Safety of Immunization during Pregnancy

A review of the evidence

Global Advisory Committee
on Vaccine Safety

World Health Organization

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1. Introduction

Vaccine-preventable infectious diseases are responsible for significant maternal, neonatal, and young infant morbidity and mortality. Changes in the immune response in pregnant women – which are thought to occur in order to allow the woman to tolerate the semi-allogeneic foetus – may interfere with the development of the specific immune response to pathogens. These immunological changes may alter the susceptibility of the woman and the foetus to certain infectious diseases (1) and increase the risk of more serious outcomes. The immature adaptive immune systems of neonates and premature infants make them particularly vulnerable to morbidity and mortality due to infection.
Immunization of pregnant women can protect them directly against vaccine-preventable infections, and in so doing potentially protect the foetus. It can also directly protect the foetus and infant via specific antibodies transferred from the mother during the pregnancy.

At its meeting in November 2011, the Strategic Advisory Group of Experts (SAGE) of WHO asked the Global Advisory Committee on Vaccine Safety (GACVS) to provide support to a review of evidence on the safety of vaccinations in pregnant and lactating women. This request related to uncertainties about the safety of vaccination – whether intended or inadvertent – of pregnant women during mass vaccination campaigns. Such evidence would be particularly important in situations where manufacturers do not recommend the vaccination of pregnant women on solely precautionary grounds. However, evidence related to this issue is limited, as pre-licensing clinical trials of vaccines do not usually include pregnant and lactating women. Reports available also provide limited post-licensing data, as once again, pregnant women are usually not included in clinical trials. This in turn has limited the ability to make evidence-based decisions and provide optimal guidance on the use of vaccines in this population.

2. Methodology

This report presents an overview of the relevant literature on the safety of vaccination of pregnant women. In addition to reviewing the published literature, GACVS contacted regulatory authorities and pharmaceutical companies to obtain results of ongoing surveillance programmes for pertussis-containing and meningococcal vaccines in pregnant women. The cut-off point for the literature review was May 2013.

The availability and amount of data were assessed, as well as their overall quality in terms of consistency, strengths, and weaknesses. The conclusions are based on expert discussion and consensus rather than on a systematic review and grading system. This report focuses on vaccines that are currently available, with priority for review given to vaccines on the basis of two key criteria:

- their potential to reduce morbidity in the pregnant woman and/or her fetus; and
- their use (or anticipated use) in vaccination campaigns targeting pregnant women as well as vaccination campaigns where pregnant women may be inadvertently vaccinated.

Once the specific vaccines for review had been selected, a standard framework was developed which addressed the following issues:

- the demonstrated or potential benefit of vaccination during pregnancy; this included evidence of disease morbidity in pregnant women and foetuses, and of the efficacy or effectiveness of the vaccine in pregnant women;
- evidence of safety of vaccination or lack of evidence of adverse pregnancy outcomes; data from clinical trials, observational studies, published case reports, case series and passive surveillance systems were assessed, as were theoretical considerations and experimental data relating to potential harm to the fetus and the mother (e.g. type of vaccine, ability of the vaccine strain to cross the placenta, risk of infection related to gestational age).

The pregnancy outcomes considered included maternal morbidity and mortality, miscarriage/stillbirth, prematurity, small size for gestational age, and congenital anomalies. The results are reported in the form of a summary of available relevant literature and an outline of methodological issues to be considered when planning clinical trials and post-marketing safety studies of vaccines in pregnant women. Recommendations for further investigations are made. The aim of this review is to guide the standardization of both the process of policy formulation and the format for recommendations for pregnant women.

3. Vaccines reviewed

3.1 Inactivated vaccines

Immunization with inactivated vaccines or toxoids during pregnancy is not expected to be associated with any increased risk to the foetus. Inactivated vaccines with novel adjuvants, however, may need to be considered and evaluated on a case-by-case basis as there is more limited experience related to those products. Safety data from vaccinated pregnant women were reviewed for seasonal trivalent inactivated influenza vaccines, H1N1 monovalent pandemic vaccines for 2009–2010, tetanus toxoid vaccines and conjugated meningococcal vaccines.

3.1.1 Non-adjuvanted inactivated trivalent seasonal and monovalent pandemic influenza vaccines

Several publications have summarized the evidence of the risks of maternal influenza disease, particularly in the second and third trimester, and the safety and effectiveness of immunization with inactivated influenza vaccines (2–5). Pregnant women are at increased risk of severe complications, their fetus of small for gestational age and preterm birth, both are at increased risk of mortality. There is widespread recognition that seasonal influenza disease is more severe in pregnant women with an underlying medical condition (6). The increased severity of disease in pregnant women infected with the 2009 pandemic influenza strain has also been widely documented, with rates of serious adverse outcomes similar to, or higher than, those of any other risk group studied, including the very young and very old (4, 7).

