Evaluation of Pharmacotherapy for Common Medical Conditions in Pregnancy

By:

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ABSTRACT

Purpose Two new scales, CORECTS and PUQE-24 are introduced and validated, and the safety and effectiveness of Proctofoam-HC® in pregnancy is demonstrated.

Method 315 of Motherisk NVP patients provided information on five clinical parameters as well as PUQE scores. 28 patients visiting a proctologist were graded for the severity of anal conditions by a proctologist before administering CORECTS. Pre and postnatal interviews were conducted with 204 pregnant women prescribed Proctofoam-HC®.

Results Strong correlations were found between the following:
PUQE-24 scores and parameters of well-being, hospitalization, and multivitamin intake; bleeding and pain components of CORECTS and the proctologist’s grade. There was no significant difference between mean birth weight of Proctofoam-HC® treated and comparison groups. There was a significant reduction in all symptoms of hemorrhoids.

Conclusion PUQE-24 and CORECTS are the first validated scales used to assess the severity of NVP and hemorrhoids. Proctofoam-HC® is safe and effective for use in pregnancy.
ACKNOWLEDGEMENTS

“Keep me away from the wisdom which does not cry, the philosophy which does not laugh and the greatness which does not bow before children.” Kahlil Gibran

Over the past several years, my intrinsic compass that pointed me to a promising destination, started to take me through dark alleys (one reason why you must always validate a scale or any measuring device); and suddenly my academic (synonym for life) journey was no longer defined by its preset destination. Instead I was forced to let opportunities that were unraveled, to light the path that I was supposedly meant to take. For some of us, the path is straight, and it would be foolish to not have faith in it, as you can already see the light at the end of your tunnel from many miles away. For some others, the twists and turns, are directions in darkness, leaving you with nothing but doubt.

Well, now that I have managed to successfully create a self impression of an unmotivated, lost, directionless, possibly hideous looking (pretty people never get lost) and miserable graduate student, I’d like to make a rather bold announcement: contrary to popular beliefs regarding graduate studies, I have been quite happy. No, I am not declaring my love for the projects I’ve completed, nor the fascinating process of writing this thesis and the world peace that will follow shortly after I submit it to the department; I do declare however, that I have been blessed with a unique opportunity, to learn things I never would have, had I not chosen this path.

When Gidi accepted me as his student and gave me the chance to join Motherisk, I was rather oblivious to the opportunity. I came in as a skeptic that was excited to do great things, but was pessimistic about the potentials. It wasn’t till I met the other students and the ongoing projects that were taking place in this very modest looking department, and it wasn’t till I started counseling pregnant women myself, that the significance of my placement really hit me. In the scientific world of drug trials and clinical investigations, where pregnant women are excluded from many potentially life saving or improving studies (you must love the irony of ethics here) I was working at Motherisk, the one and only place that solely focused on pregnant women.

No fear is more selfless, than that felt by an expecting mother for the safety of her unborn child. And no pleasure is greater, than the gratification of putting that fear into rest. At Motherisk, and only at Motherisk, have I had the good fortune to experience that kind of gratification.

Of course, this journey would not have been completed, had it not been for the key role of characters that become so important to me, and so very close to my heart. I take the opportunity here, to thank them for all that they have done. I begin with my dear friends Carolyn Tam, Moumita Sarkar and Sammy Gill, for not only sharing their skills and patiently couching me as the new student, but for their endless support and loyalty at times of difficulty. I’d like to thank all the other great graduate
students who’ve contributed to creating many great memories that will last a lifetime. Thank you to my second sisters and mothers, the Motherisk counselors, Pina Bozzo, Caroline Maltepe, Aida Erebara, and Angela Gocheco, for the love and support they have given me every single day. You have become part of my life, and your wisdom, and affections will always stay with me. Special thank you to Adrianne Einerson for sharing her incredible insights and experiences so generously, and for being a mother, friend and teacher all at once, anytime I turned to her. Many thanks to Thomas Einerson, for helping me produce this thesis. Although I spent more time making the corrections he wanted, than it took to write this thesis, the final product would not have been possible without his thorough revisions. Tom, I am indebted to all the constructive criticism you’ve provided me with as my advisor, and your humor is something I’ll always remember you by. I’d like to also thank Bhushan Kapur, not just as my advisor, but also for his fatherly advices, and sharing so much of his own experiences with me. Gideon Koren, is the reason why I ended up here, and it goes without saying that none of this would have been possible had it not been for his generous support, guidance and faith in me. I am forever grateful for the opportunities and acknowledge that any success I have in the future is rooted in my experiences here. Finally, I wish to thank my incredible family. My Mother Mahin, is the soul of my life and the incredible force that has sought me through many obstacles. She defines motherhood, and I have no greater wish than to repay her endless sacrifices one day. My sister Sana, has been my number one lawyer and best friend since birth, and despite being younger, has been standing by me since she learned to walk. My youngest sister Hoda stands guard silently in the shadows, and never seizes to amaze me with her wisdom and maturity that far surpasses her age. My father Mehdi, has played an integral role in developing my strength and independence and my ability to never give up until I find the solution. What I am, and who I will be, and the best of what I become, is all and all because of my family, and the unspeakable sacrifices they’ve made. I love you.
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LIST OF ABBREVIATIONS

NVP: Nausea and Vomiting of Pregnancy
PUQE-24: 24-hour Pregnancy Unique Quantification of Emesis Scale
HG: Hyperemesis Gravidarum
LIST OF PUBLICATIONS


CHAPTER 1.
INTRODUCTION

The nine month journey ceding the miracle of life, while a blissful event for many women, can also be a taxing emotional and physical experience. While some pains of pregnancy such as frequent urination, stretch marks, bloating, gas, heartburn, water retention, swollen feet, aching back and sore breasts, are generally minor nuisance, others can be more serious. Depression, gestational diabetes, morning sickness, constipation and hemorrhoids, are some of the medical conditions with more significant impact on the health of the childbearing mother and the developing fetus.

In this dissertation, I address two of the more common complaints of pregnancy, nausea and vomiting of pregnancy as well as hemorrhoids. Both conditions have serious impact on women’s wellbeing, and can progress into life threatening events if left untreated. Despite of their high occurrence, both NVP and hemorrhoids, tend to be considered “normal” parts of pregnancy; this expectation, combined with a general fear of using medications in pregnancy, results in inadequate management of these conditions (1-4).

As the first step for treatment and management of any medical condition, proper assessment of the severity of that condition is essential. The aim of the first two studies discussed in this manual, is to validate two scales, PUQE-24 and CORECTS, for the evaluation of severity of NVP and hemorrhoids respectively. Next we investigate the safety and effectiveness of a commonly used anti-hemorrhoid medication in pregnancy, Proctofoam-HC®. Despite of the availability of many over the counter and prescription products for treating anal conditions, none have been investigated for safety in pregnancy. Demonstrating the safety and effectiveness for a commonly used anti-hemorrhoidal product would benefit many women and healthcare providers in treating the symptoms associated with hemorrhoids.

In this chapter the statement of the problems associated with NVP and hemorrhoids, the research questions, objectives and hypotheses for each, as well as the rationales for the proposed studies, are presented.
### 1.1 STATEMENT OF THE PROBLEM

Up to 90% of women suffer from NVP in the first trimester of their pregnancy (5). While symptoms can be very mild for some women, others suffer from severe vomiting and nausea, and up to 2% will experience Hyperemesis Gravidarum (HG) (6). HG can lead to hospitalization, termination of pregnancy and even death if not treated (7, 8).

Hemorrhoids have been reported in 38% (9) and even up to 85% in specific populations of women in late pregnancy (10). Symptoms associated with hemorrhoids can also vary in severity, and may lead to secondary life threatening conditions if left untreated.

Despite of the high incidence in pregnancy, and potentially serious health consequences, the presence of tools that adequately capture the severity of the symptoms of NVP and hemorrhoids, efficiently and objectively have been lacking.

It is well established that the first step for the treatment of any medical condition requires the proper diagnosis and assessment of the severity of that condition. With both NVP and hemorrhoids recognized as common medical conditions in pregnancy, assessing the severity of the symptoms associated with each condition prior to implementing treatment is essential. Both, PUQE-24 and CORECTS are scales that were developed by Motherisk to assess the severity of NVP and hemorrhoids respectively. For the scales to be used as clinical tools by other healthcare providers in the future, the need exists to validate both these scales, to demonstrate their accuracy and validity. The first two studies in this thesis aim to validate these scales.

While mounting evidence (11-13) exists for the safety and effectiveness of Diclectin®--the only drugged approved for use in pregnancy for the treatment of NVP—there remains a substantial deficit in scientific evidence demonstrating the safety and effectiveness of
any anti-hemorrhoidal treatments. Many women seek relief from their hemorrhoid symptoms by using one or multiple of the many anti-hemorrhoidal products that are available over the counter; none of which have been evaluated for safety in pregnancy. Hence in the last study presented here, the aim is to investigate the fetal safety and effectiveness of a commonly prescribed anti-hemorrhoid medication, Proctofoam-HC® in pregnancy. This dissertation focuses on providing response to the following:

1.1.1 Research Questions

A) Is PUQE-24 a valid tool for the assessment of the severity of Nausea and Vomiting of Pregnancy?
B) Is CORECTS a valid tool for the assessment of hemorrhoid severity in pregnancy?
C) Is Proctofoam-HC® a commonly used topical anti-hemorrhoid treatment, safe for the pregnant woman and her fetus?
D) Is Proctofoam-HC® effective in treating hemorrhoidal symptoms in pregnant women?

1.2 PRIMARY OBJECTIVES

1.2.1 To validate the PUQE-24 scale, and demonstrate its ability to predict important clinical outcomes in women with NVP

1.2.2 To construct and validate the CORECTS scale and demonstrate its ability to track changes in the severity of hemorrhoid symptoms following treatment
1.2.3 First, to assess the fetal safety of Proctofoam-HC® a commonly prescribed anti-hemorrhoidal cream in the 3rd trimester of pregnancy; and second to assess its effectiveness in reducing hemorrhoid symptoms using the CORECTS scale.

1.3 **HYPOTHESES**

1.3.1 **PUQE-24**

It was hypothesized that the PUQE-24 score is an objective measure of NVP severity and an effective tool in predicting important clinical outcomes for patients with NVP.

1.3.2 **CORECTS**

It was hypothesized that CORECTS is able to assess the severity of the five cardinal symptoms associated with hemorrhoids, and is sensitive enough to changes in symptom severity following treatment of hemorrhoids.

1.3.3. **Safety and effectiveness of Proctofoam-HC® in pregnancy**

1.3.3.1 It was hypothesized that the topical use of Proctofoam-HC® in the third trimester of pregnancy, is safe for the baby and will not increase the risk for adverse fetal events.

1.3.3.2 It was hypothesized that the local use of Proctofoam-HC® in the third trimester will alleviate symptoms associated with hemorrhoids.

1.4 **STUDY RATIONALE**

Many medical conditions such as gestational diabetes, hypertension, hypothyroidism and etc., in pregnancy are known to detrimentally affect the health of the mother and
developing fetus, and hence stringent protocols exist for adequate management of such conditions. Hemorrhoids and NVP however, are considered normal parts of pregnancy, and since they are generally limited to the course of the pregnancy, they don’t receive as much attention.

The Motherisk Program, situated at Toronto’s Hospital for Sick Children, is a telephone information service that provides scientific based information, to pregnant women and their healthcare providers, on the safety of exposures in pregnancy and lactation. In our counseling of Motherisk patients, it has been repeatedly observed, that despite of the severe impact the symptoms of NVP and hemorrhoids have on women’s well-being, physicians are dismissive of these conditions. With many women suffering from both conditions, and not receiving adequate treatment, it became necessary to evaluate both conditions more closely. As the first step to adequate management and treatment, an accurate assessment of the severity of the conditions is deemed necessary. The first scales ever to capture the severity of symptoms associated with NVP and Hemorrhoids --PUQE-24 and CORECTS—are presented in this dissertation. These scales are then used to track changes in the severity of symptoms following treatment, and finally, I aim to introduce a safe and effective product that can be used for treating hemorrhoids in pregnancy.
CHAPTER 2.

BACKGROUND

This chapter provides the literature review and background knowledge needed to understand the severity and impact of NVP and Hemorrhoids in pregnancy, and the need to adequately assess and manage them. The gap in knowledge for treatment of hemorrhoids is discussed at the end of the chapter and the conflicting evidence on the safety of corticosteroids, an ingredient in most anti-hemorrhoidal products, is emphasized.

2.1 NAUSEA AND VOMITING OF PREGNANCY (NVP)

2.1.1 What is NVP?

Nausea and Vomiting of Pregnancy (NVP), also known as morning sickness, is a debilitating condition affecting many women in their pregnancy. Up to 90% of pregnant women in the first trimester suffer from NVP with varying severity, ranging from a short period of queasiness, to feeling severely noxious and experiencing multiple episodes of vomiting and retching per day. Symptoms generally start around 4 to 9 weeks of gestation and peak around the 7th to 12th weeks. Although symptoms tend to subside by the 16th week(1, 14, 15), about 20–30% of pregnant women will continue to experience symptoms beyond 20 weeks, and up to time of delivery(1, 5, 16). Up to 2% of women with NVP symptoms will develop HG, a potentially life threatening condition characterized by protracted vomiting leading to fluid and electrolyte imbalance, nutrition deficiency and a weight-loss of more than 5% of the pre-pregnancy weight, often leading to hospitalization(6). Approximately 10% of patients with HG will have symptoms persisting throughout pregnancy (1).
2.1.2 Etiology and Risk Factors

Despite many theories, the etiology of NVP remains unknown. Hormonal, immunological, anatomical and psychological contributors to NVP and HG have been proposed although inconsistently, in many studies. Results to date, remain inconclusive (6, 17), as the cause is most likely multi-factorial. Certain risk factors for experiencing NVP that have been proposed include, decreased maternal age, increased placental mass, genetic predisposition, history of HG, multipara, fetal gender, and helicobacter pylori infection (17-19). A recent study examined potential risk factors regarding timing of onset, severity and duration of NVP symptoms in more than 2000 women. It was reported that the duration of NVP is reduced in older women as well as in non-Hispanic Black and Hispanic women, and is increased with higher gravidity; severity of NVP however, was not associated with any of the aforementioned risk factors (20).

2.1.3 NVP Consequences

NVP, especially HG, can be quite traumatic, both physically and mentally, in pregnancy (7,21,22). In the absence of vomiting and retching, nausea alone can still have a detrimental effect on women’s well-being (22, 23). Negative maternal consequences have been reported even postpartum, these include: longer recovery time from pregnancy, persistence of symptoms post delivery with greater intensity for women who had extreme weight loss (24). These symptoms include postpartum gallbladder dysfunction, food aversions, muscle pain, nausea, and symptoms characteristic of post traumatic stress disorder (PTSD)(24). In addition to maternal consequences, negative impact of NVP on the fetus, family relationships, and job performance has also been documented (19,25).
The most common adverse fetal outcome with severe vomiting, is low birth weight and preterm birth; the more severe the nausea and vomiting, the lower the birth weight (17, 19). Women report that their impairment due to nausea and vomiting compromises their parenting ability, as well as job performance, and very often family relationships are strained as a result of this distress (22). Moreover, the significant psychosocial morbidity caused by severe symptoms, has resulted in elective pregnancy terminations, because women feel they cannot continue a pregnancy under these circumstances (8,17,22).

2.1.4 Treatment Options

To reduce symptoms and subsequent suffering, as soon as NVP commences, women and their healthcare providers should intervene with the appropriate treatment to prevent HG from occurring (17). A number of non-pharmacological and pharmacotherapy approaches have been proposed, investigated and recommended for the treatment of NVP. Prior to starting pharmacological therapy, women should try the appropriate dietary changes and incorporate the use of ginger and vitamin \( B_6 \), which may eliminate the need for further intervention. If these treatments are not effective, pharmacotherapy should be implemented as all the drugs used in the treatment for NVP appear to be safe for the fetus and have some degree of effectiveness.

