REVIEW ARTICLE

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Safety of Hepatitis B, Pneumococcal Polysaccharide and Meningococcal Polysaccharide Vaccines in Pregnancy

A Systematic Review

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Contents

Abstract

Immunization during pregnancy has the potential to protect the mother and the newborn from preventable diseases. Current recommendations suggest that inactivated vaccines might be considered during pregnancy when the benefits outweigh the risks.

In this review, we aimed to evaluate the safety of hepatitis B (HB) vaccine, pneumococcal polysaccharide vaccine (PPSV) and meningococcal polysaccharide vaccine (MPSV) administration during pregnancy by systematically reviewing the available evidence in PubMed and Scopus databases, as well as postmarketing surveillance data (including the Vaccine Adverse Event Reporting System [VAERS] database). A total of 18 studies were eligible for inclusion in the review. Six studies provided data on HB vaccine, six on PPSV and three on MPSV; three additional studies compared PPSV with MPSV. Additionally, 91 reports on vaccinations of pregnant women were identified

from postmarketing surveillance data (88 on HB vaccine, 2 on PPSV, 1 on MPSV). The most common complaints were local reactions, including tenderness and swelling. Overall, immunization during pregnancy did not seem to be associated with a teratogenic effect on the fetus, preterm labour or spontaneous abortion. However, the lack of randomized, placebo-controlled trials, or even large cohort studies, in addition to the inherent limitations of the reviewed observational studies with small statistical power, precluded safe conclusions. Large, prospective, population-based cohort studies are needed to elucidate this issue.

Immunization during pregnancy is an issue of great concern.[1,2] The emergence of the 2009 H1N1 pandemic, along with the increased morbidity and mortality observed in pregnant women, has once again underlined the potential benefits of vaccination during pregnancy.[3-5] However, the theoretical risks of vaccination for the fetus, the lack of explicit information regarding vaccine safety, and liability issues are major factors rendering obstetric-care providers hesitant to administer vaccines in the vulnerable period of pregnancy.[6]

Immunization of pregnant women with live virus vaccines is clearly contraindicated because of the theoretical risk of transmission of the virus to the fetus. Regarding inactivated vaccines, the main concerns include possible adverse events (AEs) of vaccine constituents (e.g. adjuvants, preservatives), as well as potential adverse pregnancy outcomes caused by the vaccine-induced immunomodulation.[7] Generally, vaccination in pregnancy should always be based on a risk-versus-benefit approach. In this context, the Centers for Disease Control and Prevention (CDC) recommend that pregnant women are routinely vaccinated against influenza. In addition, maternal immunization against tetanus and diphtheria, hepatitis B (HB), meningococcus and rabies should be considered, if indicated.[8]

The safety of maternal vaccination against influenza has already been evaluated.[9-11] Immunization against tetanus and diphtheria has been successfully implemented on a large scale in developing countries and was not associated with adverse pregnancy outcomes.[12-14] Two review articles regarding clinical experience with maternal vaccination against rabies are also available.[15,16] In this study, we sought to review available evidence regarding the safety of HB vaccine, meningococcal polysaccharide vaccine (MPSV) and pneumococcal polysaccharide vaccine (PPSV) during pregnancy, with particular focus on pregnancy and neonatal outcomes.

1. Data Sources

A systematic literature search was conducted in PubMed and Scopus databases, which were last accessed in May 2011. The search term applied to both databases was 'vaccin* AND pregnan*'. References of relevant articles were handsearched and reviewed, including relevant review papers. In addition, we reviewed the Vaccine Adverse Event Reporting System (VAERS) database, a vaccine safety surveillance programme cosponsored by the CDC and the US FDA,[17] as well as websites of pregnancy registries and surveillance programmes. Specifically, we searched the FDA list of pregnancy exposure registries, the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) and the Merck pregnancy registries.[18-20]

2. Study Selection Criteria

Two reviewers (MCM, KAP) independently searched the literature and assessed the studies for eligibility. To be considered eligible for inclusion in the review, a study should refer to HB, pneumococcal or meningococcal vaccination during pregnancy and provide data on any of the following: systemic AEs, pregnancy outcomes, delivery complications, congenital abnormalities,

neonatal mortality or developmental delay of the infant. Any reported AE was considered eligible. Study quality criteria were not implemented and no language restrictions were imposed.

