Safety and Effectiveness of Proctofoam-HC® in the Third Trimester of Pregnancy

By:

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A thesis submitted in conformity with the requirements for the degree of Master of Science (MSc)

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Abstract

Purpose: No currently used topical anti-hemorrhoidal agent has been assessed for safety or effectiveness in pregnancy. This study evaluated the fetal safety and effectiveness of Proctofoam-HC® used during the last trimester of pregnancy.

Methods: In this prospective, open-labelled, controlled observational study, pregnant women prescribed Proctofoam-HC® were asked to complete two telephone interviews. A comparison group not exposed to Proctofoam-HC® or either ingredient was recruited.

Results: 180 women completed the study, with 186 live births. Mean birth weight was 3483±408 grams in the treatment group and 3505±389 grams in the comparison group ($p=0.70$). No differences were observed in mean gestational age ($p=0.57$), labour complications ($p=0.41$), fetal distress ($p=0.34$) or adverse neonatal health ($p=0.13$). All hemorrhoidal symptoms decreased significantly ($p<0.001$).

Conclusions: No increased risk for adverse fetal events was observed. Significant improvement of symptoms was noted following treatment. Proctofoam-HC® appears to provide safe, effective treatment of hemorrhoids in pregnancy.

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CHAPTER 1: INTRODUCTION

1.1 Research Question

- What is the incidence of hemorrhoids in pregnancy?
- Is a commonly used anti-hemorrhoidal preparation, Proctofoam-HC®, safe for the mother and the fetus to be used in pregnancy?
- Is Proctofoam-HC® effective in treating hemorrhoids in pregnancy?

1.2 Statement of the Problem

Hemorrhoids are a common concern in pregnancy, affecting up to 38% of women in the third trimester of pregnancy. Since they are of low health risk, and because hemorrhoids generally resolve spontaneously after delivery, they are often overlooked. Critically, the fetal safety of any commonly used antihemorrhoidal preparations available has not been documented scientifically.

The primary objective was as follows:

1. To evaluate the fetal safety of the topical application of Proctofoam-HC® in women with hemorrhoids during the last trimester of pregnancy.

The secondary objectives were as follows:

2. To evaluate the effectiveness of treatment with Proctofoam-HC® in relieving hemorrhoidal symptoms in pregnancy.

3. To estimate the incidence of hemorrhoids in the third trimester of pregnancy

1.3 Study Hypotheses

The hypotheses for the objectives outlined above were as follows:

1. The safety of Proctofoam-HC® in the third trimester of pregnancy:

It was hypothesized that the local (rectal) use of Proctofoam-HC® is safe, for both the mother as well as the fetus, without increasing the risk for malformations or adverse fetal events.

2. The effectiveness of Proctofoam-HC® in relieving symptoms of hemorrhoids

It was hypothesized that the local use of Proctofoam-HC® alleviates symptoms of hemorrhoids in pregnancy.

3. Incidence and risk for developing hemorrhoids in pregnancy:

It was hypothesized that a large number of women in the third trimester suffer from hemorrhoidal disease. It was also hypothesized that the risk for developing hemorrhoids in pregnancy increases with gravida and previous record of hemorrhoids.

1.4 Study Rationale

Hemorrhoids are a common concern during pregnancy and can adversely affect quality of life. The incidence of hemorrhoids in pregnancy in Canada has not been determined. A few published studies reported the incidence in their respective patient population; however, none of the studies have included Canadian women. An evaluation of the incidence of symptomatic hemorrhoids in Canadian women is necessary to establish and deliver appropriate health care.

No evaluation of the maternal and fetal safety or the efficacy of currently used local antihemorrhoidal treatments is available. Since haemorrhoids are a common condition in pregnancy and are usually treated by antihemorrhoidal preparations such as Proctofoam-HC®, demonstrating its safety and efficacy in the third trimester of pregnancy will serve many pregnant women by alleviating symptoms such as pain and discomfort, and thereby improving their quality of life.

CHAPTER 2: BACKGROUND

2.1 Hemorrhoids

Hemorrhoids are swollen or enlarged veins at or near the anus and are a common ailment in the general population. It is estimated that the prevalence of hemorrhoids in the United States ranges from 4.4% to upwards of 50% of the adult population (1,2). To understand hemorrhoidal disease, it is pertinent that one understands the anatomy and physiology behind the condition.

