

OMEPRAZOLE



The Confederate Merrimack (or CSS Virginia) (left) and the Union, Monitor (right) pound each other at close range, in the Battle of Hampton Roads, 8-9 March, 1862. Chromolithograph by Louis Prang & Co., Boston 1886, Library of Congress.

“As she came plowing through the water, she looked like a huge half-submerged crocodile. At her prow. I could see the iron ram projecting straight forward”.

The Confederacy had begun the war with no navy whatsoever, but by the fall of 1861, Confederate engineers were bolting iron plates to the hull of the steam frigate Merrimack, building a warship more powerful than anything the Union had.

The news of the monster quickly reached the North. Secretary of War, Stanton feared she would steam up the Potomac and shell the White House. There was probably only one

man in America who could stop the Merrimack, and he was mad at the navy. The Swedish born inventor John Ericsson was proud, vain and cranky and felt he had been cheated out of payment for services to the Government years before, but when the secretary of the navy Gideon Welles begged him to do something to stop the Merrimack, Ericsson came up with an extraordinary design.

His ship would have only two guns to the Merrimack's ten, but they would be mounted on a revolving turret. And though his vessel would be made entirely of iron, Ericsson assured everybody that that "The seas shall ride over her, and she shall live in it like a duck!"

Professional navy men dismissed the plan, but Lincoln overruled them, and just 100 days later on January 30, 1862, Ericsson's ship slid into Manhattan's East River. He called her the Monitor, and there had never been anything like her. The single vessel contained 47 patentable inventions.

"We ran first to the New York side and then to Brooklyn, and so back and forth across the river, like a drunken man on a sidewalk we found she would not answer her rudder at all!"

(Monitor Sailor)

Once at sea, water spilled in, ventilators failed, the ship filled with gas, her crew began to faint. But the Monitor kept limping south. Four hundred miles away, off the coast of Virginia, the Merrimack was waiting.

Saturday, March 8, was wash day for the Union fleet in Hampton Roads, Virginia. Laundry was drying on the rigging of the Union warships when the Confederate Merrimack headed straight for the USS Cumberland.

The Cumberland opened fire, but the shots bounced harmlessly off the Merrimack's side. The Confederate ship rammed the Cumberland, then stood in so close, their muzzles almost touched.

The Cumberland sank in shallow water. The Merrimack went on to set the USS Congress afire, drove the USS Minnesota aground, then drew back for the night. For one day the Confederate navy ruled the sea.

At 1:00 that morning the crew of the battered Minnesota saw a strange looking ship draw up alongside them in the darkness.

"Close alongside the Minnesota, there was a craft such as the eyes of a seaman never looked upon before - an immense shingle floating on the water with a gigantic cheese box rising from its center. No sails, no wheels, no smokestack, no guns! What could it be?"

The Monitor had arrived. The next morning the epic battle of ironclads began.

Hull to hull, the two ships hammered away at each other, so close that they collided five times, as the men inside half-blind with smoke, loaded and fired.

After four and a half hours, the Merrimack drew off....

Both sides set to work building more ironclads, while Europe watched in worried fascination.

From the moment the two ships opened fire that Sunday morning, every other navy on Earth was obsolete.

David McCullough in Ken Burns', "The Civil War", 1990.