Increased fetal risks associated with maternal influenza infection have also been documented for nearly a century following well-described pandemics (2, 8–14). Specific effects of maternal influenza disease include fetal death due to maternal morbidity or premature onset of labour (15–17), as well as decreased birth weights or an increased proportion of infants born small for gestational age (11–13, 18).

The benefits of influenza vaccination to the mother and newborn, particularly if given in the second or third trimester, have been demonstrated for both seasonal influenza and influenza pandemics. In recognition of these benefits, national immunization policies in countries throughout the world incorporate influenza vaccination for pregnant women. Adequate immunological responses to inactivated influenza vaccines during pregnancy and the efficient transplacental transfer of antibodies have been demonstrated in several studies. One randomized controlled trial (RCT) and several non-randomized studies have also shown the effectiveness of seasonal inactivated influenza vaccination in pregnancy against morbidity in pregnant women and laboratory-confirmed infection in their neonates (2, 19–21). Immunogenicity studies of the 2009 pandemic influenza vaccine and documented transplacental transfer of antibodies provide indirect evidence of protection against illness in mothers and their infants (22).

Prospective trials, retrospective database assessments, post-marketing passive reporting systems, and pregnancy registries provide substantial data on the safety of non-adjuvanted inactivated influenza vaccines administered to pregnant women over many decades. For instance, from 1990 to 2009 the Vaccine Adverse Event Reporting System (VAERS) database in the United States of America reported only 20 serious adverse events following administration of trivalent influenza vaccine (TIV) to an estimated 11.8 million pregnant women (23). Studies have not found new, unusual, or unexpected patterns of serious acute events, adverse pregnancy outcomes, or congenital anomalies (2, 24–30). For example, an early study by Heinonen (24), which evaluated children born to nearly 2300 women who had received influenza vaccine during pregnancy, documented only one malignancy during the first year of life; this is comparable to expected background rates (30). A recent review by Tamma et al. (28) included ten observational studies and two RCTs that reported safety outcomes for the mother and fetus. Among over 4400 women given inactivated influenza vaccine at all stages of pregnancy, no harmful effects were identified. Ten studies in this review addressed fetal health, and identified no increase in adverse birth outcomes or congenital fetal anomalies over reported background rates. Bednarczyk and colleagues' more recent review (30) of the effects of maternal influenza immunization on the fetus included several additional studies and confirmed no increase in poor pregnancy outcomes or congenital anomalies among children born to vaccinated mothers. Similarly, the passive vaccine safety reporting system in the USA (23, 31) has noted very few fetal health complications associated with influenza vaccine, with a reporting rate of one spontaneous abortion per 1.9 million pregnant women vaccinated (23). During the 2009–2010 influenza A (H1N1) vaccination programme, clinical trials were conducted and several monitoring systems were established or enhanced to assess whether adverse events were associated with the monovalent vaccines. These evaluations did not identify any safety concerns in vaccinated pregnant women or in their infants (22, 23, 30, 32–35), even when higher doses of vaccine were given (36).

Reports to VAERS following administration of H1N1 influenza vaccines were also studied (23, 30). As with the seasonal influenza vaccine, there did not appear to be an increase over expected levels of spontaneous abortion and stillbirths (the most commonly reported outcomes).

Conclusion

Pregnant women and infants suffer disproportionately from severe outcomes of influenza. The effectiveness of influenza vaccine in pregnant women has been demonstrated, with transfer of maternally derived antibodies to the infant providing additional protection. The excellent and robust safety profile of multiple inactivated influenza vaccine preparations over many decades, and the potential complications of influenza disease during pregnancy, support WHO recommendations that pregnant women should be vaccinated. Ongoing clinical studies of the effectiveness, safety, and benefits of influenza vaccination in pregnant women in diverse settings

will provide additional data that will aid countries in assessing influenza vaccine use for their own populations.

