

A LITERATURE REVIEW OF PREGNANCY SICKNESS

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C. OBSTETRIC CONDITIONS RELATED TO NVP OR HG

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Chapter C

23. **HYPEREMESIS GRAVIDARUM AS A CAUSE OF MATERNAL MORTALITY**

1925-36 15 deaths out of 396 cases of hyperemesis gravidarum. (14)

In the whole of North West Scotland there were 14 maternal deaths due to hyperemesis gravidarum between 1931 and 1940. There was one such death between 1940 and 1956. (9)

Lupzic Clinic, Pokorny, showed falling maternal mortality due to hyperemesis gravidarum:

1900-1924	2.8%
1925-1936	0.75%
1937-1954	0.28%
1955-1959	0.0%

(10)

Results from the treatment of moderately severe and severe cases of vomiting of pregnancy at the Boston Lying-in Hospital:

Years	Deliveries	Maternal Deaths	Percentage
1930-1933	12,675	7	0.047%
1934-1937	14,600	0	

(1)

In Britain the maternal mortality from hyperemesis fell from 159 per million total births in the years 1931-40 to three per million between 1951 and 1960. (75)

Summary

Maternal mortality due to hyperemesis gravidarum became extremely rare after 1955.

24. **HYPEREMESIS GRAVIDARUM AND HYDATIDIFORM MOLE**

1. Hyperemesis gravidarum occurred in 26% of patients who had a complete hydatidiform mole, study population not included. (25)
2. 8% of patients, 6 out of 74 with complete hydatidiform mole, presented with hyperemesis gravidarum. (55)
3. 6% of women with hydatidiform mole presented with hyperemesis gravidarum. (Papua New Guinea). 37 women with hydatidiform moles. (56)
4. 23% of 39 women with hydatidiform mole presented with hyperemesis gravidarum (Guadalajara). (57)

5. Three out of 15 patients (20%) with hydatidiform mole presented with weight loss due to hyperemesis. (Barnie-Adshead, 1980, not published).
6. Six out of 40 women (15%) with hydatidiform mole presented with nausea and vomiting. (58)
7. Frequency of most common symptoms occurring prior to evacuation in patients with molar pregnancies (347 patients, 50=14%) excessive nausea and vomiting. (59)
8. Roughly 10% of 196 patients with hydatidiform mole are hospitalised with severe vomiting and weight loss. (60)
9. Hyperemesis gravidarum occurs in nil of 69 patients with trophoblastic disease. (26)

Summary

Hyperemesis gravidarum is more common in hydatidiform moles than in normal singleton pregnancies. (25) (55) (56) (57) Barnie-Adshead (58) (59) (60)

Total: Eight References

Hyperemesis gravidarum is no more common in trophoblastic disease. (26)

Total: One Reference

24a. NV AND CHORIOCARCINOMA

“Very raised serum and cerebrospinal fluid levels of human chorionic gonadotrophin occur with choriocarcinoma in the absence of nausea and vomiting, provided there are no gastrointestinal or cerebral metastases”. - Personal communication, Bagshawe, K D 1995.

25. HYPEREMESIS GRAVIDAUM (HG) AND NAUSEA AND VOMITING IN PREGNANCY (NVP) AFTER PREVIOUS UNSUCCESSFUL PREGNANCY (MISCARRIAGE, STILLBIRTH OR NEONATAL DEATH)

1. In no fewer than 41% of 207 HG patients is there a history of previous unsuccessful pregnancy. In a control population 1,719 cases (13.6%) gave a history of previous unsuccessful pregnancy. (10)
2. Among 2,500 patients evaluated in the general clinic population there were 432 multiparas with previous abortions of whom 229 vomited (53.1%). Among the remaining 2,078 patients, 707 vomited (34%). The difference between these two percentages is statistically significant (t=7.3). (3)
3. 86 women with hyperemesis gravidarum: the number of these women having a past history of abortion (24.4%) is much higher than would be expected from the general obstetric population (10%). (26)
4. 27.4% - 52/190 women with hyperemesis gravidarum reported a spontaneous abortion in a previous pregnancy compared to 17.3% 36/209, in the control group (P<0.05). (64)
5. Vomiting compared to non-vomiting was not more common among women experiencing prior fetal loss. 4,517 vomited, 3,502 did not vomit. (18)
6. No obvious correlation between emesis gravidarum and a history of previous unsuccessful pregnancy (previous abortion, ectopic pregnancy, etc) was found. 62 women complained of NVP, 28 no NVP. (27)
7. The numbers of previous pregnancies, miscarriages and terminations were not significant comparing those with the symptoms of NVP to those with no symptoms. 500 women, 380 had NVP. (27)
8. No significant association between duration of nausea and previous miscarriage. 363 women, 292 had NVP. (53)

Summary

Increased symptoms associated with previous unsuccessful pregnancy.

(10) (3) (26) (64) ▲ Three of these references refer to HG.

Total: Four References

Previous unsuccessful pregnancy not related to NVP. (18) (19) (27) (53)

Each of these references refers to NVP.