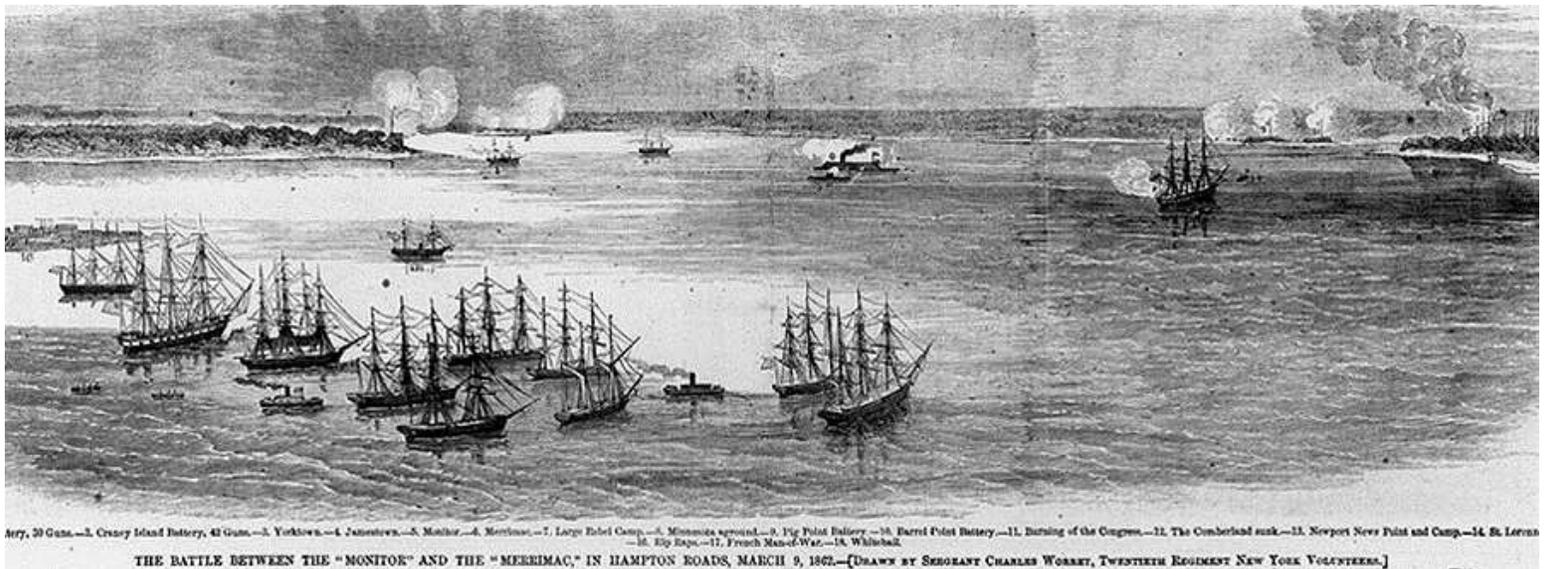
Necessity is the mother of Invention; especially in time of War. The American Civil War produced an extraordinary range of new weapons and technologies, many were prototypes for the First World War which would be fought three generations later. Perhaps the most innovative of all inventions, were the "Ironclads". At the beginning of the War, the Confederacy had no navy whatsoever. The Union with its great fleet of sailing ships ruled American waters and would eventually have the Confederacy completely blockaded. The South had to be innovative if they had any hope of challenging the Union Navy....it was, and brilliantly so. Marine engineers had designed a method of completely encasing a frigate with solid iron cladding, while still keeping the whole cumbersome structure afloat. Now cannon balls, grapeshot, canister, and shells instead of shattering timber to splinters would hit solid plate iron. Though the crew within the ironclad would receive a considerable jolt the, projectiles of the day bounced harmlessly off. The Confederates, having captured the USS steam frigate, the Merrimack, cut it down to its hull, then coated it entirely with iron plating and added a monstrous iron battering ram for good measure. Having ten heavy cannons it was a formidable vessel. When completed it was renamed the CSS Virginia

Naval commanders were at first sceptical that such a vessel could even be manoeuvred on the high seas, let alone be effective in battle. The Confederate iron monster soon dispelled any doubts. Virtually impervious to the naval weapons of the day, it proceeded to pulverise every wooden Union ship in its path. On March 8, it attacked the Union fleet in Hampton Roads, and destroyed three of them in short order, sending the pride of the fleet, the USS Cumberland to the bottom of the sea. For a day the Confederates ruled the seas. But the Union in alarmed response to reports that the South had managed to build an iron warship, had turned in desperation to the brilliant Swedish naval engineer, John Ericsson, in order to come up with an iron warship of its own that could challenge the Merrimack. Ericsson's design was extraordinary. Containing no less than 47 patented inventions his vessel rather than being iron clad was totally iron! Alarmingly it floated so low in the water it appeared it would sink at any moment, but more alarmingly still it had only two guns. This did not seem an encouraging match for the ten gunned Confederate leviathan. However Ericsson's most extraordinary innovation related to the gun turret itself. It revolved. Although outgunned, this gave the Monitor a significant advantage in its field of fire. While the Merrimack had to align broadside - as for any wooden ship of the day - to gain the full advantage of its firepower, the Monitor with its rotating turret could fire continuously no matter what position it was in.

