

Exposure to Hydroxyurea and Pregnancy Outcomes in Patients With Sickle Cell Anemia

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The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) was a randomized double-blind placebo-controlled trial to test whether hydroxyurea could reduce the rate of painful crises in adults who had at least 3 painful crises per year. Because hydroxyurea is known to be carcinogenic, mutagenic, and teratogenic in animals, a major inclusion criterion in MSH was the use of contraceptives both by females and males in order to avoid exposure of the fetus to hydroxyurea. Despite this precautionary measure, some women became pregnant while taking hydroxyurea or their male partners were on hydroxyurea. We followed surviving patients who were enrolled in the original MSH trial for up to 17 years postrandomization. Our findings suggest that exposure of the fetus to hydroxyurea does not cause teratogenic changes in those pregnancies that terminate in live birth whether full term or premature. This seems to be true whether the parent taking hydroxyurea was the mother or the father. The same argument seems to apply for exposure to opioids. However, it will take a much longer follow-up of many more hydroxyurea-exposed sickle cell disease subjects to establish the results conclusively.

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INTRODUCTION

The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) was a randomized double-blind placebo-controlled trial to test whether

hydroxyurea could reduce the rate of painful crises in adults who had at least 3 painful crises per year.¹ Hydroxyurea was the experimental agent and an active “look-alike” capsule was used as the placebo agent. Because hydroxyurea is known to be carcinogenic, mutagenic, and teratogenic in animals,²⁻⁶ a major inclusion criterion in the study was the use of contraceptives both by females and males in order to avoid exposure of the fetus to hydroxyurea. Despite this precautionary measure, some women became pregnant while taking hydroxyurea or their male partners were on hydroxyurea. Moreover, the Center for the Evaluation of Risks to Human Reproduction (CERHR) has been concerned that hydroxyurea may increase the risk for congenital anomalies or abnormalities of growth in fetuses after exposure of pregnant women and have an adverse effect on spermatogenesis in men.^{7,8} The purpose of this study is to describe the women (patients on hydroxyurea or partners of male patients on hydroxyurea) who became pregnant, determine the effect of exposure to hydroxyurea on the outcome of pregnancy, and explore the mutagenic effects of hydroxyurea, if any, in the fetuses and newborns of the women exposed to hydroxyurea. To that end, we followed surviving patients who were enrolled in the original MSH trial for up to 17 years postrandomization. In addition we explored the effect of exposure to opioids on the outcome of pregnancy and on the fetuses/newborns.

METHODS

In MSH there were 299 study participants: 153 were female (77, or 50.7%, in the hydroxyurea group; 76, or 51.7%, in the placebo group) and 146 were male (75, or 49.3%, in the hydroxyurea group; 71, or 48.3%, in the placebo group). Before randomization, all study participants (females and males) were advised by a trained counselor about the possible risks to a fetus conceived or carried during hydroxyurea therapy. A concerted effort was made to avoid pregnancy in female MSH participants or the female partners of male MSH participants throughout the trial and follow-up. Contraception advice was given and condoms were made available if needed.

Gynecological referrals were made, if requested, for the fitting of diaphragms and pelvic examinations. During the clinical trial, female subjects were asked about their last menstrual period at each clinic visit. A serum pregnancy (human chorionic gonadotropin) test was performed if amenorrhea or menstrual irregularity developed. Female subjects that became pregnant during the clinical trial were taken off further treatment (regardless of whether or not they were receiving hydroxyurea). For these female subjects, treatment assignment was unblinded, and if they were receiving hydroxyurea, they were counseled regarding the risks of teratogenicity. Female subjects taken off hydroxyurea because of pregnancy were not allowed to resume hydroxyurea treatment after delivery or termination of the pregnancy but were followed to the end of the clinical trial and patient follow-up. During the MSH patients' follow-up, the same conditions regarding contraception were in place as during the MSH clinical trial. However, study participants were seen only at annual visits. Detailed information concerning babies born during or after the MSH clinical trial to MSH patients or their partners was collected.

