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Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007–2013

Elyse Olshen Kharbanda[a,*], Gabriela Vazquez-Benitez[a], Heather S. Lipkind[b], Nicola P. Klein[c], T. Craig Cheetham[d], Allison L. Naleway[e], Grace M. Lee[f], Simon Hambidge[g], Michael L. Jackson[h], Saad B. Omer[i], Natalie McCarthy[j], James D. Nordin[a]

[a] HealthPartners Institute for Education and Research, Minneapolis, MN, United States
[b] Yale University School of Medicine, Department of Obstetrics, Gynecology, & Reproductive Sciences, New Haven, CT, United States
[c] Kaiser Permanente of Northern California, Oakland, CA, United States
[d] Kaiser Permanente of Southern California, Pasadena, CA, United States
[e] Kaiser Permanente Northwest, Portland, OR, United States
[f] Harvard Pilgrim Health Care Institute & Harvard Medical School, Boston, MA, United States
[g] Institute for Health Research, Kaiser Permanente Colorado and Department of Ambulatory Care Services, Denver Health, Denver, CO, United States
[h] Group Health Cooperative, Seattle, WA, United States
[i] Kaiser Permanente Georgia, Atlanta, GA, United States
[j] Centers for Disease Control and Prevention, Atlanta, GA, United States

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ABSTRACT

Introduction: Since October 2012, the combined tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine (Tdap) has been recommended in the United States during every pregnancy.
Methods: In this observational study from the Vaccine Safety Datalink, we describe receipt of Tdap during pregnancy among insured women with live births across seven health systems. Using a retrospective matched cohort, we evaluated risks for selected medically attended adverse events in pregnant women, occurring within 42 days of vaccination. Using a generalized estimating equation, we calculated adjusted incident rate ratios (AIRR).
Results: Our vaccine coverage cohort included 438,487 live births between January 1, 2007 and November 15, 2013. Across the coverage cohort, 14% received Tdap during pregnancy. By 2013, Tdap was administered during pregnancy in 41.7% of live births, primarily in the 3rd trimester. Our vaccine safety cohort included 53,885 vaccinated and 109,253 matched unvaccinated pregnant women. There was no increased risk for a composite outcome of medically attended acute adverse events within 3 days of vaccination. Similarly, across the safety cohort, over a 42 day window, incident neurologic events, thrombotic events, and new onset proteinuria did not differ by maternal receipt of Tdap. Among women receiving Tdap at 20 weeks gestation or later, as compared to their matched controls, there was no increased risk for gestational diabetes or cardiac events while venous thromboembolic events and thrombocytopenia were diagnosed within 42 days of vaccination at slightly decreased rates.
Conclusion: Tdap coverage during pregnancy increased from 2007 through 2013, but was still below 50%. No acute maternal safety signals were detected in this large cohort.

1. Introduction

Outbreaks of pertussis remain a persistent public health challenge across the United States and abroad [1–5]. Although pertussis may be mild in older children and adolescents, infants who contract pertussis are at risk for severe morbidity and mortality. These infants may be too young for vaccination and must rely on vaccination of close contacts (cocooning) and passive transfer of maternal antibodies for protection [6]. Third trimester maternal vaccination is likely to be the most effective strategy available for preventing pertussis in newborns [7–9].

The combined tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine (Tdap) was first recommended for routine administration during pregnancy by the California Department of

* Corresponding author. Tel.: +1 9529675038; fax: +1 9529675022.
E-mail address: Elyse.o.kharbanda@healthpartners.com (E.O. Kharbanda).

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Health in 2010 [10]. The Advisory Committee on Immunization Practices (ACIP) followed in 2011 with national recommendations to administer Tdap at 20 weeks gestation or later to all pregnant women not previously vaccinated [11]. In fall of 2012 the ACIP recommendations were revised, recommending Tdap administration in every pregnancy, preferably between 27 and 36 weeks gestation [12].

To date there are limited published data on receipt of Tdap among pregnant women, especially following the 2012 ACIP guidelines to administer Tdap to women in every pregnancy. In prior work by our group, among live births in 2012 across seven large health systems, less than 20% of women received Tdap during pregnancy [13]. Similarly, in the fall of 2011, data from the Pregnancy Risk Assessment Monitoring System demonstrated that, among women with live births in 16 states and New York City, 9.8% received pertussis vaccine during pregnancy [14]. More recent data from Texas and Wisconsin have demonstrated higher Tdap uptake for pregnant women in 2013 and 2014 [15,16].

Despite these observed increases, many women remain hesitant to receive Tdap during pregnancy due to concerns regarding safety for themselves or their babies [17,18]. Although published data to date on the safety of maternal Tdap, including from one small clinical trial [19] and several observational studies [20–25] have been generally reassuring, continued postmarketing surveillance of maternal Tdap vaccination is needed [26]. Goals of the current study were two-fold: (1) to provide updated estimates of Tdap coverage during pregnancy among insured women within the Vaccine Safety Datalink and (2) to evaluate risks for selected acute adverse events occurring 0–42 days following maternal Tdap vaccination.