Total: Four References

▲ P value recorded

26. **NVP IN RELATION TO MISCARRIAGE**

1. The significant relationship between NVP and miscarriage is a reverse one i.e. the more severe the nausea and vomiting the less tendency to abort. 100 women, 11 miscarried. (4)
2. Gravidae who do not experience NVP in the first trimester have higher abortion rates. 1,910 normal births, 27.1% no NVP, 126 miscarriages, 46.5% no NVP. (5)
3. There is a lower frequency of NVP in pregnancies resulting in spontaneous abortion. 855 singleton deliveries, 56 abortions. Frequency of emesis in pregnancies with different outcomes, Infants 70%, Spontaneous Abortions 50%. (6)
4. Hyperemesis gravidarum patients did not have any increased incidence of spontaneous abortion compared with the general obstetric population. (10)
5. Women who do not suffer nausea in early pregnancy experience abortion rates nearly three times as high as gravidas who experience NVP in early pregnancy. 4,277 gravidas. (12)
6. A deficit of prescriptions of anti-histamine (anti-emetic drugs) in women whose pregnancies ended in abortion was found in the Royal College of General Practitioners' Research Unit Outcome of Pregnancy study, conducted between 1967 and 1968, suggesting that emesis gravidarum is associated with a good prognosis for pregnancy. 9,147 pregnancies. (D M Fleming, personal communication).
7. 591 (11.9%) patients used anti-emetics out of a total patient population of 4,954 who had living normal infants, but of 423 women who later had a miscarriage, only 22 (5.2%) used anti-emetics. (16)
8. Among pregnancies carried to at least 14 weeks there were 153 miscarriages (3.4%) among the vomiting group total vomiting 4,517 pregnancies, and 184 (5.3%) among the non-vomiting group, total 3,502 pregnancies in the non-vomiting group. (18)
9. Women with no symptoms of NVP experienced a significantly greater proportion of fetal deaths. 414 pregnancies, 44 women had no NVP. (21)
10. Women with hyperemesis (419) had fewer spontaneous abortions than women who did not vomit (836). 6/419 (1.43%) hyperemesis, 25/836 (2.99%) controls. (22)
11. A statistical re-analysis confirmed the decreased risk of miscarriage associated with gestational NVP. The meta-analysis also revealed that 150 additional possibly unreported studies with contradictory evidence would be required to refute this observed association. Meta-analysis included 7 studies based on 18,464 pregnancies of 17,760 women. (30)
12. The analysis indicated that vomiting was associated with decreased risk of miscarriage ($P < 0.001$) 873 women in the study delivered a singleton birth, 31% had no NVP. There were 32 women in the miscarriage group, 20 (62.5%) had no NVP. (44)
13. 32 women miscarried and were therefore excluded from the main study. Of those 32 miscarriages, 50% were associated with no symptoms of pregnancy sickness, whereas of 363

- women in the main study, 19.6%, had no NVP (Gadsby, 1993, not published).
14. The risk of spontaneous abortion was higher in women who were not nauseated at all during pregnancy. 1,553 (a 20% sample of 7,767 pregnancies) singleton live births 29.9% no NVP. 450 miscarriages 41.1% no NVP. (51)
 15. In the 164 women in the study with hyperemesis gravidarum the risk of spontaneous abortion was 3.1% compared to a prevalence of 15% in previously reported populations (P<0.001). Thus hyperemesis gravidarum would appear to be a protective factor for spontaneous abortion. (64)
 16. 30 women with hyperemesis gravidarum causing a weight loss of greater than 5% of their pre-pregnancy weight had a spontaneous abortion rate of 2 (6.6%) compared to prevalence of 15% in the previously reported populations. (42)
 17. Women with spontaneous abortions: 52% nauseated, 46.4% no nausea; 607 women had spontaneous abortions. Controls 1,284 women: 71.7% nauseated; 28.3% not nauseated. (43)
 18. For the 160 women who completed the study, 74% reported nausea. Of the 20 who miscarried and for whom data are available (n=14), 70% reported nausea. (80)

Summary

There is a lower occurrence or severity of NVP in pregnancies resulting in spontaneous abortion. (4) (5) (6) (10) (12) Fleming (16) (18) (21) (22) (30) (42) (43) (44) Gadsby (51) (64) [▲] (80)
1,863 miscarriages involved in these 18 studies. Total: Eighteen References

MORE DETAILED SUMMARY OF NVP AND HG IN RELATION TO MISCARRIAGE

1. Women with HG have a lower risk of abortion. (22) (42) (64)
- 1a. Women with HG did not have any increased incidence of spontaneous abortion. (10)
2. Increased NVP is associated with less risk of miscarriage. (4) Fleming (16) (30)
3. Increased risk of miscarriage with no NVP. (5) (12) (18) (21) Gadsby (44) (51)
4. Lower frequency of NVP in pregnancies resulting in abortion. (6) (43) (80)

[▲] P value recorded

PLEASE NOTE

On average 25% of women who deliver a single normal infant have no symptoms of NVP. (RI 6)

27. REDUCED MATERNAL WEIGHT GAIN IN CURRENT PREGNANCY RELATED TO NVP AND HYPEREMESIS GRAVIDARUM

1. Women admitted repeatedly with hyperemesis have a more severe nutritional disturbance associated with significantly reduced maternal weight gain. 140 patients with HG, 70 admitted on only one occasion, 39 admitted on multiple occasions. 31 patients lost to follow-up. (33)
2. Women with hyperemesis gravidarum tended to gain less weight during pregnancy. 419 women with hyperemesis gravidarum. 836 women who did not vomit. (22)
3. No relation between maternal weight gain and NVP, 363 women. (53)
4. The weight gain during pregnancy for women with no NVP, nausea only and vomiting of pregnancy was not too different. 414 women, 44 had no NVP. (21)
5. Of 555 women in Cohort B (those specially requesting advice regarding the management of nausea and vomiting in pregnancy), 9.3% reported weight loss associated with vomiting in

pregnancy. There was a significant correlation between maximal number of daily episodes of vomiting and maximal weight loss ($r=0.25$ $P<0.0001$). Women with one episode of vomiting per day experienced an average of 1.5kg weight loss and those with 10 episodes per day reported a mean weight loss of 6kg. (83)

