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COMMENTARY

Safety of oral cholera vaccines during pregnancy in developing countries

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Introduction

Cholera is an acute diarrheal disease caused by toxigenic serogroups (O1 and O139) of *Vibrio cholerae* that is spread by ingestion of contaminated food or water.[1] The exact global burden of cholera is unknown due to under-reporting, but it has been estimated that 2.8 million cases and 91,000 deaths occur annually due to cholera in 51 endemic countries.[2] Cholera can cause serious complications including fetal loss at an estimated rate of 2% to 36%.[3,4] However, oral cholera vaccines (OCVs) are not recommended during pregnancy.

A few OCVs have been prequalified by the World Health Organization (WHO): (i) Dukoral (Crucell Sweden AB, Stockholm, Sweden); (ii) Shanchol (Sanofi); and (iii) Euvichol (Eubiologics, Chuncheonsi, South Korea). Dukoral is a monovalent oral killed vaccine based on whole *V. cholerae* O1 and the recombinant cholera toxin B subunit, whereas the other 2 are bivalent oral killed vaccines based on serogroup O1 and O139.[5-9] The ranges of protective efficacy for Dukoral and Shanchol according to different age groups are 66–86% at 4–6 months after vaccination, 45–62% at one year, and 58–77% at 2 y. The efficacy for Shanchol was 65% after 5 y of vaccination for individuals over 5 y of age.[10,11]

Pregnant women are vulnerable to complications in cholera, and maternal infection with cholera may adversely affect pregnancy outcomes, an observation dating back to the 19th century[12] and now strengthened with more evidence.[3,13] Maternal vaccination may boost maternal levels of pathogen-specific antibodies and provide protection to the mother as well as to newborn infant by passive transfer of antibodies.[14] Therefore, evaluation of the safety of OCVs is needed to potentially allow pregnant women to be vaccinated to prevent the complications of cholera in pregnancy.

Current evidence on the safety of OCV in pregnant women: Findings from different studies in developing countries

Several recent studies have examined pregnant women receiving the OCV. Bangladesh and some other developing countries are now considering vaccinating those at high risk of cholera. Furthermore, several mass vaccination campaigns are underway in individuals over one year of age in low-income countries. However, pregnant women were excluded from participation in most of these programs based on WHO recommendations except in a campaign conducted in Malawi. However, many pregnant women inadvertently received the OCVs.

Retrospective as well as prospective follow-up for pregnant OCV participants has now been completed. The overall aim of the studies was to assess OCV safety during pregnancy. To generate knowledge and evidence, these studies evaluated the safety of OCV in pregnancy. According to these findings, the vaccines were considered as safe during pregnancy.

Safety of recombinant OCV during pregnancy in Zanzibar

A mass oral cholera vaccination was conducted among the population over 2 y of age in an urban and a rural area in Zanzibar in 2009. After the campaign, all women residing in the study were assessed as to whether any had inadvertently received the vaccine and to investigate birth outcomes (miscarriage or live births). The objective of the study was to determine whether there was any difference between the outcomes of pregnancies exposed and not exposed to the oral rBS-WC cholera vaccine. Birth surveillance was conducted approximately 9 months after the mass vaccination campaign. There was no statistically significant evidence of a harmful effect of gestational exposure to the vaccine.[15]

Retrospective subgroup analysis following a mass vaccination campaign in Dhaka, Bangladesh

A cluster-randomized effectiveness trial of the Shanchol OCV was conducted in an urban area of Dhaka City, Bangladesh in 2011. The study captured a population of about 269,000 individuals of low socioeconomic status with poor sanitation and hygiene practices who were at high risk of cholera. Although pregnancy was an exclusion criterion, a few women received the OCV unknowingly while pregnant as ascertained at the time of the second dose. During retrospective data collection, a similar number of participants were enrolled who were pregnant during vaccination but did not receive the vaccine. The 2 groups were compared. The study end point included the adverse fetal outcomes of miscarriage, stillbirth, and congenital anomalies. There was no evidence of an elevated risk of adverse fetal outcomes in pregnant women who received the OCV.

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Pregnancy outcomes after a mass vaccination campaign with an OCV in Guinea

In 2013, a large retrospective cohort study was conducted in all residents one year of age and above in 6 sub-prefectures in Guinea. The aim of the study was to determine the risk of pregnancy loss after receiving the OCV. No association was found between fetal exposure to vaccine and risk of pregnancy loss or malformation. The study also reported that vaccination coverage was higher in women who were pregnant during the campaign than those who become pregnant after the campaign. Moreover, pregnant women may have been better informed about the vaccination campaign, were less occupied with other activities on the day of vaccination, and were more willing to follow advice.[16]

Safety of Shanchol during pregnancy in Malawi

In 2015, cholera vaccinations were given in 2 adjacent districts in Malawi to assess the safety of Shanchol during pregnancy. Individuals aged one year or older, irrespective of pregnancy status, were invited to participate. After the campaign, an observational cohort study was conducted on these large samples. Two groups were recruited from 2 different districts, of whom one group received vaccine and the other did not. Pregnancy outcomes were evaluated between the 2 groups. The primary and secondary endpoints were pregnancy loss (spontaneous miscarriage or stillbirth) and neonatal deaths and malformations, respectively. Fetal exposure to the OCV conferred no significantly increased risk of pregnancy loss, neonatal mortality, or malformation.[17]

An ongoing evaluation is being performed in a randomized controlled trial of Shanchol in over 205,000 individuals in which women who inadvertently received the OCV is being analyzed for pregnancy outcomes in a prospective cohort design.

Conclusions

These studies indicate that fetal exposure to OCV does not increase the risk of adverse pregnancy outcomes. The findings support the formulation of a recommendation on the safety of the vaccine during pregnancy. In cholera-effected regions, pregnant women are at high risk of developing cholera, and this risk can be lowered with the OCV without a clinically significant risk to the woman or her fetus. Several parenteral inactivated vaccines have substantial safety records (tetanus, acellular pertussis, and influenza vaccines) that are currently recommended for use in the third trimester of pregnancy. Although there is no evidence of a harmful effect of OCV during pregnancy, it has not yet been recommended for pregnant women.[18] Moreover, Global Task Force on Cholera Control (GTFCC) contemplate that there are little risk and considerable benefits from inclusion of pregnant women in vaccination campaigns.[19] Overall, the decision to administer the vaccine should depend on the epidemiological context and after weighing up the potential risks and benefits. On the basis of our current understanding of the vaccine and evidence from different studies, pregnant women should not be excluded from oral cholera vaccines during vaccination campaigns.[15,17,18]

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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