Design Considerations for Using the Tree-based Scan Statistic in Surveillance of Maternal Outcomes Following Medication Use During Pregnancy

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ABSTRACT

Background: TreeScan is a data-mining method to screen for thousands of adverse events and may be useful for surveillance of maternal events after drug use in pregnancy.

Research need: Assess how TreeScan performs in surveillance of maternal outcomes following medication use during pregnancy, and compare propensity score (PS) approaches for confounding control.

Main findings:

- Some alerts are identified and the alert triage is in process.
- Screening analyses should anticipate and minimize noise but should also tolerate potential false alerts to facilitate full capture of safety issues when prioritizing outcomes for targeted pharmacoepidemiology studies.

BACKGROUND

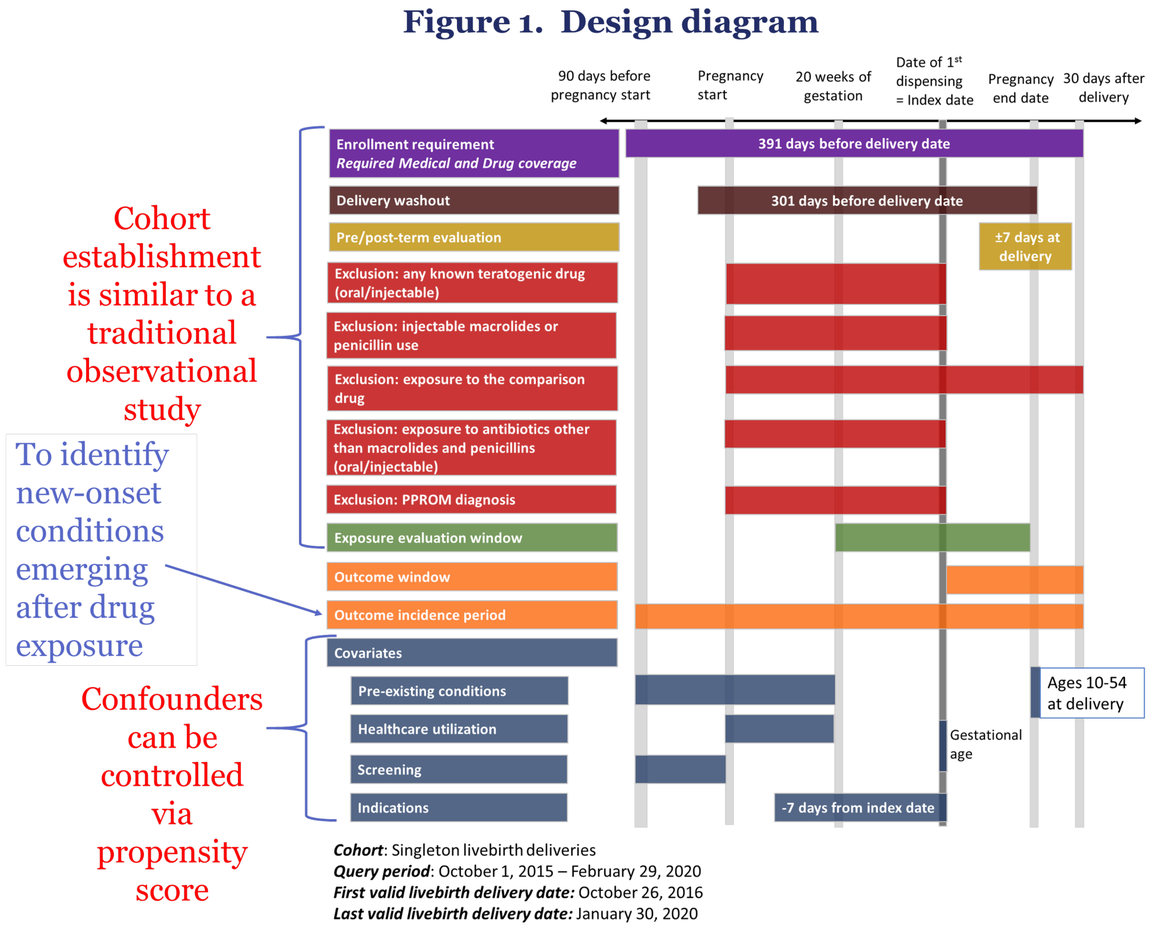
- In the US, almost 98% of medications approved from 2000 to 2010 have an undetermined teratogenic risk. More evidence is needed to guide women and clinicians in making decisions on medication use during pregnancy.
- TreeScan™ (http://www.treescan.org) is a signal identification method that evaluates thousands of outcomes simultaneously to identify potential adverse events after adjusting for multiple testing.

OBJECTIVES

To assess the performance of the TreeScan method to identify signals for **maternal and obstetric adverse outcomes** occurring from **20 weeks of gestation to 30 days** after delivery among women with livebirths exposed to **oral macrolides** compared to **oral penicillins**.