The day after the Merrimack had made short work of the Union's wooden fleet, the Monitor arrived at Hampton Roads. What followed was one of the most famous naval engagements in history - the first of iron ships. For four and a half hours the two monsters pounded each other at close range - so close the vessels actually collided five times. The smoke, noise, and bone crushing percussions of the shells hitting the iron armour almost broke the endurance of the crew of both vessels. As they hammered each other, the rest of the Union fleet could only sit back and watch the spectacle in unbelieving awe. Those present on the decks of the wooden ships were witnessing history, the Merrimack and the Monitor would be the embryonic prototypes of the stupendous British and German Dreadnoughts of the First World War.

In the end neither vessel could destroy the other, and both simply drew off. The Union Naval Command ordered the Monitor to avoid the Merrimack and the two ironclads never met in battle again. Though the engagement at Hampton Roads was inconclusive, there was no longer any uncertainty about the future of ironclads. The Confederacy did not have the industrial might to produce more ironclads, but the North did, and as it went on an ironclad building frenzy, European naval commands watched in horrified fascination - overnight every other navy on Earth had become obsolete!

By mid 1980s the H2 antagonists had become the biggest selling medications in the world. Then in 1988 the first proton pump inhibitor, omeprazole came onto the market. Just as every European Naval Command watched the Battle of Hampton Roads in fascinated horror, so H2 antagonist Big Pharmas watched the arrival of the PPIs. Overnight every H2 antagonist had become obsolete!



A contemporary illustration of the Battle of Hampton Roads, 1862, by Sergeant Charles Wollet, 20th regiment New York Volunteers. The Merrimack and the Monitor hammer each other in the distance, while every other wooden sailing ship can do no more than sit by and watch.

OMEPRAZOLE

Introduction

Omeprazole (trade name in Australia, “**Losec**”, among others) irreversibly inhibits the **proton pump** (i.e. the gastric **parietal cell** enzyme **H⁺/ K⁺ ATPase**), the final common step of gastric acid production thus resulting in a reduction of gastric acid secretion.

The proton pump inhibitors are the most potent inhibitors of acid secretion currently available.

All the current PPIs have similar efficacy and adverse effects, although they may differ in their potential to cause drug interactions.

Omeprazole is the currently preferred PPI for use in pregnancy

Omeprazole is available as **both oral** and **IV** preparations.

History

In the 1970s the newly discovered proton pump (H⁺/K⁺ ATPase) in the secretory membrane of the parietal cell was found to be the final biochemical step in stomach acid secretion

The PPIs were subsequently developed in the 1980s

Omeprazole was the first PPI to be introduced into clinical practice in 1988

Classification

The proton pump inhibitor agents include:

1. **Omeprazole**
2. Esomeprazole (This is the S-isomer of omeprazole).
3. Lansoprazole
4. Pantoprazole
5. Rabeprazole.

Chemistry

Omeprazole is a substituted benzimidazole.

Omeprazole exists as two isomers: S - omeprazole and R - omeprazole

Preparations

Omeprazole as:

Capsules:

- 10 mg
- 20 mg
- 40 mg.

Ampoules:

- Omeprazole 40 mg vial (as powder) plus 10 ml of solvent.

Ampoules should be protected from light.

Mechanism of Action

Omeprazole irreversibly inhibits the proton pump (i.e. the gastric enzyme H^+/K^+ ATPase), at the secretory surface of the gastric parietal cell. This is **the final common step** of gastric acid production.

This results in a reduction of gastric acid secretion, (see **Appendix 1 below**).

Pharmacodynamics

The degree of acid reduction is dose dependent and it effectively inhibits both basal acid secretion and stimulated acid secretion, irrespective of the stimulus to acid production

Proton pump inhibitors have a slower onset of action than histamine H_2 -receptor antagonists, but inhibition of acid secretion is greater and more sustained.

