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Pre-emptive Diclectin® therapy for the management of nausea and vomiting of pregnancy and hyperemesis gravidarum

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Disclosure

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Nausea and Vomiting of Pregnancy (NVP)

- Up to 85% of pregnant women until 12-16 wks
  - 20% will experience symptoms until time of delivery

- NVP symptoms (mild to severe)
  - Begin between 4 – 9 wks gestation
  - Peak between 7 – 12 wks gestation

- Hyperemesis gravidarum (HG)
  - Up to 2% of pregnant women
  - High recurrence rate (75-85%) of severe NVP/HG

Impact of NVP

- Physical
  - Dehydration and weight loss
  - Hospitalization(s)
  - Termination of pregnancy
  - Maternal/fetal complications
- Psychological
  - Affecting home and social life
  - Depression/anxiety, frustration and helplessness
  - Time loss from work
  - Anxiety and fear for future pregnancy(ies)
- Financial
  - High direct and indirect costs of NVP

Pre-emptive treatment of nausea and vomiting

- Prophylactic (pre-emptive) antiemetic treatment
  - Cancer chemotherapy[1]
  - Motion sickness[2]
  - Cyclic vomiting[3]

- Prospective, non randomized study on pre-emptive use of any antiemetic treatment for severe NVP and HG[4]

[1]*Mattiuzzi et al. Cancer 2010*

[2]*Gil et al. Clin Neuropharm 2012*

[3]*Hejazi and McCallum. Alim Pharm Ther 2011*

[4]*Koren and Maltepe. J Obstet Gynaecol. 2004*

Pre-emptive therapy for NVP

- A 2004 prospective, non randomized study
  - Study group: 25 women with a previous history of severe NVP or HG called when planning or early pregnancy with no symptoms of NVP
  - Control group: 35 women with a previous history of severe NVP or HG called with NVP symptoms
  - Study group counseled to start any antiemetic drug when aware of pregnancy before NVP symptoms or on first sign of NVP
- Study demonstrated:
  - Lower incidence of HG compared to previous pregnancy (P=0.01)
  - Starting any antiemetic therapy prior to or at onset of NVP reduced the severity of symptoms (P=0.01)
  - Continuous and individualized counseling very beneficial

Koren G and Maltepe C.2004 J Obstet Gynaecol

Diclectin ®

Delayed release Doxylamine succinate 10mg/Pyridoxine 10mg

- The only drug labelled for pregnancy use in Canada
- First line therapy for NVP (SOGC, ACOG &APGO)[4]
- Many studies including two meta-analyses have confirmed its safety[1,2,3,4]
- Standard dose up to 4 tabs/day. However, safety up to 12 tabs/day[1]
- Not associated with any long term effects on neurodevelopment[2]

[1] *Atanachkovic,G et al.2001 J Clin Pharmacol. Aug;41(8):842-5*

[2] *Nulman I et al. 2009 J Pediatr. 155, 45-50*

[3] *Bishai R. et al. 2000 Can J Clin Pharmacol. Autumn;7(3):138-43.*

[4] *APGO 2011 Monograph Educational series on women's health issues on nausea and vomiting of pregnancy*

