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COMMENTARY

The safety of maternal immunization

Annette K. Regan

Communicable Disease Control Directorate, Department of Health Western Australia, Perth, WA, Australia; Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Subiaco, WA, Australia

ABSTRACT

Maternal vaccination offers the opportunity to protect pregnant women and their infants against potentially serious disease. As both pregnant women and their newborns are vulnerable to severe illness, the potential public health impact of mass maternal vaccination programs is remarkable. Several high-income countries recommend seasonal influenza and acellular pertussis vaccines, and many developing countries recommend immunization against tetanus during pregnancy. There is a significant amount of literature supporting the safety of vaccination during pregnancy. As other vaccines are newly introduced for pregnant women, routine systems for monitoring vaccine safety in pregnant women are needed. To facilitate meta-analyses and comparison across systems and studies, future research and surveillance initiatives should utilize the same criteria for defining adverse events following immunization among pregnant women. At least 2 areas require further exploration: 1) identification of pregnancy outcomes associated with concomitant and closely spaced vaccines; 2) evaluation of possible improvement in birth outcomes associated with maternal vaccination. Given the public health impact of maternal vaccination, the existing evidence supporting the safety of vaccination during pregnancy should be used to reassure pregnant women and their providers and improve vaccine uptake in pregnancy.

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Maternal immunization is a public health strategy which has been shown to prevent potentially serious disease in both mothers and their infants. Maternal antibody transferred across the placenta can protect infants from infection during a time when they are most vulnerable to infection and too young to be immmunized.[1,2] Despite the potential benefits of maternal vaccination, many vaccines remain Category B drugs, as the safety and effectiveness are not established in pregnant women or nursing mothers as part of pre-licensure clinical trials. Package insert information warns providers that vaccination should only be given to pregnant women when clearly needed. This information undoubtedly contradicts the strong recommendation made by national and international health bodies and contributes to confusion among providers. Given that a provider recommendation is the strongest predictor of maternal vaccination[3] and concerns about vaccine safety are a common barrier among pregnant women,[4] well-designed safety monitoring with timely communication of results to providers and their pregnant patients is necessary for supporting antenatal and perinatal health.

Systems for monitoring the safety of maternal vaccination

Post-licensure vaccine safety monitoring allows for rapid identification of new adverse events as well as potential increases in known adverse events. Several methods are available to measure the post-licensure safety of vaccines given during pregnancy.

Pregnancy exposure registries collect and maintain post-licensure safety data on the effects of drugs and vaccines given during pregnancy or while breastfeeding.[5] Sanofi Pasteur®, GlaxoSmithKline®, CSL Biotherapies® (now Sequirus®), Merck & Co® and Novartis Vaccines and Diagnostics® each have maintained such a registry. These registries collect data on pregnancy outcomes and newborn health following vaccination. However, with the exception of reports of incidental administration,[6] few studies have been published using these data.

Passive systems, such as the Vaccine Adverse Event Reporting System (VAERS) have been used to monitor the post-licensure safety of vaccines given in the general population. These systems allow health providers, and in some cases, the public to submit reports of adverse events following immunization (AEFI) experienced. These systems are useful for monitoring vaccine safety across populations and for collecting information on post-vaccination events.[7] Active surveillance systems have also been implemented as a means of directly collecting select post-vaccination events from recently immunized pregnant women.[8,9] Systems for performing active surveillance typically enroll pregnant women at the time of vaccination and prospectively monitor them for a defined period of time. These systems are valuable in identifying the reactogenicity of vaccines and capturing pregnancy-specific outcomes in a large sample. A recent review of 47 countries indicated that all 30 countries with a national immunization policy targeting pregnant women had a passive vaccine safety surveillance system; however, only

CONTACT Annette K. Regan Annette.Regan@health.wa.gov.au Communicable Disease Control Directorate, Department of Health Western Australia, PO Box 8172, Perth Business Centre, Perth WA 6849, Australia.

11 (23%) of these countries had active surveillance systems to detect serious AEFI in pregnant women and few systems had published their findings.[10]

Observational studies can also provide important information on the occurrence of AEFI in pregnant women. For example, the Vaccine Safety Datalink (VSD), established in the 1990s, is a retrospective cohort which includes health data from 9 health care organizations, including over 9 million US individuals each year.[11] One of the initiatives of VSD included the establishment of a "pregnancy platform," a dataset used to monitor the safety of vaccines given in pregnancy. This dataset includes demographic information, birth information, vaccination records, hospital, emergency, and outpatient information, and other data. It also allows for the ability to conduct long-term follow-up of birth cohorts over multiple years.[11] Observational studies, such as the VSD, are useful, as they typically include large sample sizes and are better powered to identify less common AEFI. However, they are subject to certain biases, such as confounding and misclassification.

