Hydroxyurea and fertility in Sickle cell disease

Mariane de Montalembert

We know few things about fertility in patients with Sickle cell disease (SCD)

- Scarce reports about fertility in SCD, which was not an active field of investigation[1]
- We all know fathers and mothers affected with SCD having had children
- Infertility is defined in term of a couple and not an individual. The definition of fertility requires a couple attempting to conceive and failing after 6-12 months of regular intercourse, when the women is less than 35 or at least 35 years of age [2]

1. DeBaun MR. Expert Rev Hematol 2014
2. Practice Committee of American Society for Reproductive M. Fertil Steril 2008

Fertility in males patients with SCD

The few existing studies report a decreased fertility in men with SCD (patients not treated by hydroxyurea)

1. Osegbe DN, Lancet 1981

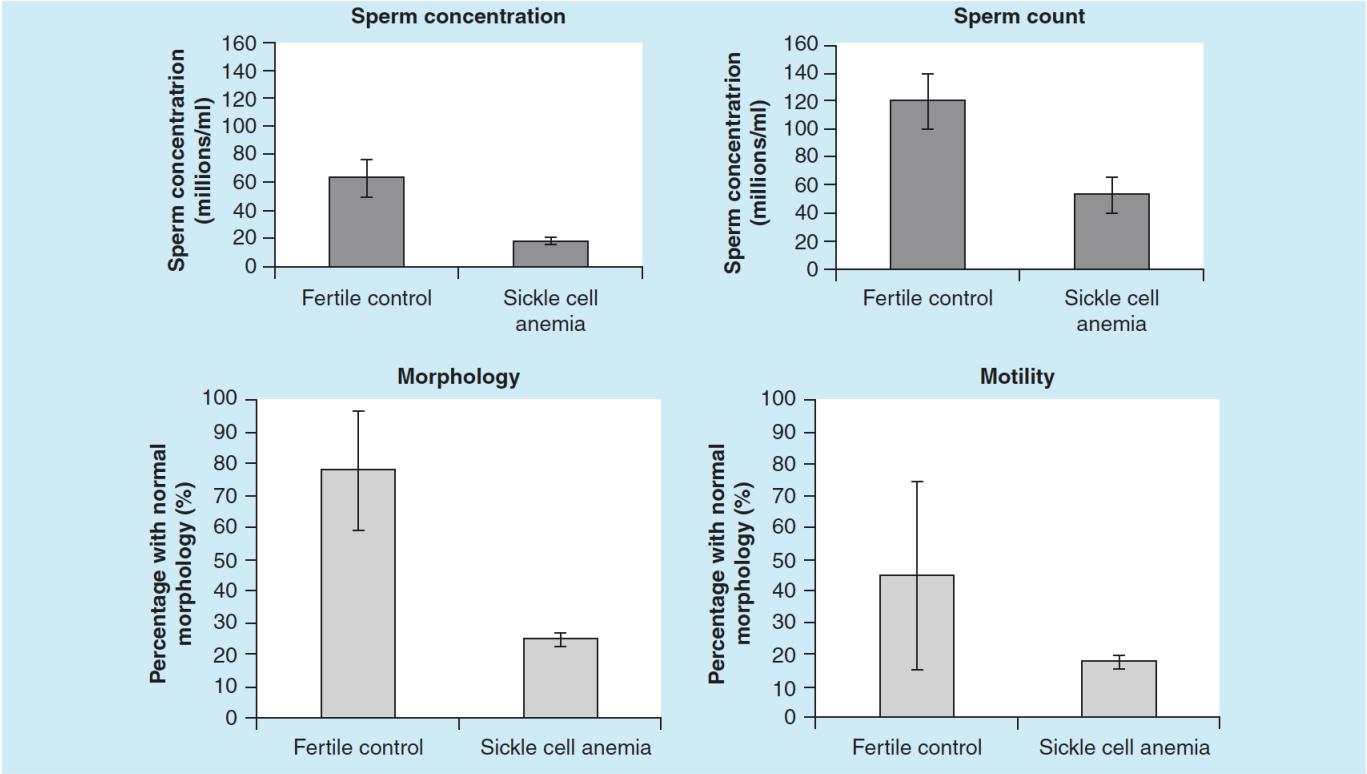


Figure 2. Semen analysis of 23 men with sickle cell anemia compared to 25 fertile men controls. The analysis demonstrated that the major qualities of semen associated with infertility are all markedly lower in men with sickle cell anemia when compared to controls [19].

The few existing studies report a decreased fertility in men with SCD (patients not treated by hydroxyurea)

2. Berthaut I, Haematologica 2008

Considering as normal (WHO guidelines)

- at least 20 millions/ml sperm concentration
- 50% minimum forward motility
- >60% sperm viability
- >30% morphologically normal spermatozoa

Less than 10% of participants had all of the sperm parameters considered as normal

- Semen analysis is not a test of fertility
-Even patients with severe abnormalities may father children.