6. Group A mothers (Hyperemesis Gravidarum with weight loss greater than 5% pre-pregnancy weight) gained 9.6 ± 2.4 kg and Group B mothers (HG with less than 5% pre-pregnancy weight gain) 13.7 ± 3.2 kg. $P<0.05$. (42)

Summary

No difference in maternal weight gain in relation to NVP. (53) (21)

Total: Two References

Hyperemesis associated with reduced weight gain. (33) (22) (83) (42)

Total: Four References

28. **PRE-ECLAMPTIC TOXAEMIA IN THE CURRENT PREGNANCY IN RELATION TO NVP OR HG**

1. No correlation between nausea and pre-eclamptic toxemia. 853 singleton deliveries. (6)
2. There is no difference in emesis gravidarum between patients with oedema and those without it. Oedema was reported in 30 patients. In late pregnancy, 5 patients developed proteinuria, 4 of them had suffered from emesis gravidarum in early pregnancy. 102 women in study. (19)
3. There was no association between hours of nausea and pre-eclamptic toxemia in current pregnancy. $P=0.89$. 363 women. (53)
4. The incidence of pre-eclampsia was not different between vomiting and non-vomiting patients. 3.0% PET with no NVP 361 women. 3.9% PET with vomiting. 922 women. (63)
5. Vomiting was not more common in women with proteinuria 2+ or greater. 4,517 women vomited, 3,502 women did not vomit. (18)
6. It would not appear that patients suffering from hyperemesis have any greater risk of developing toxemia in late pregnancy than does the general obstetric population. (10)
7. There was no significant difference in the incidence of eclampsia in the current pregnancy between women with hyperemesis and controls. 164 women with hyperemesis gravidarum, 209 controls. (64)
8. Even after controlling for chronic hypertension a modest association between severe vomiting and pre-eclampsia was still present. 1,867 subjects with single births. 1,666 had no vomiting, 201 with severe vomiting. Definition of severe vomiting not included. (65)
9. 24 women with eclampsia in 1,379 deliveries, 6 (25%) had hyperemesis gravidarum. Definition of HG not included. (68)
10. Maternal diagnosis of pre-eclampsia was less frequent when the woman had used meclizine. 16,536 women used meclizine in the first 12 weeks of pregnancy. Meclizine was mainly used for NVP. (133)

Summary

Women with pre-eclamptic toxemia no increase in NVP.

(6) (10) (18) (19) (53) ▲ (63) (64) (133)

Total: Eight References

Modest association between severe vomiting and pre-eclampsia. (65)

Total: One Reference

High incidence of hyperemesis gravidarum in eclamptic patients. (68)

Total: One Reference

29. **INTRA-UTERINE GROWTH RETARDATION IN RELATION TO NVP OR HG**

1. The foetuses of gravidas admitted for hyperemesis gravidarum are not at increased risk for growth retardation. 193 patients with hyper emesis gravidarum. 13,053 pregnant women in the study population. (61)
2. There was no significant difference in the incidence of intra-uterine growth retardation between women with hyperemesis gravidarum (164) and the control group (209). (64)
3. Women with hyperemesis gravidarum causing loss of greater than 5% of their pre-pregnancy weight, Group A (n=30), we compared to women with symptoms of nausea and vomiting but maintaining at least 95% of their pre-pregnancy body weight. Group B (n=34). Baby's growth retardation occurred in Group A. (42)
4. A modest association between severe vomiting and small for gestational age infants was identified in the present study. 201 women with severe vomiting, compared to 1,666 women with no vomiting. (65)
5. 18% of infants in the multiple admissions group were small for gestational age as compared to 7% in the single admissions group. This difference approached but did not achieve statistical significance. (33) A small for gestational age infant was diagnosed on the basis of weight <10% of age using the Brenner growth curve. (33)
6. No significant association ($P<0.05$) of freedom from nausea with intra-uterine growth retardation. 7,767 pregnancies, 2,253 pregnancies with no nausea. (51)

Summary

- A. Severe hyperemesis gravidarum association with intra-uterine growth retardation.
Total 235 women with hyperemesis. (33) (42) (65)
Total: Three References
 - B. Hyperemesis gravidarum not associated with intra-uterine growth retardation.
Total 359 women with hyper emesis. (61) (64)
Total: Two References
 - C. No association between freedom from nausea and intra-uterine growth retardation.
2,253 pregnancies no nausea. (51) ▲
Total: One Reference
- ▲ P Value Recorded

Severe hyperemesis defined as loss of greater than 5% of pre-pregnancy weight or multiple admissions to hospital for HG.

