SICKLE CELL DISEASE & PREGNANCY

Experience from a french center

Jean-Antoine Ribeil
Aurélie Stanislas
Marina Cavazzana

Necker-Enfants Malades Hospital
Biotherapy Department

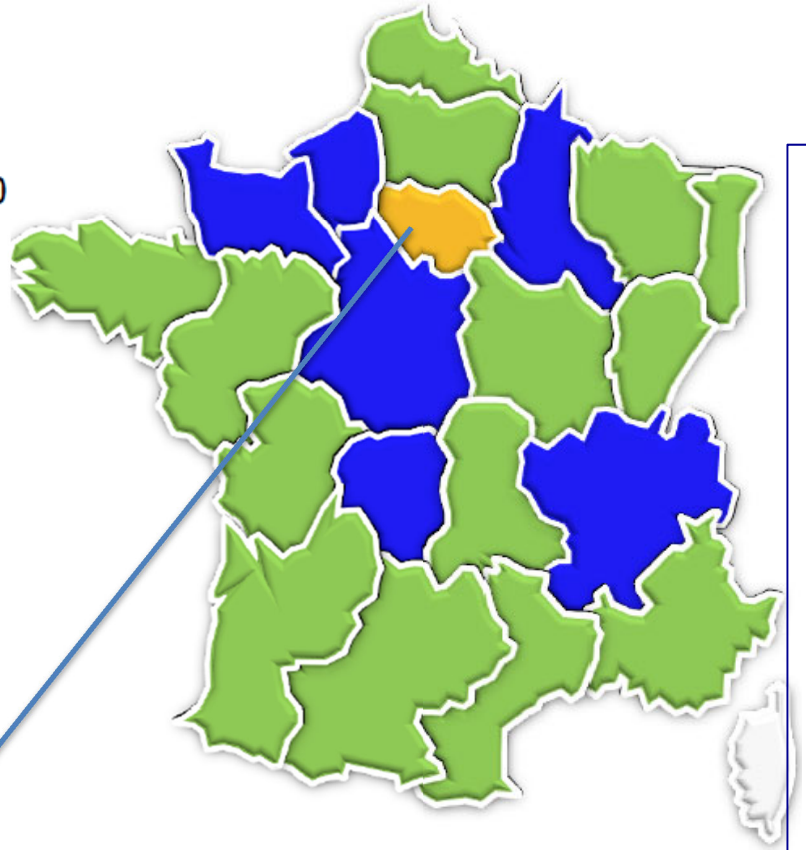
300 New born SCD / year
detected by neonatal screening

> 1/1 000

1/1 000-1/ 5 000

< 1/5 000

0



70% of the new cases are from
Paris area

Size of France = Minas Gerais

Sickle Cell Anemia

10,000 patients

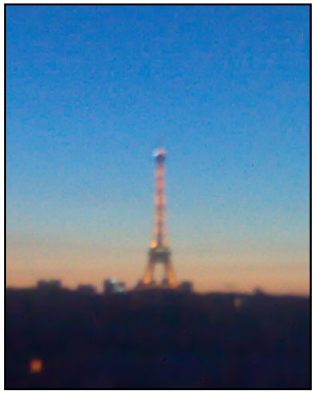
↗↗ > 20,000 in France
in the next years

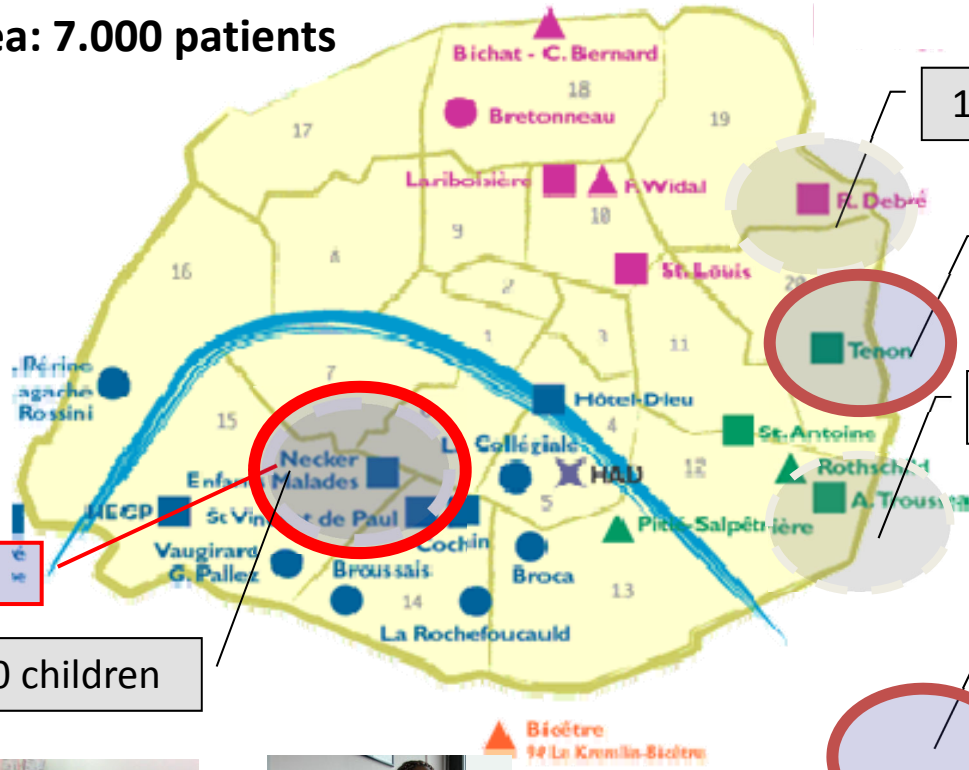
1st genetic disease

Patients from immigration

CENTER OF « EXCELLENCE » IN SICKLE CELL DISEASE

Paris Area: 7.000 patients





1000 children

600 adults

200 children

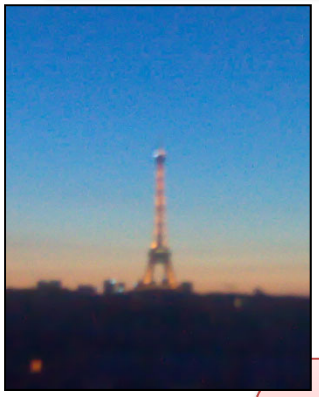
500 adults

600 children

3000 adults

500 children

NECKER & HEMOGLOBINOPATHIES



TRANSITION FROM PEDIATRIC TO ADULT MEDECINE

SICKLE CELL DISEASE & PREGNANCY

CORD BLOOD BANKING

GENE THERAPY & HEMOGLOBINOPATHIES

SICKLE CELL DISEASE & PREGNANCY
HIGH RISK SITUATION

Mortality 0.4 - 9%

Acute complications

Anaemia
Vaso-occlusive Crisis
Chest Syndrome
Infections
Thrombosis
Allo-immunization

Accentuation of chronic complications

Cardio-Pulmonary
Cerebral Vasculopathy
Retinopathy…

Integrated care sickle-obstetric units

Transfusion management?

Obstetrical complications

Pre-ecclempsia
Ecclempsia
Thrombosis

↗↗ Cesarean

Foeto-natal complications

Miscarriage
In utero Fœtal Death
Low birth weight
Pre-term delivery
Perinatal mortality

MULTIDISCIPLINARY NETWORK

Erythrapheresis

Inner medicine
&
Infectiology unit

2 High risk Maternities

Hemoglobinopathy
Reference center

Pediatrics

Genetics

Pediatric & Adult
ICU

Guidelines for management of adult sickle cell disease

Rev Med Interne. 2009;30 Suppl 3:S162–223

Lionnet F, Arlet J-B, Bartolucci P, Habibi A, Ribeil J-A, Stankovic K. Rev Med Interne. 2009;30Suppl 3:S162–223

SCD COMPLICATIONS DURING PREGNANCY

%	VOC		Acute Chest $		Transfusion		Mortality
	SS	SC	SS	SC	SS	SC	
Howard (1995) n= 78	46	27					3
Rahimy (2000) n=108	57	53	2	0	55	33	2
Leborgne-Samuel (2000) n= 68	88	27	21	3	64	3	1
Sun (2001) n=127	48	19			59	21	0
Ngo (2010) n=128	42	36	4	0	100	100	0

OBSTETRICAL COMPLICATIONS & PERINATAL OUTCOME

%	PE		IUGR		Preterm delivery		IUFD		Perinatale Mortality	
	SS	SC	SS	SC	SS	SC	SS	SC	SS	SC
Howard (1995) n=78	8	12	13	21	33	15	0		5	9
Leborgne-Samuel (2000) n=68	15	7	15	3	17	14	12	0	12	7
Sun (2001) n=127	10	3	46	17	45	22	4	2	11	2
Ngo (2010) n=128	9	0	14	3	16	12	4	0	4	0
Control	2-3		10		7-10		<1		1	

SCD & PREGNANCY FUP

- « SCD » doctor or obstetrician consultation / 2 weeks
- Blood & Urine (proteinuria & cytobacteriology) Biology analysis / 3 w
- Cardiac Echography at the 3rd trimestre
- Recent ophtalmology consultation
- Obstetrical echography : usual :12; 20; 32 WA + 28 and 36 WA
- Weekly materno-fœtal monitoring since 36 WA
- Delivery programmed at 39 WA (induced labour or cesarean section)

Make attention of expulsive delivery efforts contraindications

SCD & PREGNANCY FUP

- **Therapeutic education & hygieno-dietetic rules:**
  - Social conditions (Homeless, Corent, working conditions…)
  - Rest+++ (Home ←→Work)
  - Hydratation with alcaline water
  - Respiratory exercices: Respiflow
  - Support stockings

  - Folic Acid: 10 mg/d
  - Vitamine D: 100,000 UI/ 2 months
  - Pain killers
  - ~~Non steroidal anti-inflamatory inhibitors~~
  - Beware corticotherapy