	Before treatment (76 samples from 34 patients)	
Sperm parameter	*Mean ± standard deviation (range)*	*Percent of abnormal values*
Volume of ejaculate, mL	3.08±1.67 (0.3-8)	25.7
Spermatozoa concentration, millions/mL	38.55±43.12 (0.02-280)	38.9
Total sperm count, millions	114.17±124.12 (0.07-588)	40.3
Initial forward motility, % of motile	28.66±18.38 (0-60)	83.6
Spermatozoa morphology, % of normal	21.92±14.63 (0-53)	64.1
Vitality, % of living	59.75±21.61 (0-95)	43.1

Potential causes for decreased fertility

Testicular infarcts?

Chronic hypoxia exacerbated by VOC

Priapism (prolonged undesired erection of the penis)
(probably underreported)

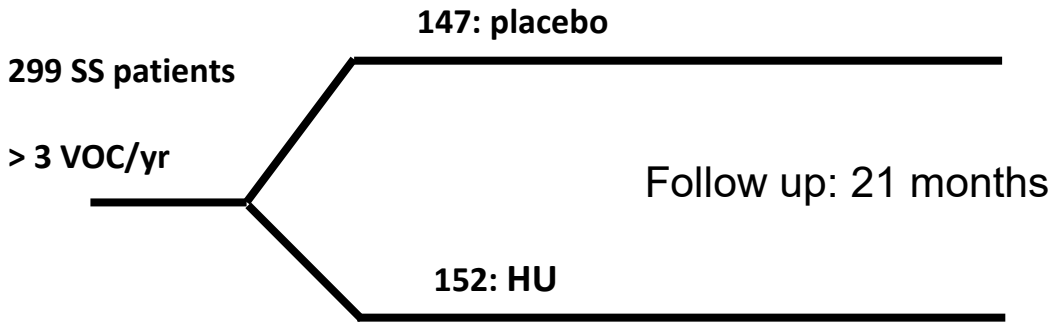
The rares studies have not taken into account
the severity of the disease, and we do not fully understand
the reasons for this decreased fertility

Hydroxyurea

I. Hydroxyurea decreases pain and increases life expectancy

Effects of HU on the frequency of painful crises in SCA MSH study

Double-blind, randomized, controlled
versus placebo study



Results		p value
Mean number of VOC/year	2.5 HU vs 4.5 placebo	< 0.001
Median number of VOC with hospitalization/year	1 Hu vs 2.5 placebo	0.0027
Number of patients with ACS	25 HU vs 51 placebo	< 0.001
Number of patients with blood transfusion	48 Hu vs 73 placebo	0.002

Charache S et al, NEJM 1995

HU in very young children with SCA
BABY HUG study

Double-blind, randomized, controlled versus placebo study

	HU	Placebo	P value
Number of Pain Events	63	121	0.004
Number of ACS	8	27	0.02
Days of Hospitalization	232	324	0.05
Number of Transfusion	20	33	0.03
Number of Dactylitis	14	42	< 0.0001