3.1.2 Adjuvanted influenza vaccines

Newer influenza vaccine formulations that contain oil-in-water adjuvants have been approved for seasonal and pandemic use in many countries. One such adjuvant produced by Novartis, MF59, has been evaluated for reproductive and developmental toxicity in animals, both alone and when formulated with an H5N1 vaccine; there was no evidence of teratogenicity or impact on fetal or early perinatal development (37, 38). Results from three studies of MF59-adjuvanted vaccines in pregnancy are available. Using the Novartis vaccines pregnancy database, Tsai and colleagues(37) found no difference in outcomes after reported exposure to MF59-adjuvanted influenza vaccines (43 pregnancies) and after exposure to non-adjuvanted influenza vaccines (60 pregnancies). A cohort study of 2295 pregnant women who received influenza A (H1N1) vaccine adjuvanted with MF59 found no differences in pregnancy outcomes from those in women who were not vaccinated, other than fewer premature births among the vaccinated women (adjusted proportional hazard, 0.69; 95% confidence interval (CI), 0.51–0.92). No differences were observed in rates of congenital anomalies after vaccination in the first (2.1%), second (2.7%), or third (2.1%) trimesters (38). Finally, a multicentre study of MF59-adjuvanted influenza vaccine in 7293 vaccinated women in Argentina suggested no difference in pregnancy outcomes (39).

Another H1N1 pandemic vaccine adjuvanted with the oil-in-water emulsion AS03 was produced by GlaxoSmithKline. The effectiveness of the vaccine against H1N1 pandemic influenza in pregnant women in the second and third trimesters was demonstrated in a large cohort study in Norway (14). In a small study in the United Kingdom, 77 pregnant women received AS03 adjuvanted vaccine in the second or third trimester; three-quarters of the newborn infants were found to have passive immunity at titres consistent with clinical protection, as a result of transplacental transfer (40).

Also in the United Kingdom, a post-authorization safety study of 267 pregnant women who received an AS03-adjuvanted monovalent H1N1 influenza vaccine noted that pregnancy outcomes were in line with expected rates (41). In a separate safety surveillance study in Scotland, 117 pregnant women received an AS03-adjuvanted H1N1 influenza vaccine. No differences in birth outcomes were seen between vaccinated and unvaccinated women (35). A Danish cohort study, of nearly 7000 pregnant women, did not find an association between exposure to an AS03-adjuvanted H1N1 monovalent vaccine during pregnancy and adverse pregnancy outcomes (42). The study also provided preliminary evidence that excluded a high risk of adverse pregnancy outcomes in 345 women vaccinated in the first trimester because of pre-existing chronic diseases. A second study in the Danish cohort also found no evidence of an increased risk of fetal death associated with exposure to the vaccine in pregnancy (43). In the United

Kingdom, 9445 women who were vaccinated before or during pregnancy, mostly with AS03-adjuvanted H1N1 pandemic vaccine, were compared with 30 218 unvaccinated pregnant women (44): there appeared to be no increase in the risk of fetal death. These data are in line with those from the large cohort study in Norway, which found no association between AS03-adjuvanted H1N1 vaccine and increased fetal mortality (14). Finally, data from the Swedish Medical Birth Register were used to evaluate the association between AS03-adjuvanted H1N1 vaccine and pregnancy outcomes, such as stillbirth, congenital anomalies, preterm birth, low birth weight, and small for gestational age (45). A total of 18 612 vaccinated women who delivered 18 844 infants were studied. Consistent with the other studies, the risks of stillbirth, preterm birth, and low birth weight were lower than in the comparison groups, and the risks of small for gestational age and congenital anomalies (after vaccination during the first trimester) did not differ from those in the comparison groups.

Conclusion

The data on vaccination during pregnancy with oil-in-water adjuvanted H1N1 vaccines indicate no adverse effects on pregnancy outcomes. However, the data are largely confined to monovalent H1N1 vaccines.

3.1.3 Meningococcal vaccines

Each year, 450 million people in the so-called "meningitis belt" of sub-Saharan Africa are at risk of death and disability from epidemic meningitis caused by serogroup A Neisseria meningitidis. A number of different polysaccharide and conjugate (mono and combined) meningococcal vaccines are available and administered to populations worldwide, including women of childbearing age.

A systematic literature search (46) conducted in 2011 identified six small studies (three prospective RCTs, one prospective cohort study and two retrospective studies). A total of 335 pregnant women received bivalent (A, C) or tetravalent (A, C, Y, W-135) polysaccharide meningococcal vaccine. The main focus of the studies was placental transfer of meningococcal antibodies and antibody titres in the infants, not pregnancy outcomes; however, no safety concerns were identified (46–49).