Current evidence supporting the safety of vaccines routinely recommended during pregnancy

Tetanus, acellular pertussis, and seasonal inactivated influenza vaccine (IIV) are routinely recommended for pregnant women in a number of countries.[10] During the 2009 influenza A/H1N1 pandemic, monovalent pandemic vaccine was also strongly recommended and made available for pregnant women. There are a growing number of published studies to support the safety of each of these vaccines.

Inactivated influenza vaccine

Post-licensure vaccine safety studies have demonstrated the safety of IIV administration during pregnancy to the mother, fetus and newborn.[12,13] Between 3–5% of women report pain or swelling at the injection site, and between 1–6% of pregnant women report a fever following seasonal influenza vaccination.[8,14,15] Where investigated, few medically-attended adverse events have been identified.[8,15] A number of studies have found no increase in pregnancy complications (e.g., gestational diabetes, pre-eclampsia, caesarean delivery,[16,17] chorioamnionitis)[18] or adverse birth outcomes, including preterm birth,[16,19,20] small for gestational age (SGA) births,[19-22] congenital anomalies and malformations,[16,23] spontaneous abortion,[24] or stillbirth.[25] Several studies have also shown no adverse effects following first trimester administration of vaccine.[21,23,26]

Following the expedited licensing of the pandemic influenza A/H1N1 vaccine and mass vaccination of pregnant women, several studies and surveillance initiatives were rapidly initiated.[9,27-30] Among 2.4 million pregnant women in the US vaccinated against 2009 influenza A/H1N1 between 2009 and 2010, 294 were associated with an adverse event report the VAERS system. Medical review of these reported events indicated there were no abnormal maternal or fetal outcomes associated with the administration of pandemic vaccine in pregnant women.[30] Similar to seasonal influenza vaccine, no adverse birth outcomes were observed following either adjuvanted or non-adjuvanted pandemic vaccination during pregnancy in prospective or retrospective cohort studies.[28,31-34]

Several studies have suggested there is a reduction in the risk or likelihood of adverse birth outcomes following IIV during pregnancy.[20,25,35] Previous cohort studies have shown seasonal influenza vaccination during pregnancy is associated with a 40-70% reduction in preterm birth, [20,23,36] SGA birth, [20] and stillbirth.[23,25] In addition to these observational studies, a randomized controlled trial in Bangladesh also showed a significant increase in the mean birth weight of infants born to vaccinated mothers compared to unvaccinated mothers and a lower proportion of infants of vaccinated mothers were born SGA.[35] Improvements in birth outcomes are thought to occur as a result of successful prevention of seasonal influenza infection during pregnancy. Two observational studies demonstrated the benefits of IIV given during pregnancy were most pronounced during or just following periods of widespread influenza activity in the community.[20,25]

Some researchers have argued these findings are due to potential uncontrolled bias.[37,38] However, the results of the randomized controlled trial from Bangladesh suggest this position is not necessarily true. Further investigation of the potential benefit to the fetus of IIV during pregnancy is needed.

Acellular pertussis vaccine

Following the introduction of antenatal pertussis vaccination programs in developed countries, published research has supported the safety of pertussis vaccination during pregnancy.[39-42] Between 1-11% of pregnant women report pain or swelling at the injection site, and between 2–3% of women report a fever following vaccination.[39,42,43] However, one prospective study reported as many as 79% of pregnant women experiencing pain or swelling at the injection site.[44] These variations may be due to differences in data collection methods.

Review of passive AEFI reporting system data have shown there is no concerning pattern with regards to maternal or fetal outcomes following pertussis vaccination during pregnancy.[41,43] Both randomized clinical trials and cohort studies also support the safety of pertussis vaccination in pregnancy, finding no increase in pregnancy complications,[42,45] preterm birth,[46,47] SGA birth,[46,47] low birthweight,[45,46,48] congenital anomalies,[46] spontaneous abortion,[46] or stillbirth.[45]

One cohort study identified a slight increase in chorioamnionitis following pertussis vaccination during pregnancy.[47] A subsequent review of the VAERS system for all reports of chorioamnionitis showed that the condition is uncommonly reported following vaccination during pregnancy and 58% of women who report chorioamnionitis had at least one risk factor predisposing them to the condition.[49] The authors concluded chorioamnionitis was unlikely to be causally linked with pertussis vaccination during pregnancy.

Some differences in the reactogenicity of pertussis-containing vaccines have been observed in comparison to IIV given during pregnancy. Observational studies have found significantly higher rates of pain or swelling at the injection site when compared to IIV,[50] and suggest co-administration with IIV was associated with a higher proportion of febrile events.[44] The authors suggested IIV could be more pyrogenic

in comparison to pertussis-containing vaccine; however, other studies in pregnant women do not support this.[50] While one study has shown the co-administration of IIV and pertussis-containing vaccines is safe to the fetus,[40] the safety of concomitant vaccination of pertussis vaccines with IIV should be further explored.