Hydroxyurea usage data were collected for all 299 MSH study participants during the trial and for the follow-up and extension periods after the trial. The relationship between hydroxyurea usage and pregnancy outcome was assessed descriptively. Since the MSH clinical trial and the MSH patients' follow-up were not designed specifically to inferentially assess the possible safety or risk potential of the use of hydroxyurea in sickle cell anemia patients with respect to pregnancy outcomes, the assessment was descriptive in nature, and no statistical testing was performed. Precise hydroxyurea exposure duration was unknown for the majority of the MSH study partici-

pants because there was a significant amount of missing hydroxyurea usage data across time for most MSH study participants during the follow-up period. Therefore, we had to restrict our definition of hydroxyurea usage to several categories: (1) hydroxyurea usage at the time of conception, ie, during the month of conception, for both female and male MSH study participants; (2) hydroxyurea usage during gestation (at least 1 month during gestation), for female MSH study participants only; (3) hydroxyurea usage at the time of the pregnancy outcome, ie, during the month of the pregnancy outcome, for female MSH study participants only; (4) probable hydroxyurea usage throughout the pregnancy (hydroxyurea usage was determined at conception, during gestation, and at the time of the pregnancy outcome), for female MSH study participants only.

For comparing hydroxyurea usage and MSH pregnancy outcomes, the following pregnancy outcomes were considered: live births, premature births, spontaneous abortions, elective abortions, and fetal deaths. All pregnancy outcomes were dichotomized as yes (the pregnancy outcome occurred) or no (the pregnancy outcome did not occur). To determine the month of conception, we subtracted the gestational age at the time of the pregnancy outcome from the date of the pregnancy outcome. If the gestational age was unknown, month of conception was unknown.

Other important exposures assessed with respect to the pregnancy outcomes were opioids prescribed and opioids given during medical contact (oral or transcutaneous); history of exposure to agents that are associated with high risk of cancer, mutagenicity, or teratogenicity; and history of exposure to levels of radiation other than background or diagnostic. In addition, neonatal abnor-

Table 1. Pregnancy Outcomes by Gender

	Total	Gender	
		Female ^a	Male ^a
	Frequency	Frequency	Frequency
Total	94	52	42
Classification			
Maternal death (stroke)+ fetal death, 22 wk	1	1	0
Live birth age/weight unknown	13	7	6
Live birth >2500 g (term)	31	10	21
Live birth >37 w <2500 g (SGA)	1	1	0
Live birth <38 w <2500 g (preemie)	7	4	3
Live birth >37 w, wt unknown	3	1	2
Fetal death >24 weeks (stillbirth)	1	1	0
Elective abortion, gestational age unknown	8	7	1
Elective abortion <24 wk	10	8	2
Spontaneous abortion, gestational age unknown	7	3	4
Spontaneous abortion <24 wk	10	8	2
Spontaneous abortion ≥24 wk	1	0	1
Twins: fetal death/live birth	1	1	0

Abbreviation: SGA, small for gestational age.

^a Female denotes the female Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) study participants, and male denotes the female partners of the male MSH study participants.

malities and delays in developmental milestones were assessed. The milestone time points were from birth through the first 36 months of life.

RESULTS

There were a total of 94 pregnancy outcomes reported during the MSH trial and the participant follow-up and extension periods after the conclusion of the MSH trial. During the MSH clinical trial, 10 pregnancy outcomes were reported: 6 for female MSH study participants and 4 for the partners of male MSH study participants. Of the 94 pregnancy outcomes, 52 were in 28 female MSH participants and 42 in female partners of 27 male MSH participants. Specifically, there were 28 female MSH participants who had 51 pregnancies (18.3% of the MSH females had at least 1 pregnancy), with 52 pregnancy outcomes (1 pregnancy produced a set of twins). The female partners of 27 male MSH participants had 40 pregnancies (18.5% of the MSH male participants had a female partner with at least 1 pregnancy). These 40 pregnancies resulted in 42 pregnancy outcomes (2 separate pregnancies produced a set of twins). No demographic or clinical information was available for the female partners of these male MSH study participants. If a male MSH study participant reported multiple pregnancies over the course of the follow-up period, it was never determined if the pregnancies were associated with a single female partner or multiple female partners. However, we report these findings even though we have limited information regarding the female partners because we can still explore the possible impact of the potential adverse effect of hydroxyurea on spermatogenesis in men receiving hydroxyurea at therapeutic doses.

