In Utero Exposure to 17α-Hydroxyprogesterone Caproate May Contribute to Increasing Incidence Rates of Early-Onset Cancer

Caitlin Murphy. *University of Texas Southwestern Medical Center*

Caitlin C. Murphy, PhD, MPH[1], Piera M. Cirillo, MPH[2], Nickilou Y. Krigbaum, MPH[2], Barbara Cohn, PhD[2]. [1]University of Texas Southwestern Medical Center, Dallas, TX, [2]Public Health Institute, Berkeley, CA.

Background: 17α-hydroxyprogesterone caproate (17-OHPC) is a synthetic progestogen introduced in the 1950s to treat habitual and threatened abortion in pregnant women. Although 17-OHPC is still available (tradename Makena), little is known about its effects on health of adult offspring, and questions concerning safety and effectiveness remain. For example, progestogens have been implicated in cancer, and trends in the use of 17-OHPC in early pregnancy during the 1950s and 60s parallel increasing incidence rates of certain cancers in young adults, such as early-onset colorectal cancer, born during that time.

Methods: We examined the effect of 17-OHPC exposure in utero on risk of cancer in adult offspring in the Child Health and Development Studies, a cohort of women receiving prenatal care between June 1959 and September 1966, with deliveries through June 1967 (n=18,751 live births excluding neonatal deaths among 14,507 mothers). Diagnosed conditions and prescribed medications were abstracted from mothers' medical records beginning 6 months prior to pregnancy through delivery. We identified mothers who received 17-OHPC (tradenames Delalutin and Proluton) in early pregnancy, defined as day 1 - 140 of gestation. Incident cancers diagnosed in offspring through 2018 were ascertained by linkage with the California Cancer Registry.

Results: Among 18,751 live births, 954 cancers were diagnosed at ages 18 - 58 years. The most frequent cancers were breast (20.9%), cervical (10.9%), colorectal (7.1%), and prostate (5.9%) cancer and melanoma (9.2%). Although few mothers (n=181, 1.0%) received 17-OHPC in early pregnancy, in utero exposure was more common in offspring diagnosed with cancer (n=18, 1.9%) compared to those without cancer (n=163, 0.9%). Conditions indicating 17-OHPC included threatened abortion (54.0%), amnionitis (9.4%), and incompetent cervix (3.0%). 17-OHPC increased risk of any cancer in offspring (OR 2.08, 95% CI 1.27, 3.40), with particularly striking associations for colorectal (OR 4.78, 95% CI 1.49, 15.41) and prostate (OR 3.83, 95% CI 0.93, 15.83) cancer. There was no association between conditions indicating 17-OHPC and risk of any cancer in offspring (threatened abortion: n=1,891 mothers, OR 1.07, 95% CI 0.87, 1.32), or with use of other progestogens within 6 months prior to pregnancy (medroxyprogesterone acetate: n=50 mothers, OR 0.38, 95% CI 0.05, 2.76).

Conclusions: Findings support susceptibility of multiple organ systems to endocrine disruption during early development and risk of cancer decades later - and may partly explain increasing rates of early-onset colorectal cancer. Even before mechanisms of carcinogenesis are elucidated, caution using 17-OHPC and other endocrine-active pharmaceuticals in early pregnancy is warranted, especially in the absence of a clear short-term benefit, and given the possible effect on risk of cancer in adult offspring.

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