Wang et al, Lancet 2011

Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa

Léon Tshilolo, M.D., Ph.D., George Tomlinson, Ph.D.,

NEJM 2018

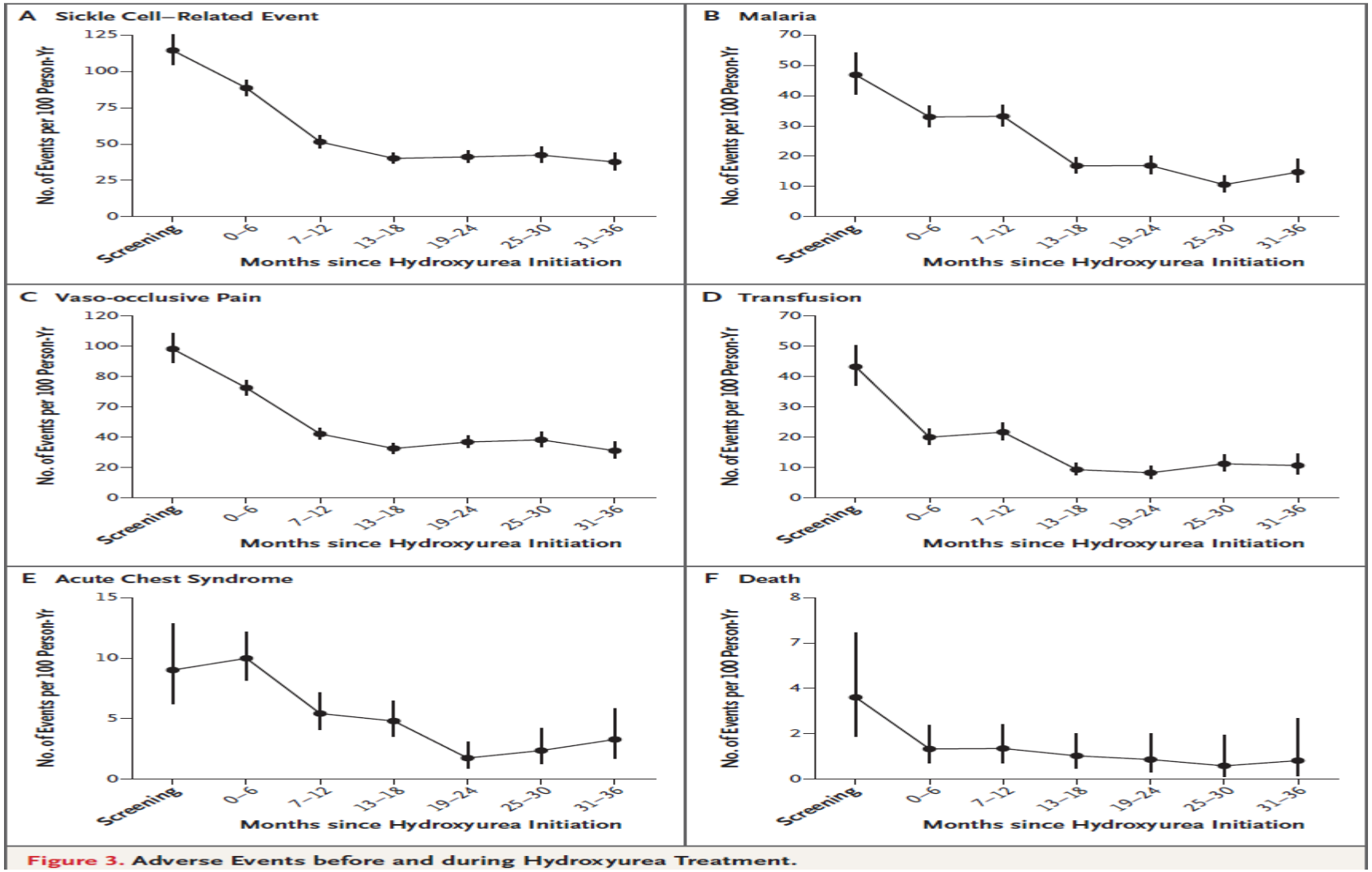
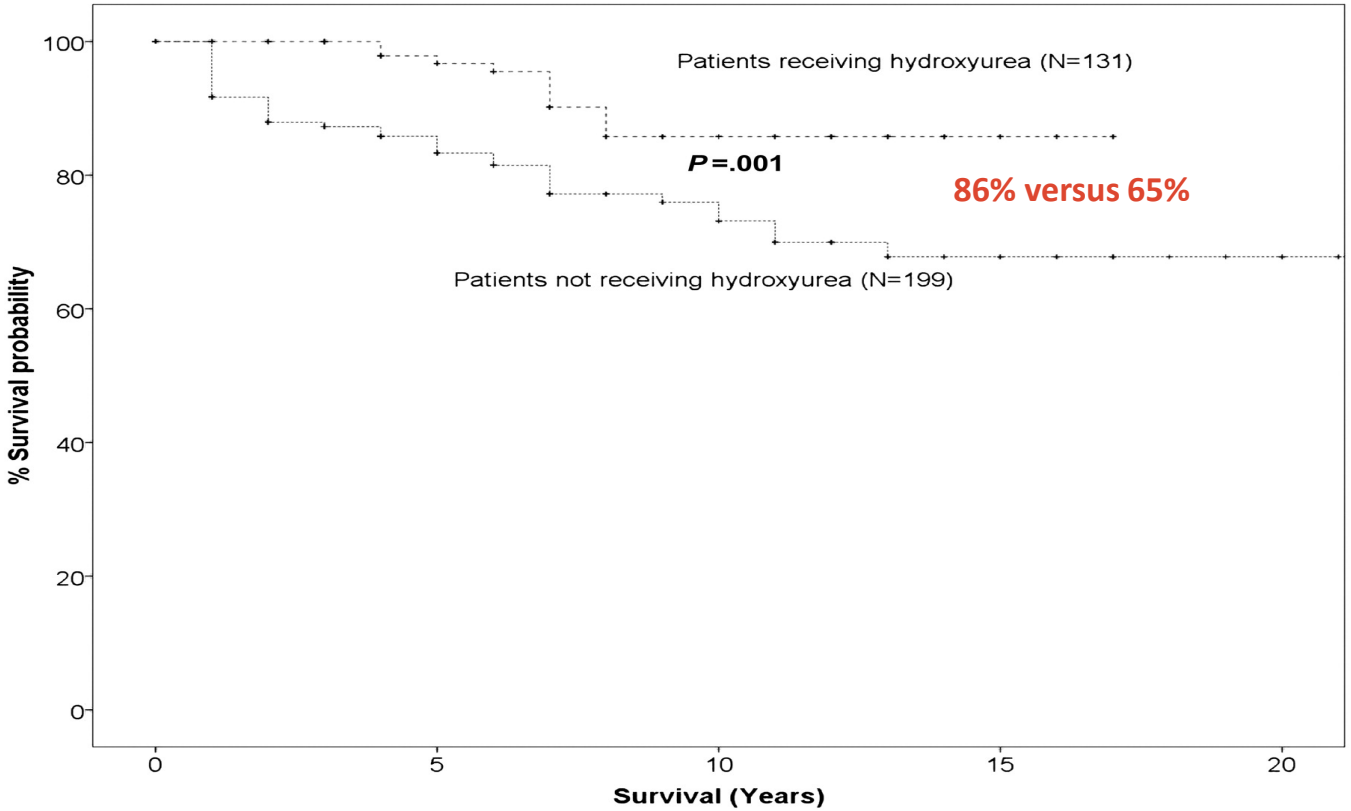


Figure 3. Adverse Events before and during Hydroxyurea Treatment.

