Exposure to hydroxyurea during pregnancy: a case series

Table 1 Our cases of HU exposure during pregnancy

	Exposure time					*Malformations*		*Complications*			*Total (%)*	
	1st trimester	*1st and 2nd trimester*	*3rd trimester*	*Throughout*	*Unknown*	*Minor*	*Major*	*IUGR*	*Prematurity*	*Neonatal respiratory distress*		
Pregnancies	22	2	2	3	2	—	—	2	—	—	31	
Outcomes	23[a]	2	2	3	2	—	—	—	—	—	32[a]	100
SA	0	0	0	0	1	—	—	—	—	—	1	3.1
VA	4	0	0	0	0	—	—	—	—	—	4	12.4
MA	1	0	0	0	0	0	0	—	—	—	1	3.1
IUFD	2[b]	0	0	0	0	0	0	—	—	—	2	6.2
LI	16	2	2	3	1	3[c]	0	—	9	5	24	92.3

IUGR, *in utero* growth retardation; SA, spontaneous abortion; VA, volunteer abortion; MA, medical abortion; IUFD, *in utero* fetal death; LI, live infant; LTF, lost to follow-up.
[a]One twice.
[b]Placentar ischemia.
[c]One pilonidal sinus, one unilateral renal dilatation, one hip dysplasia.

TO THE EDITOR

Hydroxyurea (HU) is an antineoplastic drug currently used in the management of many myeloproliferative disorders and especially in essential thombocythemia (ET). The management of pregnancy in women with a myeloproliferative disorder is a real dilemna. Being faced directly with the problem of information and counselling about HU exposure in pregnancy, we decided to collect and evaluate data on the outcome of pregnancy following exposure to hydroxyurea because of essential thrombocythemia (ET), chronic myeloid leukaemia (CML), chromic myeloid splenomegaly (CMSM) and sickle cell disease (SCD).

We collected and evaluated pregnancy outcomes of 31 women with HU exposure. Data were collected in two distinct situations, both with prospective ascertainment of exposure. First, haematologists referred patients for advice to those of us who are geneticists (CTR and ANC). We were faced directly with the problem of information and counselling about HU exposure in pregnancy. We followed these patients and their children after birth. Second, data were collected from two teratogen information services in Paris and Lyon. Telephone calls were made by clinicians seeking information about HU-related risk, then follow-up forms were sent and returned after the pregnancies ended. Overall we collected 31 cases (Table 1). Indications of HU use were ET in 22/31 cases, CML in 6/31 cases, chronic myeloid splenomegaly (CMSM) in 2/31 cases, and SCD in 1/31 cases. HU exposure occurred during the first trimester of pregnancy (weeks 1–14 after last menstruation period) in 22/31 cases, during the first and second trimester in 2/31 cases, throughout pregnancy in 3/31 cases, and in the third trimester in 2/31 cases. Precise HU exposure duration was unknown in 2/31 cases. Doses varied from 0.5 g/day to 6 g/day orally. Other drugs were associated, mostly antibiotics and aspirin. Two cases received interferon-alpha but were lost to follow-up. One woman received misulban and melphalan; she gave birth to a healthy liveborn male infant. The 31 pregnancies with HU exposure ended in 24 liveborn infants (one pregnancy was twice), five induced abortions, one spontaneous abortion and two *in utero* fetal deaths (IUFD). Intrauterine growth retardation (IUGR) was found in 2/31 cases by ultrasound. Among the 24 liveborn infants, nine were premature and three had minor abnormalities, namely hip dysplasia, unilateral renal dilatation and pilonidal sinus. Five presented neonatal respiratory distress after gravidis toxaemia or pre-eclampsia, likely to be as a result of prematurity and not pulmonary malformation. No baby had major malformations. Fetal examination did not find any malformation in the two IUFD either. Prenatal or post-natal chromosomal analysis was normal in 6/7 studied cases and 1/7 cases showed inherited inversion of chromosome 9. Alpha fetoprotein was normal in the three amniotic fluids tested.

The potential teratogenicity discourages women to become pregnant. It is the reason why the sample is small. Indeed, HU reduces the synthesis of deoxyribonucleic acid (DNA), but the mechanism is still unknown. In animals, hydroxyurea produced an increase in congenital anomalies in all species tested. Animals affected include the chick, rat, mouse, cat, and monkey.[1,2] In rats, treatment during the 9th to 12th gestational days produced defects of the central nervous system, palate, and skeleton. Hamsters exposed to hydroxyurea during gestation developed neural tube defects and heart abnormalities. The formation of reactive free radicals by hydroxyurea seems to be an important part of the embryonic cytotoxicity of this agent. Moreover, a significant blood pressure and heart rate alteration was demonstrated; the resulting reductions in uterine blood flow (77%) elicited by HU may be associated with its immediate embryotoxicity.[3] HU presented a real toxicity in all animal species. Thus it could be concluded that the antimitotic and cytotoxic effect of HU should depend on the concentration, duration of exposure and the sensitivity of the organism. Because HU induces menstrual disturbances, exposed pregnancies are also rare. Table 2 lists the 19 known human cases of exposure to HU during pregnancy reported in the literature to date. No malformation was described among documented first-trimester exposures; neither second- and third-trimester exposures resulted in any fetal anomaly. Some authors[4–7] conclude that clinical reports in humans show that the potential of fetal adverse effects is not very high and often overestimated.