3. Data Extraction

Data extracted from each of the evaluated articles included location, time period and design of each study, vaccinated populations, type, trimester and doses of vaccination, follow-up period, local and systemic AEs (i.e. fever, anaphylactic reactions), pregnancy outcomes (i.e. spontaneous abortions, preterm delivery, stillbirths, intrauterine growth restriction), and neonatal and infant complications (i.e. perinatal/neonatal mortality, developmental delay). The VAERS database was reviewed for the following information: type of vaccine administered to pregnant women, time of vaccination, reported complications, and time interval between vaccination and onset/diagnosis of complication.

4. Identification and Selection Process of the Included Studies

Figure 1 presents a flowchart of the identification process of the included studies. The literature search in PubMed generated 8090 articles, of which 539 referred to vaccination during pregnancy. The search in Scopus yielded no additional relevant articles. As shown, most of these articles

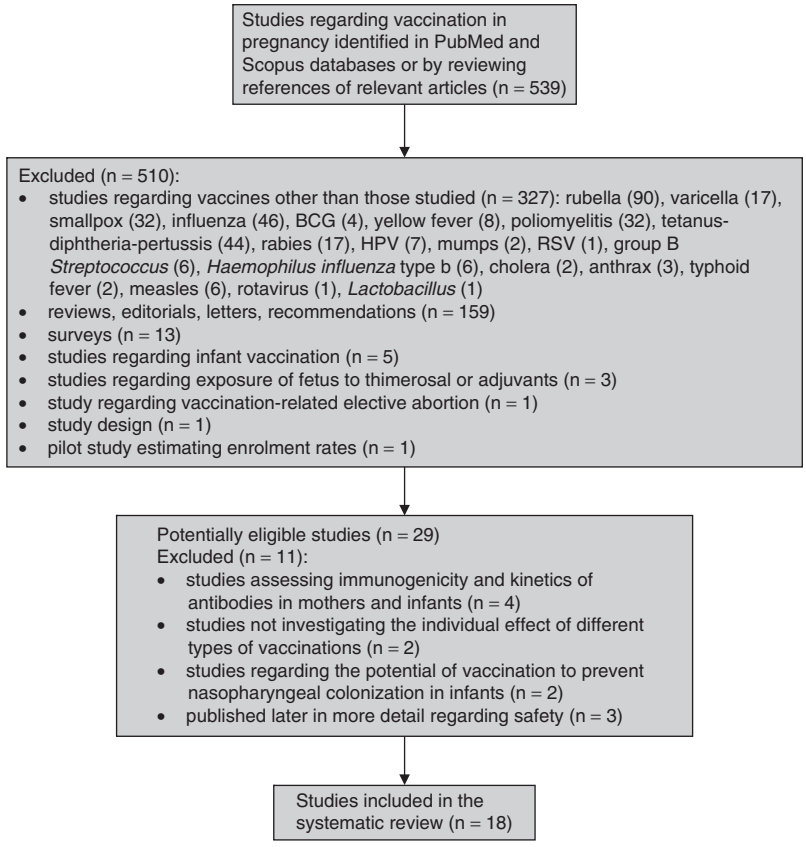

Fig. 1. Flowchart of studies identified in the literature search. **BCG** = bacillus of Calmette and Guerin tuberculosis vaccine; **HPV** = human papillomavirus; **RSV** = respiratory syncytial virus.

referred to vaccine types other than those studied; therefore, only 29 studies were selected for further evaluation. From these, four studies assessed vaccine immunogenicity and antibody kinetics,[21-24] two did not present the individual effect of different types of vaccines administered,[25,26] two studied the potential of vaccination to prevent nasopharyngeal colonization[27,28] and three were published later in more detail.[29-31] Finally, 18 studies were included in the review (table I).[32-49] From these, six referred to HB vaccine,[32-37] six to PPSV[38-43] and three to MPSV,[47-49] while three studies were randomized controlled trials (RCTs) comparing MPSV with PPSV.[44-46]

The search of the VAERS database from June 1990 through March 2011 identified 88 evaluable reports on HB vaccine, 2 on PPSV and 1 on MPSV. These case reports are presented as Appendix 1 (Supplemental Digital Content, http://links.adisonline.com/DSZ/A56). The appendix contains postmarketing passive surveillance data (1990–2011) from the VAERS on possible adverse events of maternal vaccination with the studied vaccines. For the reported events, no cause-and-effect relationship has been proven.

The search in the remaining databases yielded no additional relevant information.