Treatment with pharmacotherapy should follow the stepwise guide in Figure1; the treatments outlined are listed in alphabetical order and it is the physician’s decision to decide which order is most appropriate according to their patient’s condition. The use of antiemetics should begin with Diclectin® or any doxylamine-pyridoxine combination, as the largest body of evidence exists for their efficacy and safety. Other antiemetics can be
implemented according to the algorithm, if symptoms don’t resolve. Concurrent treatment of heartburn and acid reflux, using antacids, H₂-blockers and proton pump inhibitors, is also encouraged (26, 27).

2.1.5 Assessing The Severity of NVP

Designing an appropriate regimen for treating women with NVP depends on two factors. First, the diagnosis of NVP is clinical in nature, and although other causes of persistent nausea, retching and/or vomiting are rarely encountered, failure to distinguish them from NVP can result in serious complications (28). NVP symptoms will appear prior to ten weeks of gestation (1); women who experience NVP symptoms for the first time after 10 weeks, may be experiencing nausea and vomiting due to other medical conditions (29). Table 1 summarizes the differential diagnosis of patients with suspected NVP.
Figure 1. Stepwise Algorithm for the treatment of NVP (14)
Second, the severity of NVP determines the appropriate level of intervention. Attempts to quantify the severity of NVP symptoms started with the Rhodes scale which was originally designed for the 12 hour assessment of nausea and vomiting in cancer patients receiving chemotherapy (30). In 2002 the Pregnancy Unique Quantification of Emesis (PUQE) was developed at the Motherisk program at Toronto’s Hospital for Sick Children, from the Rhodes score and was the first scale of its kind to focus on the nausea and vomiting specific to pregnancy. This 12-hour PUQE score was validated in 2005 (31). Similar to the Rhodes scale the original PUQE scale assessed the severity of NVP by focusing on the number of hours of nausea and the number of episodes of retching and vomiting, as well as overall well-being scores in the twelve hours immediately prior to calling the Motherisk NVP line. It became apparent from the beginning that the 12 hour assessment may mostly encompass sleeping hours, and thus in 2006 the original PUQE was revised to a 24 hour scale such that the time spent sleeping was accounted for. Table 2 demonstrates the PUQE-24 scale.
Table 1. *Other potential causes of nausea and vomiting in pregnancy*

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<td>• Psychologic and psychiatric disorders</td>
<td>• Preeclampsia</td>
</tr>
<tr>
<td>• Infections</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: PUQE-24 Scoring System

<table>
<thead>
<tr>
<th>In the last 24 hrs, for how long have you felt nauseated or sick at your stomach</th>
<th>Not at all (1)</th>
<th>1 hour or less (2)</th>
<th>2-3 hours (3)</th>
<th>4-6 hours (4)</th>
<th>More than 6 hours (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the last 24 hours have you vomited or thrown up?</td>
<td>7 or more times (5)</td>
<td>5-6 times (4)</td>
<td>3-4 times (3)</td>
<td>1-2 times (2)</td>
<td>I did not throw up (1)</td>
</tr>
<tr>
<td>In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?</td>
<td>No time (1)</td>
<td>1-2 times (2)</td>
<td>3-4 times (3)</td>
<td>5-6 times (4)</td>
<td>7 or more times (5)</td>
</tr>
</tbody>
</table>

*PUQE-24 Score: Mild <6; Moderate (7-12); Severe (13-15)*
2.2 HEMORRHOIDS IN PREGNANCY

2.2.1 What are Hemorrhoids?

2.2.1.1 Anal anatomy

In the last portion of the large intestine, where the rectum passes through the levator ani muscle, lays the 3 cm structure of the anal canal. The levator ani muscle is partly responsible for maintaining the acute anorectal angle between the anus and the rectum that contributes to fecal continence. The anal columns are longitudinal folds of mucosa that are situated in the upper portion of the anal canal. The columns fuse together in the inferior portion of the canal to form anal valves, a horizontal line called the pectinate or dentate line. Above the pectinate line exists, mucus containing pockets called the anal sinuses that release lubricants when the passing stool compresses them, allowing their smooth passage during defecation. The mucosa superior to the pectinate/dentate line is innervated by visceral sensory fibers, and thus it is relatively insensitive to pain. The mucosa below the pectinate line however is innervated by somatic nerves (such as the pudendal nerve) rather than visceral, and hence very sensitive to pain (32, 33).

The wall of the anal canal contains two sphincters muscles: an internal anal sphincter of smooth muscle and an external anal sphincter of skeletal muscle. The external sphincter contracts voluntarily to inhibit defecation, whereas the internal sphincter contracts involuntarily, both to prevent feces from leaking from the anus between defecations and to inhibit defecation during emotional stress. It is the external sphincter that children learn to control during toilet training (32).
2.2.1.2 Hemorrhoidal Disease

The three arteries and veins that supply and drain the anal canal are the superior, middle and inferior hemorrhoidal arteries and veins, which stem from the internal iliac vessels (32). The fusing of these branches from these arteries and veins produce the structure of the hemorrhoidal plexuses. The superior, middle and inferior hemorrhoidal veins join to form a network of two chief plexuses of large vessels, namely, the internal and external hemorrhoidal plexuses. Both are devoid of any valves (34). The primary purpose of the hemorrhoidal plexus is the cushioning it provides for bowel control, along with the support from connective tissue framework derived from the internal anal sphincter and longitudinal muscles (35). At rest, the veins of the plexus are filled with blood and dilated, thereby absorbing any variations in abdominal pressure (such as that produced during coughing, sneezing), preventing the involuntary loss of feces. During bowel movement, the veins are compressed and drained, allowing the passage of stool (36). Thus asymptomatic hemorrhoids are considered a normal part of the anatomical structure; hemorrhoid disease however, results from excessive varicose dilations of the hemorrhoidal plexus leading to severe discomfort and bleeding. They may become thrombosed, leading to painful ulcerations (32, 33).

2.2.2 Classification of Hemorrhoids

Hemorrhoids are classified based on where they originate in the anal canal (Figure 2). The top centimeter of the canal, above the pectinate/dentate line, consists of moist simple columnar epithelium. The bottom one-thirds of the canal, below the pectinate line consists of dry stratified squamous epithelium (37,38). Swelling of the superior and
middle hemorrhoidal veins, appear above the pectinate line and are covered by *rectal* mucosa (internal hemorrhoids). Those that appear below the pectinate line represent dilations of the inferior hemorrhoidal plexus and are covered by *anal* mucosa (external hemorrhoids) (32). Both internal and external hemorrhoids can occur simultaneously (33).

### 2.2.2.1 Internal hemorrhoids

Internal hemorrhoids remain unnoticed until they are significantly enlarged and traumatized, in which case they become associated with pruritus ani, discomfort, soiling, prolapse and bleeding after defecation (37). Due to the lack of somatic innervations they are not associated with pain. Banov et al (39) created a grading system of internal hemorrhoids, based on their degree of prolapse.

- Grade I hemorrhoids project into the anal canal and often bleed but do not prolapse.
- Grade II hemorrhoids may protrude beyond the anal verge with straining or defecating but reduce spontaneously when straining ceases.
- Grade III hemorrhoids protrude spontaneously or with straining and require manual reduction.
- Grade IV hemorrhoids chronically prolapse and cannot be reduced. They usually contain both internal and external components and may present with acute thrombosis or strangulation.
2.2.2.2  External Hemorrhoids

The squamous epithelium below the pectinate line receives somatic sensory innervation from the inferior rectal nerve. Hence, external hemorrhoids may be associated with significant pain. They are also almost always accompanied with severe discomfort, pruritus ani and bleeding. External hemorrhoids are prone to thrombosis, and strangulation. When strangulation occurs, hemorrhoids are much larger and may encompass the entire anus (37, 38).

![Formation of hemorrhoids](image)

Figure 2. *Classification of hemorrhoids based on location*

Source: MedicineNet, Inc. Copyright © 2004, WebMD, Inc. All rights reserved.

2.2.3  Etiology and Risk Factors

Although it’s commonly believed that chronic constipation, prolonged sitting, and vigorous straining cause hemorrhoids, little evidence to support a causative link exists
and the absolute etiology remains unknown. Any insult that causes the deterioration of the anchoring and supporting connective tissues, and lead to increase in pressure and dilatation of the cushions can result in their excessive swelling (40). Risk factors historically associated with the development of hemorrhoids include the following:

- Pregnancy
- Lack of erect posture
- Familial tendency
- Higher socioeconomic status
- Chronic diarrhea
- Colon malignancy
- Hepatic disease
- Obesity
- Elevated anal resting pressure
- Spinal cord injury
- Loss of rectal muscle tone
- Rectal surgery
- Episiotomy
- Anal intercourse

More rarely, a secondary cause of hemorrhoids may be due to portal hypertension usually resulting from cirrhosis of the liver (33).
2.2.4 Consequences of Hemorrhoids

Internal hemorrhoids may prolapse during straining and become trapped by the compressive anal sphincter. This in turn can lead to extremely painful hemorrhagic enlargement or strangulation (33). Lack of blood supply to the strangulated hemorrhoid, can progress into gangrene formation followed by life-threatening infections. Chronic bleeding can cause iron-deficiency anemia and rarely, the requirement for transfusions (37, 38). The distended vein of internal/external hemorrhoids can rupture and lead to thrombosis which can potentially result in infarction. Thus when left untreated, hemorrhoids may lead to secondary conditions with severe consequences, potentially life threatening, and can cause a great deal of distress and discomfort, compromising daily functioning.

2.2.5 Treatment

Treatment options are tailored depending on the severity of hemorrhoids; uncomplicated Grade I internal, and non-thrombosed external hemorrhoids are generally treated with sitz baths, high-fiber and fluid intake, stool softeners, topical and systemic analgesics, proper anal hygiene, and topical steroid cream. High fiber diet help reduce severity and duration of symptoms (41). A double blind, placebo controlled study of acute hemorrhoidal symptoms found a decrease in bleeding and pain during defecation with the use of psyllium seed supplements (42). Stool softeners such as docusate sodium or docusate calcium can be taken to yield softer, less abrasive stools (37). In some countries, the use of oral micronized purified flavonoids fraction (MPFF) such as disodium flavodate, heparinoid and rutosides is implemented. These are venotonic agents derived from citrus.
fruits which increase venous tone and decrease capillary fragility, which are thought to improve acute ano-rectal symptoms (43). A meta-analysis of 14 randomized, placebo controlled trials with MPFFs found improvement in bleeding, pain, itching and recurrence of hemorrhoids (43). However the methodological quality, small sample sizes and publication bias in these studies, make their findings questionable.

The initial approach to Grade II or III hemorrhoids includes non-surgical procedures such as ablation, sclerosis, or necrosis of mucosal tissues via techniques such as: rubber band ligation, infrared coagulation, bipolar electroautey, sclerotherapy, cryotherapy, laser therapy and radiowave ablation followed by suture ligation (41). Most are performed in the clinic setting. Despite several meta-analyses there is no clear advantage of one technique over the others.

Very symptomatic grade III and grade IV hemorrhoids are best treated with surgical hemorrhoidectomy. Surgical hemorrhoidectomy is the most effective treatment for all hemorrhoids especially when non-surgical treatments fail and concomitant ano-rectal conditions (e.g. anal fissure or fistula) are present (41).

Acute thrombosed external hemorrhoids may be safely excised in patients who present within 48-72 hours of symptom onset (41).

About 5-10% of people with hemorrhoids eventually require surgical hemorrhoidectomy. Postoperative pain remains the major complication, with most patients requiring 2-4 weeks before returning to normal activities (41). Other possible complications include urinary retention, anal stenosis, and incontinence (41).
2.2.6 Hemorrhoids in Pregnancy

Pregnancy is a well known risk factor for the development of both internal and external hemorrhoids (40, 44, 45). Up to 38% of women in the third trimester of pregnancy suffer from hemorrhoids (9).

Conditions in pregnancy associated with this increased risk are as follows:

- Enlarging uterus increases intra-abdominal pressure on pelvic veins and the inferior vena cava. This excess pressure decreases blood flow to pelvic veins, hence causing vasodilation and engorgement of hemorrhoidal veins (46, 47).
- Increased blood volume by up to 50% in the third trimester contributes to venous engorgement (48).
- Elevated levels of circulating progesterone (49) have multiple effects:
  - Progesterone relaxes venous walls and reduces venous tone, thereby causing venous dilation of the cushions resulting in swelling
  - Progesterone relaxes gastric smooth muscle, which causes several gastrointestinal changes such as delayed gastric emptying, decrease tone of gastroesophageal sphincter, and decreased large intestine motility (49). Decrease in gut motility leads to constipation another well known aggravator of hemorrhoids
  - High doses of oral iron supplementation in prenatal vitamins are also thought to cause constipation (50).
Previous pregnancies also pose as a risk factor to developing hemorrhoids in recurrent pregnancy. In some populations, up to 85% of women in their second and third pregnancies suffer from hemorrhoids (10).

Vaginal deliveries with long labor, lip tears during delivery and giving birth to heavy babies have also been associated with a higher incidence of hemorrhoids (51).

### 2.2.7 Treatment of Hemorrhoids in Pregnancy

There are several challenges in treating hemorrhoids in pregnancy. Since the thalidomide incident (52), there is a heightened sense of fear of drugs in pregnancy, and many women will refuse to treat many medical conditions out of concern for harming the developing fetus (53-55).

Second, while adult life hemorrhoids are usually self-limiting, the general course of hemorrhoids in pregnancy tends to be more prolonged, they progress with the pregnancy, and usually completely resolve only postpartum (38). Because they are expected to resolve on their own, the condition is generally dismissed by many physicians and women endure the symptoms until delivery. This dismissive behavior by physicians has been a recurrent complaint by many of our Motherisk callers. In general the embarrassing nature of hemorrhoids, and anorectal conditions, has lead to a major underreporting as document in literature (56).

Third, treatment of hemorrhoids in pregnancy is symptom based and many over the counter products that claim to effectively reduce the symptoms associated with hemorrhoids do exist; none however, has been studied for safety or effectiveness in
pregnancy. A search of the Motherisk database (Jan 2006-Jan 2007), yielded a list of commonly used local anti-hemorrhoidal preparation. The eight most frequently used products by Motherisk callers included: Anusol®, Anuzinc®, Anugesic-HC®, Preparation H®, Proctofoam-HC®, Proctosedyl®, Witch hazel and Tea tree oil (Appendices C & D). Pubmed and Medline searches did not yield any eligible studies in English on the fetal safety of the above preparations during pregnancy. Thus effective pharmacotherapy for the treatment of hemorrhoids is a dilemma for many pregnant women and as a result many suffer throughout their pregnancy, enduring symptoms that impact their daily well-being.

2.2.8 Assesing Hemorrhoids in Pregnancy

Rectal bleeding, pain, pruritus, or prolapse, are non-specific symptoms that are accompanying many anorectal conditions, including hemorrhoids. Many patients wrongfully attribute any anorectal symptoms to hemorrhoids, hence a thorough medical history as well as a physical examination is generally the most appropriate way to make a conclusive diagnosis, and to rule out more serious disease such as proctitis, inflammatory bowel disease, anal cancer, colorectal tumors, and etc. (57, 58).

A thorough examination by a physician may include visual inspection of the rectum, digital rectal examination, and anoscopy or proctosigmoidoscopy (41). These procedure though painless, are embarrassing and uncomfortable for most patients and cause a great deal of distress, explaining the low diagnosis of this very common disease; less than a third of patients with hemorrhoids are thought to seek help, and only after significant impact is made on their quality of life (57, 58).
Currently no standard tool for assessment of hemorrhoids or any anorectal symptoms, and their response to therapy has been published.