30. **LENGTH OF PREGNANCY < 37 WEEKS IN RELATION TO NVP OR HG**

1. Women experiencing vomiting were less likely to experience delivery before 37 weeks. ($P=0.004$). Women who vomited carried their pregnancies approximately 1.5 days longer on average before and after adjustment. ($P<0.001$). Total vomiting group 4,517 pregnancies and 3,502 pregnancies in the non-vomiting group. (18)
2. 30 hyperemesis patients mean gestational age of delivery 39.9 weeks. (36)
3. Pregnancy outcomes between hyperemesis gravidarum patients and the general population were similar in the two groups 38 weeks. The percentage of infants born before week 37 of

- gestation was 22% in the general population, similar to 23% in the hyperemesis group. 193 women with hyperemesis gravidarum. 13,053 pregnant women in study population. (61)
4. Babies of gravidas admitted for hyperemesis gravidarum are not at increased risk of prematurity i.e. < 37 weeks. 138 patients with HG. Mild HG = n 40, 7 delivered before 37 weeks = 17.5%. Severe HG n = 98, 11 delivered before 37 weeks = 11.2%. Controls n = 12,335, delivered before 37 weeks, 1,370 (10.7%). (62)
 5. Maturity at delivery the same for patients with vomiting and those with no vomiting. No vomiting 38.9 ± 3.3 weeks. Vomiting 39.4 ± 0.8 weeks. 526 women with no vomiting, 927 women with vomiting. (63)
 6. There was no statistical difference in the length of gestation between patients with hyperemesis gravidarum and the control group. Hyperemesis 164 patients 38.8 weeks. Controls 209 patients, 39.1 weeks. (64)
 7. All infants of mothers with severe hyperemesis gravidarum (n=9) were 38 weeks or beyond at delivery. (73)
 8. Gestational age at birth, 38.7 ± 2.7 weeks. 162 patients treated for HG over three years. (82)
 9. The mean gestation at delivery in the three groups (severe HG n=46, mild HG n=26 and controls n=8,802) was not different. Controls n 8,802, 39.4 ± 1.9 weeks. Severe HG n 46, 38.9 ± 2.4 weeks. Mild HG n 26, 39.2 weeks. (28)
 10. There were no significant differences in gestational age at delivery, both 39.2 + 39.5 weeks. 64 women with HG n = Group A 30, n = Group B 34. (42)
 11. Patients with HG admitted to hospital once or those admitted more than once showed no difference in gestational age at delivery. Single admission n = 70 women, 38.9 ± 2 weeks. Multiple admission n = 39 women, 38.3 ± weeks. (33)
 12. No correlation between nausea and pre-term labour. 855 singleton deliveries. (6)
 13. NVP not related with length of gestation. 873 women in the study. 69% had NVP. (44)
 14. Our observations indicate that nausea and vomiting of pregnancy does not imply an excessive risk of pre-term birth. 309 singleton pregnancies. (13)
 15. Moderate increase in somewhat shorter pregnancies, 36-40 weeks, in hyperemesis gravidarum. But not for very short pregnancies (below 36 weeks). The excess for < 38 weeks gestation is statistically significant. (P<0.001). 3,068 women with hyperemesis. (29)
 16. Pre-term birth occurred at a reduced rate after meclizine use. 16,536 women used meclizine in the first 12 weeks of pregnancy mainly for NVP. (133)
 17. 17 Patients with hyperemesis gravidarum in the study. Apart from one premature delivery at 33 weeks, all patients gave birth between 38 and 41 weeks of gestation. (125)

Summary

Women with HG or NVP not likely to experience delivery before 37 weeks.

(6) (18) (28) (33) (36) (42) (44) (61) (62) (63) (64) (73) (82) (13) (133) (125)

Total: Sixteen References

Moderate increase in somewhat shorter pregnancies in hyperemesis gravidarum. (29)

Total: One Reference

There is therefore no association between HG or NVP and premature labour.

31. **SEX OF NEWBORN IN RELATION TO NVP OR HG**

1. No significant difference in emesis rate could be ascribed to the sex of the newborn. 102 women. (19)
2. In all results concerning the outcome of pregnancy, including the male-female ratio of the offspring, the two groups (those with and those without emesis) showed no significant difference. 500 women, 124 had no symptoms. (27)
3. The percentage of women nauseated during pregnancy was 70.1% in those who delivered a boy and 73.3% in those who delivered a girl, a difference that was not statistically significant. 7,767 pregnancies. (51)
4. There was no association between hours of nausea and sex of the baby. 363 women. (53)
5. There was no statistical significance in the gender of the offspring between the women with hyperemesis gravidarum (164 women) and the control group (209 women). (64)
6. In hyperemesis gravidarum there were fewer male infants. 3,068 women with hyperemesis gravidarum. Nearly one million births. (29)
7. There was a significant correlation between participants who later gave birth to girls and the vomiting or retching subscale ($P=0.015$). These women experience more severe vomiting or retching than those bearing male infants. $P<0.03$. The nausea subscale was not significantly correlated with gender of the infant. 100 women in study. (48)
8. There was a significant correlation between women who later gave birth to girls and the vomiting and retching subscale. 66 women with hyperemesis gravidarum. (49)
9. Although the male to female ratio of all births was 51.4/48.6, the ratio among mothers admitted to hospital for hyperemesis gravidarum during the first trimester was 44.3/55.7 $P<0.000001$ compared with all births. 1,027,213 births, 8,816 (0.79%) were preceded by a hospital admission for hyperemesis gravidarum. (66)
10. The occurrence of nausea and vomiting did not predict the sex of the child. 160 women in study. (80)
11. Pregnant women hospitalised for hyperemesis gravidarum in the first trimester had a 50% increased odds of having a female infant compared with controls (OR 1.5, 95% CI 1.4, 1.7). Women hospitalised for three or more days had the greatest odds of having a female infant compared with control women. (OR 1.8, 95% CI 1.5, 2.0). 2,110 women hospitalised for hyperemesis gravidarum. 9,783 pregnant women without hyperemesis gravidarum. (127)

Summary

No association between sex of newborn in mothers with NVP.

