The Use of Hydroxyurea During Pregnancy in Sickle Cell Anemia Women: A Case Series and Literature Review

Flávia Anchielle Carvalho Silva[1,2], Ana Laura Carneiro Gomes Ferreira[1], Luisa Martins Pimentel[1], Carlos Henrique Monteiro Maciel Lyra[1,2], Manuela Freire Hazin-Costa[1,3,4], Glaucia Lins Guerra[1], Aderson Silva Araújo[4] and Ariani Impieri Souza[1,2,*]

[1]*Instituto de Medicina Integral Prof. Fernando Figueira (IMIP), Recife, Pernambuco, Brazil*

[2]*Faculdade Pernambucana de Saúde (FPS), Recife, Pernambuco, Brazil*

[3]*Universidade Federal de Pernambuco (UFPE), Recife, Pernambuco, Brazil*

[4]*Fundação de Hematologia e Hemoterapia de Pernambuco (HEMOPE), Recife, Pernambuco, Brazil*

Abstract: Hydroxyurea (HU) has been an effective treatment for sickle cell anemia (SCA) by inducing fetal hemoglobin production as well as reducing the rate of painful crisis. The use of HU during pregnancy still has been a concerned situation due to the risk of malformation, but there is already a proposal for the possibility of the use, even during pregnancy, depending on the situation of the disease. On the other side, the potential of HU for mutagenesis and teratogenesis in humans has not been confirmed yet. This case series describe the perinatal outcomes on women at a Women's Care Center in Recife, Brazil. Women used HU early in their pregnancies and no record of malformation was report. Our sample was composed of 13 SCA women using HU just before or during pregnancy. Of these women, 4 had gotten pregnant twice by using HU and for this we have analyzed a total of 17 cases. There were no reports on malformation in any of these cases. In the literature review, we found seven studies on the use of HU in pregnancy and only one of these studies reported malformation in a fetus. We concluded that HU usage and teratogenic effects has not been confirmed in humans yet and suggested to await results of well-controlled studies to define the use of HU as a treatment for vasooculsive crises during pregnancy. Thus, we consider that this publication could be added to other cases in which have been already published where fetal malformation has not been registered yet .

Keywords: Sickle cell disease, Pregnancy, Sickle cell anemia, Congenital anomalies, Hydroxyurea.

INTRODUCTION

Hydroxyurea (HU) is used for myeloproliferative diseases treatment and has been an effective therapy for Sickle Cell Anemia (SCA) by inducing the production of fetal hemoglobin (HbF) [1, 2]. The mechanism by which HU induces HbF production is likely to be multifactorial with a major effect on the kinetics of erythroid differentiation, increasing the HbF level which is beneficial for SCA [3]. Despite studies on new treatments in sickle cell disease (SCD), long-term use of HU is still the most available drug among the disease-modifying therapy worldwide [4].

However, during pregnancy, the use of HU is not recommended [5, 6]. Studies in animals have shown that the use of HU during pregnancy has been shown to be potentially teratogenic in mammalian pregnancy due to its ability to initiate damage to genetic material [7, 8]. On the other hand, this evidence has not been demonstrated in humans. Only reports and case series have been published on the use of HU in human pregnancies and most of them did not report fetal malformation [9-12].

This study aims to describe the perinatal outcomes reported by women with SCA that became pregnant by using HU. This study was approved by the Research Ethics Committee (number CAAE: 00854918.9.0000.5201) and the Informed Consent Terms were signed by the women.

DESCRIPTION OF CASES

The data were collected face to face interviews and from medical reports during medical consultation in a gynecology service for women with SCD in a teaching and referral hospital in Recife, Brazil. Our sample was composed of 13 SCA women using HU just before or during pregnancy. Of these women, 4 had gotten pregnant twice by using HU. So, we have analyzed a total of 17 cases. The women's age ranged from 18 to 48 years old and most of them declared to be mixed race (n=9). The mean of pregnancies was 1.6 and most patients (n=10) did not plan to become pregnant while they were using HU (Cases 5, 6, 10 and 11). Sixteen of the 17 pregnancies were using HU at the time of conception and were advised to discontinue the treatment soon after the pregnancy was confirmed.