### 2.2.8.1 CORECTS

The COloRetal Evaluation and Clinical Therapeutics Scale (CORECTS) combines the five cardinal symptoms of hemorrhoids: pain, itching, swelling, bleeding and discomfort, each rated on a numeric zero to ten scale, where zero indicates no symptoms and 10 indicates worst possible symptoms (Figure 3.) In addition, CORECTS also accounts for quality of life with an “Impact on Well-being (IW) Score”, which measures the impact of hemorrhoidal symptoms on well-being; the IW score also ranges from zero (no impact) to ten (worst possible impact). In the post treatment section of the CORECTS there is also an “Overall improvement” score, which assesses the total improvement in symptoms following treatment; similarly a score of 0 indicates no improvement at all and 10 indicates maximal improvement comparable to the healthy state.

The CORECTS can be administered either by the healthcare provider or the patients themselves, as a screening tool to assess the severity of symptoms associated with hemorrhoid before necessitating a direct physical exam.
### Before Treatment

<table>
<thead>
<tr>
<th>Question</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>How much pain do you experience?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>How much itching do you experience?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>How much swelling do you experience?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>How much bleeding do you experience?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>How much discomfort do you experience?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
<tr>
<td>How much impact does your condition have on your well-being?</td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

**How do you rate the overall improvement after treatment?**

**[Post treatment]**

<table>
<thead>
<tr>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

Figure 3. CORECTS
2.3 **Safety of Proctofoam-HC® in the Third Trimester of Pregnancy**

2.3.1 What is Proctofoam-HC®?

Proctofoam-HC® is an aerosol foam canister containing the medicinal ingredients: pramoxine and hydrocortisone. It is formulated as a muco-adhesive analgesic and anti-inflammatory foam used for the temporary relief of anorectal inflammation and swelling associated with hemorrhoids, pruritus ani, anal fissures and other anorectal discomforts (59). A canister contains 36 applications; each application provides 375 mg of muco-adhesive gel with 1% hydrocortisone acetate (3.75 mg/dose) and 1% pramoxine hydrochloride (3.75 mg/dose) (59). Because of the non-leaking and non-staining nature of the gel, and the short applicator that comes with, it is assumed that women would prefer this product over others.

2.3.2 Pramoxine Hydrochloride

4-[3-(p-Butoxyphenoxy) propyl] morpholine hydrochloride or Pramoxine Hydrochloride, also known as tronolane and pramocaine hydrochloride(60) is an amino ether local analgesic and is distinctly different from the two large classes of local anesthetics (amides and esters). It is considered to be less potent locally but appears to be less irritating to tissue and possesses a considerably lower systemic toxicity than amide and esters (61), and to still be as effective as benzocaine (62).

Furthermore, due to its unique molecular structure, pramoxine cross-sensitivity is not a common problem compared to other local anesthetics (63).
Upon application, peak effects are experienced within 3 to 5 minutes (64) with a duration of action that is normally less than an hour but can last as long as five hours (60). The metabolism and clearance of pramoxine is still not fully understood.

2.3.2.1 Pramoxine Mechanism of Action

Nerve fibers most sensitive to local anesthetics are the myelinated Aδ (sharp pain) and unmyelinated C fibers (dull, throbbing pain) (65). The direct, reversible binding of pramoxine to voltage dependent sodium gated channels in these fibers, prevents the initiation and propagation of action potentials, thereby inhibiting the sensory transmission of nerve impulses. It is through this reversible binding that pramoxine blocks sensory transmission of pain, cold, warmth and deep pressure sensation (66), as well as itching since the small C nerve fibers are thought to also facilitate this sensation (67).

2.3.2.2 Pramoxine Pharmacokinetics

Typically, topical absorption of local anesthetics is very minimal, with absorption at around 1-3% (68-70). A review by Lewis (71) reported that pramoxine was generally not absorbed when used anorectally. With respect to use in pregnancy, the transfer of pramoxine through the placenta is unknown, but since other local anesthetics cross the placenta readily (72-75), it is reasonable to assume the same is true for pramoxine, though the amount transferred to the fetus is expected to be fairly negligible (76). To conclusively demonstrate its safety to the fetus, further studies are necessary.
2.3.3 Hydrocortisone Acetate

Hydrocortisone is a synthetic corticosteroid that is similar to cortisol, which is produced endogenously in the zona fasiculata of the adrenal cortex from the hydroxylation of cholesterol. It is less potent than other corticosteroids and has widespread physiologic effects such as carbohydrate, lipid and protein metabolism, immunosuppression and anti-inflammatory properties (77). Many conditions require hydrocortisone therapy and the dosage varies according to indication and typically ranging from 5-500mg in adults.

When used topically, general onset of action is seen within 7 days (78), and is cleared quickly from the body, with a plasma clearance of 362 ml/min (77). The primary function of hydrocortisone in Proctofoam-HC® is decreasing inflammation and hence the pain, swelling and discomfort symptoms secondary to inflammation.

2.3.3.1 Hydrocortisone Mechanism of Action

When Phospholipase A₂ is stimulated (i.e. via cell damage), it acts on membrane phospholipids that contain arachidonic acid which is a polyunsaturated fatty acid. The release of arachidonic acid make it a substrate to the cycloxygenase (COX) or lipoxygenase (LOX) enzymes leading to the activation of the arachidonic cascade. Oxygenated fatty acids (OFA) consisting of leukotrienes, prostaglandins and thromboxanes (collectively called the eicosanoids) are the primary precursors in the production of inflammation. The arachidonic cascade is the main pathway that yields these OFAs. Figure 4 summarizes the end products of the arachidonic cascade.

The leukotrienes are involved in the pathogenesis of several inflammatory diseases by causing vasoconstriction and increasing vasopermeability. They also induce neutrophil chemotaxis and aggregation, neutrophil-endothelial cell adhesion, neutrophil
degranulation and release of lysosomal enzymes; they mediate pain and edema and enhance mucosal secretions. The end products of the COX pathways, known as prostanoids, cause vasodilatation and increase capillary permeability, resulting in increased blood flow to the damage site leading to edema, swelling, inflammation and increased sensitization to pain. Thromboxanes cause platelet aggregation, which leads to the formation of thrombosis (77, 79).

Hydrocortisone mediates an anti-inflammatory response primarily by regulating the expression of several inflammatory initiators. One well characterized mechanism is through Lipocortin-1. Lipocortin-1, is structurally related to the family of calcium and phospholipids binding proteins, whose expression and distribution is regulated by glucocorticoids; it inhibits the activity of phospholipase A2, and hence the activation of the arachidonic cascade (Figure 5) (77,79). There are other mechanisms for the anti-inflammatory response of hydrocortisone including: decreasing the number of neutrophils, and production of monocytes, eisonophils, lymphocytes and basophils (77, 79); inhibiting late stages of inflammation by decreasing the synthesis of interleukins and tumor necrosis factor-α (TNF-α); decreasing the accumulation of macrophages in the inflammatory site (79); repressing other inflammatory mediators such as lysosomal enzymes, chemokines, basophils and fibroblasts is also repressed (77,79); and inhibition of histamine released from mast cells and basophils leading to the further reduction of vasodilation and edema (80). Hence, hydrocortisone’s anti-inflammatory property can be summarized in its role in vasoconstriction and decreasing vessel permeability leading to reduction in swelling and discomfort. It also inhibits downstream effects of inflammation and reduces pain as well as pain sensitization.
**Figure 4. Inflammatory byproducts of the arachidonic cascade**


**Figure 5. Hydrocortisone’s anti-inflammatory mechanisms**

Source: Adapted from Ophthalmology, Volume 89, Jampol, LM, Pharmacologic Therapy of Aphakic Cystoid Macular Edema, pp.894, with permission from Elsevier© 1982 (Appendix B)
2.3.3.2 Hydrocortisone pharmacokinetics

Rectal absorption of hydrocortisone in the presence of hemorrhoids in pregnancy has not been documented. The absorption through topical local use is reported to be between 3-7% (81, 82); with 2-3 applications of Proctofoam-HC® containing 1% hydrocortisone, per day, less than 1mg is thought to be systemically absorbed (83, 84). Placental transfer does occur (85, 86) but is expected to be in minimal amounts (86, 87). The placenta contains syncytial trophoblastic cells which are enriched with the enzyme 11β hydroxysteroid dehydrogenase 2 (88); this enzyme is responsible for the metabolism of active corticosteroids to the inactive 11-ketosteroids (corticosterone, 11-dehydroxycorticosterone) (89,79). However, it is not as effective with exogenous corticosteroids, and can be saturated in the presence of high levels of maternal cortisol (90, 91).

2.3.4 Hydrocortisone and Pregnancy

2.3.4.1 Teratogenicity (Systemic Corticosteroids)

Several studies have demonstrated the dose dependent teratogenic effects of oral corticosteroid use; systemic glucocorticoids have consistently produced cleft palate in animal reproductive studies (92-94). Human teratology studies in pregnancy have been conflicting. Four retrospective case-control studies have found an association with oral cleft specifically (95-98). In contrast, several prospective cohort studies have failed to show an association between exposure to corticosteroids in pregnancy and any major malformations(99-103).
In a meta-analysis conducted by Motherisk, including 5 cohort studies and 4 case controlled studies, the summary odds ratio in the combined cohort studies reporting on the total major malformations, was not significant 1.45 (95% CI:0.81-2.60) although a clustering of cleft palate among the corticosteroid exposed group was observed when compared to the controls (103); the summary odds ratio for the case-control studies examining oral clefts specifically was significant 3.35 (95% CI: 1.97-5.69). A recently published cohort study (April 2011), contributes to the findings of the aforementioned cohort studies, where no significant increase in the prevalence OR ratio 1.23 (95% CI 0.83-1.82) for cleft palate in the exposed group of women was found (104).

In the light of current data, the risk for major teratogenic risk associated with systematic exposure to corticosteroids in pregnancy, is not significant, although a small risk for oral cleft can not be ruled out at this point. Since the cleft is completely formed by the 11\textsuperscript{th} week of gestation, exposure to be minimized in the first 11 weeks of gestation and resume thereafter.

2.3.4.2 Birth Weight (systemic corticosteroids)

One of the first studies on the fetal safety of hydrocortisone was performed in 1951 by Fraser and Fainstat (105), showing marked intrauterine growth restriction (IUGR). In one study by Kalter and colleagues, a decrease of 31.2% in birth weight was observed in mice (106) with no difference in mean gestational age. In another study in rabbits, cortisone given IM produced IUGR in the pups and an increase in fetal and neonatal death (107). Several animal studies have consistently shown a dose dependent relationship with single and multiple dosing of betamethasone and birth weight reductions of 14%-26% with single dosing, and as high as 30% with three doses (108-
Dose dependent growth defects have also been observed in rabbit and mice studies with exposure to maternal glucocorticoids with more in the later stages of pregnancy (112, 113).

Several studies that have documented significant reduction in birth-weights of human subjects are summarized below:

A Motherisk prospective observational study with 187 women exposed to systemic prednisone in pregnancy found a significant difference in the birth weights of the treatment group (3112±684 grams) vs. the control group (3428±578 grams). Prematurity rates in the treatment group were also significantly higher than controls (17% vs. 6%) (103).

A prospective controlled trial with 311 exposures to systemic corticosteroids, found a significant decrease in median birth weights of the treatment group (3080 grams) vs. the control groups (3290g). Prematurity rates in the treatment group were also significantly higher than controls (22.7% vs. 10.8%). Rate of spontaneous abortions was also significantly higher in the treatment group (11.5% vs. 7.0%) (114).

Studies done on safety of corticosteroids for treatment of maternal asthma, that included oral dosing, have also been reported. A recent study by Schatz (115) on 297 women with asthma found a significant association between corticosteroid exposure and low birth weight (6.1% in the treatment group vs. 3.3% in the control group), preterm birth (6.4% in the treatment group vs. 3.8% in the control group).

In 1993, the National Institute of Health estimated that there was a risk of
antenatal corticosteroid exposure in treating asthma resulting in a 300-400 gram decrease in birth weight (116).

All of the above studies examined the administration of betamethasone, dexamethasone or both. One large retrospective study observed a 63 gram reduction in the mean birth weights (1671±574) of 8911 NICU babies from women exposed to antenatal corticosteroids (117), and another study by Bloom et al, found a decreases of 161 grams and 80 grams at weeks 30-32 and 33-34 of gestation, respectively in a cohort of 961 infants who received antenatal dexamethasone versus those who received none (118). Four other retrospective studies have contradicted the above findings, and found no difference in birth weight between one and two courses of maternal antenatal corticosteroids; all included 409, 354, 713 and 152 participants respectively (119-122). These studies however examined differences between single and multiple doses and negative controls were not used in their analyses.

The discrepancy in these studies, make the adverse effect of corticosteroids a still controversial concept, and further studies are required to make more conclusive statements with regards to its safety.

2.3.4.3 Topical and rectal applications of corticosteroids

None of the above risks for malformations and adverse fetal effects have thus far been associated with the topical use of corticosteroids. Research investigating the possibility of IUGR with topical usage is still sparse.
Rectal application is more challenging to assess. Depending on where in the anal canal the drug is applied, there may be considerable variability in systematic absorption. The lower rectal region is drained by the inferior and middle rectal veins into the inferior vena cava and directly into the systemic circulation (123). In contrast, the upper rectal region is directed into the superior rectal vein, which is directed into the portal vein and undergoes hepatic metabolism before entering into the system circulation (123). Thus lower rectal absorption of some drugs is higher than oral absorption, presumably because they bypass first-pass metabolism (123). Rectal absorption of hydrocortisone has been conducted in a few studies with large inter-individual variability; the estimated rectal bioavailability ranges from 0.4% to as high as 30% in these studies (124-126). It is possible that the application location in the anal canal, determines the degree bypassing hepatic metabolism of hydrocortisone, hence leading to such variability in these studies.

The implication for Proctofoam-HC® with rectal application hence, is the absorption level of each of the two drugs, pramoxine and hydrocortisone. Theoretically, multiple rectal applications may potentially, lead to large amounts of hydrocortisone or pramoxine entering the systemic circulation. As mentioned, multiple doses of oral corticosteroids have been associated with IUGRs, and given the lack of data on the safety of pramoxine in pregnancy, a study assessing the fetal safety of this commonly used anti-hemorrhoid medication is strongly warranted.
2.3.5 Effectiveness of Proctofoam-HC® in Treating Hemorrhoids in Pregnancy

No data is available in the current literature to assess the effectiveness, of the combination pramoxine hydrochloride and hydrocortisone acetate for the treatment of pregnancy related hemorrhoids.

For itching associated with psoriasis, pruritus ani, and experimentally histamine-induced pruritus, pramoxine has demonstrated usefulness in several studies (127-129). The studies however do not include pregnant women, nor any data to support efficacy for treatment of local pain and pruritis.

Hydrocortisone has been shown in a small number of studies in the general population to relieve some of the symptoms associated with anorectal conditions. One study using 1% hydrocortisone cream, showed a 68% decrease in anal itch compared to placebo (130). Another study demonstrated marked decrease in symptoms such as pain, bleeding and pruritus associated with anal fissures (131). Similar to pramoxine however, there are limited data on the efficacy of hydrocortisone for treatment of hemorrhoids. Hence, conducting a study to assess the effectiveness of Proctofoam-HC® for treating symptoms associated with hemorrhoids in the pregnant population is also required, in order to establish proven methods for managing hemorrhoids in pregnancy.
CHAPTER 3.
MATERIALS AND METHODS

This chapter explains how each of the studies was conducted. Details on study design, subject recruitment, type of statistical analysis and the procedure for collecting data have been explained thoroughly.

3.1 VALIDATION OF PUQE-24

3.1.1 Study Design

This was a prospective observational study.

3.1.2 Subject Recruitment

The Motherisk line is a helpline developed to provide evidence-based counseling to pregnant women and their healthcare providers about the safety of exposures. The Motherisk NVP line provides counseling specifically for women experiencing nausea and vomiting of pregnancy (NVP); strategies such as lifestyle changes, medicinal as well as non pharmacological ways for the management of NVP symptoms are discussed. The NVP counselors collect detailed information from woman once before counseling them and again during the follow up calls to evaluate their NVP management. Patients calling the Motherisk NVP line were used for this portion of the study.

