

# Pregnancy exposure registries: Prenatal testing allowed?

Susan S Roberts, PhD, MPH<sup>1,2</sup> and Jessica D Albano, PhD, MPH<sup>2</sup>

<sup>1</sup>University of NC Wilmington, North Carolina, USA <sup>2</sup>Kendle International Inc., Wilmington, North Carolina, USA

## Abstract

**Background:** Enrolling pregnant women with evidence of potential birth defects on prenatal tests as prospective patients in pregnancy exposure registries may bias risk estimates. However, limiting enrollment to pregnant women without prenatal testing can drastically reduce the pool of eligible women, limiting the feasibility of the registry.

**Objectives:** To examine enrollment and analysis practices regarding eligibility criteria, case definition, and the types of prenatal test information available at the time of enrollment.

**Methods:** We surveyed 38 currently ongoing North American pregnancy registries identified through the searches of the FDA website, internet, and literature and examined the handling of prenatal test results at the time of enrollment for eligibility (enrolled/not enrolled) and case definition (analysis population vs. analyzed separately).

**Results:** Of the 38 pregnancy registries identified, we obtained 35 completed surveys (92%). Most (n=34, 97%) allowed prior prenatal testing at the time of enrollment if the woman was currently pregnant and no abnormalities were found. Pregnant women with abnormal prenatal test results at enrollment were included in the primary analysis in 9 registries (26%); 22 (63%) analyzed these data separately; 4 (11%) excluded these women from enrollment altogether. Only 2 registries enrolled women after the pregnancy ended, regardless of birth defect status, and included these data in the primary analysis. Variations were seen in the definitions of abnormal prenatal tests such as serum screening for neural tube defect or Down syndrome and ultrasound evidence of anencephaly.

**Conclusions:** Enrolling women in pregnancy registries with normal prenatal tests and including them in the primary analysis is commonly done. Differences in eligibility criteria, case classification, and the definition of an abnormal prenatal test reduce comparability across pregnancy registries. Sensitivity analyses to examine the potential for bias are recommended.

## Background

Enrolling women in pregnancy registries early in pregnancy before prenatal testing may reduce selection bias. Standard of care varies but typically includes routine screening beginning as early as 10 weeks (Table A).<sup>1</sup> The FDA Guidance on Pregnancy Exposure Registries (2002) recognizes that the prospective orientation of such registries is a major strength in evaluating the teratogenic effects of prenatal drug exposure, however, it acknowledges the difficulty in enrolling an adequate number of eligible women who have not had prenatal testing.<sup>2</sup>

Not all abnormal findings are consistent with teratogenic effects; for example, the finding of an increased risk for Down syndrome (trisomy 18) may be attributed to maternal age and factors other than the exposure under study and may not be basis for exclusion. Further, screening results indicating an increased risk do not translate directly into a birth defect.

Table A. Typical prenatal testing schedules in the U.S.

Test	Indication/Abnormality	Gest. Age (weeks)
Chorionic villus sampling	chromosomal, genetic	10-12
Nuchal translucency ultrasound	chromosomal, genetic, structural	11-14
1st trimester serum screen	aneuploidy	11-14
Genetic amniocentesis	chromosomal, genetic	14-20
MSAFP, triple, and quadruple serum screen	neural tube defect, aneuploidy	15-20
Level II/Anatomy ultrasound	structural	15+
Fetal echocardiography	structural, functional fetal cardiac/rhythm abnormalities	18+

## Objectives

To examine enrollment and analysis practices in pregnancy registries pertaining to:

- Eligibility criteria
- Case definition
- Types of prenatal test information available at the time of enrollment

## Methods

The study population of pregnancy registries was identified through searches of the published literature, research databases, and the internet. Among registries willing to participate, a representative (e.g., PI, Project Manager) was surveyed to capture methodological practices. Standard surveys were completed by self-administration or by interview. Using descriptive statistics, we examined the handling of prenatal test results at the time of enrollment for eligibility (enrolled/not enrolled) and case definition (analysis population vs. analyzed separately).

