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MAJOR ARTICLE

Pregnancy Outcomes in Women Screened for Tuberculosis Infection in Swedish Antenatal Care

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Background. Tuberculosis (TB) disease has been associated with pregnancy complications. However, the potential impact of TB infection (TBI) on pregnancy outcome is unknown. To investigate this, we conducted a register-based study in immigrant women screened with QuantiFERON assays for TBI in antenatal care in Sweden.

Methods. Women with history of immigration from TB-endemic countries were eligible for inclusion if national identification numbers and available QuantiFERON results obtained during pregnancy from 2014 to 2018 were available. QuantiFERON results were linked to data on maternal characteristics and pregnancy outcomes from the national Pregnancy and Patient Registers. TBI was defined as nil-corrected QuantiFERON result ≥0.35 IU/mL, in the absence of TB disease. Pregnancies in women with TB disease or human immunodeficiency virus were excluded, as were multiplex pregnancies, pregnancies resulting in miscarriage, and pregnancies occurring >10 years after immigration. Odds of defined adverse pregnancy outcomes were compared by maternal TBI status using mixed effects logistic regression with adjustment for maternal age and region of origin.

Results. In total, 7408 women with 12 443 pregnancies were included. In multivariable analysis, stillbirth (adjusted odds ratio [AOR], 1.90; 95% confidence interval [CI], 1.13–3.21; $P = .016$), severe preeclampsia (AOR, 1.62; 95% CI, 1.03–2.56; $P = .036$), low birthweight (<2500 g; AOR, 1.38; 95% CI, 1.01–1.88; $P = .041$), and emergency cesarean section (AOR, 1.28; 95% CI, 1.02–1.63; $P = .033$) were significantly associated with TBI.

Conclusions. Among immigrant women seeking antenatal care in Sweden, TBI was independently associated with adverse pregnancy outcomes. Further studies are needed to corroborate these findings and to explore mechanisms involved.

Keywords. latent tuberculosis infection; tuberculosis; stillbirth; preeclampsia; pregnancy.

The incidence of severe pregnancy complications in Sweden is among the lowest in the world, with stillbirth occurring in <4/1000 births [1]. However, similar to other high-income countries, immigrants from low-income regions have higher rates of stillbirth, as well as preterm birth, with most pronounced excess incidence among women of African origin [2, 3]. The reasons underlying this discrepancy remain unclear; apart from socioeconomic conditions [2, 4], it has been suggested that infectious diseases may be involved [5, 6]. In this context, tuberculosis (TB) is of special interest because it disproportionately affects persons from low-and middle-income countries, with >90% of cases of TB disease in Sweden occurring in individuals originating from TB-endemic areas [7].

Several reciprocal interactions between TB and pregnancy exist. TB is a leading nonobstetric cause of maternal mortality globally [8, 9] and has also been associated with a range of other pregnancy complications, including preterm delivery, low birthweight, and perinatal mortality [10–12]. In addition, the incidence of TB disease is elevated in connection to pregnancy [13, 14].

TB infection (TBI) is commonly defined as immune sensitization to *Mycobacterium tuberculosis* without evidence of TB disease, and is currently regarded as a continuous spectrum, ranging from spontaneously resolved infection to incipient TB with elevated bacterial activity and risk of progression to TB disease [15, 16]. The increased incidence of TB disease reported during pregnancy and postpartum [13, 14] probably reflects progression of TBI triggered by physiological immune modifications [17]. Furthermore, recent studies (both in

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pregnant women and in other population groups) imply that TBI can be associated with systemic pro-inflammatory responses [18–20].

In this study, we aimed to explore the association between TBI and pregnancy complications, based on register linkage of women with history of immigration to Sweden from TB-endemic countries who were offered routine screening for TBI during antenatal care.

METHODS

Study Setting

Screening for TBI among women with history of immigration from TB-endemic countries (TB incidence >100/100 000 per year [21]) was implemented in antenatal care in most regions of Sweden in 2014, based on QuantiFERON (QFT) assays (QuantiFERON-TB GOLD IN-TUBE or GOLD PLUS [Qiagen, Hilden, Germany]). Women with positive QFT results and/or clinically suspected TB disease are referred to infectious disease clinics for further evaluation. Pregnancy per se is not an indication for TB preventive therapy (TPT) according to Swedish guidelines. TPT is recommended for women with recent (<2 years) contact with contagious TB or other recognized risk factors for disease progression, regardless of pregnancy status [22].