Between 2010 and 2011, the first conjugate serogroup A meningococcal vaccine (PsA-TT) developed solely for Africa was introduced in Burkina Faso, Mali, and Niger during mass campaigns. The vaccine is indicated for persons aged 1–29 years. National post-marketing enhanced passive surveillance was conducted during a vaccination campaign in Burkina Faso. Reports of adverse events following immunization (AEFIs) were collected up to 42 days after the end of the mass campaign using standardized forms (50). Overall reporting rates for any AEFI were higher than for previous vaccine introductions (12.8 per 100 000 vaccines given compared with 5.9 per 100 000 in the previous mass campaign with polysaccharide vaccine); however, very few serious AEFIs were noted. There were no reports of harmful effects on the women or their birth outcomes.

Conjugated meningococcal C vaccines and tetravalent conjugated meningococcal vaccines have been used in the United Kingdom and the United States of America in adolescents and young adults. Inadvertent vaccination during pregnancy can thus occur. A recent review of 103 reports to the US VAERs system after inadvertent administration of MenACWY-D conjugate vaccine in pregnancy found no signals suggesting harm in comparison with the proportion of adverse pregnancy outcomes or congenital anomalies after administration of inactivated trivalent influenza vaccine in pregnancy (51). Pregnancy registries have been established and are currently active for some of the vaccines.

Conclusion

Existing evidence is limited and is derived mostly from passive surveillance data for conjugated meningococcal vaccines and small studies of bi- and tetravalent polysaccharide meningococcal vaccines. The available data suggest that vaccination of pregnant women is safe and is not associated with increased risk of adverse pregnancy outcomes. However, the low statistical power of the studies, lack of sufficient follow-up of infants, and the known limitations of passive surveillance data need to be considered. Further active surveillance is warranted.

3.1.4 Tetanus toxoid vaccines

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by Clostridium tetani. Neonatal tetanus may occur in neonates who have low levels of anti-tetanus antibody due to a lack of passively transferred maternal antibody. Therefore, tetanus toxoid (TT) vaccines are recommended for use in pregnancy, particularly in developing countries, where elimination of maternal and neonatal tetanus (defined as less than one case of neonatal tetanus per 1000 live births in every district) remains a goal. WHO estimates that there were 59 000 neonatal tetanus deaths in 2008, a 92% reduction from the late 1980s and an indicator of how widely maternal TT immunization is being used. While 34 countries had still not eliminated maternal and neonatal tetanus by February 2012, TT vaccination coverage during the antenatal period has been increasing in developing countries, reaching over 95% in some countries. It is estimated that at least 100 million doses of TT vaccine were given to pregnant women in 2011 (compared with 64 million women between 1995 and 2004).

The effectiveness of TT vaccination of pregnant women in preventing neonatal tetanus deaths is well established (52). A WHO position paper on tetanus (53), published in 2006, suggested that three doses of diphtheria-tetanus-pertussis (DTP) vaccine should be given in infancy, with boosters in childhood and adolescence and a sixth dose at first pregnancy If a good immunization history is not available, pregnant women should receive two doses of vaccine four weeks apart and at least two weeks before delivery. This recommendation has resulted in widespread use of the vaccine in pregnancy, particularly in developing countries.

Preclinical and clinical studies have investigated the safety of TT vaccines in pregnancy. In an animal study on the reproductive effects of TT vaccine, a decrease in fecundity was found to be related to the adjuvant and not the vaccine (53). The first small safety study of TT in pregnancy was published in 1956 by Freda (54). Pregnant women exposed to TT were compared with non-exposed pregnant women. The frequency of complications was the same in both groups. A larger study conducted by Heinonen et al. (25) found no evidence of an increased standardized relative risk (SRR) for major and minor malformations in 337 children exposed to TT during the first 4 months of pregnancy. A study using a single-dose high-potency vaccine in women undergoing a first pregnancy identified no risk to mother or infant (55), while a Hungarian study detected no association between TT immunization and congenital anomalies (56). Similar results were reported in a hospital-based case-control study of nearly 70 000 mothers in South America (57): analysis of the ten most frequent major malformations did not find any difference between TT-exposed and non- exposed pregnancies. In a comparison of diphtheria toxoid and TT in pregnant women, no differences were found in local or systemic side-effects (58). A search of the VAERS database for 2005–2010 did not identify any concerns about maternal, infant, and foetal outcomes following vaccination with a reduced amount of diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine (dTap) (59). Recently, vaccination with dTap combined with inactivated poliovirus vaccine (IPV) has been recommended for pregnant women in the United Kingdom to protect their newborn infants against pertussis (https://www.gov.uk/goverment/publications/whooping-cough-vaccination-programme-for -pregnant-women). Results of a large safety study are awaited.

