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Review

What we do not know about pregnancy in hereditary neuromuscular disorders

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ABSTRACT

Only sparse information is available concerning the relationship between pregnancy and hereditary neuromuscular disorders. This review deals with several issues like the effects of such conditions on female fertility (myotonic dystrophy type 1 and mitochondrial disorders), on the risk to the fetus (myotonic dystrophy type 1 and Charcot-Marie-Tooth disease), on the ability to carry pregnancy and its complications (markedly increased preterm labor in myotonic dystrophies and spinal muscular atrophy), on the labor and its possible need for interventions (myotonic dystrophy type 1, facioscapulohumeral dystrophy and Charcot-Marie-Tooth disease). It also discusses the question of pregnancy effects on the course of the inherited neuromuscular disorders (myotonic dystrophies, spinal muscular atrophy, facioscapulohumeral dystrophy, Charcot-Marie-Tooth disease, congenital myopathy and limb-girdle muscular dystrophy). The aim of this critical review is to point at pregnancy-related problems that need further research.
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1. Introduction

Most physicians who follow patients with various neuromuscular disorders are faced with issues and dilemmas related to pregnancy in their female patients. Many questions are asked by the patients, their families and also by their attending obstetrician when planning pregnancy and many additional queries arise later during the pregnancy and afterwards. Yet we have little information in the medical literature to rely upon when giving answers. Although the topic of pregnancy and neuromuscular disorders has been reviewed [1,2], the focus in these reviews was on listing the available data in individual diseases. Most of the current knowledge is based on few reports which used mainly retrospective information. This is particularly true for hereditary neuromuscular diseases where the number of pregnancies recorded in the literature is small. The presently available information is not necessarily satisfactory to the many patients who do want to have children despite their illness and want medical consultation about the various aspects of pregnancy, beyond the genetic counseling, including the impact of pregnancy and having children on their clinical status.

In this review we will try to list the important pregnancy-related issues and group the known information from the various diseases in relation to these issues. We will not discuss neuromuscular diseases that are caused by pregnancy (for this see [1]). There are important additional issues related to the acquired disorders (mainly in the inflammatory or autoimmune diseases like myasthenia and myositis). The main concern in the acquired conditions, as expressed in the literature reviews, has been the effect of therapy on the fetus, during and after (lactation) the pregnancy. Also, potential aggravation of such conditions by the pregnancy is a more complicated problem because stoppage or reduction of therapy may be required and the mechanism of aggravation may also be related to the complex relationship between the immune and the hormonal systems. Because of these reasons our review will not discuss these acquired conditions and will remain limited to the hereditary disorders.

Most of the information is based on retrospective studies with questionnaires sent to the patients and their families, and certainly this would not comply with 'evidence-based medicine' criteria. Our critical review is aimed at creating a more organized way of data recording in order to make the title of the next review more positive.

2. Pregnancy-related issues for the neuromuscular patient (see Table 1)

2.1. Will the disease affect fertility?

This question is probably raised mainly in societies which cherish the family continuity and productivity. In contrast to the well-known male infertility described in myotonic dystrophy (DM), the issue of female fertility in this condition remains controversial. Some investigators found decreased fertility associated with menstrual disturbances [3], or related to gonadal dysfunction [4] expressed as poor responsiveness to controlled ovarian stimu-

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Table 1
Pregnancy-related issues in hereditary neuromuscular disorders.

		Decreased fertility in women	Increased risk of miscarriage	Preterm labor	Operative delivery	Perinatal death or other risk to fetus	Onset or worsening of muscle symptoms during pregnancy
Myotonic dystrophies	DM1	+ [3–6] – [7]	– [10]	+ [10,13,22]	+ [22]	+ [10,22]	Weakness [13], myotonia [34]
	DM2	n.r.	– [11]	+ [11]		– [11]	+ [11,33]
Non-dystrophic myotonias		n.r.	n.r.	n.r.		n.r.	+ [35–37]
Charcot-Marie-Tooth disease		n.r.	–	– [16]	+ (Forceps usage) [12]	+ (Abnormal presentations) [12]	+ [16,38]
Facioscapulohumeral dystrophy		n.r.	– [15]	– [17]	+ [17]	n.r.	+ [15,17]
Mitochondrial disorders		+ [8,9]	n.r.	n.r.		n.r.	n.r.
Spinal muscular atrophy		n.r.	n.r.	+ [14]		n.r.	+ [14]
Congenital myopathies		n.r.	n.r.	± [15]		n.r.	+ [15]
Limb-girdle muscular dystrophies		n.r.	n.r.	n.r.		n.r.	+ [15,32]