Study Design

QFT results obtained at pregnancy screening 2014–2018 from 5 Swedish regions (Skåne, Kalmar, Värmland, Östergötland, and Stockholm; total uptake population, 4.8 million) were linked to data from the Patient Register, Pregnancy Register, and Population Register. Data linkage was performed by the National Health and Welfare Board using national identification numbers (available for Swedish citizens and immigrants with permanent residence permit).

The Patient Register was used to extract data on International Classification of Diagnosis-10 (ICD-10) codes from hospital admissions and outpatient visits in specialized healthcare from 2000 to 2019 (including delivery clinics). The Pregnancy Register was introduced in 2014 and covers 97%–98% of deliveries in Sweden. This register contains demographic, medical, and obstetric information, as well as detailed pregnancy outcome data, including ICD-10 codes, from primary and specialized obstetric care for all registered pregnancies. Data were collected from the Pregnancy Register from 2014 until June 2020. Data on immigration dates and region of origin were collected from the Population Register. For individuals with ICD-10 codes indicating TB disease, data on case notification were retrieved from the Public Health Agency of Sweden.

Individuals without valid QFT results or national identification numbers were excluded, as were women who were tested outside of pregnancy, or with residence in Sweden since before 2000, and women with human immunodeficiency virus (HIV). Pregnancies occurring >10 years after immigration to Sweden, multiplex pregnancies, pregnancies ending with miscarriage or induced abortion, and pregnancies in women with TB disease before or in connection to the index pregnancy were excluded from this analysis. All pregnancies occurring for each included participant during the study period were eligible for inclusion. Separately, we characterized pregnancy outcomes in women diagnosed with TB disease in connection to pregnancy.

Study Definitions

QuantiFERON results were categorized as positive or negative, as recommended by the manufacturer, using a cutoff level of *M. tuberculosis* antigen-stimulated interferon-γ of 0.35 IU/mL (after correction for nil-tube interferon-γ levels). Only individuals with valid QFT result were eligible; indeterminate QFT results were not considered. Because of the low TB transmission rate in Sweden, we assumed that participants with negative QFT results did not acquire TB infection after the time of testing, and that participants with positive QFT results had acquired TB infection before immigration to Sweden. Episodes of TB disease were identified in the Patient Register using ICD codes (Supplementary Table 1). If these ICD codes had been assigned from clinics not routinely involved in management of TB, we also required notification in the Public Health Agency TB Register to define TB disease.

Pregnancies were identified from the Patient Register (2000–2019) as well as from the Pregnancy Register (2014–June 2020) (Supplementary Table 1). The following pregnancy complications were defined by presence of ICD-10 codes obtained from the Patient Register (Supplementary Table 1): preeclampsia, severe preeclampsia (including eclampsia and hemolysis, elevated liver enzymes, low platelet count syndrome syndrome), polyhydramnios, oligohydramnios, emergency cesarean section, stillbirth, and intrauterine growth restriction. From the Pregnancy Register the following additional outcomes were collected: birthweight (analyzed both as continuous and categorical variable [low birthweight, < 2500 g]), gestational length (analyzed both as continuous and categorical variable [prematurity, < 37 weeks of gestation]), stillbirth, neonatal death, and emergency cesarean section.

For descriptive purposes, African origin was further subdivided into Northern Africa and sub-Saharan Africa. Because of the high proportion of immigrants from the Horn of Africa in Sweden, persons with this geographical origin were described separately. Similarly, Asian origin was further subdivided into Central, Eastern, South-eastern, Southern, and Western Asia.

Statistical Analysis

Each outcome was assessed for univariate association with TBI status using simple logistic regression, followed by

multivariable analyses using generalized linear mixed modelling with binomial distribution for categorical and linear distribution for continuous outcomes. To adjust for dependence between repeated pregnancies for the same woman (ie, cluster effects), the models contained random effects for maternal identity.

The main multivariable analyses were adjusted for maternal age at delivery (categorized with five 5-year intervals) and region of origin. To allow convergence of the mixed effect regression models, the variable geographical origin was reduced to African versus non-African origin (Table 1).

