Review

Maternal Influenza Vaccination and Risk for Congenital Malformations

A Systematic Review and Meta-analysis

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OBJECTIVE: To systematically summarize the literature on maternal influenza vaccination and the risk for congenital malformations using the methodology of meta-analysis.

DATA SOURCES: PubMed, Scopus, and Embase databases (up to December 2014) as well as ClinicalTrials.gov (May 2015) and references of relevant articles were searched. The search strategy included combinations of the terms "influenza," "vaccin*," "pregnan*," "safe*," "adverse," "congenital," "malformation," "defect," and "anomal*."

METHODS OF STUDY SELECTION: Eligible studies examined the association between antepartum or preconceptional maternal immunization with inactivated influenza vaccines (seasonal trivalent or monovalent H1N1) and the risk for congenital malformations. Studies with no or inappropriate control group (comparison with population background rates or other vaccine types) were excluded.

TABULATION, INTEGRATION, AND RESULTS: The risk for congenital anomalies after influenza vaccination was examined in 15 studies: 14 cohorts (events per vaccinated compared with unvaccinated: 859/32,774 [2.6%] compared with 7,644/245,314 [3.1%]) and one case–control study (vaccinated per cases compared with controls: 1,351/3,618 [37.3%] compared with 511/1,225 [41.7%]). Eight studies reported on first-trimester immunization (events per vaccinated compared with unvaccinated: 258/4,733 [5.4%] compared with 6,470/196,054 [3.3%]). No association was found between congenital defects and influenza vaccination at any trimester of pregnancy (odds ratio [OR] 0.96, 95% confidence interval 0.86–1.07; 15 studies; $I^2=36$) or at the first trimester (OR 1.03, 0.91–1.18; eight studies; $I^2=0$). When assessing only major malformations, no increased risk was detected after immunization at any trimester (OR 0.99, 0.88–1.11; 12 studies; $I^2=31.5$) or at the first trimester (OR 0.98, 0.83–1.16; seven studies; $I^2=0$). Neither adjuvanted (OR 1.06, 0.95–1.20; five studies; $I^2=18.8$) nor unadjuvanted vaccines (OR 0.89, 0.75–1.04; seven studies; $I^2=22.6$) were associated with an increased risk for congenital defects.

CONCLUSION: This systematic review did not indicate an increased risk for congenital anomalies after maternal influenza immunization adding to the evidence base on the safety of influenza vaccination in pregnancy.

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Pregnant women are at increased risk for hospitalization, death, and adverse pregnancy outcomes after influenza infection.[1–5] Therefore, routine immunization against influenza is recommended for women who will be pregnant during the influenza season.[6,7] Evidence from randomized controlled trials suggests that antenatal immunization against influenza confers protection of both the mother and the newborn from influenza infection.[8,9] However, vaccination rates

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among pregnant women remain low mainly as a result of concerns about the safety of the influenza vaccine.[10]

Influenza vaccines are available either as live-attenuated–contraindicated during pregnancy–or as inactivated (treated with formaldehyde, β-propiolactone, detergent, ultraviolet irradiation) formulations.[11–13] During the 2009 H1N1 pandemic, a monovalent inactivated vaccine was available for maternal immunization. Currently, seasonal inactivated vaccines containing antigens from three (trivalent) or four (quadrivalent) influenza strains are recommended for pregnant women by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices.[14]

Since 2004, the Advisory Committee on Immunization Practices recommends that pregnant women be vaccinated against influenza at any stage of gestation, including the first trimester.[15] A number of studies sought to assess the safety of antenatal influenza immunization. However, most of these investigations are limited by their small sample size, which obscures the evaluation of rare events such as pregnancy loss and congenital malformations. Two recent systematic reviews suggested that antenatal influenza vaccination is safe with regard to spontaneous abortions, stillbirths, and preterm deliveries.[16,17] The aim of the present study was to systematically summarize the evidence on the risk for congenital malformations in fetuses of women vaccinated with inactivated influenza vaccines during pregnancy compared with those of unvaccinated pregnant women.

SOURCES

The systematic review has been conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines.[18] Three investigators (K.A.P., A.A.K., C.E.P.) independently conducted a systematic literature search on PubMed, Embase, and Scopus databases up to December 2014. The search strategy included combinations of the following search terms: "influenza," "vaccin*," "pregnan*," "safe*," "adverse," "congenital," "malformation," "defect," and "anomal*." After screening the title and abstract, potentially relevant studies were selected for further evaluation in full text. The same search strategy was used in ClinicalTrials.gov (May 2015). References of relevant articles were also searched to identify additional studies.

