

Supplementary Material

For “Association between use of macrolides use in pregnancy and risk of major birth defects”
Andersson et al.

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References

Definition of major birth defects.

Through the National Patient Registry, we identified outcome cases of major birth defects diagnosed within the first year of life.[1] Major malformations were defined according to the European Surveillance of Congenital Anomalies (EUROCAT) classification system of subgroups of major congenital anomalies, while excluding minor defects according EUROCAT exclusion list.[2] Major birth defects of known causes were excluded, including: genetic syndromes (ICD-10: Q447B, Q619A, Q751, Q754, Q771, Q772, Q780, Q796, Q85, Q87), malformation syndromes with known causes (ICD-10: Q86), and malformations due to chromosomal aberrations (ICD-10: Q90-99).

Supplementary Table A. Definition of covariates included in propensity score with definitions and data sources.

Variable	Categories	Data source
Age at pregnancy onset	≤19, 20-24, 25-29, 30-34, ≥35	Central Person Registry
Married or living with partner	Yes/no	Central Person Registry
Place of birth	Denmark, Europe, Outside Europe	Central Person Registry
Region of residence	The Capital Region of Denmark, Region Zealand, The Region of Southern Denmark, Central Denmark Region, The North Denmark Region	Central Person Registry
Gross household income	Quartiles	Statistic Denmark
Education level, years	≤11, 12-13, 14-15, ≥16	Statistic Denmark
Year of pregnancy onset	1997-2000, 2001-2004, 2005-2008, 2009-2012, 2013-2016	Medical Birth Registry
Parity	1,2, ≥3	Medical Birth Registry
Multiple birth pregnancy	Yes/no	Medical Birth Registry
Smoking during pregnancy	Yes/no	Medical Birth Registry
Previous pregnancy with major birth defect	Yes/no	National Patient Registry
Antidiabetic drug use in past year	ATC: A10A, A10B	Registry of Medicinal Product Statistics
Drugs used for IVF in past 3 months	ATC: G03G, G03DA04, H01CC, L02AE01	Registry of Medicinal Product Statistics
No. of drugs used in past year	0, 1-2, 3-4, ≥5	Registry of Medicinal Product Statistics
No. of days of hospitalization in past year	0, 1-2, ≥3	National Patient Registry
No. of outpatient contacts in past year	0, 1-2, ≥3	National Patient Registry

ATC: anatomic therapeutic chemical; IVF: in vitro fertilization.

Supplementary Table B. Number of missing values (percentages) for the unmatched study cohorts.

Variable	Macrolide vs penicillin (n=64,534)	Macrolide vs recent use (n=53,364)	Macrolide vs unexposed (n=1,008,692)
Age at pregnancy onset	0	0	0
Married or living with partner	164 (0.3)	135 (0.3)	13624 (1.4)
Place of birth	2 (0.0)	3 (0.0)	311 (0.0)
Region of residence	0	0	0
Gross household income	2 (0.0)	3 (0.0)	666 (0.1)
Education level, years	1643 (2.5)	1141 (2.1)	40525 (4.0)
Year of pregnancy onset	0	0	0
Parity	294 (0.5)	317 (0.6)	5420 (0.5)
Multiple birth pregnancy	0	0	0
Smoking during pregnancy	1668 (2.6)	1430 (2.7)	23550 (2.3)
Previous pregnancy with the same adverse fetal outcome	0	0	0
Antidiabetic drug use in past year	0	0	0
Drugs used for IVF in past 3 months	0	0	0
No. of drugs used in past year	0	0	0
Hospital care utilization in past year	0	0	0