- **Transfusion?**

INTERNATIONAL SICKLE CELL DISEASE OBSERVATORY

« Global Harmonization of FUP and Treatment for SCD patient »

Under the High Patronage of his Serene Highness Prince Albert II de Monaco

ISCDO

eurocord-ed

eurocord

ESH EUROPEAN SCHOOL of HAEMATOLOGY

NETCORD

DATABASE PREGNANCY-SICKLE CELL DISEASE

CLEANWEB

CleanWEB

Information
Contacts
eCRF
Annuaire
Statistiques
Configuration
Support

Patients | Nouveau Patient | Queries | Imprimer

Patient : UC----G-J Investigateur : Testeur CCH Patients: Sélectionnez

- Inclusion / Randomization
- Patient
  - Informations du patient
  - Drépanocytose
  - Situation familiale
  - Manifestation
- Etat de base
  - Antécédents d'atteinte pulmonaire
  - Atteinte Cardiaque
  - Antécédents Thrombo-emboliques
  - Antécédents Neurologiques
- Documents de fusion

Informations du patient

ETUDE RÉTROSPECTIVE D'ÉVALUATION DE LA PRISE EN CHARGE DES FEMMES ENCEINTES DRÉPANOCYT

N° Centre : UC Investigateur : Testeur CCH

Référence du patient : UC----G-J

Patient

Nom :

Prénom :

Date de naissance jj/mm/aaaa

Origine

Pays d'origine :

Pays de naissance :

Année d'arrivée en Métropole :

Grossesse

Date de début de grossesse : jj/mm/aaaa

Age lors de la grossesse ans

DATABASE PREGNANCY-SICKLE CELL DISEASE

AIMS

- **Evaluations:**
  - **Epidemiological profile of patients**
  - **Medical / obstetrical complications**
  - **Characteristics of newborn**
  - **“Conventional” care**
- **Optimization of guidelines**
- **Comparison and standardization of practices in the different countries**
- **Search for prognostic factors**

A RETROSPECTIVE STUDY
2005-2012

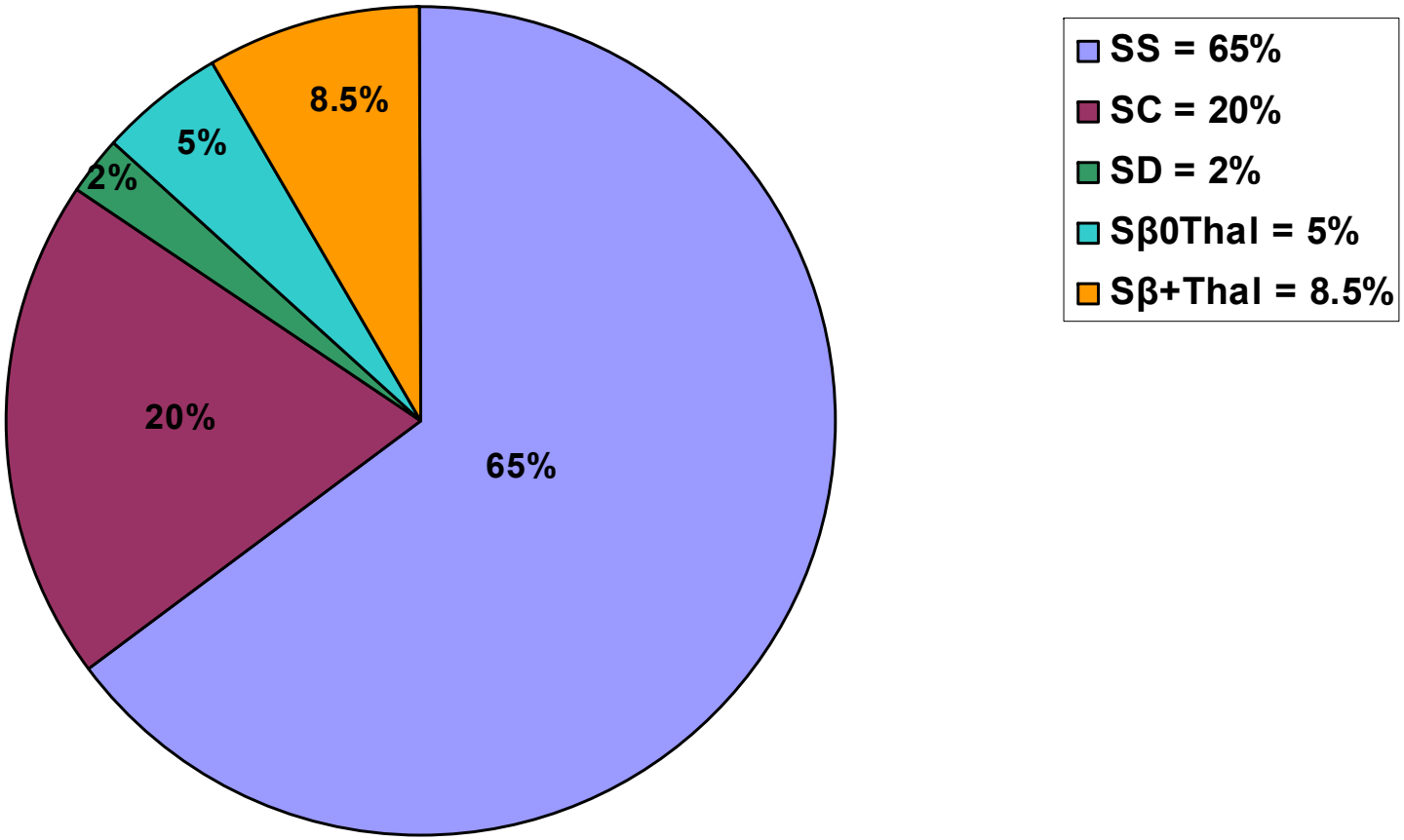
- **Sickle cell syndrome (SS, SC, Sβ, SD)**

- **Number of pregnancies : 153**

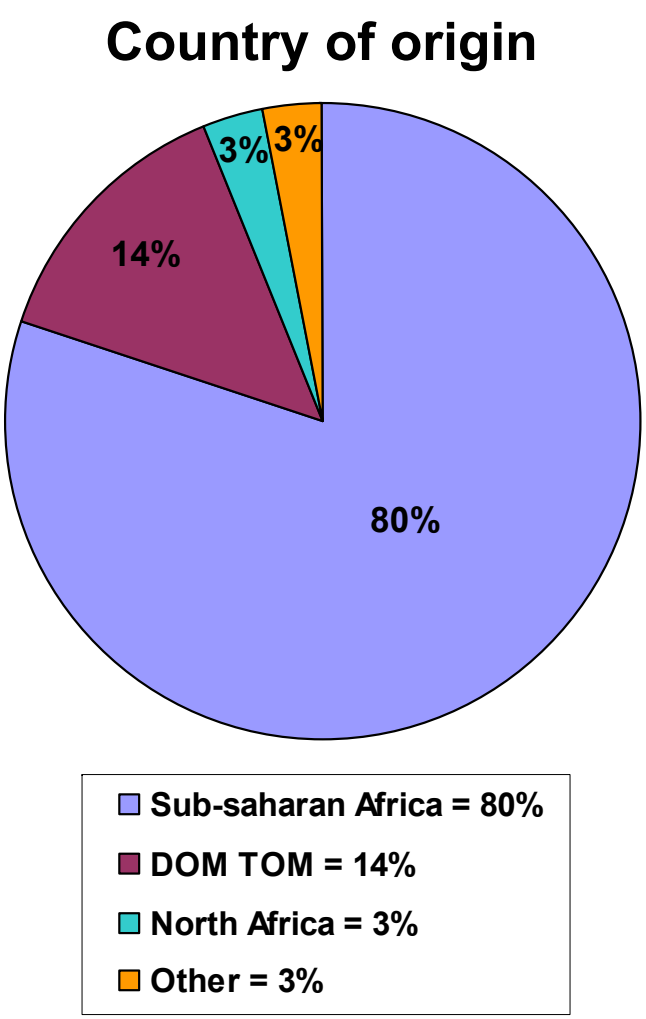
  – **Necker Hospital** (2005 to 2012)
  – **Antoine-Béclère Hospital** (2008 to 2012)

