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.

Sentinel

- 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

ICD-9-CM code	Definition	Algorithm derived gestational age	
		Weeks	Days
Preterm Birth Codes			
765.21	Less than 24 completed weeks of gestation	24	168
765.22	24 completed weeks of gestation	24	168
765.23	25-26 completed weeks of gestation	26	182
765.24	27-28 completed weeks of gestation	28	196
765.0-765.09	Extreme immaturity	28	196
765.25	29-30 completed weeks of gestation	30	210
765.26	31-32 completed weeks of gestation	32	224
765.27	33-34 completed weeks of gestation	34	238
765.28	35-36 completed weeks of gestation	36	252
765.1-765.19	Other preterm infants	35	245
765.20	Preterm with unspecified weeks of gestation	35	245
644.21	Onset of delivery before 37 completed weeks of gestation	35	245

- This table shows only the preterm birth codes
- Table from: Andrade et al, *Matern Child Health J.* 2016;20(4):895-903.

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%)   (4) letrozole (n=5,412, 0.29%)
  (2) sumatriptan (n=8,320, 0.44%)   (5) duloxetine (n=4,209, 0.25%)
  (3) lamotrigine (n=6,193, 0.33%)   (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
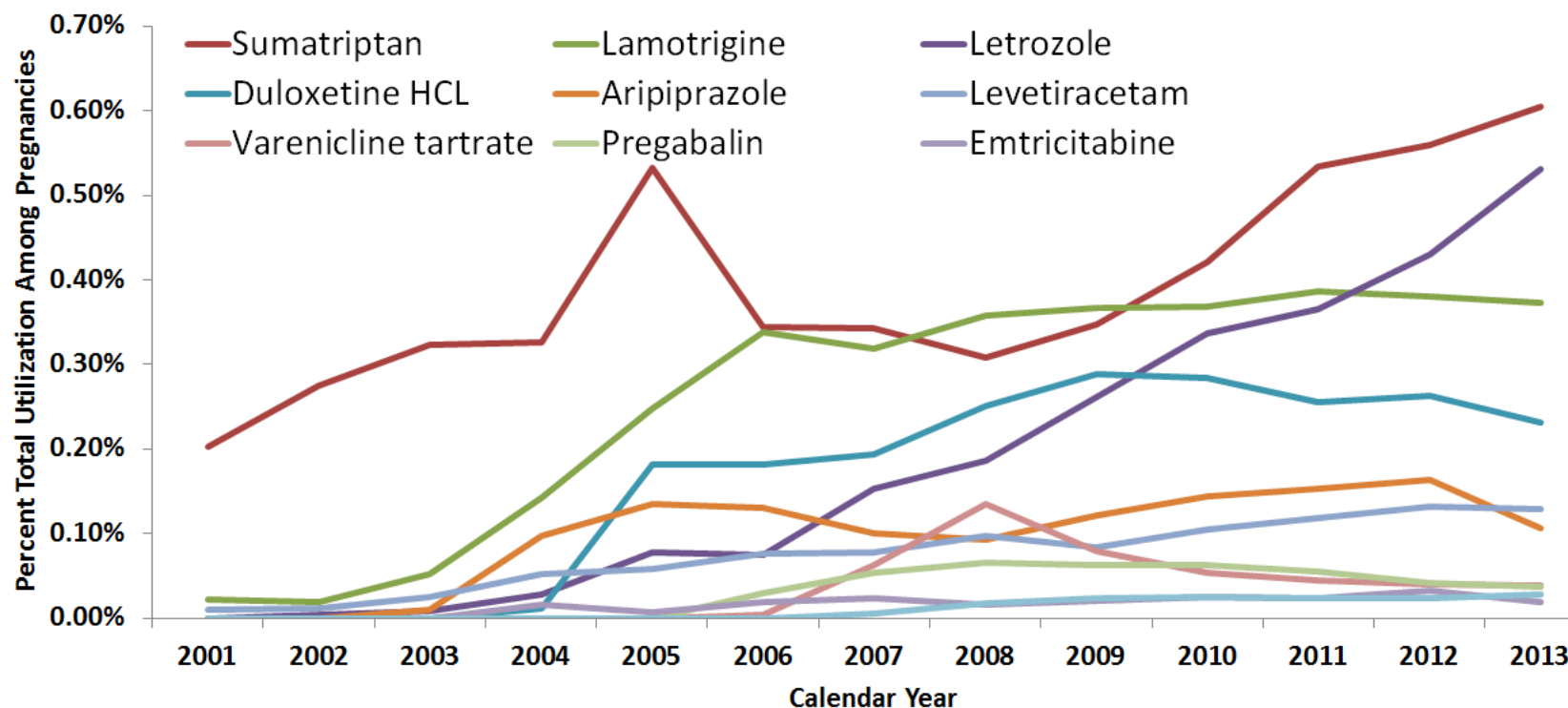
- Graph includes only products with >300 total exposures in Sentinel
- Bupropion is not shown here to avoid distorting the axis (>1% utilization)
- Not all data partners contributed data from 2001 through 2013, although trends were similar for data partners that had data for all study years

