PREGNANCY IN CADASIL: THE FLORENCE CENTER EXPERIENCE

I. Donnini[1], V. Rinnoci[1], S. Nannucci[1], R. Valenti[1], F. Pescini[2], G. Mariani[3], S. Bianchi[4], M. Dotti[4], A. Federico[4], D. Inzitari[1], L. Pantoni[1]

[1] NEUROFARBA Department - University of Florence - Florence
[2] Stroke Unit, Emergency Department - Azienda Ospedaliero Universitaria Careggi – Florence
[3] Gynecology and Obstetrics Department - University of Florence – Florence
[4] Department of Medical Surgical and Neurological Sciences - University of Siena - Siena

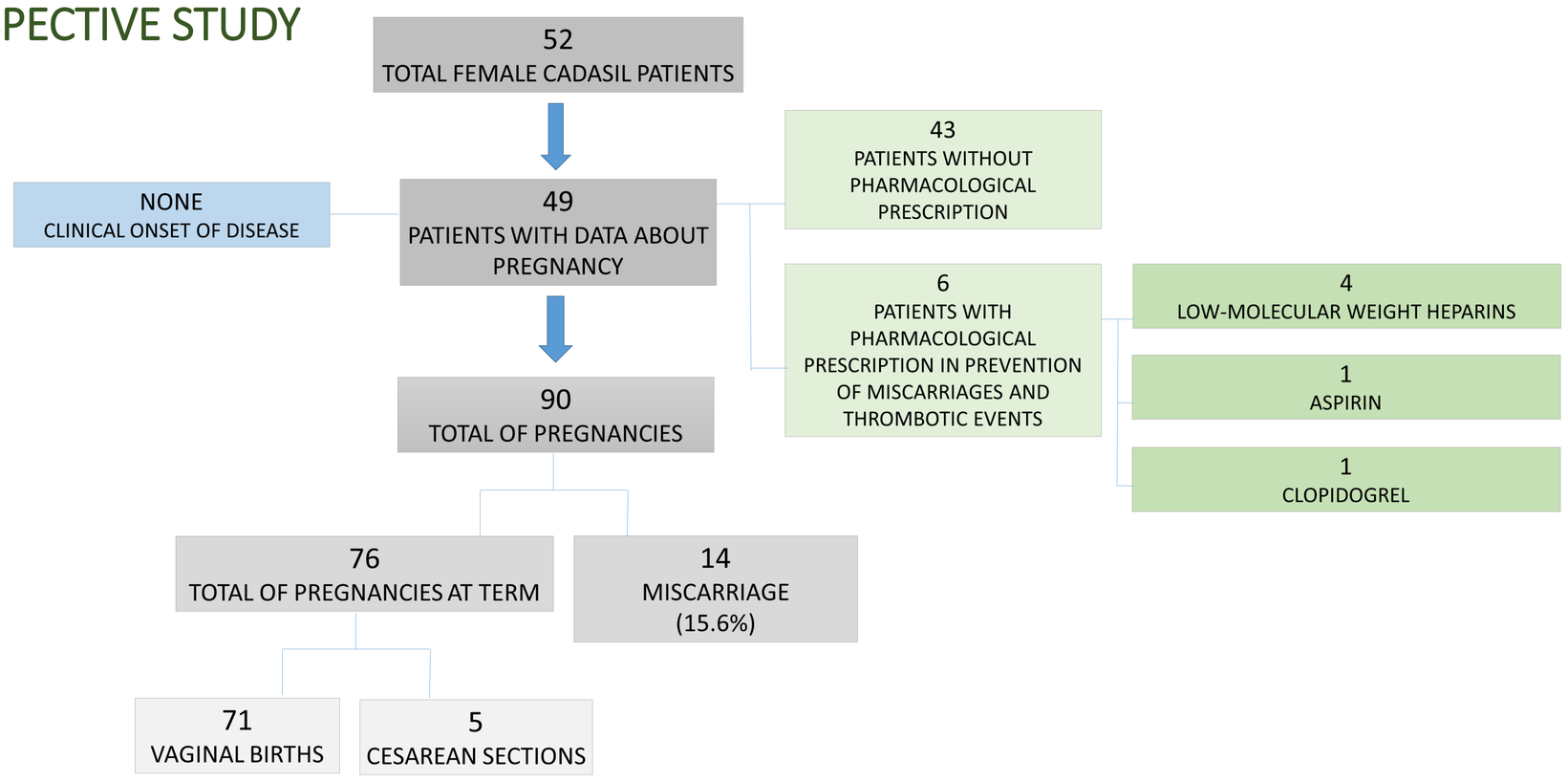
BACKGROUND

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an inherited cerebral small vessel disease caused by missense point mutations of the NOTCH3 gene and presenting with different clinical features, including migraine, mood disturbances, stroke, progressive cognitive impairment and disability. The presence of a NOTCH3 mutation in pregnant women is frequently considered to increase the thrombotic risk and these patients are often prescribed with anti-thrombotic drugs. This decision is not evidence-based because data about pregnancy outcome in women with CADASIL in comparison with the general population of pregnant women are almost lacking. [1] Therefore, it is difficult to give advice to CADASIL women who are planning pregnancy concerning the use of these drugs.

OBJECTIVE

To describe the experience in our CADASIL patient population concerning the occurrence and outcome of pregnancies.

1.RETROSPECTIVE STUDY



We reported available data about 49 pregnancies in 52 CADASIL patients.

In our sample, we recorded 15% of spontaneous pregnancy loss, in line with the epidemiologic data available for the healthy population [2].

Differently from a previous report in a Finnish population,[1] we did not record any focal neurological symptom during the gestation. In one case, the puerperium was complicated by a psychotic episode. [3]

In addition, we did not find consistent troubles in delivery, with only 5 cesarean sections, of which only two in emergency and the others three electives.

2. PROSPECTIVE STUDY

Patients	Age at pregnancy	Newborn weight (percentile)	Types of delivery	Gestational age at birth	Pregnancy complications: -Pre-eclampsia -Placental insufficiency -Glucose metabolism alterations	Drugs-administered during pregnancy	Alteration of pregnancy checkup
1	26	71th	CS	36 weeks	None	None	None
	30	74th	VD	37 weeks + 6 days			
2	34	52th	VD	40 weeks + 4 days	Flat OGT curve	LMWH until 39th weeks	Mild proteinuria during last weeks of pregnancy
