Female sexual maturation and reproduction after developmental exposure to endocrine disrupting chemicals.

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The timing of puberty has been mainly studied in females for several reasons including the possible evaluation of a precise timer i.e. menarcheal age and concerns in the high prevalence of precocity in females as opposed to males. Human evidence of altered female pubertal timing after exposure to endocrine disrupting chemicals (EDCs) is equivocal. Among limiting factors, most studies evaluate exposure to single EDCs at the time of puberty and can hardly assess the impact of lifelong exposure to mixtures of EDCs. Some rodent and ovine studies indicate a possible role of fetal and neonatal exposure to EDCs, along the concept of early origin of health and disease. Such effects are possibly involving neuroendocrine mechanisms since the hypothalamus is a site where homeostasis of reproduction as well as control of energy balance are programmed and regulated. In our previous studies, pulsatile Gonadotrophin Releasing Hormone (GnRH) secretion control through oestrogen, glutamate and aryl hydrocarbon receptors (AhR) was shown to be involved in the mechanism of sexual precocity after early postnatal exposure to the insecticide dichlorodiphenyltrichloroethane (DDT). Very recently, we have shown that neonatal exposure to the potent synthetic oestrogen diethylstilbestrol (DES) or Bisphenol A is followed by early or delayed puberty depending on the dose, with consistent changes in developmental increase of GnRH pulse frequency. Moreover, DES results in reduced leptin stimulation of GnRH secretion *in vitro,* an effect that is additive with prenatal food restriction. Thus, using puberty as an endpoint of EDC effects, it appears necessary to consider pre- and perinatal exposure to low doses and to pay attention to the other conditions of prenatal life such as energy

availability, keeping in mind the possibility that puberty could be not only advanced but also delayed through neuroendocrine mechanisms.