As a sensitivity analysis, we performed multivariable analyses with adjustment for parity (categorized at 0, 1–2, 3–5, and >5), highest level of completed education, body mass index ([BMI] categorized with thresholds at <25, 25–30, and >30 kg/m^2), and smoking status at the inclusion visit, in addition to maternal age and region of origin (for women with available information for all these variables). To allow for convergence of the expanded models, the variable parity was reduced to first versus repeated pregnancy for the analysis of 3 outcomes (severe preeclampsia, polyhydramnios, and placental ablatio). Furthermore, subgroup analyses were performed for women of African and Asian origin, respectively (Supplementary Table 2). These adjusted for age in tertiles to allow model convergence.

The distribution of birthweight and gestational length were explored with respect to maternal TBI. Besides analysis based on categorical definitions of low birthweight and prematurity, fixed effects quantile regression was applied to analyze adjusted differences on the second, third, fifth, and 10th percentiles, with similar adjustments. Quantile regression was performed to explore whether effects on these outcomes were more pronounced in a subset of participants, effects that may be diluted in analysis of average data.

Characteristics associated with stillbirths were presented descriptively by TBI status and gestational length.

Statistical analysis was performed in R, version 1.4.1717 [23]. Mixed effect models and quantile regression were preformed using the lme4 [24] and quantreg [25] R packages, respectively.

Ethical Considerations

Ethical approval was granted by the Swedish Ethical Review Authority (DNR 2019-01448).

RESULTS

Participant Characteristics

Of 10 464 women with valid QFT results and at least 1 registered pregnancy, 3056 (29.2%) were excluded, leaving 7408 women with 12 443 pregnancies for analysis (Figure 1). The proportions of women with TBI were similar among excluded and included women (16.1% vs 19.0%).

Table 1. Characteristics of Included Study Participants at Their Pregnancies

	Total	TB Uninfected	TBI
Characteristic	N = 12 443	N = 9907	N = 2536
	N (%)	N (%)	N (%)
Age (y), mean (SD)[a]	29.4 (5.4)	29.2 (5.3)	30 (5.4)
≤20	274 (2.2)	226 (2.3)	48 (1.9)
>20–25	2418 (19.4)	2001 (20.2)	417 (16.4)
>25–30	4020 (32.3)	3235 (32.7)	785 (31)
>30–35	3382 (27.2)	2631 (26.6)	751 (29.6)
>35–40	1530 (12.3)	1170 (11.8)	360 (14.2)
>40	345 (2.8)	252 (2.5)	93 (3.7)
NA	474 (3.8)	392 (4)	82 (3.2)
Time since immigration, y			
≤2	4270 (34.3)	3536 (35.7)	734 (28.9)
>2–5	4400 (35.4)	3484 (35.2)	916 (36.1)
>5–10	3773 (30.3)	2887 (29.1)	886 (34.9)
NA	0 (0)	0 (0)	0 (0)
Highest level of education completed[b]			
Less than 9 y	1518 (12.2)	1107 (11.2)	411 (16.2)
At least 9 y	2379 (19.2)	1884 (19)	495 (19.5)
Secondary school	2965 (23.8)	2408 (24.3)	557 (22)
University	2372 (19.1)	1990 (20.1)	382 (15.1)
NA	3209 (25.8)	2518 (25.4)	691 (27.2)
Geographical origin			
Africa	5700 (45.8)	4019 (40.6)	1681 (66.3)
Horn of Africa[b]	3264 (26.2)	2286 (23.1)	978 (38.9)
Other sub-Saharan Africa	857 (6.9)	588 (5.9)	269 (10.6)
North Africa	441 (3.5)	387 (3.9)	63 (2.5)
Africa, unspecified country	1138 (9.1)	767 (7.7)	371 (14.6)
Asia	5818 (46.8)	5076 (51.2)	742 (29.3)
Central	90 (1.5)	79 (0.8)	11 (0.4)
Eastern	267 (4.5)	204 (2.1)	63 (2.5)
South-Eastern	512 (8.8)	404 (4.1)	108 (4.3)
Southern	1872 (32.2)	1617 (16.3)	255 (10.1)
Western	2015 (34.6)	1834 (18.5)	181 (7.1)
Asia, unspecified country	1062 (18.2)	938 (9.5)	124 (4.9)
Europe	751 (6)	695 (7)	89 (3.5)
North America	14 (0.1)	10 (0.1)	4 (0.2)
Oceania	4 (0)	1 (0)	3 (0.1)
South America	106 (0.9)	90 (0.9)	16 (0.6)
NA	17 (0.1)	16 (0.2)	1 (0)
Parity			
0	4405 (35.4)	3596 (36.3)	809 (31.9)
1–2	5774 (46.4)	4618 (46.6)	1156 (45.6)
3–5	1534 (12.3)	1138 (11.5)	396 (15.6)
>5	226 (4.1)	145 (1.5)	81 (3.2)
NA	504 (4.1)	410 (4.1)	94 (3.7)
Sex of offspring			
Female	4660 (37.5)	3753 (37.9)	907 (35.8)
Male	4786 (38.5)	3848 (38.8)	938 (37.0)
NA	2997 (24.1)	2306 (23.3)	691 (27.3)
BMI (kg/m^2, mean [SD])[b]	25.6 (5)	25.5 (5)	26.2 (5.1)
≤25	4597 (36.9)	3793 (38.3)	804 (31.7)
>25–30	2857 (23)	2256 (22.8)	601 (23.7)
>30	1609 (12.9)	1257 (12.7)	352 (13.9)
NA	3380 (27.2)	2601 (26.3)	779 (30.7)
Smoking at enrollment			
Yes	193 (1.6)	168 (2.3)	25 (1.4)