5. Safety of Hepatitis B (HB) Vaccine during Pregnancy

Six prospective studies (one RCT,[32] five cohort studies[33-37]) evaluating the safety of HB vaccine in a total of 381 pregnant women were identified. Three studies used a recombinant HB vaccine,[32-34] while the remaining three used a vaccine containing purified, plasma-derived hepatitis B surface antigen from chronic HB carriers (Heptavax®).[35-37]

5.1 HB Recombinant Vaccine

In an RCT comparing different doses (two vs three) of HB vaccination in 100 Indian women in the second or third trimester of pregnancy, investigators stated that ''there were no side effects''.[32] A cohort study from Texas evaluated the safety of a three-dose schedule of HB vaccine in 168 pregnant women; the most prevalent complaint was soreness at the injection site, whereas the observed rates of preterm labour were similar to those seen in the general obstetric population.[33] In another cohort, 16 pregnant women who were exposed to HB virus after *in vitro* fertilization received three or four doses of a recombinant vaccine. One vaccinee had a miscarriage 2 days post-immunization and another was lost to follow-up; the remaining delivered healthy newborns, who had no developmental problems by the age of 22 months.[34]

5.2 HB Vaccine Derived from Plasma of Chronic HB virus Carriers

In a cohort study evaluating Heptavax® (two doses) in 72 Nigerian women in the third trimester of pregnancy, local and systemic AEs, as well as stillbirths (1%), were not significantly different when compared with a control group that received placebo; data on birth defects were not reported.[35] In another cohort of ten pregnant women who initiated vaccination from the first trimester, there were no congenital abnormalities or developmental problems among infants.[36] Finally, in a cohort of 15 Indian gravidas who received three doses of HB vaccine in the second and third trimester, no stillbirths or congenital defects were found.[37]

5.3 Vaccine Adverse Event Reporting System Surveillance Data

From 1990 through 2011, a total of 88 evaluable reports of pregnant women vaccinated with a recombinant HB vaccine were identified. The majority of the reports described women who found out about being pregnant shortly after receiving the vaccine; therefore, in some cases, the precise timing of vaccination with regard to conception (before or after) is not clear. Reports included cases of spontaneous abortion (n = 28), elective abortion (n = 12), stillbirths (n = 3), preterm labour (n = 3), vaginal bleeding (n = 7), chromosomal abnormalities (n = 2) and autism (n = 1), as well as local and systemic adverse reactions.

Table I. Characteristics of included studies

Study (y)	Country of origin (study period)	Study design; vax examined	No. and characteristics of vaccinated pregnant women	Follow-up	Local AEs[a]	Systemic or serious AEs	Pregnancy outcome/delivery complications [expected incidence]	Neonate/infant complications [expected incidence][a]
Gupta and Ratho[32] (2003)	India (1999–2000)	RCT; recomb. HB vax; 2 vs 3 doses (4–6 wk intervals)	52 vs 48; age range 22–27 y; trimester of vaccination: 2nd and 3rd	Mothers and infants: for 4 mo post-delivery	None	None	None	None
Sheffield et al.[33] (2011)	Texas (2000–6)	Prosp. cohort; recomb. HB vax (3 doses at a 0, 1, 4 mo schedule)	168; mean age 25 y; mean gestational age at enrolment: 17 wk	Mothers: for 5–6 mo post initial vaccination	Erythema: 6/168 (4%); soreness: 18/168 (11%); swelling: 2/168 (1%)	Fever: 0/168 (0%); fatigue: 8/168 (5%); headache: 3/168 (2%); nausea: 9/168 (5%); vomiting: 1/168 (1%); anorexia: 8/168 (5%); myalgia/arthralgia: 12/168 (7%)	Preterm labour: NR (not increased "compared with the general obstetric population")	Neonatal intensive care admissions: NR (not increased "compared with the general obstetric population")
Grosheide et al.[34] (1993)	Netherlands (1988–9)	Prosp. cohort; recomb. HB vax (4 doses at a 0, 1, 2, 6 mo schedule) + HBIG	16 pregnant (IVF) women receiving PEP; mean age 33 y; 6 received the first dose at the 1st trimester, 9 received the last dose post-delivery	Mothers: for ≥7 mo post initial vaccination; infants: 1 y (development 22 mo)	NR	None	Congenital defects: none; spontaneous abortions:[b] 1/16 (6%)	Developmental delay (22 mo): none
Ayoola and Johnson[35] (1987)	Nigeria (NR)	Prosp. cohort; Heptavax (2 doses, 1 mo apart). Control group received PL	72 (age range 19–27 y) vs 86 (PL); trimester of vaccination: 3rd	Mothers, infants: for 12 mo post-delivery	Local pain: 9/72 (12.5%) vs 11/86 (12.8%)	Fever: 2/72 (2.8%) vs 2/86 (2.3%); headache: 2/72 (2.8%) vs 2/86 (2.3%); fatigue: 2/72 (2.8%) vs 4/86 (4.6%); other (pruritus, dizziness): 3/72 (4.2%) vs 5/86 (5.8%)	Stillbirths: 1/72 (1.4%) vs 1/86 (1.2%)	NR