Supplementary Table C. Baseline characteristics of unmatched cohorts.^a

Characteristics	Unmatched pregnancy cohorts for analysis of major birth defects			
	Macrolide-exposed (n=13019)	Penicillin-exposed (n=51515)	Unexposed with recent use (n=40345)	Unexposed (n=995673)
GA at drug use initiation, median (IQR)	28 (13-54)	39 (18-62)		
Age at pregnancy onset				
≤19	586 (4.5)	637 (1.2)	1006 (2.5)	12581 (1.3)
20-24	2321 (17.8)	5966 (11.6)	5968 (14.8)	106617 (10.7)
25-29	3909 (30.0)	16636 (32.3)	12451 (30.9)	329839 (33.1)
30-34	3969 (30.5)	18776 (36.5)	13432 (33.3)	359099 (36.1)
≥35	2234 (17.2)	9500 (18.4)	7488 (18.6)	187537 (18.8)
Married or living with partner	10129 (77.8)	44776 (86.9)	33177 (82.2)	878059 (88.2)
Place of birth				
Denmark	11476 (88.2)	44434 (86.3)	35370 (87.7)	844388 (84.8)
Europe	563 (4.3)	2518 (4.9)	1813 (4.5)	54605 (5.5)
Outside of Europe	980 (7.5)	4563 (8.9)	3162 (7.8)	96680 (9.7)
Region of residence				
The Capital Region of Denmark	4241 (32.6)	15288 (29.7)	13873 (34.4)	324801 (32.6)
Region Zealand	2075 (15.9)	8121 (15.8)	6120 (15.2)	132222 (13.3)
The Region of Southern Denmark	2871 (22.1)	11036 (21.4)	8082 (20.0)	180940 (18.2)
Central Denmark Region	2589 (19.9)	11799 (22.9)	8444 (20.9)	256877 (25.8)
The North Denmark Region	1243 (9.6)	5271 (10.2)	3826 (9.5)	100833 (10.1)
Gross household income, quartile ^b				
1	4282 (32.9)	11716 (22.7)	9533 (23.6)	248037 (24.9)
2	3184 (24.5)	12961 (25.2)	10059 (24.9)	248715 (25.0)
3	2777 (21.3)	13446 (26.1)	10315 (25.6)	249315 (25.0)
4	2776 (21.3)	13392 (26.0)	10438 (25.9)	249606 (25.1)
Education level, years				
≤11	4552 (35.0)	14300 (27.8)	12043 (29.9)	206926 (20.8)
12-13	1913 (14.7)	7621 (14.8)	6051 (15.0)	147521 (14.8)
14-15	3181 (24.4)	13399 (26.0)	10266 (25.5)	256649 (25.8)
≥16	3373 (25.9)	16195 (31.4)	11985 (29.7)	384577 (38.6)
Year of pregnancy onset				
1997-2000	3799 (29.2)	11669 (22.7)	10116 (25.1)	217113 (21.8)
2001-2004	3212 (24.7)	11352 (22.0)	8747 (21.7)	213325 (21.4)
2005-2008	2459 (18.9)	11607 (22.5)	8898 (22.1)	211547 (21.3)
2009-2012	2222 (17.1)	10071 (19.6)	7928 (19.7)	195103 (19.6)
2013-2016	1327 (10.2)	6816 (13.2)	4656 (11.5)	158585 (15.9)
Parity				
1	6006 (46.1)	16079 (31.2)	17707 (43.9)	457903 (46.0)
2	4525 (34.8)	23260 (45.2)	14905 (36.9)	360694 (36.2)
≥3	2488 (19.1)	12176 (23.6)	7733 (19.2)	177076 (17.8)
Multiple birth pregnancy	459 (3.5)	1870 (3.6)	1606 (4.0)	41671 (4.2)
Smoking during pregnancy	3379 (26.0)	10813 (21.0)	9001 (22.3)	147225 (14.8)
Previous pregnancy with major birth defect	196 (1.5)	1236 (2.4)	683 (1.7)	17041 (1.7)