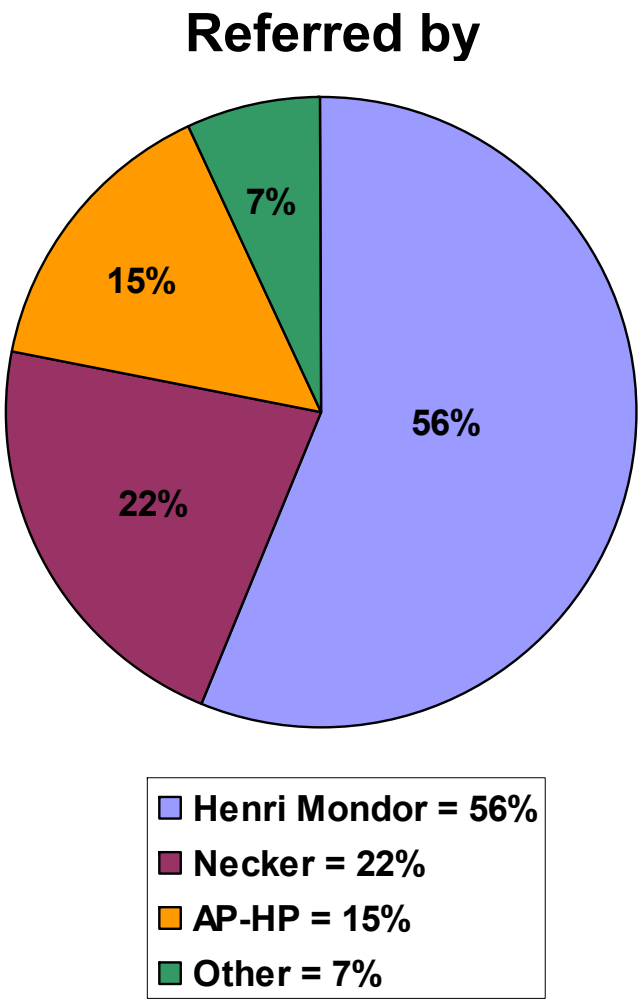
PATIENTS CHARACTERISTICS

Phenotypes

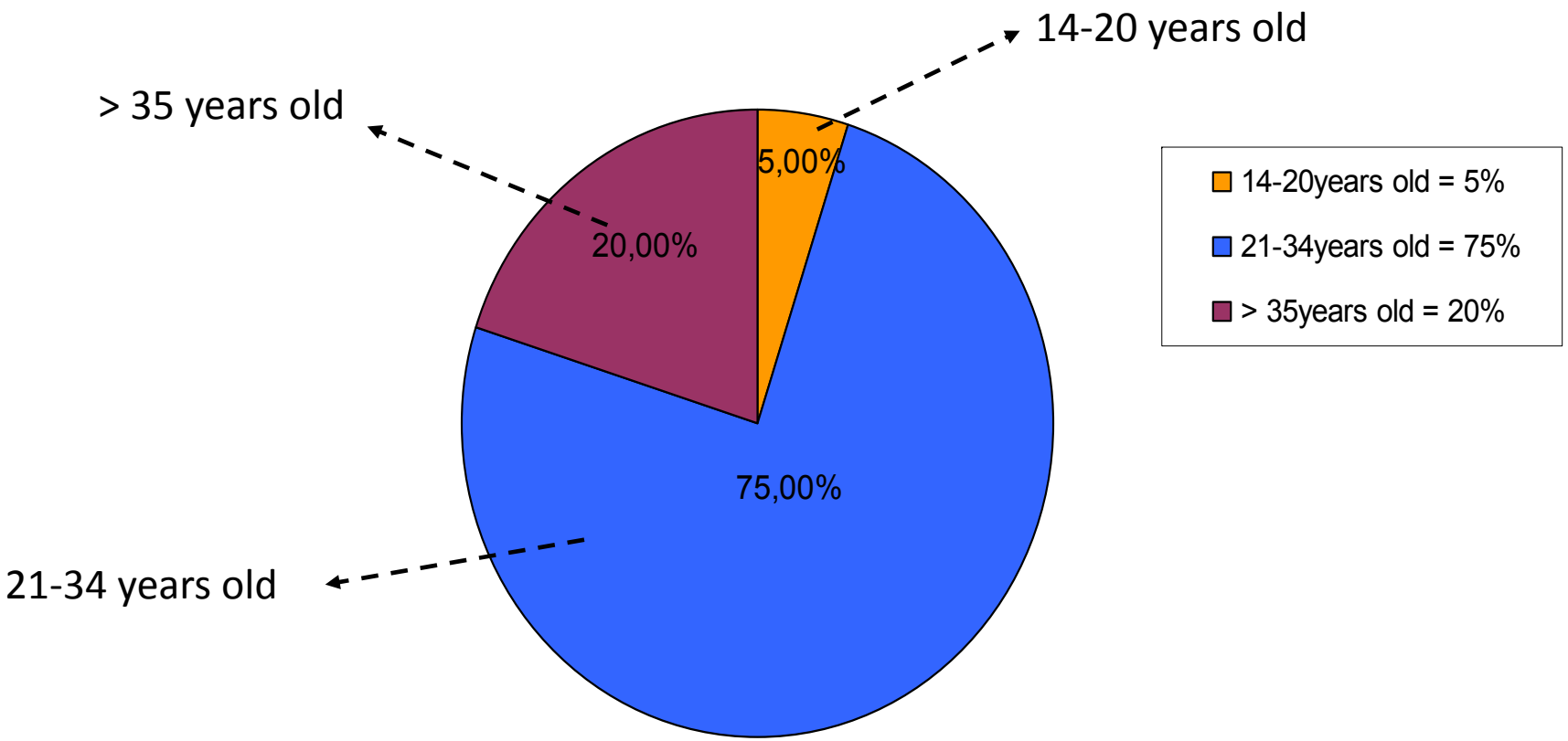


PATIENTS CHARACTERISTICS

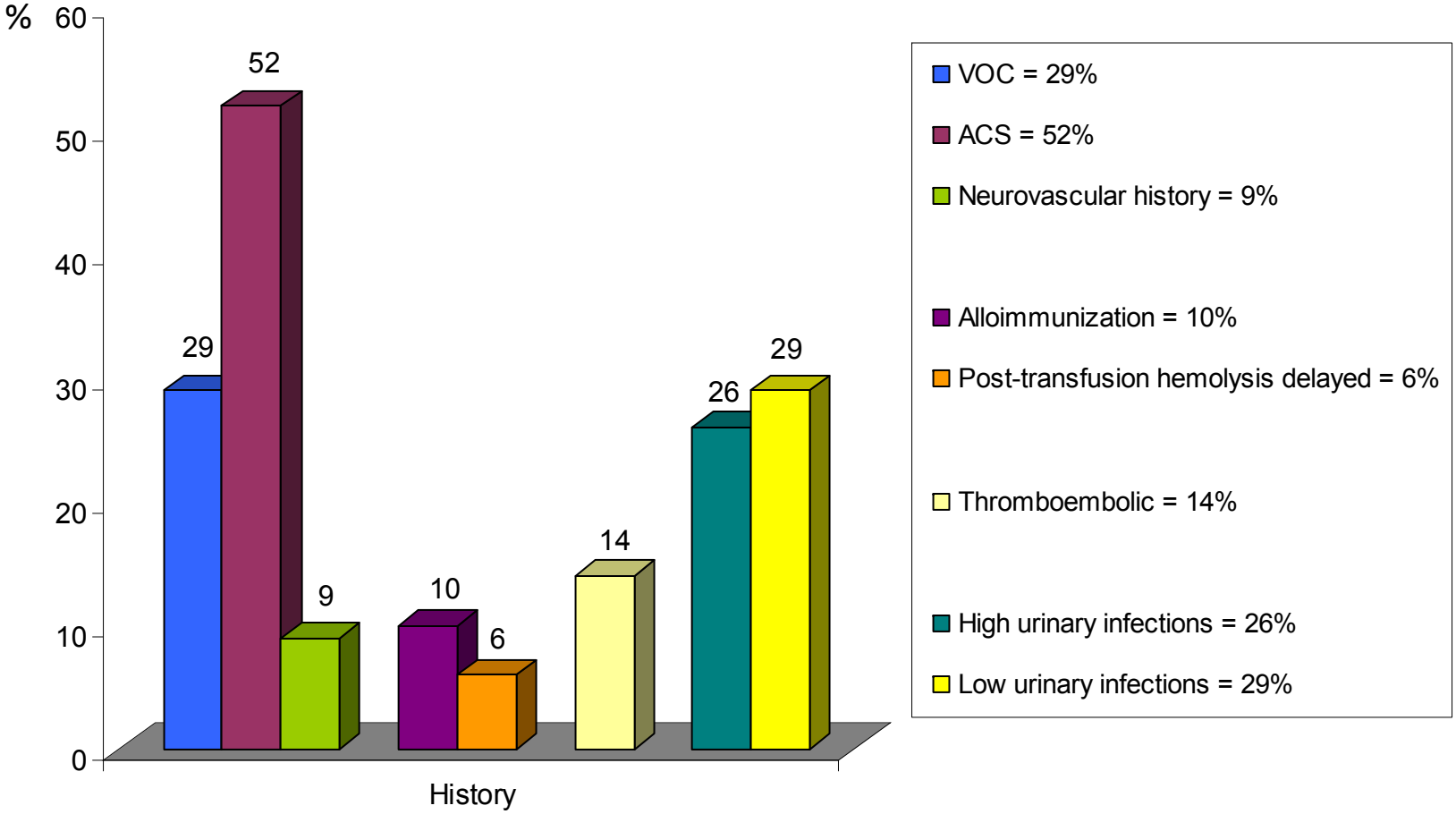




PATIENTS CHARACTERISTICS
Age distribution

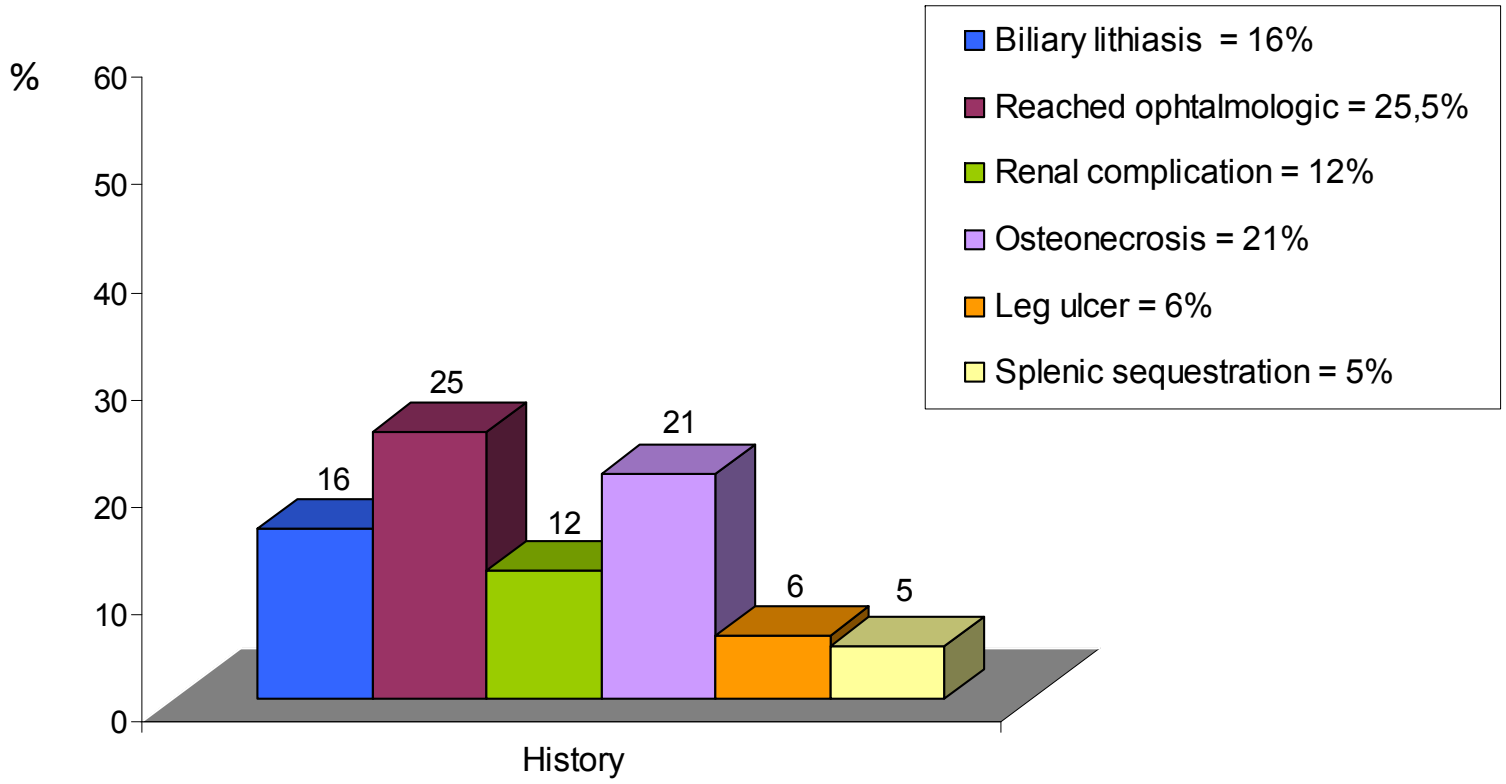


PATIENTS CHARACTERISTICS
History of acute complications



24% of patients as thorough treatment (Hydroxyurea or transfusion program)

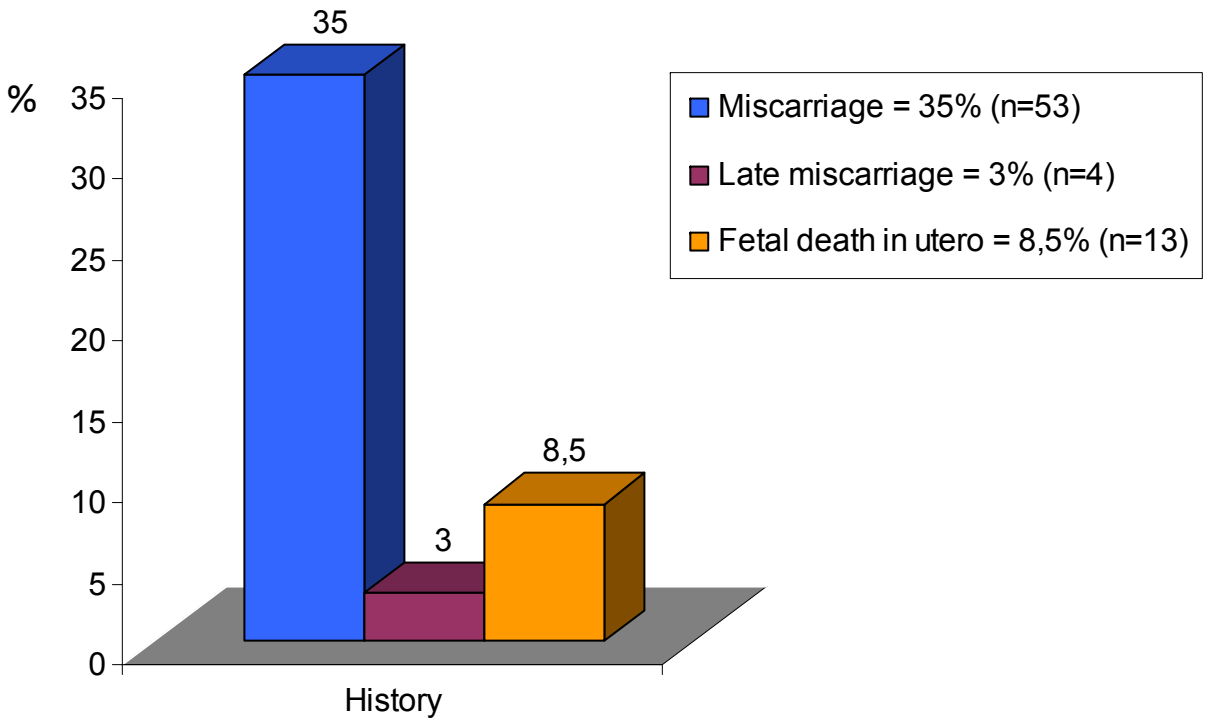
PATIENTS CHARACTERISTICS
History of chronic complications



PATIENTS CHARACTERISTICS
Obstetric history

Gestation (taking into account the current pregnancy) : **3.08**

Parity : **0.94**

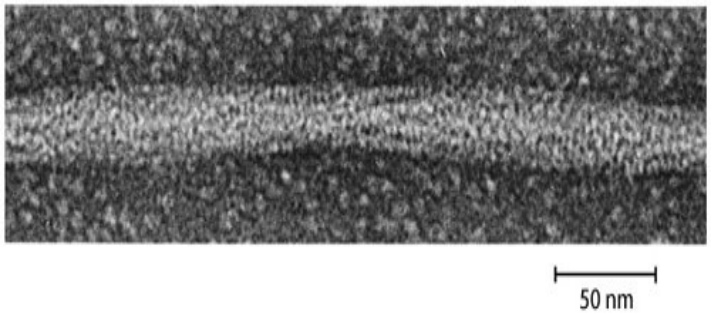


PATIENTS CHARACTERISTICS
Genetic counseling

- **Genetic counseling** : **70%**
  - Pre-conception : **32%**
