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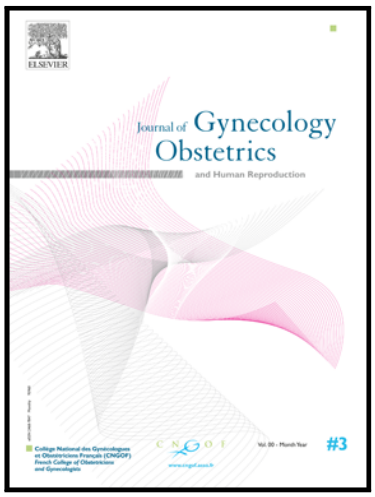

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Sickle cell disease and COVID-19 in pregnant women

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ABSTRACT

Introduction: The effect of coronavirus disease (COVID-19) on pregnancy outcome in women with sickle cell disease (SCD) is unknown.

Objectives: To analyze the severity of the SARS-CoV-2 infection in pregnant women with SCD and its impact on pregnancy.

Methods: This retrospective cohort study included SCD pregnant women tested positive for COVID-19 between March 2020 – February 2021. The primary endpoint was the severity of the COVID-19 infection. Secondary endpoints were pregnancy complications and fetal outcomes.

Results: During the study period among 82 pregnant women with SCD, 8 have presented symptoms suggestive of COVID-19 and were tested positive. A common mild clinical presentation was observed in 6 women (75%), one woman was asymptomatic and one required oxygen. The latter was admitted to the Intensive Care Unit and a cesarean section was performed in the context of an ongoing vaso-occlusive crisis and acute chest syndrome together with incidental preeclampsia. Labor was induced in another patient who developed a vaso-occlusive crisis after COVID-19 remission. Fetal outcomes were good with an average Apgar score of 10 and normal umbilical blood pH at birth. Two newborns were small-for-gestational-age as expected on the ultrasound follow-up before occurrence of COVID-19.

Conclusion: COVID-19 infection in our population of pregnant women with SCD had typical presentation and rarely triggered a sickle cell crisis or other complications. Fetal outcomes were good and did not seem to be directly influenced by the SARS-CoV-2 virus. Further studies are required to confirm these observations as compared to the population of women with SCD without COVID-19 infection.

KEYWORDS: COVID-19, pregnancy complications, sickle-cell disease

INTRODUCTION

Sickle cell disease (SCD), the most common inherited hematological disorder with a global birth prevalence of approximately 1-5 per 10,000 predominantly affects subjects of African origin (1). The condition is associated with early mortality although improved healthcare has raised the life expectancy of patients with SCD to around 50 years (2,3). The number of pregnant women with SCD is increasing along with this improvement in life expectancy. Nevertheless, despite these advances in healthcare, pregnancy in SCD patients remains associated with a greater risk of both clinical and obstetric maternal and fetal complications than in SCD-free pregnant women (1,4). Women with SCD are at a higher risk of maternal death (72.4 deaths versus 12.7 per 100,000 deliveries) and are more likely to experience gestational hypertension (5), vaso-occlusive crises (VOC) (6), deep vein thrombosis, fetal growth restriction, and systemic inflammatory response syndrome (7).

In the current pandemic, the data about the clinical course of the infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in pregnant women without comorbidities are controversial (8,9). The literature analyzing the impact of coronavirus disease 2019 (COVID-19) on obstetrical and neonatal outcomes shows also conflicting data (8,9).

Additionally, articles analyzing COVID-19 outcomes in patients with SCD conclude that patients with SCD experience a rather mild form of infection (10–12), and some even suggest a lower risk of intubation, Intensive Care Unit (ICU) admission, and death (13). Of note, subjects carrying the HbSC genotype may display a more severe course of COVID-19 (14).

However, data concerning the course of COVID-19 and pregnancy outcomes in the population of pregnant women with SCD are scarce. One single case of COVID-19 in a pregnant woman with SCD has been reported so far. The SARS-CoV-2 infection at 28 weeks of gestation (WG) triggered an acute chest syndrome (ACS) but the outcome was ultimately positive (15).

More information is therefore necessary to adapt healthcare during pregnancy for women with SCD experiencing COVID-19. The aim of this study was to describe SARS-CoV-2 infection in the potentially high-risk group of pregnant women with SCD.

