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ORIGINAL RESEARCH

Investigating Tetanus, Diphtheria, Acellular Pertussis Vaccination During Pregnancy and Risk of Congenital Anomalies

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ABSTRACT

Introduction: This observational retrospective matched cohort study evaluated the safety of a prenatal tetanus, diphtheria, acellular pertussis (Tdap) vaccination, Boostrix. We previously reported on the risk of maternal and neonatal outcomes; here we report on the risk of congenital anomalies in infants at birth through 6 months of age.

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Methods: The study included pregnant Kaiser Permanente Southern California members. Women who received the Tdap vaccine on or after the 27th week of pregnancy between January 2018 and January 2019 were matched to women who were pregnant between January 2012 and December 2014 and were not vaccinated with Tdap during pregnancy. Unadjusted and adjusted relative risks (aRRs) with 95% confidence intervals were estimated by Poisson regression. Quantitative secular trend analyses, from 2011 to 2017, were conducted on congenital anomalies with a statistically significant aRR > 1.

Results: The analysis consisted of 16,350 and 16,088 live-born infants in the Tdap-exposed and unexposed cohorts, respectively. Of the 14 congenital anomaly body systems evaluated, 8 (eye, ear/face/neck, respiratory, upper gastrointestinal, genital, renal, musculoskeletal, integument) had statistically significant elevated aRRs, with point estimates ranging from 1.17 to 2.02. The observed elevated aRRs were consistent with their respective secular increases over time.

Conclusion: Cautious interpretation of these findings is warranted as these increases may have resulted from improved identification and diagnosis. Furthermore, the biological plausibility of an association between maternal vaccine exposure in the third trimester of pregnancy and birth defects is low. The overall study findings support the safety of maternal immunization with Boostrix during the third trimester of pregnancy.

Trial Registration: ClinicalTrials.gov identifier, NCT03463577.

Keywords: Congenital anomalies; Maternal immunization; Observational study; Tdap; Vaccine safety

Key Summary Points

Why carry out this study?

We pursued this analysis to further evaluate maternal vaccination later in pregnancy to provide comprehensive safety information on the prenatal tetanus, diphtheria, acellular pertussis (Tdap) vaccination (Boostrix). As part of pharmacovigilance activities to study the safety of prenatal Tdap vaccination (Boostrix), congenital anomalies were included as pre-specified secondary safety endpoints for exploratory purposes in the study protocol as discussed with the regulatory agency.

This study evaluated the association between maternal Tdap vaccination (Boostrix) and the risk of congenital anomalies in infants at birth through 6 months of age.

What was learned from the study?

Although increased incidences of diagnoses among some congenital anomaly body systems were found after prenatal Tdap vaccination in the late second or third trimester of pregnancy, they were consistent with the secular increases over time, and the magnitude of the increases was modest and within the expected range. The most commonly identified diagnoses tended to be minor congenital anomalies.

This study provides further real-world information on the safety of prenatal Tdap vaccination in an insured, diverse Southern California population. The overall study findings support the safety of maternal immunization with Boostrix during the third trimester of pregnancy.

INTRODUCTION

Congenital anomalies, also known as birth defects, are structural or functional anomalies that develop prenatally and can lead to infant and childhood deaths, chronic illness, and disability [1]. Worldwide, almost 300,000 newborns die annually within 28 days of birth as a result of congenital anomalies [1]. In the USA, congenital anomalies account for 20% of all infant (< 1 year old) deaths [2]. Congenital anomalies include major congenital anomalies such as microcephaly, orofacial clefts, congenital heart defects, and Down syndrome; neural tube defects are considered one of the most common and most serious birth defects [3]. There are also minor congenital anomalies which include absent nails, overlapping digits, and facial asymmetry [3].