(19) (27) (51) (53) (64) (80)

Total: Six References

Infant girls more common when mother has hyperemesis gravidarum or severe NVP.

(29) (48) ▲ (49) (66) ▲ (127)

Total: Five References

▲ P Value Recorded

32. **NVP OR HG IN RELATION TO BIRTH WEIGHT OF BABY**

1. Infants of vomiting mothers were not more likely to be of low birth weight than were infants of non-vomiting mothers in either the crude or adjusted analysis. Birth weight $< 2,500g$ $p=0.45$, the mean birth weight of infants born to mothers both with and without vomiting was

- 3,203g. 4,517 women reported vomiting and 3,502 women did not vomit by 16 weeks. (18) ▲
2. There were no differences in birth weights between the two groups, those with NVP or those with no symptoms. 62 women complained of emesis gravidarum. 28 had no symptoms of NVP. (19)
 3. NVP not related to birth weight. 873 women in study, 602 women (69%) had NVP. (44)
 4. No significant relationship was found between infant birth weight and any of the subscales, i.e. nausea, vomiting or retching. Pregnancy resulted in a live birth for 100 women. (48)
 5. NVP not related to birth weight. 363 women with normal live singleton deliveries. 292 women had NVP. (53)
 6. Our observations indicate that nausea and vomiting of pregnancy does not imply an excess risk of low birth weight. 309 singleton pregnancies. (13)
 7. Birth weight, $3,286 \pm 659\text{g}$. 162 patients treated for HG over three years. (82)
 8. Birth weights of babies the same for all four groups of NVP. 1,453 women with singleton pregnancy - Gr1 No symptoms; Gr2 Nausea only; Gr3 Vomiting; Gr4 HG. (63)
 9. The occurrence of nausea and vomiting did not predict the birth weight of the child. 160 women in study. (80)
 10. No difference in birth weight for babies with morning sickness, $3,289 \pm 553\text{gms}$ (67%) and mothers with no morning sickness, $3,179 \pm 466\text{gms}$ (33%). 180 women in study. (104)
 11. There is certainly no suggestion that the patient who suffers from hyperemesis gravidarum is likely to produce an underweight baby. 105 hyperemesis gravidarum cases. (10)
 12. Average birth weight of 30 babies delivered to women with hyperemesis gravidarum. Average weight: $3.585\text{ kgm} = 7.8\text{ lbs}$. (36)
 13. Pregnancy outcome between hyperemesis gravidarum patients and the general population was similar for birth weight. 193 hyperemesis gravidarum patients, 13,053 women in study population.
 14. The mean birth weights were 3.100, 3.093, 3.160 kgms in the mild hyperemesis gravidarum, severe hyperemesis gravidarum and control groups respectively. 40 patients were diagnosed as having mild hyperemesis gravidarum and 98 as having severe hyperemesis gravidarum. 12,335 patients were defined as controls. (62)
 15. There was no statistical difference in the average birth weight of the baby between women with hyperemesis gravidarum (164) and the control group (209). 3.1229 kgms hyperemesis gravidarum, 3.1429 kgms control. (64)
 16. The birth weights of infants (n=9) with hyperemesis gravidarum attained, and slightly surpassed, the mean birth weight for gestational age. (73)
 17. The mean birth weight of the babies in the severe hyperemetic group was significantly lower than in both the mild hyperemesis gravidarum group ($P < 0.05$) and the control group ($P < 0.001$). Total hyperemesis gravidarum patients 74. 48 patients had severe hyperemesis gravidarum, one required termination, one molar pregnancy. 72 hyperemesis gravidarum patients in study population. Control group 8,802 consecutive deliveries. HG classified as severe if one or more of the following conditions was present: Ketonuria 3+ on Ketostick, increase in serum creatinine, electrolyte imbalance or increase haematocrit (>0.43). (28)
 18. In hyperemesis gravidarum increased incidence of low birth weight. 3,068 women with hyperemesis gravidarum in nearly one million births. (29)
 19. Women with hyperemesis gravidarum causing a loss of greater than 5% of their pre-pregnancy weight, Group A n=30, were compared to women with symptoms of nausea and vomiting, but maintaining at least 95% of their pregnancy weight Group B, n=34. Group A babies significantly smaller with respect to birth weight expressed as a percentage for gestational age. (42)
 20. Hyperemesis gravidarum. A comparison of single and multiple admissions. Women admitted repeatedly have babies with reduced neonatal birth weights. $2,806\text{g} \pm 676\text{g}$ compared to $3,071\text{g} \pm 477\text{g}$. Study population 140 patients, 70 were admitted on only one occasion. 39

women (28%) were admitted on multiple occasions. 31 patients were lost to follow up or elected to undergo a therapeutic abortion. (33)

21. 7.9% of gravidas who did not experience NVP were delivered of low birth weight babies, whereas only 5.6% of the N & V group had low birth weight, significant. 1,910 women experienced no N & V. 5,111 experienced N & V. (5)
22. Low birth weight associated with absence of NVP. 199 women who bore single live children, 72% experienced NVP. (11)
23. A larger proportion of low birth weight infants were delivered of women having no symptoms of NVP. 414 women, 44 women had no NVP (10.6%). (21)
24. Pregnancy outcome of 17 patients with hyperemesis gravidarum. Mean birth weight was $3,176 \pm 539$ gm. All babies weighed >2500 gm. (125)

Summary

NVP not related to birth weight of baby. (13) (18) (19) (44) (48) (53) (63) (80) (82) (104)

Total: Ten References

Hyperemesis gravidarum associated with average birth weight babies.

