

Sabine Rudnik-Schöneborn* and Miriam Elbracht

Charcot-Marie-Tooth neuropathy and pregnancy: general and specific issues

<https://doi.org/10.1515/medgen-2020-2031>

Received May 11, 2020; accepted September 2, 2020

Abstract: Background: Charcot-Marie-Tooth (CMT) neuropathies represent an important group of neuromuscular disorders and are mostly autosomal dominantly inherited. The question, if there is a higher complication rate in pregnancy and delivery in CMT neuropathy and if there is a possible influence of pregnancy on muscles and nerves themselves, is important for medical care and prepregnancy counselling of affected women.

Objectives: In this review we first address general issues of the clinical picture of CMT disease and physiological adaptations in pregnancy. In the second part of this paper we summarise specific results of two comparable studies on the obstetric history of women with CMT neuropathy in order to address the obstetric complication rate, newborn vitality, possible deterioration of CMT in or after pregnancy and personal attitudes. The results are based on two combined cohort studies with 21 and 54 participants.

Results: We documented 148 pregnancies (129 deliveries), resulting in 131 infants. There were no increased complication rates in the recorded pregnancies. Miscarriage rate was 12.8% and thus as high as in unaffected women. Deliveries were not associated with specific risks; there were no increased preterm deliveries, vaginal operations or caesarean sections, and no increased postpartum haemorrhages. Newborn vitality was normal and birth measurements were within the normal range. A deterioration of CMT related symptoms was reported in about one-third of the pregnancies and after delivery, however, the functional impact on everyday life was rather low in classical CMT. Most women expressed a positive attitude towards having own children and family life but those with a larger handicap would recommend medical advice and assistance in caring for the family.

Discussion and conclusion: Pregnancy can be safely undertaken in women with classical CMT, despite the fact that a negative influence on the disease course appears possible. The data of a Norwegian study which found

higher rates of presentation anomalies and operative deliveries and a higher risk of postpartum haemorrhage have not been confirmed in our study.

Keywords: Charcot-Marie-Tooth neuropathy, pregnancy, delivery, influence on disease course, recommendations

Introduction

Parenthood is a highly desirable aim in life for many couples, and this also applies to women affected by hereditary neuropathies. Information is still scarce about the effect of the individual neuropathy on the course of pregnancy and delivery and conversely the effect of pregnancy on muscles and nerves themselves.

Important questions are [1]: Will the disease affect fertility? Are there increased risks to the unborn or newborn child? Are there more obstetric complications during pregnancy? Will there be a need for special measures during delivery? Is there a greater risk for operative deliveries and anaesthesia? Will the course of the disease be affected by a pregnancy? Is there a genetic risk to children? How do mothers cope with their role and increasing demands of family life? In 2010 a workshop was held to address these aspects, discussing the most important issues of pregnancy and delivery in women with neuromuscular disorders of childbearing age [2].

We here summarise general aspects for pregnancy in women with neuromuscular diseases and address specific points for Charcot-Marie-Tooth (CMT) disease, based on two studies in Germany with a comparable study design [3, 4]. In the whole cohort, data were available of 75 women with clinically or genetically confirmed CMT disease, who delivered 131 children. In Norway pregnancy outcome was investigated more than 15 years ago in a series of 49 patients with known CMT neuropathy. Patient data were extracted from the Norway national birth registry [5]. In this cohort a higher risk of postpartum bleeding, uterine atony and placental anomalies and an increased rate of abnormal presentation were found. Operative deliveries were recorded to be twice as frequent in comparison to a control population.

*Corresponding author: Sabine Rudnik-Schöneborn, Institute of Human Genetics, Medical University Innsbruck, Peter-Mayr-Str. 1, 6020 Innsbruck, Austria, e-mail: sabine.rudnik@i-med.ac.at

Miriam Elbracht, Institute of Human Genetics, Medical Faculty, RWTH Aachen University, Aachen, Germany

General aspects

Clinical picture of CMT

Women with CMT who plan to have a family are mostly affected by classical CMT disease. First symptoms usually occur in childhood or early adulthood with slowly progressive distal weakness and wasting. This leads to an abnormal gait, dropped foot and foot deformities. Weakness of hand muscles and deformities of fingers usually occur later in the course of the disease. CMT disease is most frequently autosomal dominantly inherited with a broad variability of age at onset, severity of symptoms and progression of disease. Despite the fact that many patients require special walking aids, only a small proportion of less than 5 % loses the ability to walk. However, there are many rare subtypes with atypical clinical findings and specific gestational implications [4].