Antidiabetic drug use in past year	170 (1.3)	774 (1.5)	523 (1.3)	12256 (1.2)
Drugs used for IVF in past 3 months	489 (3.8)	2436 (4.7)	2110 (5.2)	62130 (6.2)
No. of drugs used in past year				
1-2	4120 (31.7)	17582 (34.1)	7660 (19.0)	408280 (41.0)
3-4	3350 (25.7)	13421 (26.1)	12590 (31.2)	208967 (21.0)
≥5	3967 (30.5)	14169 (27.5)	19211 (47.6)	148838 (15.0)
No. of hospitalization in past year				
1	1540 (11.8)	7101 (13.8)	4971 (12.3)	123273 (12.4)
2	354 (2.7)	1396 (2.7)	1098 (2.7)	21661 (2.2)
≥3	112 (0.9)	550 (1.1)	395 (1.0)	6745 (0.7)
No. of outpatient contacts in past year				
1	1822 (14.0)	7311 (14.2)	6051 (15.0)	136673 (13.7)
2	659 (5.1)	2747 (5.3)	2299 (5.7)	49286 (5.0)
≥3	290 (2.2)	1376 (2.7)	1111 (2.8)	22820 (2.3)

GA: gestational age (in days since pregnancy onset). IQR: interquartile range. IVF: in vitro fertilization. ^aValues are numbers (percentages) unless otherwise stated. Percentages may not total 100 because of rounding. ^bGross hold income quartiles presented for the macrolide-exposed pregnancies are for the main comparison of vs. penicillin-exposed pregnancies.

Supplementary Table D. Number of tablets redeemed and days of coverage.

Study antibiotic	Strength (mg), median (IQR)	No. of tablets redeemed, median (IQR)	Estimated days of coverage ^a
Azithromycin	500 (500-500)	3 (2-3)	3 days
Clarithromycin	500 (500-500)	14 (7-14)	7 days
Erythromycin	500 (500-500)	20 (20-30)	5 days
Roxithromycin	300 (150-300)	10 (7-20)	10 days
Spiramycin	500 (500-500)	24 (24-24)	6 days
Phenoxymethylpenicillin	800 (660-800)	20 (20-30)	7 days

^aDays of coverage calculated by no. of tablets redeemed divided by the required number of tablets used for the standard recommended daily doses for the individual study antibiotics, defined as: azithromycin 500mg, clarithromycin 1000mg, erythromycin 2000mg, roxithromycin 300mg, and spiramycin 2000mg daily as well as phenoxymethylpenicillin 660-800mg three times daily. IQR: interquartile range.

Supplementary Table E. Additional pregnancy outcomes for the matched main comparison between macrolide-exposed and penicillin-exposed pregnancies.