(10) (36) (61) (62) (64) (73) (125)

Total: Seven References

Severe Hyperemesis gravidarum associated with low birth weight babies.

(28) [▲] (29) (33) (42)

Total: Four References

No NVP associated with low birth weight babies. (5) (11) (21)

Total: Three References

[▲] P value recorded

33. TWINS IN RELATION TO NVP OR HG

1. Incidence of hyperemesis gravidarum in single pregnancies (90,153 pregnancies) was 3.58 per thousand. Incidence of hyperemesis gravidarum in twin pregnancies (986 twin pregnancies) 14.2 per thousand. A very highly significant relationship ($P=0.001$) between multiple pregnancy and hyperemesis gravidarum. (10)
2. We certainly have a high incidence of hyperemesis gravidarum among our patients with twin pregnancies, 25.9 per thousand for twins compared to 5.1 per thousand for singletons. (15,099 single pregnancies and 193 twin pregnancies in the study). (26)
3. 2.2 x risk of hyperemesis gravidarum in twins ($P=<0.001$), 118 twin pregnancies in this study. (29)
4. Hyperemesis gravidarum was statistically more common in twin pregnancies. (86 twin pregnancies in the study). ($P<0.001$). (18)
5. In multiple gestations (83 twin and one triplet pregnancies) 73 (86.9%) suffered from nausea and vomiting. This difference between single, as opposed to multiple gestation, is statistically significant ($P=<0.01$). (5)
6. Higher frequency of NVP seen in study for twin pregnancies. Eight twins, seven (87.5%) had NVP. 71% NVP in study population. (6)
7. Of the blacks studied, 24 had twins. 18 (75%) of them maintained that they were very sick in that pregnancy. (41)
8. Twinning rate was increased when the woman had used meclizine. 16,536 women used meclizine in the first 12 weeks of pregnancy. Meclizine was mainly used for NVP. (133)

Summary

Increased incidence of hyperemesis gravidarum in twin pregnancies.

▲ (10) ▲ (18) ▲ (26) (29) ▲

Total: Four References

Increased incidence of NVP with twin pregnancies.

(5) (6) (41) (133)

Total: Four References

▲ P value recorded

* Being a twin does not make one more liable to NVP. Information from 2,655 twin pairs who have each had a pregnancy. (47)

34. PLACENTAL WEIGHT IN RELATION TO NVP

1. Positive correlation for increased nausea was found with heavier placental weight (P=0.005). 363 women in study. (53)
2. The placental weight of subjects who had morning sickness was higher than those who had none. (P<0.002). 33% of women had no symptoms. 180 women in study. (104)
3. No obvious correlations between emesis gravidarum and placental weight were found. (NVP n=62, no NVP n=28). (19)
4. NVP not associated with placental weight. 873 women in the study, 69% had NVP. (44)
5. There was no difference in placental weight between patients with vomiting and patients with no vomiting. 1,453 formed the study population. 63% vomited, 12% did not vomit. (63)

Summary

Increased nausea associated with heavier placentae. (53) ▲ (104) ▲

Total: Two References

NVP not associated with placental weight. (14) (44) (63) Total: Three References

▲ P value recorded

PLACENTAL PATHOLOGY IN RELATION TO NVP

No statistical difference between women with hyperemesis gravidarum (n=164) and controls n=209) in terms of placental pathology. (64)

Pathologic reviews of placentas from women receiving total parenteral nutrition with fat emulsions during the study period showed no gross abnormality. Nine women with hyperemesis gravidarum. (73)

35. HYPEREMESIS GRAVIDARUM OR NVP IN RELATION TO FETAL ABNORMALITY

35a. FETAL ABNORMALITY ASSOCIATED WITH HYPEREMESIS GRAVIDARUM (Six References)

1. Studies into 60,000 births in Leipzig Clinic found deformed children after hyperemesis

exceeded the mean (Noack, 1963). He noted that these observations were made during a period when drugs now suspected of causing deformities had not yet come on the market. From Ref (10)

2. 98 cases of hyperemesis gravidarum, 6.1% deformity. In the same clinic the overall incidence of deformity 0.65%, 1949-56. Mey R. Ref from (10).
3. 165 patients with hyper emesis, 8.3% incidence of deformity. Total births in the same clinic, 0.98% incidence of deformity. 1949-59. Holbein, 1961. Ref from(10).
4. Doring and Hossfeld reported that 4% of infants of 649 women with hyperemesis were malformed, while the control group without hyperemesis (8,422 women) showed only 1.5% malformation rate. 1964. Ref from (29).
5. Fairweather points out that the definition of what constitutes a deformity clouds observations of the incidence of fetal deformity in hyperemesis. 1968. (10)
6. 6,376 pregnancies in study population, 894 women used anti-emetics. 37 women had babies with congenital dislocation of the hip (CDH) and 13 of these took anti-emetic drugs compared to the expected four. (16)
7. An increase in central nervous system and related skeletal malformations was observed in the offspring of hyperemetic women. (22)
8. Most women who reported vomiting were mothers of longitudinal limb defects. A total of 98 cases in 11 years. (97)