*Address correspondence to this author at the Instituto de Medicina Integral Prof. Fernando Figueira (IMIP) – Rua dosCoelhos, 300 Boa Vista. 50.070-550, Recife- Pernambuco, Brazil; Tel: +55 81 988227351;
E-mail: ariani@imip.org.br

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Only one woman continued using HU during pregnancy due to the severe clinical condition in her both pregnancies (Case 6). All the pregnant women referred having vaso-occlusive crisis, and seven of them were needed to be hospitalized to receive treatment (Table **1**).

We also did a research in Medline database and summarized the results of the seven published articles about the use of HU in pregnant women. These studies were conducted: one in Canada [11], two in India [13, 14], three in United States [10, 15, 16], and one in Kenya [17] (Table **2**).

DISCUSSION

HU is one of the most available disease-modifying treatments in most countries, but its use in pregnancy remains contraindicated, as there are no randomized controlled studies in pregnant women.[4] Almost all the cases published in the literature show little or no adverse results [10, 11, 13-16].

Most women reported in this case series used HU at conception or during early pregnancy did not know they were pregnant. So, the women were recommended to interrupt the use of HU after the confirmation of the pregnancy.

Table 1: Description of Cases on Women with SCA who used HU during their Pregnancy

Case	Woman's age at interview (y)	Period of HU usage	Dose of HU (mg/d)	Gestational outcome (Delivery type / Gestational age)	Newborn's weight in grams (g)	Child's current situation
1	18	First month (4 w)	Not reported	Transvaginal / 37 w	2.154g	Less than 1 year old / Healthy
2	34	First and Second trimesters (8 w)	500	cesarean section / 37 w	3.490g	2 years old / Healthy
3	24	First trimester (12 w)	1.500	cesarean section / 39 w	3.190g	7 years old / Healthy
4	36	First and Second trimesters (17 w)	1.000	Abortion / 17 w	NA*	NA*
5	48	Pregnancy1: First trimester (4 w)	Not reported	Transvaginal/ 38 w	2.700g	21 years old / Healthy
		Pregnancy2: First trimester (8 w)	Not reported	Transvaginal/ at term	2.995g	18 years old / Healthy
6	46	Pregnancy 1: Third trimester	500	cesarean section / 37 w	2.800g	23 years old/ Healthy
		Pregnancy 2: the whole pregnancy	500	cesarean section / 33 w	2.900g	22 years old / Healthy
7	29	First and Second trimesters (16 w)	Not reported	Transvaginal / 37 w	3.100g	8 years old / Healthy
8	24	First trimester (6 w)	Not reported	Transvaginal/ 37 w	3.700g	1 year old /Healthy
9	37	First trimester (4 w)	1.000	Abortion / 9 w	NA*	NA*
10	33	Both pregnancies - First trimester (8 w)	Not reported	Abortion/ no inform gestational age	NA*	NA*
			Not reported	cesarean section / 32 w	2.230g	4 years old/ Healthy
11	28	Both pregnancies - First trimester	Not reported	Transvaginal/ Stillborn with 27 w	Not reported	
			Not reported	cesarean section / 37 w	2.370g	3 years old / Healthy
12	19	Used up to 16w	500	cesarean section / 38w	2.700g	3 years old / Healthy
13	28	First month	1.000	Abortion / Cannot inform gestational age	NA*	NA*

Not applicable (NA); w= weeks.

Table 2: Results of Studies that Evaluated the use of Hydroxyurea in Pregnancy in Patients with Sickle Cell Anemia