STUDY SELECTION

To be considered for inclusion in the systematic review, a study should have examined the association between maternal vaccination with an inactivated influenza vaccine (either seasonal trivalent or monovalent H1N1, either adjuvanted or nonadjuvanted) during pregnancy or immediately before conception and congenital malformations. Studies with no or an inappropriate control group (eg, studies comparing outcomes with population background rates, studies comparing influenza vaccine with other vaccine types) were excluded. Only studies published in peer-reviewed journals were considered for inclusion. Abstracts, posters, book chapters, recommendations, review articles, and animal studies were excluded. Publications in languages other than English were not eligible for inclusion.

Two reviewers (K.A.P., A.A.K.) independently extracted the following data: first author, year of publication, country, influenza season, design, study population, effect estimates (odds ratios [ORs]) and 95% confidence intervals (CIs) of vaccine exposure, and potential confounding factors that were controlled by design or analysis. When several effect estimates were reported, that with the highest degree of control for confounding factors was selected. The quality of the eligible studies was assessed by use of the Newcastle-Ottawa scale.[19] Any disagreement was resolved by consensus in meetings that involved all authors.

Odds ratios and 95% CIs of studies that did not report effect estimates were calculated using OpenEpi.[20] Meta-analyses were conducted using Comprehensive Meta Analysis 2. Pooled ORs and 95% CIs were calculated by use of the DerSimonian-Laird random-effects model.[21] Heterogeneity was assessed by using the I^2 statistic and was considered significant if I^2 30% or greater.[22] The primary outcome was congenital malformations 1) in the total study population vaccinated at any trimester; and 2) in the subgroup exposed at the first trimester of pregnancy. A secondary analysis was conducted focusing on major congenital defects as defined by each study; for studies that did not specify whether they examined major or any malformation, we excluded minor defects according to the European registry for congenital anomalies and twins (EUROCAT).[23] Publication bias was assessed by inspection of funnel plots.[24] Sensitivity analysis was performed by excluding an old study (H1N1 A/New Jersey/76 vaccine) probably using a wide definition for congenital anomalies.[25] We also conducted subgroup analyses with regard to the use of adjuvanted or unadjuvanted vaccines and the control (by design or analysis) of at least two potential confounding factors.

RESULTS

The literature search yielded a total of 2,003 records. After exclusion of duplicates and irrelevant studies, 90

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potentially eligible studies were assessed in full text and 15 studies were included in the systematic review (Fig. 1).[25–39] Of the included studies, 10 assessed a monovalent H1N1 2009 pandemic vaccine,[26–35] two studies addressed a seasonal trivalent influenza vaccine,[38,39] two included both,[36,37] whereas an early study explored a monovalent H1N1 (A/New Jersey/76) vaccine[25] (Table 1). Twelve studies provided data on major congenital defects (Appendix 1, available online at http://links.lww.com/AOG/A694). Seven studies did not address confounding,[25,27–29,35,37,38] whereas one study controlled only for age[34] (Table 2). Maternal immunization during the first trimester was explored by eight studies,[27,30–33,35,36,38] of which three reported adjusted effect estimates.[30,32,36]

Of the 10 included studies investigating the H1N1 2009 pandemic vaccine, none demonstrated a significant risk of congenital anomalies. One study in Italy, which compared 6,131 pregnant women immunized at the second or third trimester with 23,987 matched women in a control group, showed small, nonsignificant, but positive ORs overall (adjusted OR 1.14, 0.99–1.31) and for heart defects specifically (adjusted OR 1.22, 0.98–1.51) in children born to vaccinated women.[26] No associations between maternal influenza vaccination and congenital birth defects were found in studies in Germany,[33] France,[29] the Netherlands,[31] Sweden,[30] Denmark,[32] Scotland,[35] Ireland,[27] Argentina,[28] and Taiwan.[34] Two studies provided adjusted effect estimates for congenital anomalies after first-trimester exposure.[30,32] Källén et al[30] found that 3,165 neonates exposed during the first trimester were not at increased risk for congenital anomalies compared with neonates in the unexposed control group. In propensity score-matched analysis of 660 neonates (330 exposed), Pasternak et al showed that first-trimester exposure was not associated with major birth defects.[32]