PATIENTS AND METHODS

Study setting and participants

We conducted a retrospective cohort study in Tenon Hospital (Paris, France), a secondary care unit and reference center for pregnant women with SCD, between the 1st March 2020 and 1st March 2021. During the study period the unit managed 82 deliveries in women with SCD out of a total of 2489 deliveries. Among women with SCD, 8 had symptoms suggestive of COVID-19 and were tested for SARS-Cov-2.

We enrolled all patients aged over 18 years, with an ongoing pregnancy, and diagnosed with active SARS-CoV-2 infection, and conducted a descriptive analysis in the subset of women with SCD.

Non-inclusion criteria were patients aged under 18 years, patients diagnosed with COVID-19 by a method other than a PCR nasal swab, lack of healthcare insurance, and a language barrier interfering with data collection.

Study protocol

Pregnant women monitored at Tenon Hospital or consulting at the Gynecology and Obstetrics emergency department with COVID-19 compatible symptoms were systematically tested using PCR nasal swabs.

Data from all pregnant women positive for COVID-19 with a proven infection between March 2020 and March 2021 were analyzed. Active viral infection was diagnosed by detection of

SARS-CoV-2 RNA from a nasal swab test performed by a trained practitioner. The cohort data were collected from the prospective obstetric database used routinely in the Department of Obstetrics of Tenon Hospital.

During the first wave of the pandemic (March to August 2020), patient specific data about the course of COVID-19 were collected via a daily phone call following a standardized questionnaire administered by trained obstetricians until the symptoms disappeared. From August 2020 to the end of the study period, data were obtained at regular follow-up appointments. If a patient was hospitalized for COVID-19 treatment, data were collected directly from the hospital database completed daily by the unit's physicians.

A subset of patients with SCD was identified among COVID-19 patients to study infection severity and pregnancy outcomes.

Oral informed consent for data collection was obtained from all the patients. The study was approved by the Institutional Review Board of the French College of Obstetricians and Gynecologists – CEROG (registration N° 2021-GYN-0201).

Data analysis

A descriptive analysis of the characteristics and outcomes of cases meeting the inclusion criteria was done. Descriptive analysis included frequencies and percentages for qualitative variables and means with standard deviation or medians with interquartile range (IQR) as appropriate for quantitative variables.

RESULTS

Two hundred fifty-two patients were tested for COVID-19 between March 2020 and March 2021: 162 in the first COVID-19 wave in France and the following months (March to August);

and 90 in the second wave. Four patients were excluded from the analysis because of inconclusive PCR results. Among the patients with a negative PCR nasal swab one patient was diagnosed with COVID-19 after tracheal aspirate during hospitalization in the ICU, one patient was diagnosed after a pulmonary scan, and another was considered positive as she presented with anosmia and ageusia but was not tested. Finally, 64 pregnant women with a positive PCR nasal swab test were enrolled in the cohort, eight of whom (12.5%) were patients with previously diagnosed SCD (Figure 1). None of the women included in the study was vaccinated.

Characteristics of the population

The baseline characteristics of the eight pregnant patients with SCD diagnosed with COVID-19 are detailed in Table 1. The median maternal age was 30.5 years (24.0 – 34.3). The median gestational age at COVID-19 diagnosis was 26.5 WG (20-35): three women were in the third trimester and the other five were <28 WG. All the patients were of African origin and all women except one had a normal body mass index (BMI) before the pregnancy (22 (20 – 24) kg/m^2). Only one patient was primiparous (12.5%).

Three patients had a history of cesarean section during a prior pregnancy: one for intrauterine growth restriction (IUGR) and fetal heart rate (FHR) abnormalities, the second for PE, and the third for isolated FHR abnormalities (Table A.1).

Of the eight cases, four (50%) had SS sickle cell anemia (i.e., homozygous for Hemoglobin S gene), two (25%) had double heterozygosity for HbS/ß-thal, and two (25%) had HbS/HbC disease. Seven cases (87.5%) had a previous history of VOC, which had occurred during a previous pregnancy for four. Five patients had a history of acute chest syndrome (ACS). Three patients in the cohort had long-term therapy such as exchange transfusion initiated in one patient initiated before the pregnancy and in two others during the current pregnancy, either by manual

exchange, or by erythrocytapheresis (Table A.1). Underlying pulmonary disorders were asthma (n=1), restrictive lung disease (n=1), or a history of chronic idiopathic dyspnea (n=1). None of the patients were smokers.

