A Systematic Review of Enrollment and Retention in Pregnancy Exposure Registries Compared to the Product Manufacturer's Capture of Spontaneous Reports of Exposed Pregnancies

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BACKGROUND

Pregnancy Exposure Registries (PER) and Spontaneous Reports (SR) are essential pharmacovigilance tools to evaluate medical product exposures during pregnancy.

OBJECTIVES

1) Assess patient enrollment and retention in PER compared to Sponsor's receipt of SR describing exposed pregnancies
2) Calculate PER enrollment per 100 known SR
3) Assess whether PER enrollment and SR capture increase with the following predictors:

   A) U.S. utilization levels, calculated as exposure per 100,000 live birth pregnancies (LBP)

   B) Predominant drug distribution channel

   C) Countries included in the PER

   D) Pregnancy Category in product labeling

METHODS

Systematic Review of PER

We identified PER for drug or biologic products in a previous systematic review (Gelperin et al, ICPE 2015).

Registries were included if they were designed with the primary objective to study the safety of drugs or biologics in pregnancy, they sought to enroll pregnancies prior to knowledge of the study outcome, the product was approved in the US, and the PER started prior to January 2014.

For the purpose of analyzing enrollment, multiproduct registries contributed only one product to the analysis.

Information Request to PER

From each manufacturer, we requested total and annual PER enrollment as well as data on retention of pregnancies for capture of birth outcomes.

Manufacturers of included PER were asked to provide information on the planned timeframe where infants of exposed mothers would be followed, and success rates of achieving pre-specified follow-up.

We requested from each manufacturer the number of postmarketing SR of exposed pregnancies, excluding those in the PER, received from worldwide sources since market approval, by country of origin.

Predictors of Enrollment in PER and SR Capture

1) We calculated utilization levels among pregnant women as exposures per 100,000 live birth pregnancies (LBP) using the Sentinel Distributed Database. The methodology for identification of LBPs in Sentinel has been described previously [Andrade et al, 2016;20(4):895-903].

2) The predominant distribution channel was defined for each product using the IMS National Sales Perspectives™ database [*IMS, 2017*]. This database captures the quantity of drug product sold from the manufacturer to all U.S. distribution channels.

3) We reviewed each study protocol and classified PER on whether enrollment was limited only to the U.S. or was multinational (US and ≥1 additional country).

4) We identified the Pregnancy Category (B, C, D, or X) from the product labeling.

RESULTS

Our systematic review identified 35 PER meeting study inclusion criteria, 34 (97.1%) of which responded to the questionnaire.

Median (IQR) enrollment in study registries was 36 pregnancies (5-258), with three registries enrolling 0 pregnancies and three registries enrolling >1500 pregnancies.

Table 1: Data Capture of Exposed Pregnancies and Infants

No. identified exposed pregnancies or infants	No. of PER enrolling each range of exposed pregnancies	No of PER enrolling each range of exposed infants	No. of SR databases capturing each range of SRs
	n=34 PER	n=34 PER	n=34 SR databases
0	3	6	2
1 to 20	11	14	3
21 to 100	10	5	4
101 to 500	6	6	9
501 to 1500	1	2	8
>1500	3	1	8

Median (IQR) SR capture was 450 exposed pregnancies (89-1192). Median (IQR) number of infants enrolled in PER was 12 (2-119).

Of 31 manufacturers receiving ≥1 SR, 22 (71.0%) identified a majority of SR outside the U.S.

Table 2: Data Capture in PER and Number of SR by Enrollment Predictors

	No. Registries	PER Enrollment, *median (IQR)*	Spontaneous Reports, *median (IQR)*	PER Enrollment per 100 SR, *median (IQR)*
Sentinel Exposure Threshold Categories				
>20/100,000 LBP	9	490 (92-1597)	1061 (743-1224)	44 (14-52)
0.5-20/100,000 LBP	16	36 (16-150)	541 (291-2186)	6 (3-9)
<0.05/100,000 LBP	9	3 (0-4)	41 (5-72)	5 (0-9)
Primary Distribution Channel				
Retail	14	59 (15-639)	564 (164-1183)	11 (6-52)
Mail Order	12	39 (3-150)	541 (39-2186)	6 (1-14)
Non-Retail	8	18 (13-124)	367 (188-760)	6 (5-9)
Included Countries				
United States Only	19	31 (4-113)	85 (26-417)	16 (9-48)
Multinational	15	43 (11-593)	743 (182-1143)	7 (3-52)
Pregnancy Category				
B	4	165 (22-1037)	701 (137-1407)	15 (14-31)
C	22	40 (6-266)	674 (102-1491)	7 (3-10)
D	4	11 (5-20)	225 (105-616)	3 (2-19)
X	4	83 (30-209)	318 (121-520)	25 (4-45)

Products with relatively greater utilization during pregnancy had markedly greater PER enrollment (Table 2), with median enrollment of 490 pregnancies for products used during >20/100,000 LBP, 36 pregnancies for products used during 0.5-10/100,000 LBP, and 3 pregnancies for products used during <0.05/100,000 LBP. The number of SR received by the sponsor followed a similar trend [>20/100,000: n=1061, 0.5-20/100,000: n=541,<0.5/100,000: n=41].

Products primarily dispensed in retail pharmacies had the largest median PER enrollment (59 pregnancies), although this category was correlated with higher use during pregnancy. PER with multinational enrollment had a larger median enrollment (43 pregnancies) than PER enrolling only in the U.S. (31 pregnancies).

Pregnancy category B products had greater PER enrollment than other categories (median=165 pregnancies), although Category X products had a greater proportionate capture of total known SR (25 PER enrolled / 100 known SR).

Table 3: Data Capture of Women and Infants of Exposed Mothers in PER

	No of PERs	Achieved Follow-up, *median (IQR)*	Achieved and Ongoing Follow-up, *median (IQR)*
Women	24	83.9 (72.5-94.5)	94.1 (75.7-97.3)
Children			
Perinatal	4	89.9 (81.1-97.8)	92.1 (84.5-97.8)
1 to 5 months	4	75.0 (72.0-82.1)	77.4 (75.2-82.6)
≥6 months	11	57.1 (35.0-71.6)	83.0 (67.7-92.6)

Among PER enrolling ≥10 pregnancies (n=24), median (IQR) retention rate for pregnancy outcomes was 83.9% (72.5%-94.5%) (Table 3).

For PER with data on ≥10 infants (n=19), median retention to achieve protocol-specified follow-up decreased with longer follow-up goals., This was partially accounted for by the larger percentage of pregnancies with ongoing follow-up.

CONCLUSIONS

- Relatively higher utilization among pregnant women, often associated with retail distribution, predicted greater PER enrollment.
- For drugs with low utilization during pregnancy, PER enrollment was low and differences in PER enrollment compared to worldwide SR were most pronounced. This suggests that these products may especially benefit from a combination of worldwide pharmacovigilance, PER, and additional data streams.
- Although only 19 PER enrolled ≥10 infants, achievement of postnatal follow-up was high.