3.1.3 Study procedure

For the validation of the PUQE-24 scale, 315 women who contacted the Motherisk NVP health line between 2005-2008 were selected. The following information was collected from their intake forms at their time of call:

- Their mean gestational age at the time of call
- The mean gestational age when NVP symptoms first started
• Daily liquid intake per kilogram of body weight;
• Number of hours of sleep the night before
• Quality of sleep (broken vs. good)
• Multivitamin use
• Hospitalization or emergency room visits due to NVP symptoms
• Well-being scores

The PUQE score for each patient was calculated using the original three criteria to assess severity of NVP: number of hours of nausea, and number of episodes for retching and vomiting over the last 24 hours. The PUQE score is calculated by adding the values from each category and can range from a minimum of 1 to a maximum of 15 (Table 2). The well-being score is a general self-perception score of physical and psychological health. Women were asked to rate their overall well-being in the 24 hours prior to the call, on a scale of 0 (worst possible well-being) and 10 (optimal well-being comparable to the pre-pregnancy state). Patients were also asked to provide reasoning for the well-being scores.

Information on sleep was obtained by asking the women to estimate the number of hours they slept the night before and the naps taken during the last 24 hours. Women were also asked to comment on the quality of sleep by stating if they had continuous or broken sleep; “good” sleep was described as undisturbed solid sleep, whereas “broken” was anything otherwise.

Information on multivitamin use was obtained by asking callers to state if they were using multivitamins or prenatal vitamins and the start and end date for their use. This yielded three categories of usage pattern: 1) Taking, 2) Not taking, and 3) Discontinued taking multivitamins. Patients were categorized as discontinued taking if they had
stopped using multi/prenatal vitamins within the last two weeks of the call, and were placed in *not taking* if they never took multivitamins or if they discontinued their use more than two weeks prior to making the call. The rational for this distinction was that if a woman had discontinued use of vitamins more than 2 weeks prior to calling our line, this discontinuation could not necessarily be related to the severity of her NVP symptoms at the time of call.

Patients were also asked if they had been hospitalized since the beginning of their pregnancy. The reason for their hospitalization, the length of stay at the hospital and the type of treatment received were also documented.

Information on liquid intake was gathered from reports on the number of cups of water and fluids drank the previous day. To calculated amount of liquid intake per body weight, 200 ml was used as the estimated average volume of liquid per cup, multiplied by the number of cups used and divided by the patient’s weight; this yielded a volume of liquid intake in milliliters per kilogram. Although a full cup is 250 milliliters, people typically do not fill their cups above 200 ml.

Since English is a secondary language for many pregnant patients, and can act as a barrier when discussing their symptoms, we aimed to increase the generalizablity of the PUQE-24 scale by administering it to a Spanish speaking population. Spanish is a very commonly used language by many immigrants in Toronto. We translated the PUQE questionnaire to Spanish and delivered it to ten women in their reproductive age. After the woman answered all the questions, an extensive open ended questionnaire was conducted in detail to assess their understanding of each of the PUQE questions. Comprehension was rated as “excellent” if the understanding was judged complete, “very
good”, if there was minor misunderstanding not affecting the scores, and “less than optimal” if the lack of comprehension affected the scores.

### 3.1.4 Statistical analysis

Linear regression analysis was first administered between well-being and PUQE-24 scores and between each of the well-being & PUQE-24 scores and number of hours of sleep and liquid intake. Chi square analysis was performed to compare the severity of PUQE-24 (mild, moderate, severe) and quality of sleep, multivitamin use, and rates of hospitalization.
3.2 VALIDATION OF “CORECTS” SCORES

3.2.1 Study Design

This was a prospective observational study

3.2.2 Study tool: CORECTS

The COloRetal Evaluation of Clinical Therapeutics Scale (CORECTS) combines the five cardinal symptoms of hemorrhoids: pain, itching, swelling, bleeding, and discomfort, each rated on a numeric zero to ten scale, where zero indicates no symptoms and 10 indicates worst possible symptoms (Figure 3.) In addition, CORECTS also accounts for quality of life with an “Impact on Well-being (IW) Score”, which measures the impact of hemorrhoidal symptoms on well-being; the IW score also ranges from zero (no impact) to ten (worst possible impact). In the post treatment section of the CORECTS there is also an “Overall improvement” score, which assesses the total improvement in symptoms following treatment; similarly a score of 0 indicates no improvement at all and 10 indicates maximal improvement comparable to the healthy state.

3.2.3 Subject Recruitment

For the external validation of the study we administered CORECTS to 29 adult patients visiting the Rudd anorectal clinic between September and December 2008. Their reason for their visit included hemorrhoids, anusitis, fistulas, fissures, and anal lesions. All 29 patients were directly examined by a team proctologist who routinely rates the severity of their symptoms from zero (symptom free) to 5 (maximal severity).
After verbal consent, each patient was asked to fill out the CORECTS scale by circling the number on the scale best corresponding to the severity of their symptoms. This process was repeated by the investigator delivering the questionnaire in order to evaluate the accuracy of the scale—to see whether self-assessed scores agreed with a clinician’s evaluation.

Concurrently a separate study was being conducted to evaluate the effectiveness and safety of an anti-hemorrhoidal medication: Proctofoam-HC® for the treatment of hemorrhoids in pregnancy. 209 pregnant women were recruited from obstetric and gynecology clinics in Montreal and Toronto; all women were consenting adults in the third trimester of their pregnancy and diagnosed by their physician for hemorrhoids. Majority of the patients reported great relief after using Proctofoam-HC®. As part of this study, the CORECTS scale was administered to each patient before and after treatment with Proctofoam-HC® to evaluate its effectiveness. The “Prior to Treatment” part of the CORECTS scale was filled out at the time of recruitment to assess the severity of the hemorrhoids, and the post treatment section was completed shortly after delivery; for a subgroup of patient (N=68) the post treatment section was completed within three weeks of using the product and prior to delivery. We used the CORECTS data portion of this study to evaluate its ability to track changes in hemorrhoid symptoms following treatment.

3.2.4 Statistical analysis

Linear regression and multiple regression analysis were used to correlate between the proctologist’s grade and different components of the CORECTS scale.
Paired student t-test or Wilcoxon signed rank test were performed to compare the changes in the mean or median scores of each of the components of CORECTS (i.e. pain, itching, well-being, etc.) before after treatment with Proctofoam-HC®.
3.3  SAFETY AND EFFECTIVENESS OF PROCTOFOAM-HC® IN THE 3rd TRIMESTER OF PREGNANCY

3.3.1  The Fetal Safety of Proctofoam-HC® in the Third Trimester of Pregnancy

3.3.1.1  Study Design

This was a prospective, open-labeled, controlled observational study.

3.3.1.2  Subject Recruitment

Participants were recruited from six different sites between September 2006 and December 2009. The sites included Obstetrics and Gynecology clinics at Mount Sinai Hospital, North York General Hospital, Women’s College/Sunnybrook Health Sciences and William Osler Hospital in Toronto, Ontario and the Centre Hospitalier de la Salle in La Salle, Quebec. The Motherisk general help line was also used to recruit patients.

3.3.1.3  Inclusion and Exclusion Criteria

Only consenting women in the 3rd trimester of pregnancy (27th gestational week onwards) were recruited.

Inclusion criteria were as follows:

- Low risk pregnancy with evidence of no pregnancy complications.
- Diagnosis with primary anorectal conditions (not caused by a systemic disease such as portal hypertension)
- Usage of Proctofoam-HC® alone, for treatment of their anorectal condition
Exclusion criteria were as follows:

- Women who were exposed to known teratogens during pregnancy
- Insufficient English language skills to understand the questionnaires
- Pregnant women younger than legal age of 18 years of age
- Usage of systemic corticosteroid medication
- Women with medical conditions that contraindicated Proctofoam-HC® usage (i.e. anorectal abscess, fistula, tuberculosis, varicella, Acute Herpes Simplex or fungal infections).
- History of reaction to any of the ingredients in Proctofoam-HC® (i.e. local irritation, hypertrichosis or hypo pigmentation)
- Known intrauterine growth restriction (IUGR) or known chronic conditions associated with IUGRs (i.e. systemic lupus erythematosus, placental insufficiency).
- Binge alcohol consumption.

3.3.1.4 Study Instruments

Two questionnaires were used to collect the necessary data from each patient. The Antenatal questionnaire was administered prior to delivery, and the postnatal within a few weeks postpartum. The following outlines the information collected at each interview:

Antenatal questionnaire (Appendix E)

- Detailed medical and obstetric history
- Dose, duration and indication for Proctofoam-HC® usage
• Identity and doses of any other concomitant medications
• Smoking and alcohol status

Postnatal questionnaire (Appendix F)

• Course of the pregnancy subsequent to the antenatal interview
• Changes in Proctofoam-HC® usage pattern
• Any additional medications and maternal illnesses
• Perinatal and/or postnatal complications
• Gestational age at birth, birth weight, Apgar scores, neonatal health and delivery methods.

3.3.1.5 Study Procedure

Physicians specializing in obstetrics and gynecology were approached to collaborate in the study if they routinely prescribed Proctofoam-HC® to their pregnant patients. Prior to prescribing Proctofoam-HC® to their patients, the physicians would briefly explain the ongoing study and inquire if the patient would be interested in participating. If agreement was made, the study coordinator would retrieve patient’s contact information, and call the patient to explain the full details of the study, retrieve verbal consent (Appendix G) and mail a package containing a letter with all necessary contact information and study details (Appendix H).

Motherisk callers in the third trimester of pregnancy who called between September 2006 and December 2009 to request information regarding the use of Proctofoam-HC® in pregnancy were told about the study and asked if they were interested in participating. If the caller met the inclusion criteria, the Motherisk counselor would provide details of
the study and refer the patient to speak to the study coordinator, and the above procedure was repeated.

Upon recruitment women were contacted by phone to complete the antenatal questionnaire. The second assessment, the postnatal questionnaire, was completed up to 3 months after delivery. Fetal and maternal outcomes were confirmed by sending a letter to the child’s primary care physician (Appendix I) to corroborate the mother’s information.

### 3.3.1.6 Outcome Measures

From the median weight of 1 kg at 28 weeks of gestation, the baby is expected to gain another 2 kg in the subsequent 10 weeks prior to delivery (132). This rapid weight gain process can be interrupted by certain number of insults such as cigarette smoking (133); as explained before, repeated oral doses of corticosteroids in pregnancy have been shown to cause a significant decrease in birth weight. Hence, as the primary endpoint for the safety of Proctofoam-HC®, birth weight, which is a relatively sensitive measure of fetal development in the third trimester, was used. The secondary outcomes include mode of delivery, labor complications, fetal distress and adverse events in the neonate.

### 3.3.1.7 Comparison Group

In order to ascertain the impact of Proctofoam-HC® on birth weight, a comparison group of pregnant women who were not exposed to this product or any of its ingredients were chosen. Motherisk callers who had called to receive information on non-teratogenic drugs (i.e. Diclectin®, acetaminophen, etc.), and who were not exposed to any teratogens during the course of their pregnancy, were chosen as our comparison group. None of
these women suffered from hemorrhoids at the time of call. The comparison group was matched to the Proctofoam-HC® group based on maternal age (+/- 2 years) and smoking status (+/- 2 cigarettes).

3.3.1.8 Data Analysis
Gravida, parity, alcohol use, smoking, adverse pregnancy outcome, mode of delivery, prematurity, low birth weight, major and minor malformations, fetal distress, labour complications and neonatal health were compared between the treatment and comparison groups using chi-square analysis or fisher’s Exact test for dichotomous data. Mean maternal age, gestational age at delivery, weight gain and birth weight were compared between the two groups using the Student’s t-test if the data were normally distributed or Mann Whitney Rank Sum test for non-normal distribution. α was set as 0.05 for all tests. SigmaStat (v 3.11.0 Systat Software Inc, Point Richmond, CA) was used to perform the above statistical analysis.

3.3.1.9 Sample Size
Exposure to tobacco in pregnancy has been shown to cause an average reduction of 200g in birth weight (134). Hence, to detect a clinically significant average decrease of 200g in birth weight with a power of 80% and alpha error of 5%, 155 women were required, each, in the treatment and control groups for a total of 310 subjects. During the study period, all eligible cases were recruited and the power of the available sample size is calculated in the Results section.
The study protocol was approved by the research ethics board at the Hospital for Sick Children (Appendix J), North York General Hospital (Appendix K) and Sunnybrook Health Sciences Centre (Appendix L). Verbal informed consent was obtained prior to enrolling women into this trial. The following elements were discussed prior to obtaining consent: purpose of the study, study design, potential benefits of treatment, potential side effects of treatment, voluntary participation and privacy. Enrolment in this study was voluntary, and patients were allowed to withdraw for any reason at any time during the study. Participants were assured that refusal to participate in the study would not affect the quality of health care they receive at Motherisk or at the Hospital for Sick Children. Subject to the requirement for access to subjects’ files for the purpose of source data verification by monitors, auditors and inspectors, confidentiality of all subjects was strictly maintained. All patient information was kept in a locked and secure area in the hospital. No personal identifiers were used outside the designated hospital room.
3.3.2 Effectiveness of Proctofoam-HC® in Treating Hemorrhoids in Pregnancy

3.3.2.1 Study Design

This was a prospective, observational study.

3.3.2.2 Subjects

All patients receiving Proctofoam-HC® and participating in the safety phase (section 3.1.1) were included in the effectiveness phase of the study.

3.3.2.3 Study Instrument

CORECTS, the 6 item questionnaire covering the five major symptoms of hemorrhoids: pain, itching, bleeding, swelling, discomfort, and overall impact on well-being, was the primary tool used for the assessment of effectiveness. Participants were asked to rate the severity of their hemorrhoidal symptoms, and their impact on their well-being, on a scale of 0 to 10 for each symptom listed on the CORECTS, with ‘0’ indicating ‘no symptoms/no impact on well-being’, and ‘10’ indicating ‘symptoms at their worst/worst impact’. This questionnaire was completed twice, once prior to using Proctofoam-HC® and again, after a treatment duration of at least 2 weeks. As part of the “post treatment” assessment, participants rated their overall improvement with treatment on the CORECTS; once again 0 indicated no improvement at all, and 10 indicated maximal improvement and symptom free.
3.3.2.4 Study Procedure

The same participants from the safety phase filled out the CORECTS scale at least two times – at the antenatal interview and at least 2 weeks after treatment. If the subject was scheduled to deliver prior to two weeks, the second assessment was completed during the routine postnatal interview.

3.3.2.5 Primary Outcome

Pain is the most common complaint in hemorrhoids sufferers, with the most impact on well being. Any type of untreated pain can detrimentally affect all aspects of quality of life. Hence the primary outcome for effectiveness is the ability of Proctofoam-HC® is reducing pain. The other hemorrhoidal symptoms – discomfort, itching, bleeding and swelling, as well as improvement in well-being and global improvement scores—were the secondary outcomes for the effectiveness phase of the study.

3.3.2.6 Comparison Group

No comparison group was recruited for this phase of the study.

3.3.2.7 Data Analysis

Paired Student’s t-test for normally distributed data or Wilcoxon Signed Rank test for non-normal distribution was used to compare the changes in symptoms before and after treatment with Proctofoam-HC®. The significance level α, was set at 0.05 for all tests. SigmaStat (v 3.11.0 Systat Software Inc, Point Richmond, CA) was used for the above analysis.
3.3.2.8 Sample Size

A clinically significant difference in the primary outcome, pain, is thought to be a minimum decrease in 2 points on an 11 point numerical rating scale (148). From a study employing a similar 11 point numerical scale, with a power of 95% and an alpha error of 5%, only 23 subjects would need to be needed; our sample size however far exceeds this number.