The lumen of the anal canal is surrounded by three connective tissue cushions that are fed with blood by arteries and drained by a series of veins, including the superior, middle and inferior hemorrhoidal arteries and veins (Figure 1). The inferior mesenteric artery continues to the rectum while the superior hemorrhoidal artery and middle and inferior rectal arteries stem from the internal iliac artery. The superior and middle rectal veins drain into the portal system and the inferior rectal vein drains into the systemic system, hence enabling free communication between the portal and general venous systems (3,4). The three hemorrhoidal veins form a hemorrhoidal plexus in the submucosal layer of the lower rectum. These cushions can be seen as early as the eighth week of gestation in a human embryo (5). The primary purpose of the hemorrhoidal cushions is to provide fecal continence, along with the support from connective tissue framework derived from the internal anal sphincter and longitudinal muscles (6). At rest,

they are filled with blood, thereby absorbing any variations (such as that produced during coughing, sneezing) in abdominal pressure preventing involuntary loss of faeces. During a bowel moment, the hemorrhoidal veins are compressed and drained, allowing the passage of stool (7). Since this hemorrhoidal cushion plexus is a normal anatomical structure, all adults have asymptomatic hemorrhoids. However, when these cushions enlarge and inflame beyond what is necessary to close the anal canal, they become symptomatic and constitute hemorrhoidal disease (3,4).

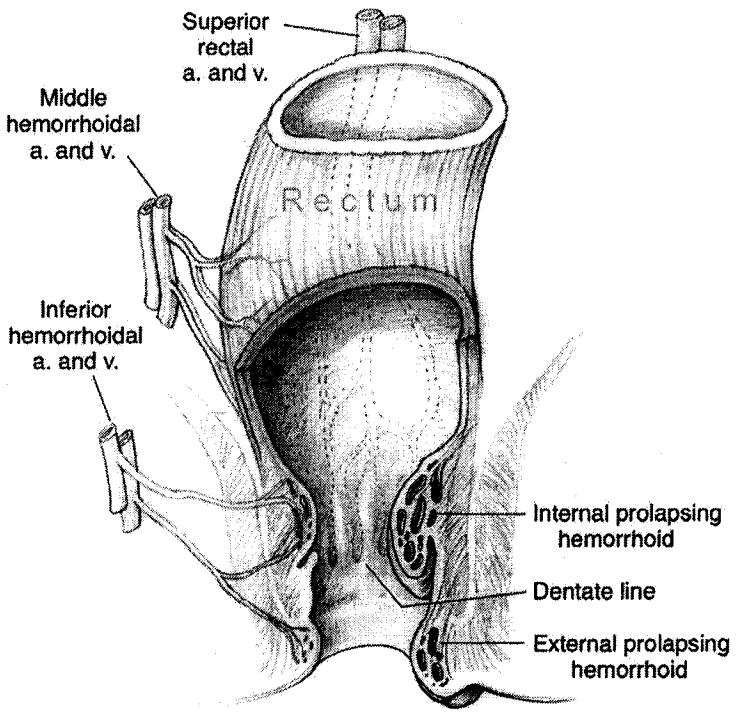

Figure 1: Schematic diagram showing blood supply to the rectum and positioning of hemorrhoids. Source: Gearhart, 2004 (6). Copyright (2004), with permission from Elsevier (Appendix A).

Hemorrhoids are classified based on where they originate in the anal canal (Figure 1). It is approximated that the anal canal is around 3 centimetres long. The top centimetre of the canal consists of moist simple columnar epithelium. The bottom two-thirds of the canal comprises dry stratified squamous epithelium (3,4). The transition between the

upper and the lower anal canal is called the pectinate line. The superior and middle hemorrhoidal arteries terminate above the pectinate line and when these veins dilate abnormally, they are called internal hemorrhoids. They can be found in three primary areas: the right posterior, right anterior and left lateral (3,4). The end branches of the superior hemorrhoidal cushion correspond to the above three haemorrhoid locations. When the inferior hemorrhoidal plexus below the pectinate line dilate abnormally, they are called external hemorrhoids (3,4). Internal and external hemorrhoids can occur simultaneously.

