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VACCINES and PREGNANCY

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The concept of vaccination has been present for over two millennia. The fundamental process involves training the immune system to recognize and ward off a pathogen before it gains a significant foothold in the body. This is achieved through inoculation, a process which originated in India or China around 200 B.C. Inoculation is the purposeful exposure of the immune system to either a component of a pathogen or the pathogen in its entirety that has been rendered inactive, thereby inducing active immunity targeted against one or more pathogen-specific antigens. In many ways it is the ultimate form of "natural" or "homeopathic" medicine.

VACCINE PHYSIOLOGY and EPIDEMIOLOGY

Vaccines come in two broad categories: live-attenuated and inactivated. The latter includes use of either the whole organism that has been rendered inactive or various protein components (i.e., antigens). Live-attenuated vaccines are, as a rule, avoided during pregnancy due to concerns about uncontrolled infection and theoretical transplacental fetal infection. The intent of inoculation is to induce an immune response and memory that can then be employed during a future pathogenic exposure. A primary immune response involves the production of antibodies by activated B lymphocytes, and it takes roughly 7 days before meaningful quantities of antibody can be detected in serum. The initial IgM antibody that is generated has relatively low affinity, but it is rapidly replaced by higher-affinity IgG antibody. Because there must be specific HLA molecules present on lymphocyte and macrophage surfaces that recognize the antigens) used in vaccines, individuals who lack the genes that encode the necessary HLA molecules can experience a primary vaccine failure (i.e., a failed immunogenic response). Patients who have a failure to respond to vaccination are classified as "non-responders."

Although the obvious benefit of vaccination is to the immunized individual, when an adequate proportion of the general population is also immunized, the pathogen in question cannot then freely circulate among the remaining susceptible individuals. This additional societal benefit is referred to as "herd immunity". A classic example of the value of herd immunity comes from Japan. In the 1970s, Japan vaccinated almost 80% of its children against pertussis. In 1974, there were 393 cases of pertussis and zero deaths. Due to various concerns about pertussis vaccine safety and a perception of a lack of need, the vaccination rate fell to 10% of infants by 1976. This led to an explosion in pertussis cases, with over 13,000 individuals affected and 41 deaths occurring during a major outbreak in 1979. By achieving as high a rate of immunization as possible, those individuals who cannot receive vaccinations due to severe allergies, or simply experience primary vaccine failure (i.e., are non-responders), are protected. One potential endpoint of maximal vaccination is the outright elimination of a pathogen altogether, thereby obviating the need for future generations to be vaccinated against it. The prime example of this has been the elimination of the smallpox virus from the human species.

THIMEROSAL and VACCINES

Despite the undeniable and tremendous public health benefits that have been achieved through nationwide and worldwide vaccination programs, developing public concern regarding vaccine safety threatens to undermine the continued widespread acceptance of vaccinations. Much of the ongoing controversy centers around the use of thimerosal in vaccine preparations and its purported link to the development of childhood autism. Thimerosal is a preservative that contains ethylmercury and has been in use since the 1930s, primarily as an antibacterial agent for multi-dose preparations of a variety of vaccinations, including those for influenza A. Due to the increasing numbers of childhood vaccinations that are now recommended and the general awareness of mercury as a neurotoxin, a causal link between thimerosal and the rising rates of diagnosis of childhood autism has been asserted by a variety of non-scientific entities and subsequently been perpetuated in the lay press. Unfortunately, the medical and scientific establishment further encouraged this dubious link. In 1999 the U.S. Food and Drug Administration (FDA) issued a statement raising concern that the cumulative doses of ethylmercury from childhood vaccinations could exceed...

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safe limits that had been previously set for *methylmercury* consumption. The U.S. Public Health Service (USPHS) and the American Association of Pediatrics (AAP) subsequently issued a joint statement advocating that pharmaceutical companies should reduce or remove thimerosal from childhood vaccinations, despite a lack of evidence linking ethylmercury in vaccinations to either mercury toxicity in children or the rising rate of childhood autism diagnoses.