Table 1. Continued

	Total	TB Uninfected	TBI
No	8857 (71.2)	7111 (97.7)	1746 (98.6)
NA	3393 (27.3)	2628 (26.5)	765 (30.2)

Each woman may be represented by more than 1 pregnancy. BMI was measured at antenatal care enrollment.

Abbreviations: BMI, body mass index; NA, not available; SD, standard deviation; TB, tuberculosis; TBI, tuberculosis infection.

[a]Continuous outcomes are represented by mean, SD, and crude and adjusted difference rather than those indicated at the table header.

[b]Ethiopia, Eritrea, Somalia, and Djibouti were considered to constitute the Horn of Africa.

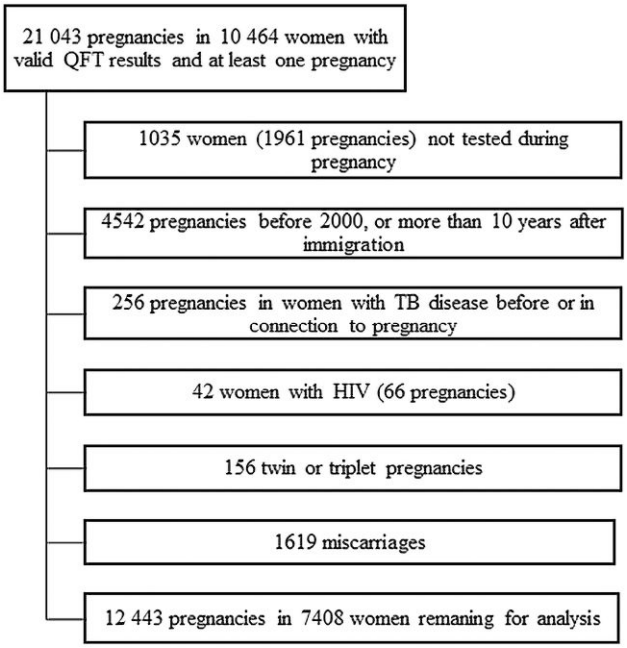

Figure 1. Flow chart of inclusion of women originating from tuberculosis (TB)-endemic countries screened for latent TB infection during pregnancy.

Among included participants, 1408 (19.0%) had TBI. In total, 2536 (20.4%) of 12 443 deliveries occurred in participants with TBI (Table 1). Women with TBI were more frequently of African origin (834/1408, 59.2% vs 2101/6000, 35.0%). Among women of African origin, 71.5% (n = 3264) were from the Horn of Africa. The distribution of TBI was comparable among women from the Horn of Africa (450/1599, 28.1%) versus other sub-Saharan countries (153/503, 30.4%). Participants with TBI were similar to TB-uninfected women with regard to mean age at registration of pregnancy (30.0 vs 29.2 years) and history of previous pregnancy (68.1% vs 64.7%). The proportion of women with >5 years' residence in Sweden was similar with respect to TBI status (34.9% vs 29.1%), as was mean BMI (26.2 kg/m^2 vs 25.5 kg/m^2). Smoking at antenatal care enrollment was less frequently reported by women with TBI (25/1771 [1.4%] vs 168/7279 [2.3%]), and women with TBI more frequently reported <9 years of formal schooling (16.2% vs 11.2%).