3.3.2.9 Ethical Considerations

The study protocol was approved by the research ethics boards at the Hospital for Sick Children, North York General Hospital and Sunnybrook Health Sciences Centre.
4.1 VALIDATION OF PUQE-24

A total of 311 women were used for this part of the study. The mean gestational age at the time of their call was 8.6 weeks, with 96% of women in their first trimester. The mean gestational age when NVP symptoms first started was 5.6 weeks (Range: 2-9.5 weeks). Results for each of the criteria used to validate the PUQE-24 are explained below.

4.1.1 Multivitamin Use

Of the 311 patients evaluated, a total of 39 patients were not taking multivitamins. Chi square analysis revealed a significant concordance between severity of NVP as defined by PUQE-24, and the propensity for not taking multivitamins. There was a significant difference between mild and severe, as well as moderate and severe PUQE scores. Table 3 outlines this comparison.

<table>
<thead>
<tr>
<th>PUQE Severity (score)</th>
<th>Percentage Not taking</th>
<th>Percentage Not taking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (3-6)</td>
<td>0/32 (0.0%)^</td>
<td></td>
</tr>
<tr>
<td>Moderate (7-12)</td>
<td>24/219 (11.0%)*</td>
<td></td>
</tr>
<tr>
<td>Severe (&gt;13)</td>
<td>15/60 (25.0%)^*</td>
<td></td>
</tr>
</tbody>
</table>

^P = 0.005 and *P = 0.001
4.1.2 Hospitalization

Of the forty cases of hospitalization and emergency visits, three were of mild NVP (9.4%), twenty one were of moderate NVP (9.6%) and sixteen were of severe NVP (25%). Chi square revealed a significant difference between hospitalization rates of moderate and severe cases by PUQE-24 (P=0.002) (Table 4.).

<table>
<thead>
<tr>
<th>PUQE Severity</th>
<th>Percentage Not taking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (3-6)</td>
<td>3/32 (9.4%)</td>
</tr>
<tr>
<td>Moderate (7-12)</td>
<td>21/219 (9.6%)*</td>
</tr>
<tr>
<td>Severe (&gt;13)</td>
<td>16/63 (25.4%)*</td>
</tr>
</tbody>
</table>

*P=0.002

4.1.3 Sleep Pattern

14/32 (43.8%) of the Mild, 112/217(51.6%) cases of the Moderate and 32/63(50.8%) of Severe cases reported broken/poor sleep. This trend was not significant among the three groups. Similarly linear regression analysis revealed no significant correlation between length of sleep and PUQE-24 nor well-being scores.

4.1.4 Well-being

Callers were asked to rate their overall physical and mental well-being on a scale of zero to ten in the 24 hours preceding the call. Linear regression analysis between well-being scores and the PUQE scores revealed highly significant correlation (P <0.001).
4.1.5 Liquid intake

134 (4 Mild, 19 Severe and 111 Moderate) callers provided information regarding their liquid intake. Women with Severe, Moderate and Mild PUQE-24 consumed 17.3, 17.34, 19.96 ml/kg/24hours of fluid respectively. After standardizing the volume of liquid consumed for the women's body weight, linear regression revealed significant correlation between well-being scores and amount of liquid intake ($r=0.189; P=0.031$); however PUQE-24 scores and amount of liquid intake did not show significant correlation.

4.1.6 Spanish Version of PUQE-24

For the validation of PUQE in Spanish, ten woman of reproductive age (5 Mexican and 5 Argentinean) were interviewed. All participants stated that they had understood the questions, and that they were straightforward and further clarification was not needed. They also stated that the questions were reasonable and they felt comfortable answering them. After the questionnaire was completed, the participants were asked in detail what they understood from each of the questions in PUQE. Responses from all participants were satisfactory from the interviewer's perspective. Some participants (two) had some difficulty answering the part “Why?” with respect to quality of sleep which was asked after the question inquiring about the number of hours of sleep in 24 hours; as they had already responded that they had slept fine and didn't know how to justify their “good” sleep. Thus this question may lead to a bit of confusion, but it is easily explainable.

Comprehension of the score questions was rated as “excellent” in 8 out of 10 of the participants, and “very good” in 2 out of 10, as evaluated by the interviewers on the basis
of the answers provided by the participants, when they were asked to explain what they had understood and what they thought the questionnaire questions meant.
4.1 VALIDATION OF CORECTS

4.2.1 External Validation with Proctologist’s Grade

Of the 29 patients visiting the Rudd clinic, 10 (34%) had symptomatic hemorrhoids, and the remaining patients were visiting conditions such as fistulae and anusitis. Significant correlation was found between the clinician’s score and the pain and bleeding components of CORECTS.

Combining the two objective components (bleeding and swelling) scores also yielded a significant correlation with the clinician’s grade.

There was also a significant correlation between Impact on Well-being (IW) scores and the pain, swelling and discomfort components of CORECTS, but no correlation with bleeding, and itching. Table 5 demonstrates these relationships.

<table>
<thead>
<tr>
<th>CORECTS Components</th>
<th>Proctologist Score P-value [R²]</th>
<th>IWB Score P-value [R²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>0.02 [0.2] §</td>
<td>0.012 [0.2] §</td>
</tr>
<tr>
<td>Itching</td>
<td>0.94 [0.0] §</td>
<td>0.24 [0.1] §</td>
</tr>
<tr>
<td>Swelling</td>
<td>0.05 [0.2] §</td>
<td>&lt;0.001 [0.4] §</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.01 [0.3] §</td>
<td>0.17 [0.1] §</td>
</tr>
<tr>
<td>Discomfort</td>
<td>0.09 [0.1] §</td>
<td>&lt;0.001 [0.4] §</td>
</tr>
<tr>
<td>Swell+Bleed</td>
<td>0.03 [0.3] *</td>
<td>&lt;0.001 [0.7] *</td>
</tr>
<tr>
<td>Swell+Bleed+Discomfort</td>
<td>0.05 [0.3] *</td>
<td>0.002 [0.4] *</td>
</tr>
<tr>
<td>Impact on WB</td>
<td>0.769[0.0]</td>
<td></td>
</tr>
</tbody>
</table>

§: Simple Linear Regression; * Multiple Linear Regression
4.2.2 Detecting changes in symptom severity following treatment with CORECTS

The mean age of the 204 pregnant women receiving Proctofoam1HC® for treatment, at conception was 31.6 (median: 32.2), the median gravidity of 2, parity of 0. A total of 175 (81%) of these women underwent a vaginal delivery. All women had symptomatic hemorrhoids with pain and swelling as their major complaints. Upon treatment with Proctofoam-HC® there was significant reduction in all parameters of the CORECTS, with a mean “overall improvement” score of 7.51 and a median of 8 (Table 6.).

Table 6. Changes in CORECTS scores before and after treatment with Proctofoam-HC®

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prior treatment Median (25-75%)</th>
<th>Post treatment Median (25-75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>6.0 (3.0-8.0)</td>
<td>0.0 (0.0-2.0)*</td>
</tr>
<tr>
<td>Itching</td>
<td>4.0 (1.8-6.0)</td>
<td>0.0 (0.0-1.0)*</td>
</tr>
<tr>
<td>Swelling</td>
<td>6.0 (5.0-8.0)</td>
<td>2.0 (0.0-4.0)*</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.0 (0-4.0)</td>
<td>0.0*</td>
</tr>
<tr>
<td>Discomfort</td>
<td>7.0 (4.0-8.3)</td>
<td>0.0 (0.0-3.0)*</td>
</tr>
<tr>
<td>Impact Wb</td>
<td>7.0 (5.0-8.0)</td>
<td>1.0 (0.0-3.0)*</td>
</tr>
<tr>
<td>Overall Improve.</td>
<td>8.0 (7.0-9.0)</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.0001 [Wilcoxon singed rank test]

For a subset of the same group of women (N=68), the CORECTS was administered three times: once prior to treatment with Proctofoam-HC®, then within 2 weeks of using Proctofoam-HC® and finally after delivery. The mean duration of treatment at the first assessment post treatment was 22.2 days, and 64.2 days at the second post treatment assessment. The third postpartum assessment was completed within 3-5 week with a mean of 29.1 days postpartum. There was a significant change in pain, itching, swelling and IW
components of CORECTS, in the third assessment (long treatment duration) group, in comparison to the second assessment. The scores at both treatment durations, was significantly different than the “prior to treatment” scores (Table 7).

Table 7. Changes in CORECTS scores following short and long treatment durations with Proctofoam-HC®

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prior to Treatment (Mean±Sd)</th>
<th>Post – treatment 1 Median (25-75%)</th>
<th>Post treatment 2 Median (25-75%)</th>
<th>P-value comparing post treatment 2 to 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (mean±sd)days</td>
<td>22.2 ± 11.7</td>
<td>64.2 ± 33.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5.0 (2.5-6.5)</td>
<td>1.0 (0.0-3.0)</td>
<td>0.0 (0.0-1.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Itching</td>
<td>4.0 (0.0-5.0)</td>
<td>1.0 (0.0-3.0)</td>
<td>0.0</td>
<td>0.0002</td>
</tr>
<tr>
<td>Swelling</td>
<td>5.0 (4.0-7.5)</td>
<td>4.0 (2.5-5.5)</td>
<td>2.0 (0.0-3.0)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0 (0-3.0)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Discomfort</td>
<td>7.0 (4.0-8.0)</td>
<td>2.5 (1.0-5.0)</td>
<td>0.0 (0.0-2.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Impact on Wb</td>
<td>7.5 (5.0-8.0)</td>
<td>3.5 (1.0-5.0)</td>
<td>0.0(0.0-3.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Overall Improvement</td>
<td>8.0 (5.0-9.0)</td>
<td>8.0 (6.3-9.0)</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Days post partum (days)</td>
<td></td>
<td></td>
<td>26.0 (21.0-35.0)</td>
<td></td>
</tr>
</tbody>
</table>
4.3 SAFETY AND EFFECTIVENESS OF PROCTOFOAM-HC® IN THE 3RD TRIMESTER OF PREGNANCY

The total number of women recruited for this study in the course of 3.5 years was 261; of which 204 fully completed the study; the remaining were either lost to follow up, discontinued using Proctofoam-HC®, or had too many missing data. The comparison group consisted of 204 pregnant Motherisk callers not exposed to any of the Proctofoam-HC® components. Seven pairs of twin pregnancies in the treatment group were included, 5 of which could not be matched for. While included in most of the analyses, the twin pregnancies were omitted from the comparison of birth weights.

Women received Proctofoam-HC® in the third trimester for a median of 6 weeks. Each woman used approximately 2 canisters of Proctofoam-HC® during their treatment duration and applied it approximate 2 to 3 times a day (Table 8).

<table>
<thead>
<tr>
<th>Treatment Details</th>
<th>Mean (SD)</th>
<th>Median (25%-75% quartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of treatment in Pregnancy [weeks]</td>
<td>6.9 (5.1)</td>
<td>6.0 (3.0-10.0)</td>
</tr>
<tr>
<td>Frequency of treatment per day</td>
<td>2.6 (0.9)</td>
<td>2.5 (2.0-3.0)</td>
</tr>
<tr>
<td>Total number of canisters used</td>
<td>2.3 (1.3)</td>
<td>2.0 (1.0-3.0)</td>
</tr>
</tbody>
</table>
4.3.1 Safety of Proctofoam-HC®

There were no differences in maternal characteristics between women in the two groups, except for more prevalent casual alcohol use and smoking in the comparison group (Table 9).

Table 9. Maternal characteristics of patients in the treatment versus comparison group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment</th>
<th>Comparison</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>203</td>
<td>204</td>
<td>0.31§</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>32 (4.9)</td>
<td>31.5 (4.9)</td>
<td></td>
</tr>
<tr>
<td>Median (25-75% quartile)</td>
<td>32.5 (28.7-35.4)</td>
<td>32.0 (28.0-35.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Gravida</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>206</td>
<td>198</td>
<td>0.2¥</td>
</tr>
<tr>
<td>Median</td>
<td>2.0 (1.0-3.0)</td>
<td>2.0 (1.0-3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>202</td>
<td>199</td>
<td>0.83¥</td>
</tr>
<tr>
<td>Median</td>
<td>1.0 (0.0-1.0)</td>
<td>0.5 (0.0-1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Casual Alcohol Use</strong></td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Yes</td>
<td>6.0 (3.0%)</td>
<td>25.0 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>198.0 (97%)</td>
<td>119.0 (82.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td>0.002*</td>
</tr>
<tr>
<td>Yes</td>
<td>15 (7.4%)</td>
<td>31 (18.3%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>189 (92.6%)</td>
<td>138 (81.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pregnancy Wgt. Gain</strong></td>
<td></td>
<td></td>
<td>0.68§</td>
</tr>
<tr>
<td>N</td>
<td>199</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.8 (5.5)</td>
<td>14.5 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Median (25-75%)</td>
<td>14.7 (11.1-17.8)</td>
<td>14.0 (11.0-18.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Chi Square analysis; § Student’s t-test; ¥ Mann Whitney Rank Sum test.
Birth weight, the primary outcome measured, did not differ between the Proctofoam-HC® and comparison group 3406.9g and 3487.7g respectively. The secondary outcomes such as prematurity, low birth weight, neonatal health, fetal distress, and gestational age at delivery were also not significantly different in either. The only outcome differing between the two groups was method of delivery with significantly more C-Sections and the need for assistance such as vacuum or forceps during delivery, in the comparison group (Table 10). Table 11 outlines the details of neonatal health complications in both groups, which did not differ significantly.
Table 10. *Pregnancy outcomes for patients exposed to Proctofoam*® *HC*® *versus comparison group*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment</th>
<th>Comparison</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method of Delivery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>173 (84.8%)</td>
<td>146 (72.6%)</td>
<td>0.003*</td>
</tr>
<tr>
<td>C-Section</td>
<td>31 (15.2%)</td>
<td>55 (27.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gest. Age at Delivery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>204</td>
<td>194</td>
<td>0.16¥</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>39.4 (1.4)</td>
<td>39.1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Median (25-75% quartile)</td>
<td>39.6 (38.4-40.6)</td>
<td>40.0 (38.0-40.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Prematurity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (4.1%)</td>
<td>10 (5.3%)</td>
<td>0.55*</td>
</tr>
<tr>
<td>No</td>
<td>193 (96.0%)</td>
<td>180 (94.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Birth Weight (grams)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>201</td>
<td>201</td>
<td>0.17§</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3406.9 (452.7)</td>
<td>3487.7 (491.4)</td>
<td></td>
</tr>
<tr>
<td>Median (25-75%)</td>
<td>3401.0 (3100.0-3730)</td>
<td>3409.0 (3180.9-3770.5)</td>
<td></td>
</tr>
<tr>
<td><strong>LBW (&lt;2500)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (3.0%)</td>
<td>3 (1.5%)</td>
<td>0.31*</td>
</tr>
<tr>
<td>No</td>
<td>194 (97.0%)</td>
<td>198 (98.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fetal Distress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (18.1%)</td>
<td>31 (17.9%)</td>
<td>0.97*</td>
</tr>
<tr>
<td>No</td>
<td>163 (81.9%)</td>
<td>142 (82.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Neonatal Health</strong></td>
<td>N= 199</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (14.1%)</td>
<td>24 (13.5%)</td>
<td>0.87*</td>
</tr>
<tr>
<td>No</td>
<td>171 (85.9%)</td>
<td>154 (86.5%)</td>
<td></td>
</tr>
</tbody>
</table>

*Chi Square analysis; § Student’s t-test; ¥ Mann Whitney Rank Sum test.
**Table 11. List of neonatal health concerns in the treatment and comparison groups**

<table>
<thead>
<tr>
<th>Neonatal Health</th>
<th>Treatment (%)</th>
<th>Comparison (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Heart murmur</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Premature Atrial</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>3</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Respiratory**

<table>
<thead>
<tr>
<th></th>
<th>Treatment (%)</th>
<th>Comparison (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Aspiration</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mild Asthma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tachypnea</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>2</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Infections**

<table>
<thead>
<tr>
<th></th>
<th>Treatment (%)</th>
<th>Comparison (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Strept B</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>High WBC count</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Skin**

<table>
<thead>
<tr>
<th></th>
<th>Treatment (%)</th>
<th>Comparison (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>3</td>
<td>0.35</td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th></th>
<th>Treatment (%)</th>
<th>Comparison (%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis</td>
<td>2</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Myopia</td>
<td>0</td>
<td>1</td>
<td>0.47</td>
</tr>
<tr>
<td>Colic</td>
<td>0</td>
<td>2</td>
<td>0.22</td>
</tr>
<tr>
<td>Milk Allergy</td>
<td>0</td>
<td>1</td>
<td>0.47</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Poor Feeding</td>
<td>1</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Poor weight gain</td>
<td>1</td>
<td>1</td>
<td>1.00</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>1</td>
<td>0.47</td>
</tr>
<tr>
<td>Kidney Stones</td>
<td>0</td>
<td>1</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*P-values determined by Fisher Exact Test*
4.3.2 Effectiveness of Proctofoam-HC®

The same group of women from the safety phase of the study happily participated in the effectiveness phase. Overall, 208 of the women in the treatment group completed the effectiveness part of the study as well. At the time of recruitment the severity of their symptoms were assessed using the CORECT scale and the assessment was repeated at least once after treatment with Proctofoam-HC®.