- **Risk of transmission** : **16%**
- **Prenatal diagnosis** : **5%**
- **Decline of prenatal diagnosis** : **11%**

PHYSIOLOGICAL CHANGES IN PREGNANCY WORSENING SCD

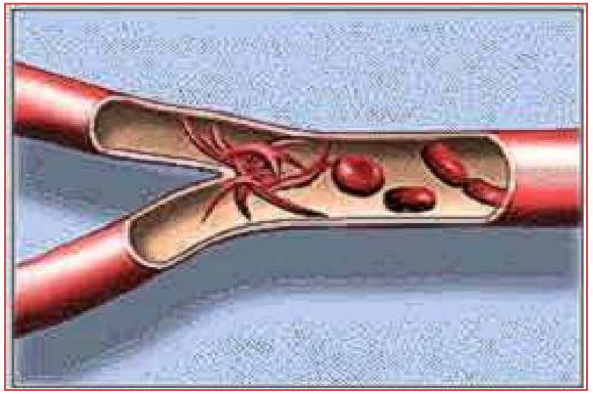
- Worsening anemia
- ↗O2 consumption
- ↘ respiratory capacity
- Acidosis



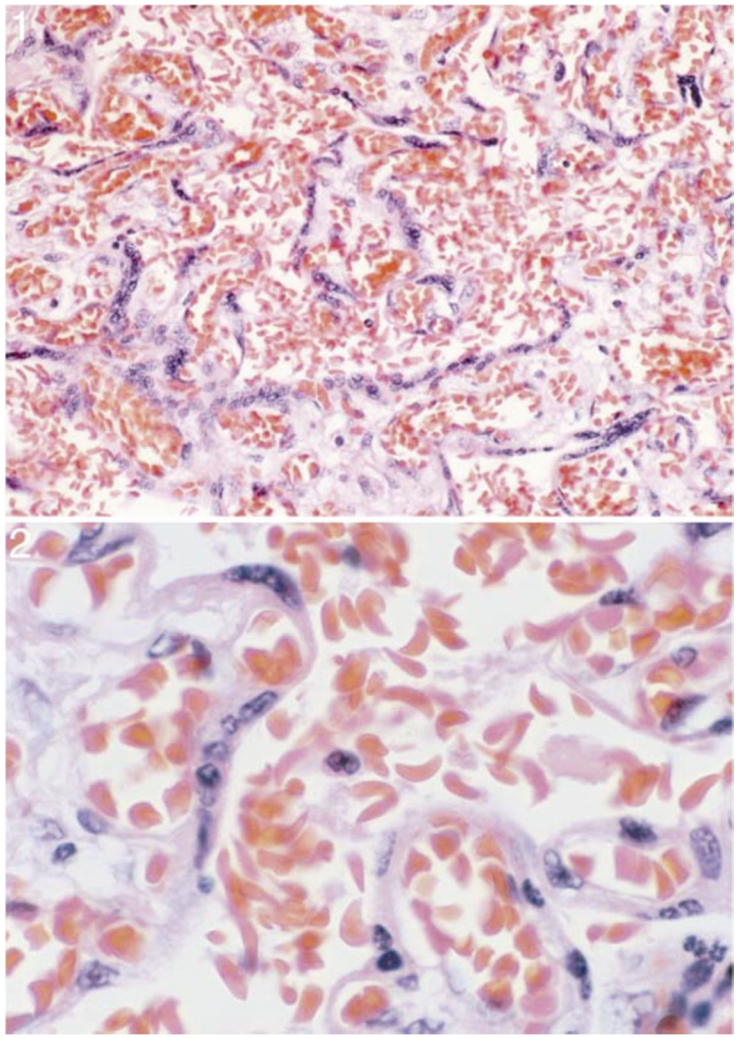
Oxy Hb ⇌ **Desoxy Hb**

Hb S polymerisation

Sickling & Vaso-occlusion



PATHOPHYSIOLOGICAL HYPOTHESIS



SCD placenta histology

Pantanowitz L et al, Arch Pathol Lab Mes, 2000

OBSTETRICAL COMPLICATIONS

Placental & Fœtal Hypoxia

- Mother

2nd-3rd T

Gravidic HTA

Pre-eclampsia

Delivery-Post-partum

Cesarean section 50-60%

VOC ++

ACS +++

- Fœtus

Micarriage

IUFD

IUGR – Low weigth

Preterm delivery

Neonatal Death

TRANSFUSION STRATEGY?