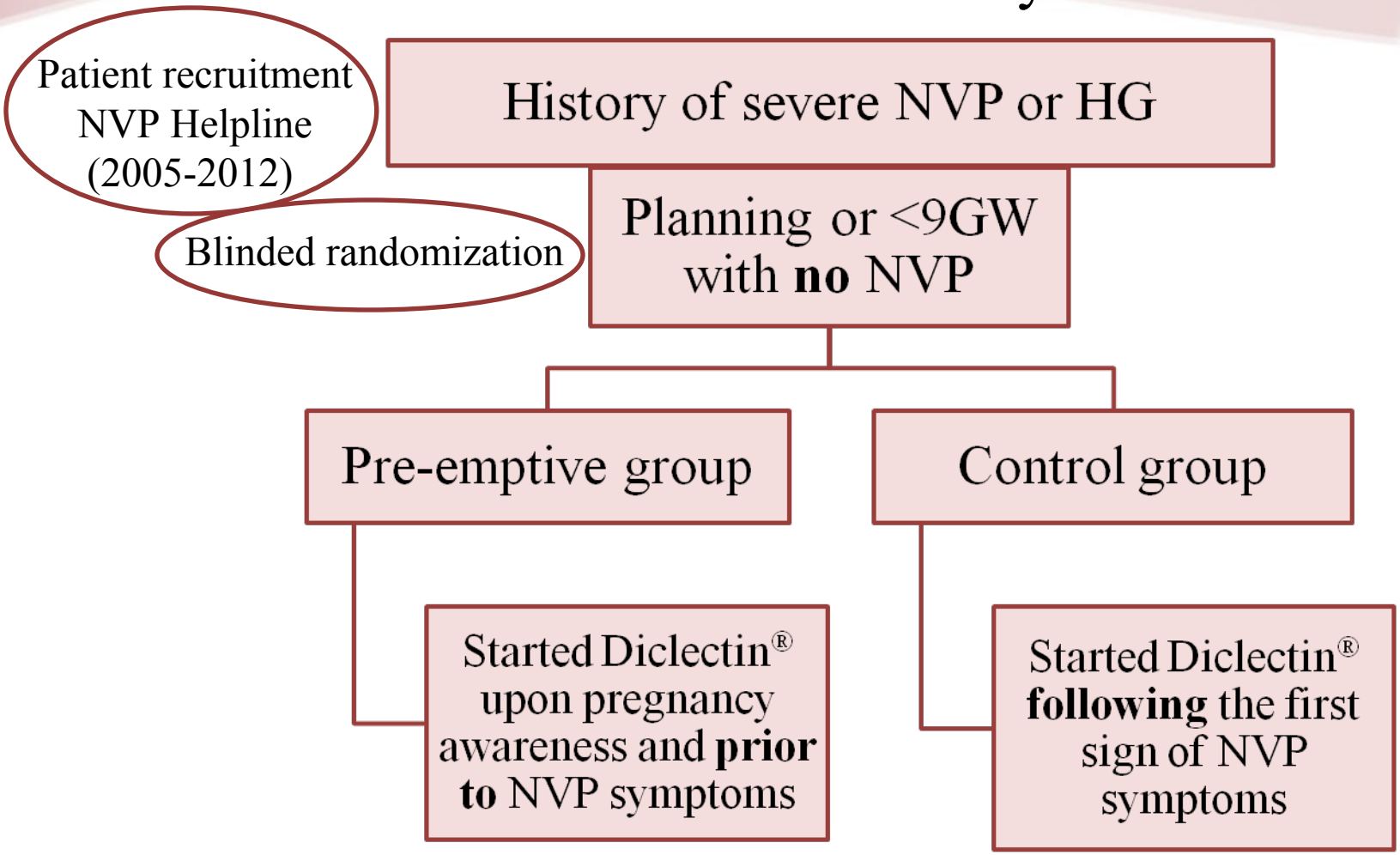
Study objectives

1. To determine the effectiveness of pre-emptive use of Diclectin® during pregnancy ***before the onset*** of NVP symptoms in women who are at a high risk for recurrence of severe NVP or HG

2. To compare this with the effects of Diclectin® started ***at the onset*** of NVP symptoms in a similar history of NVP

Methods

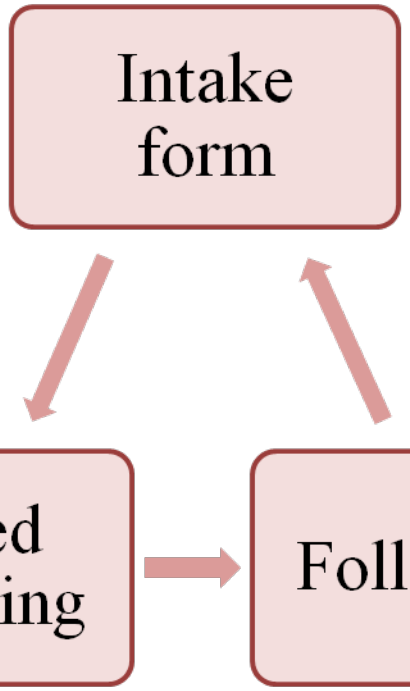
Prospective, randomized, open-label pre-emptive Diclectin® study