35b. **SPECIFIC FETAL ABNORMALITY ASSOCIATED WITH
HYPEREMESIS GRAVIDARUM**

1. Congenital Dislocation of the Hip (CDH). 6,376 pregnancies in study population, 894 women used anti-emetics. 37 women had babies with CDH and 13 of these took anti-emetic drugs compared to the expected four. (16)
2. Hip Dysplasia. 3,068 hyperemetic women in study population. 60 infants with CDH compared to the expected 47. (29)
3. Undescended Testicles. 2,068 hyperemetic women, 21 infants had undescended testicles. This figure was roughly twice the expected one, but this diagnosis in the newborn period is uncertain. (28)
4. No significant increase in congenital hernia or undescended testicles in the vomiting n=9,255 compared to the non-vomiting group n=7,143. (20)
5. Down's Syndrome. 3,068 hyperemetic women, nine women had a baby with Down's Syndrome. Three times the expected number. (29)
6. Cleft Palate deformity. Peer and Stream reported on 228 cases of cleft palate which showed that in 10% of cases the mother had suffered from hyperemesis in pregnancy. Ref from (10)
7. Cleft Palate. 3,068 hyperemetic women, no association between hyperemesis gravidarum and cleft lip or palate was found. (29)
8. An increase in central nervous system abnormalities was observed in the offspring of hyperemetic women. Hyperemesis 6/413; no vomiting 3/833. Abnormalities in hyperemetic offspring: two anencephalics, one microcephaly, one craniosynostosis, one separation of cranial sutures and one cranial suture separation with hydrocephaly. (22)
9. Most women who reported vomiting were mothers of longitudinal limb defects (98 cases) (e.g. absence of radius and thumb where longitudinal bands of limb tissue were missing). These were infants born alive with these defects within New South Wales and the Australian capital territory between 1970 and 1981 inclusive. The estimate of risk association with vomiting in the first trimester for women of the longitudinal group and their controls were significant. RR = 2.3 (CL 1.3, 4.0). (97)

35c. **SPECIFIC FETAL ABNORMALITY LESS LIKELY TO OCCUR WITH HYPEREMESIS GRAVIDARUM. CONGENITAL HEART DISEASE**

1. Cardiac defects. 3,068 hyperemetic women. There were 24 cardiac defects, close to the expected number of 22. (29)
2. 6,376 pregnancies. 894 took anti-emetic drugs. Only two of 35 women who had infants with congenital heart disease took anti-emetic drugs. (16)
3. The most severe nausea during pregnancy was associated with a lower risk for congenital heart defect (CHD) in the child compared to no nausea (or 0.81, 95% confidence interval (CI) 0.67-0.99). The lower risk tended to disappear with less severe levels of nausea and the trend was statistically significant.
998 cases mothers. 3,029 control mothers. (67)
A possible reason for the lower risk of CHD among children with mothers who took anti-nauseant medication may be that they had more severe nausea of pregnancy which could not be measured by our scale. Alternatively, maternal use of high doses of Vit B6 (contained in Bendectin) may have had a protective effect on the embryonic heart development. (67)

35d. **NO INCREASED FETAL ABNORMALITY ASSOCIATED WITH HYPEREMESIS GRAVIDARUM (Total Seven References)**

1. 246 hyperemesis patients, only 2% incidence of deformity - no greater than average incidence for the population as a whole. 1968. (10)
2. In a study of maternal states in relation to congenital malformations, in a survey of 14,813 pregnancies, found no relationship between hyperemesis gravidarum and congenital malformation. 1950. 15 patients with hyperemesis gravidarum. (84)
3. 30 patients with hyperemesis gravidarum showed no fetal deformity. 1990. (36)
4. There was no statistical difference in congenital abnormalities in babies born to women who had hyperemesis gravidarum. Hyperemesis gravidarum 1/164, controls 2/209 1%. 1995. (64)
5. The foetuses of gravidas admitted with hyperemesis gravidarum are not at increased risk of congenital abnormalities. 138 patients with hyperemesis gravidarum. 1996. (62)
6. The pregnancy outcome between hyperemesis gravidarum (193 patients) and the general population (13,053 pregnant women in the study) was similar for the incidence of fetal abnormalities. 1996. (61)
7. Major malformations, 3 (1.9%) in 162 patients treated for HG over three years. This number is comparable to our normal population. (82)
8. 20 patients with hyper emesis gravidarum, none showed any signs of congenital abnormalities. (125)

35e. **NO INCREASED FETAL ABNORMALITY ASSOCIATED WITH NVP (Four References)**

1. Vomiting during pregnancy does not increase the risk of having a malformed infant. 9,255 women vomited, 7,143 did not vomit. 1986. (20)
2. No statistically significant association observed between nausea and vomiting of pregnancy and fetal abnormality, 873 women in study population. 1989. (44)
3. Our observations indicate that nausea and vomiting of pregnancy does not imply an excess risk of malformations. 309 singleton pregnancies in study. (13)
4. There was no general increase in the risk for a congenital malformation but sooner the opposite an apparently protective effect. 16,536 women used meclizine in the first 12 weeks of pregnancy mainly for NVP. Compared to 540,660 births whose mothers did not use

meclozine. 2003. (133)

5. In a review of over 33,000 pregnancies complicated by nausea and vomiting there was no evidence that vomiting or a diagnosis of hyperemesis gravidarum was associated with an increased or decreased incidence of malformations. (147)