PROPHYLACTIC TRANSFUSION PROGRAM

OR

TARGETED TRANSFUSION

TRANSFUSION INDICATIONS GUIDELINES

PROPHYLACTIC TRANSFUSION PROGRAM

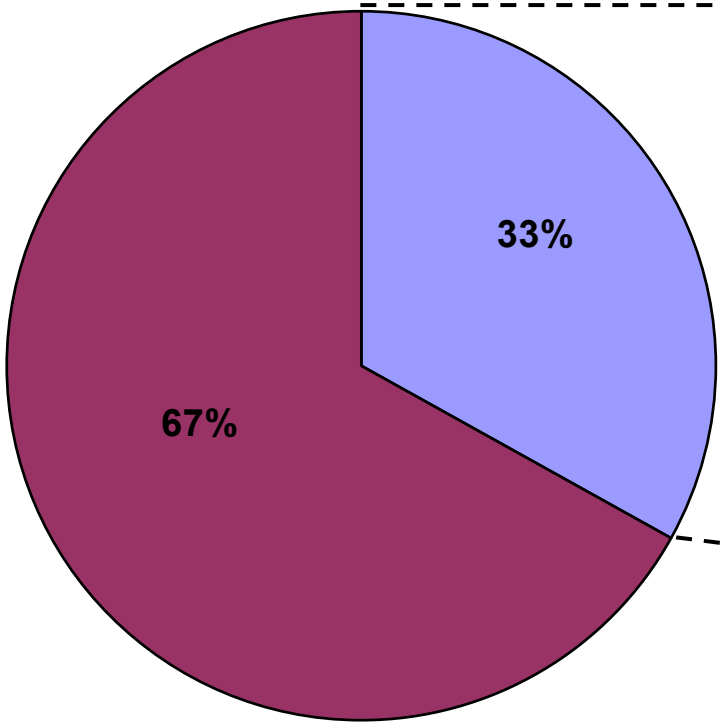
- **Systematically from 22 weeks for SS or 30 weeks for SC**

OR

- **The following indications :**
  - Pursuit of a transfusion program started before pregnancy
  - History of Acute Chest Syndrome
  - Preexisting organ failure
  - History of pre-eclampsia, IUGR, fetal death *in utero*
  - Vaso-occlusive Crisis or Acute Chest Syndrome occurred during the pregnancy
  - Hb < 8 g/dL
  - Just before delivery

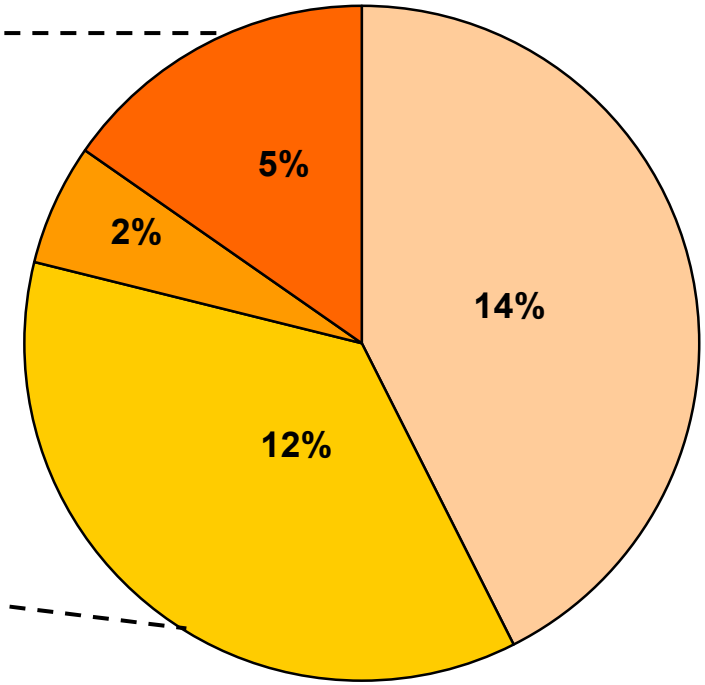
TRANSFUSION STRATEGY IN THE MANAGEMENT OF PREGNANCY

Transfusion strategy at the beginning



- Patients without transfusion = 33%
- Transfusion program during pregnancy = 67%

Reasons for non-transfusion



- Few symptoms = 14%
- Difficulty = 12%
- Decline of transfusion = 2%
- New patients = 5%

OBSTACLES TO THE TRANSFUSION PROGRAM

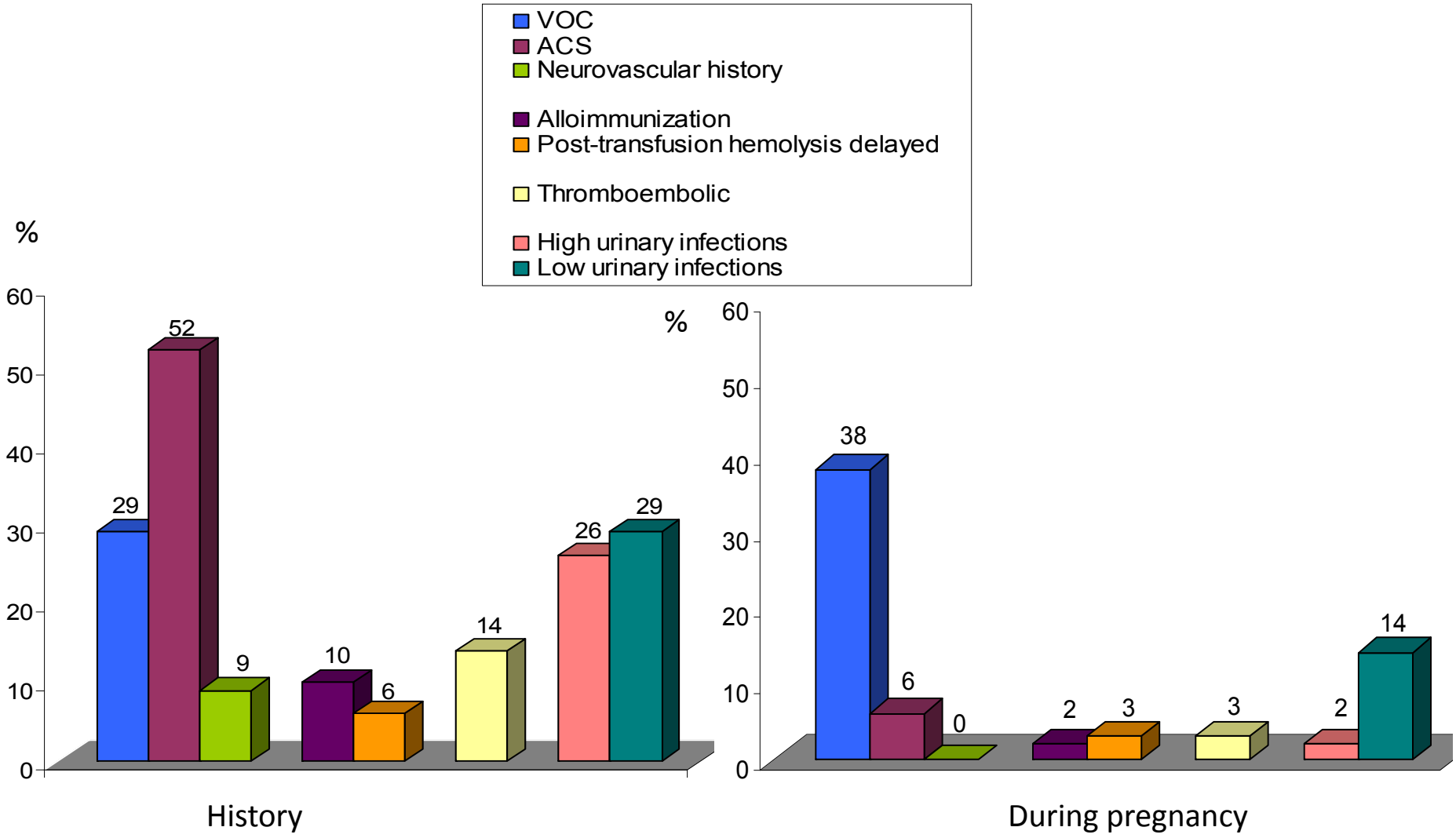
Transfusion's obstacles : **12%**

-Multi-Alloimmunization : **5%**

-Delayed hemolytic accident : **5%**

- Rare group : **6%**

SICKLE CELL COMPLICATIONS
During pregnancy studied



MATERNAL MORTALITY

1.96% maternal mortality with **3** deaths:

- 2 maternal-fetal deaths at 25 and 29 weeks
- 1 post-partum

→ **2 post-transfusions delayed hemolytic transfusion reaction**

%	VOC		Acute Chest $		Transfusion		Mortality
	SS	SC	SS	SC	SS	SC	
Howard (1995) n= 78	46	27					3
Rahimy (2000) n=108	57	53	2	0	55	33	2
Leborgne-Samuel (2000) n= 68	88	27	21	3	64	3	1
Sun (2001) n=127	48	19			59	21	0
Ngo (2010) n=128	42	36	4	0	100	100	0
ISCDO (2014) N=153	50	36	4	0	83	83	1.96

OBSTETRICAL COMPLICATIONS
During pregnancy

- **Gravidic Hypertension** : **6%**
- **Pre-eclampsia** : **10%**
- **Eclampsia** : **0%**

