Background and purpose: Systematic research on the effect of Charcot–Marie–Tooth (CMT) disease on the outcome of pregnancy and conversely the effect of pregnancy on neuropathy is still sparse.

Methods: A clinical cohort study and cross-sectional study within the German CMT-NET was conducted between 2016 and 2019. Inclusion criteria were a confirmed diagnosis of CMT and at least one completed pregnancy after 1990. All participants agreed to fill in questionnaires and have their medical files reviewed.

Results: The study group comprised 54 women with a total of 98 pregnancies. The mean age at onset of CMT disease was 12.6 years (range 0–37 years). Fifty (92%) patients had autosomal dominant CMT; two patients each (4%) had X-linked and autosomal recessive CMT. Forty patients (74%) had a PMP22 gene duplication (CMT1A). Obstetric complications did not differ significantly from a German reference population, neither in the whole group nor in the CMT1A group. Overall there was no increased newborn morbidity and mortality. About one-third of patients reported exacerbation of CMT disease in or after pregnancy. No adverse effects of anaesthesia were reported. Most participants stressed a positive attitude and awareness of challenges associated with pregnancy. Important issues were assistance and support in caring for the family.

Discussion: In line with findings from our previous study undertaken in the 1990s, there were no increased complication rates for pregnancy and delivery. These results are reassuring for the vast majority of CMT patients and are important for family planning and clinical care.
CMT patient cohort [2,3], assessments of pregnancies via a national birth registry in Norway [4] showed higher frequencies of presentation anomalies, operative deliveries and postpartum haemorrhage. There is still controversy about the appropriate options for anaesthesia and analgesia management in CMT patients, as information is limited. It can be assumed that patients with mild conditions may go through pregnancy with few difficulties. However, in more severe subtypes, the later stages of pregnancy may bring about life-threatening changes such as increasing diaphragmatic compromise in those with respiratory muscle weakness.

The underlying gene defect may significantly influence the disease course as well as the outcome of pregnancy and delivery. Previous reports were mostly based on patient cohorts from the early 1990s when information about the molecular genetic basis had not been available. Since a significant proportion of CMT patients report worsening of weakness and sensory disturbances in pregnancy, a possible hormonal influence has to be taken into account. This is important particularly for CMT1A, where progesterone was shown to have a negative influence on the disease in animal models.

In this study (i) complication rates in pregnancy and delivery of CMT patients, (ii) newborn vitality as an outcome variable of CMT pregnancies, (iii) a possible influence of pregnancy on the disease progression in CMT, (iv) a comparison of specific genetic subgroups, where applicable, and (v) a personal view of CMT mothers with regard to family planning were addressed.

Patients and methods

The CMT-NET pregnancy study was designed as a clinical cohort study and cross-sectional study based on the clinical and molecular diagnosis for patients with hereditary neuropathies, living in Germany or Austria. Recruitment of participants started in February 2016 and finished in July 2019. Inclusion criteria were women with a confirmed diagnosis of CMT who have given birth or were pregnant during the study period. Participation took place via active patient contact with the project leader. The pregnancy assessment in women with CMT was directly linked with the German CMT patient registry in Munich (www.cmt-register.de). The link to this study was implemented within the registry questionnaire.

Women who had a completed pregnancy after 1990 and agreed to take part in the study returned a signed participation form including the consent to review their medical files. The self-report questionnaires comprised information about the natural history, previous gene tests, details about the course of pregnancy and delivery, experienced influence of pregnancy on CMT severity, and assessment of personal attitudes towards having children. The questionnaires were sent out and filled in electronically and returned via email or as paper copies by postal delivery.

Sixty-one patients agreed to participate, of whom 54 (89%) fulfilled the inclusion criteria and completed all questionnaires.

The following main outcomes were analysed:

- Pregnancy and delivery complications in different genetic subgroups of CMT patients
- Assessment of newborn measurements and vitality scores
- Change of disease course in or after pregnancy
- Personal attitudes towards having children when affected by CMT

Descriptive variables included year of birth, type of obstetric institution, age of mother (completed years), sex of child, birth order (parity), birth weight (g) and gestational age in completed weeks/prematurity. The selected outcome variables included number of miscarriages or ectopic pregnancies, adverse events in all three trimesters (e.g. abnormal bleeding, infections, preeclampsia, preterm labour), induction of birth, interventions, delivery complications (e.g. prematurity, functional disorder of birth, abnormal bleeding post-partum, presentation anomalies), perinatal mortality, congenital conditions and birth defects.

As regards a possible influence of CMT disease on pregnancy, the following questions were included: ‘Did you experience a change of symptoms in pregnancy? If yes, can you fill in details?’ ‘Did you experience a change of symptoms after delivery? If yes, can you fill in details?’

Finally, the participants were asked to write down their opinion in their own words on ‘What would you personally advise other women who think about having children?’

