,12] Such historical data illustrates the importance of this population in terms of ethical prioritization.[13,14]

Limited but equally compelling data are also beginning to emerge about H5N1 infection among pregnant women. Recent

publications have highlighted that of six affected pregnant women, four died; the two survivors experienced spontaneous abortions.[15] Moreover, recent postmortem studies done on pregnant women suggest diffuse systemic dissemination of the H5N1 virus (in contrast with yearly influenza strains causing only local respiratory tract infection), including infection in the fetal-placental membranes. These reports reinforce the idea that both the mother and the fetus will likely have significant vulnerabilities from this aggressive influenza virus and that a population-specific planning approach is needed.

VULNERABILITY AS MORE THAN THE PHYSIOLOGIC CHANGES OF PREGNANCY

The prioritization of pregnant women during an impending pandemic is being acknowledged at local and national levels.[16] Although pregnant women are recognized as a priority group, many public health emergency plans have not made concessions for the ethical and practical challenges of caring for this population. Pregnancy is a special and ever-changing state in which the health of the woman and that of the fetus are intertwined in unique ways. As a result, the state of pregnancy evokes an important set of considerations about reproduction and motherhood into health care discussions that do not arise in other fields of medicine. Most notably, disagreement exists about if, how, and when the autonomous choices of a pregnant woman to decline or accept medical intervention should be superseded for the perceived interests of the fetus.[17] Historical precedent fosters real concern for the potential of a woman's interests and rights to become inappropriately diminished during pregnancy. Documented cases describe the ways in which competent pregnant patients' informed decisions to decline invasive interventions have been overridden by medical and legal establishments.[18] These types of provocative and complex issues cannot be overlooked.

Preparedness plans addressing the needs of pregnant women must also incorporate more than just the allocation strategies applicable for the general population. In addition to vulnerability resulting from physical changes of pregnancy, the gravid state introduces additional considerations about the medical management of the mother and fetus. If not addressed preemptively, these considerations could interfere with the execution of any mitigation plan. Because standard pandemic strategies have particularly relevant and weighty implications within the context of pregnancy, the generalization of existing management principles would not be an effective way to protect this population.

One of the frontline strategies for use in the general population is the distribution and use of antiviral agents. However, in the case of pregnancy, this management approach raises several important ethical and practical questions. The current influenza antiviral medications available for use are Food and Drug Administration (FDA) category C drugs.[19] This designation is given to medications whose effects in pregnant women either have not been studied in human trials or animal studies have revealed adverse effects on the fetus. In general, class C medications are used when the expected benefit to the mother or the fetus outweighs any potential risk that may occur with use. Currently, the two antivirals recommended for frontline use for H5N1 include oseltamivir (Tamiflu, F. Hoffman–La Roche Ltd, Basel, Switzerland) and zanamivir (Relenza, GlaxoSmithKline, London, England).[20] Animal studies have suggested that both drugs will likely cross the human placenta, and, in larger doses, have been shown to cause minor skeletal abnormalities in laboratory animals.[21,22] Much remains unknown about their use in pregnant humans. Label information for both agents discloses that well-designed clinical trials have not been performed among pregnant women.

Preparation for potential drug resistance should be included in any pandemic plan. Concerns about drug exposure are relevant given the propensity of influenza viruses to develop resistance to the available medications.[23,24] Resistance to amantadine (Symmetrel, Endo Pharmaceuticals, Chadds Ford, PA) and rimantadine (Flumadine, Forest Pharmaceuticals, St Louis, MO) have developed among seasonal influenza strains to such an extent that these drugs are no longer recommended for use.[23] Furthermore, there is no highly effective vaccine on the market for this specific H5N1 virus. If drug resistance to the available antivirals were to develop, rapid research, drug development, and population-level use of new antiviral medications or vaccines would be required in the midst of a pandemic. It is not unrealistic that experimental or newly developed antivirals and vaccines may be the only agents that are effective against a rapidly mutating form of the virus. In anticipation of this potentiality, the US Department of Health and Human Services has concluded that "state and local health departments should be prepared to distribute unlicensed antiviral drugs (if needed) under FDA's Investigational New Drug (IND) provisions."[20]

The clinical use of newly developed and investigational drugs among pregnant women raises a set of significant ethical issues. Although exceptions do exist, pregnant women are excluded from initial and some postmarketing stages of drug trials principally out of concern for the effects of the drug on the fetus. Consequently, many new drugs come to the market without robust safety and efficacy information for pregnant women and fetuses. This knowledge gap has important implications, because the physiological and anatomical changes that take place during pregnancy can result in unexpected and potentially harmful side effects for pregnant women and their fetuses.

The ethical challenges associated with the use of new or unlicensed pharmaceutical agents among pregnant women will quickly become an issue during a pandemic. Health care providers will be faced with operationalizing recommendations from public health officials for the use of

pharmacologic agents. Pregnant patients will then be faced with choices about the use of these agents, specifically, while weighing the benefits against the harms to themselves and their fetus by using (1) a conventional antiviral with uncertain maternal and fetal side effects and an uncertain efficacy profile, (2) an experimental agent that may be incompletely tested or untested with the hope of some benefit, or (3) no pharmaceutical agent. Currently, no literature is available about how patients will make these decisions or about how to facilitate adequate informed consent for this level of decision-making.

