Renal Teratogens

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KEYWORDS

• Kidney development • Teratogens • Pregnancy • Drug safety

KEY POINTS

- As the average age of childbearing increases, so does fetal exposure to potentially nephroteratogenic drugs.
- Renin-angiotensin system inhibitors should be avoided in pregnancy, and fetal exposure in the second half of pregnancy can cause a distinctive fetopathy, characterized by renal tubular dysplasia, oligohydramnios, hypertension, and hypocalvaria.
- Nonsteroidal antiinflammatory drugs taken late in pregnancy may cause oligohydramnios and should be avoided unless potential benefits (eg, for tocolysis) outweigh risks.
- Women of childbearing potential and their physicians should communicate clearly and frequently about the potential fetal risks of medications, and steps to avert or mitigate harm should be taken if clinically indicated.
- There is an urgent need for further research on fetal effects of maternally administered drugs, and study design, whenever possible, should include assessment of short-term and long-term renal harms.

INTRODUCTION

The average age of women at first childbirth has increased dramatically over the past several decades, having reached 30 years of age (the highest worldwide) in the United Kingdom and Germany and 25 years of age in the United States.[1] With the trend toward increased maternal age, as well as the declining state of preconception health

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among women of childbearing age, there is an increasing prevalence of maternal chronic medical conditions, such as diabetes and hypertension, requiring prescription medication, which may result in fetal drug exposure.[2] In addition, as the evidence of the developmental origins of adult chronic diseases such as hypertension accumulates, fetal renal drug safety is likely to have long-term public health significance.[3]

Existing knowledge about the effects of maternal drug exposure on fetal kidneys is limited and derives mostly from case reports and observational studies. Thus, for most medication exposures, causality of adverse fetal consequences must be indirectly inferred according to the epidemiologic principles articulated by Doll and Hill.[4,5] Using the term teratogen broadly to include any substance that has the potential, under certain exposure conditions, to have a clinically significant harmful effect on fetal formation or organ function allows one to consider both congenital malformations of the kidney and impacts on renal function as potential outcomes of exposure. To understand fully whether or not a particular drug is a teratogen, the effects of disruptions in renal development and the functional sequelae of reduced nephron number and renal function resulting from in utero exposures should be considered.

Teratogens, per the US Food and Drug Administration (FDA) recommended use of the term,[6] have the "capacity under certain exposure conditions to produce abnormal development in an embryo or fetus." Most clinicians are familiar with the FDA fetal and infant risk classification of drugs used by pregnant or lactating women according to the A, B, C, D, or X system, explained as follows: class A, adequate and well-controlled (AWC) studies failing to show risk; B, animal reproduction studies show no risk, but AWC studies are lacking; C, adverse fetal effect in animal studies, with no AWC human studies available; D, positive evidence of human fetal risk, but benefits may justify use in appropriately compelling clinical scenarios; and X, positive evidence of risk that outweighs any possible benefit.[7] However, the FDA has proposed to eliminate the foregoing classification scheme and substitute a more detailed narrative description with 3 key elements: risk summary, clinical considerations, and data,[7] with the final rule to be implemented in 2014.[8]

In this article, the existing literature on suspected human nephroteratogenic drugs is summarized and critically appraised and brief clinical considerations are presented with risk/benefit/alternative analysis for each drug class during the relevant period of pregnancy, citing currently preferred drugs or treatment strategies that are believed to minimize the potential for maternal-fetal harm. We begin, to place in developmental context the potential for nephroteratogenicity, with an illustrative case (**Box 1**). The case described in **Box 1** shows several questions that arise when an individual with preexisting hypertension who is taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) becomes pregnant. What is the risk of exposure to potentially teratogenic medication and to maternal hypertension to her baby? Which medications should be used to control blood pressure? Should the pregnancy be terminated because of conception while on valsartan? How should the infant be assessed for ARB exposure-related effect? What are the long-term effects of fetal exposure to medications that have the potential to alter kidney development?

OVERVIEW OF NEPHROGENESIS

It is useful to consider the major stages of nephrogenesis, because the timing of fetal exposure is likely to affect the observed phenotype. As shown in **Fig. 1**, kidney development in the human embryo begins before the end of the fifth week of gestation (ie, third embryonic week). Normal development is initiated with formation of the ureteric

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