Pregnancy Outcomes With Respect to TBI

In univariable analysis, pregnancies in women with TBI were more frequently associated with stillbirth (odds ratio [OR], 2.16; 95% confidence interval [CI], 1.34–3.40), preeclampsia (OR, 1.33; 95% CI, 1.03–1.70), severe preeclampsia (OR, 1.68; 95% CI, 1.17–2.38), low birthweight (OR, 1.26; 95% CI, 1.00–1.59), and emergency cesarean section (OR, 1.23; 95% CI, 1.08–1.40) compared with pregnancies in TB-uninfected women (Table 2).

In multivariable analysis adjusted for maternal age and region of origin, TBI remained associated with stillbirth (adjusted odds ratio [AOR], 1.90; 95% CI, 1.13–3.21; $P = .016$), low birthweight (AOR, 1.38; 95% CI, 1.01–1.88; $P = .041$), and emergency cesarean section (AOR, 1.28; 95% CI, 1.02–1.63; $P = .033$; Table 2). The association with preeclampsia did not reach statistical significance in multivariable analysis, but severe preeclampsia (including hemolysis, elevated liver enzymes, low platelet count syndrome and eclampsia) remained significantly associated with TBI (AOR, 1.62; 95% CI, 1.03–2.56; $P = .036$).

In subgroup analyses of women of Asian and African origin, respectively, TBI was significantly associated with stillbirth, severe preeclampsia, low birthweight, and prematurity in women of Asian origin, whereas these associations did not reach statistical significance in the subset of women originating from Africa (Supplementary Table 2).

Mean birthweight and gestational length were similar with respect to TBI. Despite this, low birthweight remained significantly associated with TBI, suggesting that an effect on birthweight might not be uniform but rather restricted to a subset of women with TBI. For this reason, multivariable quantile regression was performed for the association between maternal TBI and birthweight and for gestational age, respectively. This revealed a difference of 210 g (95% CI, 87–333 g; $P = .0008$) at the third birthweight percentile, after adjustment for age and origin (Table 2). Similarly, the third percentile of gestational age was 1.07 weeks (95% CI, .26–1.89 weeks; $P = .01$) shorter in women with TBI after adjustment for age and origin.

Multivariable regressions using the expanded set of covariates was limited by considerable proportions of missing data for some covariates. A total of 7479 (60.1%) pregnancies were included in this analysis. Confidence intervals were wider for these models. Stillbirth (AOR, 1.97; $P = .051$), severe preeclampsia (AOR, 1.83; $P = .060$), and low birthweight (AOR, 1.38; $P = .080$) did not reach statistical significance. However, adjusted OR estimates indicate similar strength of the associations between TBI and the outcomes compared with the main multivariable analysis. Quantile regression analyses with the expanded set of covariates yielded comparable results to the main analyses (Table 2).