The potential for management disagreements between patients and providers should also be considered. It is important to acknowledge the possibility of scenarios in which a patient refuses recommended pharmaceutical intervention out of concern for her own health or the health of her fetus. Although many women are prepared to take on risks to their own health in the hope of benefit to the fetus, some may have competing interests outside the pregnancy—caring for living children, for example—that lead to refusal or acceptance of medical interventions.

Advance consideration of maternal–fetal issues can mitigate contentious conflicts and harms that could result from an inadequately prepared pandemic plan. For this reason, it is vital that policymakers and health care providers develop pandemic plans in consideration of the medical management challenges associated with antepartum care. These plans should include the development of an ethical framework and mechanisms for how and when to use investigational pharmaceuticals in pregnant women. In doing so, a balance must be struck between the compromise of individual liberties for the benefit of the greater community and the protection of a population that has already sacrificed a degree of personal autonomy during the time of pregnancy. Pandemic plans that do not fully consider the uniqueness of prenatal medicine could worsen existing ethically questionable practices.

ETHICAL CHALLENGES WITHIN THE HEALTH CARE INFRASTRUCTURE

Pregnancy introduces additional barriers to the use of pandemic strategies constructed for the general population. Local medical centers will have a vital role in the prevention of illness and death for all populations. Diversion strategies will be used to direct individuals to designated facilities for the management of existing medical problems or infection to prevent the exposure of one group to another and to limit viral transmission. This strategy will be problematic if used among the pregnant population without modification. The ongoing need to prevent puerperal complications, such as postpartum hemorrhage and fetal birth trauma, will continue to be a priority in the midst of a pandemic. Although some low-risk laboring patients may be sent to other skilled birthing facilities to deliver, emergent access to specialty, tertiary centers must be maintained because an intrapartum obstetric emergency can occur even in a low-risk pregnancy. High-risk obstetric conditions, such as preeclampsia, preterm labor, and intrauterine growth restriction, will continue to occur in the general, uninfected population, and these women will also require specialized medical care found at tertiary medical centers, including the use of tocolytics, antibiotics, fetal monitoring, early delivery, and intensive nursing care.[25] Access to these specialized medical centers will mean that both infected and uninfected patients may be sent the same health care facility. Policymakers must work to preemptively devise methods to deliver ethical and scientifically sound medical care in a way that meets the needs of all pregnant patients presenting for care.

The allocation of scarce resources within medical facilities designated for the care of pregnant patients must also be addressed. The challenges of finite medical equipment and personnel cannot be met simply by perceiving pregnant women as a single unit. In a limited resource allocation scheme, it is likely that not all members of this designation can be the first-line recipients of medical attention. Resources may have to be further allocated within this population to those who are obstetrically (1) high risk and not infected, (2) high risk and infected, (3) low risk and not infected, or (4) low risk and infected. The dilemma is that each cohort represents the same set of priorities in terms of value assigned to preserving the health of the mother and the fetus. Inadequate consideration of these challenges may result in harms during the time of the emergency and also well after the pandemic has passed, particularly if the mother is disabled in such a way that she cannot care for herself or her children or the future child manifests symptoms of an antepartum or intrapartum injury.

ADDITIONAL CHALLENGES FROM THE EVER-CHANGING STATE OF PREGNANCY

All of the previously mentioned ethical issues become increasingly complex when considered within the realities of pregnancy. Pregnancy is not a static state. Instead, it is a unique period in which the anatomy and physiology of the mother and fetus are constantly changing. In terms of the mother, each organ system undergoes adaptation to support the developing fetus.[25] Changes in the cardiopulmonary, endocrine, and renal systems become more pronounced with each trimester and during times of illness. In terms of the fetus, the impact of teratogens, such as infections and drugs, varies from trimester to trimester.[25] It is undeniable that changes throughout the antepartum period make the challenges of pandemic planning even more difficult to navigate.

Policymakers and health care providers should be prepared to face difficult questions about the triage of pregnant patients. Should there be intrapregnancy differences in triage and management of women according to the trimester of pregnancy? Is there more or less at stake in early pregnancy when

maternal physiology has not undergone significant change engendering the majority of risk to infectious agents yet the developing fetus is most vulnerable to teratogens? Do these considerations change in the later trimesters once maternal physiology is such that rapid decompensation from infection is more likely and the fetus has reached viability? Given the multidimensional complexity of these issues, it is necessary to address these complicated ethical questions proactively before the occurrence of an influenza pandemic.

CONCLUSIONS

Large-scale infectious disease outbreaks present the medical community with many challenges. A key question that the medical establishment must answer is how to effectively and ethically distribute existing limited resources. Multiple factors contribute to the uniquely vulnerable and complex characteristics of the pregnant population. The medical community's preparedness efforts will be optimized when this vulnerability is recognized and addressed through sound and ethical health policy. To do so, careful consideration must be given to the design of strategies for infection control and management.

Pregnant women do not represent the only segment of the population that requires special consideration in pandemic planning. However, they are an important population to consider individually. By preparing for the needs of this population, the health of mothers, children, and the general community can be better preserved. Additionally, the challenges that arise when considering pregnant patients during pandemic planning efforts illustrates the practical and ethical considerations needed to effectively address the unique health care needs of all other populations. ■

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