Probability of 10-year overall survival in SCD patients who received HU and in SCD patients conventionally treated (LaSHS)(non randomized study)



Voskaridou E et al, Blood 2010

Hydroxyurea (HU)

II. The impact of hydroxyurea on spermatogenesis (HU is a chemotherapeutic agent)

	Before treatment (76 samples from 34 patients)		During treatment (6 samples from 5 patients)		After treatment (26 samples from 8 patients)	
Sperm parameter	Mean ± standard deviation (range)	Percent of abnormal values	Mean ± standard deviation (range)	Percent of abnormal values	Mean ± standard deviation (range)	Percent of abnormal values
Volume of ejaculate, mL	3.08±1.67 (0.3-8)	25.7	2.68±1.28 (1.5-4)	50	2.99±2.85 (0.4-15)	36
Spermatozoa concentration, millions/mL	38.55±43.12 (0.02-280)	38.9	2.66±3.75 (c*-8.75)	100	18.46 ± 26.86 (0-86)	76
Total sperm count, millions	114.17±124.12 (0.07-588)	40.3	7.02±10.18 (c*-21.9)	100	61.12±107.37 (0-387)	68
Initial forward motility, % of motile	28.66±18.38 (0-60)	83.6	30.00±5.77 (25-50)	80	29.46±20.13 (0-80)	87.5
Spermatozoa morphology, % of normal	21.92±14.63 (0-53)	64.1	34.50±21.92 (19-65)	66.7	19.16±16.3 (0-49)	75
Vitality, % of living	59.75±21.61 (0-95)	43.1	52.00±14.23 (40-68)	50	44.40±20.12 (0-90)	77

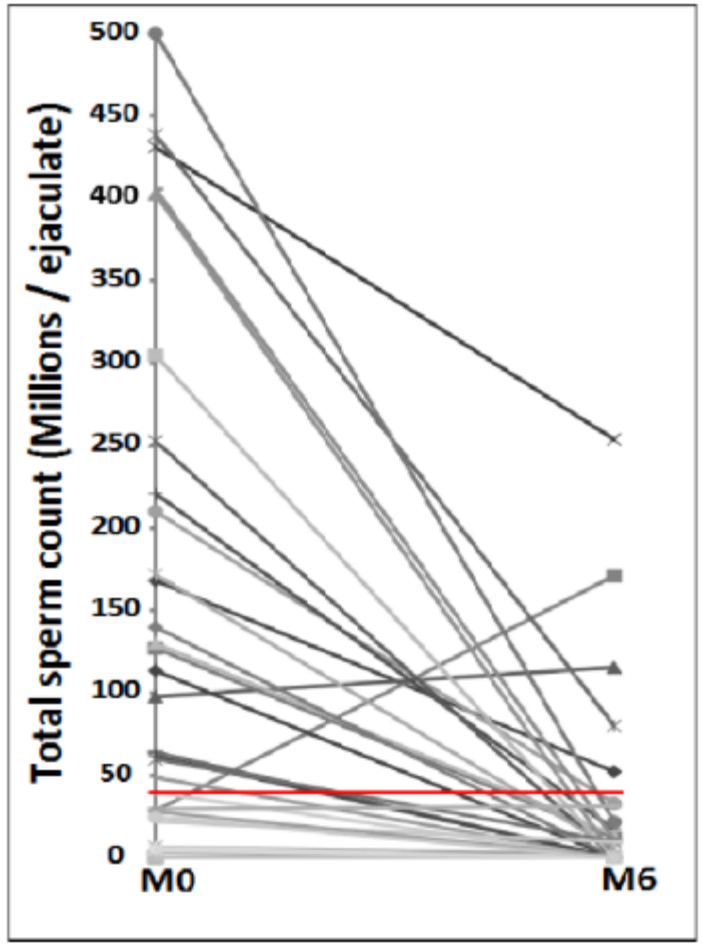
Berthaut I, Haematologica 2008

But:

- Very low number of patients
- No data about the severity of their disease

- Semen analysis is not a test of fertility
-Even patients with severe abnormalities may father children.