Internal hemorrhoids

Internal hemorrhoids are generally asymptomatic. However, when these hemorrhoids enlarge significantly, they can be irritated and traumatized easily. In such conditions, they can cause pruritus ani, discomfort, soiling, prolapse and bleeding after defecation (3). Because the anal mucosa of internal hemorrhoids lacks somatic sensory neurons, they are not associated with pain. In order to facilitate appropriate treatment, Banov et al (8) created a grading system to classify internal hemorrhoids based on the degree of prolapse. Grade I hemorrhoids do not prolapse, and may be associated with bleeding. Grade II hemorrhoids protrude during bowel movements but reduce spontaneously thereafter. Grade III hemorrhoids prolapse during defecation but need to be manually reduced. Grade IV hemorrhoids are prolapsed and cannot be reduced. Since they contain internal and external components, they can result in thrombosis or strangulation.

External Hemorrhoids

The perianal 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 (3,4).

Untreated Hemorrhoids

When hemorrhoids are left untreated, they can cause secondary diseases with severe consequences. The distended vein can rupture, resulting in a blood clot or thrombosis. This can then result in infarction. Further, a prolapsed hemorrhoid can be strangulated outside the anal canal if the anal sphincter muscle spasms. Due to the lack of blood supply, it can progress to gangrene resulting in a life-threatening infection. Chronic bleeding can cause iron-deficiency anemia and rarely, the requirement for transfusions (3,4).

Pathophysiology

While the real cause for hemorrhoids is yet unknown, there are four predominant theories:

1) Hemorrhoids have been attributed to the abnormal dilatation of the veins of the hemorrhoidal plexus (9,10)

2) Abnormal distension of the arteriovenous anastomoses has also been linked to the development of hemorrhoids (11,12).

3) Downward displacement of the anal cushions can cause inflammation and instigate hemorrhoidal disease (13,14), and finally,

4) Destruction of the anchoring connective tissue system, such as with increasing age, can also cause weak vein walls and prolapse. (15)

Risk Factors

Any insult that causes the anchoring and supporting connective tissue to deteriorate and/or initiating an increase in pressure and dilatation of the hemorrhoidal cushions can result in their engorgement and descent (16). Prolapse impairs venous return, causing irritation and inflammation, which causes pruritus and edema. Erosion of the inflamed epithelial layer causes bleeding (6). To date, several risk factors have been linked to their development. Some individuals are genetically prone to hemorrhoids due to weak vein walls and atrophied or weakened fibrocollagenous supporting tissue (16). High blood pressure may also result in increased venous pressure (17,18). Straining and holding one's breath while defecating and sitting on the toilet are all known to increase hemorrhoidal blood pressure (17,18). Constipation and hard stools cause straining, which is known to result in hemorrhoids, as well as further aggravate existing hemorrhoids (16). Diarrhea has also been shown to be another risk factor for hemorrhoids since it causes abrasions and mucosal irritation Johanson and Sonnenberg (20) Thus, unusual bowel moments with both increased and decreased gut motility can produce enlargement of anal cushions. Poor pelvic musculature, rectal surgery and decreased rectal muscle tone have

also been associated with rectal venous engorgement (16). Pregnancy is a well known cause for the development of both internal and external hemorrhoids (16-18, 20). Finally, vaginal deliveries with long labour, lip tears during delivery and giving birth to heavy babies have also been associated with a higher incidence of hemorrhoids (20).

2.2 Treatment

Conservative Treatment

Treatment of hemorrhoids is typically decided based on their severity. Treatment is primarily conservative for grade I and II hemorrhoids, consisting of a high fiber diet and adequate fluid intake. If fiber in diet is not adequate, it can be supplemented by bulk forming agents such as psyllium extracts (3,4). A double blind, placebo controlled study of acute hemorrhoidal symptoms found a decrease in bleeding and pain on defecation with the use of psyllium seed supplements (21). Stool softeners such as docusate sodium can be taken to yield softer, less abrasive stools (3). Patients are counselled to avoid sitting on the toilet seat for longer than one minute as well as avoid straining during defecation (6). Warm water bathing (40°C-50°C for 10 min) with sitz salts may also be beneficial to reduce anal pain (22).