Methods cont'd

INITIAL CALL

Motherisk NVP Helpline 1-800-436-8477



- Personal data (demographic)
- Medical and obstetric history
- Medication and vitamin use
- NVP severity assessment: PUQE, WB, self report
- Detailed symptom assessment

- Evidence-based information
- Pharmacological and non-pharmacological approaches
- Dietary and lifestyle changes

- Depending on severity of NVP
- Scheduled by the NVP counselor or initiated by patients.

Motherisk NVP algorithm

Give 10 mg of doxylamine combined with10 mg of pyridoxine (Diclectin, delayed release) up to 4 tablets daily (ie, 2 at bedtime, 1 in the morning, and 1 in the afternoon). Adjust schedule and dose according to severity of symptoms.*

↓

Add dimenhydrinate 50 to 100 mg every 4 to 6 h PO or PR up to 200 mg/d when taking 4 Diclectin tablets daily (if vomiting frequently, take 30 to 45 min before taking Diclectin); or promethazine 12.5 to 25 mg every 4 to 6 h PO or PR

↓

NO DEHYDRATION

Add any of the following:
(listed in alphabetical order)

- chlorpromazine 10 to 25 mg every 4 to 6 h PO or IM or 50 to 100 mg every 6 to 8 h PR
- metoclopramide 5 to 10 mg every 8 h IM or PO
- ondansetron 4 to 8 mg every 6 to 8 h PO
- prochlorperazine 5 to 10 mg every 6 to 8 h IM or PO
- promethazine 12.5 to 25 mg every 4 to 6 h IM, PO, or PR

DEHYDRATION

Start rehydration treatment:

- IV fluid replacement (per local protocol)†
- multivitamin IV supplementation
- dimenhydrinate 50 mg (in 50 mL of saline, over 20 min) every 4 to 6 h IV

↓

Add any of the following:
(listed in alphabetical order)

- chlorpromazine 25 to 50 mg every 4 to 6 h IV
- metoclopramide 5 to 10 mg every 8 h IV
- prochlorperazine 5 to 10 mg every 6 to 8 h IV
- promethazine 12.5 to 25 mg every 4 to 6 h IV

↓

Add 1 of the following:

- methylprednisolone 15 to 20 mg every 8 h IV or 1 mg/h continuously up to 24 h‖
- ondansetron 8 mg over 15 min every 12 h IV or 1 mg/h continuously up to 24 h

NOTE

- use of this algorithm assumes that other causes of NVP have been ruled out. At any step, when indicated, consider total parenteral nutrition.
- At any time you can add any or all of the following:
  - pyridoxine (vitamin B6) 25 to 50 mg every 8 h PO†
  - ginger root powder, capsules, or extract§ up to 1000 mg/d, and
  - accupressure or acupuncture at acupoint P6

* Study showed that up to 8 tablets daily did not increase baseline risk for major malformations or any other adverse effects.[6] Monitor for potential side effects of Diclectin and other H_1 blockers.
†No study has compared various fluid replacements for NVP.
‡Safety of up to 200 mg/d of B6 has been confirmed.[7]
§Ginger products are not standardized.
‖Steroids are not recommended during the first 10 wk of pregnancy because of possible increased risk for oral defts.

Einarson A et al. 2007 Can Fam Phys

Methods cont'd
Validated PUQE-24hrs Scoring System
(Pregnancy Unique Quantification of Emesis)

How many hours in past 24 hrs had you felt nauseated/sick to stomach?	None (1)	1 hr or less (2)	2-3 hrs (3)	4-6 hrs (4)	> 6 hrs (5)
How many times in the past 24 hrs did you vomit?	≥ 7 times (5)	5-6 times (4)	3-4 times (3)	1-2 times (2)	None (1)
How many times in the past 24 hrs did you experience gagging or retching or dry heaves?	None (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	≥ 7 times (5)

Mild: 3-6 Moderate: 7-12 Severe: ≥13

How many hours have you slept out of 24 hours? Why?_____

On a scale of 0-10 how would you rate your overall Well-Being (WB)?

