Utilization Patterns for Products with Pregnancy Exposure Registries in Pregnant Versus Non-Pregnant Women in the Sentinel Database

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Background / Study Objective

• Pregnancy Exposure Registries (PER) are typically conducted when a medical product may be used in pregnant women but has a concerning or unknown safety profile during pregnancy.

• We identified 35 Pregnancy Exposure Registries (PER) in a previous systematic review.

• Among study PERs, we sought to examine relative rates of utilization among primarily commercially insured pregnant versus non-pregnant women.
Our study was conducted in Sentinel Distributed Database.

We used electronic healthcare information from 15 data partners in a distributed database.

The study was conducted with data from 2001-2013.
Methods

• Live Birth Pregnancies
  – 1.9 million live birth pregnancies (LBP) were identified using a previously validated algorithm (Li Q et al, 2013)

• Matched Non-Pregnant Women
  – 1.9 million non-pregnant women were matched on age, calendar year, and data partner

• Outcome
  – Relative rates of utilization in pregnant vs non-pregnant women were calculated for 35 products with PERs.
Methods

• Estimated Date of Conception (i.e. date of last menstrual period, LMP)
  – Estimated as 270 days prior to delivery for full term births.
  – Date of conception was adjusted for pre-term and post-term births using billing codes shown on the following slide

• Trimesters
  – Trimesters formed as: (1) days 0-90, (2) days 91-180, and (3) days 181 to hospital admission for delivery

• Pregnancy Exposure
  – A pregnancy exposure was defined as a dispensing during pregnancy or day supply of a medication extending beyond the estimated date of conception
# Estimated Date of Conception

<table>
<thead>
<tr>
<th>ICD-9-CM code</th>
<th>Definition</th>
<th>Algorithm derived gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Weeks</td>
</tr>
<tr>
<td><strong>Preterm Birth Codes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>765.21</td>
<td>Less than 24 completed weeks of gestation</td>
<td>24</td>
</tr>
<tr>
<td>765.22</td>
<td>24 completed weeks of gestation</td>
<td>24</td>
</tr>
<tr>
<td>765.23</td>
<td>25-26 completed weeks of gestation</td>
<td>26</td>
</tr>
<tr>
<td>765.24</td>
<td>27-28 completed weeks of gestation</td>
<td>28</td>
</tr>
<tr>
<td>765.0-765.09</td>
<td>Extreme immaturity</td>
<td>28</td>
</tr>
<tr>
<td>765.25</td>
<td>29-30 completed weeks of gestation</td>
<td>30</td>
</tr>
<tr>
<td>765.26</td>
<td>31-32 completed weeks of gestation</td>
<td>32</td>
</tr>
<tr>
<td>765.27</td>
<td>33-34 completed weeks of gestation</td>
<td>34</td>
</tr>
<tr>
<td>765.28</td>
<td>35-36 completed weeks of gestation</td>
<td>36</td>
</tr>
<tr>
<td>765.1-765.19</td>
<td>Other preterm infants</td>
<td>35</td>
</tr>
<tr>
<td>765.20</td>
<td>Preterm with unspecified weeks of gestation</td>
<td>35</td>
</tr>
<tr>
<td>644.21</td>
<td>Onset of delivery before 37 completed weeks of gestation</td>
<td>35</td>
</tr>
</tbody>
</table>

- This table shows only the preterm birth codes
Results

• Among 35 products with PERs, the most common exposures, calculated as a percentage of total pregnancies (total n=1,895,597), were:
  
  (1) bupropion (n=20,690, 1.09%)  
  (2) sumatriptan (n=8,320, 0.44%)  
  (3) lamotrigine (n=6,193, 0.33%)  
  (4) letrozole (n=5,412, 0.29%)  
  (5) duloxetine (n=4,209, 0.25%)  
  (6) aripiprazole (n= 2,256, 0.13%)

• The median (interquartile range, IQR) relative differential use between pregnant versus non-pregnant women for these products was:
  
  – RR 0.23 (IQR: 0.15-0.31)

• The median (IQR) relative differential use during the 90 days prior to pregnancy between pregnant vs non-pregnant women was:
  
  – RR 0.44 (IQR: 0.32-0.54)
Utilization of Products with PER by Calendar Year

- Graph includes only products with >300 total exposures in Sentinel
- Bupropion is not shown here to avoid distorting the axis (>1% utilization)
- Not all data partners contributed data from 2001 through 2013, although trends were similar for data partners that had data for all study years
Letrozole Therapeutic Use

• Approved Indication
  – Treatment of postmenopausal women with hormone receptor positive breast cancer

• Off-label Use
  – Ovulation Stimulation
    • Given on days 3-7 of menstrual cycle for ovulation induction
    • 2.5mg/day, 5mg/day, or 7.5mg/day x 5 days
Letrozole Exposure During Pregnancy

- Are these true pregnancy exposures or an artifact of misclassification in our estimated date of conception?