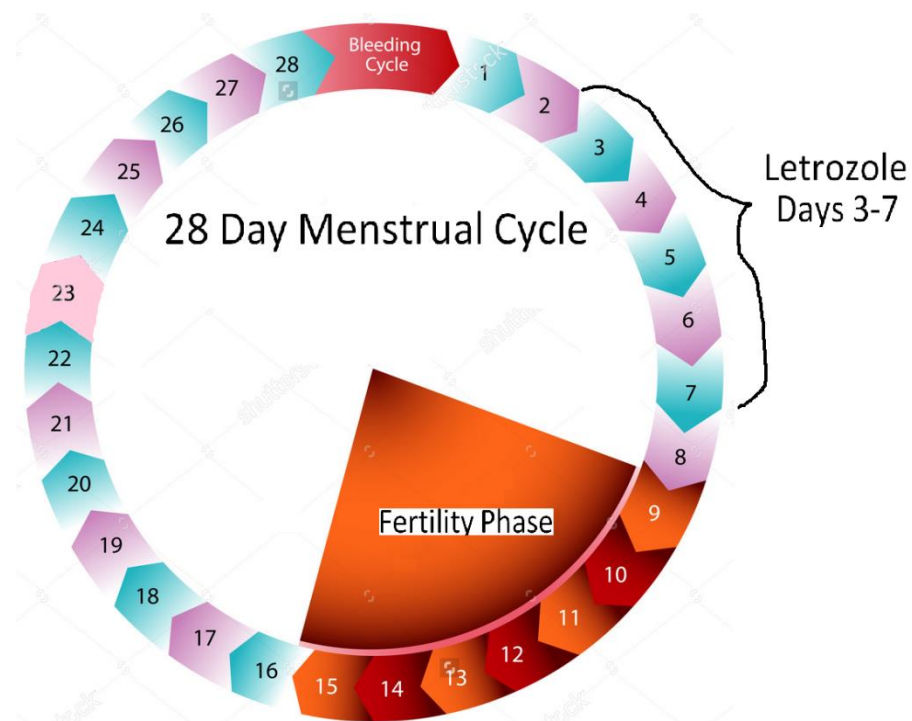# Letrozole Therapeutic Use

- 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 