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
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

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

Patient recruitment NVP Helpline (2005-2012)

Blinded randomization

History of severe NVP or HG

Planning or <9GW with no NVP

Pre-emptive group

Started Diclectin® upon pregnancy awareness and prior to NVP symptoms

Control group

Started Diclectin® following the first sign of NVP symptoms
INITIAL CALL
Motherisk NVP Helpline 1-800-436-8477

Intake form

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

Tailored Counseling

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

Follow up(s)

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

Give 10 mg of doxylamine combined with 10 mg of pyridoxine (Diclectin, delayed release) up to 4 tablets daily (i.e., 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

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

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.† Monitor for potential side effects of Diclectin and other H2 blockers.
† No study has compared various fluid replacements for NVP.
‡ Safety of up to 200 mg/d of B6 has been confirmed.
§ Ginger products are not standardized.
‖ Steroids are not recommended during the first 10 wk of pregnancy because of possible increased risk for oral defts.
Methods cont’d
Validated PUQE-24hrs Scoring System
(Pregnancy Unique Quantification of Emesis)

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

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)

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 (43% in the pre-emptive group vs 17% in 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, etc)
- Mean Diclectin® dose (range 2-9 tablets)
- Mean of 8 follow-up calls/counseling
Comparison of effectiveness between the two arms

<table>
<thead>
<tr>
<th></th>
<th>Pre-emptive (n=30)</th>
<th>Control (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rates (%) of PUQE $\geq 11$ in first 3 weeks of NVP</td>
<td>4 (15%) (n=26)</td>
<td>9 (39%) (n=23)</td>
<td>$&lt;0.04$</td>
</tr>
<tr>
<td>NVP resolved before labor</td>
<td>18/23 (78%)</td>
<td>11/22 (50%)</td>
<td>$&lt;0.002$</td>
</tr>
<tr>
<td>Resolution of NVP (median weeks)</td>
<td>26</td>
<td>33</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Distribution of HG in previous vs. present pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Previous</th>
<th>Present</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HG in previous pregnancy</td>
<td>19 (63%)</td>
<td>11 (38%)</td>
<td>$0.047$</td>
</tr>
</tbody>
</table>
### Study characteristics of the women in both groups

<table>
<thead>
<tr>
<th></th>
<th>Pre-emptive (n=30)</th>
<th>Control (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age-yr (SD)</td>
<td>32.2(4.7)</td>
<td>31.3(3.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>25.2(5.7)</td>
<td>27.3(6.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean daily dose of Diclectin® (mg/ kg) (SD)</td>
<td>0.65(0.23)</td>
<td>0.56(0.24)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean gestational age (in weeks) when NVP symptoms began (SD)</td>
<td>5.30( 1.02)</td>
<td>5.45(1.88)</td>
<td></td>
</tr>
<tr>
<td>Mean start of pre-emptive therapy (SD)</td>
<td>3.8(0.98)</td>
<td></td>
<td></td>
</tr>
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</table>

### Some associated medical conditions

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Pre-emptive</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motion sickness</td>
<td>7</td>
<td>4</td>
<td>N.S.</td>
</tr>
<tr>
<td>Acid Reflux/Indigestion</td>
<td>23</td>
<td>27</td>
<td>N.S.</td>
</tr>
<tr>
<td>Depression/Anxiety</td>
<td>8</td>
<td>16</td>
<td>0.04</td>
</tr>
<tr>
<td>Low iron/anemia</td>
<td>15</td>
<td>9</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
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

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

*P=0.01; **P=0.05.