Utility of prenatal tests and fertility coding to estimate pregnancy start in the Sentinel Distributed Database

Taylor LG[1], Bird ST[1], Stojanovic D[1], Toh D[2], Fazio-Eynullayeva E[2], Petrone A[2], Rajbhandari R[2], Lyons JG[2]

[1]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

[2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA

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Disclaimer

- The views expressed in this presentation are those of the authors and not necessarily those of the FDA
- No conflicts

Background

- Studies of medication safety during pregnancy are typically limited to live-birth pregnancies (LBP)

  - LBP validate well in claims data (*Raebel 2005; Li 2013*)

  - Algorithms are available to estimate gestational age (GA) at delivery and to estimate pregnancy start and trimester dates

    - A common approach is to assume a term birth occurs at a GA of 273 days and then use ICD codes, when available, to adjust GA

- GA coding available at delivery

  - ICD-9 era: GA codes for live births only

  - ICD-10 era: GA codes for all pregnancies, but validity largely uninvestigated in U.S. sources

  - Coding for prenatal tests and fertility procedures may represent an avenue to identify GA when this information is not available (*Margulis 2013; Matcho 2018*)

Objectives

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- To develop an algorithm to estimate gestational age using diagnostic and procedure codes for clinically-indicated, often routine, prenatal tests/scans and coding for fertility procedures, separately, for live births and stillbirths, in the Sentinel Distributed Database.

- To evaluate performance of the ***prenatal test algorithm***:
  - Live Birth Pregnancies
    - Against a traditional ***delivery coding algorithm***
  - Stillbirth
    - Against national data on GA at stillbirth

Methods: Study Population

- Live Birth Pregnancy Cohort
  - Comprised of pregnancies ending in live birth among women ages 15-45 years identified in 16 Sentinel data partners from Jan 2006 – Jan 2018
    - Enrollment coverage for at least 43 weeks before delivery; Gaps in coverage up to 45 days
  - Pregnancy identification and GA based on validated algorithm (*Raebel 2005; Li 2013*)
  - **~4.7 million live birth pregnancies in Sentinel**
- Stillbirth Cohort
  - Comprised of pregnancies ending in stillbirth among women aged 15-45 years identified in 16 Sentinel data partners from Jan 2006 – Jan 2018
    - Enrollment coverage for at least 43 weeks before stillbirth with no stillbirth in prior 140 days; Gaps in coverage up to 45 days
  - Stillbirth identification in the inpatient setting based on validated ICD9 codes (*Likis, 2013*) and unvalidated ICD10 codes
  - **40,484 probable stillbirths in Sentinel**

Methods: Prenatal Tests and Procedures

- Fertility procedures:
  - 1: In-Vitro Fertilization (IVF) or In-Utero Insemination (IUI)
- Prenatal Tests and Scans
  - 1: Amniocentesis
  - 2: Chorionic Villus Sampling
  - 3: First Trimester Ultrasound
  - 4: Second/Third Trimester Ultrasound
  - 5: Fetal Anatomic Exam
  - 6: Nuchal Translucency
  - 7: Fetal Echo/Doppler
  - 8: Fetal Aneuploidy test

9: Alpha-fetoprotein

10: Assay of Estriol

11: PAPP-A Serum

12: Chorionic Gonadotropin

13: Inhibin A

14: Group B Strep

15: Glucose

Methods: Live birth Pregnancies

- Calculation of GA with traditional delivery coding algorithm
  - Algorithm previously shown to classify 77% of pregnancies within two weeks of the clinical estimate of last menstrual period (*Li 2013*).