At baseline, almost all of the participants complained of hemorrhoid swelling (98%) and anal discomfort (96%). Pain was reported in 87%, itching in 72% while bleeding was present in 51% of these women. 98% of the women reported IW due to symptoms associated with hemorrhoids. Tables 6 and 7 from the CORECTS validation study, provide the median scores at the time of recruitment and again after treatment with Proctofoam-HC®.

For a subset of the women (N=68) in the study, the assessment was completed twice after treatment with Proctofoam-HC®. The median duration of treatment at the time of the first assessment was 22 days at which there was a significant reduction in all symptoms. The second assessment was completed after median treatment duration of 65 days in which there was a further reduction in severity of all symptoms. When compared to the first assessment at 22 days, the further reduction in symptoms was significant for pain, itching, swelling and discomfort but not for bleeding which did not change from zero.

It should be noted that at the second post treatment assessment 50% of women were within 26 days postpartum. Thus the further reduction in symptoms may have partially been due to the ending of pregnancy and not just the effectiveness of treatment. The
overall improvement reported however, did not differ significantly with longer treatment, although the impact on well-being due to symptoms was still further reduced.
CHAPTER 5.
DISCUSSION

5.1 NAUSEA AND VOMITING OF PREGNANCY (NVP)

The validation of PUQE-24, a tool that assesses one of the most common medical conditions specific to pregnancy, NVP, was my initial Master’s thesis objective. The original twelve hour PUQE scale –developed from the original Rhodes scale which assesses the severity of nausea and vomiting in chemotherapy patients– had been validated and used for a number of years; however it performed the assessment in the last twelve hours prior to patients' calling the Motherisk line. It became apparent that during the last 12 hours a woman may mostly have been sleeping, and hence it was not sufficient in capturing the daily severity of NVP. In order to capture the extent of NVP in a whole day, we modified the twelve hour scale to the new 24 hour PUQE, such that we would be able to account for the time spent sleeping.

In order to validate the modified PUQE scale, we used external parameters that reflect clinically the severity of the woman's symptoms. One of these parameters, multivitamin use, is indicative of the severity of NVP, since women tend to discontinue prenatal vitamin use when experiencing severe nausea or gastrointestinal adversities related to the iron content in the multivitamins (31). This discontinuation occurs despite women’s awareness of the importance of multivitamins in pregnancy and their initial attempts to take them regularly. As shown in our results, PUQE-24 scores were highly predictive of the inability to take multivitamins in cases of severe nausea, with women trying to avoid foods and supplements that may worsen their already severe NVP.

A second parameter examined by us was the rate of hospitalization or visits to emergency rooms attributable to NVP. This endpoint was also highly correlated with PUQE-24
scores. High PUQE-24 scores were not only associated with higher hospitalization rates, but were also able to distinguish between severe NVP cases--most likely due to HG--and mild and moderate cases. This increases the power of this new tool to not only predict hospitalization but to also identify the more vulnerable group of women at risk for experiencing HG, and thus, can provide women and their health-care providers an opportunity to intervene prior to worsening of symptoms.

Another parameter, well-being, is a subjective parameter developed by Motherisk to capture women’s overall mental, physical and emotional health, reflecting their quality of life at the time of questioning. NVP symptoms, especially retching, tend to cause great distress in pregnancy (135), and well-being scores are primarily reflective of the extent of distress when women call our NVP line. Our results show that PUQE 24 correlates strongly with this self rated measure and thus is an important tool in assessing the degree of distress experienced by pregnant women.

The amount of liquid intake is another important parameter, as women with severe NVP tend to be dehydrated and avoid liquids. Although the amount of liquid intake per kilogram of body weight did not correlate significantly with PUQE-scores, it did so with well-being scores. Since well-being scores is administered as part of the PUQE and was shown to strongly correlate with PUQE-24 scores, it is deducible that PUQE-24 is also predictive of the hydration sufficiency in these women.

With respect to the sleep parameter, it is intuitive that women who achieve sufficient quality sleep feel better during the day. In contrast poor sleep is associated with more fatigue and worsening of NVP experience. Despite of this, we did not find a strong correlation between PUQE score and either the quality nor the number of hours of sleep.
A possible explanation for this lack of correlation may be due to the acquisition of sleep data. In our counseling women are asked to state the number of hours they slept in the past 24 hours including naps, and the quality of sleep by simply stating whether it was broken or good. The top reasons reported by women for broken sleep were, frequent urination; younger children waking up, anxiety, and lastly, NVP. The NVP unrelated reasons for broken sleep thus, interfere with PUQE’s ability to predict sleep quality. On the other hand good sleep is considered to be uninterrupted sleep, which states little about the quality and restfulness of the sleep. Furthermore, women with NVP tend to feel the need to lie down when feeling nauseous and may have to take frequent naps. When asked about the number of hours they have slept in the past 24 hours, their reports may be inaccurate and the amount of sleep they get may be overestimated, for example: five one-hour naps during the day does not equate to five solid hours of night sleep. Finally, the mainstay of anti-emetic therapy for NVP in Canada is Diclectin®(14, 25, 135), containing the sedative doxylamine which naturally disrupts the correlation between the severity of NVP and sleep; in fact better control of NVP with more Diclectin® may be associated with more sleepiness (11).

A major strength of our study is that the majority of women who call our NVP line are highly motivated to improve their NVP symptoms, and thus we are confident in the overall accuracy of the information they provide our counselors with, especially since the information is collected in real time and recall bias is not a confounding factor.(136).
5.1.1 Overall Study Limitations

- Unspecific questioning for one of the parameters: Sleep. The sleep quality should be assessed using more detailed questioning and not just brokenness but the number of naps taken during the day and the number of solid hours slept at night.
  - Diclectin® is a confounding factor in good sleepers

- Use of Motherisk callers for the validation may reduce the generalizability of the scale to all women experiencing NVP –majority of Motherisk callers consist of well educated, upper socioeconomic class older women. Validation in the Spanish population should be expanded to other ethnic and socioeconomic classes.

- Well-being is a subjective measure of overall health and does not distinguish between psychological and physiological impact of NVP, and other confounding factors (i.e. Sickness, trauma, spousal discourse etc.)

- The liquid intake may not fully predict hydration status, especially if the source consists primarily, of caffeinated, sugary or dairy drinks. The unit of measure for most women was in cups to which the arbitrary value of 200ml was assigned per cup, thus the exact amount may have been over or under estimated in these women. A more detailed questioning may have resolved this problem.
5.2 ASSESSING HEMORRHOIDS IN PREGNANCY: VALIDATION OF THE CORECT SCALE

For the validation of this scale, we intuitively expected a significant correlation between the objective symptoms of CORECTS (bleeding and swelling) and the grade assigned by a clinician after direct examination. Indeed, significant correlation was found between the physician’s score and the pain and bleeding components of the CORECTS, but not with swelling. The degree of pain experienced by the patient avidly reflects the clinician’s score.

The lack of correlation between swelling, an objective symptom, and the physician’s score may be explained by the small sample size, and the fact that the symptom of swelling was not pertinent to every patient’s condition. For example, anusitis is accompanied by a burning sensation around the anus, pain, tenderness and bleeding, but no swelling. Furthermore, once the scores for swelling and bleeding were combined, a significant correlation between patients’ and physician’s scores was observed. Hence with a larger sample size that covers a wider range of anorectal symptoms, a strong correlation with swelling is expected to be observed.

As mentioned, CORECTS was used in the effectiveness study of Proctofoam-HC®. Prior to CORECTS, no validated tool to measure the effectiveness of any anti-hemorrhoidal treatment existed. Several efficacy studies on oral and local preparations for the treatment of symptomatic hemorrhoids used a 4 point scoring scale (137-139), where 0=none, 1=mild, 2=moderate and 3=severe and others used a Likert-type scale that included two or three options from: maximum improvement, no improvement and worsening of symptoms(140-142) and a few used a combination of the two(143, 144). However,
neither of these scales deemed adequate in capturing the full range of symptoms associated with hemorrhoids. CORECTS, an 11 point numeric scale, includes all major symptoms of hemorrhoids, as well as their impact on well-being, and thus thought to be better a more appropriate scale. Finally, global improvement scores can help quantify the impact of treatment on anorectal symptoms.

The CORECTS data from the effectiveness portion of the study, revealed a highly significant correlation between pain, swelling and discomfort scores and the impact women reported on their well-being (Table 5). In contrast, the itching and bleeding scores did not correlate with the IW scores, suggesting that these symptoms of hemorrhoids do not contribute as strongly to quality of life.

As shown by our results, CORECTS is sensitive in capturing changes in symptoms following treatment with an anti-hemorrhoidal medication. The further reduction in CORECTS scores, observed at the second post treatment assessment (longer treatment group) was significant for pain, itching and swelling, and an overall less impact on well-being; this demonstrate the sensitivity of the CORECTS scale to detect even small differences with the disease progress.

The subjectivity of symptoms such as pain, itching, and discomfort, pose a challenge to quantitative assessment of these symptoms, hence questioning the accuracy of CORECTS. However, despite of the individual difference in thresholds for subjective symptoms, changes in severity is still captured with CORECTS, which can be important clinically. Although no scale can replace a direct examination by a physician, the availability of a tool like this at the initial assessment, may facilitate diagnosis, especially when a direct examination is not possible due to women’s embarrassment.
Furthermore, CORECTS can be used by clinicians and researchers to assess the effectiveness of different treatments for common anorectal conditions. The majority of over the counter medications for the treatment of anorectal conditions have not been assessed for effectiveness, making the choice of the right medication, a cumbersome and expensive trial and error process for most patients. More studies are required to provide guidelines for effective pharmacotherapy, and the availability of a standard tool such as CORECTS, can be helpful for such studies.

The concordance of CORECTS with direct assessment by a proctologist, as well as its sensitivity in capturing small changes in symptom severity following treatment, make it a unique and efficient tool for assessing this also very common medical condition in pregnancy by clinicians.

5.2.1 Overall Study Limitations

- Sample size. Only a small fraction of our 29 patients had hemorrhoids, and despite of the overlap between hemorrhoidal symptoms and other anorectal conditions, the specificity of CORECTS for hemorrhoids symptoms, requires a larger sample with only hemorrhoids as their primary anal condition

- The questioning for some of the symptoms needs to be more specific. Primarily with bleeding, patients were unsure if they should rate based on frequency of bleeding or amount of blood loss per bleeding episode.

- The questionnaire should include a duration of treatment in the post treatment assessment
5.3 TREATING HEMORRHOIDS IN PREGNANCY

5.3.1 The Fetal Safety of Proctofoam-HC® in the Third Trimester of Pregnancy

Altogether, 408 women were recruited to this phase of the study, with 204 in each of the treatment and comparison groups. It was calculated that in order to detect a 200 gram difference in mean birth weight with a standard deviation of 621 grams (derived from tobacco studies) a sample size of 155 would be necessary – the power of the study with this sample size would be 80% with an alpha error of 5%. However with our sample size of 204, the power of the study was determined to be close to 91%, and it appears that our sample size is more than adequate.

Upon comparing the treatment and comparison group, no significant differences were apparent in any of the endpoints analyzed. All pregnancies lead to a live birth in both groups and the primary endpoint, birth weight, was very similar. The mean gestational age at delivery, fetal distress and neonatal health, were not different between the two groups either. There were similar percentages of low birth weight (<2500g) babies in both groups, and in most of them an objective etiology was identified (multiple birth, smoking).

The rate of malformations, 12 and 14 in the exposed and control group respectively did not differ significantly. With the exception of one cleft palate case in the comparison group, the remaining defects were of minor nature. At 27 weeks gestation, the fetus is considered to be completely developed (145), and since treatment with Proctofoam-HC® was limited to the third trimester of pregnancy, it is not expected to increase the rate of malformations.
In essence, rectal use of Proctofoam-HC® in pregnancy does not appear to produce any adverse changes in birth weight, or adverse neonatal outcomes.

It may be argued that the higher number of smokers and drinkers in the comparison group may contribute to the lack of difference in the above endpoints. It must be noted however, the unmatched smokers, were all light smokers (N=16) reporting on one smoke a day, with the exception of one that smoked 10 a day. The mean birth weight within this group alone was 3490g with only one low birth weight, below 2500g at 35 weeks. Hence the impact, if any would be negligible.

With respect to alcohol use, the women in the comparison group answered yes to alcohol exposure, even if minimal. Except for one woman who reported three drinks, the remainder reported on one alcohol use throughout the whole pregnancy. Most likely these exposures occurred at the very early stage of pregnancy prior to women finding out if they were pregnant, and was discontinued soon after realizing.

The higher number of C-Sections and delivery complications (use of forceps, vacuum, etc.) was also significantly higher in the comparison group. As mentioned the comparison group consisted of Motherisk callers who had participated as controls for various studies. By nature these women may be anticipating complicated pregnancies and are under more supervision which is why they contact Motherisk. Hence the higher rate of C-Sections and minor complications is not surprising.

Our primary endpoint, birth weight, in the treatment group was still consistent with the expected birth weight of full term babies in Canada (Means: 3372grams, Median 3400grams; Statistics Canada, 2007) (146). Hence our comparison group, even if not ideal, is adequate for this study.
Since hemorrhoids are progressive in nature during the course of pregnancy, many women experience significant impact on their quality of life with symptomatic hemorrhoids, especially in the later stages of their pregnancy. Generally, depending on the type of hemorrhoid (internal or external) symptoms can vary, many patients initially report to a physician when experiencing bleeding, itching and pain (58). Left untreated, severe hemorrhoids can lead to secondary complications--incarcerated hemorrhoids may thrombose, become ischemic and eventually gangrenous from vascular insufficiency--iron-deficiency as a result of chronic blood loss, and not to mention the severe pain and discomfort that often accompanies them, tend to severely compromise a woman’s daily functioning(38,147). There have been no published studies on the fetal safety of any topically used anti-hemorrhoidal preparations in pregnancy. While this study adds to the limited literature on this topic, there are issues that warrant further investigation. Firstly the percentage of women who applied Proctofoam-HC® internally, and moreover, the positioning of the applicator in the anal canal, is unknown. As discussed previously, there is substantial variability in the absorption of medication administered in the lower rectal region versus the upper rectal region; and this difference in absorption needs to be quantified.

