Neuromuscular diseases and pregnancy

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Learning objectives

At the end of this lecture

- The learner knows the risks of pregnancy in females with neuromuscular disorders
- The learner knows about practical clinical management issues related to pregnancy in women with neuromuscular disorders

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Review

What we do not know about pregnancy in hereditary neuromuscular disorders

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Workshop report

179th ENMC international workshop: Pregnancy in women with neuromuscular disorders 5–7 November 2010, Naarden, The Netherlands

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Physiological changes during normal pregnancy

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- Haematological effects (dilutional anaemia, reduction in total plasma proteins and an increased thromboembolic risk).
- Cardiological changes (a rise in heart rate, stroke volume and thus a rise in cardiac output by 50%).
- Respiratory changes including a rise in tidal volume and oxygen consumption. As a general rule, women with a VC<1L are advised against pregnancy. Where maternal hypoxia results in oxygen saturations <85%, livebirth rate is only 12%.
- Immunological changes causing infections
- Musculoskeletal alterations with collagen softening in ligaments and joints.

Prevalence of neuromuscular disorders

- myotonic dystrophies (DM1, DM2)
- dystrophinopathies (DMD, BMD)
- facioscapulohumeral muscular dystrophy (FSHD)
- spinal muscular atrophy (SMA)
- limb girdle muscular dystrophies (LGMDs)
- hereditary motor and sensory/Charcot-Marie-Tooth neuropathies
- mitochondrial myopathies
- Norwood F, Brain 2009;132:3175–86.

Pregnancy-related issues for the neuromuscular patient

1. Will the disease affect fertility?
2. Are there special risks to the fetus (beside the genetic implications)?
3. Will the disease affect the ability to carry a pregnancy?
4. Are there more obstetric complications during pregnancy?
5. Will there be a need for special measures during labor and delivery (birth complications)?
6. Will the course of disease be affected by pregnancy?

Pregnancy-related issues for the neuromuscular patient

		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]

Zohar and De Visser. Neuromusc Disord 2009;19:675

1. Will the disease affect fertility?

- Not systematically investgated.
- Some investigators found decreased fertility associated with menstrual disturbances or related to gonadal dysfunction expressed as poor responsiveness to controlled ovarian stimulation even in mildly affected DM females.
- Others did not find a relationship between DM1 and female fertility.
- Case reports of gonadal dysfunction (premature menopause) in mitochondrial disorders, in particular in progressive external ophthalmoplegia due to POLG mutations.

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Zohar and De Visser. Neuromusc Disord 2009;19:675

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

- Increased perinatal death (up to 15%) in DM1, mainly due to the occurrence of congenital DM in conjunction with pregnancy complications.
- A significantly increased frequency of abnormal presentations (e.g. breech or abnormal cephalic presentations) is observed in Charcot-Marie-Tooth disease.

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Will the disease affect the ability to carry a pregnancy?

- Is there an increased risk of miscarriage?
  - In DM1 miscarriage rate is 11%, within range of normal population
  - 13% of 96 pregnancies in DM2 ended in early miscarriage.
- No increased early miscarriage rate in FSHD, CMT
- Late spontaneous abortions in 4% of clinically symptomatic DM1 women.
- Preterm labour is common in DM1 and DM2, and also observed in SMA, but not in FSHD and CMT.
- Reduction of respiratory function to about 50% of predicted values was associated with successful pregnancies in SMA (risky pregnancies!).

3. Are there more obstetric complications during pregnancy?

- Risk of pre-ecclampsia in DM1
- 10-fold increase in risk of placenta previa in DM1
- Increased rate of urinary tract infections in DM1 (13%) and rarely in SMA

Pregnancy-related issues for the neuromuscular patient

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Zohar and De Visser. Neuromusc Disord 2009;19:675

4. Will there be a need for special measures during labor and delivery (birth complications)?

- In DM1 increase in cesarean sections (uterine muscle abnormality)
- Increased forceps usage in CMT1
- In FSHD increase in cesarean sections and operative vaginal deliveries (abdominal muscle weakness)
- Increased postpartum hemorrhage rate probably due to atonic uterus in DM1 and CMT1

- In disorders of lipid metabolism (CPT2 or VLCAD deficiency) rhabdomyolysis can be triggered by prolonged exercise or fasting

A patient with spinal muscular atrophy type III

Pregnancy-related issues for the neuromuscular patient

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Zohar and De Visser. Neuromusc Disord 2009;19:675