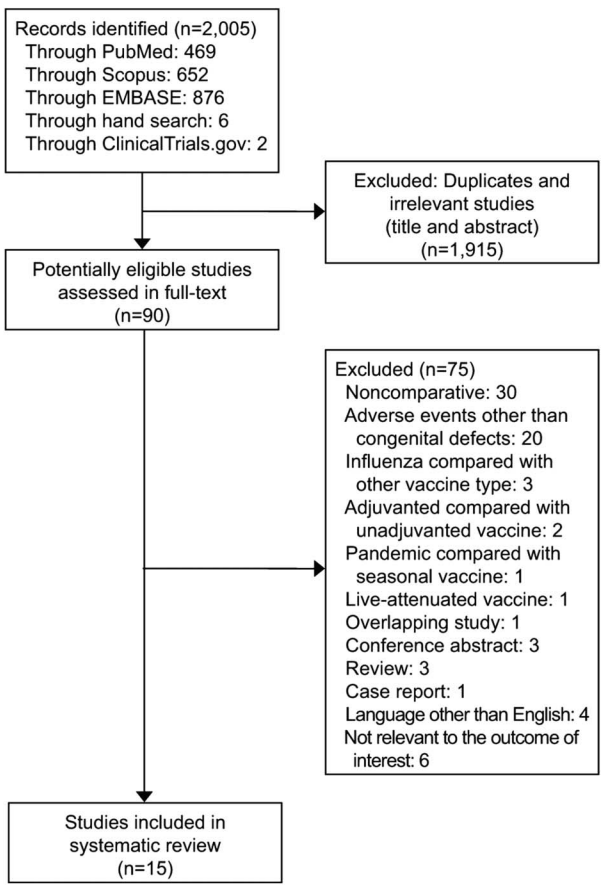

Fig. 1. Flow diagram of the study selection process.
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Two studies assessed the safety of H1N1 2009 pandemic vaccine provided either as monovalent vaccine (2009–2010) or as part of a seasonal trivalent influenza vaccine (2010–2012).[36,37] A prospective cohort study investigated the safety of first-trimester immunization in 328 vaccinated and 188 unvaccinated women and found no increased risk for major malformations.[36] In a case–control study including 3,104 malformed case participants and 1,087 control participants, maternal influenza vaccination did not increase the rate of overall congenital anomalies. Notably, logistic regression analysis of specific defects found an increased risk for anopthalmia or micropthalmia in neonates of exposed women (OR 8.67, 1.10–68.5). However, this estimate was based on very few cases and had wide CIs.[37]

Two retrospective cohort studies in the United States examined the potential teratogenicity of antenatal immunization with seasonal trivalent influenza vaccines.[38,39] The first study (1998–2003) compared 225 pregnant women vaccinated at the second or third trimester with a control group of 826 unvaccinated pregnant women matched by age, month of delivery, and type of medical insurance. No congenital defects were reported in the vaccinated group compared with 15 (1.8%) events in the control group.[39] The second study (2003–2008), including 8,864 immunized and 76,919 unimmunized pregnant women, found no increased risk for major malformations regardless of trimester of vaccination. Importantly, a separate analysis showed no association between first-trimester exposure and congenital anomalies.[38]

During a national immunization program in the United States in 1976–1977, a prospective study investigated the safety of monovalent inactivated influenza A/New Jersey/76 virus vaccine during pregnancy.[25] In

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Table 1. Characteristics of the Included Studies