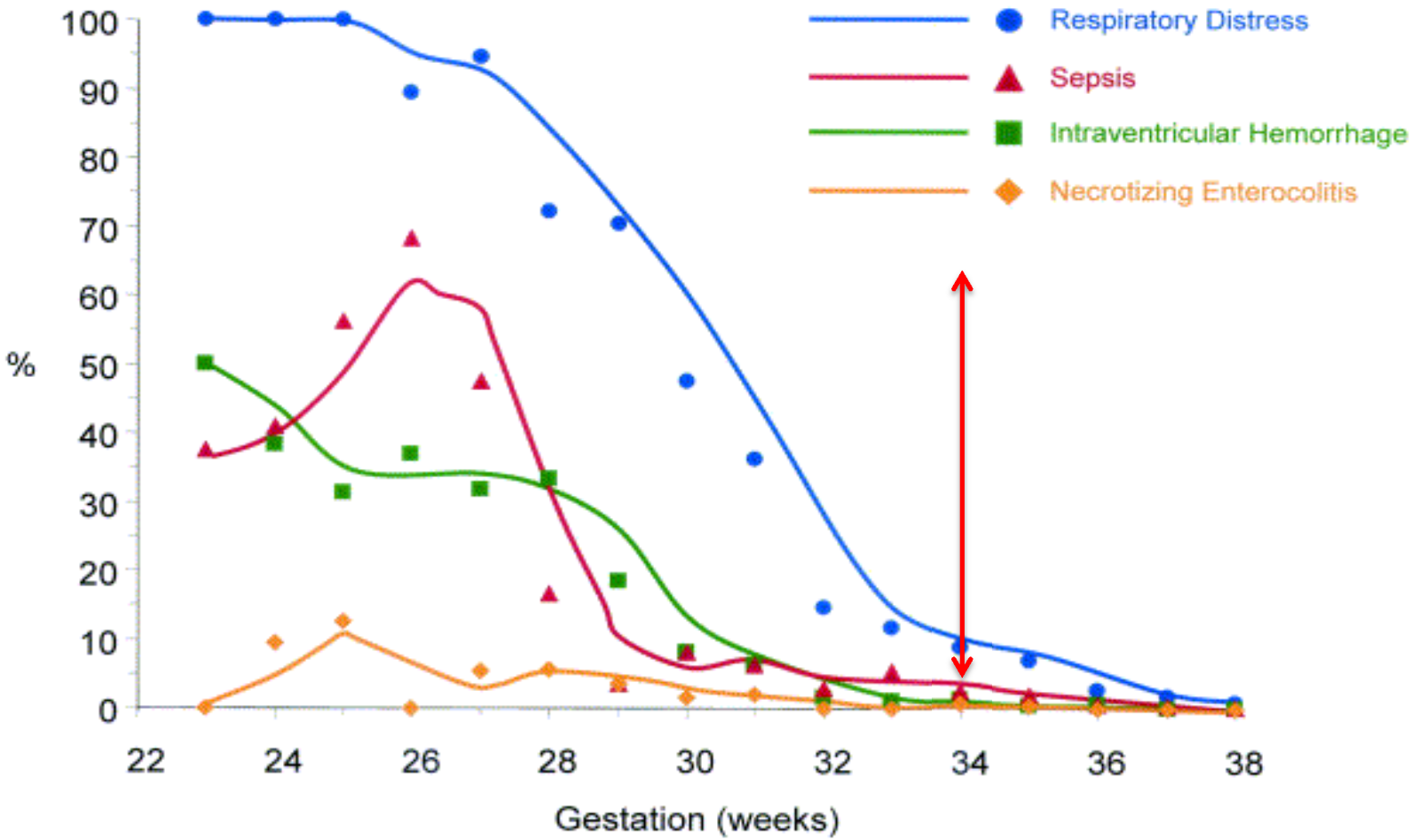
%	PE		IUGR		Preterm delivery		IUFD		Perinatale Mortality	
	SS	SC	SS	SC	SS	SC	SS	SC	SS	SC
Howard (1995) n=78 TT	8	12	13	21	33	15	0		5	9
Leborgne-Samuel (2000) n=68	15	7	15	3	17	14	12	0	12	7
Sun (2001) n=127	10	3	46	17	45	22	4	2	11	2
Ngo (2010) n=128	9	0	14	3	16	12	4	0	4	0
ISCDO (2014) N=153	8	13	7	0	35	7	1	3	0	7
Control	2-3		10		7-10		<1		1	

DELIVERY & NEWBORN CHARACTERISTICS

- Cesarean : 68%
- Delivery at < 37 weeks : 27%
- Delivery at < 34 weeks : 7%
- Newborn hypotrophy : 4%
- Transfer to intensive care unit : 19%

%	PE		IUGR		Preterm delivery		IUFD		Perinatale Mortality	
	SS	SC	SS	SC	SS	SC	SS	SC	SS	SC
Howard (1995) n=78 TT	8	12	13	21	33	15	0		5	9
Leborgne-Samuel (2000) n=68	15	7	15	3	17	14	12	0	12	7
Sun (2001) n=127	10	3	46	17	45	22	4	2	11	2
Ngo (2010) n=128	9	0	14	3	16	12	4	0	4	0
ISCDO (2014) N=153	8	13	7	0	35	7	1	3	0	7
Control	2-3		10		7-10		<1		1	

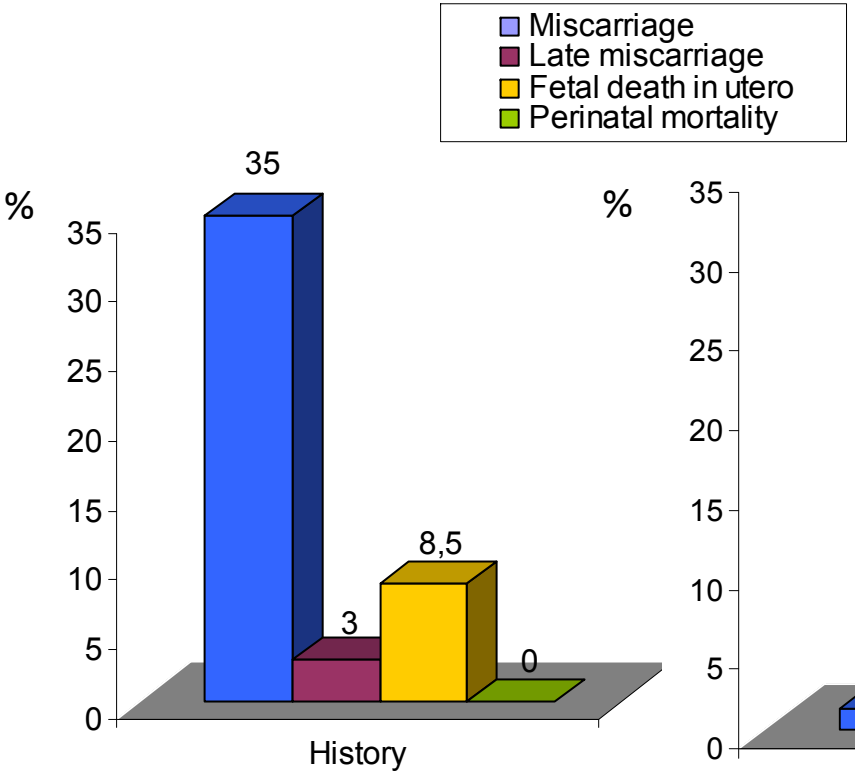
Neonatal Morbidity in 8523 NB between 1997–1998



B. Mercer.

OBSTETRIC COMPLICATIONS
During pregnancy studied

- Late Miscarriage : **0.7% (n= 1)**
- Fetal death *in utero* : **1.3% (n= 2)**
- Perinatal mortality : **1.3% (n= 2)**
- Neonatal mortality : **0.7% (n= 1)**



POST-TRANSFUSION COMPLICATIONS DURING PREGNANCY

- **Allo-immunisation**
  - Miller 1981 : 36%
  - Koshy 1988 : 23.6-29%
  - Howard 1995 : 12%
  - Ngo 2010 : 5%

  - ISCDO : 3%
    2% DHTR → 2 deaths

/3

COMMENTS
Evolution of Transfusion Indications

« Caractéristiques et évolution de 78 épisodes d'hémolyse post transfusionnelle retardée (HPTR) chez des patients atteints d'un syndrome drépanocytaire majeur »

Anoosha Habibi, C.Guillaud, M.Michel, K. Razazi, C. Rieux, P. Bartolucci, D.Bachir,J.Gellen-Dautremer, A. Mekontso-Dessap, B.Godeau, F. Noizat-Pirenne, F.Galacteros.

- **30% of post-transfusion hemolysis delayed readings occurring during pregnancy :**
  - 24% prophylactic program
  - 6% treatment of vaso-occlusive complication

PROBABLY UNDER DIAGNOSED

TRANSFUSION STRATEGY SWITCH
during the pregnancy studied

- **Transfusion strategy switch : 27%**

- **Prophylactic Transfusion switch : 5%**
  - **DHTR : 60%**
  - **Allo-immunisation: 40%**

- **Not transfused SCD Pregnancy women → Transfused : 65%**
  - **Patientes with transfusion obstacles but finally transfused: 36%**
    - SCD or obstetrical complications: 71%
    - Before delivery : 29%
  - **Patientes few symptomatic before pregnancy but finally transfused : 90%**
    - SCD or obstetrical complications: 77%
    - Before delivery :23%

GUIDELINES - 2014
TRANSFUSION INDICATIONS

- **PROPHYLACTIC :**
  - Pursuit of a transfusion program if started before pregnancy
  - Treatment by Hydroxyurea
  - Preexisting organ failure
  - History of severe obstetrical complications

- **TARGETED :**
  - Severe anemia with foeto-maternal clinical impact
  - Repeated Vaso-occlusive Crisis or Acute Chest Syndrome occurring during the pregnancy
  - ~~Just before delivery~~

OXYGEN AT HOME
PROPHYLACTIC ALTERNATIVE ?