5. Will the course of disease be affected by pregnancy?

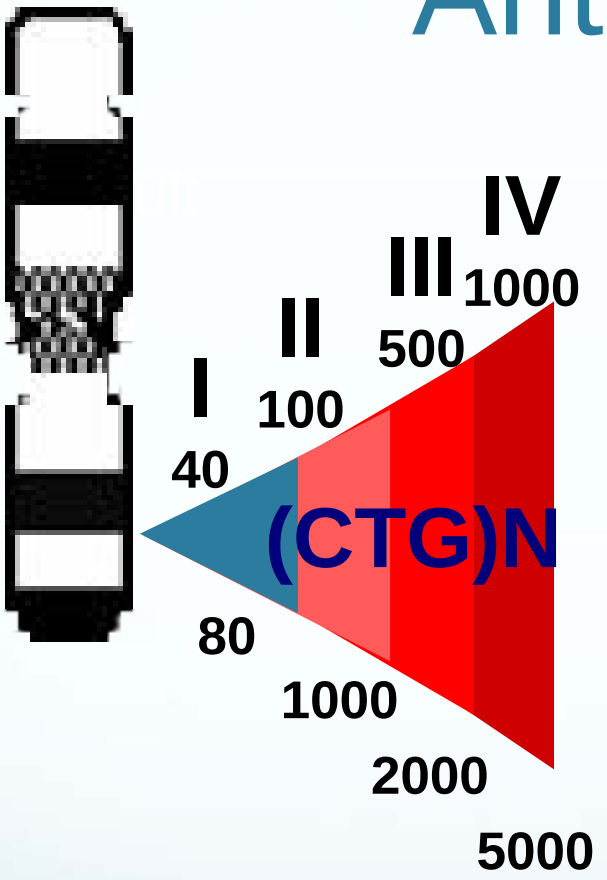
- Pregnancy-related worsening of muscular symptoms found in 30% of women with DM1
- Also observed in FSHD (25%), LGMD, SMA, CMT1 (40%), congenital myopathies, Bethlem myopathy (anecdotal cases)
- Sometimes transient
- Aggravation of clinical myotonia during pregnancy in DM1, DM2 and also non-dystrophic myotonias