0 (Worst possible)_____10 (The best you felt before pregnancy)

Ebrahimi N et al. 2009, J Obstet Gynaecol Can

Methods cont'd

- Both pre-emptive and control groups started with 2 tablets of Diclectin® at bedtime with gradual increase of their dose according to symptom escalation
- Both pre-emptive and control groups were continuously followed up and received intensive protocolized counseling
- PUQE-24 and WB scores were used at enrolment and each follow up to measure the severity of NVP

Results

- Significant reduction of HG with pre-emptive Diclectin ® treatment (4.3% the pre-emptive group vs 17% the control group)
- 70% reduction of cases with moderate-severe NVP (PUQE≥11) in the 3 first weeks of NVP in the pre-emptive group (*p<0.04*)
- Significant negative correlation between peak PUQE and Well-Being (WB) scores
- Earlier resolution of NVP symptoms in the pre-emptive group (Mean GA of 26 wks vs 33 wks for control group)

- Both study groups had similar:
  - Demographic characteristics
    (Age, BMI, history of severe NVP/HG, ect)
  - Mean Diclectin® dose (range 2-9 tablets)
  - Mean of 8 follow-up calls/counseling

Comparison of effectiveness between the two arms

	Pre-emptive (n=30)	Control (n=29)	P
Rates (%) of PUQE ≥11 in first 3 weeks of NVP	4 (15%) (n=26)	9 (39%) (n=23)	**<0.04**
NVP resolved before labor	18/23 (78%)	11/22 (50%)	**<0.002**
Resolution of NVP (median weeks)	26	33	0.18

Distribution of HG in previous vs. present pregnancy

HG in previous pregnancy	19 (63%)	11 (38%)	**0.047**

Study characteristics of the women in both groups

	Pre-emptive (n=30)	Control (n=29)	P
Mean age-yr (SD)	32.2(4.7)	31.3(3.2)	0.37
BMI (SD)	25.2(5.7)	27.3(6.6)	0.2
Mean daily dose of Diclectin® (mg/ kg) (SD)	0.65(0.23)	0.56(0.24)	0.2
Mean gestational age (in weeks) when NVP symptoms began (SD)	5.30(1.02)	5.45(1.88)	
Mean start of pre-emptive therapy (SD)	3.8(0.98)		
<u>Some associated medical conditions</u>			
Motion sickness	7	4	N.S.
Acid Reflux/Indigestion	23	27	N.S.

Conclusions

- Pre-emptive Diclectin® treatment prevents severe NVP from recurring in a subsequent pregnancy
- Reduces symptoms by implementing:
  - Dietary and lifestyles strategies
  - Non-pharmacological and pharmacological approaches
  - Improves maternal quality of life

Study impact

- Prevent maternal and fetal complications
- Reduce the need for enteral and parenteral therapy and their associated risks
- Reduce the costs associated with severe NVP/HG
  - Time loss of work
  - Hospitalization




Thank you




PUQE and WB correlation

- Significant negative correlation between peak PUQE score and Well-Being (WB) score among participants.
  - Women with PUQE of 13-15 had a median WB score of 1.5/10
  - Women with PUQE of 7-12 had a median WB score of 5/10
  - Women with PUQE of 3-6 had a median WB score of 7.5/10

Pre-emptive therapy for NVP

Results

	Pre-emptive (study) group	*Control group*	P
Number	25	35	
Age (years) (mean range)	32.3 ± 4.2 (21–43)	31.9 ± 4.8 (21–39)	0.74
No change in severity (i.e. severe–severe)	12 (48%)*	28 (80%)*	Overall Fisher exact test: $P = 0.01$
Improvement from (severe–moderate)	5 (20%)	5 (14%)	
Improvement (severe–mild)	8 (32%)**	2 (13.8%)**	
No. of cases with HG	18/8	5/3	
(previous pregnancy *versus* now)	$p = 0.01$	(ns)	

*P=0.01; **P=0.05.

Koren G and Maltepe C.2004 J Obstet Gynaecol