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Table I. Contd

Study (y)	Country of origin (study period)	Study design; vax examined	No. and characteristics of vaccinated pregnant women	Follow-up	Local AEs[a]	Systemic or serious AEs	Pregnancy outcome/delivery complications [expected incidence]	Neonate/infant complications [expected incidence][a]
Levy and Koren[36] (1991)	Canada (NR)	Prosp. cohort; Heptavax	10; no of doses: 2 or 3; 9 women received at least one dose in the 1st trimester, 7 received the last dose post-delivery	Mothers and infants: for 12 mo post-delivery	NR	NR	NR	Developmental delay (12 mo): none
Reddy et al.[37] (1994)	India (NR)	Prosp. cohort; Heptavax (3 doses at 4–6 wk intervals)	15 (age range 22–27 y); trimester of vaccination: 2nd and 3rd	Mothers and infants: for 6 mo post-delivery	Local pain and pruritus: common	None	Stillbirths: none; congenital defects: none; preterm labour: none	None
Almeida et al.[38] (2009)	Brazil (NR)	Prosp. cohort; PPSV (23-valent)[c]	46 HIV-infected women; trimester of vaccination: 3rd	Infants: 6 mo	Mild local reactions: 3/44 (6.8%)	None	Stillbirths: 0/46 (0%)	Infant deaths: 0/46; HIV infection during the first mo of life: 2/46 (4.4%)
Lehmann et al.[39] (2002)	Papua New Guinea (1991–4)	Prosp. cohort; PPSV (23-valent);[c] control group: unimmunized women	279 (mean age 29 y[d]); control group: 202 (mean age 29 y); trimester of vaccination: 3rd	NR	NR	NR	Stillbirths: 3/279 (1.1%) [1.5%]; Mean birthweight:[e] 3.1 kg vs 3.09 kg	Mortality:[e] <1 wk: 0/235 vs 0/202; 1 wk–6 mo: 7/235 (3%) vs 8/202 (4%); 6–12 mo: 0/235 (0%) vs 1/202 (0.5%); 0–12 mo: 29.8/1000 vs 44.6/1000
Riley and Douglas[40] (1981)	Papua New Guinea (1973–6)	RCT; PPSV (14-valent) vs PL	187 vs 167; trimester of vaccination: NR	Infants: 3 y	NR	Spontaneous abortions: 2/187 (1.1%) vs 0/167 (0%)	Stillbirths: 6/187 (3.2%) vs 4/167 (2.4%)	Congenital defects: 1/187 (0.5%) vs 2/167 (1.2%); 1 wk mortality: 2/187 (1.1%) vs 1/167 (0.6%); 3 y mortality: 13/187 (6.9%) vs 11/167 (6.6%)
Lopes et al.[41] (2009)	Brazil (2005–6)	RCT; PPSV (23-valent) during pregnancy vs PPSV post-delivery vs no vax	50 vs 50 vs 50; trimester of vaccination: 3rd	Infants: 6 mo	''Only 2 pregnant women complained of local pain''	Fever: none; ''No relevant adverse effects … in groups 1 and 2''	Preterm labour: 3/50 (6%) vs 0/50 (0%) vs 1/50 (2%)	NR