High oxygen environment during pregnancy rescues sickle cell anemia mice from prenatal death

Table 1
Yield of sickle cell anemia mice

Environment	Number of mother	Number of pups born			Alive SS [a]	
		Total	SB (+SS) [b]	Alive	Number	Percent
50% O_2	45	238	23 (5)	215	75	35
Room air	14	93	38 (20)	55	1	1.8

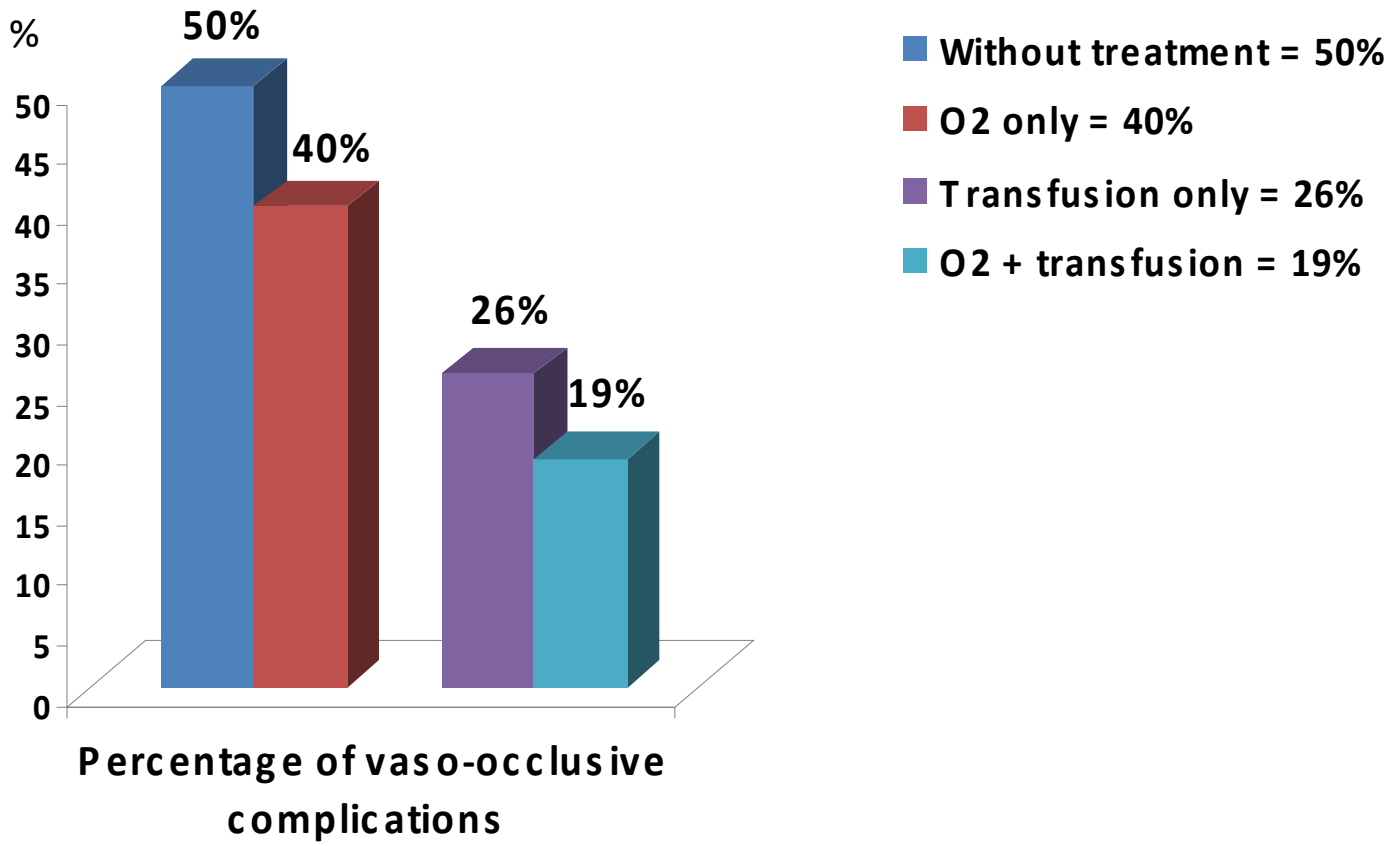
[a] SS: Sickle cell anemia.
[b] SB (+SS): Stillbirths with SS.

Fig. 1. Oxygen chamber containing 4 mouse cages. The oxygen percentage within the chamber is shown in the inset.

Blood Cells Mol Dis. 2008;41(1):67–72.

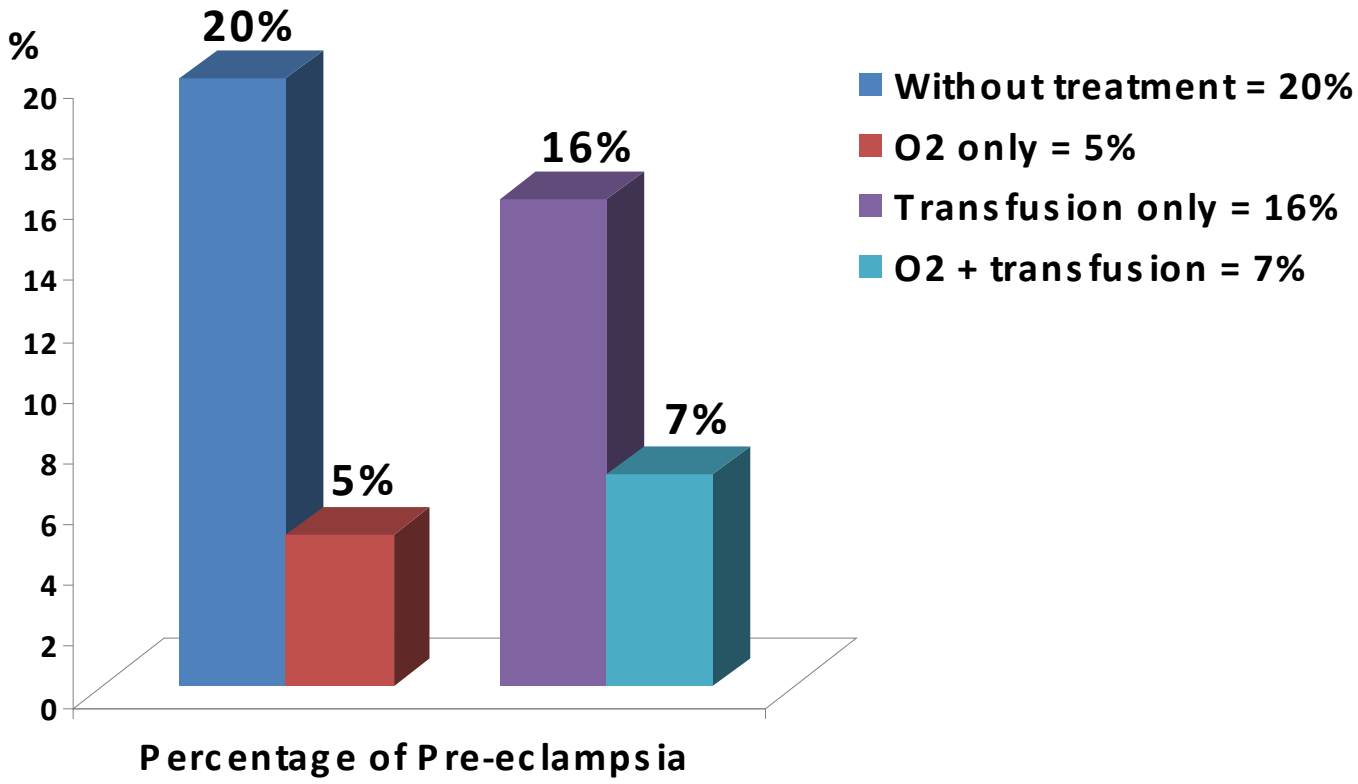
OXYGEN AT HOME
PROPHYLACTIC THERAPEUTIC ?

RETROSPECTIVE STUDY 2010-2012
79 PREGNANCIES



OXYGEN AT HOME
PROPHYLACTIC THERAPEUTIC ?

RETROSPECTIVE STUDY 2010-2012
79 PREGNANCIES



DATABASE "PREGNANCY & SCD"