On diagnosis of COVID-19, two patients were using low-dose aspirin: one because of a history of IUGR, and the other because of SCD cerebral vasculopathy. The latter (patient #2) was also receiving anti-epileptic drugs (Levetiracetam 500mg twice a day and Lamotrigine 150mg twice a day) and inhaled fluticasone/salmeterol due to asthma. One patient (patient #7) used daily hydroxychloroquine (200mg twice a day, orally) because of a history of repeated spontaneous miscarriages and fetal death at 5 months of gestation.

The four hospitalized patients (50%) were administered low-molecular-weight heparin (LMWH) (enoxaparin sodium) at a prophylactic dose. Two out of four patients presenting with fever received preventive antibiotic treatment for presumptive exposure to Listeria (amoxicillin) until the reception of COVID-19 PCR result. Overall, only one of the infected patients (#8) received active, full-course antibiotic treatment by cefotaxime and spiramycin for the treatment of concomitant ACS. One patient received influenza antiviral medication by oseltamivir which was interrupted on day 3 after admission when a negative nasal swab result was obtained.

Short term course of COVID-19

Common clinical symptoms were reported by seven of the eight patients (88%) and included fever, cough, rhinitis, and headache (Table 2). One patient had no symptoms but had a positive PCR test result from a routine nasal swab after admission for ongoing VOC and suspicion of ACS.

The symptoms persisted for a median of 5.5 days (3.0 – 12.5) and all the patients but one (patient #8) were followed up as outpatients or rapidly discharged from hospital (median hospital

stay 4.5 days (3.5-7.25)). On admission of patient #8 COVID-19 symptoms were mild, but dyspnea and PE occurred over the following days. She was admitted to the ICU and high flow oxygen therapy was administered for 4 days. A CT scan of the chest showed an aspect suggesting ACS lesions, but COVID-19 related involvement could not be excluded.

None of the patients required a supplementary transfusion related to COVID-19. From the biological point of view the mean hemoglobin level at the moment of COVID-19 was 9.0 ± 1.0 g/dl compared to 9.4 ± 1.0 g/dl 1 month before COVID-19 infection (p = 0.5).

Obstetrical course after COVID-19 remission

The median gestational age at childbirth was 38 WG (37-38) (Table 3). Two patients (25%) had preterm labor at 35 WG: patient #2 had labor induction for previously diagnosed IUGR associated with labiopalatoschisis, and patient #8 had a cesarean section at 35 WG because of incidental PE after ICU admission. Patient #8 was discharged without requirement of supplemental oxygen on postpartum day 14 and fetal outcome was favorable despite the preterm birth.

Labor induction for VOC was indicated in patient #1.

At the end of the study, one patient had not yet delivered, one patient (14%) had spontaneous onset of the labor, one patient had a cesarian section (patient #8) and five patients had labor induction (71%) due to cholestasis of pregnancy (n=2), previously diagnosed IUGR (n=1), isolated proteinuria (n=1), and VOC (n=1).

Fetal outcomes were mostly favorable with an average Apgar score of 10/10 5 minutes after birth and normal umbilical cord arterial blood pH (mean 7.31 ± 0.05). The median birth weight was 2770g (2455 – 3545) which corresponded to 56th percentile (18 – 69). Birth weight was normal except for two newborns (25%), previously diagnosed with IUGR.

DISCUSSION

During the study period, eight pregnant women with SCD were diagnosed with COVID-19. Both maternal and fetal outcomes were favorable despite high-risk pregnancy status and maternal comorbidities. Complications of SCD after COVID-19 were observed in one case admitted to ICU.

Pregnant women are especially susceptible to severe manifestations of viral infections including pneumonias because of immunologic alterations and physiological adaptive changes during pregnancy (16). In contrast, in our population pregnancy and SCD were not a risk factor of the severe form of COVID-19. The hypothesis that a chronic inflammatory background and the hemolytic and anemic state in SCD patients might have a protective impact on COVID-19 progression has already been reported (14,17). On the other hand, the exchange transfusion could have also played a protective role, as it was performed in 38% of women.

The clinical characteristics of COVID-19 in our cohort were similar to those reported by Zaigham et al for pregnant patients without SCD. In a cohort of 108 patients, most of the mothers (97%) were discharged without any major complications. However they also reported cases of severe maternal morbidity with ICU admission as a result of COVID-19 (18).