Study (Location)	Design (Flu Season)	n	Vaccine Type	Trimester of Vaccination (%)	Quality (Newcastle-Ottawa Scale)
Trotta et al, 2014[26] (Italy)	Retrospective cohort (2009–2010)	30,118	H1N1 2009 pandemic, MF59-adjuvanted	T1 (1.2), T2 (40.9), T3 (57.9)*	8
Cleary et al, 2014[27] (Ireland)	Retrospective cohort (2009–2010)	6,894	H1N1 2009 pandemic, nonadjuvanted or AS03-adjuvanted	T1 (8.2), T2 (57), T3 (34.5)	6
Rubinstein et al, 2013[28] (Argentina)	Cross-sectional (2010–2011)	30,488	H1N1 2009 pandemic, MF59-adjuvanted	T1 (39.4), T2 (48.6), T3 (10.1), unknown (1.9)	6
Launay et al, 2012[29] (France)	Prospective cohort (2009–2010)	877	H1N1 2009 pandemic, nonadjuvanted	T2 (81), T3 (19)†	6
Källén et al, 2012[30] (Sweden)	Retrospective cohort (2009–2010)	114,494	H1N1 2009 pandemic, AS03-adjuvanted	T1 (100)	8
Heikkinen et al, 2012[31] (the Netherlands, Italy, Argentina)	Prospective cohort (2009–2010)	4,508	H1N1 2009 pandemic, MF59-adjuvanted	T1 (4), T2 (56.9), T3 (38.7), unknown (0.3)	8
Pasternak et al, 2012[32] (Denmark)	Retrospective cohort (2009–2010)	660	H1N1 2009 pandemic, AS03-adjuvanted	T1 (100)	8
Oppermann et al, 2012[33] (Germany)	Prospective cohort (2009–2010)	1,652	H1N1 2009 pandemic, nonadjuvanted, AS03- or MF59-adjuvanted	Immediately before conception (6.2), T1 (17), T2 (44.6), T3 (32.2)	8
Lin et al, 2012[34] (Taiwan)	Retrospective cohort (2009–2010)	396	H1N1 2009 pandemic, nonadjuvanted	T1 (5.1), T2 (41.4), T3 (53.5)	7
Mackenzie et al, 2011[35] (United Kingdom)	Prospective cohort (2009–2010)	97	H1N1 2009 pandemic, nonadjuvanted or AS03-adjuvanted	Immediately before conception (9.3), T1 (15.1), T2 (50), T3 (25.6)	5
Chambers et al, 2013[36] (United States, Canada)	Prospective cohort (2009–2012)	539	H1N1 2009 pandemic or trivalent influenza vaccine, nonadjuvanted	T1 (100)	8
Louik et al, 2013[37] (United States)	Case–control study (2009–2011)	4,191‡	H1N1 2009 pandemic or trivalent influenza vaccine, nonadjuvanted	T1, T2, or T3	7
Sheffield et al, 2012[38] (United States)	Retrospective cohort (2003–2008)	84,843	Trivalent influenza vaccine, nonadjuvanted	T1 (5.1), T2/T3 (94.9)	6
Munoz et al, 2005[39] (United States)	Retrospective cohort (1998–2003)	1,051	Trivalent influenza vaccine, nonadjuvanted	T2, T3	8
Deinard et al, 1981[25] (United States)	Prospective cohort (1976–77)	706	H1N1 (A/New Jersey/76), nonadjuvanted	Immediately before conception (6.9), T1 (21.7), T2 (30.7), T3 (40.7)	5

T1, first trimester; T2, second trimester; T3, third trimester.
* Percentages refer to vaccinated pregnant women before matching by propensity score and gestational age.
† Percentages refer to gestational age at enrollment of the total study population (vaccinated and unvaccinated).
‡ Case–control study including 3,104 participants in the case group and 1,087 in the control group.

a cohort of 189 immunized (at any trimester) and 517 unimmunized pregnant women, no association was found between maternal vaccination and risk for congenital anomalies.[25]

In the overall meta-analysis of 14 cohorts (events per vaccinated compared with events per unvaccinated: 859/32,774 [2.6%] compared with 7,644/245,314 [3.1%]) and one case–control study (vaccinated per cases compared with vaccinated per controls: 1,351/3,618 [37.3%] compared with 511/1,225 [41.7%]), maternal influenza immunization at any trimester of pregnancy did not increase the risk for congenital defects (OR 0.96, 0.86–1.07; 15 studies; $I^2=36$) (Fig. 2A). Immunization during the first trimester (events per vaccinated compared with events per unvaccinated: 258/4,733 [5.4%] compared with 6,470/196,054 [3.3%]) was not associated with increased risk for congenital malformations (OR 1.03, 0.91–1.18; eight studies; $I^2=0$) (Fig. 2B). In a secondary analysis addressing major birth defects, no association was detected either after

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Table 2. Outcomes of the Included Studies on the Association Between Maternal Influenza Vaccination and Congenital Anomalies