+ Indicates present.
– Indicates absent.
n.r. Indicates not recorded.
± Indicates suspected to be present.
Refs. = references between brackets

lation even in mildly affected DM females [5,6]. In contrast, in a case-controlled study in an area known for its exceptionally high DM type1 (DM1) prevalence, no relationship between female fertility and the disease could be found [7]. If a relationship between DM and women's infertility does exist, its rate is unknown and the contribution of each of the above-mentioned potential mechanisms to the problem is not clear. It is of note that despite the observed ovarian abnormality many women with DM1 do have apparent normal fertilization rate. The fertility topic was not studied systematically in any other hereditary disease, but there are case reports of gonadal dysfunction in mitochondrial disorders as well [8], and in particular in patients with progressive external ophthalmoplegia due to DNA polymerase γ (POLG) mutations who have premature menopause (around age 30) [9]. In the DM1 study [5], carriers of X-linked diseases including Duchenne dystrophy were used as control group and normal response to ovarian stimulation was found.

2.2. Are there special risks to the fetus (beside the genetic implications)?

There is an observation of increased perinatal death (up to 15%) in DM1, but it seems to be mainly due to fetuses affected by congenital DM in conjunction with pregnancy complications [10]. Thus, this risk is mainly related to the overall genetic risk. This conclusion is partly supported by the fact that in the milder DM type 2 (DM2) none of 79 pregnancies was associated with perinatal death [11].

A significant increased frequency of abnormal presentations (e.g. breech or abnormal cephalic presentations) is observed in Charcot-Marie-Tooth (CMT) disease. The authors hypothesize that this is perhaps due to decreased motility in fetuses with the dominantly transmitted CMT genotype [12], although it cannot be ruled out that the maternal condition is the cause. It should be noted that perinatal mortality was not increased in the CMT study [12].

2.3. Will the disease affect the ability to carry a pregnancy?

This in our experience is an issue raised not only by the patients but also by the gynecological/obstetrician colleagues. They look for professional reassurance, especially in the clearly symptomatic patients, and for objective measures to assess the problem. Unfortunately it is currently difficult to provide such data.

The first question is whether there is an increased risk of miscarriage in patients with muscle weakness. In DM1 11% miscarriage rate was recorded and considered to be within the range of normal population [10]. Similarly 13% of 96 pregnancies in DM2 ended in early miscarriage [11]. Increased early miscarriage rate was also not observed in other hereditary neuromuscular conditions (e.g. fascioscapulohumeral dystrophy (FSHD) and CMT), thus it seems safe to assume that it is not a risk feature in this group of diseases. However, late spontaneous abortions were seen in 4% of DM1 women who were already clinically symptomatic, thus this may be a specific risk in this condition. Increased risk of ectopic pregnancies (4% of all gestations) is suspected in DM1, possibly related to impaired tube motility due to smooth muscle involvement in this disorder [10]. The involvement of smooth muscle in DM1 seems to be unique among the various hereditary myopathies, but the issue was not formally studied in any other such muscle disease.

Preterm labor is common in several, but not all, hereditary neuromuscular disorders. Its rate is markedly increased in DM1 and only half of the pregnancies in this condition reach a full completion. Of the 50% preterm pregnancies, about 30% do reach the 'safer' length of 35–38 weeks and only 20% are terminated before week 34 [10]. The above figures are true only for DM1 women with clinical signs of the disease already at pregnancy time. Importantly, the increased risk of preterm labor was mainly found in pregnancies with affected fetuses (i.e. carrying the DM1 gene defect) [13], suggesting that the fetus status determines this complication. However, in DM2 preterm labor is also a frequent feature, as 50% of pregnancies in mothers with overt signs are terminated before their expected time [11]. Since congenital DM2 is extremely rare (if at all existing) there must be another explanation for the inability to reach term in the myotonic dystrophies. Increased incidence of premature delivery was also recorded in spinal muscular atrophy (SMA) [14] and it was suspected to be the case in a group of patients with congenital myopathies [15], but the numbers were too small to draw firm conclusions for these conditions. In contrast no increase in pre-

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