In the USA, moderate to severe local reactions have been associated with high levels of tetanus and diphtheria antitoxin when tetanus toxoid was administered with a reduced amount of diphtheria toxoid. However, because of the potential benefits of maternal pertussis immunization and the lack of monovalent acellular pertussis vaccine, the Advisory Committee on Immunization Practices (ACIP) has recently recommended that pregnant women receive Tdap boosters during each pregnancy (60). The American Congress of Obstetricians and Gynaecologists also recommends giving diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine to pregnant women (61).

Conclusion

Although data from high quality studies are currently limited, widespread use of TT-containing vaccines in many countries has not produced any signal of possible harm to pregnant women or their foetuses. The safety of widespread tetanus toxoid vaccine use over the past 40 years, as well as the substantial decrease in neonatal tetanus and increase in neonatal survival, supports vaccine use.

3.2 Live attenuated vaccines

Theoretically, live attenuated virus vaccines given to pregnant women might be capable of crossing the placenta and infecting the foetus. As a result, most live attenuated vaccines are contraindicated or not recommended during pregnancy. However, because live attenuated viral vaccines are used in mass vaccination campaigns, inadvertent vaccination of pregnant women has been documented.

3.2.1 Rubella mono and combined live attenuated vaccines

Rubella vaccine, containing a live attenuated virus, has been licensed for general use since the late 1960s. The vaccine may be given alone or, more commonly, in combination with measles and mumps vaccines (MMR). Rubella infection in a susceptible (non-immune) woman during the months of pregnancy can lead to congenital rubella syndrome (CRS) in the neonate. The occurrence of congenital anomalies is as high as 85% if maternal infection occurs during the first 12 weeks of gestation, 54% if infection occurs during weeks 13–16, and 25% if infection occurs at the end of the second trimester.
Since the introduction of vaccination in the late 1960s, the incidence of rubella and CRS has decreased dramatically and large-scale epidemics of rubella no longer occur in immunized populations.

The incidence of CRS following inadvertent vaccination of pregnant women has been evaluated through rubella registries in the USA and Europe (e.g. Germany, Sweden and United Kingdom), a prospective controlled study in Canada and surveillance for cases during mass vaccination campaigns in Latin America and the Islamic Republic of Iran (62–69). The combined data from the registries were reviewed by the United States ACIP (70). Among 680 live births to rubella-susceptible women, none of the infants was found to have CRS. The same was true in a smaller prospective controlled study of 94 women in Canada who had received rubella or MMR vaccination in early pregnancy or up to 3 months prior to conception (62).

The incidence of CRS and asymptomatic congenital rubella infection was also evaluated in the setting of large mass vaccination campaigns in Latin America and the Islamic Republic of Iran (mostly with measles and rubella (MR) vaccines) (68, 71). In these settings, cord blood from rubella-susceptible women who had been inadvertently vaccinated was tested for antirubella immunoglobulin M (IgM) as an indicator of maternal–fetal rubella transmission. If the serological test was positive, the infants were evaluated for clinical signs of CRS. In Latin America, 2894 women who were rubella-susceptible, as indicated by serum IgG and IgM titres, and who became pregnant up to one month after receiving rubella vaccination were identified; 1980 of these pregnancies resulted in a live birth. Cord blood serum was positive for anti-rubella IgM in 70 cases (3.5%). None of the infants showed signs or features of CRS. On the basis of these data, a maximum theoretical risk for CRS of 0.2% was estimated following inadvertent vaccination with rubella vaccine during pregnancy. In the Islamic Republic of Iran, a study identified 117

rubella-susceptible women who had been inadvertently vaccinated during pregnancy. All had normal pregnancies and deliveries, without evidence of CRS over a 6-month follow-up period. Cord blood from 35 subjects was tested for anti-rubella IgM and two (5.7%) were positive. These data are consistent with those in the above-mentioned studies in Latin America (71).

In several studies, rubella vaccine-like virus has been isolated from the products of conception, obtained from women who had been inadvertently vaccinated with rubella vaccine during pregnancy and subsequently experienced a spontaneous or induced abortion (73–77). In these case reports or case series, published in the 1970s, a presumptive identification of vaccine strain, as opposed to wild-type rubella virus, was made by comparing the growth characteristics of the isolate with those of reference strains in cell culture. Definitive identification of vaccine-strain virus was not possible because of a lack of appropriate available technologies at that time. Vertical transmission of the vaccine virus determined by nucleotide sequence analysis from the susceptible mother to foetus was demonstrated in 2000 (72). The infection of the foetus did not result in a congenital defect.

