

# Reviewing the Evidence for Using Continuous Subcutaneous Metoclopramide and Ondansetron To Treat Nausea & Vomiting During Pregnancy

**A review of the available research identifies payment for services in the absence of high-quality scientific evidence and presents an opportunity to use evidence-based medicine to develop a clinical coverage guideline**

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## ABSTRACT

**Objective:** To examine the medical evidence regarding the clinical efficacy and cost-effectiveness of the application of continuous subcutaneous metoclopramide and ondansetron to treat nausea and vomiting during pregnancy.

**Study design:** All of the published peer-reviewed articles on the subject were assembled and assigned a level of evidence based on research design. The search uncovered one level II matched, controlled trial and three level III uncontrolled, retrospective case series published in peer review journals, as well as a book chapter. The book chapter, although not subjected to the peer-review process, is included in this review due to the paucity of other evidence.

**Results:** The matched cohort trial

showed that continuous subcutaneous metoclopramide is significantly less-tolerated than continuous subcutaneous ondansetron (31.8% vs. 4.4%;  $P < 0.001$ ). The four case series reported complete symptom resolution for 63.9% to 75% of the patients. Complications arose in 24.9% to 30.5% of the selected cases that were severe enough to require discontinuation of therapy. Complications included side effects of a worsening of symptoms.

All of the trials are retrospective and observational in nature and, therefore, subject to the limitations inherent in the research design. Absent the benefit of meaningful cohort controls, comparative statements effectiveness cannot be substantiated with the available data.

**Conclusion:** Randomized, controlled trials of sufficient power are necessary before long-term continuous subcutaneous metoclopramide or ondansetron can be used on a widespread basis to treat nausea and vomiting during pregnancy.

Cost approximations in the case series are reported and, when compared to the cost of other methods of treatment previously published in the medical literature, the therapy appears to be cost-prohibitive. However, definitive statements cannot be made regarding cost-effectiveness until clinical efficacy is demonstrated through a sufficiently powered, well-designed, randomized control trial (RCT). Until such time, the therapy

should remain experimental and coverage be restricted to intractable hyperemesis gravidarum (HG) that is unresponsive to more-conventional treatment options.

**Keywords:** metoclopramide (Reglan), ondansetron (Zofran), hyperemesis gravidarum, reglan pump, Zofran, nausea and vomiting of pregnancy

## INTRODUCTION

In the mid-eighties, continuous subcutaneous antiemetic therapy began to creep into clinical practice for treating nausea and vomiting during pregnancy without the benefit of published clinical evidence to support the intervention. At that time, physicians began prescribing continuous subcutaneous metoclopramide (Reglan) via a portable, programmable micro-infusion pump (MiniMed 404SP-MiniMed Technologies, Sylmar, Ca.) called the Reglan pump.

In the late nineties, after ondansetron (Zofran) was widely promoted as an anti-emetic for patients with chemotherapy-induced nausea and vomiting, obstetricians began prescribing it in much the same way as had been done a decade earlier with metoclopramide. This became commonly referred to as a Zofran Pump.

The purpose of this analysis is to assemble all of the medical evidence on the therapy and assess its clinical efficacy, safety, and cost-effectiveness. To our knowledge, this is the first ex-

## Disclosure/conflict of interest

The authors report no conflicts of interest in developing, preparing, and writing this article.

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haustive review of the medical evidence on the use of continuous subcutaneous anti-emetic therapy to treat nausea and vomiting during pregnancy (NVP).

## MATERIALS AND METHODS

Using Google Scholar (<http://www.google.com/scholar>) and Pub Med (<http://www.ncbi.nlm.nih.gov/pubmed>), we conducted a literature search using the key search terms of *subcutaneous metoclopramide (Reglan)*, *subcutaneous ondansetron (Zofran)*, *Zofran pump*, *Reglan pump*, and *pharmaceutical treatment for nausea and vomiting of pregnancy*. The search was not constrained by either search dates or language limitations. A manual search of references was subsequently performed to discover additional articles. All authors' names on relevant identified articles were searched to further mitigate the possibility of inadvertently omitting any published work on the topic. All identified articles are included in this review; none were excluded.

## EVIDENCE REVIEW

The published medical evidence on continuous subcutaneous anti-emetic therapy consists of one level II retrospective non-randomized matched cohort study, four level III uncontrolled retrospective descriptive case series, three published peer

reviewed articles, and a book chapter (Table 1). No comparative trials containing conventional lower-cost treatments as controls have been published to date.