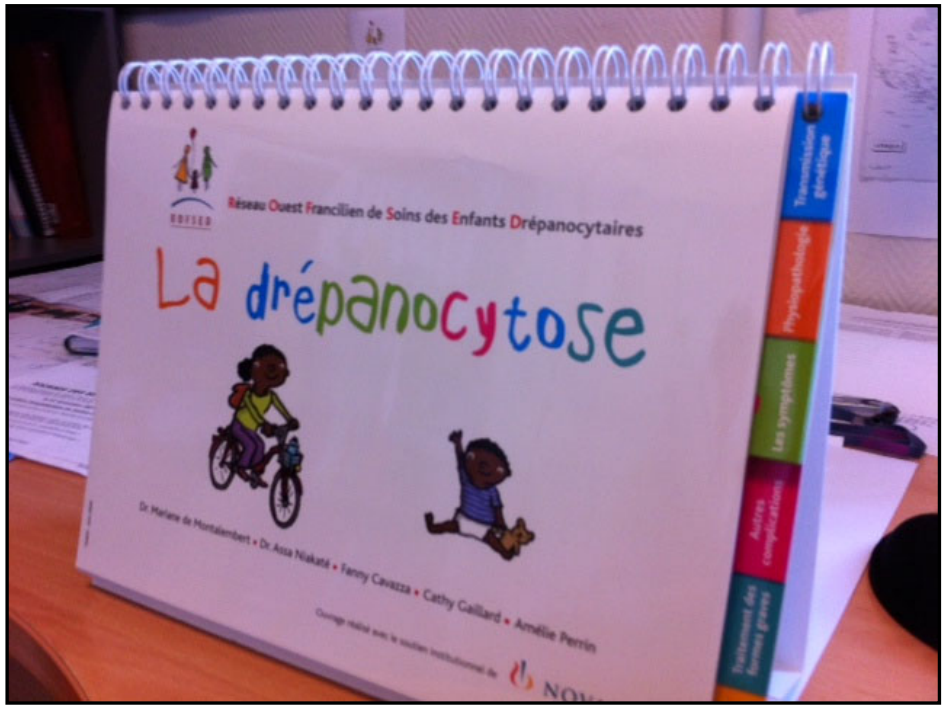
PERSPECTIVES

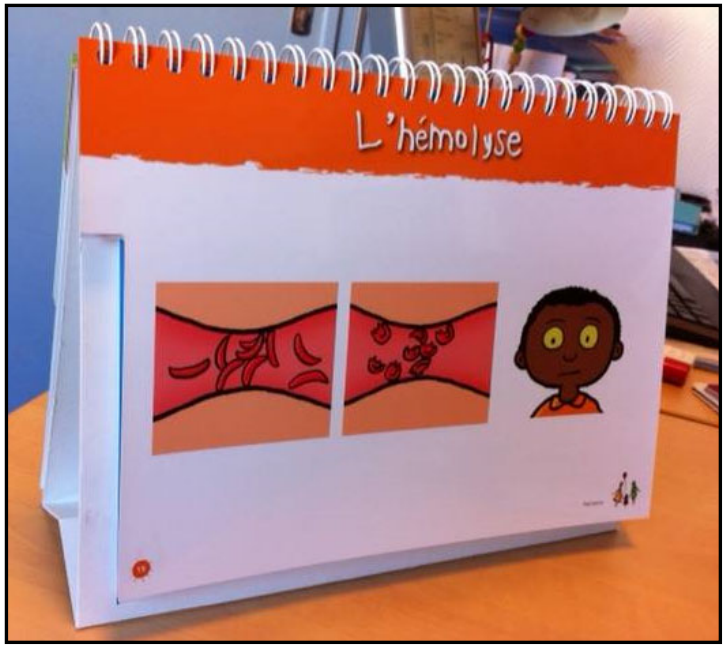
- **Multicenter & international prospective database**
- **Optimization & Homogenization of guidelines**
- **Dissemination with therapeutic education**
- **Setting up of a randomized clinical study : 300 pregnancies/years in Paris**
  - Impact of home Oxygen
  - Search for prognostic factors
  - Monitoring urinary tract infections

THERAPEUTIC EDUCATION

PICTURE FILE

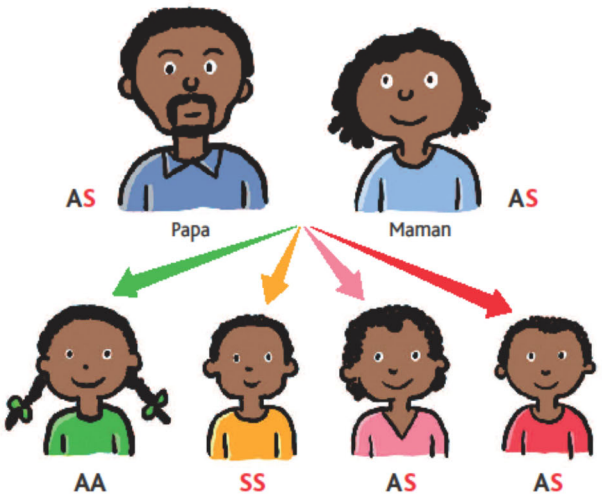
- For professionnal
- Sponsorised by NOVARTIS



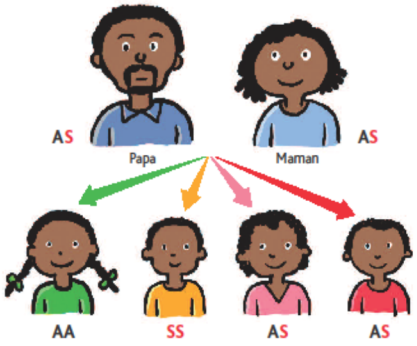


Picture File

Drépanocytose homozygote SS



La transmission génétique SS



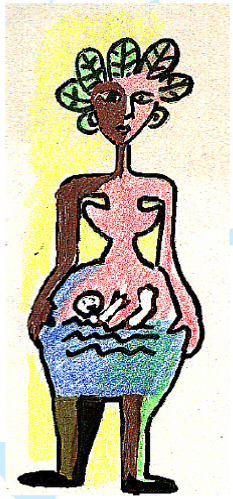
AA : Non malade
AS : Porteur sain
SS : Drépanocytaire (homozygotie)

Autres formes : SC - Sβ°- Sβ+ ...

- Mode autosomique récessif (50 % garçon et 50 % fille).
- Les deux parents doivent être porteurs d'une mutation de l'hémoglobine pour que l'enfant soit atteint.
- Risque de transmission à chaque grossesse = 1 enfant sur quatre atteint.

"La drépanocytose". R. Girot, P. Begué, F. Galactéros. Ed. John Libbey. Eurotext. Juillet 2003.

Drépanocytose et grossesse



La grossesse chez la femme drépanocytaire

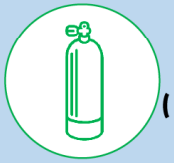
PETITS CONSEILS POUR FEMME ENCEINTE DREPANOCYTAIRE

Necker

Vous devez

BOIRE BOIRE & BOIRE BEAUCOUP D' EAU
(et de l'eau de Vichy, c'est encore mieux)

AVOIR UNE BONNE HYGIENE DES DENTS
(pour eviter les infections)



UTILISER VOTRE INHALATEUR D'O_2
(pour eviter les crises vaso occlusives)

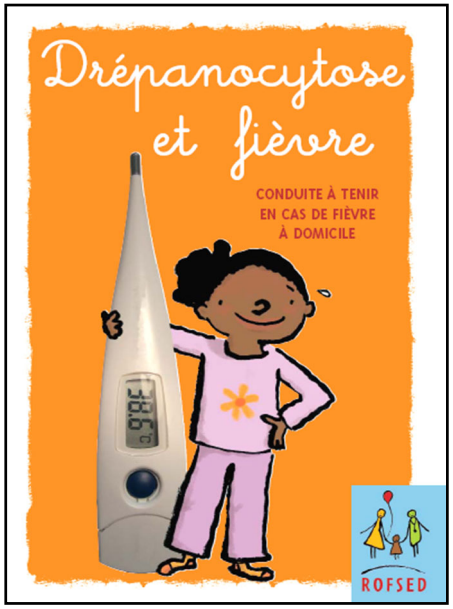
PORTER DES BAS DE CONTENTION
(pour favoriser la circulation sanguine)

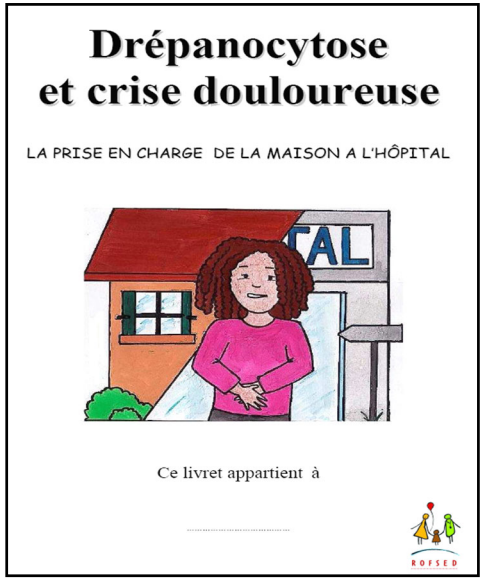
Vous ne devez pas

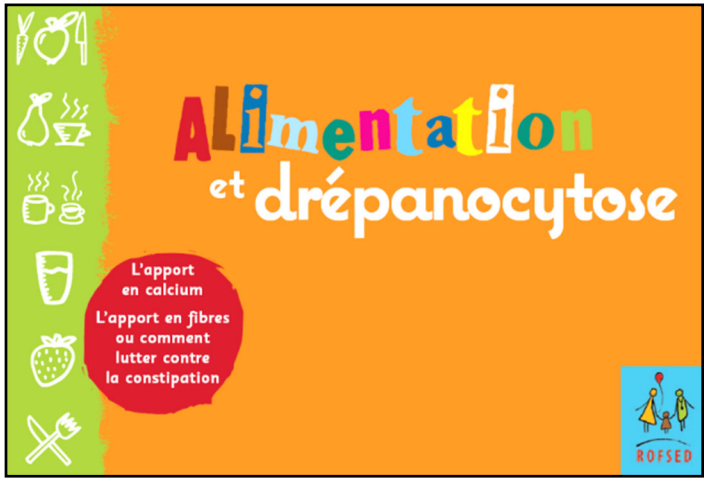
VOUS EXPOSER NI AU FROID NI A LA CHALEUR
(vos globules rouges n'aiment pas ça)

NI BOIRE D' ALCOOL NI FUMER
(vos globules rouges et votre bébé n'aiment pas ça)

FAIRE DES EFFORTS INUTILES
(mais oui, laissez votre mari faire la vaisselle)







http://www.rofsed.fr

THANKS

NECKER-ENFANTS MALADE Hospital:

-Department of Biotherapy: Aurélie Stanislas,

Marina Cavazzana

-Maternity: Benjamin Deloison, Yves Ville

-Department of Infectious Diseases: Caroline Charlier, Olivier Lortholary

-Clinical Research Unit: Jean-Marc Treluyer and Fabrice Gourmelon

-Unit of Pediatric Immuno-Hematology: Stéphane Blanche

-SCA Pediatric reference center: Mariane de Montalembert

ANTOINE BÉCLÈRE HOSPITAL:

Maternity: Alexandra Benachi

SAINT ANTOINE:

Department of Statistics: Myriam Labopin

HENRI-MONDOR:

Genetic Diseases Unit of Red Blood Cell: Frédéric Galacteros

OBRIGADO!