

Hyperemesis gravidarum, Tetanic Syndrome and Hypomagnesemia

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Zusammenfassung

Nach ihrer Entbindung wurden 40 Frauen mit Hyperemesis gravidarum auf Symptome des tetanischen Syndroms hin untersucht und mit einer Kontrollgruppe verglichen. Es wurden klinische Daten, elektromyographische Provokationstests und Elektrolyt-Messungen im Serum und den Erythrozyten angewandt. Eine tetanische Disposition wurde bei 80% der Frauen mit Hyperemesis gravidarum und bei 15% der Kontrollgruppe diagnostiziert. Dies wurde durch den Beweis der spezifischen Änderungen in den Elektromyogrammen und den verringerten Magnesiumkonzentrationen in Serum und Erythrozyten bestätigt. Tetanische Dispositionen und Hypomagnesiämie sollten als bedeutender Risikofaktor der Hyperemesis gravidarum angesehen werden.

Summary

After delivery 40 women with hyperemesis gravidarum were examined for symptoms of tetanic syndrome and compared to a control group. Clinical data, electromyographic provocation tests and electrolyte measurements in serum and erythrocytes were used. A tetanic disposition was diagnosed in 80% of women with hyperemesis gravidarum and in 15% of the control group. This was confirmed by the evidence of specific alterations in the electromyogramme and decreased magnesium concentrations in serum and erythrocytes. Tetanic disposition and hypomagnesemia should be considered as an important risk of hyperemesis gravidarum.

Résumé

Après leur accouchement 40 femmes souffrant de hyperémèse gravidarum étaient examinées pour des symptômes du syndrome tétanique et comparées à un groupe de contrôle. On se servit de données cliniques, de tests électromyographiques provocatives et de mesurages électrolytes dans le sérum et dans les érythrocytes. Une disposition tétanique était diagnostiquée chez 80% des femmes souffrant de hyperémèse gravidarum et chez 15% des femmes du groupe de contrôle. Cette disposition a été confirmée par l'évidence des changements spécifiques dans l'électromyogramme et par les concentrations de magnésium réduites dans le sérum et les érythrocytes. La disposition tétanique et la hypermagnésiémie devraient donc être considérées comme risque important du hyperémèse gravidarum.

Introduction

Hyperemesis gravidarum is a relatively rare but serious complication of pregnancy. The common pathophysiological pathway is well known. Severe vomiting results in weight loss and dehydration. Dehydration leads to fluid and electrolyte complications, particularly alkalosis from loss of hydrochloric acid. Starvation causes hypoproteinemia, hypovitaminosis, ketacidosis and other signs of nutritional deficiency (Benson, 1984, Pritchard et al., 1985).

There are no proved causes of vomiting in pregnancy. The etiology of hyperemesis gravidarum has been the subject of many speculations. It has been suggested to be of psychogenic or organic origin or both. The opinion is widely held that the disorder is psychogenic in nature and that vomiting is a defense against undesired pregnancy (Molinski, 1972). On the other hand there are the following somatogenic hypotheses:

Endocrine causes such as HCG (Kaupila et al. 1979, 1984), hyperthyroidism (Bouillon et al., 1982) (Chin and Lao, 1988) and elevated estrogen levels (Depue et al., 1987) being discussed. An incompatibility of hormonal contraception has been described (Järfeld-Samsioe et al., 1983). Nausea and vomiting were found to be unrelated to the serum level of chorionic gonadotropin (Soles et al., 1980) and to thyroid function (Evans et al., 1986). Increased aller-

gic reactions in patients with hyperemesis gravidarum suggest that immunological factors are involved (Fairweather et al., 1968). In about 1000 patients suffering from a tetanic syndrome (synonyms: hyperventilation syndrome, spasmophilia) the following disorders could be observed:

1. a disposition to vomiting manifested by a high irritability of subcortical structures,
2. an incompatibility of hormonal contraception,
3. frequent allergic reactions,
4. neurotic or psychosomatic phenomena,
5. hypomagnesemia (Fehlinger et al., 1985).

The hypothesis was established that there might be a relationship between hyperemesis gravidarum, the tetanic syndrome and hypomagnesemia.