Several topical preparations containing varying proportions of anesthetics, astringents and corticosteroids are also available for symptomatic relief of hemorrhoids. Mild topical astringents, such as zinc sulphate and Hamamelis virginiana (Witch Hazel) may be helpful to shrink hemorrhoids. To reduce inflammation and pruritus, ointments and suppositories containing corticosteroids such as hydrocortisone, benzocaine and

lidocaine are often used. Pain can be reduced by the use of topical anesthetics such as pramoxine hydrochloride. However, there are no randomized trials that suggest topical treatments reduce hemorrhoidal symptoms, such as bleeding and prolapse in patients.

In some countries, treatment of hemorrhoids with oral medications is commonly employed. A few studies have shown the use of oral micronized purified flavonoids fraction (MPFF) such as disodium flavodate, heparinoid and rutosides, which are venotonic agents derived from citrus fruits, helpful to treat hemorrhoids. Flavanoids increase venous tone and decrease capillary fragility, which are thought to improve acute ano-rectal symptoms (23). A meta-analysis of 14 randomized, placebo controlled trials with MPFFs found improvement in bleeding, pain, itching and recurrence of hemorrhoids (23). However, there were several limitations of the studies in question, such as issues on methodological quality, small sample sizes and publication bias, which raise doubt about the true efficacy of MPFFs.

Invasive Treatment

If hemorrhoids are persistent and do not resolve after one month with conservative treatment, definitive non-operative therapy can be tried (24). First and second degree hemorrhoids do not require a procedure to remove the redundant hemorrhoidal tissue. However, third and fourth degree hemorrhoids do require therapy, which typically initiate thrombosis followed by complete removal of the mucosa. Several such modalities exist.

Rubber band ligation is a commonly used outpatient procedure that results in complete removal of hemorrhoidal tissue. A tight band is placed over the tissue stopping

blood flow in the pinched-off portion with ulcerates and forms scar tissue. This procedure works best on first, second and few third degree hemorrhoids (3,16).

Sclerotherapy utilizes the injecting of 5% sclerosant solution, such as sodium morrhuate or 5% phenol, into the submucosa surrounding the hemorrhoid. This results in acute inflammation and scarring and finally eliminating the submucosal layer. This technique works best on first and second degree hemorrhoids (3,16).

Photocoagulation with infrared or lasers coagulates the tissue, causing necrosis and shrinkage of the hemorrhoid. Electrocoagulation and heat coagulation use direct current and heat to treat hemorrhoids respectively (3,16).

Cryotherapy causes local tissue destruction and necrosis by deep freezing of submucosal cushions using an agent such as liquid nitrogen (3,16).

When necessary, surgical treatment of hemorrhoids can also be performed. If third and fourth degree hemorrhoids have persisted with the above treatments or if strangulation has occurred, the hemorrhoids may need to be surgically removed via a hemorrhoidectomy. Several procedures exist, with the primary focus on removal of all hemorrhoid tissue without damage to surrounding tissues and anal sphincter. The wounds can also be sutured or left open for drainage (3,16).

Finally, chronic hemorrhoids may be benefited by two methods: dilation of the anal sphincter, causing the weakening of the sphincter and sphincterotomy where the internal section of the sphincter is cut off. Both surgical procedures result in a decrease in anal sphincter pressure (3,16).

2.3 Hemorrhoids in Pregnancy

Pregnancy is a known risk factor for hemorrhoids. Studies have found that hemorrhoids affect up to 38% of women in the third trimester of pregnancy (25). A combination of several factors makes it a common occurrence in pregnancy. Firstly, the 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 (26,27). Secondly, there is an increase in circulating blood volume in pregnancy by 40-50% in the third trimester (28). This increase in blood volume further contributes to venous engorgement. Thirdly, high levels of the hormone progesterone circulate in pregnancy (29). Progesterone relaxes venous walls and reduces venous tone, thereby causing venous dilation of the cushions causing them to enlarge and swell. Also, 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 (29). This decrease in gut motility leads to constipation, which, as stated above, makes pregnant women more prone to hemorrhoids. High doses of oral iron supplementation in prenatal vitamins are also thought to cause constipation (30). Previous pregnancies also pose as a risk factor to develop hemorrhoids in recurrent pregnancy. In some populations, up to 85% of women in their second and third pregnancies suffer from hemorrhoids (31).