Author/ Year/ Country	Study design	Period of HU used	Dose of HU	Gestational outcome	Newborn's outcome
Charache e*t al.,* 1995 [15] USA	A case report within a Randomized clinical trial (n = 1)	Not informed	15mg/Kg/dia	Abortion	-------
Diav-Citrin *et al*., 1999 [11] Canada	Case report (n=1)	9 w	1g/day	Induced delivery at 39w	Fetal weight: 3.240g Healthy
Byrd *et al*., 1999 [10] USA	Case report (n=2)	Case 1 -use until 5w Case 2 – use until 4w	Case 1 – 1g/day Case 2 – 500mg/day	Case 1 - cesarean section Case 2 – cesarean sectionin 32w,	Case 1: 2.750g Case 2: 1.365g IUGR, ICU for ventilatory support, Hospital discharge at 6 days of life
Ballas *et al*., 2009 [16] USA	A case series report within a Randomized clinical trial (n=6)	Not informed	Not informed	1 full term (live birth) 1 full term (preterm) 3 induced abortions 1 spontaneos abortion	1 newborn with IUGR
Italia *et al*., 2010 [13] India	Case report (n=2)	Case 1 -until 9 w Case 2 – 2nd trimester until delivery	Caso 2 - 10-15 mg/kg/dia	Case 1: normal delivery (38 w) Case 2: cesarean section (39 w)	2.680g 2.750g
Daigavane *et al*., 2013 [14] India	Case series (n=6)	After 12 w	Not informed	2 preterms 4 terms (Type of delivery - not informed)	Not informed
Poli *et al*., 2020 [17] Kenya	Case report (n=1)	Used until 26 w	1.5g/day	Pregnancy interruption at 30 w	Multiples congenital malformations and passed on few hours later

w = weeks.

Some cases in the literature reported pregnant women used HU due to severe clinical conditions and after the first trimester of pregnancy [13, 14]. In two other studies, women had participated of a randomized control trials (RCT) and become pregnant with the use of HU during the study, were recommended to not get pregnant during the study. Despite this, there were no complications or malformation reported in these pregnancies [15, 16]. In France, a study evaluated the tolerance of HU in children and adolescents with SCD and reported a 19-year-old pregnant woman who received HU for 50 months and gave birth to a healthy child [12].

On the other hand, we found a more recent study where the authors reported a case of malformation in a woman who used HU during pregnancy [17]. Even in this case, where a malformation fetus was found, we do not know what the cause was. We know that congenital malformations are multifactorial and include genetic predisposition and environmental factors, including different drugs [18]. In fact, it is necessary to maintain surveillance among women with SCD using HU.

Anyway, we do not have well-controlled studies on the use of HU among pregnant women and in most of these situations, in the first- second- or third-trimester did not demonstrate any fetal toxic effects [13, 14]. However, the current recommendation is to discontinue the use of HU during pregnancy due to the lack of evidence about its safety during this period and is also a current recommendation in Brazil [15, 19]. Despite this, Montironi *et al*. [6] proposed a protocol to treat SCD pregnant women using HU after the 2nd or 3rd trimester according to the patients sickle cell history and the severity of the disease.

It is important to note that the dose of HU and the route of its administration in the studies in animals [7] were different than those used in humans [20]. Some studies presented mutagenic and genotoxic effects of the usage of HU at pregnancy were carried out in animals with doses fivefold higher than those used in

humans [7, 20]. However, to define the optimal dose of HU usage in pregnancy is still necessary more robust evidence.

The dose of HU used by women in our case series was similar to those found in the literature review, which is an average of 1 g/day [10, 11, 20] and compatible with the recommended dose by the American Society of Hematology to control SCA severity in adults [5, 15].

In our case series, we observed some unfavorable obstetric outcomes, as four miscarriages, however, we cannot know if this had some association with the use of HU. In the literature cases, abortions were related as a medical abortion due to the teratogenicity risks of HU usage, as this has already been described in animals [7]. Furthermore, studies have shown that abortion is an obstetric complication related to SCA, and is probably due to vascular alterations of the placenta [21-24] and we cannot know what caused the abortion.

Among our 17 cases, 10 were at term and there were no reports on malformation in any of these cases. At the time of the interview, the women reported that all live births were healthy, ranging from 1 to 23 years old. We must consider a possibility of bias, because of the long period between the moment of the pregnancy and the interview, in some of the cases.

CONCLUSION

Regarding potential carcinogenesis and mutagenesis in the use of HU demonstrated in animals, our findings suggest that the relation between HU usage and any neonatal abnormalities or teratogenic effects is not confirmed in humans yet. There is also a need for additional evidences on the optimal and safety use of HU in pregnant women with SCA.

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