Healing of erosive oesophagitis and peptic ulcers by PPIs is superior to histamine H_2 -receptor antagonists and other antiulcer drugs

Omeprazole has **no** effect on acetylcholine or histamine receptors.

When PPIs are stopped, acid secretion is only restored by the synthesis of new hydrogen/potassium ATPase.

Pharmacokinetics

Absorption:

- Can be given orally or IV, (esomeprazole, and pantoprazole can also be given orally or intravenously).

Oral absorption is rapid.

Systemic bioavailability of omeprazole from a single oral dose is approximately 35%.

After a single oral dose the onset of antisecretory effect occurs within one hour and is maximal within 2 hours.

PPIs are acid-labile and require enteric-coated dose forms for oral absorption. Dispersible tablets, capsules and sachets contain enteric-coated pellets. Suspensions can be made from these formulations.

Distribution:

- The plasma protein binding of omeprazole is approximately 95%.
- Omeprazole can cross the human placenta
- Omeprazole is excreted into human breast milk.

Metabolism and excretion:

- Omeprazole is entirely metabolized by the cytochrome P450 system mainly in the liver.

Indications

Indications include:

1. Dyspepsia
2. Peptic ulcer:
 - Prophylaxis against peptic ulcer
 - Treatment of peptic ulcer
3. Oesophagitis:
 - Due to GORD or other causes, (such as scleroderma).
 - Omeprazole is also the *preferred* PPI for use in **pregnancy**.
4. Zollinger-Ellison syndrome
5. Acute upper gastrointestinal bleeding

- 6 Adjunct to *H. pylori* eradication:
 - Omeprazole does not eradicate *H.pylori* in its own right, but acts synergistically with antibiotics to do so.
 - Optimal eradication rates are achieved when omeprazole is combined with two antimicrobial agents.
- 7 The prevention or treatment of gastric and duodenal ulcers and erosions associated with NSAIDs.
- 8 In selected patients for stress ulcer prophylaxis
9. Prevention of *acid* aspiration

Contraindications/ Precautions

These include:

- 1 Hypersensitivity to omeprazole
- 2 Caution should be exercised in the use of the PPIs in the presumptive diagnosis of “dyspepsia” without prior endoscopy

Important diagnoses to keep in mind include:

Possible upper GIT malignancy:

- Caution as PPIs may alleviate symptoms and thereby delay diagnosis.

Possible *H. Pylori* Infection:

- Infection must be treated in order to cure the underlying cause of the symptoms.

Pregnancy

Omeprazole is a category B3 drug with respect to pregnancy.

B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Omeprazole use during pregnancy has not been associated with an increased risk for congenital malformations, spontaneous abortions or preterm delivery.

While omeprazole has the **most reported safety experience** in human pregnancy studies, lifestyle modifications (including dietary changes), antacids and histamine-2 antagonists (such as ranitidine) should be trialed before omeprazole is used for the treatment of heartburn and gastro-oesophageal reflux disease during pregnancy.

Breastfeeding

All PPIs are acid labile; small amount in milk is likely to be destroyed by acid in infant's stomach.

Omeprazole is excreted into breast milk, but maternal use is not expected to cause adverse effects in the breastfed infant.

However, lifestyle modifications (including dietary changes), antacids and histamine-2 antagonists should be trialed before omeprazole is used for the treatment of heartburn and gastro-oesophageal reflux disease during breastfeeding.

Adverse Effects

PPIs are generally well tolerated.

1. GIT upset may occasionally occur
2. Hypersensitivity reactions, (rare)
 - Allergic / anaphylactic.
 - Skin reactions:
 - ♥ Stevens-Johnson syndrome/ toxic epidermal necrolysis
3. Some *epidemiological* studies have suggested *possible* associations between PPI use and increased risk of:
 - Enteric infections (including Clostridium difficile-associated disease)
 - Pneumonia
 - Decreased serum vitamin B12 concentration (long-term use)
 - Fracture (long-term use); for patients at risk of osteoporosis and taking PPIs long term (>1 year), consider daily calcium intake and vitamin D status.