It is difficult to extrapolate concerns pertaining to methylmercury toxicity to thimerosal for the following reasons. First, ethylmercury has a much shorter half-life than methylmercury and is not actively transported across the blood-brain barrier, unlike methylmercury. Second, methylmercury toxicity has not been shown to cause autism, despite clinically sharing a few similarities with this disorder. Third, multiple sizable epidemiologic studies and systematic reviews have found no conclusive evidence that establishes a causal relationship between inoculations with thimerosal-preserved vaccines and the development of autism. Fourth, the amount of ethylmercury currently used in vaccines is significantly lower than the amount used in the 1930s and 1940s. However, the increase in the rate of diagnosis of autism and autism spectrum disorders has occurred despite the reduction in the amount of thimerosal per vaccine, as well as the overall availability of thimerosal-containing vaccines. In fact, the rate of increase in diagnosis has been greatest only over the past 15 – 20 years, while thimerosal has been in use for seventy years. Given all of these arguments, the World Health Organization has stated that it is safe to continue using thimerosal-containing vaccines, and the Institute of Medicine has rejected a causal relationship between thimerosal exposure and the development of autism. Despite the lack of scientific data, the USPHS and AAP joint statement of potential risk has unnecessarily frightened parents and patients. Given the very real threat posed by a variety of infections to pregnant mothers' well-being, the theoretical risks posed by thimerosal should not prevent administration of thimerosal-containing vaccinations to this high risk group of patients.

While immunizations are important for all people to receive, pregnant patients and newborns are particularly vulnerable to several kinds of infections. The following is a partial review of recommendations pertaining to those infections. While there are a great number of available vaccines, and since particular patients may have needs beyond what is covered below, additional resources are recommended for review. These include a variety of American College of Obstetrics and Gynecology (ACOG) documents pertaining to pregnancy and vaccinations, as well as the Centers for Disease Control (CDC) website.

PANDEMIC H1N1 INFLUENZA AND SEASONAL INFLUENZA

Of particular importance this year is immunization against pandemic H1N1 influenza A virus, which was referred to early on as "swine flu" due to 6 of its 8 gene segments being similar to those seen in prior swine influenza viruses from pigs. The actual genetic make-up of this H1N1 virus is a quadruple reassortment of 2 swine strains, one human strain, and one avian strain of influenza. It is believed that a descendent strain virus from the 1918 influenza pandemic contributed genetic material to the current H1N1 virus. Risk factors for severe complications include chronic respiratory illnesses (e.g., asthma, COPD), immunosuppressive states, cardiac disease, pregnancy (including patients who are up to 2 weeks postpartum as well as those who have had a pregnancy loss), diabetes mellitus, and obesity. Pregnant women infected with this virus have a higher than expected mortality rate; indeed, 6% of deaths from H1N1 virus in the U.S. have occurred in pregnant patients, while at any given time only 1% of the population is pregnant. Increased morbidity includes a higher risk of respiratory failure, ARDS, pneumonia, spontaneous abortion, preterm labor and premature rupture of membranes. Inactivated H1N1 vaccine is now available for pregnant patients, and its administration to pregnant patients as well as parents of infants less than 6 months of age is strongly recommended by the CDC and other international medical organizations. A single dose appears to be highly effective at generating an appropriate immune response as measured by the antibody titer generated. Pregnant woman are also strongly recommended to receive the seasonal influenza vaccine as well.

PERTUSSIS

Consideration needs to be given to administration of the Tdap vaccine, especially in the postpartum period. Adults who develop pertussis can transmit the infection to neonates who have considerable risk of morbidity and mortality from this disease. Greater than 50% of infants with pertussis contract the infection from their parents, and primarily from their mothers. Booster vaccination of mothers and primary care providers is recommended to prevent infection in infants by removing an adult reservoir of infection. Immunizing individuals of all ages could prevent 3000 to 15,000 cases among infants less than 1 year of age and could save billions of dollars in treatment costs. By containing lower amounts of the diphtheria and pertussis components, Tdap vaccines have fewer side

Vaccines and pregnancy continued...

effects (fever, headaches, fatigue, and pain) in adults than DTaP vaccines and are the pertussis vaccine of choice in the adult population. Details on the CDC's Advisory Committee on Immunization Practices (ACIP) recommendations, which have been endorsed by the Committee on Obstetric Practice of the ACOG, can be found elsewhere (Murphy, et al., *MMWR* 2008; 57:1; ACOG Committee Opinion No. 438, *Obstet Gynecol* 2009; 114:398). These recommendations depend upon whether a woman has been immunized in the past or not, and if she has, whether that immunization occurred less than or greater than 10 years ago.

If not previously vaccinated with Tdap, one dose should be administered to new mothers in the immediate postpartum period.