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Table I. Contd

Study (y)	Country of origin (study period)	Study design; vax examined	No. and characteristics of vaccinated pregnant women	Follow-up	Local AEs[a]	Systemic or serious AEs	Pregnancy outcome/delivery complications [expected incidence]	Neonate/infant complications [expected incidence][a]
Quiambao et al.[42] (2007)	Philippines (1994–5)	RCT; PPSV (23-valent) + cHibV + TT vs TT only	106 (mean age 27 y) vs 54 (mean age 27 y); trimester of vaccination: 2nd or 3rd	Mothers and infants: 1 d	≥1 local reaction: 79/106 (74.5%) vs NR; redness:[f] 12/106 (11.3%) vs 10/106 (9.4%); **swelling:**[f] 33/106 (31%) vs 21/106 (19.8%); **induration:**[f] 34/106 (32%) vs 24/106 (22.6%); pain:[f] 76/106 (72%) vs 69/106 (65%)	Fever: 1/106 (0.9%) vs 1/54 (1.8%); facial redness/swelling: 1/106 (0.9%) vs 0/54 (0%)	NR	NR
Munoz et al.[43] (2001)	Texas (1995–6)	RCT; PPSV (23-valent) vs cHibV	20 (mean age 30 y) vs 40 (mean age 32 y); trimester of vaccination: 3rd	Mothers and infants: 16 mo	**Tenderness: day 1:** 6/20 (30%) vs 1/40 (2%); day 2–3: NS difference; redness and swelling: <5% in each group	No fever; no serious adverse reactions; non-specific, mild systemic events (nasal congestion, cough, shortness of breath, headache, weakness nausea) during the first 3 d: 5–30% in both groups	Stillbirths: 0/20 (0%) vs 0/40 (0%); any perinatal event: 11/20 (55%) vs 16/40 (40%) [69%]; preterm labour (<37 wk): 0/20 (0%) vs 1/40 (2.5%) [6.2%]; IUGR: 1/20 (5%) vs 0/40 (0%) [NR]; LGA: 1/20 (5%) vs 4/40 (10%) [5.3%]; C-section: 5/20 (25%) vs 5/40 (12.5%) [21%]; minor benign anatomic defects: 0/20 (0%) vs 2/40 (5%) [6.2%]	Jaundice: 3/20 (15%) vs 2/40 (5%) [11%]; respiratory distress: 3/20 (15%) vs 4/40 (10%) [8.6%]; hospitalization >48 h: 3/20 (15%) vs 3/40 (7.5%) [25%]; pyloric stenosis: 1/20 (5%) vs 0/40 (0%); developmental delay 1/20 (5%) vs 0/40 (0%); hydronephrosis: 0/20 (0%) vs 1/40 (2.5%); pneumococcal sepsis: 0/20 (0%) vs 1/40 (2.5%); infant deaths: none

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Table I. Contd

Study (y)	Country of origin (study period)	Study design; vax examined	No. and characteristics of vaccinated pregnant women	Follow-up	Local AEs[a]	Systemic or serious AEs	Pregnancy outcome/delivery complications [expected incidence]	Neonate/infant complications [expected incidence][a]
Shahid et al.[44] (2002)[d]	Bangladesh (1995, 1998)	RCT; MPSV (A,C,Y,W-135) vs PPSV (23-valent)[c]	75 (mean age 26 y) vs 82 (mean age 26 y); trimester of vaccination: 3rd	Mothers: 72 h post-vaccination; infants: 22 wk post-delivery	Tenderness: 22/75 (29%) vs 24/82 (29%); swelling:[g] 12/34 (36%) vs 13/36 (35%) ''Symptoms resolved by 72 h in all subjects''	None	Stillbirths: 0/75 (0%) vs 2/82 (2.4%); LBW (<2.5 kg): 2/75 (2.6%) vs 4/82 (5%); prematurity (<37 wk gestation): 1/75 (1.3%) vs 1/82 (1.2%); fetal distress: 1/75 (1.3%) vs 6/82 (7.3%); prolonged labour: 12/75 (16%) vs 6/82 (7.3%); pre-eclamptic toxaemia: 5/75 (6.7%) vs 1/82 (1.2%); haemorrhage: 2/75 (2.7%) vs 1/82 (1.2%); leaking membrane: 3/75 (4%) vs 1/82 (1.2%); C-sections: 33/75 (44%) vs 29/82 (35%)	None
O'Dempsey et al.[45] (1996)	Gambia (1991–2)	RCT; MPSV (A,C) vs PPSV (23-valent)	75 (mean age 22 y) vs 75 (mean age NR); trimester of vaccination: 3rd	Infants: 1 y post-delivery	Soreness at the injection side: rate not specified	None	Stillbirths:[h] 3/75 (4%) vs 1/75 (1.3%)	Neonatal deaths:[h] 1/75 (1.3%) vs 2/74 (2.7%); infant deaths (<5 mo): 2/75 (2.7%) vs 4/74 (5.4%)
Obaro et al.[46] (2004)	Gambia (1995–6)	RCT; MPSV (A,C) vs PPSV (23-valent)	57 vs 56; trimester of vaccination: 2nd or 3rd	Mothers and infants: 6 mo post-delivery	NR	None	Stillbirths:[i] 5/57 (8.8%) vs 3/56 (5.3%); LBW (<2.5 kg): 11/57 (19.3%) vs 11/56 (19.6%)	1 wk mortality:[i] 0/52 (0%) vs 2/53 (3.8%); 6 mo mortality:[i] 0/52 (0%) vs 4/53 (7.5%) [neonatal mortality: 37.1/1000]