Dosing

Exact dosing and duration depends on the condition being treated as well as its severity.

A standard regimen in adults is:

Oral:

- Omeprazole 20 mg daily

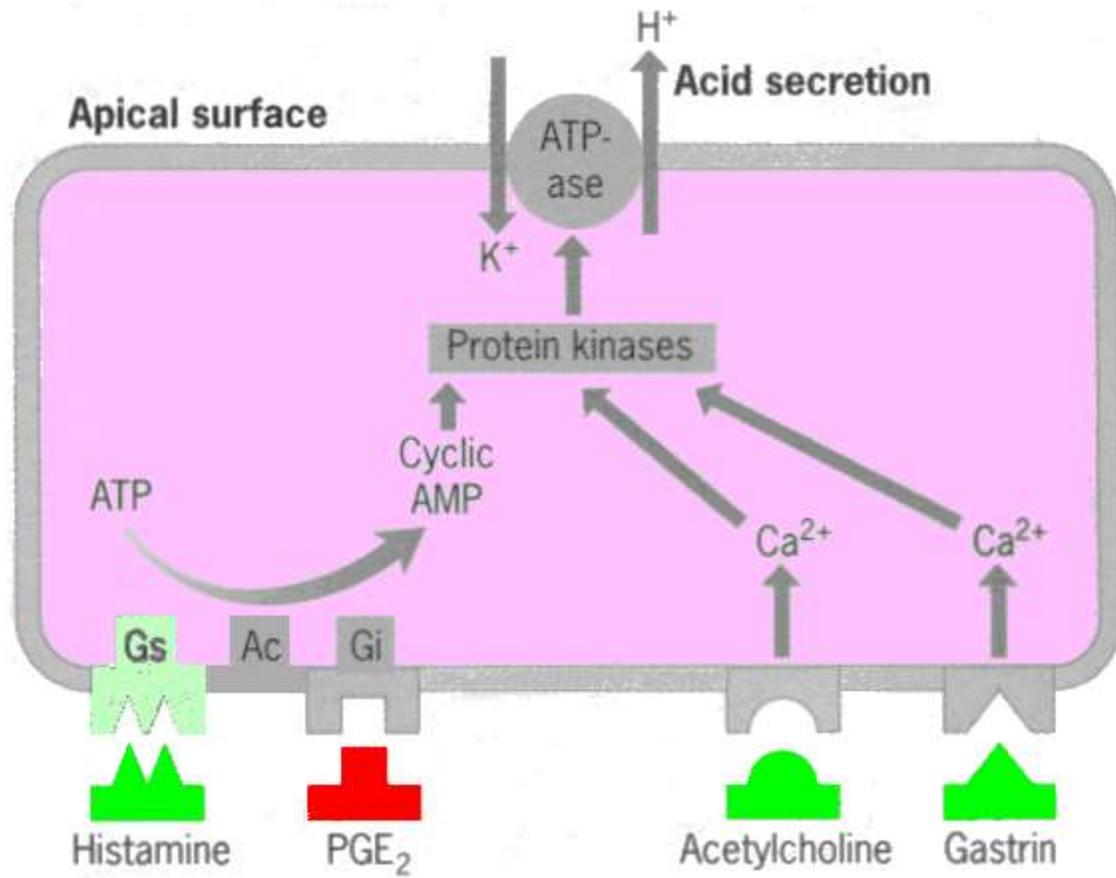
With repeated once daily dosing the maximum effect is usually achieved within 4 days of commencing treatment. ²

IV:

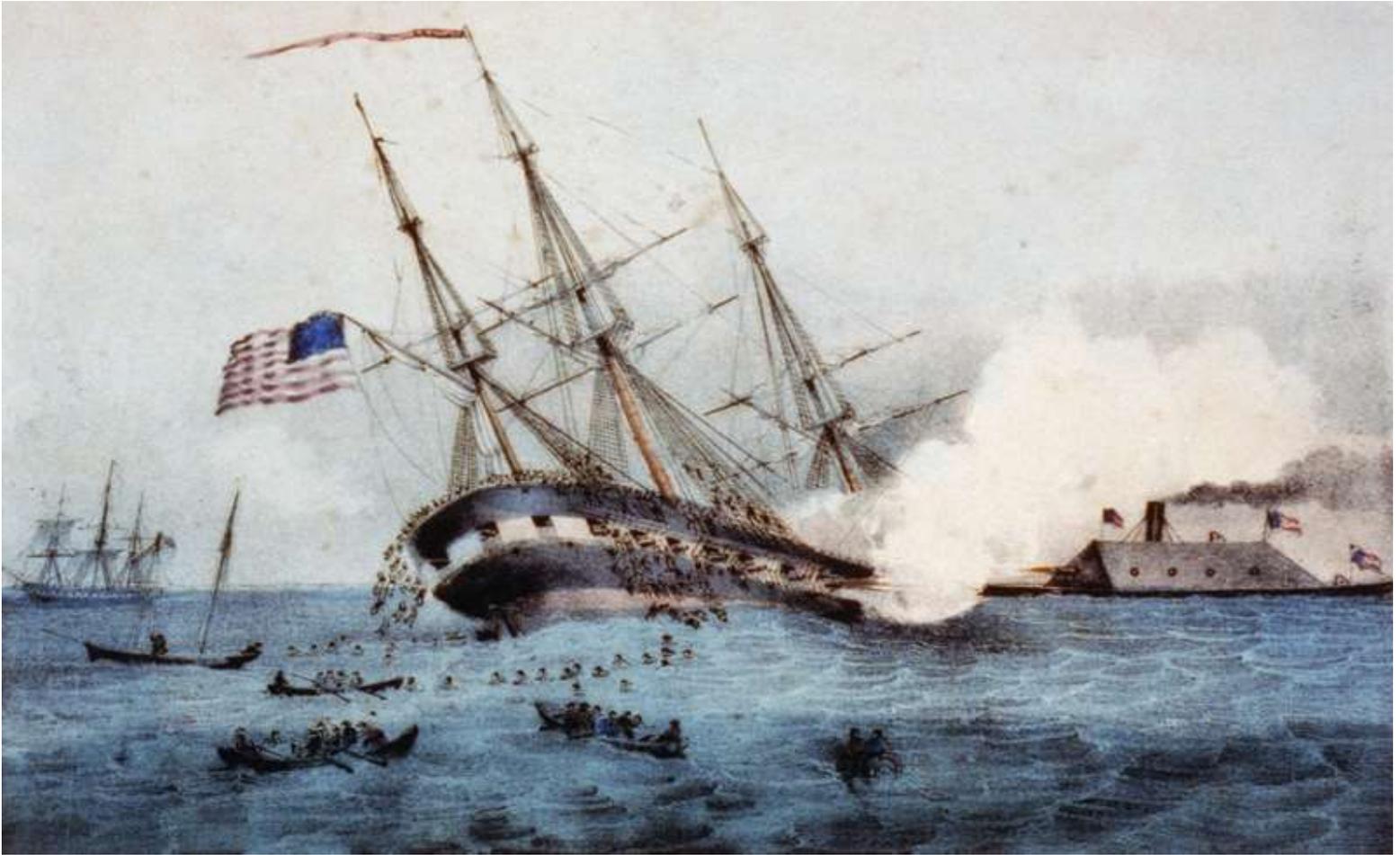
- 40 mg IV once daily. ³
- For upper GIT bleeding:
 - ♥ **Omeprazole 80 mg IV over 15 to 30 minutes, then 8 mg/hour by IV infusion, for up to 3 days, followed by oral therapy after this.** ¹

Appendix 1

The Gastric Proton Pump:



The Proton Pump, (School of Biochemistry and Microbiology University of Leeds).



The Sinking of the USS Cumberland by the Merrimack, hand coloured lithograph, 1862.



Photograph taken on the deck of the USS Monitor. Behind the sailors is the famous rotating gun turret.

References

1. eTG - March 2017
2. Omeprazole in MIMs, November 2013.
3. Omeprazole in Australian Medicine's Handbook, December 2013.
4. Omeprazole in RWH Pregnancy & Breastfeeding guidelines, 16 June 2016.

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