Study	Events/No. Vaccinated	Events/No. Unvaccinated	Effect Estimate (95% CI)	Factors Controlled or Adjusted*
Trotta et al, 2014[26]	276/6,131	945/23,987	aOR 1.14 (0.99–1.31)	Propensity score (age, nationality, education, occupational and civil status, previous deliveries, previous live births, previous cesarean deliveries, comorbidities, drugs, no. of drugs in the past 6 mo, no. of in-hospital deliveries), gestational age at vaccination
Cleary et al, 2014[27]	66/2,996 (T1: 9/246)	110/3,898	OR 0.78 (0.57–1.05) (T1: OR 1.31 [0.65–2.61])	—
Rubinstein et al, 2013[28]	35/7,293	137/23,195	OR 0.81 (0.56–1.18)	—
Launay et al, 2012[29]	4/320	3/557	OR 2.34 (0.52–10.5)	—
Källén et al, 2012[30]	T1: 200/3,197 (severe: 121/3,197)	4,997/111,297 (severe: 4,546/111,297)	aOR 1.00 (0.86–1.15) (severe: aOR 0.94 [0.78–1.13])	Age, BMI, parity, smoking
Heikkinen et al, 2012[31]	56/2,295 (T1: 2/94)	41/2,213	aOR 1.33 (0.88–2.00) (T1: OR 1.15 [0.27–4.83])	Age, parity, smoking, alcohol use, enrollment type, type of health care practitioner enrolling, ethnicity, history of the outcome of interest
Pasternak et al, 2012[32]	T1: 18/330	15/330	pOR 1.21 (0.60–2.45)	Propensity score (age, BMI, birthplace, urban area, parity, smoking, history of birth defects, preterm birth, spontaneous abortion and SGA, comorbidities, use of drugs, health care utilization, no. of hospital admissions and hospital outpatient visits in the past 3 y, no. of drugs used in the past 6 mo)
Oppermann et al, 2012[33]	All: 30/321 (T1: 8/70); major: 10/320 (T1: 2/69)	All: 138/1,198; major: 43/1,196	All: aOR 0.92 (0.58–1.46) (T1: OR 0.99 [0.46–2.11]); major: aOR 1.11 (0.51–2.42) (T1: OR 0.80 [0.19–3.37])	Propensity score (age, BMI, alcohol consumption, smoking, drug consumption, no. of previous pregnancies, no. of previous fetal losses, no. of previous malformed children, other diseases, family medical history)
Lin et al, 2012[34]	4/202	7/206	OR 0.57 (0.17–1.99)	Age
Mackenzie et al, 2011[35]	All: 6/86 (T1 or immediately before conception: 2/21); major: 4/86 (T1: 1/21)	0/11	OR 1.86 (0.10–35.2) (T1: OR 2.95 [0.13–66.94]); major: OR 1.25 [0.06–24.85] (T1: OR 1.68 [0.06–44.76])	—

(*continued*)

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Table 2. Outcomes of the Included Studies on the Association Between Maternal Influenza Vaccination and Congenital Anomalies (*continued*)

Study	Events/No. Vaccinated	Events/No. Unvaccinated	Effect Estimate (95% CI)	Factors Controlled or Adjusted*
Chambers et al, 2013[36]	T1: 9/328	6/188	T1: aOR 0.79 (0.26–2.42)	Age, BMI, race–ethnicity, socioeconomic status, smoking, alcohol, vitamin supplementation, pregnancy history, previous preterm delivery, infection, fever, asthma, depression, autoimmune disease, hypertension, and seasonal vaccine not containing the H1N1 2009 pandemic strain
Louik et al, 2013[37,†]	2009–2010: 709/1,750; 2010–2011: 642/1,868; 2009–2011: 1,351/3,618	2009–2010: 267/570; 2010–2011: 244/655; 2009–2011: 511/1,225	2009–2010: OR 0.77 (0.64–0.93). 2010–2011: OR 0.88 (0.73–1.06). 2009–2011: OR 0.83 (0.73–0.95)	—
Sheffield et al, 2012[38]	136/8,864 (T1: 10/447)	1,163/76,919	OR 1.02 (0.85–1.21) (T1: OR 1.49 [0.79–2.78])	—
Munoz et al, 2005[39]	0/225 (major: 0/225)	15/826 (major: 7/826)	OR 0.12 (0.01–1.95) (major: OR 0.24 [0.01–4.26])	Age, month of delivery, type of medical insurance
Deinard et al, 1981[25]	19/186 (major: 5/186)	67/489 (major: 22/489)	OR 0.72 (0.42–1.23) (major: OR 0.59 [0.22–1.57])	—

CI, confidence interval; aOR, adjusted odds ratio; OR, odds ratio; pOR, prevalence odds ratio; T1, first trimester. BMI, body mass index; SGA, small for gestational age.