Profile at M0 and M6 of HU treatment of the total sperm count (millions / ejaculate) for each patient
35 men with severe form of SCD, Berthaut I, et al. Blood 2017



It is very likely that, in many patients, HU decreases fertility while it is taken, but

- Surely less than bone marrow transplant and gene therapy, which both need myeloablative conditioning and induce azoospermia

  Sperm banking may be proposed before treatment for pubere boys

- **The major question is to know whether hypofertility resolves after cessation of treatment**

ORIGINAL ARTICLE

Study of Seminal Fluid Parameters and Fertility of Male Sickle Cell Disease Patients and Potential Impact of Hydroxyurea Treatment

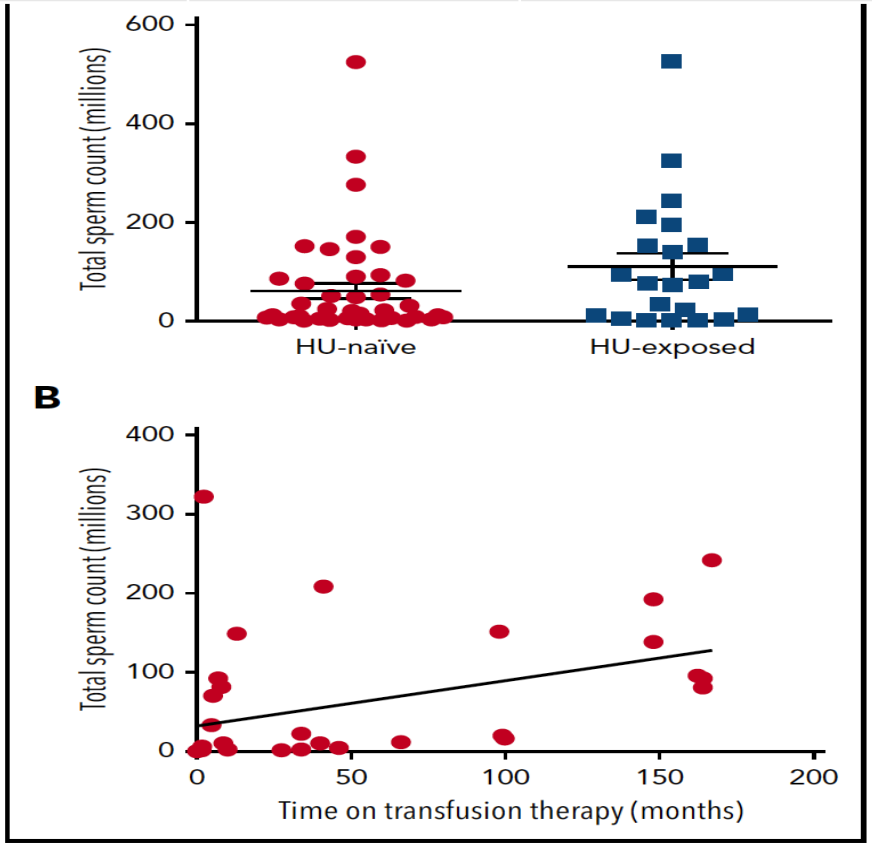
Lulup Kumar Sahoo[1], Bipin Kishore Kullu[2], Siris Patel[3], Nayan Kumar Patel[4], Pragyan Rout[5], Prasanta Purohit[6], Satyabrata Meher[6]

Material and methods: This was a prospective study done at a tertiary care hospital over 26 months between September 2011 to October 2013. 100 male sickle cell disease patients of age group 15 to 45 years were recruited in the study. We evaluated seminal fluid indices in all patients and the effect of hydroxyurea on seminal fluid parameters. Hydroxyurea was given at low dose of 10mg/kg/day orally to patients with frequent vaso-occlusive crisis and frequent need of blood transfusion. Seminal fluid analysis was done according to WHO criteria before starting hydroxyurea and every 3 months after initiation of hydroxyurea. Patients with abnormal seminal parameters before hydroxyurea therapy were not given hydroxyurea therapy. Patients with abnormal sperm parameters were subjected for FNAC of testis. In sickle cell disease patients with hydroxyurea

Results: Among Sickle cell disease patients without hydroxyurea therapy, 18% of patients developed oligospermia and 4% developed azoospermia. Among sickle cell disease patients with hydroxyurea therapy, 20% of patients developed oligospermia and 10% developed azoospermia. Seminal fluid parameters reverted back to normal after stoppage of hydroxyurea for 3 months in 73% of patients.

N patients	23 HU-naive	15 HU-exposed
Transfusion program at time of semen analysis -% -duration of Tx program before semen analysis, y	 52 0 (0-8)	 100 3 (0-13)
HU		Age at HU initiation: 6 (1-14) yrs Duration of HU tt before analysis: 4 (0.5-10) yrs Wash-out period: 2.5 (0-13)y

Joseph L, et al, Blood 2021



→ No difference

→ Positive correlation between duration of transfusion and semen analysis

Current protocol used in Necker-enfants malades Hospital

- Storage of frozen sperm proposed to mature boys and adults before beginning HU

- When HU started in infancy, possibility, when required by patient, to stop HU while introducing a period of monthly transfusion, in order to perform sperm banking