Pregnant patient with DM1

Preconceptional counseling of DM1 Genetic aspects

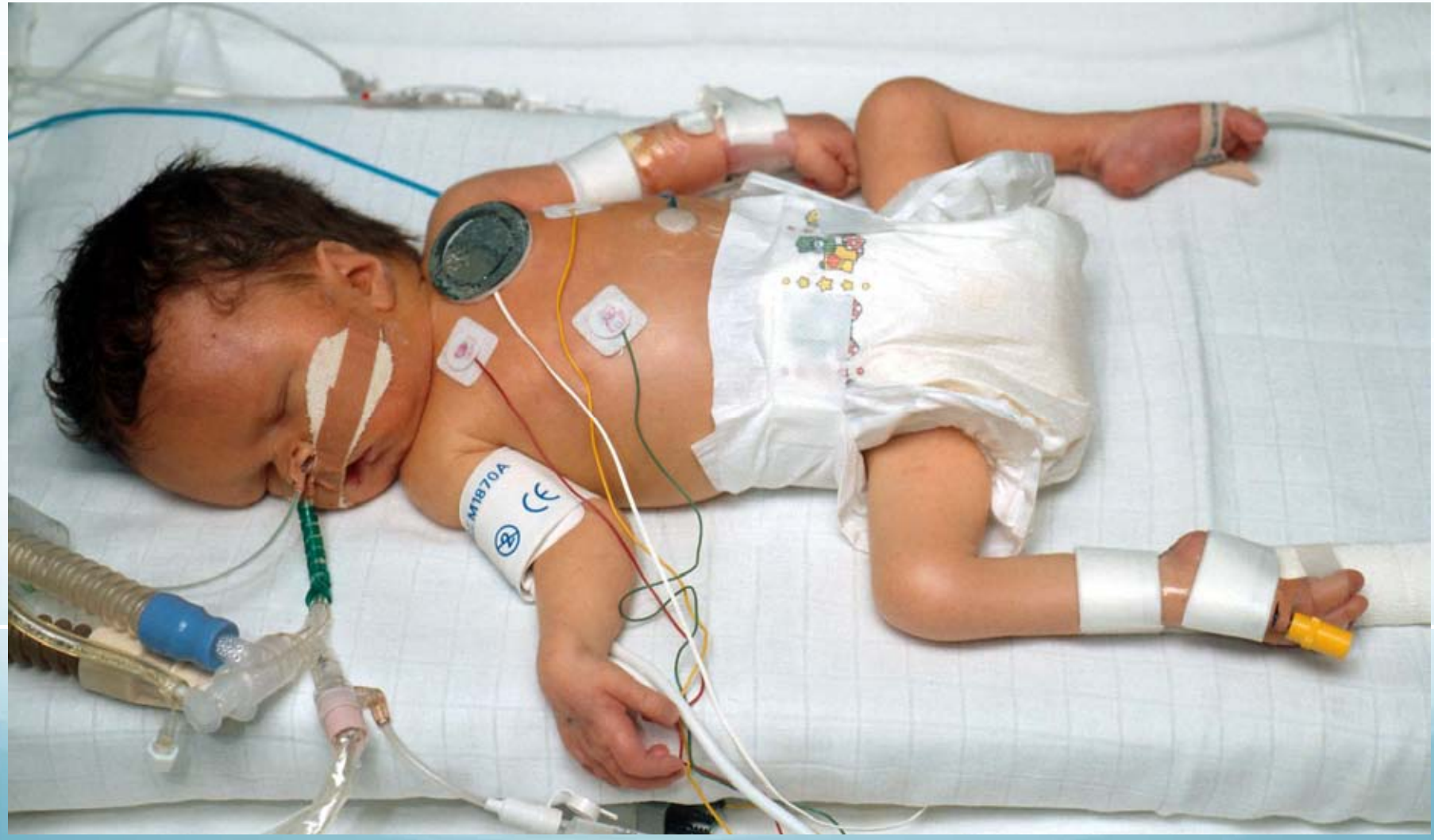
- Myotonic dystrophy (DM1): prevalence of 1 in 8000 among Western Europeans
- Marked inter- and intrafamilial variability caused by dynamic mutation of DM protein kinase (DMPK) gene on chromosome 19q: expansion of a CTG repeat (n 5-37, affecteds 50-several 1000s)
- CTG repeat is unstable and increases in length when transmitted from generation to generation (anticipation): clinical picture more severe in successive generations