Physiological changes in pregnancy

There are significant physiological changes occurring early in pregnancy and continuing throughout gestation [6]. The increase in plasma volume of 45–50 % has haematological effects such as a dilutional anaemia and a reduction in total plasma proteins. Thromboembolic risks are higher due to hormonal related increased clotting (and venous stasis). Maternal heart rate increases by about 20 %, and other cardiological changes include a rise in stroke volume and cardiac output by 30–50 %, while there are only minor changes in blood pressure. Respiratory changes include a rise in tidal volume and oxygen consumption starting in the second half of pregnancy, however routine spirometric tests remain essentially unchanged. There are immunological changes in pregnancy with infections being more common. Hormonal adaptations of the musculoskeletal system result in softening of ligaments, joints and smooth muscles but with no significant changes in skeletal muscles.

Due to the physiological adaptations and the increasing weight in pregnancy many patients with neuromuscular diseases experience a loss of mobility and strength during their second half of pregnancy which usually improves within weeks or months after delivery. The question of a lasting deterioration of muscle weakness caused by pregnancy and delivery is difficult to assess, since most hereditary disorders are progressive. The situation in pregnancy is more likely to remain unchanged if the patient has had long phases of clinical stability in her disease course.

Decisions when contemplating pregnancy

The process of decision making when contemplating pregnancy should start with the alternatives in the preconception planning phase [2]. Since CMT disease is most frequently autosomal dominantly inherited, there is often a 50 % recurrence risk to offspring. Prenatal or preimplantation genetic diagnosis may be discussed in the context of genetic counselling. Different pregnancy periods have to be considered in maternity care: the embryonic phase in the first trimester (miscarriage risk, teratogenicity of medication, prenatal testing), the foetal period in the second and third trimesters (foetal growth and development), delivery (presentation of foetus, spontaneous or operative delivery) and the postpartum period.

Results of two subsequent pregnancy studies in CMT disease

In Germany a pro- and retrospective assessment of pregnancy and delivery in patients with various hereditary neuromuscular disorders has been conducted since the early 1990s. It requires active participation of patients and has been successfully applied to many different conditions [7]. Patients who had completed at least one pregnancy are invited to fill in questionnaires on their diagnosis, natural history and pregnancy experiences. Upon consent further medical data are recorded for the neurological disease, genetic diagnosis (if applicable) and the obstetric histories. For CMT disease data of two cohorts were available: In the first cohort, data of 21 German and Australian women were documented retrospectively in the first half of 1992 [3]. Diagnosis of CMT relied on clinical criteria in the first cohort, since a genetic diagnosis was not possible before 1992. The second cohort of 54 women was recruited within a cross-sectional study of the German CMT NET between 2016 and 2019 [4]. In 51 of 54 patients a genetic diagnosis was established, of whom 40 (78.4 %) had a *PMP22* duplication, corresponding to CMT1A. The combined CMT cohort comprises 75 patients who had a total of 148 pregnancies and 129 deliveries (Fig. 1).

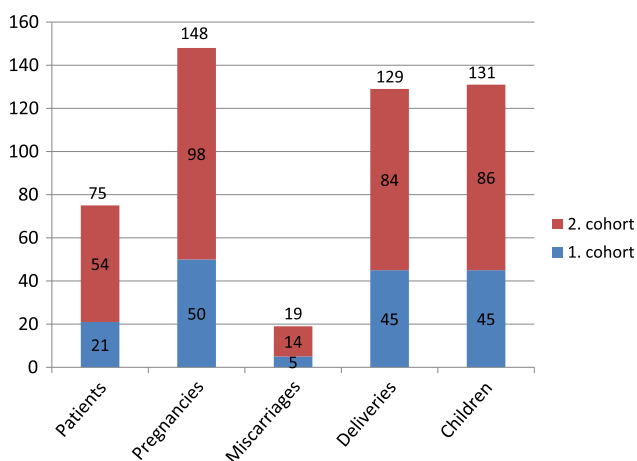
Course of pregnancy and delivery

Obstetric complications in both cohorts were not significantly different from a normal reference population (Table 1) [7]. Miscarriages occurred in 12.8 % of gestations. Only 2.2 % patients had gestosis/hypertensive disease in

Table 1: Obstetrical complications in the two CMT study cohorts and in the combined cohort compared with the normal reference population [7].