Errors in embryogenesis during critical periods of fetal development can lead to structural anomalies [4]. While the first trimester (gestational age 1–13 weeks) is the highest risk period, the critical exposure period during pregnancy can vary depending on the type of anomaly and organ system [4]. There is also variability in embryonic development as it has been suggested that embryos may develop at different rates, and there may be inexactness in determination of gestational age in some pregnancies [5]. The Brighton Collaboration Congenital Anomalies Working Group recommends a relevant exposure period for the evaluation of maternal vaccination safety from 30 days prior to conception to 20 weeks gestational age [4]. This allows for a wider window of teratogen effects and accounts for potential errors in defining the conception date and gestational age, while focusing on the most plausible period for the development of congenital anomalies [4].

Maternal tetanus, diphtheria, acellular pertussis (Tdap) immunization has been shown to be an effective strategy in reducing the incidence of pertussis [6], a highly contagious respiratory disease, that is most severe in infants too young to be fully vaccinated. Since 2012, the Advisory Committee on Immunization Practices (ACIP) has been recommending Tdap vaccines (Adacel [Sanofi Pasteur] and Boostrix [GSK]) to be administered to all pregnant women in the USA, irrespective of prior Tdap vaccination [7, 8]. To optimize transplacental transfer of anti-pertussis antibodies to the fetus, and to help protect the newborn prior to primary childhood vaccination, Tdap vaccine administration between 27 and 36 weeks' gestation is recommended, although Tdap vaccine may be given at any time during pregnancy [8].

There are limited observational studies on Boostrix safety during pregnancy in the USA. Our previous study found no elevated risks of maternal and neonatal outcomes associated with Boostrix vaccination on or after 27 weeks of pregnancy [9]. Even though the third trimester of pregnancy is less sensitive to disruptions in fetal development than earlier in pregnancy, exposure to certain teratogens in late pregnancy can impact organogenesis, resulting in congenital anomalies, including functional defects and minor anomalies [10].

As part of pharmacovigilance activities to study the safety of Boostrix in pregnancy, congenital anomalies were included as pre-specified secondary safety endpoints for exploratory purposes in the study protocol, as discussed with the regulatory agency. In the current publication, we present real-world data on the risk of congenital anomalies identified at birth through 6 months of age among infants born to women receiving Boostrix on or after 27 weeks of pregnancy.

METHODS

Setting

The study was conducted at Kaiser Permanente Southern California (KPSC), an integrated health care system with over 4.6 million members. The demographic make-up of the KPSC membership closely mirrors the Southern California population and the California census population [11, 12]. Data were extracted from the electronic health records (EHR) system which inputs data from outpatient, emergency department, and hospital settings; these data include demographics, diagnoses, procedures,

and vaccinations. In December 2012, KPSC implemented ACIP guidance and recommended Tdap immunization at 27 to 36 weeks' gestation for all pregnant women during each pregnancy, irrespective of the patient's prior history of receiving Tdap vaccine. Prior to the introduction of Boostrix at KPSC in 2018, Adacel was the only Tdap vaccine product used at KPSC. Vaccinations were provided at no cost to KPSC members and were ultimately the decision of the member informed by their physician. The study was approved by the KPSC Institutional Review Board (#11537). A waiver of informed consent was obtained as the Tdap vaccine was a licensed and recommended vaccine for eligible members' routine clinical care and the study involved no direct intervention with the enrolled members. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Study Design

The study design is described in greater detail elsewhere. In short, this was an observational retrospective matched cohort study of pregnant KPSC members, and their infants born at KPSC hospitals (NCT03463577). The exposed cohort consisted of women who received the Tdap vaccine (Boostrix) at KPSC as routine care on or after the first day of the 27th week of pregnancy during the vaccination period January 1, 2018 to January 31, 2019. Although the use of a concurrent unvaccinated comparator was considered, we anticipated that Tdap vaccine uptake in pregnant women at KPSC would exceed 80% during January 2018 to January 2019, making concurrent unvaccinated individuals a select group that would not be representative of pregnant women in general. Instead, we used an unvaccinated comparison group from a historical period when Tdap vaccine uptake in pregnancy remained low. This approach minimized confounding by indication and made it feasible to achieve balanced matching. The exposed cohort was matched 1:1 to the unexposed historical cohort consisting of women who were pregnant at least 1 day during the period January 1, 2012 to December 31, 2014, and were unvaccinated with any Tdap vaccine throughout their pregnancy. Matching variables included maternal age at pregnancy start, race/ethnicity, and multiple gestation. Every unexposed woman was assigned an index date that was determined by the number of days from pregnancy start to the Tdap vaccination date of her matched exposed woman. Continuous membership was required for both the exposed and unexposed cohorts between the first day of the 27th week of pregnancy and the index (vaccination) date to avoid misclassification of vaccination status.

