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Review of the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act – what can the obstetric community learn from the pediatric experience?

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Abstract

Children have been called therapeutic orphans as they have been excluded from drug research and new drug development resulting in the lack of proper labels for majority of the drugs for pediatric use. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) are two legislative mandates to improve pediatric drug labeling. The BPCA legislation authorizes the National Institutes of Health (NIH) to implement research programs through funding clinical trials to study off patent drugs in pediatric population. Obstetric pharmacology research gaps are in many ways similar to those in pediatrics, including off-label use of common medications, and lack of knowledge of appropriate dosing, safety, and efficacy of drugs. Much research is needed to define mechanisms of disease and drug actions in pregnant women to fill the knowledge gaps.

Children have been called therapeutic or pharmaceutical orphans as they have generally been excluded from drug research and new drug development¹. This has been due, in part, to technical and ethical concerns, and the lack of financial incentives. The lack of proper labeling of medications for children has led to serious medical consequences and tragedies².

The U.S. FDA and Congress have attempted to improve pediatric labeling through a series of initiatives including the 1994 Pediatric Rule, 1997 FDA Modernization Act (FDAMA), 1998 Pediatric Rule, and 2002 Best Pharmaceuticals for Children Act (BPCA) and the 2003 Pediatric Research Equity Act (PREA).

The 1997 FDA Modernization Act (FDAMA) provided a 6-month extension to existing marketing exclusivity for pharmaceutical companies to study medications in pediatric populations as requested by the FDA in a Written Request (WR)³. This left a gap for studies needed to improve pediatric labeling for off-patent products, or for products where the

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manufacturer declined to perform the requested studies. In 2002, the Best Pharmaceuticals for Children Act (BPCA) was signed into law, which expanded the program to include a role for the National Institutes of Health (NIH) to cover this gap. In 2003, the Pediatric Research Equity Act (PREA) was enacted to require manufacturers to complete studies in children, when the pediatric and adult indications are the same, and when the medications were expected to be used in a substantial number of children⁴. Both BPCA and PREA were reauthorized by Congress in 2007. In 2012, PREA and the FDA-related portion of BPCA were made permanent. Section 409I of BPCA which relates to NIH expires in 2017 unless reauthorized.

The BPCA legislation authorized a research program with implementation through the NIH, specifically to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Under the BPCA mandate, the NICHD, in consultation with the FDA and experts in pediatrics, is responsible for (1) identifying and publishing a list of drugs (and, in 2007, therapeutic areas) of highest priority for study in pediatric populations; (2) sponsoring relevant pediatric clinical trials; and (3) submitting resulting data to FDA for consideration of pediatric labeling changes. The first priority list, including 12 off-patent drugs requiring further investigation was published in January 2003⁵. The most recent list outlining priority needs in pediatric therapeutics for multiple therapeutic areas was published in August 2014⁶.

Under the BPCA legislation, FDA issues Written Requests (WR) to drug manufacturers (both New Drug Application (NDA) and abbreviated (aNDA) holders) to conduct pediatric drug studies. If a WR is declined by a drug manufacturer, then the FDA has the option to refer the WR to NIH for clinical studies. Alternatively, NIH can submit draft Written Requests, or Proposed Pediatric Study Requests (PPSRs), to FDA outlining the design, study population and proposed endpoints for clinical studies to be conducted. Since the BPCA inception, the NICHD has sponsored 25 clinical trials with 59 drugs; the results of eight clinical trials have been submitted to FDA for consideration of labeling changes. More drugs are being studied and data will soon to be submitted to the FDA. In 2007, the BPCA mandate also included a means to improve pediatric infrastructure. NICHD has expanded its support of pediatric clinical pharmacology training grants, and awarded a Pediatric Trials Network contract.

With several decades of the development of pediatric initiatives, and the strong support from various advocate groups and the pediatric community, pediatric drug research has made significant strides. As a proof of concept, NICHD supported the Pediatric Pharmacology Research Units (PPRU) (www.ppru.org), a multisite research network to demonstrate that pediatric clinical trials could be performed ethically. The PPRU performed more than 260 studies and contributed data on 23 drugs which led to the pediatric labeling. Although gaps in knowledge in understanding the mechanisms of disease characteristics and developmental pharmacology in drug disposition and response still remain, results from clinical studies/ trials have led to significant pediatric labeling changes by FDA.

Obstetric pharmacology research parallels the pediatric situation in several ways: there is significant off-label use of common medications, and lack of sufficient scientific knowledge

of appropriate dosing, safety, and efficacy. There is a lack of basic science to define mechanisms of disease; genotypic and phenotypic disease characteristics; and developmental pharmacology in drug disposition and response. Specifically for obstetrics, scientific knowledge gaps include: when and on what basis extrapolation from pre-clinical models could be done for appropriate drug dosing, safety and teratogenicity, and efficacy; placental transport; drug disposition across pregnancy; and drug safety and efficacy across pregnancy.

Federal agencies have addressed the issues in obstetric therapeutics through initiatives including the NICHD Maternal-Fetal Medicines Units Network (MFMU) and Obstetric Pharmacology Research Units Network (OPRU), and the CDC Treating for Two Initiative. Much as the original paradigm for pediatric clinical trials participation has evolved from “not ethical” to “not ethical not to”, the same will hopefully occur in obstetrics, and off-label prescribing will no longer be the norm.

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