Biometric concept/statistical analyses

Statistical analysis included contingency tables and variance analysis for comparisons of delivery complications and newborn parameters between the CMT sample and reference data from the normal population and between genetic subgroups of CMT and the reference data. For qualitative variables, CMT and reference groups were compared using cross-tables with the Pearson $\chi^2$ test. Two-sided $P$ values of $<0.05$ were interpreted as significant. Normal values for the German reference population have been published previously [3]. Mean age at first delivery was compared with the German population between 1995 and
Labour was defined as preterm before 37 weeks gestation leading to hospital admission or medical intervention (i.e. tocolysis) [6]. Small for gestational age was recorded when birth weight was below the 10th centile of the normal range for the German population [7]. Analyses were performed using the statistics software R-Studio Version 1.2.1335 2009–2019, (RStudio, Vienna, Austria).

**Ethical considerations**

Patients actively participated upon informed consent. Confidentiality measures for the storage of patients’ data were ensured. The study holds a positive vote by the Ethical Board of the Medical Faculty, RWTH Aachen, Germany (2012) and by the Ethical Board of the Ludwig-Maximilian University of Munich, Germany (2016).

**Results**

The study group comprised 54 women who had a total of 98 pregnancies. Mean age at onset of CMT disease was 12.6 years (SD 10.8; range 0–37 years). Miscarriage rate was 14.2% (n = 14) and therefore within normal limits. Altogether, 84 completed gestations were counted, resulting in 86 children (82 singletons and two pairs of twins). Median age at first delivery was 28 years, mean 28.5 years (SD 5.68), which did not differ significantly from the German reference population who had a mean age at first delivery rising from 28.2 years in 1995 to 29.2 years in 2010. Since data from a medical birth registry in the Norwegian study were surveyed in women with a known diagnosis of CMT [4], this subgroup of patients was analysed (n = 26), being aware of their diagnosis, affecting 40 gestations, separately for the complications reported as being statistically increased.

**Genetic subtypes**

Following the information in the medical files and the family histories, 50 (92%) patients had autosomal dominant CMT; in two patients each (4%) X-linked and autosomal recessive inheritance was documented. In 51 (94%) patients the underlying genetic defect was identified (Fig. 1). On account of the research focus of the CMT-NET on CMT1A, most participants (n = 40, 74%) had a PMP22 gene duplication. Therefore only the CMT1A subgroup was calculated separately from the total cohort.

**Obstetric aspects**

Obstetric complications were not significantly different from a German reference population, either for the whole group or for the CMT1A subgroup (Table 1, Fig. 2). Only two patients (2.4%) had hypertensive disease in pregnancy. There were no reports of polyhydramnios or placentation anomalies (placenta praevia or placenta accreta). Preterm delivery (<37 weeks gestation) occurred in 7.1% (n = 6). The mean number of gestational weeks until delivery was 38.5 weeks (SD 0.94). Presentation anomalies were documented in 9.5% (breech presentation, n = 6; transverse presentation, n = 2), instrumental delivery (vacuum or forceps delivery) in 3.6% (n = 3) of completed pregnancies. In 36.9% (n = 31) of deliveries a caesarean section took place, of which 19.0% (n = 16) were primary and 17.9% (n = 15) secondary sections.

In all caesarean sections, details of anaesthesia were documented: spinal anaesthesia was administered in 80.6% (n = 25, 13 primary and 12 secondary) of sections and general anaesthesia in 19.4% (n = 6, three primary and three secondary) of sections. There was no evidence of increased postpartum haemorrhage (3.6%, n = 3).

The subgroup of 26 patients who were aware of the diagnosis when becoming pregnant did not have a higher rate of presentation anomalies (7.5%, n = 3), operative deliveries (none), postpartum haemorrhage (5%, n = 2) or overall obstetric complications (32.5%, n = 13) in 40 analysed gestations.

**Newborn vitality**

Overall there was no increased neonatal morbidity and mortality as regards birth measurements, Apgar scores and clinical information. Mean Apgar scores were 8.7 at 1 min (SD 1.30), 9.57 at 5 min (SD 1.15) and 9.85 at

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**Figure 1** Overview of the genetic diagnosis in the 54 patients. CMT1A: PMP22 duplication (heterozygous), HNPP: PMP22 deletion (heterozygous), CMTX: GJB1 mutation (heterozygous), CMT2A: MFN2 mutation (heterozygous), CMT1B: MPZ mutation (heterozygous), CMT2C: TRPV4 mutation (heterozygous), CMT4C: SH3TC2 mutation (compound heterozygous), NMAN: HINT1 mutation (compound heterozygous).
10 min (SD 0.42). Mean birth measurements were weight 3236.45 g (SD 613.48), length 50.72 cm (SD 3.05) and head circumference 34.54 cm (SD 2.1). No tendency towards abnormal birth weights was found in our cohort in comparison to the normal population (Fig. 3).