* Either by study design (eg, matching) or in the analysis (eg, multivariate regression).

† This is a case–control study, and ratios refer to the percentages of exposed patients among those in the case group and those in the control group. The authors report rates for 2009–2010 and 2010–2011 season separately. We added the numbers, although patients with pregnancies overlapping both seasons were included in both analyses.

exposure at any stage of pregnancy (OR 0.99, 0.88–1.11; 12 studies; $I^2=31.5$) or after first-trimester exposure (OR 0.98, 0.83–1.16; seven studies; $I^2=0$) (Appendix 2, available online at http://links.lww.com/AOG/A695). Inspection of funnel plots did not suggest that publication bias could influence the results (Appendix 3, available online at http://links.lww.com/AOG/A696). In a separate analysis of studies of the H1N1 2009 pandemic vaccine, exposure at any trimester (OR 1.02, 0.91–1.14; 10 studies; $I^2=18.1$]) or first-trimester exposure (OR 1.02, 0.89–1.17; six studies; $I^2=0$) was not associated with congenital defects (Appendix 4, available online at http://links.lww.com/AOG/A697). Finally, the results of the meta-analyses did not change after exclusion of the early study on monovalent inactivated A/New Jersey/76 influenza vaccine (data not shown).[25]

Neither adjuvanted (OR 1.06, 0.95–1.20; five studies; $I^2=18.8$) nor unadjuvanted vaccines (OR 0.89, 0.75–1.04; seven studies; $I^2=22.6$) were associated with congenital malformations (Fig. 3). In subgroup analysis based on the adjustment of confounding bias, any-trimester vaccination did not increase the risk for congenital defects in studies that controlled for confounders (OR 1.07, 0.98–1.18; seven studies; $I^2=0$) and was protective in studies not addressing confounding (OR 0.87, 0.79–0.96; eight studies; $I^2=0$) (Appendix 5A, available online at http://links.lww.com/AOG/A698). Regarding first-trimester exposure, no increased risk for malformations was found in either studies that controlled for confounding (OR 1.00, 0.87–1.16; three studies; $I^2=0$) or those that did not (OR 1.28, 0.88–1.88; five studies; $I^2=0$) (Appendix 5B, available online at http://links.lww.com/AOG/A698).

DISCUSSION

In view of the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists recommendations on routine immunization of pregnant women at any time during pregnancy,

