REPRODUCTIVE CHALLENGES FOR FEMALE SICKLE CELL PATIENTS ON HYDROXYUREA

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Abstract: Sickle cell disease is effectively treated with hydroxyurea (HU), an S-phase antineoplastic agent. However, women are advised not to attempt pregnancy while on HU due to the teratogenic effects of this agent, based on results obtained from animal studies. In fact, several case reports suggest that HU may have minimal teratogenic effects on the developing human fetus. Fourteen cases of HU therapy in pregnant patients diagnosed with acute or chronic myelogenous leukemia, primary thrombocytopenia, or sickle cell disease have been reported (Byrd et al., 1999; Pharmacotherapy, 19:1459-62). Three pregnancies were terminated by elective abortion; one woman developed eclampsia and delivered a phenotypically normal stillborn infant. All other patients delivered live, healthy infants without congenital anomalies. We therefore hypothesize that case studies such as this cannot effectively address the adverse effect of HU on embryo resilience. Because of the case nature of these studies with limited number of subjects, we sort to assess the risks associated with a clinically relevant dose of HU used for the treatment of SCD, on ovulation rate and embryo development, using adult C57BL/6J female mice. In Expt 1, 30 day-old female mice were randomly assigned to a treatment or a control group (N=20/gp). Treatment consisted of oral HU (30 mg/kg) for 30 days; while control mice received saline (HU carrier). Four days to the cessation of HU dosing, all mice were subjected to folliculogenesis induction with PMSG (2.5 IU; IP). Ten mice/gp were anesthetized at 48 hours post PMSG to facilitate blood collection via cardiac puncture for E2 measurement by RIA. Ovulation was induced in the remaining mice at 48 hours post PMSG with hCG (2.5 IU; IP) and the mice immediately caged with adult males for mating. Sixteen hours post hCG, mated mice were sacrificed, ovaries excised and weighed and embryos harvested and cultured in Whitten’s medium supplemented with CZBt (WCZBt). In Expts 2 and 3, (N=10/Expt) folliculogenesis and ovulation were induced in untreated mice followed by mating as described above. Recovered embryos were either cultured continuously (Expt 2) or intermittently (Expt 3) in the presence or absence of bioavailable HU (18 μg HU/ml of WCZBt). Treated mice sustained decreased ovarian wt, ovulation rate and circulating E2 compared with controls (P<0.05). Fewer embryos retrieved from HU-treated mice developed to blastocyst stage (32%) compared with those from controls (60%; P<0.05). Furthermore, continuous (HU, 10 vs control, 63%; P<0.05) or intermittent (HU, 20 vs control, 62%; P<0.05) in vitro exposures of embryos to HU also resulted in reduced development to blastocyst stage, with embryos exposed continuously to HU in vitro fairing worse. Even though HU is beneficial for the alleviation of the clinical manifestations of SCD, our data suggest that it compromises folliculogenesis and the ability of generated embryos to develop. Therefore, designed studies with larger numbers of patients receiving HU during pregnancy, with longer follow-up of exposed children and more careful assessment of embryo/fetotoxic effects, are required before this agent can be promoted as safe in pregnancy.

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