- Coding Performance Evaluation
  1. Identify prenatal tests and fertility procedures using ICD 9 and 10 coding
  2. Examine A) prevalence of each test and B) distribution of test by GA (using traditional algorithm above),
     only first occurrence of each prenatal test and last fertility procedure evaluated
  3. Assigned a specific gestational day to each test, selected as the day with the highest percentage of tests occurring within ±14 days of that gestational day
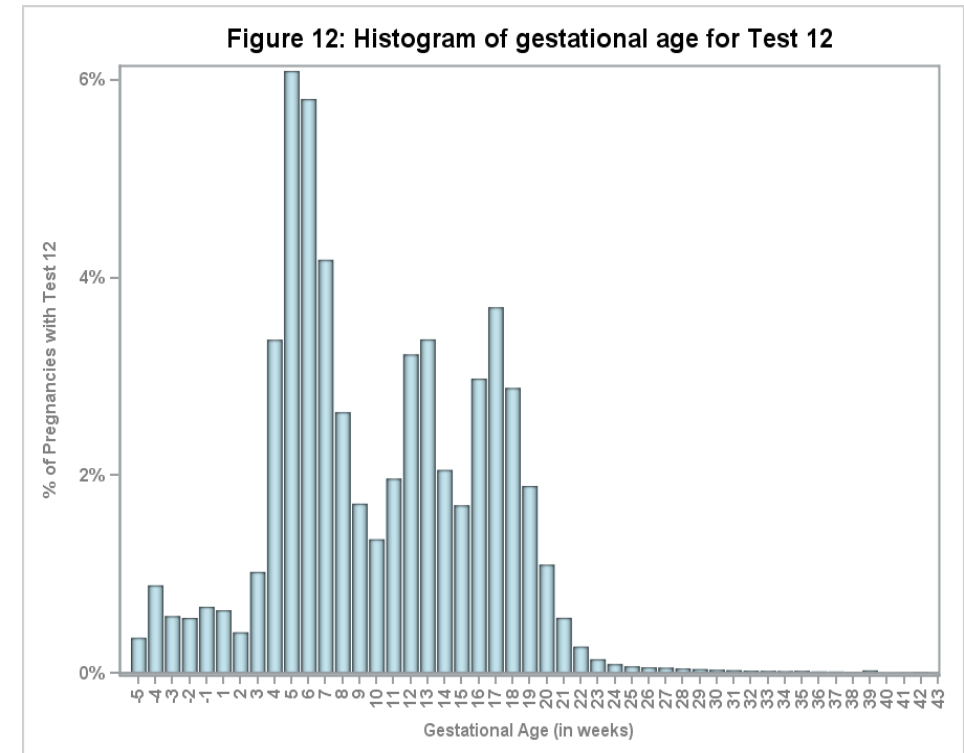
Results: Example Distributions

Good test

Figure 6: Histogram of gestational age for Test 6
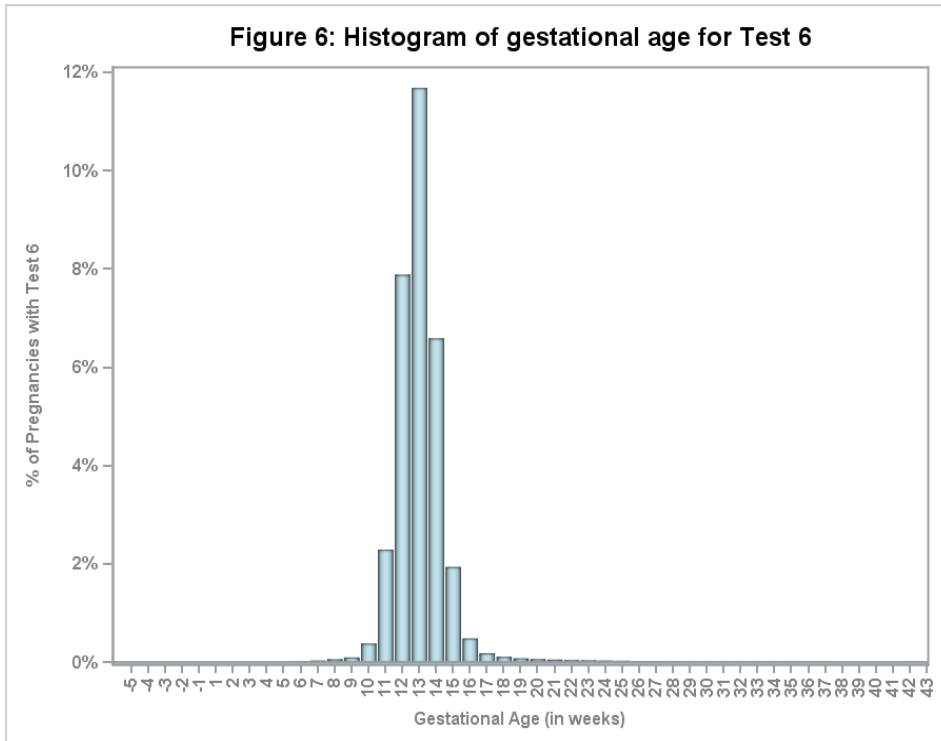
Nuchal translucency; ACOG rec 11-14 weeks