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Tab. 1: Characteristics of the Hyperemesis gravidarum and of the control group.

| | Hyperemesis gravidarum (n = 40) | | | Control (n = 40) | | | Significance |
|---|------------------------------------|-------|-----------------|---------------------|-------|-----------------|--------------|
| | mean | SD | CI 95% | mean | SD | CI 95% | |
| Age | 27.17 | 4.52 | 25.73 - 28.62 | 27.17 | 3.93 | 25.92 - 28.43 | n.s. |
| Time of examination after delivery (months) | 25.3 | 11.27 | 21.70 - 28.90 | 25.35 | 10.11 | 22.12 - 28.58 | n.s. |
| Body weight (kg) | 57.78 | 9.20 | 54.83 - 60.72 | 58.48 | 5.48 | 56.60 - 60.35 | n.s. |
| Body length (cm) | 166.9 | 5.27 | 165.22 - 168.58 | 166.6 | 5.36 | 164.88 - 168.32 | n.s. |

SD - Standard Deviation, CI - Confidence Interval, n.s. - not significant

Subjects and Methods

About one year after delivery 40 women hospitalized between 1984 and 1988 because of hyperemesis gravidarum as well as a control group of 40 women without vomiting and nausea in pregnancy were recalled for a retrospective examination.

Since there is no clear boundary between mild pregnancy-induced sickness and hyperemesis gravidarum, we defined hyperemesis gravidarum as a condition requiring admission to hospital and intravenous therapy.

On admission, besides a general and common gynaecological history, symptoms and signs of tetanic syndrome and data of pregnancy and fetal outcome are documented. Serum potassium and calcium concentrations are analyzed by flamephotometry (Flapho 40, Zeiss, Jena, FRG). Magnesium in serum and whole blood was determined by atomic absorption spectrophotometry (ASS 1, Zeiss, Jena, FRG). Magnesium in erythrocytes was calculated by haematocrit, plasma and whole blood concentration:

$$\frac{(Mg^{Blood} - Mg^{Plasma})}{Haematocrit} + Mg^{Plasma} = Mg^{Erythrocyte}$$

Tab. 2: Medical history.

| | Hyperemesis gravidarum (n = 40) | | Control (n = 40) | | Significance p = |
|----------------------|------------------------------------|------|---------------------|------|---------------------|
| | n | % | n | % | |
| Migraine | 15 | 37.5 | 7 | 17.5 | 0.046 |
| Pyelonephritis | 15 | 37.5 | 7 | 17.5 | 0.046 |
| Goiter | 14 | 35.0 | 5 | 12.5 | 0.018 |
| Allergic reactions | 15 | 37.5 | 9 | 22.5 | 0.147 |
| Abdominal complaints | 7 | 17.5 | 3 | 7.5 | 0.179 |
| Recurrent infections | 5 | 12.5 | 1 | 2.5 | 0.088 |

Neuromuscular hyperirritability was tested by electromyographic provocation tests according to *Alajuanine* et al., 1954.

A bipolar needle-electrode was inserted into the first interosseous dorsal muscle of left hand and electrical activity was recorded. After the control of electrical activity at rest ischemia was produced for 5 minutes. The blood pressure cuff was wrapped around the upper arm to suppress radial pulse. A postischemic interval of 5 minutes was followed by 5 minutes of voluntary hyperventilation.

Electromyographic signs of tetanic syndrome were considered as positive if regular repetitive activity persisted for 2 minutes (uniplets, doublets, multiplets) at least during one of these three intervals (ischemic, postischemic, hyperventilation).

Statistical Analysis

A distribution of variables was described by mean, standard deviation and 95% confidence interval. Differences

between groups were compared by student's test if the Kolmogorov-Smirnov goodness of Fit test showed normal distribution. Categorical variables were analyzed by the Chi²-test. Differences were considered significant at a 5% level (p < 0.05).

Results

During the study period from August 1984 to December 1988 the incidence of hyperemesis gravidarum was 4‰. 91 women suffering from hyperemesis gravidarum were asked to participate in the study. The period between delivery and examination was 10 to 50 months. Women with hyperemesis gravidarum were compared with the same number of controls matched in age and time after delivery. There was no difference in regard to age, body weight and height (tab. 1). Women with hyperemesis gravidarum suffer significantly more often from goiter, migraine and pyelonephritis (tab. 2). Characteristic

Tab. 3: Data of gynaecological history characteristic of tetanic syndrome.