### Continuous subcutaneous metoclopramide

In 1998, the first report was published on 301 patients receiving continuous subcutaneous metoclopramide administered in the home. This retrospective chart review reported encouraging results, although, without controls, it is impossible to determine the treatment effect of the intervention, if any existed. Authors reported that 64.8% of patients had complete resolution of symptoms, 10.6% discontinued therapy due to side effects, and 14.3% discontinued therapy as a result of worsening symptoms. An additional 5.2% discontinued therapy for nonspecific reasons. A total of 54.5% suffered some side effects from the therapy and 11 patients experienced extrapyramidal symptoms (Buttino, 1998).

Two years later, the same author published another case series on continuous subcutaneous metoclopramide. This study contained 646 women with hyperemesis gravidarum. Similarly to previously reported results, 63.9% of patients experienced complete resolution of

symptoms and 30.5% reported at least one side effect related to the treatment. The author concluded from the uncontrolled retrospective case series that the therapy appeared to be safe and effective (Buttino, 2000a).

Later in the year, the same author wrote a book chapter describing home continuous subcutaneous metoclopramide administration for treatment of nausea and vomiting of pregnancy. The evidential weight of this book chapter is compromised by the fact that 82.1% of the patients were previously reported in the first two published case series and the chapter, therefore, suffers from redundancy of publication (Buttino, 2000b).

Another case series that looked at patients who were switched from metoclopramide to ondansetron appeared in a managed care journal several years later (Lombardi, 2004). This case series contained 428 women and reported the incidence of treatment failure, hospitalizations/ER visits, ketonuria, and pregnancy-unique quantification of emesis and nausea (PUQUE) score at the therapy start/stop. Symptoms of NVP improved for 89.3% of patients, while 10.7% were switched to continuous subcutaneous ondansetron administration.

The PUQUE score, hospital/ER

**TABLE 1**  
**Continuous subcutaneous anti-emetic pump evidence**

Study	N	Research design	Level of evidence	Symptom resolution	Symptom improvement	Failed therapy	Side effect rate
Buttino 1998	301	Case series	III	195 (64.8%)	-	91 (30.1%)	164 (54.5%)
Buttino 2000 <sub>a</sub>	646	Case series	III	413 (63.9%)	-	NR	192
Buttino 2000 <sub>b</sub>	1154 <sup>1</sup>	Case series	III	N/A	N/A	N/A	N/A
Lombardi 2004 <sup>2</sup>	428	Case series	III		382 (89.3%)	NR	167 (39%)
Klauser 2011	355 –CSMT <sup>3</sup> 521 – CSOT <sup>3</sup>	Matched cohort	II	68.2% 95.8%	NR NR	31.8% 4.4%	NR NR

N/A, not applicable; NR, not reported.

<sup>1</sup>947 (82.1%) of the patients were previously reported in the first two trials.

<sup>2</sup>Included patients receiving subcutaneous metoclopramide as well as patients moved to continuous subcutaneous ondansetron. Reported results rendered continuous subcutaneous ondansetron outcomes indiscernible.

<sup>3</sup>CSMT = Continuous subcutaneous metoclopramide and CSOT = Continuous subcutaneous ondansetron.

visits, and ketonuria decreased significantly from initiation of therapy to completion as expected, since NVP is a self-limited condition. No control group was used as a comparison cohort, so it is not possible to determine if either intervention would perform better than other inexpensive or less-invasive therapies (Lombardi, 2004).

### **Continuous subcutaneous ondansetron**

There exists one retrospective non-randomized, descriptive level II trial and one level III retrospective uncontrolled case series included patients who were administered continuous subcutaneous ondansetron (Klauser, 2011; Lombardi, 2004). Once previously discussed descriptive analysis moved patients who failed to see symptoms resolved from continuous subcutaneous metoclopramide to ondansetron. Of the 428 patients who were originally administered continuous subcutaneous metoclopramide, 46 (10.7%) women were subsequently switched to continuous subcutaneous ondansetron. These patients were reportedly more acute because they previously failed continuous subcutaneous metoclopramide, although no differences were noted between patients who failed initial therapy and those who did not.

Patients remained on therapy for a mean of 22.3 +/- 20.2 days. No outcomes were reported for the subset of patients who failed continuous subcutaneous metoclopramide and subsequently started on continuous subcutaneous ondansetron; their results were reported in conjunction with patients who remained on the original therapy (Lombardi, 2004).