2. Methods

2.1. Overview

In this observational cohort study of pregnancies at seven Vaccine Safety Datalink sites, we described Tdap coverage during pregnancy and, using a matched cohort design, we evaluated risks for acute maternal adverse events following maternal Tdap vaccination.

2.2. Study population: Vaccine coverage and vaccine safety cohorts

The Vaccine Safety Datalink (VSD) is a collaboration between the Centers for Disease Control and Prevention's Immunization Safety Office and nine large integrated health care systems in the United States [27]. For the current study, among seven participating VSD sites, with members in six states (California, Colorado, Minnesota, Oregon, Washington and Wisconsin), pregnancies were identified from claims, administrative and electronic health data, using a validated algorithm [28]. This algorithm, used in several prior studies of vaccine coverage [13,29] and vaccine safety during pregnancy [20,30,31], identifies pregnancies, pregnancy outcomes, pregnancy end dates and gestational age at end of pregnancy. The algorithm uses gestational age at end of pregnancy and pregnancy end date to estimate the pregnancy start date, equivalent to the last menstrual period (LMP). Cases of gestational trophoblastic disease, ectopic pregnancy, and pregnancies ending in spontaneous abortion, therapeutic abortion, stillbirth, or with an unknown pregnancy outcome were excluded.

For our *vaccine coverage cohort*, we first identified pregnancies with live births between January 1, 2007 and November 15, 2013. Each pregnancy was recorded as a unique event. Women with 2 or more pregnancies during the observation period could be included more than once. To ensure capture of data on vaccine exposures, women were required to have continuous insurance enrollment for the period 6 months prior to pregnancy start, through pregnancy and 6 weeks following the end of pregnancy or postpartum. For the remaining eligible pregnancies, with a live birth outcome and continuous insurance enrollment, we then obtained all vaccine records from the standardized VSD vaccine files. These files capture vaccines primarily through EHR-linked registries as well as from medical or pharmacy claims and state-based vaccine registries. Similar to prior studies, Tdap vaccines were classified as occurring during pregnancy if administered starting 8 days after LMP through 7 days before delivery [13]. These cut-offs were assigned to account for uncertainty regarding the LMP and specifically to avoid misclassification of postpartum vaccinations as occurring during pregnancy. For Tdap vaccines administered during pregnancy, gestational week of vaccination was defined by subtracting the vaccination date from the estimated pregnancy start date. First trimester was defined as <14 weeks gestation, second trimester as 14 weeks to <28 weeks and third trimester as ≥28 weeks gestation.

For the *vaccine safety cohort*, we started with the vaccine coverage cohort, including both vaccinated and unvaccinated women, and applied the following additional exclusions: multiple gestation pregnancies, women with no medical care during pregnancy and women who received a live virus vaccine. Women receiving Tdap during pregnancy were matched with up to 3 unexposed women using an optimal matching algorithm. Match variables were maternal age (within 1 year), site, and estimated pregnancy start date (within 7 days). Unvaccinated women were assigned an index date equivalent to the gestational age at vaccination for their match.

Covariates of interest included: the Kotelchuck Adequacy of Prenatal Care Utilization Index (APNCU) [32,33] derived from administrative and electronic health record data within the VSD, the number of hospitalizations from LMP to vaccine/index date, and maternal age at delivery. In addition, we evaluated census tract poverty level, defined for each subject as the percent of families in their census tract with income below 150% of the federal poverty level.

2.3. Safety outcomes, exposure periods and risk windows

Outcomes, exposure periods and risk windows were chosen a priori based on prior work by our group on vaccine safety during pregnancy [25,30,31], biologic plausibility [34], and the expected timing of both Tdap vaccination [12] and specific outcomes during pregnancy. All outcomes were identified using diagnostic codes (ICD-9 codes) assigned at inpatient, emergency department or outpatient visits. Washout periods or specific exclusions were applied to ensure that outcomes were incident or new events and not conditions present prior to vaccination/index date in unvaccinated. These outcome specific exclusions are defined in Appendix Table 1. For all pregnancies, we evaluated risks for medically attended allergic reactions, fever, malaise, seizures, altered mental status and local and other reactions for 0–3 days following vaccination/index date. We also evaluated risks for medically attended neurologic events (autonomic disorders, cranial nerve disorders, CNS degeneration/demyelinating conditions, peripheral neuropathy, Guillain-Barré syndrome, meningoencephalitides, movement disorders, paralytic syndromes, and spinocerebellar disease), proteinuria, and venous thromboembolism for 0–42 days following vaccination. Events occurring on the day of vaccination were limited to emergency department or inpatient visits.

For the subset of women vaccinated at 20 weeks gestation or later, (consistent with the 2011 ACIP recommendations) we evaluated risks for incident gestational diabetes, thrombocytopenia, cardiac events (cardiomyopathy, myocarditis, pericarditis, and heart failure), and venous thromboembolism within 42 days of vaccination. Risk windows were truncated at delivery, except for