Infant congenital anomalies were identified from the mother's EHR or from the EHR of infants born at KPSC hospitals. Since most congenital anomalies are diagnosed by 6 months of age [4], we identified congenital anomalies at birth through 6 months of age. Congenital anomalies were categorized by body system: nervous; eye; ear, face, or neck; cardiovascular; respiratory; clefts; upper gastrointestinal; lower gastrointestinal; genital organs; renal; musculoskeletal; limb; integument; and other/unspecified. Chromosomal abnormalities were excluded.

International Classification of Diseases, 9th and 10th revision (ICD-9 and ICD-10) codes from the National Birth Defects Prevention Network were used to identify congenital anomaly diagnoses during the infant's 6-month observation period [13]. Cases were chart-reviewed by trained research associates, and for more difficult cases by co-author BKA, a medical doctor, to confirm the diagnosis and onset date (when applicable).

Statistical Analysis

The incidence of congenital anomalies (overall, by type) was calculated as the number of infants with a congenital anomaly in the numerator and the total number of infants born in KPSC hospitals in the denominator during the exposed and unexposed study period. The unadjusted and adjusted relative risks (aRRs) with 95% confidence intervals (CIs) were estimated by Poisson regression models, or modified Poisson regression models with robust error

variances if incidence was greater than 2%, with and without adjustment for potential confounders (e.g., diabetes, hypertension, obesity, Medicaid insurance, prior health care utilization, number of previous pregnancies, history of pregnancy loss, month of pregnancy start, receipt of other vaccines from pregnancy start to index date, receipt of vaccines containing Tdap antigens in the year prior to pregnancy start). Analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

Per protocol, we calculated the frequencies of congenital anomaly ICD codes in the exposed and unexposed cohorts for congenital anomalies with statistically significant elevated aRR.

To inform the interpretation of study results, secular trend plots of background rates of congenital anomalies among all KPSC live-born infants between January 2011 and March 2020 were generated, irrespective of Tdap vaccination status during pregnancy. Methods for the plots are further explained in Supplementary Material 1.

Quantitative secular trend analyses were conducted on the congenital anomalies with a statistically significant aRR > 1. For endpoints with a linear trend over time, the total percentage change of events was estimated on the basis of a linear model established from 2011 to 2017 (prior to the exposed period) and applied an average interval of 5.36 years between the index date of the historical cohort and the Tdap-exposed cohort. For endpoints with no clear linear trend, the total percentage change was estimated by comparing the average rates between 2016–2017 and 2012–2014. Each estimated total percentage change was adjusted for age and race/ethnicity. The total percentage change in the secular trend analyses was used to understand the congenital anomaly background rates by comparing it to the aRR to assess if the direction and magnitude of the trends were consistent. The events for secular trend analyses were not chart-reviewed.

RESULTS

The study population and its characteristics have been described elsewhere in detail [9]. In summary, the exposed cohort consisted of 16,606 pregnant women vaccinated with Tdap in their 27th week of pregnancy or later, matched to an unexposed historical cohort of 16,606 pregnant women. In the exposed and unexposed cohorts there were 16,350 and 16,088 live-born infants, respectively. For the total cohort, the median age at pregnancy start was 30.0 years, and 58.35% of the women were Hispanic, 17.91% were White, 12.91% were Asian, 7.67% were Black, and 3.16% were Other. In the exposed cohort, 6.86% of the live-born infants were born before 37 weeks' gestation, while 9.42% in the unexposed cohort were born before 37 weeks' gestation.