2.4 The Incidence of Developing Hemorrhoids in Pregnancy

The estimated overall prevalence of hemorrhoids in women is around 25%, which is thought to increase during the childbearing years (17). Despite the lack in precise data on the prevalence of symptomatic haemorrhoids in pregnancy, it is expected to be much greater than non-pregnant women of the same age (32,33). A few studies have evaluated the incidence of symptomatic hemorrhoids in pregnancy, each differing significantly from the other. One study by Abramowitz (20) observed a risk of 7.9%, whereas Pradel (34) estimated a 24% risk and Simmons found a 38% risk (25). None of these studies reported on Canadian women. An evaluation of the incidence of symptomatic hemorrhoids among Canadian women is necessary to establish and deliver appropriate health care. There may be significant diversity in the incidence of hemorrhoids in Canadians due to differing lifestyles, diet and genetics in this population. Furthermore, multigravid women are at a greater risk for recurring hemorrhoids in subsequent pregnancies. In one study, hemorrhoids were diagnosed in 85% of women in Serbia and Montenegro in their second and third pregnancies (31). In a second study, 70% of women diagnosed with hemorrhoids had one or more prior pregnancies (35).

It is important to estimate what are some of the risk factors of developing hemorrhoids in pregnancy as well as what percentage of Canadian women suffer from hemorrhoids in the third trimester of pregnancy.

2.5 Treatment of Hemorrhoids in Pregnancy

In pregnancy, treatment is typically conservative and primarily symptomatic whereas surgical and invasive hemorrhoid therapies are usually avoided. Very little data exists describing the safety of definitive treatment, and guidelines generally suggest that surgery should only be performed if absolutely necessary and postponed to the third trimester when the fetus is completely developed. (4) In a small study, Saleeby et al conducted hemorrhoidectomies for removal of hemorrhoids and observed no maternal or fetal complications (36). However, it is suggested that almost 25% of women who undergo hemorrhoidectomy during pregnancy require additional treatment subsequently (6). Whereas, adult life hemorrhoids are usually self-limiting, the general course of hemorrhoids in pregnancy tends to be more prolonged and usually completely resolve only postpartum (4). Thus, due to the prolonged nature of pregnancy related hemorrhoids as well as concerns regarding fetal safety, such therapy is restricted to the time period post delivery when symptoms persist (6, 37).

An increase in fiber and water intake is recommended to prevent straining due to constipation (38,39). If this measure alone does not suffice, osmotic laxatives can also be used (40). Stimulant laxatives should be avoided due to potential risk of uterine contractions (41). To mitigate the symptoms of hemorrhoids, warm water bathing is suggested. Training in toilet habits is also recommended to prevent worsening of symptoms. In some countries, oral micronized purified flavonoid fractions (MPFF) are also used in pregnancy (23). Topical preparations have also been suggested to alleviate symptoms of hemorrhoidal disease (3,4,16).

2.5.1 Issues with Treating Hemorrhoids in Pregnancy

First line conservative treatment such as fiber and fluid intake is generally slower acting and targeted towards long term prevention of hemorrhoids. Prolapse is not likely to improve with fiber supplementation alone, since it involves structural change and damage to connective tissue supporting the hemorrhoidal cushions (42). There is little data that support the effectiveness of warm water bathing. Toilet training primarily prevents further prolapse of existing symptomatic hemorrhoids. There is some literature that suggests MPFF's are effective in reducing symptomatic hemorrhoids in pregnancy, however, the safety as well as efficacy of these MPFFs is still not fully established (23). Furthermore, MPFFs are not available readily in North America. Most are not approved by Food and Drug Administration (FDA) or Health Canada, although a few other varieties of flavanoids are available in some health food stores. There is also little evidence to support either safety or efficacy of any of the more commonly used antihemorrhoidal preparations containing analgesics, anesthetics and corticosteroids.

Additionally, there is no information on the safety of any of the commonly used anti-hemorrhoidal preparations. A literature review was conducted on the safety of topical anti-hemorrhoidal preparation. The Motherisk database (Jan 2006-Jan 2007) was searched and a list of commonly used local anti-hemorrhoidal preparation was developed. The Motherisk Program is a service provided out of the Hospital for Sick Children that provides evidence based information via telephone on the. The eight most frequently used local treatment by Motherisk callers included Anusol®, Anuzinc®, Anugesic-HC® , Preparation H®, Proctofoam-HC®, Proctosedyl®, Witch hazel and Tea tree oil. Pubmed and Medline searches did not yield any eligible studies in English on the fetal

safety of the above preparations during pregnancy. It was concluded that there was not enough data on any of the commonly used anti-hemorrhoidal preparations by Canadian women (Appendix B). The ingredients present in each of the above mentioned preparations have been listed in Appendix C.