The average age for the female MSH study participants considered in this analysis was 27 years (SD, 4.1 years) and the average age for the male MSH study participants was 29.8 years (SD, 4.6 years). Table 1 enumerates the pregnancy outcomes by gender (where female denotes the female MSH study participants and male denotes the female partners of the male MSH study participants). The following discussion refers to Table 2.

For the female MSH study participants, the 6 pregnancy outcomes that had known hydroxyurea usage at conception and sometime during gestation resulted in 1 live birth (full term), 1 live birth (premature), 3 elective abortions (gestational age <24 weeks), and 1 spontaneous abortion (gestational age <24 weeks).

For the female MSH study participants, the 3 pregnancy outcomes that had probable hydroxyurea usage throughout the entire pregnancy (known hydroxyurea usage at conception, known hydroxyurea usage sometime during gestation and known hydroxyurea usage at the time of the pregnancy outcome) resulted in 2 elective abortions (gestational age <24 weeks), and 1 spontaneous abortion (gestational age <24 weeks).

It should be noted that the MSH data coordinating center received no reports why the elective abortions were performed. Therefore, it is not known if any of the elective abortions were performed because of suspected or established fetal abnormalities.

As Table 3 illustrates, for male MSH study participants who had known hydroxyurea usage at conception, the 10 pregnancy outcomes of the female partners resulted in 4 live births (full term), 1 live birth (premature), 1 live birth (gestational age >37 weeks but weight unknown), 2 elective abortions (gestational age <24

Table 2. Pregnancy Outcomes for the Female Multicenter Study of Hydroxyurea in Sickle Cell Anemia Study

	Hydroxyurea at Conception			
	Total	Unknown	No Hydroxyurea	Hydroxyurea
			Exposure	Exposure
Frequency	Frequency	Frequency	Frequency	
Total	52	26	20	6
Classification				
Maternal death (stroke) + fetal death, 22 wk	1	0	1	0
Live birth age/weight unknown	7	7	0	0
Live birth >2500 g (term)	10	2	7	1
Live birth >37 wk <2500 g (SGA)	1	0	1	0
Live birth <38 wk <2500 g (preemie)	4	0	3	1
Live birth >37 wk, weight unknown	1	0	1	0
Fetal death >24 wk (still birth)	1	1	0	0
Elective abortion, gestational age unknown	7	7	0	0
Elective abortion <24 wk	8	3	2	3
Spontaneous abortion, gestational age unknown	3	3	0	0
Spontaneous abortion <24 wk	8	3	4	1
Twins: fetal death/live birth	1	0	1	0

Abbreviation: SGA, small for gestational age.

weeks), and 2 spontaneous abortions (gestational age <24 weeks).

The 28 MSH female participants had the following history of pregnancy during the MSH experience: 14 had a single pregnancy, 9 had 2 pregnancies (1 of the 9 resulted in twins), 2 had 3 pregnancies, 2 had 4 pregnancies, and 1 had 5 pregnancies. The 27 MSH male participants had the following history of pregnancy during the MSH experience: 21 had a single pregnancy (2 of the 21 resulted in twins), 3 had 2 pregnancies, 1 had 3 pregnancies, 1 had 4 pregnancies, and 1 had 6 pregnancies.

Two neonatal abnormalities were reported: (1) MSH female patient offspring: live birth, preemie; and (2) MSH male patient offspring: live birth, >37 weeks but weight unknown—also not considered a full-term birth in the MSH study. Both neonatal abnormalities were not from a parent exposed to hydroxyurea at conception, during gestation, or throughout pregnancy.

History of Exposure to Toxic Agents

In terms of MSH participants who had a history of exposure to agents that are associated with high risk of cancer, mutagenicity, or teratogenicity, there was 1 MSH female participant who experienced an elective abortion <24 weeks (out of 8 elective abortions <24 weeks reported). Hydroxyurea usage was unknown at conception, during gestation, and throughout pregnancy for her. There was 1 MSH male participant whose female partner experienced a live birth >2500 g (term) (out of 21 reported). He had used hydroxyurea at conception.