In the exposed and unexposed cohorts, 21.91% versus 16.34% of the infants had one congenital anomaly, 3.43% versus 2.09% of the infants had two congenital anomalies, and overall, less than 1% of the infants had three or more congenital anomalies (Table 1). The majority of the infants in both the exposed and unexposed cohorts had no detected congenital anomalies, 74.02% versus 81.22%, respectively. The incidence of congenital anomalies of the eye was the highest in both groups, with 69.85 per 1000 persons (95% CI 66.05–73.87) in the exposed cohort versus 60.48 per 1000 persons (56.91–64.28) in the unexposed cohort. The second highest was the incidence of congenital anomalies of the upper gastrointestinal system with 67.83 per 1000 persons (64.08–71.79) in the exposed cohort compared to 37.85 per 1000 persons (35.02–40.92) in the unexposed cohort.

There were eight congenital body systems with statistically significant elevated aRRs comparing the exposed versus unexposed cohorts, with point estimates ranging from 1.17 to 2.02: eye (aRR 1.17, 95% CI 1.06–1.29); ear, face, or neck (2.02, 1.59–2.55); respiratory (1.34, 1.07–1.68); upper gastrointestinal (1.75, 1.57–1.95); genital organs (1.19, 1.01–1.42); renal (1.40; 1.04–1.88); musculoskeletal (1.50; 1.21–1.86); and integument (1.98, 1.76–2.23) (Table 1). The aRRs of the six other congenital anomaly body systems were not significantly elevated.

For each of the eight body systems with elevated aRRs, ICD-9 and ICD-10 diagnosis codes are described in Supplementary Material 2. For

Table 1 Incidence and relative risk of congenital anomalies comparing Tdap-exposed and unexposed cohorts

Congenital anomalies system	Exposed (*N* = 16,350)		Unexposed (*N* = 16,088)		Relative risk (Wald 95% CI)	
	Number of events	Incidence per 1000 persons (95% CI)	Number of events	Incidence per 1000 persons (95% CI)	Unadjusted	Adjusted[b]
Congenital anomalies at birth through 6 months of age[a]	4247	259.76 (253.12–266.56)	3022	187.84 (181.90–193.98)	N/A	N/A
Nervous system	46	2.81 (2.11–3.76)	38	2.36 (1.72–3.25)	1.19 (0.78–1.83)	1.35 (0.81–2.24)
Eye[c]	1142	69.85 (66.05–73.87)	973	60.48 (56.91–64.28)	1.15 (1.06–1.25)	1.17 (1.06–1.29)
Ear, face, or neck	266	16.27 (14.43–18.35)	131	8.14 (6.86–9.66)	2.00 (1.62–2.46)	2.02 (1.59–2.55)
Cardiovascular system[c]	399	24.40 (22.15–26.89)	351	21.82 (19.67–24.20)	1.12 (0.97–1.29)	1.12 (0.96–1.31)
Respiratory system	225	13.76 (12.08–15.68)	166	10.32 (8.86–12.01)	1.33 (1.09–1.63)	1.34 (1.07–1.68)
Clefts	32	1.96 (1.38–2.77)	24	1.49 (1.00–2.23)	1.31 (0.77–2.23)	1.41 (0.78–2.57)
Upper gastrointestinal system[c]	1109	67.83 (64.08–71.79)	609	37.85 (35.02–40.92)	1.79 (1.63–1.97)	1.75 (1.57–1.95)
Lower gastrointestinal system	22	1.35 (0.89–2.04)	37	2.30 (1.67–3.17)	0.59 (0.35–0.99)	0.63 (0.36–1.12)
Genital organs	355	21.71 (19.57–24.09)	297	18.46 (16.48–20.68)	1.18 (1.01–1.37)	1.19 (1.01–1.42)
Renal system	128	7.83 (6.58–9.31)	95	5.91 (4.83–7.22)	1.33 (1.02–1.73)	1.40 (1.04–1.88)
Musculoskeletal system	266	16.27 (14.43–18.35)	171	10.63 (9.15–12.35)	1.53 (1.26–1.85)	1.50 (1.21–1.86)
Limb	116	7.09 (5.91–8.51)	111	6.90 (5.73–8.31)	1.03 (0.79–1.33)	1.13 (0.85–1.52)
Integument[c]	949	58.04 (54.57–61.74)	477	29.65 (27.14–32.39)	1.96 (1.76–2.18)	1.98 (1.76–2.23)
Other and unspecified congenital anomalies	32	1.96 (1.38–2.77)	33	2.05 (1.46–2.89)	0.95 (0.59–1.55)	1.09 (0.64–1.85)