In summary, while traditionally conservative therapy is usually advocated in pregnancy, there is no evidence to show either fetal safety or effectiveness of any of these treatment modalities.

2.6 Fear of Drugs in Pregnancy

Ever since thalidomide caused widespread teratogenicity in the 50s and 60s, women and health care providers have been exercising extra caution with prenatal exposures. In fact, many women are advised by their healthcare practitioners to discontinue medications that may not have any additional risk to the fetus (43). Women also self-discontinue medications for the same reason. Studies have shown that the perception of teratogenic risk is much higher than the actual risk, in both women as well as care-givers (43). To reduce perceived risks and to enable proper management of disease, it is imperative to establish the fetal safety of medications commonly used by women. If studies show the medication is safe in pregnancy, women can be reassured and will be more likely to continue treatment. Reducing risk perception may offer optimal therapy of ailments in pregnancy and may also improve well-being and quality of life (43).

2.7 Safety of Proctofoam-HC® in the Third Trimester of Pregnancy

2.7.1 Proctofoam-HC®

Proctofoam-HC® is a mucoadhesive 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 (44). Each aerosol foam canister contains 18g of a mixture of 1% hydrocortisone acetate and 1% pramoxine hydrochloride in a hydrophilic base formulated with cetyl alcohol, emulsifying wax, methylparaben, polyoxyetlheylene-10 stearyl ether, propylene, glycol, propylparaben, purified water, trolamine, and inert propellants isobutane and propane. A canister contains 36 applications; each application provides 375 mg of hydrocortisone acetate (3.75 mg/dose) and 375 mg of pramoxine hydrochloride (3.75 mg/dose) (44). Every canister contains a topical applicator, thus avoiding direct touch to the inflamed area. The foam is thought to adhere to the surface without staining or leaking. Thus, due to its hygienic and non-greasy nature, it was assumed that more women might prefer to use this product over other similar preparations.

2.7.2 Pramoxine Hydrochloride

The local anesthetic, pramoxine hydrochloride is 4-[3-(p-Butoxyphenoxy) propyl] morpholine hydrochloride. It is also named tronolane and pramocaine hydrochloride (45). Pramoxine does not belong to either of the two large classes of local anesthetics (amides and esters). Rather, it is classified as an amino-ether. Pramoxine is less potent locally than other commonly used topical anaesthetics, but is thought to be as effective as

benzocaine (46). Pramoxine appears to be less irritating to the tissue and possesses a considerably lower systemic toxicity than amide and ester local anesthetics (47). In addition, there is no cross-sensitivity with pramoxine due to its unique molecular structure compared to other local anesthetics (48).

Peak effects are usually seen 3-5 minutes after application (49) and the duration of action is typically under one hour, but may last up to 5 hours depending on the amount of drug applied (45). The metabolism and clearance of pramoxine is still not fully understood. Another amino-ether, fomocaine, which is a morphiline derivative similar to pramoxine is thought to undergo biotransformation to hydrophilic metabolites via N-oxidation, which are then excreted by the kidney (50). Metabolism of fomocaine is not fully understood either, however acknowledging similar chemical structures, pramoxine might share a common biotransformation pathway with fomocaine.

Mechanism of Action

As with other local anesthetics, pramoxine blocks sensory transmission of pain, cold, warmth and deep pressure sensation. Pramoxine provides pain relief by providing localized, reversible inhibition of the initiation and conduction of nerve impulses by binding directly to voltage-dependant sodium channels. By decreasing the neuronal membrane's permeability to sodium channels, the flow of sodium ions into the neuron is interrupted. This slows the rate of depolarization, thus decreasing the rate of rise and height of the action potential. Consequently, the rate of axonal conduction slows, finally resulting in the failure to propagate an action potential. Thus, subsequent conduction of nerve impulses is blocked (50). Small nerve fibres such as the myelinated Aδ fibers

(facilitate sharp pain) and unmyelinated C fibers (facilitate dull throbbing pain) are most susceptible to local anesthetics (51). Further, since these small C nerve fibres also facilitate the pathway of itching sensation (52), pramoxine is also believed to help relieve pruritus and pain associated with hemorrhoids.

