Neuroscience and Biobehavioral Reviews 77 (2017) 107–121

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Risk mitigation for children exposed to drugs during gestation: A critical role for animal preclinical behavioral testing

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ARTICLE INFO

Article history:
Received 27 November 2016
Accepted 8 March 2017
Available online 16 March 2017

Keywords:
Human pregnancy
Off-label drugs
Cognitive deficits
Child development
Rodent animal models
Autism
Attention deficit hyperactivity disorder
Depression

ABSTRACT

Many drugs with unknown safety profiles are administered to pregnant women, placing their offspring at risk. I assessed whether behavioral outcomes for children exposed during gestation to antidepressants, anxiolytics, anti-seizure, analgesic, anti-nausea and sedative medications can be predicted by more extensive animal studies than are part of the FDA approval process. Human plus rodent data were available for only 8 of 33 CNS-active drugs examined. Similar behavioral and cognitive deficits, including autism and ADHD emerged in human offspring and in animal models of these disorders after exposure to fluoxetine, valproic acid, carbamazepine, phenytoin, phenobarbital and acetaminophen. Rodent data helpful in identifying and predicting adverse effects of prenatal drug exposure in children were first generated many years after drugs were FDA-approved and administered to pregnant women. I recommend that enhanced behavioral testing of rodent offspring exposed to drugs prenatally should begin during preclinical drug evaluation and continue during Phase I clinical trials, with findings communicated to physicians and patients in drug labels.

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http://dx.doi.org/10.1016/j.neubiorev.2017.03.005
0149-7634/

1. Introduction

Pregnant women are excluded from virtually all clinical trials that establish the safety of drugs by the US Food and Drug Administration (FDA). Nevertheless, hundreds of drugs of undetermined safety for fetuses (Lo and Friedman, 2002). are administered to pregnant women for treatment of multiple diseases (Briggs and Freeman, 2014). There is no specific guidance from drug manufacturers or the FDA, other than recommendations that the pregnant patient discuss the issue with her physician, who in most instances has little solid evidence for prescribing practice in pregnant women (Schonfeld, 2013).

The pregnant woman with serious medical challenges faces a difficult choice. Drugs that ease the maternal burden of depression or seizures, for example, may present long-term behavioral risks to her fetus, but untreated depression and epileptic activity also are associated with offspring risks. Uncertainty regarding drug use will remain as long as pregnant women are not enrolled in clinical trials.

The reluctance to include pregnant women in clinical trials is influenced by adverse effects revealed decades ago in treating pregnant women with the synthetic estrogen diethylstilbestrol (DES), which rendered offspring at increased risk for cancer, and by thalidomide, which produced upper and lower limb defects in fetuses after gestational exposure. Orally administered stilbestrol induced breast tumors in mice (Shimkin and Grady, 1940) and studies in multiple animal species treated with thalidomide documented a syndrome that included complete absence of lower extremities (Di Paolo, 1963; Homburger et al., 1965; Hamilton and Poswillo, 1972; Hendrickx et al., 1966). Unfortunately, definitive animal studies were not performed until after pregnant women were treated with these drugs. The value of extensive animal research has repeatedly been confirmed but would be of much greater utility if performed before rather after drugs are administered to pregnant women.

1.1. Post-marketing findings and drug registries

Information on the safety of drugs for pregnant women is primarily available from post-marketing reports and drug registries. It takes years to accrue sufficient information to warrant FDA intervention, during which time patients and their physicians lack reliable information concerning individual drugs. The identification of risks from registries is presently limited by insufficient sample sizes (Gliklich et al., 2014); most newly marketed drugs have no human pregnancy data (Briggs et al., 2015). An average of 6 years elapsed after FDA approval before the teratogenic risk of pregnancy drugs became known, and 9 or more years elapsed before a treatment was designated as likely risk-free (Lo and Friedman, 2002; Adam et al., 2011).

1.2. Ethics of clinical trials in pregnant women

Evidence gathered in a randomized controlled trial would expose fewer pregnant women and their fetuses to risk than the larger number of pregnant women currently exposed to medications once drugs come to market and are administered off-label (Schonfeld, 2013). From a public health perspective, including pregnant women in drug trials would be beneficial; from the perspective of an individual woman, ample reasons predispose her to avoid participation in such trials. Unless desperate and lacking other options, pregnant women are unlikely to voluntarily enroll in a clinical trial of an unproven new drug. This dilemma has no obvious solution; however, off-label administration of drugs with no known safety profile to pregnant women is tantamount to enrollment in an unregulated experiment, without the safeguards of a well-controlled clinical trial.