Table 2. Pregnancy Outcomes by Maternal TBI Status

	TB Uninfected	TBI	Crude Analysis			Adjusted Analysis			Expanded Adjusted Analysis		
Categorical outcomes	N (%)	N (%)	COR	95% CI	*P*	AOR	95% CI	*P*	AOR	95% CI	*P*
Stillbirth	51 (0.51)	28 (1.1)	2.16	1.34–3.40	.001	1.90	1.13–3.21	.016	1.97	1.00–3.91	.051
Neonatal death	7 (0.09)	4 (0.22)	2.35	.62–7.81	.17	1.90	.54–6.68	.32	2.98	.57–15.6	.20
Preeclampsia	246 (2.5)	83 (3.3)	1.33	1.03–1.70	.028	1.27	.79–2.04	.32	1.22	.65–2.26	.54
Severe preeclampsia[a]	103 (1.0)	44 (1.7)	1.68	1.17–2.38	.004	1.62	1.03–2.56	.036	1.85	.98–3.49	.060
Emergency cesarean section	1119 (11.3)	344 (13.6)	1.23	1.08–1.40	.002	1.28	1.02–1.63	.033	1.68	1.23–2.28	.0009
Placental ablation	37 (0.4)	13 (0.5)	1.37	.70–2.52	.33	1.34	.61–2.98	.46	1.41	.62–3.24	.41
Polyhydramnios	55 (0.6)	21 (0.8)	1.50	.88–2.44	.12	1.29	.65–2.58	.47	1.40	.60–3.23	.43
Oligohydramnios	283 (2.9)	73 (2.9)	1.01	.77–1.30	.95	.91	.66–1.25	.56	1.02	.67–1.53	.94
Low birthweight[b]	319 (4.2)	97 (5.3)	1.26	1.00–1.59	.049	1.38	1.01–1.88	.041	1.38	.96–1.98	.080
Prematurity[c]	356 (4.7)	97 (5.3)	1.13	.89–1.42	.29	1.23	.92–1.64	.16	1.32	.96–1.81	.087
IUGR[d]	486 (4.9)	126 (5.0)	1.01	.83–1.23	.90	1.04	.79–1.36	.79	1.18	.82–1.69	.38
Continuous outcomes	Value	Value	Diff.	95% CI	*P*	Adj. diff.	95% CI	*P*	Adj. diff.	95% CI	*P*
Birthweight (g), mean (SD)	3407 (560)	3424 (607)	16	−13–45	.27	−3.5	−37–30	.84	−11	−48–26	.56
Birthweight 2nd percentile	2094	1866	−228	−514–34	.086	−145	−426–136	.31	−269	−412 – −124	.0003
Birthweight 3rd percentile	2345	2155	−190	−323 – −57	.0052	−210	−333 – −87	.0008	−191	−336 – −48	.009
Birthweight 5th percentile	2570	2460	−110	−244–24	.10	−114	−237–9	.0069	−119	−240–1	.052
Birthweight 10th percentile	2790	2760	−30	−85–25	.10	−62	−123 – −1	.045	−45	−98–8	.095
Gestation (wk), mean (SD)	39.7 (2.0)	39.7 (2.2)	0.00	−.10–.10	.98	−0.09	−.20–.02	.17	−0.11	−.23–.01	.10
Gestation 2nd percentile	34.6	34.0	−.60	−2.1–.99	.47	−1.29	−2.7–.16	.082	−1.27	−2.39 – −.15	.027
Gestation 3rd percentile	36.0	35.1	−.90	−1.89 – −.12	.026	−1.07	−1.89 – −.26	.0099	−1.14	−2.34–.05	.060
Gestation 5th percentile	37.0	36.9	−.10	−.73–.44	.63	−0.42	−.99–.13	.13	−0.57	−1.03 – −.11	.016
Gestation 10th percentile	38.0	37.9	−.10	−.40–.11	.27	−0.14	−.37–.09	.22	−0.20	−.44–.04	.11

Adjustments were made for maternal age and African origin, with random effects fitted for maternal study code to account for repeated observations. Because of missing data, the adjusted models excluded 481 (3.9%) pregnancies. The expanded adjusted analyses also include covariates maternal education, parity, body mass index, and smoking; because of missing data, 4964 (39.9%) pregnancies were excluded from these models. Quantile regression models for percentiles of birthweight and gestational age did not include random effects.

Abbreviations: Adj. diff., adjusted difference; AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; Diff., crude difference; HELLP, hemolysis, elevated liver enzymes, low platelet count syndrome; ICD, International Classification of Disease; IUGR, intrauterine growth restriction; NA, not available; SD, standard deviation; SGA, small for gestational age; TB, tuberculosis; TBI, TB infection.

[a]Severe preeclampsia, HELLP syndrome, or eclampsia. This model required parity to be categorized at 0 or >0 to allow model convergence.

[b]IUGR defined by presence of ICD-10 code O365 (maternity care due to known or suspected IUGR).

[c]Low birthweight was defined as birthweight <2500 g.

[d]Prematurity was defined as gestational length <37 weeks.

Characteristics of stillbirths in women with TBI were compared with those of TB-uninfected women, further disaggregated by prematurity, as shown in Table 3. Proportions of preterm delivery were higher in stillbirths with maternal TBI (14/28, 50% vs 17/51, 33%; not significant). Gestational diabetes mellitus was recorded in 6 (11.8%) stillbirths of TB-uninfected participants and none in participants with TBI (NS). Two cases of chorioamnionitis were recorded in preterm stillbirths of women with TBI.