Local Anesthetics in Pregnancy - General

Typically, local anesthesia has not been shown to increase the risk for congenital malformations or other neonatal adverse effects. Local anesthetics are used for a variety of indications in pregnancy, the most common being lumbar epidural anesthesia. Anesthetics such as lidocaine are also used systemically to treat ventricular arrhythmias.

Several animal studies investigating the safety of local anesthesia in pregnancy have been performed. In rats and rabbits, reproductive studies with ropivacaine have found no teratogenic effects (53). Similarly, in pregnant sheep given ropivacaine, bupivacaine or levobupivacaine, no adverse effects were observed (54). Reproduction studies in rats receiving lidocaine found no evidence of teratogenicity (55), whereas chronic exposure to high doses of lidocaine in pregnant rats did not produce any adverse reproductive or congenital anomalies (56,57). Several animal models and *in vitro* data documented that high concentrations of local anesthetics can cause changes in uterine blood flow (58) and result in fetal convulsions (59). Another animal study has raised some concern with changes in umbilical blood flow and fetal heart rate with bupivacaine exposure in pregnant sheep (60). An *in vitro* study identified a restriction in umbilical arteries and veins with high concentrations of bupivacaine (61)

Most of the human data available on local anesthetics stems from epidural analgesia during labour, mostly with ropivacaine (62-69). No neonatal adverse outcomes have been documented in any of the studies. The Collaborative Perinatal Project followed 293 women with exposure to lidocaine in the first trimester. No major malformations were observed. The same study also found no increased risks for major or minor malformations in 947 exposures of lidocaine anytime in pregnancy (70). Similarly, no increase in major or minor malformations has been associated with the use of bupivacaine in pregnancy (71-78). The Collaborate Perinatal Project also did not find an increased risk for congenital anomalies with the use of benzocaine in 47 women treated during the first trimester of pregnancy and 238 women treated anytime during pregnancy (70). Most human studies with lidocaine epidural analgesia have failed to find any evidence of neonatal adverse effects or changes in neurobehaviour (71-78). Neurobehavioral studies with bupivacaine found mostly no effects or mild and transient effects in some cases (79-86). None of the human studies with lidocaine concluded that there were any concerns with respect to decreased uterine blood flow or fetal convulsions (87-89). Similarly, none of the human studies could identify any differences in umbilical blood flow (90-92).

To date there has been no published study on the safety of pramoxine in pregnancy.

Pharmacokinetics:

Typically, topical absorption of local anesthetics is very minimal, with absorption at around 1-3% (93-95). A study done by Jouppila (96) looking at the epicutaneous

absorption of ketocaine for relieving referred lower back pain observed very minimal amounts present in the umbilical/maternal vein and artery. A review by Lewis (97) reported that pramoxine was generally not absorbed when used anorectally. Since other local anesthetics cross the placenta readily (87, 98-100), it is reasonable to assume the same for pramoxine. However, as noted by Briggs (101), even if small amounts were to be absorbed systemically in the maternal circulation, the amount transferred to the fetus would be fairly negligible. However, further studies are required to document conclusive fetal safety of the use of pramoxine hydrochloride use in pregnancy.

2.7.3 Hydrocortisone Acetate

Hydrocortisone is a synthetic corticosteroid that is similar to the endogenously produced cortisol. Cortisol is produced in the zona fasciculata of the adrenal cortex from cholesterol via hydroxylation mediated by the enzyme 11B hydroxylase. Hydrocortisone is less potent compared to most other corticosteroids, and possesses both glucocorticoid and mineralocorticoid properties. Hydrocortisone has widespread physiologic effects, including but not limited to, carbohydrate, lipid and protein metabolism, immunosuppression and most importantly, anti-inflammatory properties (102).