There is also much need for pharmacokinetic studies to examine what percentage of hydrocortisone entering the systemic circulation following internal rectal application in different sections of the anal canal. Finally, longitudinal studies are warranted to investigate the long-term neurodevelopment and health outcomes of in utero hydrocortisone exposure.
5.3.2 Effectiveness of Proctofoam-HC® in Treating Hemorrhoids in Pregnancy

To detect a clinically significant decrease in the primary outcome, pain, only 23 patients were required. All the women from the safety phase of the study agreed to participate in this section of the study as well, as administering the CORECTS took only a few minutes, and most participants were eager to share their experience with Proctofoam-HC®. In the present study, local treatment with Proctofoam-HC® was found to be very effective in reducing all symptoms related to hemorrhoids.

A 2 point decrease in pain scores from the reported baseline, on an 11-point pain intensity numerical rating scale is considered to be clinically significant (148). One study found that patients only considered a 50% improvement in pain as a ‘treatment success’ (149). As our primary outcome for effectiveness of treatment, we did observe a reduction of 6.0 points in pain, from baseline, which is three times greater than what is considered significant. In fact dramatic decrease in all symptom severity was observed with half the women scoring zero on pain, itching, swelling and discomfort after treatment with Proctofoam-HC®; this significant reduction in symptom severity is also reflected in the significant increase in IW and Overall Improvement scores—1 and 8 respectively.

It may be argued that the great improvement postpartum, maybe due to the completion of pregnancy itself and not entirely due to the treatment. Hemorrhoids do tend to reduce on their own after delivery, due to the relief from intra-abdominal pressure and the venous congestion during pregnancy. The postpartum assessment however, was completed within only a few weeks after delivery (less than 4 weeks in 50% of women), which is not sufficient for symptoms to resolve fully; most hemorrhoids are still persistence 8 weeks postpartum (150). Furthermore, in our subgroup of 68 women whom
we assessed three times, the first post treatment assessment was completed after a mean of 22 days of treatment (prior to delivery); substantial improvement in all parameters of CORECTS in comparison to the prior to treatment assessment was still observed (P<0.001), strongly corroborating the effectiveness of the medication Proctofoam-HC® for hemorrhoids in pregnancy. However we do acknowledge that the significant difference demonstrated in Table 7, between post treatment two and one, may be confounded by the completion of pregnancy, and may not be entirely due to the effectiveness of longer treatment parse.

The major limitation of this study was the lack of a placebo group. The literature on interventional anti-hemorrhoidal trials with a placebo group was systemically reviewed. A total of 11 studies were available (58,137-144,151-153); only two included pregnant women (140, 144). The duration of the 9 studies ranged from at least 7 days to up to two months. It is well established that adult-life hemorrhoids are self-limiting and can heal without medication (154). In one study, mean healing time without any treatment was 5.6 and 6.5 days for anal bleeding and pain, respectively (139). Other studies have shown 7 to 24 days for remission of thrombosed hemorrhoids (38,40). With spontaneous remission known to occur prior to study completion, it is quite possible that these non-pregnant patients experienced a high placebo effect. Since hemorrhoids in pregnancy are chronic in nature, the chance of spontaneous improvement appears to be slim; suggesting that the effect size that was observed in our study was probably due to the true measure of effectiveness and not due to any significant placebo effect. Even if a placebo effect did exist it is unlikely that it is to the same extent as the placebo effect observed in non pregnant population. To address the placebo effect in the pregnant group with
hemorrhoids, only the two remaining trials focusing on pregnant women were included. Both studies randomized pregnant women to receive oral rutosides and observed them two times, once at 2 weeks and again at 4 weeks post treatment. The first study (144) only included patients with grade 1 and grade 2 hemorrhoids. Grade 1 and 2 hemorrhoids, as mentioned previously, are typically associated with very mild symptoms and hence often go undiagnosed unless they worsen and present with bleeding and prolapse. Most first degree hemorrhoids are easily treated by lifestyle changes and resolve faster than more severe hemorrhoids (38,40). Since significant swelling and bleeding was observed in the sample population in the effectiveness study, it is probable that a large percentage had some degree of prolapse, and thus at least a grade 3 and possibly grade 4, hemorrhoids. Hence, the first placebo study in pregnancy would not be reflective of our pregnant population. In the second study a 12% and 14% improvement at week 2 and 4 respectively, in the placebo, were observed. Most of the women included in the study had grade 2 or 3 hemorrhoids. The results of our effectiveness study were re-analyzed after taking into consideration a potential 12-14% placebo effect. Since this group did not use a symptom scoring scale, the average of the total improvement (13%) was subtracted from every symptom in the effectiveness study. The reduction in symptoms scores was still significant.

In essence, these results suggest that Proctofoam-HC® enabled significant global improvement, and was highly effective in treating hemorrhoidal symptoms in majority of the pregnant patients in this study sample.
5.3.3 **Overall Study Limitation**

- Details on how the product was applied would have provided some insight on where most of the absorption occurred. Hence we could conclusively say if the lack of difference in birth weight occurred despite of the higher absorption in the lower anal canal.
- Including postpartum women in the effectiveness study may act as a confounder
- Extent of the effectiveness was hindered by the lack of a placebo group specific to our study
- A direct examination by a proctologist before and after treatment may have strengthened the evidence for effectiveness of Proctofoam-HC®
CHAPTER 6.
CONCLUSION

6.1 ASSESSING NAUSEA AND VOMITING OF PREGNANCY (NVP)

PUQE-24 appears to be a reliable tool for the assessment of the severity of NVP symptoms. The simplicity of its use and its specificity to NVP symptoms make it a valuable tool for health-care providers and researchers. The modification of the original PUQE yields a more accurate reflection of the severity of NVP symptoms in one day, while capturing all aspects of daily life, without compromising the quality of data due to recall errors, since the captured period is still a short one.

The PUQE-24 scoring system has also been recently corroborated by other groups of researchers who have used it in clinical and research settings (155, 156).

6.2 ASSESSING SEVERITY OF HEMORRHOIDS IN PREGNANCY

The CORECTS is the first tool to encompass all major symptoms associated with hemorrhoids and to include a measure of quality of life. Since the five symptoms associated with hemorrhoids overlap with symptoms from other common anorectal conditions, the use of the scale can be justified in patients with other conditions such as fistulas, fissures, and pruritis ani. Its visual analogue nature, as well as its ability to track even small changes in symptoms, makes it a highly efficient and simple scale to use by clinicians and even patients. Although it does not replace a direct examination by a physician, the availability of a non invasive tool like this, may help target the more shy patients who are too embarrassed to address the problem.
Since pregnancy is considered a risk factor for a very common anorectal condition, and many pregnant patients suffer relentlessly, the existence of such a scale should allow for the adequate evaluation of the patient’s status and the implementation of effective treatments for this commonly ignored condition.

6.3 TREATING HEMORRHOIDS IN PREGNANCY

Hemorrhoids are a common concern in pregnancy, affecting over a third of women in their third trimester. Exposure to Proctofoam-HC® does not appear to cause any adverse fetal effects, and is highly effective in relieving all symptoms of hemorrhoidal disease. This makes Proctofoam-HC®, the first anti-hemorrhoidal medication to be approved for use in pregnancy, and provides a feasible, sure and safe way for many women who suffer relentlessly, to treat this embarrassing condition. This is the first study to examine fetal safety of any local anti-hemorrhoidal preparation.

6.4 FUTURE DIRECTIONS

PUQE-24 has already been used by researchers in different studies as the primary scale to assess severity of symptoms with NVP in different populations and countries, and when counseling and treatment is implemented. As NVP is universal and up to 90% of women suffer from it in their 1st trimester, this tool can be used to detect cultural, dietary, life style differences, as well as other conditions that can affect NVP.

CORECTS offers the first tool to address symptoms associated with hemorrhoids, and the Proctofoam-HC® was the first study where its use was implemented. It is hoped
that clinicians would recognize its importance and accepting it as the tool of choice in future studies addressing any anorectal conditions and their progress with dietary changes and treatment. Considering the embarrassing nature of the condition, it is highly suspected that many patients are under diagnosed, and perhaps CORECTS will be used as a non invasive screening tool to bring attention to this area.

A further addition to the safety study of Proctofoam-HC® should be made to follow up on the neonates. Growth milestones including neurodevelopment of all children should be monitored, short-term as well as long-term. Pharmacokinetics of drug absorption from the upper and lower rectal region would be necessary to comprehend complete exposure of any medication used rectally.

### 6.5 CONFLICT OF INTEREST

The Proctofoam-HC® studies were supported by a grant from Duchesnay Inc., producer of Proctofoam-HC®. To eliminate any potential bias, Duchesnay Inc. was at an arm’s length from the research stage of this study while being conducted at the Motherisk Program. The study protocol was devised at the Motherisk Program. All recruitment, collection of data and data analysis were performed by myself and Sabina Vohra, the study coordinator at the Motherisk Program. All data collected are the property of the Hospital for Sick Children. The Duchesnay Inc., also supports the Motherisk NVP line where data for the PUQE-24 validation study were collected. However the company had no part in the planning, conduct or analysis of data.
REFERENCES


59. Duchesnay Inc. Product information: Proctofoam-HC® rectal anti-inflammatory foam, hydrocortisone acetate and pramoxine HCL.

60. Ross Labs CP. Product information: Tronolane®, pramoxine.


APPENDICES

Appendix A. Permission to include Figure 4. Inflammatory byproducts of the arachidonic cascade

Date: April 20/2011

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Figure 35-1 Major products of the cyclooxygenase (COX) and lipoxygenase branches of the arachidonic acid cascade. PGD, prostaglandin D; 5HpETE, hydroxyperoxyeicosatrienoic acid.


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Sincerely

Neda Ebrahimi
neda.ebrahimi@utoronto.ca
MSc. Candidate
University of Toronto, Pharmaceutical Sciences
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this e-mail I forward to Mica Haley.

Regards,

George Siegel, MD
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Fax: 312-9438430
Editor in Chief, 7th Edition, Basic Neurochemistry: Molecular, Cellular and Medical
Aspects.
Appendix B: Permission to include Figure 5. *Hydrocortisone’s Anti-inflammatory mechanism*

Date: April 20/2011

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**neda.ebrahimi@utoronto.ca**
MSc. Candidate
University of Toronto
Pharmaceutical Sciences
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Appendix C: Literature review: Motherisk commonly used anti-hemorrhoidal medication

The safety of commonly used anti-hemorrhoidal preparations in pregnancy
Vohra S1,2, Koren G1,2,3
1Motherisk Program, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Canada, 2Department of Pharmaceutical Sciences, University of Toronto, Toronto, Canada, 3Ivery Chair in Molecular Toxicology, University of Western Ontario, London, Canada
Corresponding Author: sabina.vohra@utoronto.ca
Funding Source: Duchesnay Inc.

Background: Up to 24% of women suffer from hemorrhoids during the third trimester of pregnancy. Pregnant women are more prone to hemorrhoids because of increased circulating blood volume, constipation due to high progesterone levels and increased pressure by the growing uterus; all resulting in venous engorgement. Typically, management during pregnancy is conservative in nature. The objective of this study was to evaluate the safety of commonly used local treatments by Motherisk callers.

Methods: The Motherisk database was searched (2006-2007) and a list of commonly used local antihemorrhoidal preparations was generated. Medline (1950-2007) and PubMed (1950-2007) were searched for clinical studies evaluating the safety of any of the above treatments. Title and abstracts were reviewed. Only articles written in the English language were included.

Results: The eight most frequently used local treatments by Motherisk callers include Anusol®, Anuzinc®, Anugesic-HC®, Preparation H®, Proctofoam-HC®, Proctosedyl®, Witch hazel (Hamamelis Virginiana) and Tea tree oil (Oleum Melaleuca). Pubmed and Medline search did not yield even a single eligible study on the safety or efficacy of the above preparations during pregnancy.

Conclusions: Hemorrhoids are a common concern during pregnancy and can potentially affect quality of life. No evaluation of the maternal and fetal safety of currently used local antihemorrhoidal treatments is available. It is critical to study the safety and efficacy of antihemorrhoidal treatments used by over 100,000 pregnant Canadian women every year.

Keywords: hemorrhoids, pregnancy
## Appendix D: List of ingredients in the Motherisk commonly used antihemorrhoidal medications

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anusol®</td>
<td>Zinc Sulfate (0.5%) / Zinc Sulfate (0.5%) + Pramoxine Hydrochloride (1%)</td>
</tr>
<tr>
<td>Anuzinc®</td>
<td>Zinc Sulfate (0.5%) / Zinc Sulfate (0.5%) + Hydrocortisone Acetate (0.5%) / Hydrocortisone Acetate (0.5%) + Pramoxine Hydrochloride (1%) + Zinc Sulfate (0.5%)</td>
</tr>
<tr>
<td>Anugesic-HC®</td>
<td>Hydrocortisone Acetate (0.5%) + Pramoxine Hydrochloride (1%) + Zinc Sulfate (0.5%)</td>
</tr>
<tr>
<td>Preparation H®</td>
<td>Hamamelis Virginiana (50%) + Phenylephrine Hydrochloride (0.25%)</td>
</tr>
<tr>
<td>Proctofoam-HC®</td>
<td>Hydrocortisone Acetate (1%) + Pramoxine Hydrochloride (1%)</td>
</tr>
<tr>
<td>Proctosedyl®</td>
<td>Dibucaine Hydrochloride (0.5%) + Esculin (1%) + Framycetin Sulfate (1%) + Hydrocortisone Acetate (0.5%)</td>
</tr>
<tr>
<td>Witch-Hazel</td>
<td>Hamamelis Virginiana</td>
</tr>
<tr>
<td>Tea tree oil</td>
<td>Oleum Melaleuca</td>
</tr>
</tbody>
</table>
Antenatal Questionnaire

our date of birth: ____________
What is the current gestational age? _____ (weeks) ____ (days), or _________ (months).
When was the first day of your last menstrual period? ____________
What is your Due date? ____________

Race/ethnicity

Living arrangements

Education

Occupation

What is your job? ____________

Pregnancy History:

How many times (including this one) have you been pregnant? ________
How many children do you have? ________
What was the mode of delivery in the past pregnancies?
- Cesarean section (how many)? ________
- Normal vaginal delivery? How many? ________
- Did you ever have a miscarriage, and how many times? ________
- Did you ever have an abortion, and how many times? ________
- How many children live with you at home? ________

103
Did you ever suffer any of the following medical conditions:

<table>
<thead>
<tr>
<th>☐ Heart ☐ Liver ☐ Kidney</th>
<th>☐ Infectious Diseases (specify)</th>
<th>☐ Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Hypothyroid ☐ Hyperthyroid</td>
<td>☐ Hypertension ☐ Hypotension</td>
<td>☐ Anemia</td>
</tr>
<tr>
<td>☐ Crohn's ☐ Ulcerative colitis</td>
<td>☐ Peptic/duodenal ulcer ☐ Reflux</td>
<td>☐ Previous surgery/hospitalizations</td>
</tr>
</tbody>
</table>
| ☐ Irritable colon ☐ Irritable bowel | ☐ Celiac Disease ☐ Other | ☐ Depression ☐ Bipolar ☐ Anxiety ☐ Other | ☐ Other

☐ Does anyone in your family have medical problems?