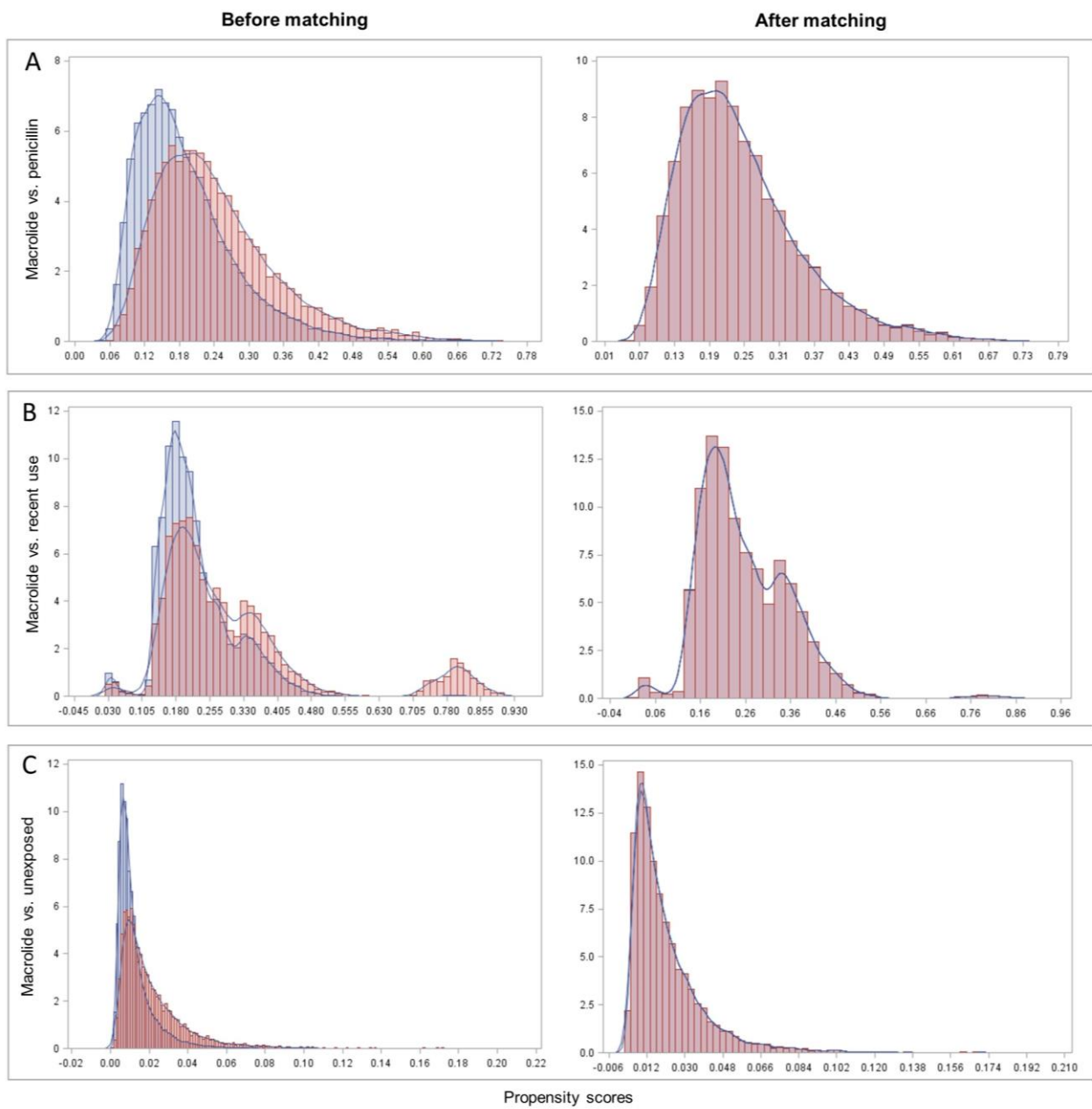
Other pregnancy outcomes	Macrolide-exposed (n=13017)	Penicillin-exposed (n=13017)	p-value
Preterm birth (n / %)	985 / 7.6	941 / 7.2	0.30
Small for gestational age (n / %)	1439 / 11.1	1372 / 10.5	0.18
Cesarean section (n / %)	2764 / 21.2	2712 / 20.8	0.43
Placental weight (kg) (mean / IQR)	659.4 / 550-650	660.5 / 550-650	0.65
Length at birth (cm) (mean / IQR)	51.2 / 50-53	51.2 / 50-53	0.85
Head circumference (cm) (mean / IQR)	34.1 / 34-35	34.0 / 34-35	0.75
Low Apgar score after 5 minutes (<7) (n / %)[3]	154 / 1.2	171 / 1.3	0.34
Perinatal death (n / %)	33 / 0.3	48 / 0.4	0.09

Supplementary Table F. Standardized differences before and after propensity score matching.

