

**Discontinuation of long-established Hydroxyprogesterone Caproate; call for awareness and drug-substitutes: A Letter to the Editor**Muhammad Affan<sup>1</sup>, Erum Ilyas<sup>2</sup>

*Madam*, 17-Hydroxyprogesterone caproate is a synthetic progestin medication used to prevent preterm birth in pregnant women with a prior history of preterm birth. The drug has been used worldwide, including in Pakistan (local brand names Gravibinan and Proluton) for the prevention of PTBs and recurrent miscarriages. The drug is potent, cost-effective and readily available as IM injections. The FDA approved drug in 2011 after the Meis trial was regarded as a game-changer.<sup>1</sup> But many subsequent trials showed that the drug did not significantly lowered the risks of preterm births.

The PROLONG study, much larger than the Meis trial, that was conducted in association with the FDA between 2009 and 2018 as a confirmatory trial showed practice-changing results that 17 OHPC did not significantly reduce the risk of PTB and neonatal morbidity, hence not confirming treatment efficacy.<sup>2</sup> The FDA ultimately in 2023 issued a statement recalling Makena (17-OHPC) and its generics from the market stating that the drug had no significant role in reducing the risk of PTBs and has potential risks to the offspring in the long term.<sup>3</sup> A study by C. Murphy et. al published in the American Journal of Obstetrics and Gynecology showed an increased risk of prostate, colorectal and paediatric brain cancer in offspring exposed to 17 OHPC especially during the first trimester.<sup>4</sup>

Micronized progesterones (locally available as Progefik and U-Progest) on the contrary, are chemically similar to human progesterone and are therefore regarded as 'body-identical'. They are administered orally or vaginally and have similar effects as 17-OHPC in the prevention of PTB. A comparative study in India by Shambhavi et.al was one of the various studies to show that no significant difference in the two medications for the prevention of PTB and neonatal morbidity.<sup>5</sup> Micronized progesterone has largely gained popularity in recent years and has replaced 17-OHPC in preventing PTBs especially in women with short cervix.

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17-OHPC is still being widely prescribed in Pakistan. Efforts should be made to spread awareness among the healthcare practitioners regarding the disapproval by FDA for continued use of 17-OHPC. Pakistan's Drug Regulation Authority needs to act accordingly regarding the continued approval of the drug in the country and spread awareness about its substitutes with better potency and reduced risks. Moreover, continued research about the efficacy of other progesterones administered to reduce PTBs and their potential risk factors in the long run is needed.

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