Number of congenital anomalies (based on body system) per infant	Number of events	Proportion of infants, % (95% CI)	Number of events	Proportion of infants, % (95% CI)		
0	12,103	74.02 (73.36–74.70)	13,066	81.22 (80.61–81.82)	N/A	N/A
1	3582	21.91 (21.28–22.55)	2629	16.34 (15.78–16.92)	N/A	N/A
2	560	3.43 (3.16–3.72)	337	2.09 (1.88–2.33)	N/A	N/A
3	66	0.40 (0.32–0.51)	36	0.22 (0.16–0.31)	N/A	N/A
≥ 4	39	0.24 (0.17–0.33)	20	0.12 (0.08–0.19)	N/A	N/A

CI confidence interval, *N* sample size, *N/A* not applicable, *Tdap* tetanus, diphtheria, acellular pertussis

[a]Identified among Kaiser Permanente Southern California (KPSC) live-born infants

[b]Adjusted for covariates (diabetes, pre-existing hypertension, Medicaid insurance, any hospitalization or emergency department visit from pregnancy start to index date, number of outpatient visits from pregnancy start to index date, number of previous pregnancies, history of pregnancy loss, month of pregnancy start, received other vaccines from pregnancy start to index date, received vaccines containing diphtheria, tetanus toxoid, or pertussis antigens within 1 year before pregnancy, and pre-pregnancy obesity) in the model for each endpoint except for model of congenital anomalies of nervous system where number of outpatient visits from pregnancy start to index date was removed from model because of convergence issues, and models of congenital anomalies of lower gastrointestinal system and other and unspecified congenital anomalies where number of previous pregnancies was removed from model because of convergence issues

[c]Poisson regression model with robust variance estimate

the eye, the most common diagnosis was congenital stenosis and stricture of the lacrimal duct (i.e., excessive tearing) in the exposed group (93.35%) and specified congenital anomalies of lacrimal passages (i.e., blocked tear duct) in the unexposed group (92.39%). For the ear, face, and neck, the most common diagnosis was accessory auricle in the exposed group (29.32%) and in the unexposed group (41.98%). In the respiratory system, the most common diagnosis was congenital laryngomalacia (i.e., noisy breathing) in the exposed group (87.11%) and other anomalies of larynx, trachea, and bronchus in the unexposed group (87.95%). In the upper gastrointestinal system, the most common diagnosis was ankyloglossia (i.e., tongue-tie) in the exposed group (95.85%) and tongue-tie in the unexposed group (92.45%). For the genital organs, the most common diagnosis was unspecified undescended testicle, unilateral in the exposed group (22.54%) and undescended testis in the unexposed group (34.68%). Within the renal system, the most common diagnosis was congenital hydronephrosis (i.e., build-up of urine in the kidneys) in the exposed group (85.16%) and other obstructive defects of renal pelvis and ureter in the unexposed group (70.53%). In the musculoskeletal system, the most common diagnosis was macrocephaly in the exposed group (18.05%) and anomalies of skull and face bones in the unexposed group (14.04%). For the integument, the most common diagnosis was other specified congenital malformations of the skin (e.g., Mongolian spot) in the exposed group (42.26%) and congenital pigmentary anomalies of skin in the unexposed group (45.70%).