Characteristics	Macrolide-exposed vs penicillin-exposed pregnancies		Macrolide-exposed vs unexposed pregnancies with recent prior use		Macrolide-exposed vs unexposed pregnancies	
	Before matching	After matching	Before matching	After matching	Before matching	After matching
Age at pregnancy onset						
≤19	19.7	5.2	10.9	0.7	19.4	0.8
20-24	17.7	1.1	8.2	0.1	20.5	1.1
25-29	4.9	2.4	1.8	1.3	6.7	0.3
30-34	12.7	1.2	6.0	0.3	11.9	0.1
≥35	3.4	0.5	3.7	0.7	4.4	1.2
Married or living with partner	24.1	2.9	11.1	1.8	27.9	0.2
Place of birth						
Denmark	5.7	0.9	1.5	3.7	9.8	2.3
Europe	2.7	1.4	0.8	2.6	5.4	1.8
Outside of Europe	4.9	0.1	1.2	2.5	7.8	1.4
Region of residence						
The Capital Region of Denmark	6.3	1.2	3.8	2.0	0.1	0.1
Region Zealand	0.5	0.7	2.1	0.4	7.5	0.2
The Region of Southern Denmark	1.5	1.4	5.0	0.2	9.7	0.0
Central Denmark Region	7.4	1.0	2.6	0.8	14.1	0.4
The North Denmark Region	2.3	1.7	0.2	1.3	2.0	1.2
Gross household income, quartile						
1	22.8	3.0	12.8	1.9	23.5	0.1
2	1.6	0.4	0.6	2.4	0.7	0.2
3	11.2	1.5	5.4	2.1	10.4	0.1
4	11.0	1.6	8.4	2.4	16.1	0.2
Education level, years						
<12	15.6	2.3	10.9	2.0	32.0	1.2
12-13	0.3	0.3	0.9	0.4	0.3	1.0
14-15	3.6	1.4	2.3	0.4	3.1	0.1
>15	12.3	0.9	8.5	2.1	27.5	0.7
Year of pregnancy onset						
1997-2000	14.9	1.4	9.3	2.1	17.0	0.6
2001-2004	6.2	0.9	7.1	1.5	7.7	0.4
2005-2008	9.0	0.4	7.9	1.4	5.9	0.3
2009-2012	6.4	1.3	6.7	1.3	6.5	0.3
2013-2016	9.5	1.3	4.3	1.3	17.1	1.1
Parity						
1	30.0	0.1	4.5	2.0	0.3	2.6
2	20.3	0.9	4.6	0.2	3.1	1.5
≥3	11.1	1.2	0.1	2.8	3.4	1.5
Multiple birth pregnancy	0.6	2.1	2.4	7.4	3.4	4.5
Smoking during pregnancy	11.7	2.7	8.5	2.0	28.0	1.4

Previous pregnancy with major birth defect	6.5	1.6	1.5	1.5	1.6	3.0
Antidiabetic drugs use in past year	1.7	0.5	0.1	1.8	0.7	3.3
Drugs used for IVF in past 3 months	4.8	1.3	7.1	0.4	11.4	2.0
No. of drugs used in past year						
1-2	8.3	0.3	26.6	4.1	19.6	1.6
3-4	0.9	0.4	10.6	0.7	11.2	1.6
≥5	11.1	1.3	31.4	0.1	37.7	2.4
No. of hospitalization in past year						
1	5.9	1.2	1.5	3.2	1.7	4.2
2	0.1	0.6	0.0	2.1	3.5	3.5
≥3	2.1	1.2	1.2	1.2	2.1	2.8
No. of outpatient contacts in past year						
1	0.6	0.3	2.9	3.9	0.8	3.8
2	1.2	0.4	2.8	2.4	0.5	5.1
≥3	2.9	1.3	3.4	2.7	0.4	2.9

Supplementary Figure (A-C). Distribution of propensity scores before and after matching.^a



^aRed color denotes macrolide-exposed pregnancies and blue color denotes the respective comparison groups.

Supplementary Table G. Cases of major birth defects and absolute risk differences per 1000 pregnancies among macrolide-exposed compared with penicillin-exposed pregnancies.