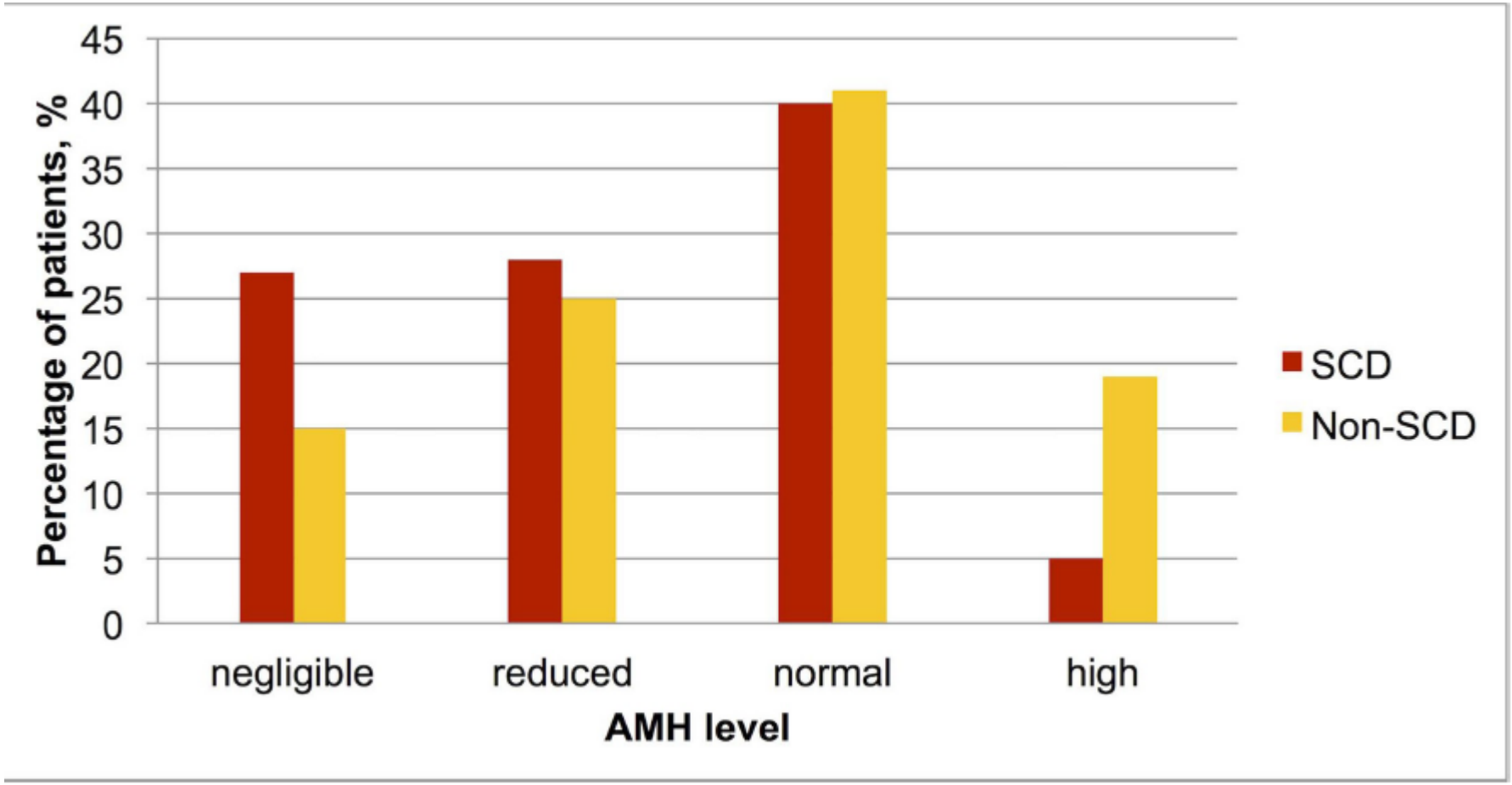
Fertility in females patients with SCD

We know few things about fertility in females with Sickle cell disease (SCD)

- Publications[1]
  - Onset of menarche delayed (puberty delay)
  - Many women experience dysmenorrhea and VOC with the onset of their menses
  - Possibility of primary ovarian insufficiency (with risk of premature menopause (< 40 yrs)) in women with SCD evoked [2]
- We all know fathers and mothers affected with SCD

1. Ghafuri DL, et al. Expert Rev Hematol 2017
2. Kopelia J, et al. PLoS One 2019

Decreased levels of anti-Mullerian hormone (AMH), marker of ovarian function in women with SCD



ig 1. Distribution of different AMH categories in patients with and without SCD. AMH categories: negligible–less than 1.5 pmol/l; reduced -1.5 to 6.5 pmol/l; ormal- 6.6 to 19.8 pmol/l; high–above 19.8 pmol/l.