The observed increased risks in the exposed compared to the unexposed cohorts in the study were consistent with and fell within the expected range of the total percentage change estimated from the secular trends (irrespective of prenatal Tdap vaccination) of congenital

Table 2 Secular trends analyses of congenital anomalies among KPSC live-born infants of all pregnant women

Congenital anomalies	Adjusted relative risk (Wald 95% CI)[a]	Total percentage change (5.36 years)[b,c,d] (%, 95% CI)
Congenital anomalies of eye[e]	1.17 (1.06–1.29)	3.6 (0.4–6.8)
Congenital anomalies of ear, face, or neck[f]	2.02 (1.59–2.55)	75.0 (57.7–94.1)
Congenital anomalies of respiratory system[e]	1.34 (1.07–1.68)	5.4 (− 3.1 to 14.6)
Congenital anomalies of upper gastrointestinal system[f]	1.75 (1.57–1.95)	56.6 (50.2–63.2)
Congenital anomalies of genital organs[e]	1.19 (1.01–1.42)	4.1 (− 2.5 to 11.1)
Congenital anomalies of renal system[e]	1.40 (1.04–1.88)	37.0 (24.7–50.6)
Congenital anomalies of musculoskeletal system[f]	1.50 (1.21–1.86)	63.4 (57.7–69.2)
Congenital anomalies of integument[f]	1.98 (1.76–2.23)	101 (91.4–111)

CI confidence interval, *KPSC* Kaiser Permanente Southern California

[a]From Table 1 presented for side-by-side comparison

[b]Average days (years) between index dates of historical cohort and exposed cohort was 1957.6 days (5.36 years)

[c]Adjusted for age and race/ethnicity

[d]Analysis was based on automated data

[e]The total percentage change was estimated by comparing the average rates between 2016–2017 vs. 2012–2014

[f]The total percentage change was estimated on the basis of a model with a linear trend from 2011 to 2017

anomalies of the renal system (37.0%, 95% CI 24.7–50.6), musculoskeletal system (63.4%, 57.7–69.2), and integument (101%, 91.4–111) (Table 2). For the remaining five congenital anomaly body systems with increased aRRs (eye; ear, face, or neck; respiratory system; upper gastrointestinal system; and genital organs), the total percentage change estimated from the secular trends was generally lower than the magnitude of increased risk; however, the pattern of increasing incidence of diagnoses over time appeared consistent with the observed increased aRRs. The secular trends of congenital anomalies are displayed in Supplementary Material 3. There were some secular increases in the background rates of certain congenital anomalies spanning the historical comparator period to the Tdap-exposed study period.

DISCUSSION

This study provides information on the safety of a prenatal Tdap vaccination with regards to several congenital anomalies in a large, diverse cohort at an integrated healthcare organization. Historically, pregnant women have been excluded from pre-licensure vaccine safety studies despite an increasing number of vaccines now being recommended during pregnancy [14, 15]. Even post-licensure, pregnant women may hesitate to get vaccinated because of concerns about safety for the fetus and long-term risks to the infant [16, 17]. Thus, it is important to evaluate vaccine safety at all stages of pregnancy to provide pertinent information regarding risks and benefits. This study shows that, overall, although increased incidences were observed for some congenital anomalies in the Tdap-exposed study period as compared to the historical comparator period, similar secular increases in the background rates of these diagnoses were also observed over time.

Congenital anomalies can be major or minor. Major anomalies account for substantial death, morbidity and disability in infants, and can have significant adverse impacts on an infant's life expectancy, health status, and functional, anatomical, psychological, and social well-being [4, 18]. Variability in severity of the clinical presentation of the anomaly can have emotional, financial, and medical implications for patients and their families [19]. Major anomalies can present externally (e.g., neural tube defects, microcephaly, clefts), internally (e.g., congenital heart defects, renal agenesis/hypoplasia), or chromosomally (Down syndrome) [18]. In contrast, minor congenital anomalies are less severe, do not significantly affect the infant's health, and can have minor social or cosmetic presentations; some examples include absent nails, facial asymmetry, overlapping digits, or umbilical hernia [18]. While previous studies tended to focus only on Tdap vaccination and risk of major congenital anomalies, for this study, all congenital anomalies, regardless of whether they were major or minor, were investigated per Brighton Collaboration recommendations [20].