There was no MSH participant associated with a pregnancy outcome that had ever been exposed to levels of radiation other than background or diagnostic. In

addition to monitoring pregnancy outcomes, another major emphasis of the MSH patients' follow-up was to monitor MSH offspring health and developmental milestones. Specific case report forms collected physician-based evaluations of each MSH offspring's developmental progress. There was no report of delays in developmental milestones by 6 months, by 9 months, by 12 months, by 18 months, by 24 months, or by 36 months of life for any of the MSH offspring.

DISCUSSION

Pregnancy in patients with sickle cell disease presents a challenge both to patients and providers. Historically, we know that pregnancy in women with sickle cell disease, in general, and sickle cell anemia, in particular, is associated with increased maternal morbidity and high fetal morbidity and mortality.⁸⁻¹⁴ Reported fetal complications included small size for gestational age, premature delivery, stillbirth, and spontaneous abortion. Pregnant women with sickle cell disease who also take hydroxyurea could increase the already high risk of fetal morbidity and mortality. The potential of hydroxyurea for mutagenesis, teratogenesis, and carcinogenesis in humans, however, is controversial. Alterations in sperm have been reported in laboratory rodents⁵ and teratogenesis in a variety of laboratory pregnant animals, including rats, hamsters, cats, and rhesus monkey.^{6,15-17} The dose of hydroxyurea and the route of its administration in animals, however, were different than those in humans. In most animals, hydroxyurea was given parenterally, and the dose varied from 50 mg intravenously on gestational days 9, 10, or 11 in hamsters to 1000 mg/kg intravenously on gestational days 9, 10, 11, or 12 in rats.^{6,15}

Participants With Respect to the 3 Hydroxyurea Usage Categories

Hydroxyurea During Gestation			Hydroxyurea Throughout		
Unknown	No Hydroxyurea Exposure	Hydroxyurea Exposure	Unknown	No	Yes
Frequency	Frequency	Frequency	Frequency	Frequency	Frequency
23	23	6	8	41	3
0	1	0	0	1	0
7	0	0	3	4	0
0	9	1	0	10	0
0	1	0	0	1	0
0	3	1	0	4	0
0	1	0	0	1	0
1	0	0	0	1	0
7	0	0	1	6	0
2	3	3	2	4	2
3	0	0	1	2	0
3	4	1	1	6	1
0	1	0	0	1	0

The risk of teratogenesis in humans is unknown and may have been overestimated. Normal pregnancy outcomes were reported in 19 women who took hydroxyurea, and there have been no reports of teratogenicity or mutagenesis in their newborns.^{1,7,18-28} Four of the reported women had sickle cell disease.^{1,21}

Because there was a substantial amount of unknown hydroxyurea usage for many of the pregnancy outcomes examined, our conclusions can only focus on those pregnancy outcomes where the hydroxyurea usage status was known. Therefore, this paper is a case series report, and as such, our results and conclusions regarding hydroxyurea usage may be limited. However, for those pregnancy outcomes with known status for hydroxyurea usage, we did not find a relationship between hydroxyurea usage and neonatal abnormalities or teratogenic effects. Fetuses of those pregnancies that were not terminated and resulted in full-term or premature live births were normal with no evidence of any neonatal abnormalities or teratogenic effects. This seems to be true whether the parent taking hydroxyurea was the mother or father. However, since we do not know why elective abortions were performed, this finding is limited in nature. In addition, the use of hydroxyurea at conception, sometime during gestation, or throughout pregnancy did not result in any delays in development milestones for any offspring of MSH participants (female or male).

The Cooperative Study of Sickle Cell Disease (CSSCD) reported similar pregnancy outcomes. CSSCD noted that “overall, 28.8% of the reported pregnancies ended in voluntary abortions, 6.5% ended in miscarriages, 0.7% ended in stillbirths, and 63.6% ended in live births.”²⁹ Referring to Table 1, it can be seen that the female MSH study participants have a similar elective abortion rate (CSSCD, 28.0%; MSH females, 28.9%); a higher spontaneous abortion rate (CSSCD, 6.5%; MSH

females, 21.2%); a lower still birth rate (CSSCD, 0.7%; MSH females, 0.02%); and a lower live birth rate (CSSCD, 63.6%; MSH females, 42.2%).