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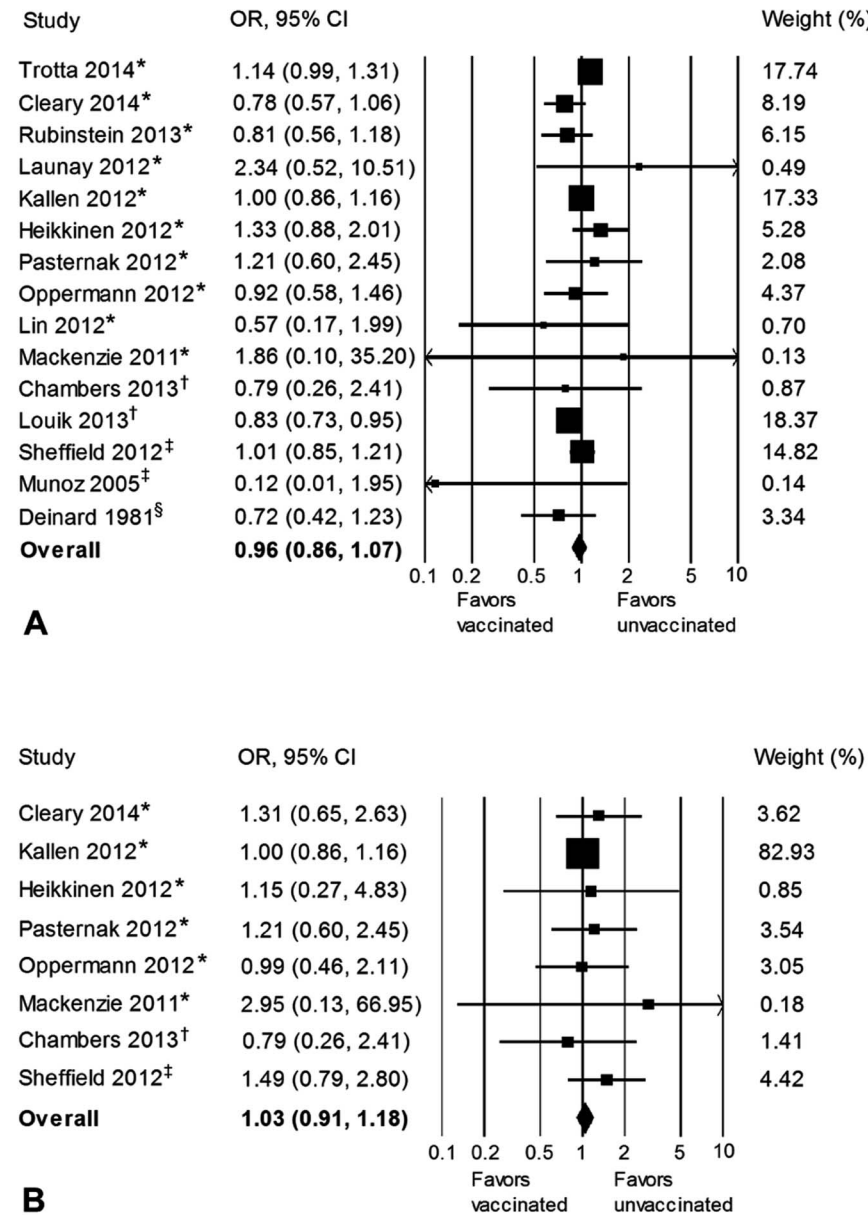

Fig. 2. Forest plots for congenital anomalies associated with maternal influenza immunization at any trimester (**A**) or at the first trimester (**B**) of pregnancy. *Squares* indicate odds ratios (ORs), *horizontal lines* indicate 95% confidence intervals (CIs), *diamonds* indicate pooled ORs. *H1N1pdm09; †H1N1pdm09 or trivalent influenza vaccine; ‡trivalent influenza vaccine; §H1N1 (A/New Jersey/76).

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a theoretical risk for congenital anomalies must be addressed. This systematic review including 15 nonrandomized studies (14 cohorts [278,088 patients; 32,774 vaccinated compared with 245,314 unvaccinated]; one case–control study [4,843 patients; 3,618 in the case group compared with 1,225 in the control group]) found no association between maternal influenza vaccination at any trimester, including the first, and overall or major congenital malformations. No association was also obtained in subgroup analyses with regard to the use of adjuvants and the control of confounding.

The first trimester of pregnancy is the crucial period of organogenesis, and therefore many obstetricians administer the influenza vaccine later in the course of pregnancy. Based on eight studies (4,733 vaccinated compared with 196,054 unvaccinated), our meta-analysis did not indicate an increased risk for malformations associated with first-trimester exposure. Importantly, none of the three studies adjusting for confounding indicated an association between first-trimester exposure and major birth defects.[30,32,36] A limitation is that our analysis was dominated by one large study,[30] thus underscoring the need for further studies assessing first-trimester immunization.

In a previous meta-analysis of seven studies, Jefferson and colleagues[40] assessed potential harms

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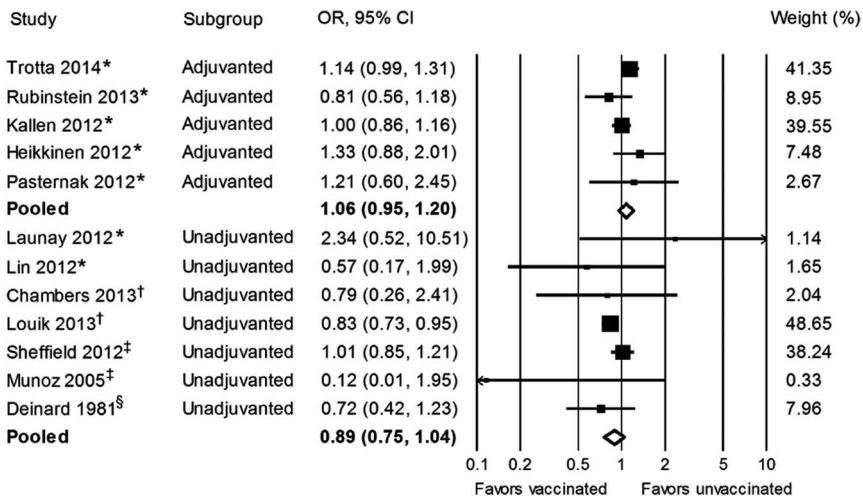