Previous studies have suggested that COVID-19 is more likely to progress into a severe and critical stage in the presence of risk factors such as older age, male gender, or underlying comorbidities such as hypertension, diabetes, obesity, or pregnancy (19). In our cohort the only constant risk factors were pregnancy and SCD comorbidities.

One patient in our study, patient #8 with HbSS genotype, was hospitalized due to VOC associated with ACS. However, in this patient a history of PE and VOC during a previous pregnancy already constituted a risk factor in itself (20,21). She had already been hospitalized

169 twice for VOC at 24 and 32 WG of the current pregnancy. A CT scan performed during the ICU
170 stay showed images of bilateral ground-glass opacities associated with
171 pulmonary condensation in the inferior lobes. Reports were inconclusive about the exact etiology
172 of these abnormalities although SARS-CoV-2 implication could not be excluded. Hence, it is
173 difficult to establish a causality but a hypothesis of the trigger effect of COVID-19 seems
174 plausible as infections participate in the pathogenesis of VOC (22).

175 In contrast with the literature data (14), none of the two women with HbSC genotype
176 presented with severe symptoms.

177 The association between VOC and COVID-19 in patient #1 is debatable. The VOC
178 occurred 10 days after the last symptom of COVID-19 in this patient and 20 days after a positive
179 PCR nasal swab. In some cases, SARS-CoV-2 can be detected in follow-up nasal swabs for a
180 longer period of time (23). However, no control PCR was performed in this case.

181 Another severe complication of COVID-19 is blood clotting abnormalities leading to
182 deep vein thrombosis, PE, and stroke (24) which is why we administered LMWH as preventative
183 treatment to all of our hospitalized patients. However, to date there is insufficient evidence to
184 determine the risks and benefits of prophylactic anticoagulants for patients hospitalized for
185 COVID-19 (25) and this subject has not yet been studied in the SCD population.

186 Daily low-dose aspirin for the prevention of an embolic event was prescribed for two of
187 our patients. However, the results of a recent meta-analysis suggest no association between the
188 use of aspirin and mortality in patients with COVID-19 (26) which was confirmed by a
189 randomized controlled trial (27).

190 Hydroxychloroquine, prescribed in patient #7 as a treatment of repeated spontaneous
191 miscarriages, is no longer considered to be an effective COVID-19 treatment (28).

Finally, some authors recommend that pregnant women with COVID-19 be monitored for fetal growth restriction (29). In this article, IUGR was related to the patient's history or had differential diagnosis confirmed by additional explorations.

The limitations of our study include a small sample size and its retrospective design. Another limitation is the heterogeneous study period. At the beginning of the pandemic, pregnant women with SCD without any severity criteria were systematically admitted to hospital. As we gained more knowledge about the course of COVID-19, outpatient treatment was preferred. This tendency could have influenced the analysis by overestimating the real need and length of hospitalization. Finally, confounding factors were numerous such as medical history and ongoing treatments.

In conclusion, in our study pregnant women with SCD mainly presented a mild form of COVID-19, independently of the genotype of SCD. COVID-19 impact on pregnancy outcomes was moderate and its course did not seem to differ from that reported in SCD-free patients. Further studies are needed to confirm these results. Comparison of the course of COVID-19 infection in this complex population of patients with that in a general population could contribute to a better understanding of the physiopathology of both diseases. Despite those reassuring data, the anti-COVID vaccination in this population of pregnant women seems crucial.

CONTRIBUTION STATEMENT

Concept and design of the study: KK, NCB, ED and MB; acquisition of data: KK, RV, FL, AS, SJ and YD; analysis and interpretation of data KK, RV, FL, YD, ED and MB; drafting the article

KK, RV and MB; revising it critically for important intellectual content: FL, AS, SJ, YD, NCB, ED and MB. All authors approved the final version of the manuscript to be submitted.