The Jamaican Cohort Study reported pregnancy outcome rates for mothers with homozygous sickle cell disease (subjects) and mothers with a normal hemoglobin genotype (controls).³⁰ Two controls were selected for each of the first 125 babies with a phenotype consistent with homozygous sickle cell disease. The Jamaican Cohort Study had 52 subjects with 94 pregnancies and 68 controls with 157 pregnancies. The spontaneous abortion and elective abortion rates of this Jamaican cohort were compared to those of the female MSH study participants.

The elective abortion rate for the Jamaican cohort was 10.6% for the subjects and 8.2% for the controls. It was 28.9% for the MSH female patients. When comparing the Jamaican subjects to the MSH females, the elective abortion rate was lower for the Jamaican subjects. When comparing the Jamaican controls to the MSH females, the elective abortion rate for the Jamaican controls was lower.

The spontaneous abortion rate for the Jamaican cohort was 35.7% for the subjects and 10.4% for the controls. It was 21.2% for the MSH female patients. When comparing the Jamaican subjects to the MSH females, the spontaneous abortion rate was higher for the Jamaican subjects. When comparing the Jamaican controls to the MSH females, the spontaneous abortion rate was lower for the Jamaican controls.

The stillbirth rate for the Jamaican cohort was 1.2% for the subjects and 0.7% for the controls. It was 0.02% for the MSH female patients. When comparing the Jamaican subjects to the MSH females, the stillbirth rate was higher for the Jamaican subjects. When comparing the Jamaican controls to the MSH females, the stillbirth

Table 3. Pregnancy Outcomes for the Female Partners of the Male Multicenter Study of Hydroxyurea in Sickle Cell Anemia Study Participants With Respect to the Hydroxyurea Usage Category “Hydroxyurea Usage at Conception”

	Hydroxyurea at Conception			
	Total	Unknown	No Hydroxyurea Exposure	
			Hydroxyurea Exposure	Hydroxyurea Exposure
Frequency	Frequency	Frequency	Frequency	
Total	42	19	13	10
Classification				
Live birth age/weight unknown	6	6	0	0
Live birth >2500 g (term)	21	7	10	4
Live birth <38 wk <2500 g (preemie)	3	1	1	1
Live birth >37 wk, weight unknown	2	0	1	1
Elective abortion, gestational age unknown	1	1	0	0
Elective abortion <24 wk	2	0	0	2
Spontaneous abortion, gestational age unknown	4	4	0	0
Spontaneous abortion <24 wk	2	0	0	2
Spontaneous abortion ≥24 wk	1	0	1	0

rate was higher for the Jamaican controls.

The live birth rate for the Jamaican cohort was 57.1% for the subjects and 88.8% for the controls. It was 44.2% for the MSH female patients. When comparing the Jamaican subjects to the MSH females, the live birth rate was higher for the Jamaican subjects. When comparing the Jamaican controls to the MSH females, the live birth rate was higher for the Jamaican controls.

The reasons why pregnancy in sickle cell disease is associated with increased maternal morbidity and high fetal morbidity and mortality are unknown. Recently it was reported³¹ that maternal serum granulocyte colony-stimulating factor (G-CSF) level is significantly associated with gestational age at birth and with spontaneous preterm birth. Given that sickle cell disease is associated with leukocytosis due to increased bone marrow activity, it is possible that the level of G-CSF is increased and causes some of the complications observed in pregnant patients with sickle cell disease. Since hydroxyurea is known to decrease the white blood cell count and to have an inhibitory effect on bone marrow activity,³² it is possible that hydroxyurea could have a salutary effect in preventing or decreasing the incidence of small gestational age and spontaneous preterm birth. Needless to say, this hypothesis has to be studied in depth in animals.

Together, our findings suggest that exposure of the fetus to hydroxyurea does not cause teratogenic changes in those pregnancies that terminate in live birth whether full term or premature. This seems to be true whether the parent taking hydroxyurea was the mother or the father. The same argument seems to apply for exposure to opioids. However, it will take a much longer follow-up of many more hydroxyurea-exposed sickle cell disease subjects to establish the results conclusively.

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