**Influence on disease course**

As regards own experiences of a possible influence of pregnancy on the disease course, self-assessed information was available from 82 gestations. In 31 gestations (37.8%) a deterioration was reported, in three (3.7%) improvement, and in 48 (58.5%) no change of CMT during pregnancy. After delivery, deterioration was reported in 30 (37.5%), improvement in four (5.0%) and no change of CMT symptoms in 46 (57.5%) instances. The second pregnancy was never better than the first, i.e. a progression was either experienced as similar or worse in later pregnancies. Three of the four deliveries associated with improvement followed a pregnancy with exacerbation.

No adverse effects of anaesthesia were reported. There was no statistical difference in the proportion of patients who experienced a deterioration after delivery when spinal anaesthesia (nine of 23, 39.1%) and general anaesthesia (two of six, 33.3%) were compared ($P > 0.05$).

**Specific case reports**

A more severe phenotype with additional clinical features. The following case reports illustrate the obstetric histories in rare subtypes of CMT.

**Patient with autosomal dominant CMT2C**

This 38-year-old woman had congenital contractures (arthrogryposis multiplex congenita, AMC) and had never been able to walk. She had severe scoliosis and reduced lung function in her first pregnancy at age 30, when AMC was also seen on ultrasound in her unborn son. Her pulmonary situation worsened markedly in her view during the last 2–3 months of pregnancy; however, lung function tests were not undertaken until age 33. She delivered at 37 + 1 gestational weeks via primary caesarean section due to breech presentation and for maternal reasons. Birth measurements were 48 cm, 2650 g and 36 cm, Apgar 9/9. Newborn vitality was normal apart from the presence of AMC (hips, knees and talipes) in her son. Two years after her first pregnancy the patient and her son were diagnosed to have autosomal dominant CMT2C (heterozygous TRPV4 mutation c.806G>A, p.Arg269His). Due to exertional shortness of breath, spirometry was performed at age 33 revealing a severe restrictive lung disease with forced vital capacity...
(FVC) 1.4 l (45%), forced expiratory volume in 1 s (FEV1) 1.2 l (46%) in a sitting position and FVC 1.0 l (33%), FEV1 0.9 l (34%) when lying supine. Lung function remained stable with similar reduced values at age 34 and 37 years. At age 38 (after completion of recruitment for this study) she had a second pregnancy which was uneventful until her last weeks when she developed increasing dyspnoea. She was seen in hospital at 36 + 6 weeks gestation and was advised to have an emergency caesarean section on account of her respiratory situation and transverse position of the foetus. The male newborn was healthy but small for gestational age (2220 g, 43 cm, 35 cm) and initially had reduced Apgar scores of 1/8/9. His mother never received assisted ventilation or oxygen treatment up to the time when last contacted. In her personal review, the patient reported no long-lasting influence of her pregnancies on the disease course. She stressed the importance of coping to accept the need of support and the overall positive emotions associated with a fulfilled family life. In addition, she felt that more physical exercise (swimming) in her second pregnancy prevented an earlier respiratory dysfunction in comparison with her first pregnancy.

**Patient with autosomal recessive CMT4C**

This 37-year-old woman had first walking difficulties and difficulties in sports at school in her teenage years. It was not until her second delivery that she sought medical advice for increasing muscle weakness in her arms and legs. She was unable to hold her second son in her arms and to push the baby stroller. Her first pregnancy at age 27 was largely uneventful until her due date when foetal heart beats were found to decrease under labour induction. Her son was delivered after 40 + 2 weeks gestation by caesarean section and showed no neonatal abnormalities (Apgar 10/10, birth measurements 54 cm, 2650 g, 32 cm). The patient had a second pregnancy at age 32, when she noticed general fatigue, leg muscle weakness and muscle cramps. Her second son was delivered by elective re-section at 37 + 4 weeks gestation. He was fine with normal Apgar scores (10/10) and normal birth measurements (2670 g, 51 cm, 33.5 cm). Since the mother’s condition had worsened considerably after delivery, she underwent neurological examinations and genetic testing. Diagnosis of autosomal recessive CMT4C was confirmed by compound heterozygous *SH3TC2* mutations (c.2860C>T, c.610G>A). In retrospect the patient would advise not having children if there is not sufficient familial or professional support. Nonetheless, she is very happy with her sons. In her view, the children grow up with a different responsibility facing their mother’s handicap.