35f. **FREEDOM FROM NVP NOT RELATED TO FETAL ABNORMALITY**

1. No significant association for freedom of nausea with fetal abnormality. 7,767 pregnancies, 2,253 no nausea. (51)
2. Here were no major malformations among the offspring of 130 women not experiencing nausea and vomiting. There were two major malformations among 246 women experiencing vomiting (0.81%). (123)

Summary

- a. Fetal abnormality associated with hyperemesis gravidarum.
(10) (plus 2 references from 10) (29) (16) (22) (97) Seven References
- b. Specific fetal abnormality associated with hyperemesis gravidarum.
Congenital dislocation of the hip 1 positive reference (16) One Reference
Hip Dysplasia 1 positive reference (29) One Reference
Undescended testicles 1 positive, 1 negative reference
each (28) (20) Two References
Down's Syndrome 1 positive reference (29) One Reference
Cleft palate 1 positive, 1 negative reference (10) (29) Two References
Central nervous system 1 positive reference (22) One Reference
Skeletal malformations 1 positive reference (97) One Reference
Total: Seven References
- c. Specific fetal abnormalities less likely to occur with hyperemesis gravidarum.
Congenital hernia 1 reference (20) One Reference
Cardiac defects 3 references (29) (16) (67) Three References
Total: Four References
- d. No increased fetal abnormality associated with hyperemesis gravidarum.
(10) (36) (61) (62) (64) (82) (84) (125) Eight References
- e. No increased risk of fetal abnormality associated with pregnancy nausea and vomiting.
(13) (20) (44) (133) Four References
- f. No significant association with freedom from nausea and fetal abnormality.
(51) (123) Two References

Conclusion

The spread of evidence in these papers suggest there is no positive correlation between NVP or HG and congenital abnormalities.

35g. **INCIDENCE OF MAJOR CONGENITAL DEFECTS IN THE GENERAL POPULATION**

Major malformations defined as the presence of any congenital anomaly that has an adverse effect on either the function or social acceptability of the individual. (135)

1. Major congenital defects occur in 1-3% of the general population at birth. Careful follow up

- increases the number detected to up to 5% later in life. (130)
2. In summary it is probably not far wrong to say that 2 to 3 percent of all live born infants show one or more significant congenital malformations and that at the end of one year this figure is doubled by the discovery of malformations not manifest at birth. (131)
 3. In the cohort of women (n=187) exposed to ginger during pregnancy all of whom used it during the first trimester the results do not suggest that there is a higher risk of major malformations above the base-line rate of (1-3%). (135)
 4. In all pregnancies there is a base-line risk of 1-3% of having a baby with a major congenital abnormality. (136)
 5. Percentage of all congenital malformations to total births in Northern Ireland.

1966	3.3%	
1976	3.2%	(137)
 6. The rate of congenital disorders diagnosed at birth among infants exposed to Bendectin (14 of 1000) is identical to that among infants who were not exposed (14 of 1000). (138)
 7. The 2-3% risk that any pregnancy has just by chance for serious malformation. (139)
 8. Of 291 women in study a total of 9 babies (3%) were born with a major or minor congenital abnormality. In the year 2000 there were 770 (4.3%) birth defects in South Australia, this included minor and major malformations. (140)

Summary

In all pregnancies there is a base-line risk of 1-3% of the baby having a major congenital abnormality at birth.

Eight References

36. STILLBIRTHS AND PERINATAL MORTALITY IN RELATION TO NAUSEA AND VOMITING OF CURRENT PREGNANCY

1. Hyperemesis patients did not have any increased risk of stillbirth or neonatal death. (10)
2. Women with hyperemesis (419) had a significantly reduced risk of stillbirth (>20 week) compared to 836 women who did not vomit. $6/419 = 1.43\%$, $25/836 = 3\%$. (22)
3. No excess of perinatal death rate in hyperemesis gravidarum. 3,068 women with hyperemesis gravidarum. (29)
4. No statistically significant association was observed between nausea and vomiting of pregnancy and perinatal mortality. 873 women in study, 69% had NVP. (44)
5. Pregnancy outcome between hyperemesis patients (193) and the general population (13,053 women in study) was similar for perinatal mortality. (61)
6. There was no statistical difference in perinatal mortality between women with hyperemesis gravidarum and the control group. Hyperemesis gravidarum 1.9%, 3/164. Control 1.9%, 4/209. (64)
7. There were no stillbirths or neonatal deaths in 64 women with HG. (42)
8. The evidence from reanalysis and meta-analysis indicates that the decreased mortality risk associated with NVP was restricted to the first 20 weeks gestation, and was not detected during the last 20 weeks or in the neonatal period. (30)
9. No significant association of freedom from nausea with stillbirth. 7,767 pregnancies in study, 29%, i.e. 2,252 pregnancies had no nausea. (51)
10. An association between higher neonatal and perinatal mortality rates and the absence of nausea and vomiting during the first trimester is demonstrated. 7,027 women in study. (5)

Summary

1. No increased risk of stillbirth or perinatal mortality with NVP or HG.
(10) (29) (42) (44) (61) (64) (30) Seven References
2. Significant reduced risk of stillbirth in women with hyperemesis gravidarum. (22)
One Reference
3. No significant association of freedom from nausea and stillbirth. (51)
One Reference
4. Higher neonatal and perinatal mortality rates and the absence of nausea and vomiting are demonstrated. (5)
One Reference