Bad test

Figure 12: Histogram of gestational age for Test 12

hCG test; ACOG rec 11-14 weeks quad screen; other reasons

Results: Test Performance

Test Type	% of live births with test, n=4,701,207	Gestational day with peak 2-week sensitivity	% codes within ±2 weeks
Fertility Coding, IVF/IUI*	2.7%	14	78.3%
Amniocentesis	0.04%	259	30.2%
Chorionic villus sampling	**0.8%**	**84**	**84.4%**
First Trimester Ultrasound	43.0%	80	20.9%
Second/Third Trimester Ultrasound	68.2%	128	63.8%
Fetal anatomic exam	42.5%	138	70.4%
Nuchal translucency	**32.3%**	**88**	**90.6%**
Fetal echo/doppler	7.6%	148	44.6%
Fetal Aneuploidy test	2.6%	85	72.6%
Alpha-fetoprotein	1.8%	120	68.4%
Assay of estriol	**31.8%**	**119**	**79.6%**
PAPP-A serum	**28.8%**	**85**	**82.6%**
Chorionic gonadotop	56.6%	38	35.5%
Inhibin A	30.5%	119	78.1%
Group B strep	**61.1%**	**252**	**82.2%**
Glucose	77.7%	190	66.4%

*Fertility coding tested in later version of data containing 4,727,266 live births

Methods: Live birth Pregnancies

- Algorithm Development
  - If fertility procedures were present, pregnancy start was assigned to the procedures with closest proximity to the delivery date (*Bird, 2018*)
  - In absence of fertility procedures, prenatal tests were ranked by performance, calculated as the two-week sensitivity, as a measure of central tendency, at the assigned gestational day.
  - The algorithm was developed in a stepwise fashion, where the fertility procedures and each prenatal test where added one at a time to the algorithm, with evaluation at each stage.

- Algorithm Evaluation
  - The **prenatal test algorithm** was tested against the traditional **delivery coding algorithm** at each stepwise addition, calculating:
    - 1) sensitivity (i.e., live birth pregnancies assigned a GA)
    - 2) agreement (i.e., difference in estimates of pregnancy start between the two algorithms)

  ICD9/10 coding evaluated combined and separately

Results: Algorithm Development and Evaluation

Prenatal Test(s)	% of live births assigned a gestational age	% of live births with ±2 weeks agreement in pregnancy start between algorithms	Difference pregnancy start between algorithms - Mean No. days
Procedure 1	2.7%	74.5%	-0.2
Proc 1 or Test 6	34.1%	90.1%	0.9
Proc 1 or Test 6 or 2	34.6%	90.1%	0.9
Proc 1 or Test 6, 2, or 11	37.9%	89.0%	1.2
Proc 1 or Test 6, 2, 11, or 14	76.6%	87.4%	-6.3
Proc 1 or Test 6, 2, 11, 14, or 10	81.9%	86.4%	-5.5
Proc 1 or Test 6, 2, 11, 14, 10, or 13	81.9%	86.4%	-5.5
Proc 1 or Test 6, 2, 11, 14, 10, 13, or 8	82.6%	86.3%	-5.4
Proc 1 or Test 6, 2, 11, 14, 10, 13, 8, or 5	87.6%	84.9%	-4.4
Proc 1 or Test 6, 2, 11, 14, 10, 13, 8, 5, or 9	87.6%	84.8%	-4.4
Proc 1 or Test 6, 2, 11, 14, 10, 13, 8, 5, 9, or 15	94.7%	83.3%	-4.4
Proc 1 or Test 6, 2, 11, 14, 10, 13, 8, 5, 9, 15, or 4	97.9%	82.5%	-3.7
Remaining pregnancies not meeting any algorithm[3]	2.1%	-	-

Methods: Stillbirth

- Algorithm Implementation
  - The prenatal testing and fertility procedure code algorithm developed in live birth pregnancies was applied to our cohort of stillbirths
- Evaluation
  - No reference GA for stillbirth analysis
 - We compared our GA estimates for stillbirth in Sentinel to that of national data