**Patient with autosomal recessive neuromyotonia and axonal neuropathy (NMAN)**

This 32-year-old woman had muscle cramps, myalgia, myotonia and distally pronounced leg weakness from 7–8 years of age. When becoming pregnant at age 29, she had myotonic stiffness, dystonic contractures in her ankles and walking difficulties. She had been hospitalized at 18 weeks gestation for hyperemesis gravidarum and vaginal bleeding. Following a fall, she was examined again at 30 weeks gestation. There were no abnormal findings. Six weeks later she was referred to hospital on account of foetal growth restriction, oedema and increasing blood pressure, indicating a beginning preeclampsia. A healthy boy was delivered by secondary caesarean section at 36 + 3 weeks gestation with Apgar scores 8/9/9 and birth measurements of 2545 g, 48 cm, 34 cm. The boy had respiratory adaptation problems and a newborn infection which improved shortly thereafter. During her pregnancy the patient underwent *HINT1* gene sequencing which revealed compound heterozygous mutations c.110G>C, p.Arg37Pro, and c.356G>A, p.Arg119Gln, confirming autosomal recessive NMAN. The patient reported worsening of her neuropathy during pregnancy, followed by symptom relief after delivery. Her advice was to seek competent medical control, professional assistance and a good social network to cope with the increasing demands of having a child.

**Recommendations**

The question ‘What would you advise other women who think about having children?’ was answered by 44 patients, who gave a total of 89 recommendations (mean 2.0, range 1–5). The majority (n = 21, 47.7%) of women stressed the importance of a positive attitude, but 16 (36.4%) advised to be aware of the challenges associated with pregnancy. Medical advice and expert opinion for specific medical interventions were recommended by 11 (25.0%) patients. For 27 mothers (61.4%), who gave recommendations, important issues were assistance and support in caring for the family, whilst physical activity in or before pregnancy was recommended only by five (11.4%) women.

**Discussion**

In a previous retrospective cohort study, undertaken in the 1990s in Germany and Australia, comprising 21 patients and 45 gestations with demyelinating CMT, no increased complication rates for pregnancy and delivery were found [2]. Having a basically identical study design, but with no overlap in the patient cohorts, this study yielded similar results. These
results are reassuring for the vast majority of CMT patients. Nonetheless, the study design may be biased towards an ascertainment of active patients who participate in registries and may have had more positive experiences with their pregnancies than those patients who do not participate. In the Norwegian study [4] the total obstetric complication rate in 108 deliveries of 49 CMT mothers was 42.6% and comprised presentation anomalies occurring in 9.3% and operative deliveries in 29.6% indicating statistically significantly increased complications compared to a reference population. In a European workshop on pregnancy in neuromuscular disorders in 2010 [8], it was agreed that the discrepancy of complication rates might have been related to the different ascertainment of data. It is likely that more severely affected CMT patients were assessed in the Norwegian study than in the German study. No information of the genetic subtype was released in the Medical Birth Registry of Norway.

In our cohort CMT1A (caused by PMP22 duplication) made up the vast majority (74%) of patients, whilst the proportion of PMP22 duplication amongst all CMT cases in a large German series comprised 40%–50% [9]. Of the remaining genes known to cause demyelinating CMT, mutations in GJB1 (CMTX1) and MPZ (CMT1B) are the most frequent. In axonal CMT, mutations in GJB1 (CMTX1) and MFN2 (CMT2A) account for 10%–20% of patients, whilst other CMT2 genes are responsible for a very small minority of cases. The obstetric histories were comparably uneventful in classical CMT1A, HNPP, CMTX1 and CMT1B. However, specific genetic subtypes with congenital or infantile features warrant individual medical supervision as seen in our case reports. Interestingly, despite severe congenital contractures, scoliosis and reduced lung function with vital capacity of about 1 l, repeated pregnancies had been successfully completed in our patient with CMT2C without much intervention.

In our study adverse effects of general or spinal anaesthesia used for operative deliveries were not detected, nor was an influence on the disease course reported by either anaesthesia. Generally, it was recommended to prefer regional anaesthesia at caesarean section above general anaesthesia in patients with neuromuscular disorders [8,10–11]. Regarding analgesia and anaesthesia, medications with neurotoxic side effects have to be avoided [10]. Information as to whether there might be an influence of gestation on the course of CMT disease was available only in the German cohorts. The proportion of exacerbation in pregnancy was 37.8% (17 of 45) and 31.1% (14 of 45) after pregnancy in the previous study. The corresponding figures were remarkably similar with 37.8% and 37.5% in this study, even in a different cohort more than 25 years later. However, it has to be noted that a possible relationship between deterioration in pregnancy and after delivery was not specifically addressed. Self-assessment of the natural history is prone to reporting bias and may result in an overestimation or underestimation of real changes of symptoms in pregnancy. This problem can only be solved by administering prospective studies of pregnant patients with assessment of severity scores before, in and after pregnancy.

The results of our study contribute further knowledge to better predict and manage possible complications of CMT disease in pregnancy. This information is important for family planning and clinical care.

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The principal investigator confirms that she had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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