Thirty-two pregnancies were recorded in women with TB disease in connection to pregnancy. None of these resulted in stillbirth. Three women with TB disease (9.4%) had preeclampsia, 1 had oligohydramnios, 6 (18.8%) were delivered by emergency cesarean section, and 1 had intrauterine growth restriction.

DISCUSSION

In this study, we investigated whether TBI contributes to the excess burden of adverse pregnancy outcomes in women with history of immigration to Sweden from TB-endemic countries. We found significantly increased incidence of stillbirth, severe preeclampsia, emergency cesarean section, and low infant birthweight in pregnancies of women with TBI.

The differences remained in multivariable analysis after adjustment for maternal age and African versus non-African region of origin.

TB disease has been associated with a range of adverse pregnancy outcomes, although the pathogenesis has not been elucidated. Different mechanisms have been implicated for the impact of other microbes on pregnancy; either direct invasion of the fetus or placenta or effects mediated by pathogen-induced immune responses [26, 27]. The placental vascularization may be affected by maternal immune alterations [27], which in turn could have adverse impact on pregnancy outcome [27, 28]. Similar mechanisms have been proposed to be involved in pregnant women with TB disease [29].

Both epidemiological and laboratory data suggest that the balance of immune control in women with TBI changes during pregnancy [13, 14, 17]. The elevated incidence of TB disease in

Table 3. Characteristics of Pregnancies Complicated by Stillbirths by TBI Status

Characteristics	TB-uninfected		TBI	
	≥37 wk	<37 wk	≥37 wk	<37 wk
Age (y)	N = 34	N = 17	N = 14	N = 14
≤20	0	1 (5.9)	0	0
21–25	4 (11.8)	2 (11.8)	4 (28.6)	1 (7.1)
26–30	6 (17.6)	5 (29.4)	5 (35.7)	4 (28.6)
31–35	13 (38.2)	4 (23.5)	2 (14.3)	8 (57.1)
36–40	7 (20.6	3 (17.6)	1 (7.1)	1 (7.1)
>40	1 (2.9)	1 (5.9)	0	0
NA	3 (8.8)	1 (5.9)	2 (14.3)	0
Parity				
0	13 (38.2)	5 (29.4)	8 (57.1)	4 (28.6)
1–2	10 (29.4)	9 (52.9)	4 (28.6)	6 (42.9)
3–5	8 (23.5)	1 (5.9)	0	4 (28.6)
>5	0	1 (5.9)	0	0
NA	3 (8.8)	1 (5.9)	2 (14.3)	0
Gestational age, wk				
<27	0	6 (35.3)	0	3 (21.4)
27–36 + 6	0	9 (35.3)	0	10 (71.4)
37–41 + 6	18 (52.9)	0	5 (35.7)	0
≥42	2 (5.9)	0	0	0
NA	14 (41.2)	2 (11.8)	9 (64.3)	1 (7.1)
IUGR[a]	1 (2.9)	3 (17.6)	0	2 (14.3)
Gestational DM	5 (14.7)	1 (5.9)	0	0
PPROM	1 (2.9)	1 (5.9)	0	1 (7.1)
Ablation	3 (8.8)	0	1 (7.1)	1 (7.1)
Emergency cesarean section	5 (14.7)	2 (11.8)	1 (7.1)	0
Maternal sepsis	0	0	0	0
Bacterial chorioamnionitis	0	0	0	2 (14.3)
Puerperal infection[b]	6 (17.6)	1 (5.9)	2 (14.3)	1 (7.1)

In this table, stratification by preterm birth was based on (1) gestational age and, if absent, (2) presence of ICD-10 codes indicating preterm birth.

Abbreviations: HELLP syndrome, hemolysis, elevated liver enzymes, low platelet count syndrome; ICD, International Classification of Disease; IUGR, intrauterine growth restriction; NA, not available; PROM, premature preterm rupture of membranes; TB, tuberculosis; TBI, tuberculosis infection.

[a]IUGR defined by presence of ICD-10 code O365 (maternity care due to known or suspected IUGR).