Results: Stillbirth

Prenatal test(s) within 280 days of index event	No. of stillbirths assigned a gestational age	% of stillbirths assigned a gestational age
Number of probable stillbirths	n = 40,484	
Proc 1	1,928	4.8%
Proc 1 or Test 6	13,491	33.3%
Proc 1, Test 6 or 2	13,736	33.9%
Proc 1, Test 6,2 or 11	14,672	36.2%
Proc 1, Test 6,2,11 or 14	21,142	52.2%
Proc 1, Test 6,2,11,14 or 10	25,666	63.4%
Proc 1, Test 6,2,11,14,10 or 13	25,682	63.4%
Proc 1, Test 6,2,11,14,10,13 or 8	26,842	66.3%
Proc 1, Test 6,2,11,14,10,13,8 or 5	31,691	78.3%
Proc 1, Test 6,2,11,14,10,13,8,5, or 9	31,799	78.5%
Proc 1, Test 6,2,11,14,10,13,8,5,9, or 15	34,100	84.2%
Proc 1, Test 6,2,11,14,10,13,8,5,9,15 or 4	37,498	92.6%
No recorded prenatal tests	2,986	7.4%

# Results: Stillbirth by gestational age

The proportion of stillbirths by gestational week:
A comparison of the Sentinel prenatal test algorithm versus CDC WONDER estimates

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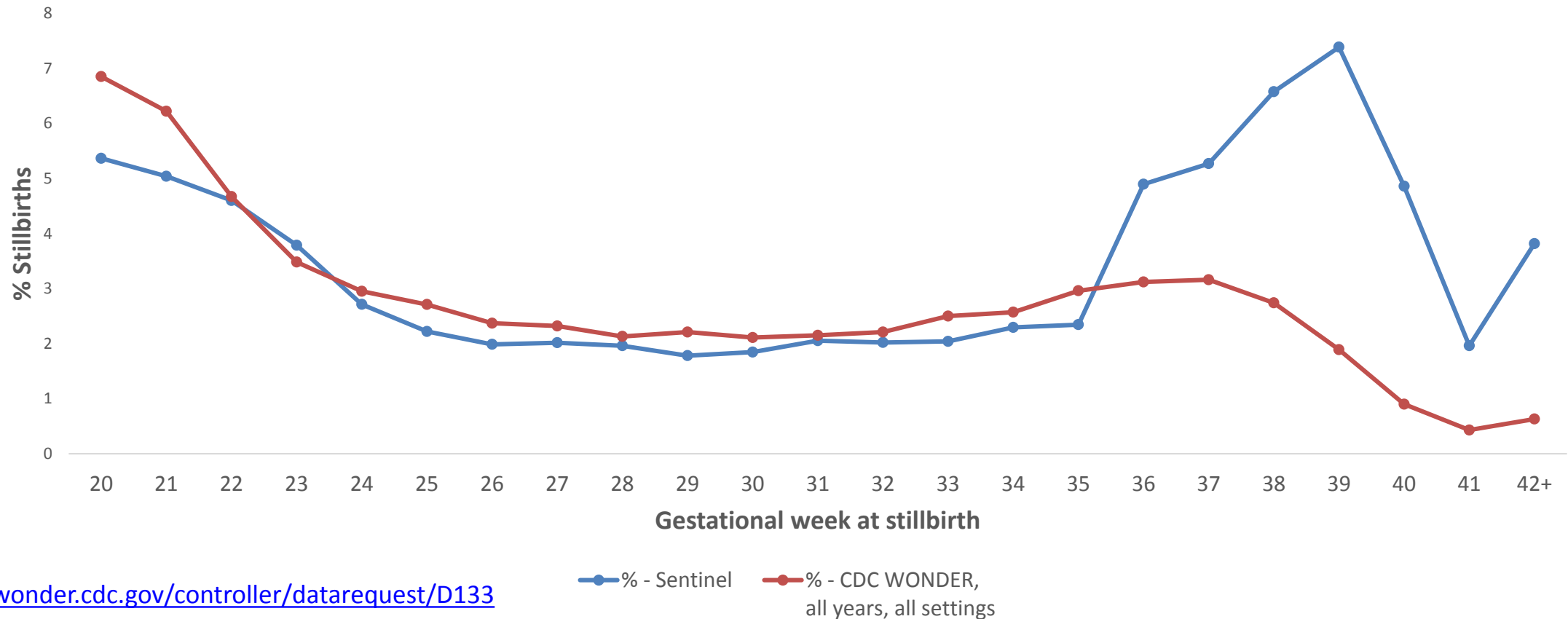
Discussion