Currently, there is limited safety information for the use of Tdap vaccination during pregnancy. If vaccination is required in pregnancy, Td alone is preferable to Tdap, with Tdap administration held until the postpartum period. If not previously vaccinated with Tdap, one dose should be administered to new mothers in the immediate postpartum period. Healthcare workers are also at risk for being exposed to pertussis in inpatient and outpatient settings. Infected workers can then expose at-risk neonates, children, and adults. Tdap vaccination in adult healthcare workers has been shown to be effective in controlling nosocomial outbreaks of pertussis. Thus, obstetrical care providers should seek to remain up-to-date on their Tdap vaccinations as well.

RUBELLA

The MMR vaccine should be administered in the postpartum period to women found not to be immune to rubella on their initial prenatal laboratory assessment. If a woman tests rubella "non-immune," but has received two doses of the MMR vaccine in the past, then repeat vaccination is not recommended. However, if she has received only one dose of the vaccine and had a failed response, then it is worth repeating a vaccination. MMR vaccination is contraindicated within 3 months of conception and during pregnancy as it contains live-attenuated virus. The theoretical risk for congenital rubella syndrome (CRS) with inadvertent administration of the MMR vaccine has been calculated by the CDC to range from 0 to 1.2%. However, there have been no reported cases of CRS among patients who have received this vaccine during pregnancy. As a result, inadvertent vaccination should not be considered an indication for pregnancy termination.

STREPTOCOCCAL PNEUMONIA

Pregnant patients who have an increased risk of invasive pneumococcal disease should receive the pneumococcal vaccine. Per CDC guidelines this includes patient with chronic cardiovascular disease, chronic pulmonary disease (including asthma), diabetes mellitus, as well as those with HIV infection, malignancy, chronic renal disease, nephrotic syndrome, congenital immunodeficiency, surgical or acquired asplenia (e.g., sickle cell anemia), and those receiving immunosuppressive chemotherapy. The safety profile of pneumovax is unclear with first trimester immunization, and thus vaccination is best reserved for the second or third trimesters.

VARICELLA

At the time of the initial prenatal visit pregnant patients should be screened for varicella susceptibility. Traditionally, if patients recall having had a chicken pox infection in the past they do not require antibody confirmation of immunity. However, if a patient does not recall having a past infection, she should undergo varicella IgG testing to determine her immunity. If she is found to be non-immune, then appropriate behavioral precautions should be provided to the patient. More recently, due to recommendation for universal varicella vaccination in newborns, a new generation of individuals reaching childbearing age will soon not have had chicken pox infection in their medical histories. There are no current guidelines as to whether to screen these patients for confirmation of their immunity during the initial prenatal visit, but it certainly could be considered.

Since the varicella vaccination contains live-attenuated virus, non-immune patients should receive the vaccination in the postpartum period. Inadvertent administration of the varicella vaccine within 3 months of conception or in the first trimester has not been shown to cause congenital varicella syndrome, and thus is a theoretical risk only. Thus, inadvertent vaccination should not be considered an indication for pregnancy termination. However, such an administration should be reported to the Varivax Pregnancy Registry (800-986-8999) so that further data can be collected regarding varicella vaccine safety. Overall, vaccination programs have successfully reduced a great deal of maternal and neonatal morbidity and mortality. Obstetrical health care providers ought to be familiar with relevant recommendations as well as the appropriate use of a variety of vaccines in their patients, both during and after pregnancy.

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Dr. Pandipati was born in India. His family moved to the United States when he was three, and eventually settled in Maryland. He received both his bachelor's degree in biomedical sciences and his medical training from the University of Michigan in Ann Arbor. After medical school, he completed a residency in obstetrics and gynecology at the University of Washington Medical Center in Seattle. He subsequently did his fellowship in maternal-fetal medicine at the University of Colorado Health Sciences Center in Denver. Dr. Pandipati has received many honors during his medical training, including election to Alpha Omega Alpha and Best Teaching Resident. He is board certified in obstetrics and gynecology, and in maternal-fetal medicine.

Dr. Pandipati loves maternal-fetal medicine for the blend of medical, surgical, and radiologic practice it affords. He enjoys the challenge of providing skillful and compassionate care for both mother and fetus. His specific clinical interests include intrauterine growth restriction, hypertensive disorders of pregnancy, critical care obstetrics, and Doppler ultrasound.

Away from work, Dr. Pandipati enjoys spending time with his wife and two daughters, as well as experimenting with cooking, exercising, philosophizing, and taking his beloved golden retriever on long walks.

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