Are you currently taking any medications? (Please specify) _____________________________

Do you have any allergies to medications/food? _____________________________

Do you have regular bowel movement habits? _____________________________

How often do you have bowel movements? ________/day_____/ week

Any recent change in bowel habits? _____________________________

Is there any blood? _____________________________

Any difficulty passing stool? _____________________________

Any pain? _____________________________

Any discomfort? _____________________________

Anal conditions:

Were you ever in the past diagnosed with any anal/rectal condition? (Hemorrhoids/Piles, anal fissure, other...) _____________________________

Have you ever (in the past) been treated with a rectal cream/ointment? (Please specify name) _____________________________

Have you ever (in the past - prior to this pregnancy) felt anal itching/pain? _____________________________

Do you currently experience any anal symptoms like pain? _____________________________

If yes - for how long? _____________________________

Did you receive any treatment? (Please specify) _____________________________
Appendix F: Postnatal questionnaire used in the safety study

**POSTNATAL QUESTIONNAIRE:**
The Safety of Proctofoam-HC® in the Third Trimester of Pregnancy

<table>
<thead>
<tr>
<th>FOLLOW-UP</th>
<th>Date:</th>
</tr>
</thead>
</table>

**PREGNANCY OUTCOME:**

<table>
<thead>
<tr>
<th>Due Date:</th>
<th>Tel: (H)</th>
<th>(W)</th>
<th>Live Birth [ ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td></td>
<td></td>
<td>Miscarriage (&lt;20wks) [ ]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fetal Death (&gt;=20wks) [ ]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Elective Abortion [ ]</td>
</tr>
</tbody>
</table>

*If miscarriage, fetal death or elective abortion:*
- How many weeks? ___________
- Were defects detected? [ ] No [ ] Yes (describe) ____________________________
- How? By: [ ] ultrasound [ ] amniocentesis
- Done at: ____________________ wks

*If live birth:*
- Child's first name: _______________ Child's last name: ______________________
- Child's DOB: _______________ Child's Doctor: ______________________
- Address: ______________________

**DISEASES COMPLICATING PREGNANCY AND EXPOSURES**

<table>
<thead>
<tr>
<th>Anemia/fld Alter'n</th>
<th>Y / N</th>
<th>Infections Diseases</th>
<th>Y / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Y / N</td>
<td>Gastro-Intestinal</td>
<td>Y / N</td>
</tr>
<tr>
<td>Central Nerv Syst.</td>
<td>Y / N</td>
<td>Genito-Intestinal</td>
<td>Y / N</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Y / N</td>
<td>Hematology</td>
<td>Y / N</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y / N</td>
<td>Musculo-Skeletal</td>
<td>Y / N</td>
</tr>
<tr>
<td>Ear,Eye,Nose,Throat</td>
<td>Y / N</td>
<td>UGK Growth Problems</td>
<td>Y / N</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Y / N</td>
<td>Respirator</td>
<td>Y / N</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Y / N</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please record other medications, prescription or over-the-counter:

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>INDICATION</th>
<th>START</th>
<th>STOP</th>
<th>DOSE/FREQ</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
</table>


USE
Please record use of following:

<table>
<thead>
<tr>
<th></th>
<th>START</th>
<th>STOP</th>
<th>DOSE/REQ</th>
<th>DECREASE</th>
<th>VITAMIN USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VITAMIN USE
Please record vitamin use

Taste during pregnancy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Use</th>
<th>Reason</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amniocentesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose tolerance test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorionic villus sampling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Delivery information

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pregnancy weight:</td>
<td>Hospital City:</td>
</tr>
<tr>
<td>Weight at delivery:</td>
<td></td>
</tr>
<tr>
<td>Total length of labour:</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth:</td>
<td></td>
</tr>
<tr>
<td>Premature rupture of membranes?</td>
<td>Birth weight:</td>
</tr>
<tr>
<td>Method:</td>
<td>Birth time:</td>
</tr>
<tr>
<td>Assistance:</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage?</td>
<td>Time:</td>
</tr>
<tr>
<td>Transfusion?</td>
<td></td>
</tr>
<tr>
<td>Pain relief?</td>
<td></td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td></td>
</tr>
<tr>
<td>Analgesic</td>
<td></td>
</tr>
</tbody>
</table>

For our documentation which will help other women exposed to the same drug that you were exposed to, would you share with us whether your child was born with any birth defects?
DEFECTS: No [ ] Yes [ ]
If yes, what: ________________________________
Refined to answer: [ ]
### NEONATAL HEALTH

| Disease                  | Details | Medication | Hospitalization*
|--------------------------|---------|------------|-------------------
| Cardiovascular           | Y / N   |            |                   
| CNS                      | Y / N   |            |                   
| Dermatology              | Y / N   |            |                   
| Diabetes                 | Y / N   |            |                   
| Ears, Eyes, Nose, Throat | Y / N   |            |                   
| Endocrine                | Y / N   |            |                   
| Infectious Diseases      | Y / N   |            |                   
| Gastro-Intestinal        | Y / N   |            |                   
| Genito-Intestinal        | Y / N   |            |                   
| Hematology               | Y / N   |            |                   
| Musculo-Skeletal         | Y / N   |            |                   
| IUGR/Growth Problems     | Y / N   |            |                   
| Respiratory              | Y / N   |            |                   

### Proctofoam Details:

- When did you start Proctofoam: __________________________
- When did you stop Proctofoam: __________________________
- How long did you use Proctofoam: ________________________
- How frequently (in a day): _____________________________
- How many samples of Proctofoam did you use in total: ________________________
- Regular bowel movements? ___________________________
- How often? _______/day _______/week. Any recent changes? ________________________
- Any blood? ________________________ Any difficulty passing stool? ________________________
- Anal itching, pain? ________________________
- Did Proctofoam improve your condition even if? ________________________
- Did you use anything else to treat hemorrhoids during this pregnancy? ________________________
- If yes: What? ________________________, Duration and frequency: ________________________

### CONSENT

We would like to send a letter to your child’s doctor to confirm medical details of this follow-up. May we have your verbal permission to send this?  
☐ No  ☐ Yes

*Please enter Doctor’s contact number on the front page of this form.
Appendix G: Oral consent form to participate in the safety study

Introduction

“Hi, I am Neda Ebrahimi, and am calling on behalf of the Motherisk Program at the Hospital for Sick Children in Toronto, Ontario.”

Purpose of the Study

“We are currently conducting a research study to evaluate the safety and effectiveness of using Proctofoam-HC® in treating hemorrhoids during the third trimester of pregnancy. Upto 35% of women suffer from hemorroids during pregnancy. Growing uterus as well as high levels of a female hormone called Progesterone result in causing or aggravating hemorrhoids or other anorectal symptoms. Surprisingly, there has been no study done to assess the safety and efficacy of any anti-hemorrhoidal preparations in pregnancy. We, at Motherisk, would like to change that. The study is supervised by Dr. Gideon Koren, who is the director of the Motherisk Program here at the Hospital for Sick Children.”

Study Procedures

“If you agree to participate, you will be telephoned twice during the course of the study in order to complete two questionnaires. The first questionnaire would be completed before delivery and will include questions on your medical and obstetric history as well as the time, indication, dose and duration of use of Proctofoam-HC®. The second would be completed after delivery and will ask questions on any pregnancy complications, birth weight, gestational age and health of your baby. We will also complete a hemorrhoid scale to score how your symptoms are doing at each telephone conversation. With your permission, we will contact your obstetrician and pediatrician to confirm information provided by the questionnaire.”

Risks

“Oral repeated doses of hydrocortisone have shown to increase the risk for oral cleft slightly over the general baseline risk. Since the palate is completely formed by week 12 of gestation, corticosteroid therapy appears to be safe to be used thereafter without a risk for major malformations. However, when applied locally, such as on the skin or in the rectum, the systemic effects of topical corticosteroids are generally limited. This is because only about 3%-7% of the medication is absorbed in to the body following 8 hours of contact with normal skin.”
Data on safety of topical corticosteroids is sparse. One study found that treatment with topical corticosteroids during pregnancy did not increase risk of congenital abnormalities in humans.”

**Cost**

“Proctofoam-HC® samples will be provided to you through the course of your pregnancy by your physician or by contacting us. However, if you have already bought Proctofoam-HC®, we will not compensate or reimburse you for the cost. The study will also not cover the cost of prescriptions and any other non-study drugs that you are already taking.”

**Confidentiality**

“All information concerning your participation in this study, including your medical records, will be kept completely confidential.”

**Participation in the Study**

“Participation in this study is entirely voluntary. You do not have to take part in this study. If you do not take part in this study or if you participate in the study and then decide to withdraw, it will not affect the quality of health care you receive at Motherisk or at the Hospital for Sick Children.”

“Do you have any questions for me at this time?”

“Would you like to participate in the study? You may think about your decision and let us know within a week.”

**Consent:**

This confirms that ________________________________ was recruited to the study on ________________________________ and has provided oral consent to participate in the study conducted at the Motherisk Program, Hospital for Sick Children.

The study procedure, purpose, risks and benefits were explained to the above in full detail.

_____________________

Neda Ebrahimi (Study co-ordinator)

_____________________

Dr. Gideon Koren, MD (Study Principal Investigator)
Appendix H: Information letter mailed to the participant

Dear Participant,

Up to 25% of women suffer from hemorrhoids during pregnancy. Growing uterus as well as high levels of a female hormone called Progesterone result in causing or aggravating hemorrhoids or other anorectal symptoms. Surprisingly, there has been no study done to assess the safety and efficacy of any anti-hemorrhoidal preparations in pregnancy. We, at Motherisk, would like to change that.

The Motherisk Program at the Hospital for Sick Children in Toronto is conducting a study to assess the safety of Proctofoam-HC®, an anti-hemorrhoidal medication, in the third trimester of pregnancy. Participation will consist of initial telephone interview and follow-ups during the pregnancy and after the baby is born. All telephone interviews will take no longer than 10 minutes. Constant contact with your family physician and OB/GYN will also be maintained.

Proctofoam-HC® has been on the market for 25 years and since it is local acting, extremely negligible amounts are absorbed into the body. However, we would like to document this scientifically, so as to encourage other pregnant women to consider treatment during pregnancy to ensure a comfortable pregnancy. Furthermore, we would also like to assess how effective Proctofoam-HC® is in treating pregnancy related hemorrhoids. As well, the good thing about Proctofoam-HC® is that it’s a dry foam, so it doesn’t leak or stain. Application is more convenient and sanitary, since it has a shorter applicator.

This study is supervised by Dr. Gideon Koren, Director of Motherisk. If you have any questions or concerns, or would like to participate in the study, please contact the Study Coordinator, Neda Ebrahimi, at (416)813-7283 (mailbox 5) or e-mail at: neda.ebrahimi@utoronto.ca

Thank you for your time. We believe that together with your help, we can help pregnant women!

Sincerely,

Neda Ebrahimi
Motherisk Program
Division of Clinical Pharmacology and Toxicology
Hospital for Sick Children
(416) 813-7283; mailbox 5 neda.ebrahimi@utoronto.ca
Appendix I: Letter sent to the child’s primary care physician

Dear Dr. [name of physician],

Re: [Name of child]

On [date], [Mother’s name], your patient’s mother, was counselled by the Motherisk Program at the Hospital for Sick Children. During a telephone interview to ascertain pregnancy outcome, we were given verbal consent to contact you to corroborate the medical details of [name of child] health.

If available, would you send us a copy of the hospital’s labour and delivery forms and a copy of the hospital’s neonatal assessment forms? In addition, would you please complete the attached form and return it to us at the Motherisk Program? For your convenience you may fax us at 416-813-7562.

Thank you for your anticipated co-operation.

Sincerely,

Neda Ebrahimi

(416)813-7283 [Mailbox 5]

ned.ebrahimi@utoronto.ca

Motherisk Program
Division of Clinical Pharmacology and Toxicology
Hospital for sick Children

[Name of physician]
[Address of physician]
[Address of physician]
[Address of physician]

sent by fax to:
Follow Up Report
MOTHERISK PROGRAM

Child’s Name:

Regarding the development of this child:

A. Major anomalies [ ] no [ ] yes
   Description: ______________________________________
   ______________________________________
   ______________________________________
   ______________________________________

B. Minor anomalies [ ] no [ ] yes
   Description: ______________________________________
   ______________________________________
   ______________________________________
   ______________________________________

C. This child was last examined on ________________ (dd.mm.yy). At that visit:
   weight ________________
   height / length ________________
   head circumference ________________

D. Hospital labour & delivery forms are included [ ] yes [ ] no
   Hospital neonatal assessment forms are included [ ] yes [ ] no

Signature of physician: __________________________

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Appendix J: Ethics approval from the Hospital for Sick Children

February 06, 2006

Dr. Gideon Koren
Clinical Pharmacology & Toxicology
The Hospital for Sick Children

Dear Dr. Koren:

Your study “The Safety of Proclofoam-HC in the Third Trimester of Pregnancy”

REB File No.: 10000006452

On behalf of the REB, I am writing to confirm that the above noted study was re-approved by the
REB for one year ending in February 2009. The REB approved continuing review at level II. As
necessary, the Clinical Research Office will be contacting you to arrange follow-up.

Please note that, in accordance with the Personal Health Information Protection Act of Ontario, you
are responsible for adhering to all conditions and restrictions imposed by the REB governing the use,
security, disclosure, return and disposal of the research subjects’ personal health information. You
are also responsible for reporting immediately any privacy breaches to the REB Chair and to Janice
Campbell, the Sick Kids privacy officer.

Yours truly,

Richard Sugarman
Chair, Research Ethics Board

Co-Investigator(s): Alon Shim

555 University Ave
Toronto, Ontario
Canada M5G 1X8

www.sickkids.ca
Appendix K: Ethics approval from North York General Hospital

North York General Hospital
Including the IODE Children's Centre
Embracing Health

June 7, 2007

Dr. Nicholas Pairaudeau
402 - 1100 Sheppard Ave. E.
Toronto ON M2K 2W1

Dear Dr. Pairaudeau

Re: NYGH REB #: 06 0050
The Incidence of Ano Rectal Problems in Pregnancy A Survey: The Efficacy and Safety of Proctofoam-HC for Hemorrhoids in Pregnancy

The above-named protocol and the consent form were reviewed at a meeting of the North York General Hospital Research Ethics Board. At the time of the meeting, members of the Research Ethics Board requested additional information. The information requested has been received and reviewed. This submission was reviewed at a meeting of the Board where a quorum was maintained. The proposal is approved for the next 12 months. If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must also be notified of the completion or termination of this study and a final report provided.

If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives annual re-approval. The REB must also be notified of the completion or termination of this study and a final report provided.

If, during the course of the research, there are any serious adverse events, changes in the approved protocol or consent form, or any new information that must be considered with respect to the study, these should be brought to the immediate attention of the Board. As the Principal Investigator, you are responsible for the ethical conduct of this study.
The REB of NYGH functions under the guidance of the Tri-Council Policy Statement and the ICH/GCP Guidelines.

Sincerely,

David Kaplan, MSc (Health Policy & Bioethics), MD, CCFP  
Interim Chief, Family & Community Medicine  
Chair, Research Ethics Board  
North York General Hospital  
Assistant Professor, Family and Community Medicine, University of Toronto

June 7, 2007  
Date of Approval  

June 7, 2008  
Expiry Date  

DK:da
MEMORANDUM

To: Dr. H. Akoury
    Women's College Hospital
    60 Grosvenor Street
    Toronto, ON
    M5S 1B6

From: Philip Hébert MD

Date: January 10, 2008

Subject: The Safety of Proctofoam-HC in the Third Trimester of Pregnancy

Project Identification Number: 300-2007
Approval Date: January 10, 2008

The Research Ethics Board of Sunnybrook Health Sciences Centre has conducted a Full Board review of the research protocol referenced above on the above captioned date and approved the involvement of human subjects as specified in the protocol.

The approval of this study includes the following documents:

- Protocol dated December 16, 2005
- Product Monograph dated February 11, 1976
- Prescribing Information dated November 8, 2005
- Electronic CPS Monograph 2007
- Information sheet/Consent form dated November 20, 2007
- Letter to Patients Physician
- Antenatal and Postnatal Questionnaires
- Hemorrhoid Survey Scale

The quorum for approval did not involve any member associated with this project.

The Research Ethics Board of Sunnybrook Health Sciences Centre Operates in Compliance with the Tri-Council Policy Statement, the ICH/GCP Guidelines and Division 5 of the Food and Drug Regulations.

Fully affiliated with the University of Toronto
Should your study continue for more than one year you must request a renewal on or before one year from the approval date. Please advise the Board of the progress of your research annually and/or any adverse reactions or deviations which may occur in the future.

The above Project Identification Number has been assigned to your project. Please use this number on all future correspondence.

Philip C. Lebert, MD PhD FCFPC
Chair, Research Ethics Board

[Signature]