The second trial, containing patients receiving continuous subcutaneous ondansetron, was published recently and compared those patients with a group receiving continuous subcutaneous metoclopramide (Klauser, 2011). The

retrospective, non-randomized, matched cohort study compared 355 women in the metoclopramide group to 521 in the ondansetron group. The major scientific contribution of this trial is that significantly fewer women tolerated metoclopramide administered via subcutaneous pump than those receiving ondansetron in a similar fashion (31.8% vs. 4.4%  $P < 0.001$ ).

The authors acknowledge, "The retrospective, non-randomized descriptive design of our study limits our ability to make conclusions regarding superiority of one medication versus the other. We are unable to prove that either intervention is effective or ineffective without a control group ..." (Klauser, 2011).

### **COST CONSIDERATIONS**

A recently published article on cost-effective pharmacologic treatments for nausea and vomiting of pregnancy (Reichmann, 2008) compared the published cost of continuous subcutaneous anti-emetic therapy to cost of hospitalization or intermittent homecare for the treatment of hyperemesis gravidarum (Neaf, 1995) and the costs were \$4,432, \$2,701, and \$701 respectively. Given this high relative cost of therapy, cost-effectiveness may be difficult to establish.

### **DISCUSSION**

Studies often are designed, conducted, analyzed, and written by industry employees or people paid directly or indirectly by industry (Kassirer, 2006; Dietz, 2007). Unfortunately, a growing body of evidence demonstrates that industry-sponsored trials are much more likely to find in favor of the studied intervention than independently funded studies (Bekelman, 2003; Buchkowsky, 2004; Als-Nielsen, 2003; Goetzsehe, 2005; McHenry, 2010).

This bias is demonstrated to be present in cohort-controlled trials and is much more likely to be present

in uncontrolled case series produced and authored by industry, particularly when the selection process is not well-described by the authors. In addition, physicians sometimes fail to discount for conflict of interest when evaluating medical literature (Silverman, 2010; Chaudry, 2002).

While recognizing the important role that case series play in the advancement of obstetrics, the American College of Obstetricians and Gynecologists (ACOG) issued a committee opinion, cautioning that, "Practitioners need to be careful not to adopt innovative procedures or diagnostic tests on the basis of promotional and marketing campaigns when the value of such procedures and tests has not yet been proved" and that "innovations should be subjected to systematic formal research as soon as feasible" (ACOG Committee on Ethics, 2006).

The findings from these promising studies should be used to formulate a hypothesis for trials containing meaningful comparative controls and adequate randomization. It may be difficult to conduct a randomized, placebo-controlled trial regarding the treatment of hyperemesis gravidarum, but evidence exists that a trial comparing unproven therapies to a well-accepted conventional one can be executed, even with extreme cases (Sullivan, 1996).

### **MANAGED CARE PERSPECTIVE**

WellCare Health Plans, Inc. has put a Clinical Coverage Guideline in place for "Treatment of Nausea and Vomiting (Hyperemesis Gravidarum) during Pregnancy with Subcutaneous Microinfusion Pump." The guideline applies to women diagnosed with HG after nine weeks of gestation when all other causes of NVP have been ruled out. A continuous subcutaneous anti-emetic pump is considered not medically necessary unless all other pharmacologic treatment has been attempted and failed, including:

1. Prochlorperazine (Compazine IM/PO);
2. Trimethobenzamide (Tigan PR) (No longer available; see Federal Register, 2007, FDA Withdrawal of Approval);
3. Promethazine (Phenergan IM/PO/PR);
4. Metoclopramide (Reglan PO); or
5. Ondansetron (Zofran PO).

Another requirement is that intravenous metoclopramide (Reglan) or intravenous ondansetron (Zofran) have been attempted and failed (WellCare Health Plans, Clinical Coverage Guideline Number HS-016, 2008).

An extensive Internet search revealed no additional health plans that have published clinical coverage guidelines to ensure that only appropriate patients are administered this expensive and as yet unproven therapy. An additional, previously published recommendation called for a failed trial of Zofran ODT before authorizing continuous subcutaneous anti-emetic pump (Reichmann, 2008).

## CONCLUSION

The entire body of evidence involving continuous subcutaneous anti-emetic therapy for treatment of nausea and vomiting during pregnancy consists of five industry-sponsored and -authored non-randomized reports.

These therapies do not appear, based on published payment levels, to be cost-effective when compared to conventional treatment alternatives including episodic hospitalization (Reichmann, 2008). Managed care organizations that design evidence-based clinical coverage guidelines may want to limit the use to extremely recalcitrant cases of hyperemesis gravidarum until sufficiently powered, independent, randomized, controlled trials demonstrate clinical efficacy and cost-effectiveness.

