PEDIATRICS PERSPECTIVES

Hormonal Contraceptive Agents: A Need for Pediatric-Specific Studies

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Adolescents are frequently prescribed hormonal contraceptive agents for both contraceptive and noncontraceptive purposes. Over half of all sexually experienced females aged 15 to 19 have used some form of hormonal contraception: 56% oral contraceptive pills (OCPs), 20% injectable, 14% emergency, 10% patch, and 5% ring.[1] Given that 50% of adolescent girls have been sexually active before age 18, ~1 in 4 adolescent girls will be exposed to hormonal contraceptives by age 18.[2] Additionally, teenagers are more likely than adult women to use hormonal contraceptives for purposes other than birth control: 33% of adolescents on OCPs use the method solely for noncontraceptive purposes.[3]

Hormonal contraceptive agents have many noncontraceptive benefits that are of particular importance during adolescence. They decrease menstrual flow, anemia, painful periods, acne, functional ovarian cysts, as well as other menstrual-related symptoms such as premenstrual syndrome, headaches, and epilepsy. Menstrual irregularity is common among adolescent girls, particularly in the first 2 years after menarche. These irregular periods can lead to prolonged excessive bleeding. In girls with bleeding disorders, sickle cell disease, polycystic ovary syndrome, or developmental delays, menstrual control may be essential to well-being and indicated soon after menarche. The median age at menarche is 12 to 13 years old. Given this median, girls 10 to 12 years of age could be menstruating and have reason to be prescribed hormonal contraceptive agents. Especially few data are available regarding hormonal contraceptive use in girls under the age of 13.

Despite their widespread use, the overwhelming majority of hormonal contraceptive agents have not been adequately studied in pediatric populations. Pharmacokinetic data are lacking, as few industry-sponsored trials have enrolled subjects younger than 18 years of age. Trials that have included adolescents typically exclude those younger than 16. Efficacy is generally extrapolated from adult data and expected to be the same for postpubertal adolescents as for adults. This assumption ignores not only distinctive physiologic factors of pediatric populations, but also unique characteristics that impact "real-life" efficacy such as lower health literacy and reduced adherence. Adolescents are more likely than adult women to discontinue, restart, or change hormonal contraceptive methods.

Pediatric pharmacodynamic studies, where available, demonstrate that adult data are not adequate to determine pediatric safety. Depot medroxyprogesterone acetate and OCPs impair peak bone mass acquisition in young adolescents.[4] This is not of as much concern in adult women in whom peak bone mass has been achieved. Whereas baseline obesity has been found to be a risk factor for weight gain in adolescents administered depot medroxyprogesterone acetate, it has been found to be protective in adults.[5] The mechanisms of contraceptive-associated weight gain in adolescents are likely distinct from those in adult women in whom body composition is more stable. Although adolescents are generally considered low risk, up to 5.9% of contraceptive-related venous thromboembolisms are seen in this population.[6] While we are aware of no studies evaluating coagulation profile changes associated with hormonal contraceptive use in patients younger than the age of 18, it is known that the coagulation profile of adolescents differs from that of adults.[7] The consequences, if any, of the unique physiologic state of adolescence on the safety of hormonal contraceptives and the lasting effects of hormonal contraceptive use in these formative years are not known.

Federal law and US Food and Drug Administration (FDA) regulations require that new pharmaceuticals be tested in specific populations before approval for clinical use. Testing in pediatric populations, however, has historically been lacking, and as such, drugs are frequently used "off-label" in this population. The Best Pharmaceuticals for Children Act (BPCA) was signed into law in 2002 to promote pharmaceutical studies in children and encourage the development of new drugs for use in pediatric populations. The BPCA offered 6 additional months of patent exclusivity for drugs being tested for pediatric use and established mechanisms for studying off-patent drugs in children. The BPCA tasked the National Institutes of Health with identifying and prioritizing drugs in need of pediatric study and requesting or conducting trials not initiated by manufacturers. In 2007, the BPCA was reauthorized and expanded. Under the BPCA 2007, the National Institutes of Health must publish a priority needs list every 3 years, which includes both drugs and indications needing pediatric study. The BPCA 2007 also gave the FDA further power to issue written requests to drug manufacturers for pediatric testing.

Although the BPCA encourages voluntary pediatric studies, the Pediatric Research Equity Act (PREA) mandates pediatric testing for drugs likely to be used in pediatric populations unless a waiver or deferral is granted. Waivers may be granted in the following cases: where pediatric assessments would be impossible or highly impractical to conduct, the drug does not represent a meaningful benefit to children as compared with existing therapies, or pediatric use is anticipated to be insubstantial or nonexistent (eg, a prostate cancer treatment drug).

Despite the significant advancements in pediatric pharmaceutical testing brought on by the BPCA and PREA, hormonal contraceptive testing has seen limited to no advancement in this patient population. Hormonal contraceptive agents have not been included in priority needs lists or studies requested under the BPCA. Although a BPCA-related Adolescent Therapeutics Working Group has been in existence since 2009, no specific drugs, including hormonal contraceptives, have been identified as priorities for study. Working Groups in other areas have generated specific drug lists, but hormonal contraceptives have not been, and are unlikely to be, included because they do not fall within these groups' scopes of practice. Although the merits of generating a list of specific drugs were weighed by the Adolescent Therapeutics Working Group, concerns were raised that such a list would impose limits on adolescent pharmacology research. We counter that for drugs that carry existing stigma, such as hormonal contraceptives, a specific recommendation by a working group would be the impetus necessary to overcome current reluctance.

PREA's requirement for pediatric testing would be expected to apply to hormonal contraceptives as they represent a meaningful benefit to children and are commonly used in pediatric populations. However, manufacturers are not routinely conducting hormonal contraceptive clinical trials in children. Whether this is due to sponsor denial or requirement waiver is not known. Study requests declined by sponsors are unlikely to be carried out by the FDA. This lack of testing has resulted in a dearth of data for multiple hormonal contraceptive agents that are commonly used in the clinical care of pediatric and adolescent females.

Given that ~1 in 4 adolescent females will be exposed to hormonal contraceptives by the age of 18, reluctance to conduct pediatric contraceptive testing can no longer be justified. The time has come for pediatric and contraceptive trials networks to begin to perform pharmacokinetic/pharmacodynamic studies in this important population. Specific Requests for Applications calling for pediatric data, as well as the FDA prioritizing and mandating pediatric data for new hormonal contraceptive drug approvals, are needed. Those who provide care to pediatric and adolescent girls, as well as their professional societies, must begin lobbying for trials in this population. Hormonal contraceptives represent one of the few drug classes taken long-term by otherwise healthy adolescents. The neglect of pediatric patients in hormonal contraceptive testing represents an indefensible

health disparity that must be remedied. This health disparity will likely worsen should the current situation continue.

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