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Table I. Contd

Study (y)	Country of origin (study period)	Study design; vax examined	No. and characteristics of vaccinated pregnant women	Follow-up	Local AEs[a]	Systemic or serious AEs	Pregnancy outcome/delivery complications [expected incidence]	Neonate/infant complications [expected incidence][a]
McCormick et al.[47] (1980)	Brazil (1974–5)	Prosp. cohort; MPSV (A,C)	51; trimester of vaccination: NR	NR	NR	NR	Stillbirths: none; congenital defects: none	NR
Letson et al.[48] (1998)	USA (1994–5)	Retro. cohort; MPSV (A,C,Y, W-135)	34 (mean age 27 y); trimester of vaccination: 1st: 4/34; 2nd: 17/34; 3rd: 13/34	Infants: average 13.2 mo	NR	NR	Stillbirths: 0/34 (0%); prematurity (<32 wk): 1/34 (2.9%) [3.2%]; SGA: 1/34 (2.9%) [5.9%]	TTN: 1/34 (2.9%) [1.1%]; umbilical hernia: 2/34 (5.9% [>7.5%]; persistent umbilicus: 1/34 (2.9%) [10%]; pneumonia: 1/34 (2.9%) [10%]; congenital pigmented nevus: 1/34 (2.9%) [1%]; **cardiac murmur:** 1/34 (2.9%) [28%]; **physiological jaundice:** 10/34 (29.4%) [50–60%]; conjunctivitis: 1/34 (2.9%) [8–25%]; strabismus: 1/34 (2.9%) [3%]; cephalhematoma 1/34 (2.9%) [2.5%]; **charlie M syndrome:** 1/34 (2.9%) [<1%]; no infant had significant growth or developmental delays during follow-up
Adam and Abdalla[49] (2005)	Sudan (2001–3)	Cross-sect. (retro.); MPSV (A,C)	43 (mean age 33 y); trimester of vaccination: 1st: 12/43; 2nd: 22/43; 3rd: 9/43	NR	NR	NR	Congenital defects: none	Mortality (7 mo): 1/43 (2.3%); developmental delay: none

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a Comparisons that showed a statistically significant difference ($p < 0.05$) are outlined in bold.

b Similar rates of spontaneous abortions after IVF were observed in a control group and a control period.

c Women in these studies also received TT during pregnancy.

d This RCT was conducted on two cohorts (1995, 1998) comprising 157 pregnant women.

e Birthweights and mortality rates referred to the subset of pneumococcal vax recipients who delivered at hospital (n = 235).

f Comparison of local reactions between the sites of PPSV and TT vaccination among 106 vaccinated mothers.

g Rates of swelling at the injection site were available only for one of the two cohorts that comprised the total population of the RCT.

h According to the authors, the observed rates of stillbirths and neonatal mortality were "less that might have been expected".

i According to the authors, "stillbirths and infant death rates observed in this study were within expected ranges".

AEs = adverse events; **cHibV** = conjugate *Haemophilus influenzae* type b vax; **C-section** = caesarean section; **cross-sect.** = cross-sectional; **HB** = hepatitis B; **HBIG** = HB immunoglobulin; **IUGR** = intrauterine growth restriction; **IVF** = *in vitro* fertilization; **LBW** = low birthweight; **LGA** = large for gestational age; **MPSV** = meningococcal polysaccharide vax; **NR** = not reported; **NS** = not statistically significant; **PEP** = post-exposure prophylaxis; **PL** = placebo; **PPSV** = pneumococcal polysaccharide vax; **prosp.** = prospective; **RCT** = randomized controlled trial; **recomb.** = recombinant; **retro.** = retrospective; **SGA** = small gestational age; **TT** = tetanus toxoid vax; **TTN** = transient tachypnoea of the newborn; **vax** = vaccine.

6. Safety of Pneumococcal Polysaccharide Vaccine during Pregnancy

In total, nine prospective studies (two cohort studies,[38,39] seven RCTs,[40-46]) evaluated the safety of PPSV in 795 pregnant women. Only two of the included RCTs had an arm that received placebo or no vaccination,[40,41] while the remaining RCTs compared PPSV with another vaccine during pregnancy.[42-46] All studies used a 23-valent PPSV at the second or third trimester of pregnancy,[38,39,41-46] except for one that used a 14-valent PPSV and for which trimester was not reported.[40]