Teratogenic effects were searched for after first trimester exposures. No major malformation is described in our case series during this period. In fact, no major malformation was found among the 24 liveborns and the two *in utero* fetal deaths. Hip dysplasia and unilateral renal dilatation are not rare and there is no argument to correlate them with HU exposure. Cases of respiratory distress were as a result of prematurity and not pulmonary dysplasia or malformations. No chromosomal abnormalities were found. However, there was a significant number of intrauterine growth retardation, fetal death *in utero* and prematurate infants. Nevertheless, these complications might be

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Table 2 Review of reported cases on HU exposure during pregnancy

Author/Ref.	*Indications*	*Exposure time*	*Dose (g/day)*	*Other drugs*	*Outcome*
Doney *et al* 1979[9]	AML	1: 2nd trimester	1:8 iv	Daunorubicin, ara-c, vincristine, prednisone, 6-thioguanine, cephalothin, gentamycin, platelet transfusions, carbenicillin	MA, fetus 307 g, NP
Doney *et al* 1979[9]	AML	1: 2nd trimester	1:8 iv	Daunorubicin, ara-c, vincristine, 6-thioguanine	1 LI: 31 wg, 2 kg 130, NP hyponatremic, hypocalcemic and hypoglycemic during the first 2 days of life
Patel *et al* 1991[10]	CML	throughout	0.5–1		1 LI: 34 wg, 2 kg 670, NP
Tertian *et al* 1992	CML	0–37 wg	1–3	any	1 LI: 36 wg, 3 kg 100, NP, hip dislocation
Delmer *et al* 1992[11]	CML	throughout	1.5		1 LI: NP
Jackson *et al* 1993[12]	CML	throughout	1.5		1 LI: 38 wg, 3 kg 200, NP
Fitzgerald and McCann 1993[13]	CML	0–2 wg + 4.5 mths until 8 mths	NA	any	1 LI: 38 wg, 3 kg 400, NP
Szanto and Kovacs 1993[14]	CML	throughout	1.5–2.5		1 LI: at term, 3 kg 440, NP
Cinkotai *et al* 1994	ET	0–6 wg	1–2		1 LI: 35 wg, 3 kg 000, NP
Fernandez *et al* 1994[15]	ET	NA	NA	aspirin	MA
Charache *et al* 1995[16]	SCD	1st trimester	NA		MA
Charache *et al* 1995	SCD	1st trimester	NA		MA
Charache *et al* 1995	SCD	1st trimester	NA		1 LI: at term
Dell'Isola *et al* 1997	ET	18–28 wg	0.5–1		1 LI: 37 wg, 2 kg 970, NP
Diav-Citrin *et al* 1999	SCD	0–9 wg	1	Folic acid, oxygen, ceftriaxone, erythromycin, meperidine	1 LI: 39 wg, 3 kg 240, NP, FU: 15 mths, NP
Byrd *et al* 1999[17]	SCD	0–5 wg	0.5	Hydrocodone, cefuroxime folic acid, ferrous sulfate, amoxicillin, promethazine blood transfusions	1 LI: 37 wg, 2 kg 750, NP, mild respiratory distress, lactose intolerance with feeding difficulties; FU: 17 mths, NP
Byrd *et al* 1999	SCD	0–4 wg	0.5	Folic acid, ranitidine, penicillin V, potassium, promethazine, hydrocodone, albuterol inhaler, droperidol, meperidine	1 LI: 32.5 wg, 1 kg 365, NP, respiratory distress, apnea, sepsis, bradycardia, hyperbilirubinema, patent ductus arteriosus, FU: 21 mths, NP
Bayhal *et al* 2000[18]	CML	18–31 wg 34 wg until birth	1.5	Interferon alpha, steroid	1 LI: 37 wg, 2 kg 450, NP
Celiloglu *et al* 2000[19]	CML	20 wg until birth	1.5	any	1 LI: 38 wg, 3 kg 400, NP

CML, chronic myeloid leukaemia; ET, essential thrombocythaemia; SCD, sickle cell disease; wg, weeks of gestation; LI, liveborn infant; MA, medical abortion; IUFD, *in utero* fetal death; NP, normal phenotype; FU, follow-up; NA, not available; IV, intravenous.

related to the underlying haematological condition not to HU exposure. Indeed, maternal disease has to be considered in the evaluation of the teratogenic potentency of hydroxyurea. Some pathologies such as CML and CMSM are usually associated with blood hyperviscosity and SCD with increased risk of vascular or ischaemic complications. ET seems to improve during pregnancy by spontaneous platelet numeration decrease. Fetal death in one case was as a result of severe placental ischaemia and haemorrhage, which could be directly secondary to SCD. In another case, retroplacental haematoma could have explained the fetal death.