The current study found a higher incidence of congenital anomalies than is typically observed in the literature. One study combining data from 39 US population-based birth defects surveillance programs to calculate pooled prevalence estimates found an adjusted national prevalence per 10,000 live births of 16.9 for clubfoot and 19.9 for 12 congenital heart defects [21]. In the current study, in the exposed cohort, congenital anomalies of the musculoskeletal system and cardiovascular system had an incidence of 163/10,000 persons and 244/10,000 persons, respectively. The higher incidences observed in the current study could have been, in part, due to the inclusion of minor congenital anomalies, alongside the major ones. Furthermore, the rates of congenital anomalies from this study may not be directly comparable to the rates in the literature as a result of methodological differences. Studies varied in the use of active or passive surveillance, types of congenital anomalies selected for inclusion, length of follow-up, completion of case confirmation, geographic region, and study period [21–24].

There were several body systems with elevated aRRs; within those systems, the most common congenital anomaly diagnosed tended to be minor. For example, we found the highest aRR to be 2.02 for congenital anomalies of the

ear, face, or neck. Within this body system, the most common diagnosis in both the exposed and unexposed cohorts was for accessory auricle (e.g., preauricular skin tag), a benign malformation. Other benign diagnoses observed in body systems with elevated aRRs included blocked tear duct, tongue-tie, and skin pigment anomalies. We also observed an elevated aRR for the genital organs, with undescended testis as the most common diagnosis identified in both the exposed and the unexposed groups. Other studies such as that done by Kerr et al., using data from the Slone Epidemiology Center Birth Defects Study, found that for second or third trimester Tdap vaccine exposure, there was no evidence of appreciable risks for 15 birth defects including minor ones (e.g., undescended testicle) [25]. However, that study evaluated the aRRs for individual outcomes, rather than whole body systems like in this current study.

Conversely, we did not observe statistically significant elevated aRRs for the nervous or cardiovascular systems, body systems generally associated with major structural birth defects. Similarly, a study by DeSilva et al. found no increased risk of Tdap vaccination in the third trimester of pregnancy for both microcephaly (a condition of the nervous system) and various major structural birth defects such as spina bifida and severe congenital heart disease [26]. Hall et al., looked at pregnant US military women who were exposed to Tdap vaccine or unexposed at 0–13 weeks' gestation [27]. Maternal exposure to Tdap vaccine in the first trimester was not associated with any major structural birth defect, including cardiovascular birth defects. Other studies, such as the Kerr et al. study mentioned previously, also found no evidence of appreciable risks for major (e.g., clubfoot) birth defects associated with Tdap vaccine exposure during pregnancy [25]. On the other hand, another study by Mai et al. found there was increasing prevalence of gastroschisis, a hole in the abdominal wall next to the belly button (part of the musculoskeletal system) over time [21]. This current study found an elevated aRR of congenital anomalies of the musculoskeletal system. However, the aRR was consistent with the total percentage change estimated from the secular trends. Further still, Sancovski et al. evaluated the safety of Boostrix vaccination among 1203 vaccinated and 1259 unvaccinated pregnant women in Brazil and found no increased risk of congenital anomalies [28]; however, the study was greatly underpowered, and the incidence rate ratio estimates had wide CIs. Several other studies still found no increased risk of infant congenital anomalies or birth defects with maternal Tdap vaccination [29–31].

