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

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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.[2-4]
- 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.
- In July 2018, the Dutch STRIDER trial was terminated prematurely due to excessive neonatal deaths in babies whose mothers were treated with sildenafil for EO-FGR of placental origin.[5]
- Maternal exposure to phosphodiesterase type 5 (PDE5) inhibitor during pregnancy for both indicated use (pulmonary arterial hypertension in adults, 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 using 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).
- 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,[7] 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.

RESULTS

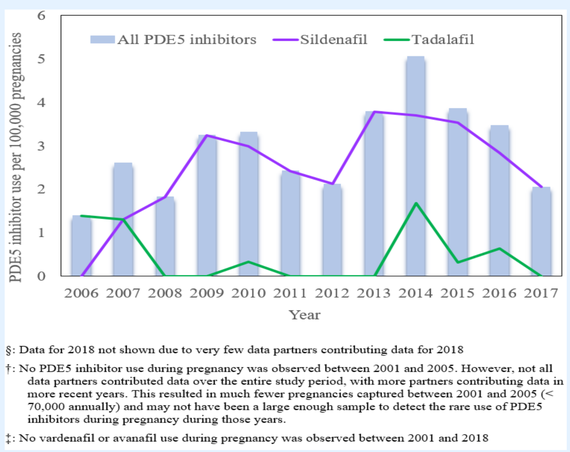
- In Sentinel, we identified 2,776,562 women with 3,373,369 pregnancies that resulted in a live birth. The mean age at the time of delivery was 30.5 years.
- When pooled across the entire study period (January 2001 through March 2018), PDE5 inhibitor use occurred in 96 pregnancies, a prevalence of 2.85 per 100,000 live-born pregnancies (95% CI: 2.31-3.48).
- The prevalence of PDE5 inhibitor use during the first, second, or third trimester was 2.61, 0.62, and 0.62 per 100,000 live-born pregnancies, respectively (Table 1).
- No PDE5 inhibitor use was observed from 2001-2005. No consistent trends in PDE5 inhibitor use were observed in 2006-2018 and the annual prevalence of PDE5 inhibitor use showed considerable variation (Figure 1).
- Women aged 45-50 years were most likely to fill a prescription for a PDE5 inhibitor during pregnancy and women aged 15-24 years were least likely (Figure 2).
- Among women exposed to a PDE5 inhibitor from 90 days before the estimated last menstrual period (LMP) to the end of pregnancy, 25.0%, 31.1% and 15.5% had a diagnosis code for FGR, preeclampsia, or PAH, respectively.
- During 2001-2018, we identified approximately 48 million insured US women of reproductive age in the Sentinel data. Among them, 7,066 women had at least one recorded dispensing of PDE5 inhibitor, with an overall prevalence of use of 14.72 per 100,000 eligible women.
- In IQVIA's TPT, an estimated 58,000 women received prescriptions for PDE5 inhibitors from U.S. retail pharmacies in 2017. Approximately 31% of women who received dispensed PDE5 inhibitor prescriptions were aged 50 years or younger, while 26% (15,000 patients) were 15-50 years old.
- In IQVIA's NPA, 78% of an estimated 170,000 prescriptions dispensed to women from U.S. retail pharmacies during the 12-month period ending in August 2018 were reimbursed by third party insurance, the remainder of which was covered by Medicare, Medicaid or cash.

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=3,373,369)†

	Use in 90 days before pregnancy	Any use during pregnancy	Use in 1st trimester	Use in 2nd trimester	Use in 3rd trimester‡	Use in all three trimesters
Any PDE5 inhibitor	91 (2.70)	96 (2.85)	88 (2.61)	21 (0.62)	21 (0.62)	16 (0.48)
Sildenafil	83 (2.46)	85 (2.52)	81 (2.40)	13 (0.39)	12 (0.36)	10 (0.30)
Tadalafil	8 (0.24)	12 (0.36)	7 (0.21)	8 (0.24)	10 (0.30)	6 (0.18)
Vardenafil	1 (0.03)	0	0	0	0	0
Avanafil	0	0	0	0	0	0

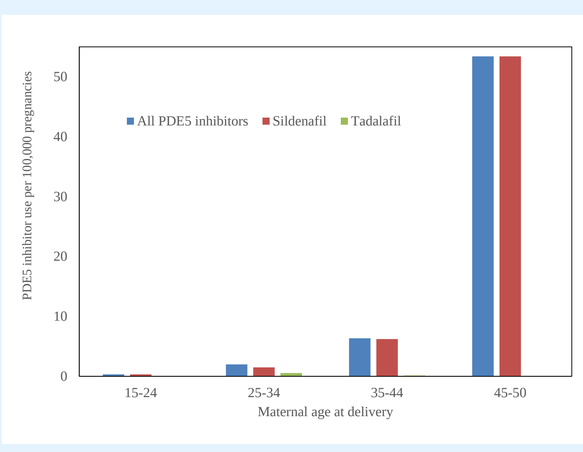
† Numbers in parentheses represent the prevalence of use (number of pregnancies with PDE5 inhibitor use per 100,000 eligible live birth pregnancies)
‡ Total number of pregnancies is lower for third trimester exposures (n=3,368,587) because some live births occurred in the second trimester

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



§: Data for 2018 not shown due to very few data partners contributing data for 2018
†: No PDE5 inhibitor use during pregnancy was observed between 2001 and 2005. However, not all data partners contributed data over the entire study period, with more partners contributing data in more recent years. This resulted in much fewer pregnancies captured between 2001 and 2005 (< 70,000 annually) and may not have been a large enough sample to detect the rare use of PDE5 inhibitors during pregnancy during those years.
‡: No vardenafil or avanafil use during pregnancy was observed between 2001 and 2018

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, preeclampsia, 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 dispensed prescription claims 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.

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