In contrast to rubella and mumps, measles wild virus has not been shown to cross the placenta and infect the fetus. No teratogenic effects have been associated with measles or mumps virus infection during pregnancy (78). Measles infection in pregnancy is associated with an increased risk of severe pregnancy outcomes, such as prematurity and miscarriage (78).

No studies have been conducted on the pregnancy outcomes of susceptible women who were vaccinated with measles- or mumps-containing vaccines. The observational studies in Latin America, the Islamic Republic of Iran and Canada, as well as the case series in the USA and several European countries in which MR or MMR vaccines were used, may provide some indirect evidence of the safety of these vaccines for pregnant women.

Data from spontaneous reporting of MMR exposure prior to conception and during pregnancy do not indicate an increased risk of congenital malformation or spontaneous abortion, but there is not sufficient information to exclude such a risk.

Conclusion

The attenuated rubella and mumps viruses can cross the placenta and infect the fetus (72, 78). Fetal damage has not been documented when measles or mumps vaccines have been given to pregnant women. Although more than 3500 susceptible women have been inadvertently vaccinated against rubella shortly before or in the early stages of pregnancy, no cases of CRS had been reported by the end of 2012. Thus, available data from observational studies, case series, and spontaneous reports in passive surveillance systems do not demonstrate

a teratogenic risk of rubella vaccination in pregnant women. However, there is evidence of asymptomatic congenital rubella infection from both cord blood anti-rubella IgM testing and reverse transcription polymerase chain reaction (RT-PCR) testing (72).

MMR vaccines are usually contraindicated in pregnant women because they are live attenuated vaccines, although this is a purely precautionary measure. Inadvertent administration of MMR vaccines is not considered an indication for termination of the pregnancy, as there is no evidence of harm to the fetus.

3.2.2 Oral poliovirus vaccines

Oral poliovirus vaccine (OPV), containing live attenuated poliovirus types 1, 2, and 3, has been shown to be highly effective in preventing poliomyelitis. Introduced in the early 1960s, OPV has been widely used to protect pregnant women and neonates against poliomyelitis. The possible development of viraemia following immunization (79) and cases suggestive of vaccination-associated anomalies have been reported (80). However, no population-based controlled studies are available to confirm the significance of these individual reports. In contrast, mass immunization programmes that included thousands of pregnant women, prompted by poliovirus epidemics in Finland (81, 82) and Israel (83, 84) failed to show any association between maternal immunization with OPV and congenital anomalies or adverse pregnancy outcomes (85, 86). In Finland, a wild-type poliovirus 3 epidemic broke out in autumn 1984, and in early 1985, OPV was given to 94% of the entire population, including pregnant women, among whom the refusal rate was only 2% (87). In a retrospective cohort study, the outcome of 21 500 pregnancies was evaluated. In addition, data from the Finnish national Register of Congenital Malformations on 6500 children with anomalies born in Finland in 1982–1986 were studied. There was no observed increase in the rates of growth retardation, perinatal deaths, prematurity or congenital anomalies in the infants exposed to OPV in utero in comparison with the expected rates (87). In Israel, 90% of the population was given OPV in 1988 to protect against a wild-type poliovirus 3 epidemic. In a pre-epidemic versus post-epidemic comparison of 15 021 and 15 696 live births, respectively, there were no significant differences in prematurity or anomalies (83, 88).

Conclusion

A number of large studies in different countries have demonstrated the safety of oral poliovirus vaccine for infants born to vaccinated women and there is no evidence of increased rates of adverse pregnancy outcomes, despite the fact that OPV could theoretically infect the foetus. However, there remains a small theoretical risk of adverse effects of OPV immunization during pregnancy.

Immunization of adults with poliovirus vaccine is not routinely recommended if a series of poliovirus vaccinations has been completed in childhood. However,

immunization of pregnant women at high risk of endemic or epidemic exposure is recommended by SAGE and several national immunization technical advisory groups. Such immunization is currently being carried out in several countries that still suffer from wild-type poliovirus circulation.

3.2.3 Yellow fever vaccines

Yellow fever vaccines are not recommended for pregnant women and lactating mothers, unless there is an epidemic or the woman is travelling to a high-risk area (89). Yellow fever vaccination is generally regarded as safe and effective; in vaccine-naïve subjects, mild reactions – low-grade fever, mild headache, arthralgia and myalgia are seen in 15–20% of vaccinees. Some serious side-effects –neurological syndromes and viscerotropic disease – have been described, but rarely reported and confirmed (90).

