Use of Hydroxyprogesterone Caproate and Progesterone During the 2nd and/or 3rd Trimester Among Pregnancies with Live Birth Deliveries in the Sentinel Distributed Database

Huei-Ting Tsai, Ph.D.

Epidemiologist
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration

Clinical Background

- Preterm birth (PTB) occurs in ~10% of all births, resulting in neonatal mortality and morbidity.
- To date, no drugs are approved for reducing neonatal morbidity and mortality associated with PTB.
- Progesterone has been used off-label to prevent PTB
- **Makena®** (hydroxyprogesterone caproate injection, HPC) is the only product approved for reducing the risk of recurrent PTB.

Regulatory History

- Makena received accelerated approval in 2011. Full approval is contingent upon a successful confirmatory trial to verify its clinical benefit in improving neonatal morbidity and mortality.
- The confirmatory trial (PROLONG) completed in 2018 showed Makena had no clinical benefit and failed to reduce the risk of recurrent PTB.
- FDA convened an Advisory Committee (AC) meeting in 2019 to discuss the evidence on Makena's efficacy and to inform FDA’s regulatory decision-making for this product.

Sentinel Study Objectives

To inform AC members on the utilization and reasons for Makena use, we initiated a Sentinel analysis with the following objectives

1) Drug utilization:

   To determine the percentage of live-birth pregnancies used injectable HPC or progesterone during 2nd and/or 3rd trimesters

2) Possible reasons for use:

   To determine the percentage of live-birth pregnancies used injectable HPC or progesterone that also had at least one obstetrical condition related to PTB

Methods

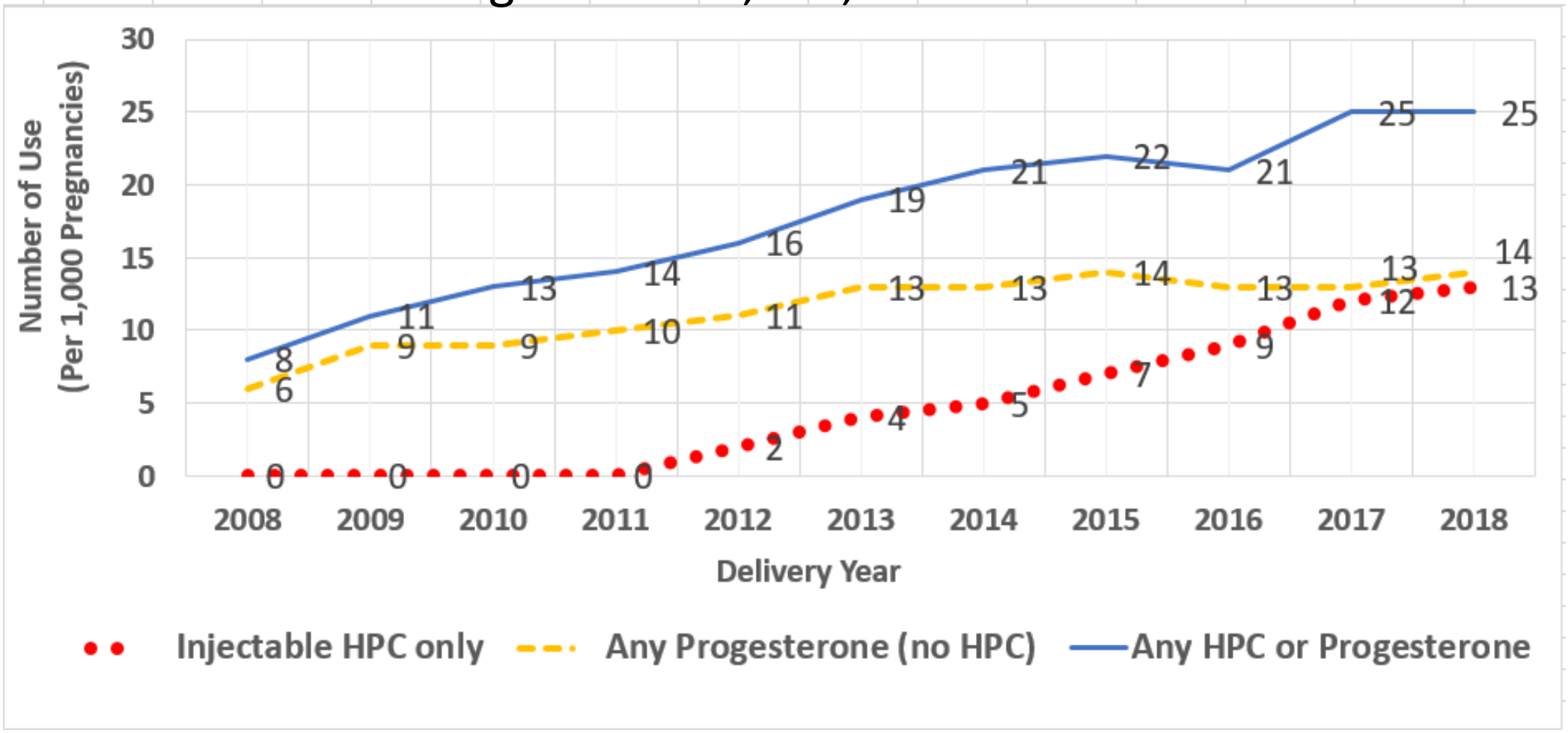
- Database: Sentinel Distributed Database
  - ❖ Primarily composed of commercially-insured patients
- Population: Women with live-birth deliveries b/w Jan 2008 -Apr 2019
  - ❖ Pregnancy duration and trimester periods are estimated using a validated algorithm
- Medications of interest: HPC and progesterone
  - ❖ Ascertained through NDC and HCPCS codes
  - ❖ HPC in injectable or bulk powder formulation
  - ❖ Progesterone in vaginal, oral, injectable, or bulk powder formulation