	Macrolide (n=13017)	Penicillin (n=13017)	Absolute risk differences (95% CI) per 1000 pregnancies
	Per 1000 pregnancies	Per 1000 pregnancies	
Any major birth defects	35.1	37.0	-1.8 (-6.4 to 2.7)
Specific birth defect subgroups			
Of the nervous system	1.5	2.2	-0.7 (-1.7 to 0.3)
Of the eye	0.9	1.6	-0.7 (-1.6 to 0.2)
Of the face, ear, and neck	0.3	0.3	0.0 (-0.4 to 0.4)
Of the heart	9.8	9.9	-0.2 (-2.6 to 2.2)
Orofacial cleft	2.1	1.8	0.2 (-0.8 to 1.3)
Of the digestive system	1.8	2.5	-0.8 (-1.9 to 0.4)
Of the urinary system	3.3	2.9	0.4 (-1.0 to 1.7)
Of the external genital organs	2.8	3.2	-0.4 (-1.7 to 1.0)
Of the limbs	10.6	10.6	0.0 (-2.5 to 2.5)
Of the musculoskeletal system	1.6	1.2	0.5 (-0.4 to 1.4)
Of the respiratory system	1.8	1.4	0.4 (-0.6 to 1.3)
Other major birth defects	1.3	1.8	-0.5 (-1.5 to 0.4)

Supplementary Table H. Cases of major birth defects and absolute risk differences per 1000 pregnancies among macrolide-exposed compared with unexposed pregnancies with recent use.

	Macrolide (n=11908)	Recent use (n=11908)	Absolute risk differences (95% CI) per 1000 pregnancies
	Per 1000 pregnancies	Per 1000 pregnancies	
Any major birth defects	36.4	36.4	-0.1 (-4.8 to 4.7)
Specific birth defect subgroups			
Of the nervous system	1.6	0.8	0.8 (-0.1 to 1.6)
Of the eye	0.9	1.2	-0.3 (-1.1 to 0.6)
Of the face, ear, and neck	0.3	0.4	-0.1 (-0.6 to 0.4)
Of the heart	10.1	9.0	1.1 (-1.4 to 3.6)
Orofacial cleft	2.2	1.4	0.8 (-0.3 to 1.8)
Of the digestive system	1.8	2.0	-0.2 (-1.3 to 0.9)
Of the urinary system	3.0	2.9	0.1 (-1.3 to 1.5)
Of the external genital organs	2.9	2.9	0.0 (-1.4 to 1.4)
Of the limbs	11.3	11.2	0.1 (-2.6 to 2.8)
Of the musculoskeletal system	1.6	1.8	-0.3 (-1.3 to 0.8)
Of the respiratory system	1.9	1.7	0.3 (-0.8 to 1.3)
Other major birth defects	1.4	1.6	-0.2 (-1.2 to 0.8)

Supplementary Table I. Cases of major birth defects and absolute risk differences per 1000 pregnancies among macrolide-exposed compared with unexposed pregnancies.

	Macrolide (n=13019)	Unexposed (n=52075)	Absolute risk differences (95% CI) per 1000 pregnancies
	Per 1000 pregnancies	Per 1000 pregnancies	
Any major birth defects	35.2	33.4	1.8 (-1.7 to 5.3)
Specific birth defect subgroups			
Of the nervous system	1.5	1.3	0.1 (-0.6 to 0.9)
Of the eye	0.9	1.0	-0.1 (-0.7 to 0.5)
Of the face, ear, and neck	0.3	0.4	-0.1 (-0.4 to 0.3)
Of the heart	9.8	8.5	1.3 (-0.6 to 3.1)
Orofacial cleft	2.1	1.8	0.3 (-0.6 to 1.2)
Of the digestive system	1.8	2.2	-0.4 (-1.2 to 0.4)
Of the urinary system	3.3	2.9	0.4 (-0.7 to 1.5)
Of the external genital organs	2.8	3.3	-0.5 (-1.5 to 0.5)
Of the limbs	10.6	10.5	0.1 (-1.8 to 2.1)
Of the musculoskeletal system	1.6	1.2	0.4 (-0.4 to 1.1)
Of the respiratory system	1.8	1.2	0.6 (-0.2 to 1.4)
Other major birth defects	1.3	1.3	0.0 (-0.7 to 0.7)

Supplementary Table J. Cases of major birth defects and absolute risk differences per 1000 pregnancies among azithromycin-exposed compared with penicillin-exposed pregnancies.