	Miscarriages	Gestosis	Preterm delivery (<37 weeks gestation)	Non-vertex presentation of foetus	Caesarean section	Operative delivery
First cohort	5/50 11.1 %	1/45 2.2 %	1/45 2.2 %	1/18* 5.6 %	5/45 11.1 %	4/45 8.9 %
Second cohort	14/98 14.2 %	2/84 1.7 %	6/84 7.1 %	8/84 9.5 %	31/84 36.9 %	3/84 3.6 %
CMT-Combined	19/148 12.8 %	3/129 2.2 %	7/129 5.4 %	9/102 8.8 %	36/129 27.9 %	7/129 5.4 %
Reference population	15 %	7 %	7 %	4 % (at term) 12 % (preterm)	15–30 %	6–8 %

* Data not systematically assessed and extracted from ref. [7].

**Figure 1:** Overview of the different study cohorts.

pregnancy, and there were no reports of polyhydramnios or placentation anomalies (placenta praevia or placenta accreta). Preterm delivery (below 37 weeks gestation) occurred in both cohorts with a slightly lower frequency than expected in the normal population. Presentation anomalies (breech or transverse presentation) were documented in 8.8 % and instrumental delivery (vacuum or forceps delivery) in 5.4 % of completed pregnancies (Table 1). The number of caesarean deliveries increased in the reference population during the study period from 15 % to 30 % and was within normal limits in our two study cohorts (11.1 % and 36.9 %). The proportion of primary and secondary caesarean sections was largely constant comprising about 50 % of each. In all caesarean sections, where details of anaesthesia were documented, spinal anaesthesia was administered in about 80 % and general anaesthesia in about 20 % of sections [4]. Generally, following Orphanet recommendations [8], regional anaesthesia is preferred over general anaesthesia in women with CMT neuropathy, however

there is no clear rationale for this recommendation. In our study we did not find an adverse effect of general anaesthesia [4]. This is important information for patients who may have contraindications for epidural anaesthesia, e. g., patients with severe scoliosis or after spinal operation. In terms of analgesia or other medications, it has to be taken into account that neurotoxic substances should be avoided in CMT disease [8].

Newborn vitality

In both cohorts there was no increased neonatal morbidity and mortality as regards birth measurements, Apgar scores and clinical information. One newborn twin died of neonatal asphyxia in the context of prematurity being born at 29 weeks of gestation.

Influence on disease course

The severity of the disease – more progression rather than age at onset – influences the observation of any pregnancy related changes. The proportion of women who experienced a deterioration of symptoms in pregnancy was remarkably similar in both cohorts, comprising 37.8 % of pregnancies. After delivery worsening of neuropathy was reported in 31.1 % of gestations of the first cohort and in 37.5 % of the second cohort. However, in retrospect it was not possible to further evaluate an aggravating effect of gestation on the natural history of CMT disease. In the total cohort a deterioration was reported in pregnancy in 37.8 % (48 of 127) and after delivery in 34.6 % (44 of 127) of instances. Only in 2.4 % (3 of 127) of gestations an improvement in pregnancy or in 9.4 % (12 of 127) an improvement after delivery was noticed. For most patients deterioration

had no significant impact on the handicap in everyday life. No adverse effects of anaesthesia were reported. While we found a correlation between age at onset and a negative influence of pregnancy on the disease course in the first cohort, this was not the case in the second cohort. Walking was maintained in nearly all patients who were still mobile at the beginning of pregnancy. There were four patients with a classical CMT disease who required walking aids at the time of delivery. One patient experienced significant worsening in and after pregnancy and was confined to a wheelchair and unable to rise from a sitting position following her first delivery (patient 2 from ref. [3]). Three patients were documented in the second cohort [4]. One patient with CMT2A used walking aids from early adulthood and did not report a change in mobility in her only pregnancy. Two patients with CMT1A were partly chairbound from youth and felt that there was no change or rather an improvement of motor functions in and after pregnancy.