| | Hyperemesis gravidarum (n = 40) | | Control (n = 40) | | Significance p = |
|---|------------------------------------|----|---------------------|----|---------------------|
| | n | % | n | % | |
| Irregularity of menstruation | 23 | 58 | 8 | 20 | < 0.001 |
| Hypermenorrhoea | 27 | 68 | 5 | 13 | << 0.001 |
| Dysmenorrhoea | 17 | 43 | 4 | 10 | 0.001 |
| Miscarriages | 11 | 28 | 2 | 5 | 0.006 |
| Hormonal contraceptives | 17 | 43 | 30 | 75 | 0.003 |
| Number of previous deliveries ¹⁾ | 26 | | 32 | | 0.138 |
| ¹⁾ with h.g.* | 17 | | 0 | | << 0.001 |

* h.g. = hyperemesis gravidarum

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data of gynaecological history are enlisted in (tab. 3). As a typical pattern of the tetanic syndrome, irregular menstruation, hypermenorrhoea and dysmenorrhoea were significantly more common in the hyperemesis gravidarum group. In addition the number of miscarriages is significantly increased. Hormonal contraception is less often tolerated.

Women with hyperemesis gravidarum had a higher risk of abnormal pregnancy. Preterm labour, hypertension and delivery before completed 37 weeks of gestation were significantly more frequent in this group. There were no differences in birthweight and height of the children. The duration of pregnancy was slightly but significantly reduced in the hyperemesis gravidarum group (tab. 4). Moreover, there were two perinatal death (tab. 5). In the hyperemesis gravidarum group one preterm infant died 7 days after delivery because of immaturity and one with Potter syndrome died 4 hours after delivery.

Tab. 5: Perinatal problems – diseases of children.

| | Hyperemesis gravidarum | Control |
|---------------------------------------|------------------------|---------|
| Frequent infections | 4 | 1 |
| Delay of neonatal motoric development | 3 | 0 |
| Perinatal death ¹⁾ | 2 | 0 |
| Endogenous eczema | 2 | 1 |
| Malformation ²⁾ | 1 | 0 |
| Icterus | 0 | 1 |
| Fits after delivery | 1 | 0 |
| Coeliac disease | 1 | 0 |
| Pneumothorax | 1 | 0 |

¹⁾ immaturity, Potter syndrome

²⁾ myopia and nystagmus

Tab. 6: Clinical signs of hyperirritability.

| | Hyperemesis gravidarum (n = 40) | | Control (n = 40) | | Significance p = |
|-----------------|---------------------------------|----|------------------|----|------------------|
| | n | % | n | % | |
| Cramps | 21 | 53 | 6 | 15 | < 0.001 |
| Paraesthesia | 17 | 43 | 6 | 15 | 0.007 |
| Chvostek's sign | 11 | 28 | 1 | 3 | 0.002 |

Tab. 4: Complications during pregnancy.

| | Hyperemesis gravidarum (n = 40) | | Control (n = 40) | | Significance p = |
|----------------------------------|---------------------------------|------|------------------|------|------------------|
| | n | % | n | % | |
| Haemorrhage ante partum | 4 | 10 | 1 | 2.5 | 0.168 |
| Pyelonephritis | 4 | 10 | 3 | 7.5 | 0.7 |
| Incompetent cervix | 10 | 25 | 4 | 10 | 0.078 |
| Preterm labour | 6 | 15 | 1 | 2.5 | 0.048 |
| Hypertension | 7 | 17.5 | 0 | 0 | 0.005 |
| Preeclampsia | 3 | 7.5 | 0 | 0 | 0.078 |
| Delivery < 37 weeks of gestation | 5 | 12.5 | 0 | 0 | 0.021 |
| | weeks | SD | weeks | SD | p |
| Duration of gestation (weeks) | 39.12 | 2.19 | 39.90 | 0.38 | < 0.05 |

These women reported frequently symptoms and signs attributed to a tetanic disposition like cramps, paraesthesia and Chvostek's sign (tab. 6). Tab. 7 shows the results of the EMG provocation test indicating an enhanced neuromuscular irritability.

Patients with hyperemesis gravidarum suffer from decreased efficiency and an increased need of sleep. They notice significantly more often a distinct loss of hair and a brittleness of fingernails (tab. 8).

There were no differences between the two groups in respect to serum potassium and calcium concentration. The mean serum and erythrocyte magnesium concentration were significantly lower in the hyperemesis gravidarum group (tab. 9).

Discussion

These data clearly establish that tetanic

syndrome is more frequent in women suffering from hyperemesis gravidarum than in normal pregnancy. In the presence of hyperemesis gravidarum, serum and red cell magnesium concentrations are even lower than in normal pregnancy. It therefore seems reasonable to assume that hyperemesis gravidarum, tetanic syndrome and magnesium deficiency are in some way associated.