A prospective cohort study assessing PPSV at the third trimester of pregnancy found that stillbirth rates (0.1%) among 279 pregnant women were similar to those expected in this population (0.15%).[39] Furthermore, in a double-blinded RCT among 12 000 adults, Riley and Douglas[40] found no significant difference in spontaneous abortions (2/187 vs 0/167; $p = 0.6$), stillbirths (6/187 vs 4/167; $p = 0.9$) and congenital defects (1/187 vs 2/167; $p = 0.9$) between 187 and 167 pregnant women who received PPSV and placebo, respectively. Another RCT found no significant difference in prematurity rates among 150 pregnant women who were allocated to three groups (PPSV in the third trimester, PPSV postpartum or no vaccine).[41]

Among studies with available relevant data, local tenderness or pain ranged between 4% and 72%;[41-44] swelling ranged from <5% to 36% between studies;[42-44] fever ranged from 0% to 0.9% between studies;[41-44] stillbirths ranged from 0% to 5.3% between studies,[38-40,43-46] occurred only in Papua New Guinea (9/466; 1.9%)[39,40] and Gambia (4/130; 3.1%),[45,46] and were within expected ranges; preterm deliveries occurred in 1 of 82 (1.2%) vaccinees in Bangladesh;[44] in Texas there were no premature births and most of the delivery complications and perinatal events were within expected ranges;[43] low birthweight was reported in 4 of 82 (4.9%) births in Bangladesh[44] and 11 of 56 (19.6%) births in Gambia;[46] and neonatal mortality ranged from 0% to 3.8% between studies.[38,43-46]

7. Safety of Meningococcal Polysaccharide Vaccine during Pregnancy

A total of six studies, involving 335 women, evaluated the safety of the MPSV in pregnancy.[44-49] Four studies were prospective (three RCTs,[44-46] one cohort[47]), while the remaining two were retrospective (one cohort,[48] one cross-sectional study[49]). Furthermore, four studies examined a tetravalent (A,C,Y,W-135) MPSV,[44,47-49] whereas the remaining two examined a bivalent (A,C) MPSV.[45,46]

Three RCTs (one from Bangladesh,[44] two from Gambia[45,46]) allocated pregnant women to either MPSV or PPSV. As no conclusion could be drawn by comparing MPSV- with PPSV-related AEs, in this review we present data on MPSV. In Bangladesh, there were no stillbirths or serious neonatal illnesses among 75 MPSV pregnant recipients; preterm delivery occurred in a single case (1.3%) and low birthweight occurred in two cases (2.6%).[44] In Gambia, stillbirth rates observed by O'Dempsey et al.[45] (4%) and Obaro et al.[46] (8.8%) in MPSV recipients were, according to the authors, lower than or within that expected for the population ranges; neonatal mortality in both studies (1.3% and 0%, respectively) was also within expected ranges.

A prospective cohort study conducted in Brazil in 1974 followed through delivery 51 pregnant women vaccinated with a bivalent MPSV and recorded no physical abnormalities among newborns.[47] In a retrospective study from Wyoming, the infants of 34 vaccinated pregnant women were evaluated for birth defects and evidence of developmental or neurological abnormalities. The investigators found neither a teratogenic effect of the vaccine on the fetus nor a negative impact on psychomotor development during a 2-year follow-up period. Most of the illnesses diagnosed in hospital were within the expected ranges.[48] In another study, which interviewed 43 women who had been administered an MPSV during pregnancy, no congenital abnormalities or developmental delay were reported.[49]

8. Discussion

Although the interpretation of our findings may be limited by the amount of published studies, the existing evidence suggests that minor local reactions are the most prevalent complaints and that a teratogenic effect on the fetus cannot be directly attributed to the vaccine.

On the other hand, an increased risk for adverse birth outcomes, including spontaneous abortion, preterm labour and stillbirth, cannot be excluded, based on the limited evidence. The studies we reviewed only enrolled a total of 318, 335 and 795 pregnant women for HB vaccine, MPSV and PPSV, respectively.

Regarding HB vaccine, the CDC and the American College of Obstetricians and Gynecologists (ACOG), aiming at preventing perinatal HB transmission and therefore chronic infection, recommend HB vaccination be considered for pregnant women at risk for infection (injection-drug users, women with sexually transmitted diseases, multiple sex partners, household contacts with HB chronic infection).[8,50] Our study showed that the risks from HB vaccination during pregnancy have not been evaluated in any RCT, and that available safety data derive from cohort studies with limited statistical power to detect a negative effect on pregnancy outcome. Additionally, half of the studies regarding HB vaccination used a vaccine deriving from the plasma of chronic hepatitis B carriers. This vaccine has been discontinued since 1990 as it was replaced by recombinant DNA vaccines. Nevertheless, available data on safety suggest that the benefits from HB vaccination outweigh the risks in the above-mentioned cases.