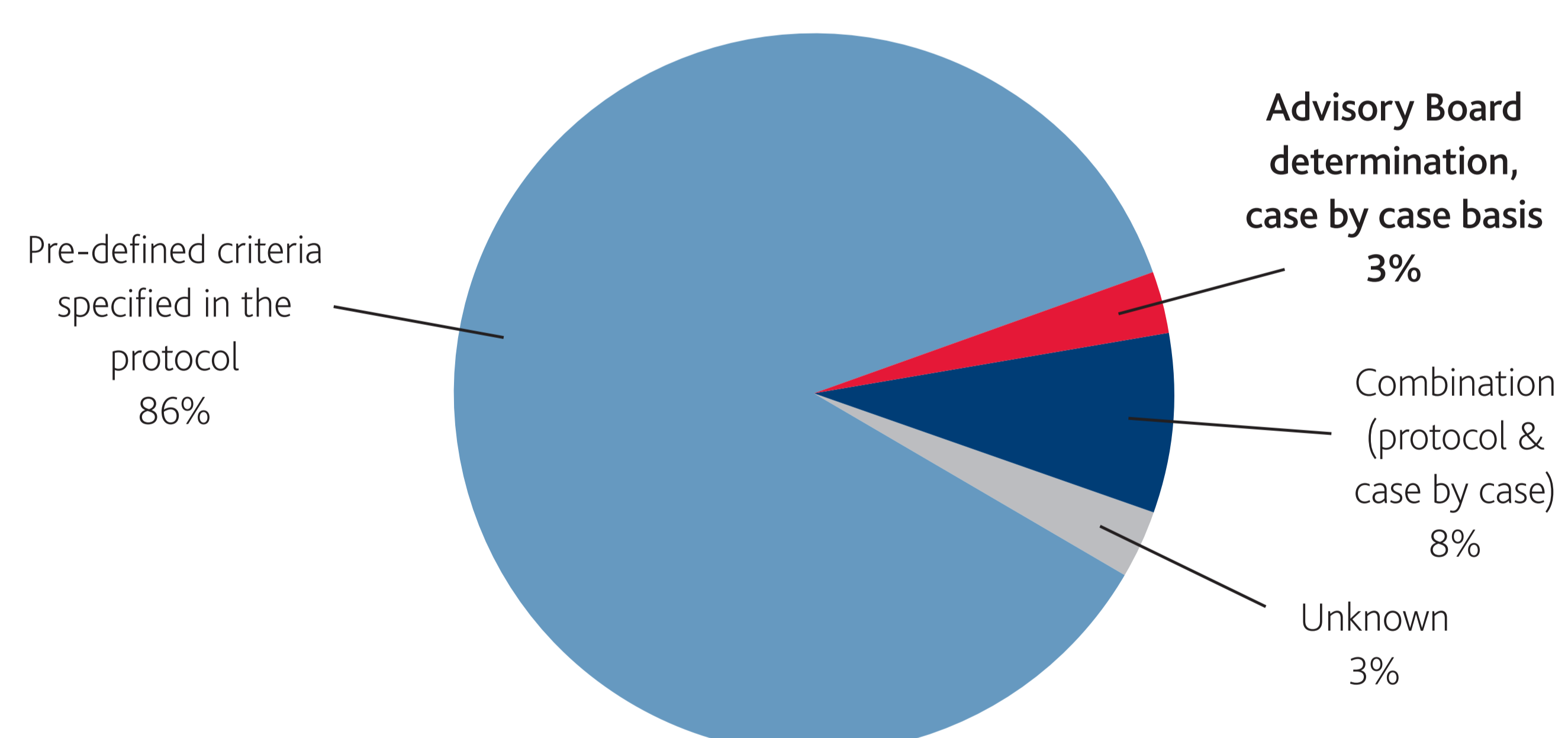
## Results

- Of the 38 registries surveyed, 35 (92%) responded to the survey.
- Geographically, 40% (n=14) were U.S. only; 40% (n=14) were U.S. and other countries; and 20% (n=7) were global pregnancy registries.

Table 1. Summary of prenatal testing status by enrollment and case classification.

At the time of enrollment:	Patient Data Captured		Patient Data Not Captured
	Included in Primary Analysis	Analyzed/Reported Separately	
<b>Currently pregnant</b>			
No prenatal testing done	35 (100%)	0 (-)	0 (-)
Prenatal testing: no abnormalities	34 (97%)	1 (3%)	0 (-)
Prenatal testing: abnormalities	9 (26%)	22 (63%)	4 (11%)
<b>Pregnancy has ended</b>			
No birth defects noted in infant/fetus	2 (6%)	13 (37%)	20 (57%)
Birth defects noted in infant/fetus	2 (6%)	18 (51%)	15 (43%)
<b>Type of abnormal test results</b>			
Structural congenital anomaly	9 (26%)	22 (63%)	4 (11%)
Serum screening for aneuploidy: increased risk for Down syndrome	15 (43%)	17 (49%)	3 (9%)
Choroid plexus cyst detected by ultrasound	16 (46%)	16 (46%)	3 (9%)
Anencephaly detected by ultrasound	9 (26%)	22 (63%)	4 (11%)
Serum screening: increased risk for neural tube defect	15 (43%)	17 (43%)	3 (9%)

Figure 1. Method of determining enrollment eligibility and case status categorization for analysis.



## Conclusions

Among the surveyed registries, a variety of methods are used to define the analysis population with regard to prenatal testing and case eligibility. The impact on the overall birth defect rate is not known. Allowing the analysis population to contain women with "normal" results may bias the point estimate toward the null. Conversely, allowing "all comers" regardless of prenatal testing results may inflate the point estimate through selection bias. These variations also have implications for interpreting the results compared to commonly used population-based estimates.

Enrolling women with normal prenatal tests as prospective patients is a feasible solution as long as the potential for bias is examined in subgroup analysis. Enrollments **early in pregnancy** can minimize the prevalence of prior prenatal testing. Early enrollments can be facilitated by an active awareness plan, efficient study designs, and user-friendly operational procedures.

Pregnancy registries vary greatly in the selection of the analysis population; this limits the ability to compare results across registries. Standardization through updated FDA guidance would help to improve usefulness of pregnancy registry data.

## References

1. Roberts SS *et al*, 2006. Prenatal Testing Prior to Enrollment in Pregnancy Exposure Registries. PDS 2006;15(Supp):S12.
2. U.S. FDA Guidance for Industry: Establishing Pregnancy Exposure Registries. August 2002 [online]. <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133332.pdf>

## Disclosure

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