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SAFETY OF ORAL CHOLERA VACCINES IN PREGNANCY:A REVIEW

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ABSTRACT

Cholera is a rapidly dehydrating diarrhoeal disease caused by ingestion of toxigenic serogroups of *Vibrio cholerae*. Cholera in pregnancy is associated with serious complication leading to fetal loss in 2-36% cases. Safety evaluations done in pregnant women during cholera outbreaks suggest that OCV'S are safe during pregnancy. WHO recommend killed whole celled vaccines to reduce the risk of cholera which include Dukoral and Shancol. According to the 2010 WHO Position Paper on cholera vaccines, mention pregnant women as a group that is "especially vulnerable to severe disease and for which the vaccines are not contraindicated", and thus a possible target for vaccination as well. Use of OCV'S in pregnancy is associated with many risk and benefits. Based on the analysis of risk and benefit, there are considerable benefits and very few risks from including pregnant women in vaccine campaign.

KEYWORDS: *Vibrio cholera*, Dukoral and Shancol.

INTRODUCTION

Cholera is a rapidly dehydrating diarrhoeal disease caused by ingestion of toxigenic serogroups (O1 and less commonly O139) of *Vibrio cholerae*. Humans are the only known natural host for *V. cholerae*, and the disease is spread mainly by faecal contamination of water and food. Direct transmission from person to person is uncommon. Cholera is a disease of poverty and closely linked to poor sanitation and a lack of clean drinking water. The disease burden is characterized by both endemic disease and epidemics. Endemic cholera refers to cholera that recurs in time and place, whereas epidemic cholera denotes cholera that occurs unpredictably with respect to these variables. Cholera occurs endemically in south and south-east Asia and in Africa, but may also cause major outbreaks. Throughout history, devastating outbreaks of cholera have resulted in millions of cases and hundreds of thousands of deaths.[1] Cholera in pregnancy is associated with serious complication leading to fetal loss in 2-36% cases.[5] OCV'S have been widely used for the prevention of cholera. Safety evaluations done in pregnant women during cholera outbreaks suggest that OCV'S are safe during pregnancy.

OCV'S (Oral Cholera Vaccines)

WHO recommend killed whole celled vaccines to reduce the risk of cholera which include Dukoral and Shancol.[2]

Dukoral (WC-rBS): It was developed in Sweden and first licensed in 1991.

Type of vaccine: It is a monovalent vaccine based on formalin and heat-killed whole cells (WC) of V. cholera O1 plus recombinant cholera toxin B subunit. (To protect the toxin B subunit from being destroyed by gastric acid, the vaccine must be given with a bicarbonate buffer).

Age: From 2 years of age. Dukoral is not licensed for children aged <2 years.

Packaging or Presentation: The vaccine is provided in 3 ml single-dose vials together with the bicarbonate buffer (effervescent granules in sachets).

Buffer: Dilution in 150 ml of water (chlorinated or not) for persons aged >5 years and in 75 ml of water for children aged 2–5 years.

Shelf life and Storage: 3 years of shelf life at 2–8°C and remains stable for 1 month at 37°C and 2 weeks at < 27°C.

Vaccine schedule and administration

Primary immunization

Adults and Children aged ≥6 years should receive 2 oral doses given >7 days apart (but <6 weeks apart).

Children aged 2–5 years should receive 3 doses >7 days apart (but <6 weeks apart).

Intake of food and drink should be avoided for 1 hour before and after vaccination. If the interval between the primary immunization doses is delayed for >6 weeks,

primary immunization should be restarted. Protection may be expected about 1 week after the last scheduled dose.

Booster dose
Adults and Children aged ≥6 years 1 booster dose is recommended after 2 years. If the interval between the primary series and booster immunization is >2 years, primary immunization must be repeated.

Children aged 2–5 years 1 booster dose is recommended every 6 months. If the interval between primary immunization and the booster is >6 months, primary immunization must be repeated. Dukoral is not licensed for children aged <2 years.

Vaccine safety in pregnancy: Dukoral can be administered to pregnant and lactating women although no clinical studies reported the effect of this vaccine in the reproductive toxicity. Since, Dukoral is also an inactive vaccine theoretically it is safe to administer in pregnancy after considering the risks and benefits. The adverse events of Dukoral are mild abdominal discomfort, pain or diarrhea, all of which attributed to bicarbonate buffer which is given along with the vaccine.

Immunogenicity: Dukoral stimulates the production of both antibacterial and antitoxin antibodies, including immunoglobulin A antibodies produced locally in the intestines.

Clinical efficacy and effectiveness, and duration of protection: The vaccine has been tested in randomized placebo controlled double blind pre licensure efficacy trials in both Bangladesh and Peru. The protective efficacy of Dukoral varies among young children and older children and adults. Among children aged 2–5 years, the level of protection was 100% at 4–6 months following vaccination; 38% at the end of 1 year, 47% during the second year and to 0% thereafter. The protective efficacy for people aged >5 years was 78% at 1 year and 63% during the second year following immunization. Two doses of the WC-BS vaccine were as protective as 3 doses in people aged >6 years.