misopristol 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
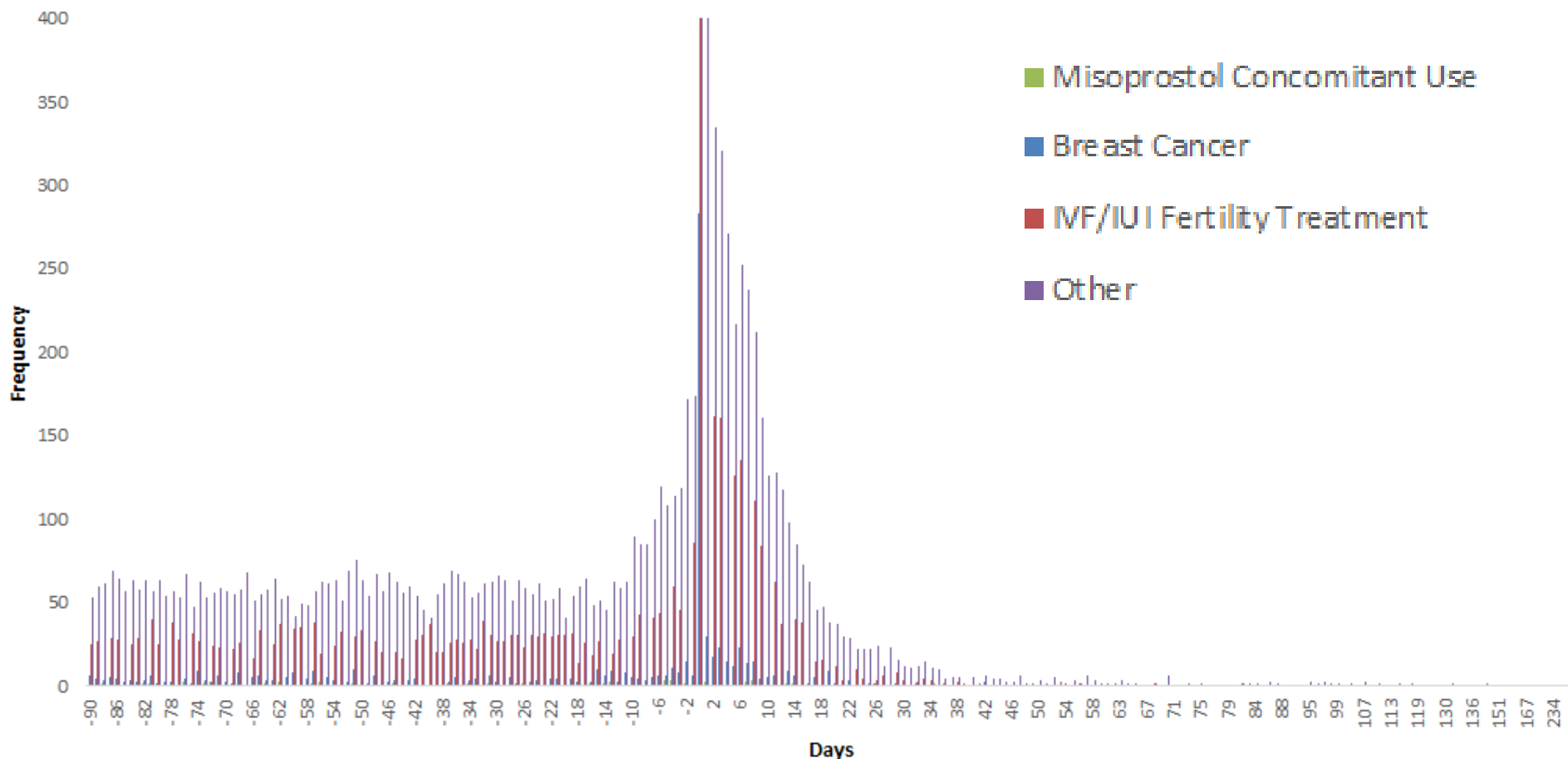