Kopelia J, et al. PLoS One 2019

AMH levels decrease more quickly in women with SCD

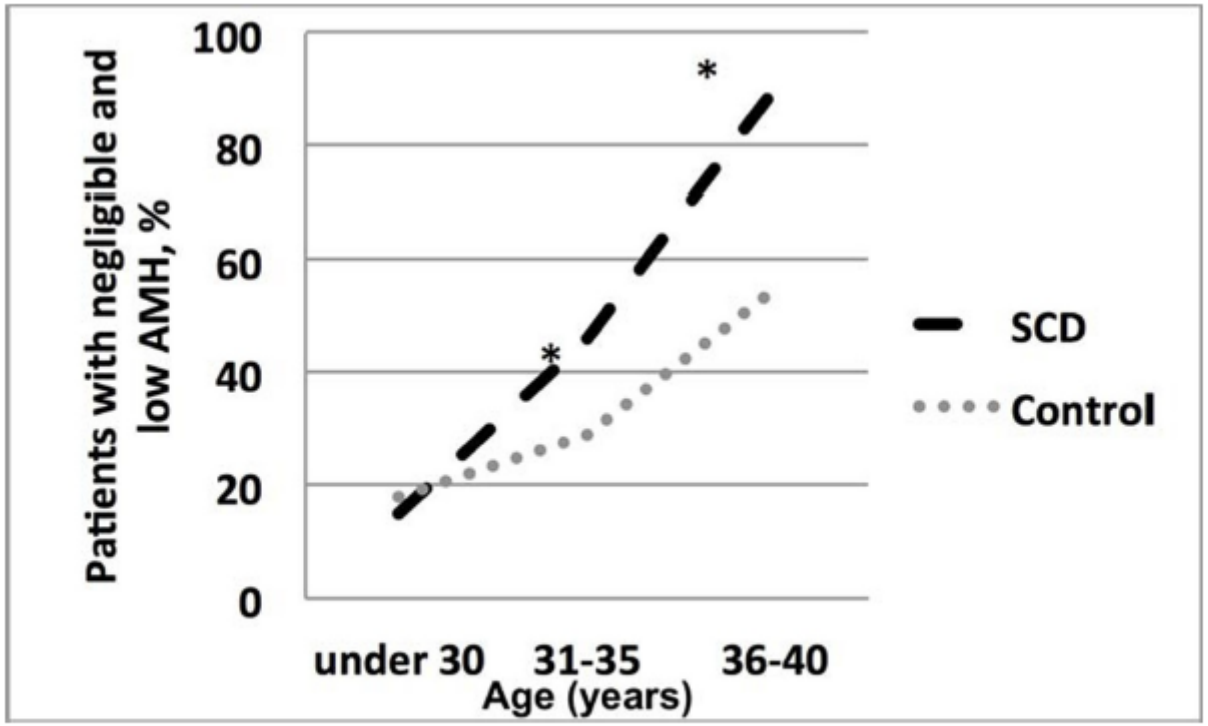


Fig 2. Prevalence of patients with negligible (<1.5 pmol/l) and reduced (1.5–6.5 pmol/l) AMH among SCD and control patients (* $p \leq 0.5$).

Kopelia J, et al. PLoS One 2019

Impact of Hydroxyurea (HU) in female patients with SCD

II. The impact of hydroxyurea on fertility in females has been very rarely studied

Information about whether sickle cell anemia (SCA) and its treatments affect female fertility is needed.[1] Diminished ovarian reserve (DOR) describes low egg supply, is considered irreversible in women with cancer,[2] and is a risk factor for recurrent pregnancy loss,[3] miscarriage,[4] and infertility.[5] Women with SCA (>30 years old) have higher rates of DOR than age-matched controls.[6-8] In a study of 10- to 21-year-old females with SCA, DOR occurred in 24% (8 of 33) of the hydroxyurea-treated subjects and none of the 14 untreated subjects.[9] In cancer,

Pecker LH et al, Blood 2022

The effects of hydroxyurea and bone marrow transplant on Anti-Müllerian hormone (AMH) levels in females with sickle cell anemia

Table 2
Ovarian reserve and function by age group and SCA treatment.

SCA treatment groups	N	Normal AMH		Low AMH < 5%				p-Value
		Normal ovarian reserve		Diminished ovarian reserve Non-menopausal FSH		Premature ovarian insufficiency Menopausal FSH		
		n	%	n	%	n	%	
All age groups								
SCA-SC	14	14	100.0%	0	0.0%	0	0.0%	<0.001
SCA-HU	33	25	75.8%	8	24.2%	0	0.0%	
SCA-BMT	9	0	0.0%	1	11.1%	8	88.9%	
10–13 years old								
SCA-SC	7	7	100.0%	0	0.0%	0	0.0%	<0.001
SCA-HU	12	11	91.7%	1	8.3%	0	0.0%	
SCA-BMT	6	0	0.0%	1	16.7%	5	83.3%	
14–17 years old								
SCA-SC	6	6	100.0%	0	0.0%	0	0.0%	0.001
SCA-HU	20	14	70.0%	6	30.0%	0	0.0%	
SCA-BMT	2	0	0.0%	0	0.0%	2	100.0%	
18–21 years old								
SCA-SC	1	1	100.0%	0	0.0%	0	0.0%	–
SCA-HU	1	0	0.0%	1	100.0%	0	0.0%	
SCA-BMT	1	0	0.0%	0	0.0%	1	100.0%	

Low AMH was defined at <5th percentile using age-specific healthy controls. Menopausal FSH is >40 IU/L.