Shanchol (BivWC): It was developed in Viet Nam and first licensed in 1991 as ORCVAX. In 2009 this vaccine was licensed as mORCVAX in Viet Nam and as Shanchol in India.

Type of vaccine: Killed bivalent whole-cell vaccine suspension based on serogroups O1 and O139. Unlike Dukoral, these vaccines do not contain the bacterial toxin B subunit.

Age: From 1 year of age.

Packaging or Presentation: Shanchol is provided in 1.5ml single dose vials (in 3 ml glass vial with aluminum cap).

Buffer: No buffer needed. Water may be offered following ingestion of the vaccine, but is not required.

Shelf life and Storage: 2 years of shelf life at 2–8°C and Stable for 21 days at 37°C.

Vaccine schedule and administration
Primary immunization
For individuals aged ≥1 year: orally in 2 liquid doses 14 days apart.

Booster dose
A booster dose is recommended after 2 years.

Vaccine safety in pregnancy: No clinical studies have been performed to evaluate the safety of Shancol. Since Shancol is killed vaccine, when orally given act on intestine and does not replicate it should not produce any harmful effect to human fetus. so it can given to pregnant women after careful consideration of risks and benefits in epidemics.

Immunogenicity: Following the addition of the O139 strain, the resulting bivalent vaccine was shown in non inferiority trials to be safe and immunogenic against both O1 and O139 infection.

Clinical efficacy and effectiveness, and duration of protection: The protective efficacy of the vaccine for all ages after 2 doses was 66%. The overall effectiveness of this vaccine 3–5 years after vaccination was 50%. Earliest onset of protection is for 7-10 days after 2nd dose.

Who Recommendations Concerning Use of OCV'S In Pregnency
According to the 2010 WHO Position Paper on cholera vaccines, preschool-aged and school-aged children are the primary targets for cholera vaccination in many endemic areas. However, the paper also specifically mentions pregnant women as a group that is "especially vulnerable to severe disease and for which the vaccines are not contraindicated", and thus a possible target for vaccination as well.[1]

Criterias for OCV'S Use in Pregnant Women
OCV'S can be used in pregnant women only after considering following criteria's.[4]
1. Is cholera increase risk of maternal or fetal death or other complications in pregnant women?
2. Is benefits of OCV'S out weights the risk of OCV'S in pregnant women?
3. Is vaccination with OCV'S providing any protection to fetus?
4. Is there any evidence suggesting the safety of OCV'S in pregnancy?

Risk Associated with Cholera in Pregnant Women
Cholera in pregnancy is associated with high risk of fetal loss and miscarriage. Evidence from studies shows

reported fetal loss in women with cholera range from 8 – 33%, where still birth rates alone where found to 5.5 times (Haiti) and 1.8 times (Senegal) higher than estimated national still birth rates.[3]

Studies conducted in Bangladesh in 1960's and studies from Senegal and Nigeria found higher rates of premature delivery and fetal loss in women with cholera in their 2nd or 3rd trimester.[5] This studies shows that severe dehydration due to rapid reduction in blood volume is a major risk factor for fetal loss and premature delivery. Reduction in blood volume leads to decreased blood flow to placenta which in turn causes fetal asphyxia. These changes are further severed by metabolic acidosis which occurs due to severe bicarbonate loss in stool during diarrhea.

Risk Associated with OCV'S In Pregnancy

- Pregnant women are not included in any controlled trials of OCV'S. Retrospective studies conducted in 2012 in guinea and Zanzibar does not shows the evidence of increasing maternal adverse effects in vaccinated woman compared to non vaccinated women.[2]
- There is no up- to-date evidence to show that OCV'S are harmful to pregnant women, CI in pregnancy and adversely affect fetus and mother.[6]
- Posts marketing surveillance data as well as surveillance data have not indicated any enhancement in adverse effect although there is a few reports of their use in pregnancy.

Benefit Associated with OCV'S In Pregnancy

- OCV'S will protect against cholera which causes severe dehydration and fetal loss.
- Several studies reveal that in pregnant women with cholera there is a delay in seeking treatment so OCV'S helps to avoid complications in these women who may not receive treatment in time.
- Vaccination with OCV'S before, during or after pregnancy will help to reduce the risk of transmission of cholera from mother to children.

CONCLUSION

Cholera causes miscarriage and still birth in pregnant women. Large number of evidences suggests vaccination with OCV'S for the prevention of cholera in pregnant women. Based on the analysis of risk and benefit, the GTFCC consider that there are considerable benefits and very few risks from including pregnant women in vaccine campaign.

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