Although HU is reported as a teratogen for experimental animals, doses administered are up to 10 to 100 times higher than the therapeutic ones. Because of this dose difference, extrapolation from animal species to humans is doubtful. The cytotoxic effect on HU in animals depends on the concentration, duration of exposure and the sensitivity of the organism. Teratogenicity in humans probably depends on HU doses and duration exposure as well. Associated drug exposures should also be evaluated separately and correlated to pregnancy outcome. Fetal death is more likely to be due to captopril exposure, which is a recognized risk factor.[8]

In practice, despite previously reported teratogenicity in animals with high doses, we did not find any major malformation among the 31 human pregnancies exposed to therapeutic doses of HU. Although the sample presented here is too small to establish the safety of HU in pregnancy, it is a valuable source of additional information for counselling patients inadvertently exposed during pregnancy. Our opinion is that such an exposure should never be an indication for termination of pregnancy, but for a careful follow-up with good clinical, biological and ultrasonographic examinations. Fetal chromosomal analysis should also be proposed because of findings in animal literature. The limited available human data nevertheless lead to the conclusion that pregnancy in women exposed to HU should be avoided when possible until more experience is accumulated.

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Intraventricular thrombosis during all-*trans* retinoic acid treatment in acute promyelocytic leukemia

TO THE EDITOR

The introduction of all-*trans* retinoic acid (ATRA) treatment in association with chemotherapy has markedly improved prognosis of acute promyelocytic leukemia (APL), with significant higher complete remission (CR) rates and longer disease-free survivals.[1–3]

However, in a few patients (<15%) ATRA showed a severe toxicity characterized by fever, weight gain, dyspnea and lung infiltrates (ATRA syndrome).[4] Moreover, an increased occurrence of thrombotic events expecially in the coronaric district has been reported in the elderly.[5] This toxicity might in part be mediated by an increased expression of adhesion molecules that facilitate adhesion of cells to the vascular endothelium, therefore promoting localized coagulation.[6]

We report two patients with APL, who during induction treatment with ATRA plus idarubicin (AIDA protocol)[3] developed an unusual thrombosis of the right ventriculum.

Patient 1 was a 50.7-year-old male, diagnosed with APL in November 1996. At diagnosis WBC were 14.9×10^9/l with blasts >90%, Hb levels 10.4 g/dl and platelets 17×10^9/l; echocardiographic examination was normal. He started therapy according to the AIDA protocol.[3] On day +11, he suddenly developed a respiratory syndrome with hypoxemia (pO_2 55 mm Hg), pulmonary infiltrates and arterial hypotension without fever and thoracic pain. He was pancytopenic (WBC 2.9×10^9/l, platelets 11×10^9/l); coagulation parameters were normal. Cardiological examination did not show any abnormal finding. High-dose dexamethasone (10 mg twice a day) was started, with prompt resolution of clinical and radiological signs. Eight days later, echocardiographic examination showed a 3-cm dishomogeneous mass in the right ventriculum (Figure 1a), tight to the corda of papillar muscle and floating, without functional involvement of the tricuspidal valve. A thrombus was suspected and subcutaneous low-weight heparin (LWH) was started, with a consistent reduction of the mass after 17 days (Figure 1b). After 20 days of LWH treatment, oral anticoagulant therapy was started, with a further reduction of the mass the following year.

The patient achieved a morphological CR and continued post-remission treatment according to the AIDA protocol; molecular remission was achieved after the second consolidation course. After 8 months of maintenance with alternating cycles of ATRA and methotrexate + 6-mercaptopurine he had a molecular relapse (PCR positivity for PML/RARα hybrid gene without morphological signs of disease) and started ATRA treatment for 35 days, with negativization of molecular marker. He then received a consolidation course (mitoxantrone 6 mg/m^2 + cytosine arabinoside 1 g/m^2 for 4 days) but died during the aplastic phase from cerebral hemorrhage.

Patient 2 was a 32-year-old female, diagnosed with APL in July 1997. WBC were 76.5×10^9/l with blasts >90%, Hb levels 12.6 g/dl and platelets 56×10^9/l. Echocardiographic examination was normal. She was treated according to the AIDA protocol[3] but on day +3 she

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