Women affected with tetanic syndrome exhibit both the characteristic neuromuscular and sensory hyperirritability (muscle cramps and acral paraesthesia) and increased irritability of subcortical structures (Gabersek et al., 1969). This latter disorder is manifested clinically by an increased need of sleep and a substantial liability to dizziness, nausea and vomiting.

Tab. 7: Number of positive results indicating an enhanced neuromuscular irritability during EMG provocation test.

| | Hyperemesis gravidarum (n = 40) | | Control (n = 40) | | Significance p = |
|-------------------------|---------------------------------|----|------------------|----|------------------|
| | n | % | n | % | |
| Ischemic period | 7 | 18 | 0 | | 0.005 |
| Postischemic period | 3 ¹⁾ | 8 | 0 | | 0.078 |
| Hyperventilation period | 29 | 73 | 14 | 35 | < 0.001 |

¹⁾ because of threatening seizures indicated by carpopedal spasms, the test was done without hyperventilation in one case.

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Tab. 8: Clinical signs of tetanic disposition.

| | Hyperemesis gravidarum (n = 40) | | Control (n = 40) | | Significance p = |
|-------------------------------------|---------------------------------|----|------------------|----|------------------|
| | n | % | n | % | |
| Decreased efficiency | 23 | 57 | 8 | 20 | < 0.001 |
| Hypersomnia ¹⁾ | 18 | 45 | 6 | 15 | 0.003 |
| Distinct loss of hair | 6 | 15 | 0 | 0 | 0.010 |
| Distinct brittleness of fingernails | 14 | 35 | 4 | 10 | 0.007 |

¹⁾ need of sleep \leq 10 h/d

The effectiveness of high-dose oral magnesium in the management of the tetanic syndrome has been proved by various placebo-controlled double-blind trials. In addition to other target parameters such as relief of muscle cramps, increase in muscular power and performance of the brain, the calming effect on the irritability of subcortical structures was demonstrated by electronystagmographic studies (Fehlinger et al., 1981).

In the present study, abnormalities such as preterm labour and premature delivery were found to be more frequent in patients suffering from hyperemesis gravidarum. It appears reasonable to assume that there is a relationship between these disorders and magnesium deficiency, since preterm labour and premature delivery were less frequent in pregnant women receiving magnesium replacement (Spätling and Spätling, 1988). Moreover, electromyographic signs of the tetanic syndrome are more commonly observed in patients with premature delivery (Fehlinger et al., 1984). In pregnancy, latent magnesium deficiency is aggravated, since increased magnesium demands are associated with augmented magnesium excretion in the

urine (Spätling et al., 1985). Thus, the large variety of symptoms of subclinical magnesium deficiency may become manifest in pregnancy.

Since the tetanic syndrome may be controlled by magnesium replacement, magnesium might have a beneficial effect on hyperemesis gravidarum. Further studies should be performed to elucidate this question. Intravenous therapy is imperative in the management of hyperemesis gravidarum. Thus, the infusion of some 40 mmol daily would be no problem.

As stated above, the factors causing hyperemesis gravidarum are complex. Nevertheless, it is conceivable that the irritability of subcortical structures resulting from magnesium deficiency increases the sensitivity to certain alterations including the appearance of hyperemesis gravidarum.

To discover patients at risk for tetanic syndrome, more attention should be directed during prenatal care toward this disorder, which is characterized by a large variety of anamnestic and clinical features (Fehlinger et al., 1985).

In addition to general recommendations regarding magnesium replacement during pregnancy, patients with symptoms suggestive of tetanic syn-

drome should be given the largest tolerable amounts of oral magnesium until they produce a soft stool.