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Table 1. Characteristics of the study population

Baseline variables	**SCD + (n=8)**
Age (years), median (IQR)	30.5 (24 – 34.25)
BMI, median (IQR)	22 (20 – 24.25)
Ethnicity	
African, n (%)	8 (100%)
Primiparous, n (%)	1 (12.5%)
Previous obstetric complications	
History of FDIU/IUGR/PE	3 (37.5%)
History of cesarian section	3 (37.5%)
Sickle cell genotype	
SS, n (%)	4 (50%)
SC, n (%)	2 (25%)
Sbeta, n (%)	2 (25%)
History of VOC/ACS, n (%)	7 (87.5%)
Long term SCD therapy, n (%)	4 (50%)
Chronic respiratory disease, n (%)	3 (37.5%)
Smoking, n (%)	0 (0%)
Other therapies*	
Acetylsalicylic acid	2 (25%)
Hydroxychloroquine	1 (12.5%)
EADs	1 (12.5%)
ICS	1 (12.5%)
Gestational age on infection, median (IQR)	26.5 (20.25 – 35)
Treatment during Covid19 infection	
Enoxaparin	4 (50%)
Antibiotics†	1 (12.5%)

ACS – acute chest syndrome
EADs – anti-epileptic drugs
FDIU – fetal death in utero
ICS – inhaled corticosteroids
IUGR – intrauterine growth restriction
PE – preeclampsia
SDC – sickle cell disease
VOC – vaso-occlusive crisis
*Onset of these therapies was previous to current pregnancy or no later than 8 weeks of pregnancy
†Only antibiotics prescribed as active, full-length therapy are taken in consideration.

Table 2. Severity and outcome of the COVID 19 infection

COVID-19 outcomes	**SCD + (n=8)**
Days with persistent symptomatology, median (IQR)	5.5 (3 – 12.5)
Fever	4 (50%)
Cough	3 (37.5%)
Anosmia/ageusia	2 (25%)
Rhinitis	5 (62.5%)
Headache	3 (37.5%)
Hospitalization, n (%)	4 (50%)
Days of hospitalization, median (IQR)	4.5 (3.5 – 7,25)
Pulmonary affection, n (%)	1 (12.5%)
VOC/ACS complications during COVID infection, n (%)	1 (12.5%)
Requirement of supplemental O_2, n (%)	1 (12.5%)
Admission to ICU, n (%)	1 (12.5%)

ACS – acute chest syndrome
ICU – intensive care unit
SDC – sickle cell disease
VOC – vaso-occlusive crisis

Table 3. Obstetric complications and neonatal status

Pregnancy outcomes	**SCD + (n=8)**
Gestational age at birth, median (IQR)	38 (36 – 38)
Obstetric complications after remission	
Pre-eclampsia	1 (12.5%)
Preterm birth	2 (25%)
VOC	2 (25%)
Childbirth delivery methods (n=7)	
Labor induction, n (%)	5 (71%)
Cesarean section, n (%)	1 (14 %)
Fetal weight at birth (g), median (IQR)	2770 (2455 – 3545)
Fetal weight at birth (percentile), median (IQR)	56 (18 – 69)
Apgar, median (IQR)	10
pH, mean (SD)	7.31 (0.05)

SDC – sickle cell disease
VOC – vaso-occlusive crisis

Figure 1. Flow chart

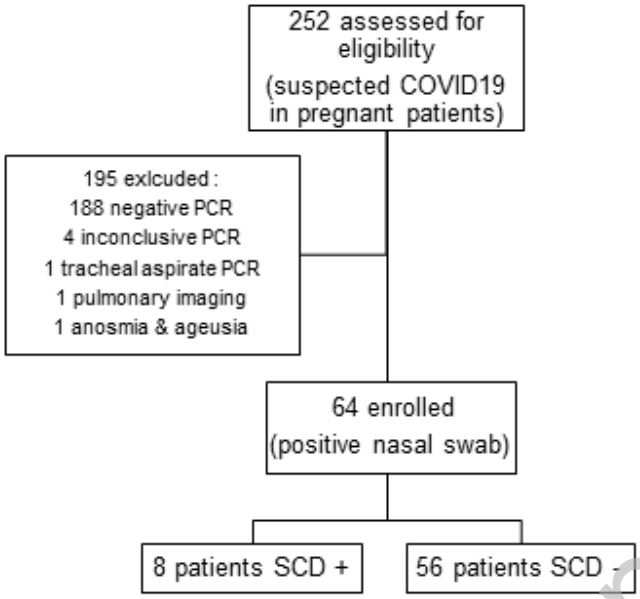

Table A.1. Overview of the 8 cases demographics, history of the illness and their respective pregnancy outcome.