Current evidence evaluating the safety of vaccines not recommended during pregnancy

Varicella and measles-mumps-rubella (MMR) vaccines are contraindicated in pregnancy due to the theoretical risk of congenital infection from live virus. Previous studies of incidental administration of these vaccines have shown no aberrant pattern in AEFI reported. A review of VAERS data has shown there were no adverse events associated reports of incidental administration of MMR during pregnancy.[51] A review of the Pregnancy Registry for VARIVAX (Merck & Co®) following 362 pregnancies inadvertently exposed to varicella vaccine showed there was no case of congenital varicella syndrome and no abnormal features or birth defects in the infants.[6] A total of 30,139 pregnant women in 6 South American countries who were inadvertently administered rubella vaccine during a large elimination program were prospectively monitored. No congenital rubella syndrome was identified in the infants exposed to rubella vaccine in utero.[52] While these studies have demonstrated there were no unanticipated adverse outcomes following receipt of contraindicated vaccines, these studies are few and the theoretical risk of congenital infection following administration of live vaccines remains.

Recommendations for future research and surveillance of maternal vaccination

While a large body of evidence overwhelmingly supports the safety of maternal vaccination, there remain a few areas important for future research. Well-controlled, high quality randomized trial data are needed to appropriately determine whether there are true reductions in adverse birth outcomes following IIV in pregnancy. Such trials may be difficult to implement, particularly in countries where vaccination is standard of care, as randomized trials would not be ethical in such settings. Randomized controlled trials currently underway in Nepal, Mali, and South Africa plan to collect birth outcome information and may provide better evidence to address this issue.[53]

Few studies have been conducted evaluating concomitant or closely spaced doses in successive pregnancies. One study in Western Australia followed up a sample of 4,437 pregnant women who received both IIV and pertussis vaccine during their pregnancy.[50] This study also collected AEFI information for 70 women who had received a recent (e.g., within 5 year) dose of pertussis vaccine. While they observed no serious AEFI associated with concomitant vaccination, women with a history of recent pertussis vaccination reported local reactions twice more frequently than women with no history of recent pertussis vaccination.[50] This study included a small number of women with a recent history of pertussis vaccination and did not collect information on pregnancy outcome. Another observational study of 36,844 pregnancies in the US showed that acute adverse events were rare following concomitant vaccination and there was no difference in preterm delivery, low birth weight, or SGA births among women who received pertussis and seasonal influenza vaccine concomitantly.[40] These studies suggest concomitant vaccination is safe; however, additional research is needed, particularly with regards to pregnancy outcomes.

Several vaccines not routinely recommended during pregnancy have been listed as high priority for investigation for use in pregnancy. These including Group B Streptococcus (GBS) conjugate, *Haemophilus influenzae* type B (Hib) conjugate, Hib polysaccharide, meningococcal conjugate, pneumococcal conjugate and respiratory syncytial virus (RSV).[54] Current systems for monitoring routine vaccination in pregnancy would be useful in evaluating the safety of any newly recommended vaccines for pregnant women.

A number of surveillance and research platforms exist which can be used to routinely monitor the safety of any vaccine given during pregnancy. Future research and surveillance in this area should conform to consistent definitions of AEFI in pregnant women. In an effort to harmonize AEFI definitions for pregnant women globally, the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) was established by the Bill and Melinda Gates foundation.[55] This collaboration has established a set of consistent case definitions for measuring AEFI in pregnant women and created data collection tools for monitoring maternal vaccination programs. These tools and recommendations for AEFI measurement will allow for better comparison between studies and enable appropriate meta-analyses in future.

Future research and surveillance should consider background rates of adverse events (e.g., spontaneous abortion) when interpreting reports of post-vaccination events among pregnant women. Given a certain number of adverse events is expected in a population of pregnant women, it is possible to misinterpret temporally associated events as vaccine-causal.[56] It will be important to ensure causality is not inferred, as such misinterpretations may be harmful to vaccine confidence among pregnant women.

Conclusions

Maternal vaccination offers the unique opportunity to prevent vulnerable populations from potentially lethal disease, and existing research strongly supports the safety of maternal vaccination. Healthcare providers play a critical role in promoting maternal vaccination.[3] Women commonly cite concerns about the safety of vaccination to the fetus when refusing vaccination during pregnancy; results from studies evaluating adverse pregnancy outcomes should reassure pregnant patients that maternal vaccination is safe to the fetus. Healthcare providers may find results from studies measuring the reactogenicity of vaccination during pregnancy useful when communicating to pregnant women what to expect following vaccination. To support this potentially game-changing public health strategy, continued monitoring and communication of safety information to health care providers and their patients is critical.

Abbreviations

AEFI	Adverse events following immunization
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
SGA	Small for gestational age
MMR	Measles-mumps-rubella
RSV	Respiratory syncytial virus

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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