Phosphodiesterase type 5 (PDE-5) inhibitor use among pregnant women and women of reproductive age in the United States

Wei Liu1, Talia Menzin2, Corinne M Woods3, Nicole Haug3, Jie Li3, Justin A Mathew4, Christine P Nguyen5, Grace P Chai5, David Moen5, and Mayura Shinde6

1 Division of Epidemiology II, CDER, FDA, Silver Spring, MD; 2 Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; 3 Division of Bone, Reproductive and Urologic Products, CDER, FDA

INTRODUCTION

- Early-onset fetal growth restriction (EO-FGR) due to placental insufficiency is associated with significant perinatal morbidity and mortality. No effective treatments are currently available to treat the condition.1
- It’s hypothesized that sildenafil citrate may improve the uteroplacental blood flow in pregnancies complicated by EO-FGR of placental origin.1,2
- The STRIDER is an international consortium of randomized controlled trials to investigate whether maternal treatment with oral sildenafil would improve pregnancy and birth outcomes in EO-FGR affected pregnancies.3
- In July 2018, the Dutch STRIDER trial was terminated prematurely due to excessive early deaths in babies whose mothers were treated with sildenafil for EO-FGR of placental origin.4
- Maternal exposure to phosphodiesterase type 5 (PDE5) inhibitor during pregnancy for the indication used in severe pulmonary arterial hypertension (PAH) and off-label use are expected; despite this, population-based studies to examine PDE5 inhibitor use in reproductive-age women, including pregnant women, are lacking.

Objective

To assess the prevalence and indications of PDE5 inhibitor use in pregnant women in the United States.

METHODS

Data Sources

- Sentinel Distributed Database which contains electronic health care data for primarily commercially-insured patients from 16 data partners.
- IQVIA’s National Prescription Audit™ (NPA) and Total Patient Tracker™ (TPT).
- We identified PDE5 inhibitor prescriptions using National Drug Codes or a HCPCS code.

Study Population:

- In Sentinel, we identified pregnancies ending in a live birth in women aged 15-50 years from 1/1/2001 to 3/31/2018, used a validated algorithm.6
- Eligible women had continuous health plan memberships for at least 391 days before hospital admission for birth (allowing ≤ 30 days enrollment gaps).

RESULTS

- In Sentinel, we estimated prevalence of total PDE5 inhibitor use in live-born pregnancies, as well as by individual products, calendar year of delivery, maternal age at delivery, and pregnancy trimesters.
- Potential indications, labeled (PAH) and off-label, associated with PDE5 inhibitor use, using pre-defined ICD9/10 diagnosis codes were also assessed.
- IQVIA’s NPA data source provided national estimates of dispensed prescriptions for PDE5 inhibitors (Sept 2017-Aug 2018) and TPT data source provided the estimated number of women aged 15-50 with a dispensed PDE5 inhibitor prescription from outpatient retail pharmacies in 2013-2017.

Table 1. Utilization of PDE5 inhibitors among pregnancies ending in a live birth identified in Sentinel data, 1/1/2001 through 3/31/2018 (n=3,733,369)

<table>
<thead>
<tr>
<th>PDE5 Inhibitor</th>
<th>Use in 90 days before pregnancy</th>
<th>Use any during pregnancy</th>
<th>Use in 1st trimester</th>
<th>Use in 2nd trimester</th>
<th>Use in 3rd trimester</th>
<th>Use in all three trimesters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>2 (0.06)</td>
<td>1 (0.03)</td>
<td>1 (0.03)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
</tbody>
</table>

*In Sentinel, we identified pregnancies ending in a live birth in women aged 15-50 years from 1/1/2001 to 3/31/2018, used a validated algorithm.6

Figure 1. Utilization of PDE5 Inhibitor among live birth pregnancies, by year

Figure 2. Utilization of PDE5 Inhibitor among live birth pregnancies, by maternal age at delivery

DISCUSSION

- Overall, we identified a low prevalent use of PDE5 inhibitor among primarily privately insured, pregnant women over the 17-year study period (2.85 per 100,000 livebirth pregnancies) with most women possibly receiving PDE5 inhibitor treatment for FGR, pre-eclampsia, or PAH.
- Annually, an estimated 15,000-23,000 reproductive-age women received PDE5 inhibitor prescriptions from U.S. outpatient retail pharmacies 2013-2017.
- The Sentinel analysis has several limitations. First, we cannot evaluate PDE5 inhibitor use in pregnancies not ending in a live birth (e.g., spontaneous or therapeutic abortion); second, our results may not be generalizable to women enrolled in Medicaid; third, ICD9/10 codes may not be the gold-standard marker for diagnosis/indication. Also, since we only captured PDE5 inhibitor use in a study sample that was reimbursed by third party insurance, use patterns may not be representative of the total population.
- Nationally projected data on drug utilization using a proprietary prescription database suggested a low prevalence of PDE5 inhibitor use in women, particularly between the ages of 15-50 years of age, which corroborates findings from the Sentinel data.

CONCLUSION

- In conclusion, the use of PDE5 inhibitors in reproductive aged women overall and in pregnant women specifically appeared to be relatively low during the study period. This study provided relevant evidence to assess the potential public health impact of PDE5 inhibitor exposure in pregnancies in the US and inform our regulatory decision-making.

Acknowledgement: The authors thank the Sentinel Data Partners who provided data used in the analysis. The Sentinel Initiative is funded by the US Food and Drug Administration through the Department of Health and Human Services contract number HHSF223200100061E. The views expressed in this abstract are those of the author and not intended to convey official US Food and Drug Administration policy or guidance.

References

5. Haeke, N. Trial of Viagra for fetal growth restriction is halted after baby deaths. BMJ. 2018; 352:k3247.