№	Age	BMI	Parturition	Obstetric anamnesis	SCD genotype	Previous VOC/ACS	Long term SCD therapy	Other comorbidities/ treatments**	GA at infection	Treatment during Covid19	Days with persistent symptoms	Covid19 severity criteria	Hospital stay (days)	Pregnancy outcome & childbirth details (GA)	Fetus weight at birth (percentile)
1	29	22	2	No	SC	Yes (VOC +, VOC while pregnant +, ACS+)	No (exchange transfusion during previous pregnancies)	Chronic dyspnea	35	0	14 (rhinitis, sore throat, fever)	No	N/A	Labor induction for VOC 20 days after positive PCR, suspicion of ACS (38 weeks)	2770g (26p)
2	20	25	0	No	SS	No	Exchange transfusion, erythro - cytapheresis	Cerebral vasculopathy (aspirin); minor alpha thalassemia ; Epilepsy (FLNA gene) (EADs); Asthma (ICS) ; Splenectomy and cholecystectomy	22	0	3 (cough, rhinitis, muscle pain, anosmia)	No	N/A	Labor induction for IUGR¥ (35 weeks)	1950g (14p)
3	35	20	1	Caesarian for FHRA	Sß+	Yes (VOC +, ACS +)	No	No	26	LMWH† Oseltamivir‡ Amoxicillin‡	22 (fever, cough, rhinitis)	No (unspecified abnormalities on X-ray)	2	Spontaneous onset of labor (40 weeks)	3570g (56p)
4	24	27	2	No	SC	Yes (VOC +)	No	No	27	LMWH† Amoxicillin ‡	4 (fever, muscle pain, headache)	No	4	Labor induction for isolated proteinuria (38 weeks)	3580g (80p)
5	39	19	2	No	SS	Yes (VOC +, VOC while pregnant +)	Bloodletting	Restrictive lung disease	36	LMWH†	0 (asymptomatic)	No	5	Labor induction for cholestasis of pregnancy (37 weeks)	3520g (78p)
6	32	24	2	UIGR, caesarian for FHRA	Sß+	Yes (ACS +)	Exchange transfusion during this pregnancy	SCD retinopathy, ocular toxoplasmosis, Aspirin (history of IUGR)	15	0	3 (fever, fatigue, headache, sore throat)	No	N/A	VOC at 26 GA Labor induction for cholestasis of pregnancy , IUGR (38 weeks)	2540g (10p)
7	34	22	1	FDIU at GA of 5	SS	Yes (VOC +,	Hydroxy-urea	Hepatitis B, Hydroxychloroqu	8	0	7 (rhinitis,	No	N/A	IUGR (16 weeks)	N/A

№	Age	BMI	Parturition	Obstetric anamnesis	SCD genotype	Previous VOC/ACS	Long term SCD therapy	Other comorbidities/ treatments**	GA at infection	Treatment during Covid19	Days with persistent symptoms	Covid19 severity criteria	Hospital stay (days)	Pregnancy outcome & childbirth details (GA)	Fetus weight at birth (percentile)
				months*, 3 miscarriages		ACS +)	previously, exchange transfusion during this pregnancy	ne (obstetrical history)			headache, muscle pain, anosmia)				
8	24	20	1	Caesarian section for PE	SS	Yes (VOC+, VOC while pregnant +, current pregnancy with VOC+, ACS+)	No	factor XI deficiency	35	LMWH† Cefotaxime Spiramycin	12 (cough, rhinitis initially, dyspnea, VOC and ACS afterwards)	Admission to ICU, O2 therapy, VOC and ACS	14	Cesarean section for VOC/ Covid19/ Pre-eclampsia (35 weeks)	2115g (60p)

FHRA = fetal heart rate abnormalities, IUGR = intrauterine growth restriction , FDIU = fetal death in utero, , PE = preeclampsia ; VOC = vaso-occlusive crisis , ACS = acute chest syndrome, EADs = anti-epileptic drugs; ICS = inhaled corticosteroids; LMWH = low-molecular weight heparin; ICU = intensive care unit; * clinical assessment and laboratory investigations did not find underlying pathological cause ;** Onset of these therapies was previous to current pregnancy or no later than 8 weeks of pregnancy; † LMWH was prescribed at prophylaxis dose for all patient admitted to hospital; ‡ Antibiotics were initially prescribed to treat Listeriosis and stopped as soon as the etiology of the fever was found as guidelines suggest; antiviral were prescribed until influenza nasal swabs results came negative.¥ Genetic analysis showed FLNA gene mutation probably explaining the IUGR and the orofacial in fetus clefs which was found on ultrasound exam as well as the mother's epilepsy