*Calculated as: letrozole dispensing date – estimated date of conception

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
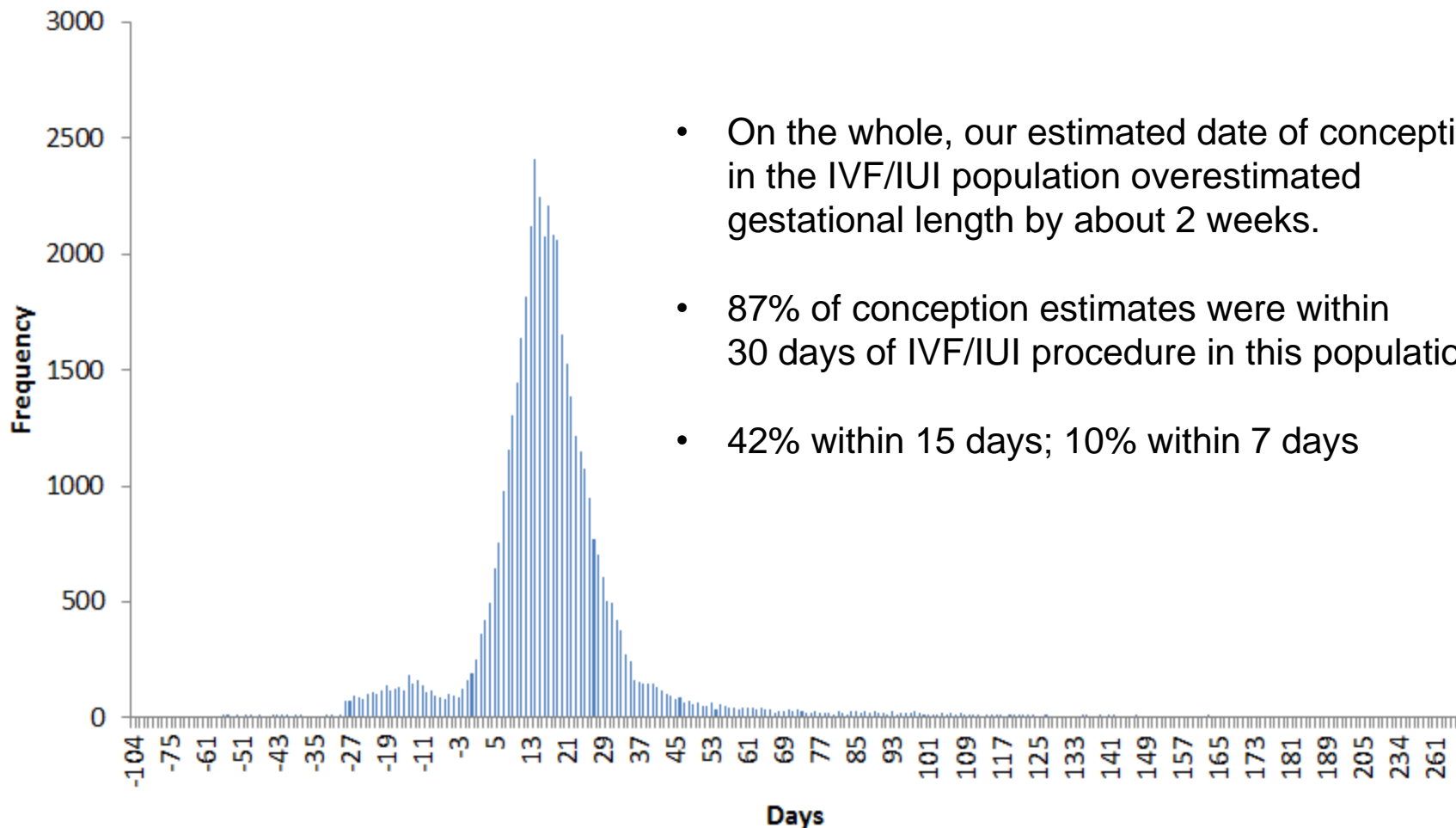
- On the whole, our estimated date of conception in the IVF/IUI population overestimated gestational length by about 2 weeks.