METHODS

Figure 1. Design diagram



Cohort: Singleton livebirth deliveries
Query period: October 1, 2015 – February 29, 2020
First valid livebirth delivery date: October 26, 2016
Last valid livebirth delivery date: January 30, 2020

Data source: MarketScan® Commercial Claims data

Statistical analysis

- After trimming non-overlapping regions of the PS, the cohort was stratified based on different combinations of PS quartiles or deciles and windows of gestational age at treatment initiation to balance on covariates and gestational age of treatment.
- Sensitivity analyses were implemented to reduce spurious alerts.
- We used conditional Poisson TreeScan analysis & set alert threshold at alpha=0.05.

Table 1. Stratification analysis scenarios and sensitivity analyses

#	Analysis scenarios	Strata of gestational age	Strata of propensity score
1-3	Vary strata of gestational age at treatment initiation	Every 2/4/6 weeks	Quartiles
4	Vary strata of PS	Every 6 weeks	Deciles
5	Restrict to patients with respiratory tract infections (RTI)	Every 6 weeks	Deciles
6	Restrict to patients with RTI and outcomes in inpatient or emergency department (IP/ED) visits	Every 6 weeks	Deciles

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- The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.
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RESULTS

- The final cohort included 13,215 macrolide and 18,554 penicillin users.
- We could not identify indications for 52% macrolide and 39% penicillin users.
- The indications were the only covariates that were imbalanced before adjustment.
- The indications for antibiotic use were only balanced when using propensity score deciles (Table 2).

Table 2. Indication balances after propensity score stratification

Characteristics	Standardized difference					
	Unadjusted	4 weeks GA- quartile PS	2 weeks GA - quartile PS	6 weeks GA - quartile PS	6 weeks GA - decile PS	RTI restriction
Upper RTIs	-0.324	0.011	0.011	0.007	0.007	-0.022
Gastrointestinal infections	-0.015	0.005	0.004	0.004	0.006	0.005
Lower RTIs	0.234	0.094	0.093	0.091	0.035	0.015
Sexual tract infections	0.097	0.064	0.064	0.063	0.049	-0.003
Other indications	-0.092	-0.057	-0.058	-0.053	-0.046	-0.014
Pelvic diseases	-0.01	0.003	0.002	0.006	0.004	-0.002
Skin infections	-0.107	-0.065	-0.066	-0.065	-0.048	-0.034
Urinary tract infections	-0.196	-0.122	-0.122	-0.122	-0.092	-0.019

Table 3. Macrolide alert patterns

Node description	Decile PS (Analysis #4)	RTI (Analysis #5)	IP/ED settings (Analysis #6)
Total alerts	**10**	**2**	**1**
Infections related	1		
Maternal care for pelvis problem or excessive fetal growth	5	1	1
Preterm labor without delivery	1	1	
Gestational hypertension	1		
Fetal anemia and thrombocytopenia	1		
Unspecific/non-actionable alerts	1		

Note: Shading indicates different clinical groups of alerts; PS: propensity score; RTI: respiratory tract infections; IP/ED: inpatient/emergency department

Table 4. Penicillin alert patterns

Node description	Decile PS (Analysis #4)	RTI (Analysis #5)	IP/ED settings (Analysis #6)
Total alerts	**23**	**16**	**20**
Infections related	7	4	3
Antepartum hemorrhage		1	1
Placenta related conditions		2	1
Chorioamnionitis		1	1
Oligohydramnios			1
Pre-eclampsia	1	1	
Premature rupture of membranes		1	1
Gestational diabetes			2
Post-term pregnancy	1		
Obesity complicating pregnancy			1
Obstructed labor due to pelvic abnormality	1	1	1
Third degree perineal laceration		1	1
Other vomiting complicating pregnancy	1		
Superficial thrombophlebitis	1	1	1
Nonpurulent mastitis	2		
Cracked nipple/Hypogalactia			3
Maternal care for abnormal fetal heart rate or other fetal problems			
Unspecific/non-actionable alerts	7	3	3

Note: Shading indicates different clinical groups of alerts; PS: propensity score; RTI: respiratory tract infections; IP/ED: inpatient/emergency department

CONCLUSION

The alert triage is in process. Alert screening and review of specific cases suggested several pathways for false positive alerts:

- As TreeScan evaluates hypotheses one-sided, exposure group comparisons were repeated with each antibiotic class. Some alerts related to the similar conditions were identified for both macrolide and penicillin users.
- Several alerts appeared to be exacerbations of the initial indication.
- Given intention-to-treat design, some exposure/outcome pairs were not in close proximity and had limited biological plausibility.

Screening analyses should anticipate and minimize noise but should also tolerate potential false alerts to facilitate full capture of safety issues when prioritizing signals for targeted pharmacoepidemiology studies.

LIMITATIONS

- Not accounting for competing risks
- Only evaluating outcomes among pregnant persons with livebirths
- Only including pregnant persons with enrollment until 30 days after delivery