[b]Puerperal infection defined by presence of ICD-10 codes O85 and O86.

connection to pregnancy observed in low-endemic countries is likely to be due to pregnancy-induced progression of TBI [13, 14]. Furthermore, we and other researchers have found altered *M. tuberculosis*–specific immune responses during pregnancy [17, 20, 30, 31], suggesting that the host–pathogen interaction changes during pregnancy [17, 20].This register-based study was not designed to investigate mechanisms involved in these phenomena. Yet, we speculate that low-grade inflammation triggered by TBI during pregnancy might be involved in the association between TBI and pregnancy complications observed in our study population [26, 27, 32]. Interestingly, analysis of continuous variables using quantile regression revealed that while mean birthweight and gestational length were almost identical with respect to TBI status, there were substantial differences in the lower-end distribution of these variables, especially around the third percentiles. This suggests that the effect of TBI on gestational length and birthweight is concentrated in a subset of pregnancies.

In subanalysis of women originating from Asia (constituting 47% of the study population and 29% of women with TBI), several pregnancy complications showed strong associations with TBI, supporting the association between TBI and pregnancy complications. However, these associations did not reach statistical significance among women of African origin. The reasons underlying this discrepancy cannot be determined from our study design. Because most these women originated from the Horn of Africa, it is possible that other factors (eg, socioeconomic condition) had a stronger impact on pregnancy outcome in this subpopulation. In line with this, the burden of stillbirth and severe preeclampsia were lower among Asian compared with African TB uninfected women.

To our knowledge, the association between TBI and pregnancy outcome has not been studied previously using a similar design. In a small study performed in Ethiopia, we found higher rates of stillbirth in women with TBI (4.0% vs 2.7%); however, this difference did not reach statistical significance [33].

Further studies are needed, both to corroborate our findings from other settings and to investigate the mechanisms involved in the association between TBI and pregnancy complications observed in our study.

Our study was based on immigrant women seeking antenatal care in Sweden who met indications for routine TBI screening, which was performed using interferon-γ release assays. We excluded women with TB disease before in connection to the pregnancy for a reliable definition of TBI. These data were linked to national registers containing detailed information on pregnancy outcomes as well as factors that may contribute to these outcomes, minimizing the risk of confounding. Importantly, all women in the target population had equal access to antenatal care, with nearly all deliveries in Sweden taking place within the public healthcare system.

Certain limitations should be considered. To reduce the risk of residual confounding, we chose to limit the study population to women originating from TB-endemic countries, all of whom were eligible for TB screening during pregnancy according to Swedish guidelines. Data on potentially confounding variables, such as socioeconomic status, were not available. For some covariates, data were missing from relatively high proportions of women; for example, information on BMI was not available in 27.2% of pregnancies. For this reason, we performed 2 sets of multivariable analyses. Although multivariable analysis based on the expanded set of covariates had reduced power because of lower study sample, the OR estimates were similar, indicating that these covariates did not explain the observed association between TBI and pregnancy outcome. In support of this, a literature review performed by Gissler et al. [4] concluded that socioeconomic background characteristics explain only a minor proportion of the excess risk of perinatal mortality in immigrant groups in industrialized countries.

Similar to other studies on TBI, we were unable to categorize participants with regard to degree of bacterial activity and persistence. It is probable that some study participants with TBI had spontaneously resolved infection [16], whereas others could have had incipient TB that did not progress to clinically overt active disease. In addition, we did not have information on receipt of TPT. Recent trials in women with HIV have shown inconsistent results regarding the effect of TPT on pregnancy outcomes [34, 35]. In light of this, and that TPT is not generally recommended for pregnant women in Swedish guidelines, we consider it unlikely that TPT would explain the observed differences in pregnancy outcomes. Furthermore, our data sources did not allow for analysis of the potential impact of TBI on fetal deaths occurring before 22 gestational weeks.

CONCLUSION

In women immigrating to Sweden from TB-endemic countries and who underwent routine TBI screening during antenatal care, TBI was independently associated with increased risk of stillbirth, severe preeclampsia, emergency cesarean section, and low birthweight. Further studies are needed to corroborate these findings and to explore pathophysiological mechanisms.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Conflicts of interest. P. B. reports private donation to Lund University for research in tuberculosis/human immunodeficiency virus (TB/HIV) in Ethiopia (not related to the current work); payment for lectures to author from Gilead Inc; participation in advisory board for Gilead Inc (payment to author; not related to TB); unpaid board member of Physicians against AIDS research committee (until 2022); donation of Quantiferon enzyme-linked immunosorbent assay kits for research projects in Ethiopia (not related to current work). E. S. and J. W. report donation of Quantiferon enzyme-linked immunosorbent assay kits for research projects in Ethiopia (not related to current work). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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