Anticipation



I = Mild
II = Adult
III = Childhood
IV = Congenital

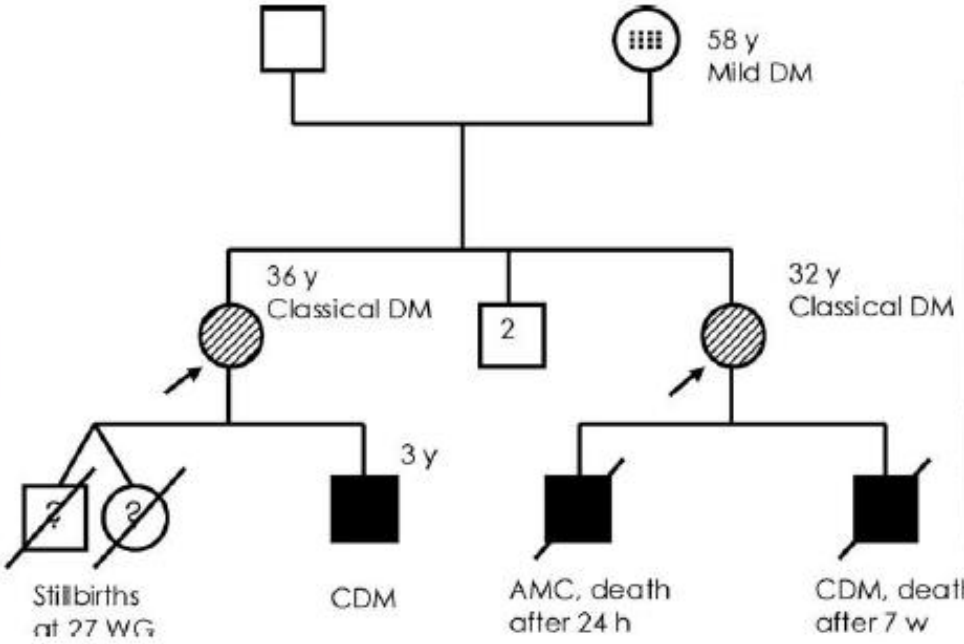
Congenital myotonic dystrophy

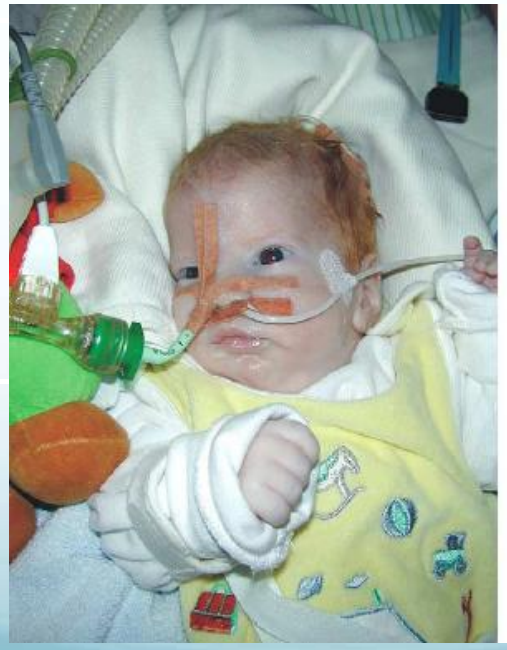


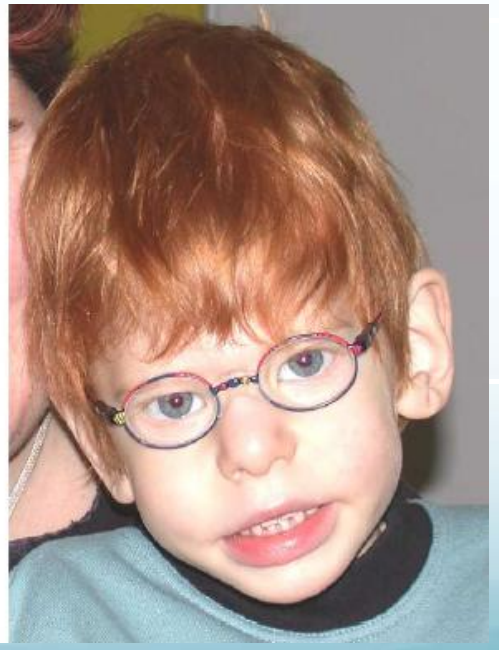
Question 1

Congenital myotonic dystrophy occurs if

1. The mother has myotonic dystrophy with a CTG expansion of 1-4 kb
2. The mother is subclinically affected (CTG expansion < 1kb)
3. Both answers are correct







Rudnik-Schöneborn S, Zerres K. Eur J Obst Gynec Reprod Biol 2004;114: 44

Genetic aspects of DM1

- A priori risk of a CDM pregnancy is 59–100% if maternal CTG expansion is 1-4 kb, the risk is 17% if the expansion is <1 kb.
- Even subclinically affected women with repeat sizes <75 can give birth to CDM offspring.
- In more than one third of families, it is the affected child that brought the mother to the attention of a neurologist.
- Recurrence risk to further children is nearly 100% if the mother has given birth to a CDM child.
- Prenatal testing or pre-implantation genetic diagnosis can be helpful.

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Myasthenia gravis and pregnancy

- Occurs in women of child-bearing age
- Diagnosed in 1:20.000 pregnancies
- Pregnancy has a variable effect: relapse in 41%, remission in 29%
- Pregnancy does not worsen the long-term outcome
- Overall maternal mortality risk: 4%.
- Risk factors: respiratory failure, cholinergic crises, postpartum hemorrhage, treatment with magnesium for eclampsia
- Perinatal mortality is 5 x that of uncomplicated births

Interventions during labor and obstetric complications in MG

Procedure	MG group, n (%)	Reference group, %	Rate ratio	*p* Value*
Total intervention during birth	43 (33.9)	20.0	1.7	<0.001
Cesarean section				
Total	22 (17.3)	8.6	2.0	0.001
Elective†	11 (17.2)	4.6	3.7	<0.001
Vaginal intervention (forceps/vacuum)	11 (8.7)	6.3	1.4	0.4
Total occurrence of complications	52 (40.9)	32.9	1.2	0.05
Preterm rupture of amniotic membranes	7 (5.5)	1.7	3.2	0.001
Functional disorder of birth	12 (9.4)	6.5	1.4	0.2
Injuries in birth canal	8 (6.3)	3.7	1.7	0.1
Bleeding postpartum	7 (5.5)	5.3	1.0	0.9
Obstruction of birth process	2 (1.6)	2.0	0.8	0.8
Umbilical cord complications	17 (13.4)	12.6	1.1	0.8