In a Nigerian vaccination campaign during a yellow fever outbreak in 1986–87, 101 pregnant women aged between 15 and 50 years were inadvertently immunized with 17D vaccine. The children born from these pregnancies were followed up for 4 years. No child showed any physical or psychological abnormality or growth retardation. There was no statement about data quality and no assessment of any clinical symptoms attributable to yellow fever vaccine. Measurement of neutralizing antibody levels before and after vaccination showed that the antibody responses of the pregnant women were much lower than those of non-pregnant women in a comparable control group (91).

After a campaign in Brazil in which over 2 million people were vaccinated, 312 pregnant women who had received 17D vaccine were followed up. Ten major malformations were noted in 304 children born to vaccinated mothers. When compared with 10 961 births in the same region during 1997–99, the only significant difference in the rates of major malformations was for Down syndrome (3 cases among those exposed in utero). Minor dysmorphisms, especially naevi, were significantly more frequent ($P < 0.001$) than in the reference population, but this was thought to be a result of evaluation bias (92). In another report from Brazil, 480 pregnant women who received 17DD yellow fever vaccine were followed up via at least three antenatal visits and their children were examined at 3, 6 and 12 months. A 12-month serological follow-up of the infants and an examination to detect congenital abnormalities were offered to the pregnant women. The women had received the vaccine at a mean of 5.7 weeks (95% CI 5.2–6.2) of gestation. After at least six weeks, 98.2% of the women were IgG-positive. A total of 19.6% of the women reported mild adverse effects, such as headache, fever or myalgia (93).

To determine whether yellow fever vaccine administered in pregnancy causes fetal infection, women who were vaccinated during unrecognized pregnancy in a mass campaign in Trinidad were studied retrospectively. Maternal and cord or infant blood were tested for IgM and neutralizing antibodies to yellow fever and dengue viruses. Of 41 infants, one had IgM and elevated neutralizing antibodies to yellow fever virus,

indicating congenital infection. The infant, whose mother had been immunized in the first trimester, was delivered after an uncomplicated full-term pregnancy and appeared normal (94).

Among six pregnant women who received yellow fever and other vaccines at a travel clinic in Switzerland, there were no adverse outcomes for the mothers or their children (95).

Follow-up information in the European Network of Teratology Information Services for 74 pregnant women (58 pregnant women with complete follow up) who received 17D vaccine indicated two major and three minor malformations among the 46 live births and 7 spontaneous abortions (96). The rates of major malformation, as well as the frequency of spontaneous abortion, were consistent with expected rates in the general population. The three minor malformations were of different kinds and, according to the authors, unrelated to vaccination.

In a Brazilian university hospital, following a campaign in which some pregnant women inadvertently received yellow fever vaccine, 39 immunized women with spontaneous abortion were compared with a control group of 79 women at the antenatal clinic. The odds ratio for spontaneous abortion after yellow fever vaccine, after controlling for potential confounders, was 2.29 (95% CI=0.65–8.03). No serological tests were reported and the statistical power was low (97).

These seven studies have been discussed in a systematic review of adverse events associated with yellow fever vaccine in vulnerable populations, including pregnant women (98).

Conclusion

Yellow fever vaccination has been documented in several hundred pregnant women. The risks of adverse outcome of pregnancy and childbirth appear to be similar to those in the general population, except in one study, which used passive surveillance data and had low statistical power.

4. Obstacles to accurate assessment of risk

Vaccine safety in pregnancy must be assessed in the context of the substantial risk of infection for the pregnant woman and her fetus in the absence of immunization. In addition, it may be difficult to dissociate risks inherent in pregnancy from those associated with a vaccine. Knowledge of background rates of adverse pregnancy outcomes is critical when assessing adverse events after vaccination in order to interpret the data for causality. Information on background rates is non-existent in many parts of the world (99).

While there is emerging scientific evidence, as well as theoretical reasons, indicating that certain vaccines are safe for pregnant women and foetuses, policy formulation is challenging because the evidence base to guide decisions is still limited for some vaccines. With newer vaccines, the data are even more limited, because pregnant women are excluded from clinical trials and there is a lack of systematic investigation of the post-licensing experience.