Related obstetrical conditions (possible reasons for use)

- Identified by ICD-9 and ICD-10 codes in inpatient or outpatient records
  - Narrow definition:
    - Preterm delivery in a prior pregnancy
    - Preterm labor in a current pregnancy
    - Cervical shortening in a current pregnancy
  - Broad definition:
    - Same three obstetrical conditions above recorded in a prior pregnancy or the current pregnancy

Temporal Trend on Number of Pregnancies With injectable HPC Use Per 1,000 Pregnancies

- Total Live-Birth Pregnancies: 3,451,121



[1] Data from 2019 was incomplete and excluded from the figure

Most Injectable HPC Users Had a Related Obstetrical Diagnosis Code

Related Obstetrical Conditions	Injectable HPC (N=16,535)	Progesterone (N= 40,144)	Any HPC or Progesterone (N= 61,615)
Narrow Definition			
1. Preterm delivery in a past pregancy	39%	11%	20%
2. Preterm labor in a current pregnancy	49%	45%	47%
3. Cervical shortening in a current pregnancy	20%	32%	27%
Any of the conditions above	73%	61%	65%
Broad Definition			
1. Preterm labor or delivery in a past pregnancy	95%	37%	56%
2. Preterm labor or delivery in a current pregnancy	54%	55%	56%
3. Cervical shortening in a past or current pregnancy	24%	33%	29%
Any of the conditions above	98%	75%	83%

Limitations

- Might not be generalizable to women without a commercial health plan
- Unspecified timing between related obstetrical conditions and injectable HPC use
- Inability to capture medication use paid for by patients as they are not billed to health plans

Conclusions

- In the Sentinel Distributed Database
  - Overall modest use of HPC (~1.3 % in 2018) and progesterone (~1.4% in 2018) during 2nd or 3rd trimesters in live-birth pregnancies
  - Most (at least 73%) of the pregnant women using injectable HPC had a related obstetrical condition recorded before or during the current pregnancy.

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