Hoff JM et al. Eur J Neurol 2007:14:38-43

Question 2

The delivery of a mother with myasthenia gravis should take place in the hospital, because the newborn is at risk

1. To develop neonatal myasthenia due to the transplacental transmission of IgG-antibodies
2. To have myasthenia gravis as well since MG is often familial
3. To have neonatal myasthenia due to the use of pyridostigmine by the mother

Myasthenia gravis and pregnancy
Which complications can occur?

- Weakness during labor necessitating assisted delivery or c-section (twice that of controls).
- Neonatal MG (9-27%): develops 24-48 hours after delivery and resolves usually within 1 month due to transplacental transmission of IgG-antibodies.
  - Clinical picture: poor sucking and swallowing, generalized hypotonia, respiratory distress.
  - No relationship with severity of mother's MG.
  - Neonates of mothers who underwent thymectomy less likely to develop neonatal MG.
  - Treatment: supportive care, anticholinesterases, plasmapheresis in severe cases.

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Myasthenia gravis and pregnancy
Which complications can occur?

Arthrogryposis congenita: multiple joint contractions develop due to lack of movement *in utero*. Increased neonatal death due to pulmonary hypoplasia and polyhydramnios.

Mother has serum antibodies that inhibit fetal acetylcholine receptor function,

High recurrence rate in subsequent pregnancies despite the lack of myasthenia in the mother.

Barnes et al. Neuromusc Disord 1995;5:59
Norwood F, et al. J Neurol Neurosurg Psychiat 2013, June 11 online

Question 3

Females with myasthenia gravis who are on prednisone and azathioprine medication in addition to pyridostigmine should be given the advice:

1. To continue the medication during the pregnancy
2. To stop the azathioprine and increase the prednisone
3. To stop both prednisone and azathioprine and increase pyridostigmine

Myasthenia gravis and pregnancy
Which drugs can be used?

- Anticholinesterase medication
- Corticosteroids (also during lactation)
- Azathioprine is believed to be relatively safe
- Severe exacerbations can be treated with intravenous immunoglobulins and plasmapheresis
- Avoid muscle relaxants and magnesium

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Other neuromuscular complications during pregnancy and delivery

- CTS (most frequent complication: 2-35%)
  - Most frequently in 3d trimester
  - More than half of untreated patients still had symptoms one year after delivery
- Lumbosacral radiculopathy (more often back pain)
  - In case of root involvement MRI is allowed
- Meralgia paresthetica (common, 80% unilateral)
- Mononeuropathies (femoral, obturator, peroneal, facial, intercostal, radial)
  - femoral neuropathy probably underrecognised; usually good recovery

Pregnancy in neuromuscular patients with cardiac involvement

- The main limiting factor for pregnancy is cardiac systolic dysfunction, as haemodynamic changes during pregnancy, can lead to decompensated heartfailure
- The 3^{d} trimester, labour and delivery are the periods with the highest risk of cardiac complications.
- Generally speaking, an ECG an echocardiogram is recommended in all patients at risk for cardiac disease. If the left ventricular ejection fraction is <45% it might be advisable to discourage pregnancy due to a increased risk of death/pulmonary oedema/stroke

Pregnancy in nm patients with reduced lung function

- In patients with NMDs, there is a risk of alveolar hypoventilation which increases the risk of chronic respiratory failure and therefore careful planning is essential.
- In the third trimester and at the time of delivery:
  High aspiration risk
  a. Increased intrabdominal pressure
  b. Reduced gastro-oesophageal sphincter tone
  c. Gastric insufflation with non-invasive ventilation
  High risk of worsening respiratory failure
  a. Expulsive phase requires isometric diaphragm contractions which may precipitate muscle failure
- b. Opiate analgesia reducing respiratory drive

Conclusions

- Serious neuromuscular complications are rare during pregnancy
- Our knowledge is mostly from anecdotal cases or (relatively) small series
- Awareness of these complications can improve outcome
- Active management prior to and during pregnancy, labour and delivery is recommended
- More research is needed

Recommendations

- Preconception planning
- Care in each stage of pregnancy
- Postpartum period
- Specific recommendations
  - Respiratory
  - Cardiac

A healthy baby was born!

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