- Results suggest that algorithms using prenatal tests can be used to reliably estimate pregnancy start in absence of information on GA among live births

  - Tests added in order of performance. Addition of each test is a balance between increased sensitivity and decreased accuracy
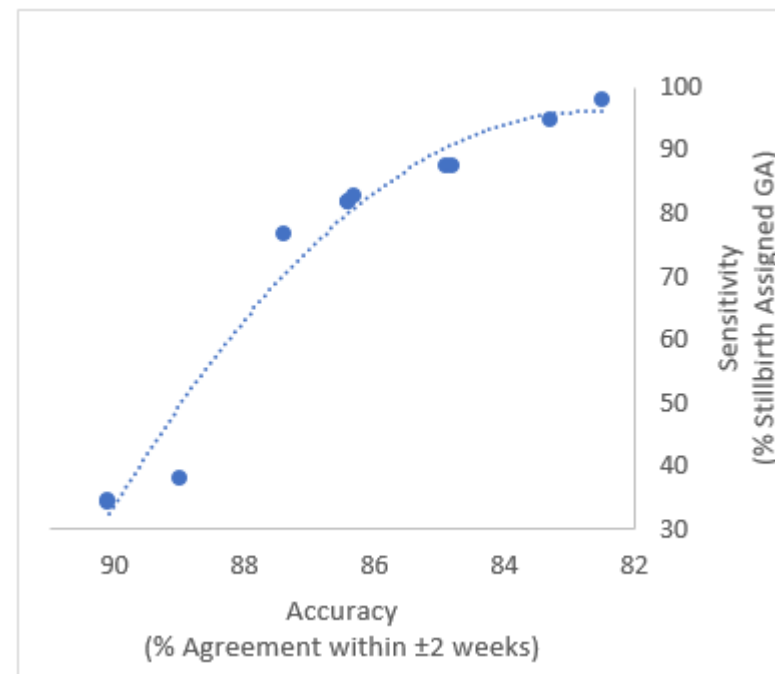
- Prenatal tests were commonly performed among our population of probable stillbirths

  - The distribution of GA at stillbirth using our prenatal test algorithm was similar to that of a national estimate (CDC, NCHS).

Discussion

FDA

- Limitations
  - We evaluated our GA algorithm using prenatal testing against another validated algorithm, not directly against birth certificate data
    - May have resulted in misclassification of GA, but likely minimal
  - Stillbirth definition unvalidated and limited to inpatient settings
    - Difficult to differentiate timing of stillbirth diagnosis from delivery (misclassification <1 week)
  - We tested our algorithm in live birth pregnancies and applied it to stillbirths.
    - This assumes clinical management, particularly in early pregnancy, is similar for pregnancies that end in live birth versus stillbirth
    - Early detection of pregnancy complications / fetal abnormalities may bias toward increased prenatal testing among pregnancies ending in stillbirth

Conclusions

FDA

- In the absence of information on GA, use of prenatal tests and fertility procedure coding may provide reliable estimation of pregnancy start among stillbirths and live births.

- Ongoing work
  - Formal validation of ICD-10 stillbirth coding, GA among stillbirths, and the performance of this algorithm among validated stillbirths is ongoing.

  - If successful, the mainstay of drug utilization analyses in Sentinel can be conducted among a cohort of pregnancies surviving 20+ weeks

References

- Bird et al. Misclassification in assessment of first trimester in-utero exposure to drugs used proximally to conception; the example of letrozole utilization and infertility treatment. *Am J Epidemiol* 2019;188(2):418-425.

- Li Q et al. Validation of an algorithm to estimate gestational age in electronic health plan databases. *PDS* 2013; 22: 524-532.

- Likis et al. A systematic review of unvalidated methods to capture stillbirth and spontaneous abortion using administrative claims data. *Vaccine* 2013; 31 Suppl 10:K74-82.

- Margulis et al. Algorithms to estimate the beginning of pregnancy in administrative databases. *PDS* 2013; 22(1): 16-24.

- Matcho et al. Inferring pregnancy episodes and outcomes within a network of observational databases. *PLoS ONE* 2018: 13(2) e0192033.

- Raebel et al. Evaluation of gestational age and admission date assumptions used to determine prenatal drug exposure from administrative data. *PDS* 2005; 14(12): 829-836.

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