Elchuri SV, et al. Blood cells, Molecules and Diseases 2015

Prevention of teratogenicity : current recommendations

No malformation has been evidenced in babies born from mothers treated whith HU during pregnancy, but the current recommendations are

- ✓The use of effective contraception
- ✓If a women becomes pregnant while taking HU, she should be advised of the potential risk to the fœtus
- ✓Breast-feeding must be discontinued while taking HU

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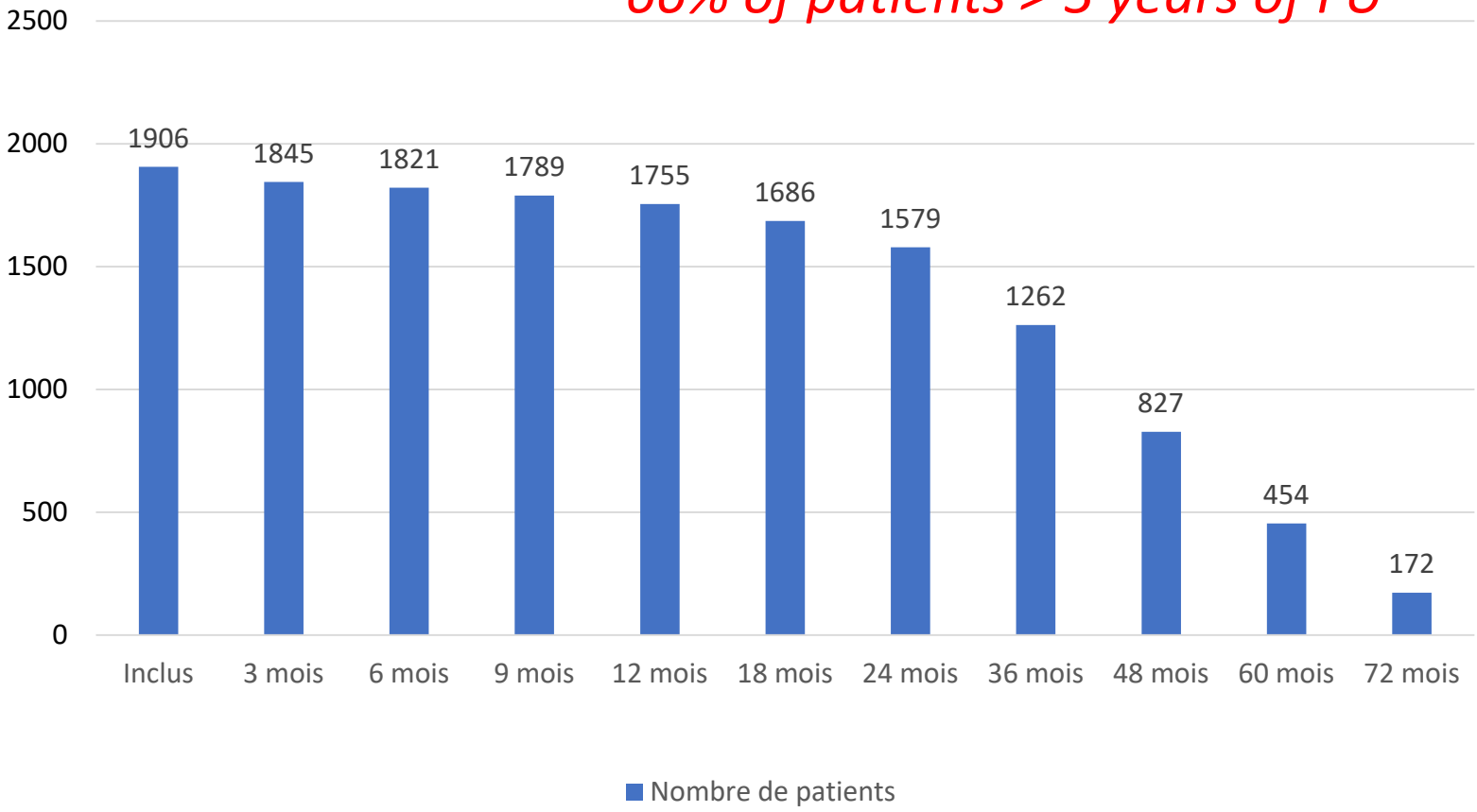
RESEARCH ARTICLE

Real-Life experience with hydroxyurea in patients with sickle cell disease: Results from the prospective ESCORT-HU cohort study

Mariane de Montalembert[1] | Ersi Voskaridou[2] | Lena Oevermann[3] | Giovanna Cannas[4] | Anoosha Habibi[5] | Gylna Loko[6] | Laure Joseph[7] | Raffaella Colombatti[8] | Pablo Bartolucci[5] | Valentine Brousse[1] | Frédéric Galactéros[5] | All ESCORT HU Investigators

Duration of Follow-up

66% of patients > 3 years of FU



1903 patients,
1054>18 years

Median duration of participation in the study: 3.8 years
In naïve patients: 43 ± 23 months/In non naïve patients: 124 ± 63 months
7309 patient-years of duration of HU exposure

Fertility issues

- 125 pregnancies in 101 women: 110 with exposure to HU
  - 77 live births, + spontaneous and elective terminations and ongoing pregnancies
  - No malformations among neonates
- 12 pregnancies of partners of male patients treated with HU

In conclusion

We are **sure** that

HU decreases pain and ACS

Positive impact on fertility

We have observed that HU may decrease spermatogenesis

But preliminary studies suggest that this effect may be reversed when HU is stopped