	Azithromycin (n=4711)	Penicillin (n=4711)	Absolute risk differences (95% CI) per 1000 pregnancies
	Per 1000 pregnancies	Per 1000 pregnancies	
Any major birth defects	40.8	39.1	1.7 (-6.2 to 9.6)
Specific birth defect subgroups			
Of the nervous system	1.1	2.1	-1.1 (-2.7 to 0.5)
Of the eye	1.1	2.3	-1.3 (-2.9 to 0.4)
Of the face, ear, and neck	NE		
Of the heart	12.5	9.8	2.8 (-1.5 to 7.0)
Orofacial cleft	1.9	1.9	0.0 (-1.8 to 1.8)
Of the digestive system	2.1	2.8	-0.6 (-2.6 to 1.4)
Of the urinary system	3.6	2.5	1.1 (-1.2 to 3.3)
Of the external genital organs	3.0	3.4	-0.4 (-2.7 to 1.9)
Of the limbs	11.9	11.9	0.0 (-4.4 to 4.4)
Of the musculoskeletal system	2.3	1.3	1.1 (-0.7 to 2.8)
Of the respiratory system	3.0	2.1	0.8 (-1.2 to 2.9)
Other major birth defects	1.3	1.9	-0.6 (-2.2 to 1.0)

NE: not estimated.

Supplementary Table K. Cases of major birth defects and absolute risk differences per 1000 pregnancies among erythromycin-exposed compared with penicillin-exposed pregnancies.

	Erythromycin (n=5458)	Penicillin (n=5458)	Absolute risk differences (95% CI) per 1000 pregnancies
	Per 1000 pregnancies	Per 1000 pregnancies	
Any major birth defects	30.0	36.6	-6.6 (-13.3 to 0.1)
Specific birth defect subgroups			
Of the nervous system	1.8	1.6	0.2 (-1.4 to 1.7)
Of the eye	NE		
Of the face, ear, and neck	NE		
Of the heart	7.3	10.8	-3.5 (-7.0 to 0.1)
Orofacial cleft	2.2	2.2	0.0 (-1.8 to 1.8)
Of the digestive system	1.5	2.9	-1.5 (-3.2 to 0.3)
Of the urinary system	2.7	2.7	0.0 (-2.0 to 2.0)
Of the external genital organs	2.4	3.1	-0.7 (-2.7 to 1.2)
Of the limbs	9.5	9.5	0.0 (-3.6 to 3.6)
Of the musculoskeletal system	1.1	1.1	0.0 (-1.2 to 1.2)
Of the respiratory system	1.5	1.5	0.0 (-1.4 to 1.4)
Other major birth defects	0.9	2.2	-1.3 (-2.8 to 0.2)

NE: not estimated.

Supplementary Table L. Cases of major birth defects and absolute risk differences per 1000 pregnancies among roxithromycin-exposed compared with penicillin-exposed pregnancies.