Personal attitude and recommendations to other patients

The majority of participants stressed the value of a fulfilled family life and had a positive view of having children, despite being aware of the challenges associated with pregnancy (Fig. 2). Medical advice and expert opinion for specific medical interventions are recommended. Important issues are assistance and support in caring for the family. Women with a significant handicap will generally need help in the household and may have limited physical reserves for their tasks as a mother. Personal recommenda-



Figure 2: Family picture of a study participant with CMTX who stressed the importance of medical advice and the awareness of challenges associated with pregnancy and who is active in her local self-support group.

tions include a positive attitude and trust in own abilities. In the view of many mothers, children grow up in a different responsibility facing her mother's handicap.

Practical conclusions

- There are no increased complication rates in pregnancies of women with classical CMT neuropathy. Miscarriage rate is within normal limits.
- Deliveries in women with CMT disease do not warrant specific measures; there are (i) no increased preterm deliveries, (ii) normal rates of vaginal operations and caesarean sections and (iii) no increased postpartum haemorrhages.
- Newborn vitality is normal, birth measurements are within the normal range.
- A deterioration of CMT related symptoms are recorded in about one-third of the pregnancies and after delivery, and we consider the functional impact of this observation on everyday life rather low in classical CMT. We did not find an adverse effect of regional or general anaesthesia on the outcome of pregnancy or the disease course.
- Most women have a positive attitude towards having own children and family life but would recommend medical advice and assistance in caring for the family.
- Women with CMT disease who become pregnant should seek advice of an interdisciplinary care team, including obstetricians, neurologists, geneticists, anaesthetists and midwives, if possible.

To conclude, pregnancy and delivery seem to be safe for the vast majority of classical CMT patients, specifically for women with *PMP22* gene duplication. Nonetheless, further studies on clinical and genetically subdivided groups are required to further identify patients who may have specific gestational risks in order to improve medical care in women with hereditary neuropathies.

Funding: The study has been supported by the German network on Charcot-Marie-Tooth neuropathies (CMT NET, 01GM1511B and 01GM1511D) funded by the German Federal Ministry of Education and Research.

Conflict of interest: The authors report no conflict of interest.

References

- [1] Argov Z, de Visser M. What we do not know about pregnancy in hereditary neuromuscular disorders. *Neuromuscul Disord.* 2009;19:675–9.
- [2] Norwood F, Rudnik-Schöneborn S. 179th ENMC international workshop: Pregnancy in women with neuromuscular disorders. 5–7 November 2010, Naarden, The Netherlands. *Neuromuscul Disord.* 2012;22:183–90.
- [3] Rudnik-Schöneborn S, Röhrig D, Nicholson G, Zerres K. Pregnancy and delivery in Charcot-Marie-Tooth disease type 1. *Neurology.* 1993;43:2011–6.
- [4] Rudnik-Schöneborn S, Schöneborn R, Thiele S, Walter M, Reinecke L, Sereda MW, Elbracht M. Pregnancy outcome in Charcot-Marie-Tooth disease: results of the CMT NET cohort study in Germany. *Eur J Neurol.* 2020;27:1390–6.
- [5] Midelfart Hoff J, Gilhus NE, Daltveit AK. Pregnancies and deliveries in patients with Charcot-Marie-Tooth disease. *Neurology.* 2005;64:459–62.
- [6] O'Day M. Cardio-respiratory physiological adaptation of pregnancy. *Sem Perinatal.* 1997;21:268–75.
- [7] Awater C, Zerres K, Rudnik-Schöneborn S. Pregnancy course and outcomes in women with hereditary neuromuscular disorders: comparison of obstetric risks in 178 patients. *Eur J Obstet Gynecol.* 2012;162:153–9.
- [8] Orphanet. Handlungsempfehlung zur Anästhesie bei Patienten mit Charcot-Marie-Tooth Erkrankung. https://www.orpha.net/data/patho/Ans/de/Charcot-Marie-ToothSyndrom_ES_de_ANS_ORPHA166.pdf. Accessed on 19/03/2020.

Prof. Dr. med. Sabine Rudnik-Schöneborn

Institute of Human Genetics, Medical University Innsbruck,
Peter-Mayr-Str. 1, 6020 Innsbruck, Austria
sabine.rudnik@i-med.ac.at

Dr. med. Miriam Elbracht

Institute of Human Genetics, Medical Faculty, RWTH Aachen
University, Aachen, Germany