## REFERENCES

- ACOG Committee on Ethics. ACOG Committee Opinion No. 352: Innovative practice: ethical guidelines. *Obstet Gynecol.* 2006; 108:1589–95.
- Als-Nielsen B, Chen W, Gluud C, Kjær-gard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *JAMA.* 2003; 290(7):921–8.
- Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA.* 2003; 289: 454–65.
- Buchkowsky SS, Jewesson PJ. Industry sponsorship and authorship over 20 years. *Ann Pharmacother.* 2004; 38(4):579–585.
- Buttino L, Gambon C. Home subcutaneous metoclopramide therapy for hyperemesis gravidarum. *Prim Care Update Ob Gyns.* 1998; 5(4):189.
- Buttino L Jr., Coleman SK, Bergauer NK, Gambon C, Stanziano GJ. Home subcutaneous metoclopramide therapy for hyperemesis gravidarum. *J Perinatol.* 2000; 20(6):359–62.
- Buttino L Jr., Gambon C, Coleman S. Home subcutaneous metoclopramide therapy for hyperemesis gravidarum. In: Koren G, Bishai R, editors. *Nausea and vomiting of pregnancy: state of the art 2000. First International Conference on Nausea and Vomiting of Pregnancy.* Toronto: Motherisk; 2000 P 84–9.
- Chaudry S, Schroter S, Smith R, et al. Does declaration of competing interests affect readers' perceptions? A trial. *BMJ.* 2002;325:1391–2.
- Dietz HP. Bias in research and conflict of interest: Why should we care? *Int Urogynecol J Pelvic Floor Dysfunct.* 2007; 18(3):241–3.
- Goetzsehe P. Research integrity and pharmaceutical industry sponsorship. *Med J Aust.* 2005. 182(11):549.
- Kassirer J. Physicians on the take. *Med-GenMed.* 2006; 8(1):74.
- Klauser CK, Fox NS, Istwan N, Rhea D, Rebarber A, Desch C, Palmer B, Saltzman D. Treatment of severe nausea and vomiting of pregnancy with subcutaneous medications. *Am J Perinatol.* 2011 Oct; 28(9):715–22.
- Lombardi DG, Istwan NB, Rhea DJ, O'Brien JM. Measuring outpatient outcomes of emesis and nausea management in pregnant women. *Manag Care.* 2004; 13(11):48–51.
- McHenry L. Of sophists and spin-doctors: Industry-sponsored ghostwriting and the crisis of academic medicine. 2010; In: *Psychopharmacology Today: Some Issues* (A.R. Singh and S.A. Singh, eds.), MSM, 8, Jan-Dec 2010, p129–145.
- Neaf RW III, Chauhan SP, Roach H, Roberts WE, Travis KH, Morrison JC. Treatment for hyperemesis gravidarum in the home: an alternative to hospitalization. *J Perinatol.* 1995; 15(4):289–92.
- Reichmann JP, Kirkbride MS. Nausea and vomiting of pregnancy—cost effective pharmacologic treatments. *Manag Care.* 2008 Dec; 17(12):41–45.
- Silverman GK, Loewenstein GF, Anderson BL, Ubel PA, Zinberg S, Schulkin J. Failure to discount for conflict of interest when evaluating medical literature: a trial of physicians. *J Med Ethics.* 2010; 36:265–270.
- Sullivan CA, Johnson CA, Martin RN, Stewart DK, Morrison JC. A pilot study of ondansetron for hyperemesis gravidarum. *Am J Obstet Gynecol.* 1996; 174:1565–8.
- “Trimethobenzamide Hydrochloride Suppositories; Withdrawal of Approval.” *Federal Register* 72 (April 9, 2007). <http://www.gpoaccess.gov/fr/index> (accessed on April 13, 2011).
- WellCare Health Plans, Inc. Coverage Guideline, Treatment of Nausea and Vomiting (Hyperemesis Gravidarum) during Pregnancy with Subcutaneous Misroinfusion Pump, Guideline Number: HS-016, Original effective date: 4/3/2008; Revision Date: 6/5/2009. Available at: [http://www.wellcare.com/WCAssets/corporate/assets/HS016\\_Treatment\\_of\\_%20Nausea\\_and\\_Vomiting\\_in\\_Pregnancy\\_with\\_Subcutaneous\\_Pump.pdf](http://www.wellcare.com/WCAssets/corporate/assets/HS016_Treatment_of_%20Nausea_and_Vomiting_in_Pregnancy_with_Subcutaneous_Pump.pdf). Retrieved October 27, 2010.