This study has several strengths. It was conducted among members of a prepaid health plan (KPSC), reducing the likelihood of differential access to healthcare between the vaccinated and unvaccinated cohorts. A historical unvaccinated cohort was used to reduce confounding by indication as vaccine uptake was lower during that period compared to the vaccinated cohort period. The study was EHR-based, rather than relying on claims data, which allowed for detailed review of medical records of congenital anomalies. Lastly, we evaluated the secular trends of congenital anomaly diagnoses over time to better understand background rates and to facilitate the interpretation of findings.

There are also limitations to this study. While Brighton Collaboration recommends assessing congenital anomalies possibly associated with maternal vaccination from − 30 days to 20 weeks' gestation, in the USA, Tdap is recommended at 27 weeks' gestation or later, a period when the biological plausibility of an association between maternal vaccination and major birth defects is low. Nevertheless, congenital anomalies can still occur as a result of exposures later in pregnancy during organogenesis. Other studies have evaluated the risk of major birth defects following maternal Tdap vaccination occurring during similar pregnancy exposure periods [4, 25, 26]. Also, by using a historical comparison group, secular confounding may have been introduced. However, given the lower Tdap vaccine uptake during this historical period, the historical unvaccinated cohort was likely more representative of unvaccinated pregnant women. During the alternative Tdap-exposed study period, the prenatal Tdap vaccine uptake was over 80% and an unvaccinated concurrent comparator would

yield a small and selective sample that would not be broadly representative of unvaccinated pregnant women. To avoid confounding by indication, we used a historical comparison group during a time when Tdap vaccination uptake was slowly increasing. Moreover, there may have been different background rates for the events identified from the exposed and unexposed cohorts; these could have been different because of care improvement, as well as changes in diagnostic criteria, health-seeking behavior, and the coding system (ICD-9 to ICD-10 transition). Trend analyses were completed to examine background rates. In addition, within each body system, ICD codes were used to identify the most common diagnoses in the exposed versus the unexposed groups; these tended to be for minor congenital anomalies. Over time, congenital anomaly coding and reporting might have continued to improve [21, 32], leading to increased capture and diagnosis of minor conditions; the capture of major congenital anomalies might not have been significantly affected by these changes as their diagnoses might have been more well-established. To further minimize bias, several potential confounders were controlled for in the multivariable analyses. Lastly, the study population consisted of individuals who were part of a prepaid integrated healthcare system which might limit the generalizability of the study results. The results might not be applicable to uninsured or underinsured populations where access to vaccine and prenatal care is scarce. The study population was also representative of Southern California's racial/ethnic make-up, which might not be representative of other parts of the USA.

CONCLUSIONS

This study provides further real-world information on the safety of prenatal Tdap vaccination in an insured Southern California population. Although an increased incidence of diagnoses among some congenital anomaly body systems was found after prenatal Tdap vaccination in the late second or third trimester of pregnancy, the elevations were consistent with the secular increases over time, and the magnitude of the increases was modest and within the expected range. In addition, the most commonly identified diagnoses in the Tdap vaccine-exposed cohort tended to be minor congenital anomalies that may have occurred owing to improved identification and diagnosis over time. The increases should thus be interpreted with caution. Reassuringly, minor congenital anomalies tend to have no significant medical or major cosmetic consequences. Furthermore, per the Brighton Collaboration, maternal vaccination after 20 weeks' gestation is unlikely to be within the risk window for congenital anomalies. The biological plausibility of an association between maternal vaccine exposure in the third trimester of pregnancy and birth defects is low. Nevertheless, we pursued this analysis to further evaluate maternal vaccination later in pregnancy to provide comprehensive safety information on the Boostrix vaccine. The overall study findings support the safety of maternal immunization with Boostrix during the third trimester of pregnancy.

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Compliance with Ethics Guidelines. The study was approved by the KPSC Institutional Review Board (#11537). A waiver of informed consent was obtained as the Tdap vaccine was a licensed and recommended vaccine for eligible members' routine clinical care and the study involved no direct intervention with the enrolled members. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to privacy concerns.

Trademarks. Adacel is a trademark owned by or licensed to Sanofi Pasteur. Boostrix is a trademark owned by or licensed to the GSK group of companies.

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