Fig. 3. Subgroup analysis of studies using adjuvanted or unadjuvanted influenza vaccines. Forest plot for congenital anomalies associated with any-trimester influenza immunization. *Squares* indicate odds ratios (ORs), *horizontal lines* indicate 95% confidence intervals (CIs), *open diamonds* indicate pooled ORs for each subgroup. *H1N1pdm09; †H1N1pdm09 or trivalent influenza vaccine; ‡trivalent influenza vaccine; §H1N1 (A/New Jersey/76).

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associated with influenza vaccination during pregnancy and found no increased risk for congenital malformations. Our meta-analysis including 15 studies updates this earlier study, which analyzed total (major and minor) anomalies associated with maternal vaccination at any trimester. In addition, our analysis addressed first-trimester exposure and major congenital malformations adding to the evidence on the safety of maternal influenza immunization.

Adjuvants–compounds that enhance the immune response to vaccination–are frequently used during pandemics as means to spare antigen and meet the demand for mass production. Such compounds have been used for decades in various vaccine types with no evidence of serious or long-term adverse events.[41] During the H1N1 2009 pandemic outbreak, adjuvanted influenza vaccines were licensed in Europe and Canada and administered in pregnant women without being linked with excessive reactogenicity or adverse pregnancy outcomes.[26,30–32,42] In the current meta-analysis, neither adjuvanted nor unadjuvanted influenza vaccines were associated with increased risk for congenital anomalies.

Trotta et al[26] reported a nonsignificant increase in congenital heart defects associated with antenatal influenza immunization. Importantly, nearly 99% of immunized women in this study were vaccinated during the second and third trimesters. The fact that the majority of such defects occur during the first 10 weeks of pregnancy renders a causal association unlikely. Moreover, vaccination was more likely to be administered to women with comorbidities–confounders that may affect the effect estimates if not adequately adjusted. The importance of comparability of study arms in observational studies is illustrated by the heterogeneity between studies with or without confounding bias.

It should be mentioned that there was a limited number of studies assessing trivalent influenza vaccines; the majority of the included studies assessed the monovalent H1N1 2009 pandemic vaccine. A retrospective study among pregnant U.S. military women found similar rates of major birth defects in more than 16,000 newborns exposed either to H1N1 2009 pandemic vaccine or trivalent influenza vaccine (2.1% compared with 2%, respectively; adjusted OR 1.08, 0.87–1.35).[43] In addition, this systematic review excluded studies using population background rates as reference for comparisons. Such studies did not report higher rates of congenital defects after influenza vaccination during pregnancy.[42,44,45]

This meta-analysis has several limitations. First, modest statistical heterogeneity was detected in the analysis of congenital anomalies after vaccination at any trimester of pregnancy. Notably, heterogeneity decreased in a separate analysis of H1N1 2009 pandemic vaccines or in subgroup analysis of adjuvanted compared with unadjuvanted formulations and disappeared after excluding studies that did not address confounding. Second, studies assessing the monovalent H1N1 2009 pandemic vaccine dominated in our pooled analysis. Third, the total number of first-trimester exposed patients in our analysis might not have provided the power to detect small effects, and few studies addressing confounding explored first-trimester vaccination. Finally, in the case–control study providing data on influenza seasons 2009–2010 and 2010–2011 separately, we added the numbers although there was a small overlap between seasons.[37]

In conclusion, this systematic review provided additional evidence on the safety of influenza vaccination during pregnancy with regard to congenital malformations. Given the methodologic limitations of

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observational studies, further research focusing primarily on the risk of first-trimester immunization with trivalent influenza vaccines and adjusting for potential confounders is warranted to better characterize the safety of immunization of pregnant women and increase the vaccination coverage in this high-risk group.

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