- A true pregnancy exposure would be highly concerning:
  1. This product is Category X with a contraindication in pregnancy
  2. Letrozole has been studied for use with misoprostol in early pregnancy termination
  3. Premenopausal breast cancer treatment is an off-label use
Letrozole Therapeutic Use

• A second updated evaluation of letrozole (2001-2015) was conducted among 2.3 million live birth pregnancies
  – n=7,827 (0.33%) exposures to letrozole anytime during pregnancy
  – n=7,749 first trimester exposures

• Ovulation Stimulation
  – 65.3%% had a 5 day supply
  – 9.5%% had a 10 day supply
  – 7.6% had a 28 day supply

• Premenopausal Breast Cancer Treatment
  – 9.0% had a 30 day supply;
  – 5.3% have breast cancer coding (algorithm from Nattinger et al)

• Ongoing effort will cross tabulate day supply with tablets dispensed
Difference in Days Between Most Recent Letrozole Exposure and Estimated Date of Conception

*Calculated as: letrozole dispensing date – estimated date of conception*
IVF/IUI Population

- We identified a cohort of live birth pregnancies who had an In Vitro Fertilization (IVF) or Intrauterine Insemination (IUI) procedure; n=47,390
  - We can estimate an accurate gestational length in this population
  - This population is enriched with letrozole users
  - This population is known to have a higher rate of preterm births than the general population

- We calculated the difference between the date of the IVF/IUI procedure and the estimated date of conception from ICD-9 coding

- Calculated as:
  - IVF/IUI procedure date - Estimated date of conception (i.e. LMP)
Timing Between IVF/IUI Procedure and Estimated Date of Conception; Among 47,390 Women with an IVF/IUI

- On the whole, our estimated date of conception in the IVF/IUI population overestimated gestational length by about 2 weeks.
- 87% of conception estimates were within 30 days of IVF/IUI procedure in this population
- 42% within 15 days; 10% within 7 days
Difference in Days Between IVF/IUI Procedure and Most Recent Letrozole Exposure
Conclusions

• Lower rates of utilization were observed during pregnancy and immediately prior to pregnancy for all study products with Pregnancy Exposure Registries, except letrozole.

• As expected, we found the estimated date of conception in an IVF/IUI population overestimated the true length of gestation by approximately two weeks on average.
  • This likely explains a large portion of the letrozole pregnancy exposures.

• Misclassification in the estimated date of conception leads to difficulties in assessing exposure intended to occur immediately prior to conception.

• Ongoing work is being conducted to better characterize letrozole exposures during pregnancy.
Questions?
## IVF/IUI Procedural Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Full Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>58974</td>
<td>Embryo transfer, intrauterine</td>
</tr>
<tr>
<td>S4011</td>
<td>In vitro fertilization; including but not limited to identification and incubation of mature oocytes, fertilization with sperm, incubation of embryo(s), and subsequent visualization for determination of development</td>
</tr>
<tr>
<td>S4013</td>
<td>Complete cycle, gamete intrafallopian transfer (GIFT), case rate</td>
</tr>
<tr>
<td>S4014</td>
<td>Complete cycle, zygote intrafallopian transfer (ZIFT), case rate</td>
</tr>
<tr>
<td>S4015</td>
<td>Complete in vitro fertilization cycle, not otherwise specified, case rate</td>
</tr>
<tr>
<td>S4016</td>
<td>Frozen in vitro fertilization cycle, case rate</td>
</tr>
<tr>
<td>S4022</td>
<td>Assisted oocyte fertilization, case rate</td>
</tr>
<tr>
<td>58321</td>
<td>Artificial insemination; intra-cervical</td>
</tr>
<tr>
<td>58322</td>
<td>Artificial insemination; intra-uterine</td>
</tr>
<tr>
<td>S4035</td>
<td>Stimulated intrauterine insemination (IUI), case rate</td>
</tr>
</tbody>
</table>