- 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
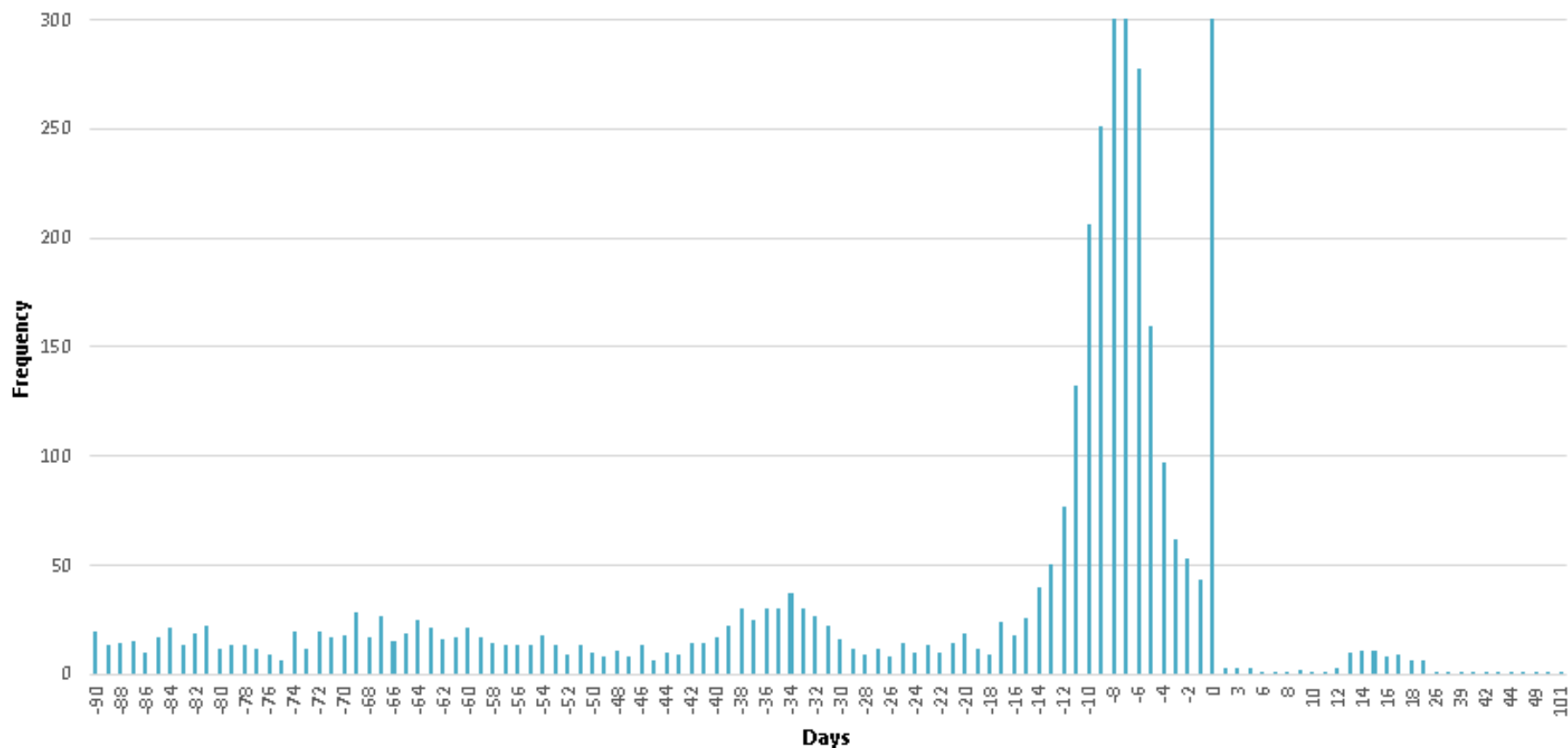
Conclusions

- 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

Code	Full Description
58974	Embryo transfer, intrauterine
S4011	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
S4013	Complete cycle, gamete intrafallopian transfer (GIFT), case rate
S4014	Complete cycle, zygote intrafallopian transfer (ZIFT), case rate
S4015	Complete in vitro fertilization cycle, not otherwise specified, case rate
S4016	Frozen in vitro fertilization cycle, case rate
S4022	Assisted oocyte fertilization, case rate
58321	Artificial insemination; intra-cervical
58322	Artificial insemination; intra-uterine
S4035	Stimulated intrauterine insemination (IUI), case rate