3	30	17th	VD	40 weeks + 3 days	None	None	None
4	35	39th	VD	42 weeks	None	LMWH started 1st trimester stopped at the labour	None
5	34	19th	VA VD	39 weeks	None	None	None
6	31	90th	CS	41 weeks	Hyperinsulinemia	LMWH	Albuminuria in renal failure due to minimal change glomerulopathy
	34	84th	CS	38 weeks + 3 days	Pre-eclampsia	LMWH + ASA 100 mg/day until the 5th month.	

VD (vaginal delivery); CS (cesarean section); VA (Vacuum-assisted); OGT (oral glucose tolerance), LMWH (low-molecular-weight heparin: Enoxaparin sodium 4000 UI/day)

Our prospectively experience of pregnancy in 6 CADASIL patients does not permit to reach definitive conclusions but give us some suggestions :

- CADASIL does not appear to correlate with gestational complications (we recorded only 3 patients with disorder of glycaemia tolerance and one pre-eclampsia status in story of renal failure),
- birth weight adjusted for gestational age follows a normal distribution, included between 10th to 90th percentile (in line with the standard values of the healthy population),
- antithrombotic drugs were administered only in few cases and basically for the miscarriage prevention in predisposed patients (even if in two cases, they were prescribed only for the presence of the CADASIL pathology).

DISCUSSION

These data support the hypothesis that CADASIL is not associate with severe pregnancy problems or miscarriage related to vascular alterations.
In support of this assertion, a histopathological study comparing fetal tissues in CADASIL and controls (brain, heart, skin, muscle, and placenta) did not reveal positive NOTCH3 staining of vessels or other structures. Moreover, CADASIL fetal vessels did not contain GOM, the morphology of the smooth muscle cells (VSMC) was not different from that of the control fetus, and no changes were seen in other vascular wall structures, including the endothelium suggesting that arterial wall and VSMC abnormalities in CADASIL initiate later in the course of the disease. [4]

CONCLUSION

A diagnosis of CADASIL is not associated with an unfavorable outcome of pregnancy either for women and fetuses.
CADASIL patients and treating physicians should be reassured that pregnancy can be safely initiated in this disease.
There is no clear evidence to support a specific preventive antithrombotic treatment during pregnancy in CADASIL.
Further larger studies are needed to definitely confirm these conclusions.

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