Brief Notes on Pregnancy, Prenatal Diagnosis, and Preimplantation Procedures in NF1

20

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Contents

Few reports in literature have investigated pregnancy in NF1. Some of them remain anecdotal, other are small case series published many years ago regarding only severe cases in which are described a high rate of hypertension, preeclampsia, intrauterine growth restriction, preterm labor, and cesarean delivery in NF1 pregnancies [1, 2]. On the contrary, in 1996 a further study on 105 patients failed to confirm these data and more recent reviews in 2010 and 2017 dedicate to this topic only brief comments [3–5].

Nevertheless, Terry et al. in 2013 decided to fill this gap using a large population-based US national registry (United States National Inpatient Sample, NIS) to investigate pregnancy complications in women with NF1, collecting data from 1988 to

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G. Tadini et al. (eds.), *Multidisciplinary Approach to Neurofibromatosis Type 1*,
https://doi.org/10.1007/978-3-319-92450-2_20

Table 20.1 Odds ratio for outcomes of interest between NF1 patients and healthy controls

	NF1 (%)	Control (%)
Gestational hypertension	3.5	2.3
Preeclampsia	9.7	3.5
IUGR[a]	7.9	1.5
Preterm labor	12.4	6.9
Cesarean delivery	43.3	25.7
Stillbirth	0.9	0.5

[a]*IUGR* Intrauterine growth retardation

2009. During this period, NIS registered 19,750,702 pregnancy-related admissions and 1533 were associated with a diagnosis of NF1 [6].

Using data from this study, fertility seems to be normal in NF1 women and they will experience one or more pregnancies. Usually, higher mortality rate related to the disease does not comprise the reproductive years. NF1 pregnant women at the time of hospital admission were in majority between 20 and 35 years of age, 1 year younger than control population and they came from lower socio-economic group. Furthermore, they had a higher rate of pre-existing hypertension (4.7% vs 1.8%) and renal disease (0.8% vs 0.3%).

The odds ratio for outcomes of interest by at-risk group is presented in Table 20.1.

Moreover, NF1 patients experienced more commonly cerebrovascular events both during pregnancy and in the peripartum period. In contrast, no acute cardiac complications were observed and the in-hospital mortality rate was the same in two groups.

Data from Table 20.1 show clearly the higher rate of gestational hypertension and preeclampsia, IUGR, and preterm labor. Even analyzing NF1 group excluding patients with pre-existing hypertension and vascular renal disorders, the results confirm that higher risk of pregnancy complications is not due to pre-existing conditions.

Cesarean sections (43.3% vs 25.7%) were more frequent in NF1 population, even if the authors recommend being cautious analyzing this data because of the preference for more conservative management in NF1 patients even in the absence of complications.

In summary, we can consider that this large analysis (>1500 patients) identified increased risks for many complications that were unreported in previous literature and claimed for counsel in NF1 affected families planning for spontaneous or assisted conception. Furthermore, this study was unable to obtain information on neonatal course.

Finally, we have to remember that there are at least two well-established phenomena during NF1 pregnancy:

1. The increase in number and size of cutaneous neurofibromas and plexiform lesions during pregnancy
2. The rare presence of plexiform tumors on external genitalia and retroperitoneal and/or pelvic masses may interfere with the course of gestation and/or complicate delivery

20.1 Prenatal and Preimplantation Genetic Diagnosis

Also on this argument medical literature is far to be abundant. First, we have to underline that couples at risk for NF1 recur to the prenatal diagnosis (PD) rarely. PD is possible in NF1 families at risk only when molecular analysis reveals pathogenic variants. Usually, detection of family segregated mutation is performed using chorionic villi sample analysis and less frequently with fetal blood sampling [7, 8].

In a recent study performed in the Netherlands [9] analyzing molecular diagnosis of NF1 in a span of 18 years, about 2000 index cases were analyzed. Among them, 46 (2.4%) prenatal diagnoses were performed in 28 families at risk for NF1. Twenty-nine of forty-six index cases received a diagnosis of heterozygosity for the familial pathogenic mutation: from these data the authors emphasize there is a need for prenatal NF1 testing.

Ultrasound and RMI are also used in selected cases for prenatal diagnostic purposes [10].

Preimplantation genetic diagnosis (PDG) allows testing an embryo generated from in vitro fertilization before uterine transfer for specific mutations. In contrast, preimplantation genetic screening may detect chromosomal aneuploidies.

A recent study [11] on a cohort of 1356 embryos obtained from in vitro fertilizations at risk for NF1, 1322 were available for further studies and 1080 obtained a diagnosis. From these 1080 diagnoses, 483 were unaffected and 577 were affected with NF1. In the unaffected generated cycles, 22 had a confirmed unaffected live birth.

Finally, the association of pregnancy complications seen in NF1 women claims for adequate attention in patients who use assisted reproductive technologies because of the increased risk of multiple pregnancies.

Funding Sources None.

Conflict of Interest None declared.

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