Over the last 2 decades, a total of 88 reports regarding possible AEs of maternal immunization with HB vaccine have been identified in the VAERS database. Interestingly, spontaneous abortions, stillbirths, congenital abnormalities and preterm labour accounted for approximately 50% of reports. Most women were inadvertently vaccinated either shortly before or after conception. Extreme caution is required in the interpretation of the VAERS data. Although numerous significant AEs are reported, no causality can be established. Additionally, one could mention that the reported cases of AEs are few for a 20-year period; however, this may also reflect either underreporting or the fact that pregnant women are

rarely vaccinated against HB. Moreover, a number of AEs is normally expected in the general pregnant population, irrespective of vaccination. For instance, ten stillbirths may be expected if 1000 women had been evaluated (current rate of approximately 1% in the US).

Regarding pneumococcal vaccination in pregnancy, current research is focused on the potential of transplacental IgG antibodies and breastfeeding-acquired secretory IgA antibodies to prevent serious infections in the neonate.[27,28] In the case of MPSV, maternal immunization might be considered during outbreaks caused by vaccine preventable serotypes and among travellers to pandemic areas (e.g. sub-Saharan Africa).[51] Notably, polysaccharide vaccines, although superseded by the more immunogenic conjugate vaccines, are those recommended during pregnancy because of availability of data on safety. Among pregnant women vaccinated with MPSV or PPSV, rates of stillbirth and preterm labour in Bangladesh were rather low for a country with traditionally high rates of pregnancy complications.[44,52] Similarly, stillbirth rates reported in two studies from Gambia were found within expected ranges. Although available data suggest that these vaccines are safe during pregnancy, the small sample size as well as confounding factors (better antenatal care, hospital delivery among study participants) do not allow us to reach firm conclusions.[45,46]

Vaccination during pregnancy always raised concerns. In a study conducted in the US between 1957 and 1966, over 50 000 pregnant women were followed through delivery, and their children were followed for 7 years. No association was found between vaccination (e.g. influenza, poliomyelitis, tetanus and diphtheria vaccines) and pregnancy outcomes or increased risk for infant disability.[53]

Another important issue is the theoretical concern regarding the effects of vaccines' constituents, particularly thiomersal (thimerosal), on the fetus. Thiomersal, an organomercury compound that is used as a preservative in vaccines, has been hypothesized to be associated with a harmful effect on embryonic neurodevelopment.[54] However, clinical studies found no association between prenatal mercury exposure from thiomersal-containing vaccines and neuropsychological problems.[55-57] In addition, in the last decade, manufacturers have been urged to remove thiomersal from vaccine preparations.[57] Nevertheless, it would be prudent to avoid immunization in the first trimester of pregnancy, when the nervous system develops. Lastly, gynaecologists should carefully review the vaccines' excipients and avoid vaccinating women with a history of hypersensitivity to any of these substances.

The role of gynaecologists/obstetricians is crucial for counselling pregnant women toward vaccination. Interestingly, in a recent survey among fellows of ACOG, one-third of the responding physicians agreed that the medical community underestimates the effects of vaccines on the fetus, while the majority stated that their immunization training was inadequate and that their practice would benefit from continuing medical education courses on immunization.[58] The ideal scenario would be for women of childbearing age to have their immunization status reviewed and optimized before pregnancy, when seeking gynaecological healthcare.

Our study has specific limitations that should be taken into consideration in the interpretation of its findings. Apart from the inherent limitations of observational studies and the small sample sizes of included studies, which have already been discussed, most of the reviewed studies primarily aimed at assessing the immunogenicity of vaccination; safety evaluation was a secondary objective that was not always thoroughly addressed. In addition, the evaluation of adverse reactions mostly depended on self-reporting rather than active follow-up. The duration of follow-up also varied; therefore, long-term adverse outcomes may have been missed. Furthermore, one should not underestimate the lack of randomized, placebo-controlled trials and studies in developed countries, which could provide more solid data on this subject. Finally, it should be mentioned that pregnant women may not be a prime target for these vaccines.

9. Conclusions

In summary, the lack of randomized, placebo-controlled trials, as well as the small statistical

power of the reviewed studies, hampered the establishment of any firm conclusions regarding the safety of HB vaccines, PPSVs and MPSVs during pregnancy. In a case-by-case approach, however, the benefits from vaccination in certain circumstances, especially against HB, might outweigh potential AEs. Ethical issues regarding the development of RCTs comparing pregnant women underline the need for large, population-based cohort studies with active follow-up to assess the potential risks of maternal immunization by trimester of vaccination.

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