GACVS has noted a number of methodological challenges in post-licensing safety studies – low statistical power due to limited sample sizes notwithstanding – that are inherent in the variety of adverse pregnancy outcomes that occur such as preterm birth, anomalies (major and minor), caesarean section, and pregnancy loss (miscarriages and stillbirths). Variations in both exposure to infection or vaccination and incidence of outcomes over the gestational period may also create challenges as a result of the changing risk over the course of a pregnancy. For instance, a substantial percentage of conceptions are lost prior to clinical recognition. Thus, a primary problem when studying miscarriages is the wide scope for bias introduced by the incomplete and varying ascertainment of implantation failures and early embryonic deaths (100), since in several developing country settings most women only seek antenatal care well beyond the first trimester of pregnancy. Long-term follow-up of infants and their postnatal care needs is also required to assess congenital anomalies. For example, minor heart malformations may be detected only by cardiac ultrasound, and developmental delay may be diagnosed months or years after birth. If these issues are not appropriately assessed and accounted for, risk estimates may be profoundly biased.

4.1 Summary and overall recommendations

GACVS has evaluated the data on the safety of immunization of pregnant women for several inactivated and live attenuated vaccines. There is no evidence of adverse pregnancy outcomes from the vaccination of pregnant women with inactivated virus, bacterial vaccine, or toxoid. Therefore, pregnancy should not preclude women from immunization with these vaccines, if medically indicated (Table 1).

Live vaccines may pose a theoretical risk to the fetus. However, there is a substantial literature describing the safety of live attenuated vaccines, including monovalent rubella vaccines, combined measles-mumps-rubella vaccines, yellow fever and oral poliovirus vaccines. No significant adverse effects on the fetus have been reported following administration of these live attenuated vaccines. Thus, the contraindication of MMR-containing vaccines can be considered a purely precautionary measure. Inadvertent vaccination of pregnant women with MMR-containing vaccines is not considered an indication for termination of the pregnancy.

The benefits of vaccinating pregnant women generally outweigh the potential risks, if they are at high risk of being exposed to a particular infection and the disease would pose a risk for the woman or her unborn child, and if the vaccine is unlikely to cause harm. The use of selected vaccines in pregnancy is an important aspect of prenatal care, which not only protects maternal health but also benefits the neonate.

Table 1. Summary of vaccines reviewed and level of evidence concerning vaccine safety

Vaccine	Increased risk or severity of disease in pregnant women	Risk of disease to fetus or young infant	WHO recommendation on vaccination during pregnancy	Vaccine safety concerns	Level of evidence on vaccine safety
Inactivated vaccines					
Seasonal TIV or H1N1 2009–2010 monovalent, non-adjuvanted vaccines Oil-in-water adjuvanted, monovalent H1N1 vaccines	More severe disease especially in second and third trimester and increased risk of death in a pandemic	Possible increased spontaneous abortion rate and increased preterm delivery. No malformations confirmed.	Yes Yes	No safety concern identified No safety concern identified	++++ +++
Tetanus toxoid vaccines	Incidence depends on region; unaltered by pregnancy	Neonatal tetanus mortality 60%	Yes	No safety concern identified	++
Meningococcal polysaccharide vaccines Meningococcal conjugate vaccines	Incidence not altered by pregnancy	Unknown for fetus; infants may develop significant morbidity and mortality.	No As part of mass campaigns.	No safety concern identified No safety concern identified	++ +
Live attenuated vaccines					
Rubella vaccine	Incidence not altered by pregnancy	Abortion and congenital rubella syndrome (CRS)	No	No CRS identified in children born to inadvertently vaccinated susceptible pregnant women	+++
Measles vaccines	More severe disease; low mortality	Possible higher abortion rate, infrequently congenital measles and if premature possible high case fatality rate	No	No safety concern identified	Indirect data from combined MR vaccines
Mumps vaccine	Incidence not altered by pregnancy	Probable increased rate of abortion in the first trimester	No	No safety concern identified	Indirect data from combined MMR vaccines
Oral poliovirus vaccine	Increased risk of paralytic disease	Anoxic fetal damage reported; 50% mortality in neonatal disease	No	No safety concern identified	+++
Yellow fever	Incidence not altered by pregnancy	Unknown	During epidemics and when travel to endemic areas cannot be avoided	No safety concern identified	+++

++++ Substantial evidence from RCTs, large observational studies or registries with pregnancy follow-up and passive surveillance.
+++ Evidence from observational studies or registries with pregnancy follow-up and passive surveillance.
+ + Some evidence from studies with lower power, lack of information on some relevant pregnancy outcomes, short follow-up of offspring or other limitations of study design and passive surveillance.
+ Passive surveillance data.
- No data.

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