References

- Alajouanine, Th.; Contamin, F.; Cathala, H.P.; Scherrer, J.: Contribution électromyographique a une delimitation de la tétanie de l'adulte. *Presse méd.* **62** (1954) 339-342.
- Benson, R.C.: Gastrointestinal disorders. In: Benson, R.C. (ed.): *Current Obstetrics & Gynecologic diagnosis & treatment*. Lange Medical Publication, California 1984, pp. 897-899.
- Bouillon, R.; Naesens, M.; VanAssche, F.A.; DeKeyser, L.; DeMoor, F.: Thyroid function in patients with hyperemesis gravidarum. *Am. J. Obstet. Gynecol.* **143** (1982) 922-926.
- Chin, R.K.H.; Los, T.T.H.: Thyroxine concentration and outcome of hyperemesis pregnancies. *Brit. J. Obstet. Gynaecol.* **95** (1988) 507-509.
- Depue, R.H.; Bernstein, L.; Ross, R.K.; Judd, H.L.; Henderson, B.E.: Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome and other maternal factors. *Am. J. Obstet. Gynecol.* **156** (1987) 1137-1141.
- Evans, A.J.; Li, T.C.; Selby, C.; Jeffcoate, W.J.: Morning sickness and thyroid function. *Brit. J. Obstet. Gynaecol.* **93** (1986) 520-522.
- Fairwether, D.V.I.: Nausea and vomiting in pregnancy. *Am. J. Obstet. Gynecol.* **102** (1968) 135-175.
- Fehlinger, R.; Franke, L.; Glatzel, E.; Meyer, E.; Michalik, M.; Rapoport, S.M.; Rüstow, M.; Schulz, Ch.; Schumann, G.: Klinische Studien zur Magnesiumbehandlung des tetanischen Syndroms. *Mag. Bull.* **3** (1981) 298-306.
- Fehlinger, R.; Kemnitz, C.; Dreißig, P.; Egert, M.; Seidel, K.: Frühgeburtlichkeit, tetanische Reaktionsbereitschaft und Magnesiummangel: Eine retrospektive Untersuchung an 132 Müttern. *Mag. Bull.* **6** (1984) 52-59.
- Fehlinger, R.; Seidel, K.: The Hyperventilation Syndrome: A Neurosis or a Manifestation of Magnesium Imbalance? *Magnesium* **4** (1985) 129-136.
- Gabersek, V.; Durlach, J.: Electronystagmogramme et forme de spasmophilie

Tab. 9: Mineral concentration (mmol/l) in serum and erythrocytes.

| | Hyperemesis gravidarum (n = 40) | | | mean | Control (n = 40) | | Significance |
|--------------------------|---------------------------------|------|-----------|------|------------------|-----------|--------------|
| | mean | SD | CI 95% | | SD | CI 95% | |
| Potassium in serum | 4.61 | 0.41 | 4.48-4.74 | 4.55 | 0.36 | 4.44-4.66 | n.s. |
| Calcium in serum | 2.45 | 0.10 | 2.43-2.49 | 2.44 | 0.10 | 2.40-2.47 | n.s. |
| Magnesium in serum | 0.79 | 0.05 | 0.77-0.80 | 0.85 | 0.05 | 0.84-0.89 | p < 0.05 |
| Magnesium in erythrocyte | 2.00 | 0.16 | 1.95-2.05 | 2.18 | 0.16 | 2.13-2.23 | p < 0.05 |

SD - Standard Deviation, CI - Confidence Interval, n.s. - not significant

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- du déficit magnésique. *J. méd. Besancon* 5 (1969) 361-370.
- Järmfeld-Samsioe, A.; Samsioe, G.; Velinder, G.-M.*: Nausea and vomiting in pregnancy. — A contribution to its epidemiology. *Gynec. Obstet. Invest.* 16 (1983) 221-229.
- Kauppila, A.; Huhtanemi, J.; Ylikorkala, O.*: Raised human chorionic gonadotropin concentrations in hyperemesis gravidarum. *Br. med. J.* 1 (1979) 1670-1671.
- Kauppila, A.; Heikinheimo, M.; Lohela, H.; Ylikorkala, O.*: Human Chorionic Gonadotropin and Pregnancy specific Beta-1 Glycoprotein in Predicting Pregnancy outcome. *Gyn. Obstet. Inrest.* 18 (1984) 49-53.
- Molinski, H.*: Die unbewußte Angst vor dem Kinde. Kindler, München 1972.
- Pritchard, J.A.; MacDonald, P.C.; Gant, N.F.*: Williams Obstetrics, Vol. 17, Appleton century crofts, Norwalk Connecticut 1985, p. 613.
- Soules, M.R.; Hughes jr., C.L.; Garcia, J.A.; Livengood, Ch.; Prystowski, M.R.; Alexander, E.*: Nausea and vomiting of pregnancy: Role of human chorionic gonadotropin and 17-hydroxy-progesterone. *Obstet. Gynecol.* 55 (1980) 696-700.
- Spätling, L.; Kunz, P.A.; Huch, R.; Huch, A.*: Magnesium and calcium excretion during pregnancy. *Mag. Bull.* 7 (1985) 91-93.
- Spätling, L.; Spätling, G.*: Magnesium supplementation in pregnancy. A double-blind study. *Brit. J. Obstet. Gynaecol.* 95 (1988) 111-116.

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