	Roxithromycin (n=2375)	Penicillin (n=2375)	Absolute risk differences (95% CI) per 1000 pregnancies
	Per 1000 pregnancies	Per 1000 pregnancies	
Any major birth defects	36.2	32.8	3.4 (-7.0 to 13.8)
Specific birth defect subgroups			
Of the nervous system	1.3	3.4	-2.1 (-4.8 to 0.6)
Of the eye	2.1	1.7	0.4 (-2.1 to 2.9)
Of the face, ear, and neck	NE		
Of the heart	8.8	8.4	0.4 (-4.8 to 5.7)
Orofacial cleft	NE		
Of the digestive system	1.7	1.7	0.0 (-2.3 to 2.3)
Of the urinary system	4.2	3.4	0.8 (-2.7 to 4.3)
Of the external genital organs	4.2	3.4	0.8 (-2.7 to 4.3)
Of the limbs	10.5	10.1	0.4 (-5.3 to 6.2)
Of the musculoskeletal system	NE		
Of the respiratory system	NE		
Other major birth defects	1.7	1.3	0.4 (-1.8 to 2.6)

Supplementary Table M. Sensitivity analyses for the association between macrolide exposure in pregnancies and risk of any major birth defects compared with penicillin exposure in the first trimester of pregnancy.

	Macrolide-exposed		Penicillin-exposed		Relative Risk Ratio (95% CI)
	No. pregnancies	No. cases (%)	No. pregnancies	No. cases (%)	
Any major birth defects					
Filled prescription in gestational week 3-8	6493	213 (3.3)	6513	240 (3.7)	0.89 (0.74 to 1.07)
Among singleton pregnancies only	12558	421 (3.4)	12608	460 (3.7)	0.92 (0.81 to 1.05)
Among first-time pregnancies only	5940	221 (3.7)	5945	240 (4.0)	0.92 (0.77 to 1.10)
Among first pregnancies exposed to study antibiotic only	12463	425 (3.4)	12739	464 (3.6)	0.94 (0.82 to 1.07)
Among pregnancies with no recent (<1 month) antibiotic use ^a	11447	402 (3.5)	11846	429 (3.6)	0.97 (0.85 to 1.11)
Among pregnancies with no other antibiotic use in pregnancy ^a	11358	397 (3.5)	11441	416 (3.6)	0.96 (0.83 to 1.10)
Cohort of live birth and induced abortion pregnancies ^b	6892	296 (4.3)	6892	328 (4.8)	0.90 (0.77 to 1.05)
Defects of the heart					
Filled prescription in gestational week 3-8	6493	64 (1.0)	6513	75 (1.2)	0.86 (0.61 to 1.19)
Among pregnancies with no recent (<1 month) antibiotic use ^a	11447	109 (1.0)	11846	117 (1.0)	0.96 (0.74 to 1.25)
Among pregnancies with no other antibiotic use in pregnancy ^a	11358	105 (0.9)	11441	111 (1.0)	0.95 (0.73 to 1.24)

^aDefined as no use of any antibiotics (ATC: J01 and P01AB01) in the 1 month prior to pregnancy onset. ^bData only available for live births and induced abortions (ICD-10 codes: O053 and O054) between 1 January 2004 and 31 December 2016. Identified cases of induced abortions with a confirmed birth defect occurred in 28 macrolide-exposed and 33 penicillin-exposed pregnancies, which was defined as previously described.[4] Of note, the registration of defects among induced abortions have not been validated.

Supplementary Table N. Post-hoc analysis for the association between macrolide exposure in any trimester or in 2nd and 3rd trimester only and risk of any major birth defects and defects of external genital organs.

	Macrolide-exposed		Penicillin-exposed		Relative Risk Ratio (95% CI)
	No. pregnancies	No. cases (%)	No. pregnancies	No. cases (%)	
Exposure in any trimester					
Any major birth defects	23996	827 (3.5)	23996	810 (3.4)	1.02 (0.93 to 1.12)
Defects of the external genital organs	23996	76 (0.3)	23996	82 (0.3)	0.93 (0.68 to 1.27)
Exposure in 2nd and 3rd trimester only					
Any major birth defects	12327	419 (3.4)	12318	398 (3.2)	1.05 (0.92 to 1.20)
Defects of the external genital organs	12327	46 (0.4)	12318	39 (0.3)	1.18 (0.77 to 1.80)

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