Adult dosage of hydrocortisone can be anywhere between 5mg and 500mg depending on the indication. When used topically, general onset of action is seen within 7 days (103). Hydrocortisone is metabolized extensively in the liver and kidney, with an elimination half-life of 1 to 2 hours. Despite its short half-life, hydrocortisone has a much longer biologic half-life due to the nature of action of glucocorticoids (102). Glucocorticoids induce the modification of genes and messenger ribonucleic acids

(mRNS), lasting significantly longer than the plasma half-life of the glucocorticoid. Cortisol binds primarily to corticosteroid binding globulin (CBG), and to some extent to albumin. Typically, 75% of circulating hydrocortisone is bound to CBG, while only 15% is bound to albumin. The remainder circulates freely (102). Cortisol is metabolized primarily in the liver and excreted predominantly by the kidney. Cortisol is first inactivated by a ring reduction to tetrahydrocortisol, and then further reduced to cortol. Cortol conjugates with glucoronic acid, a reaction catalyzed by β-glucoronidase. The hydrolysed metabolites, being extremely hydrophilic, are excreted through the kidney. Hydrocortisone is cleared quickly from the body, with a plasma clearance of 362 ml/min (102).

As all other glucocorticoids, hydrocortisone/cortisol has several physiological effects, including, but not limited to metabolic, anti-inflammatory and immunosuppressive effects. The primary function of hydrocortisone in Proctofoam-HC® is in decreasing inflammation, pain, swelling and discomfort resulting from the inflammation.

Mechanism of Action

Hydrocortisone mediates an anti-inflammatory response by inhibiting the production of multiple factors and mediators of inflammation. Hydrocortisone causes an increase in circulating neutrophilic leukocytes (thus decreasing the number of neutrophils at the site of inflammation), while decreasing the production of monocytes, eisonophils, lymphocytes and basophils (102,104).

The arachidonic acid cascade is the main pathway for the production of oxygenated fatty acids known as eicosanoids consisting of leukotrienes, postaglandins and thromboxanes, which are the primary precursors in the production of inflammation. The first pathway is modulated by the enzyme 5-lipooxygenase, which converts arachidoic acid to LTA4, LTB4, LTC4, LTD4 and LTE4. These 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. Finally, leukotrienes mediate pain and edema and enhance mucosal secretions. The second pathway is catalyzed by the enzyme cyclooxygenase, which converts arachidonic acid to prostaglandin G2 (PGG2) and prostaglandin H2 (PGH). Prostaglandin H2 is further broken down to prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostaglandin F2A and F1A (PGF2A, PGF1A), prostacyclin (PGI2) and thromboaxane A2 (TXA2). The end products, known as prostanoids, cause vasodilation and increase capillary permeability, resulting in increased blood flow to the area which then causes edema, swelling, inflammation and pain. Prostanoids also cause increased sensitization to pain. Thromboxanes also cause platelet aggregation, which leads to the formation of thrombosis (102,104).

Hydrocortisone binds to a cytosolic glucocorticoid receptor. This receptor-ligand complex then translocates into the nucleus and binds to glucocorticoid response elements (GRE) in the promoter region of certain genes, regulating the expression of several inflammatory initiators, one of which being Lipocortin-1. Lipocortin-1 inhibits the activity of phospholipase A2, thus inhibiting production of arachidonic acids. This

prevents the release of prostaglandins leukotrienes and thromboxanes inhibiting the manifestations of the above mentioned inflammatory process (102,104).

Hydrocortisone also inhibits the late stages of inflammation. The synthesis of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which in turn produces nuclear factor-kappa B (NF-kB) are decreased. The action of another cytokine, migration inhibition factor (MIF), is also impaired, resulting in the decreased accumulation of macrophages in the inflammatory site (104).

Hydrocortisone also stimulates the migration of lipocortin-1 into the extracellular space, binds to the leukocyte membrane receptors and thus inhibits cell migration, epithelial adhesion and chemotaxis. The release of other inflammatory mediators such as lysosomal enzymes, chemokines, basophils and fibroblasts is also repressed (102,104). As well, decreased action of bradykinin and serotonin and inhibition of histamine released from mast cells and basophils by hydrocortisone further decreases vasodilation and edema (105).

To summarize, hydrocortisone reverses the effects of inflammation by causing vasoconstriction and decreasing vessel permeability, thus reducing serum extravasation, swelling and discomfort. It also inhibits downstream effects of inflammation and reduces pain as well as pain sensitization.

Hydrocortisone and Pregnancy

Oral Corticosteroids

1- Teratogenicity:

Animal experiments with various glucocorticoids have shown specific dose-dependant teratogenic effects. Systemic glucocorticoids have consistently produced cleft palate in animal reproductive studies (106-108). Human teratology studies of systemic corticosteroid use in pregnancy have been conflicting. Four retrospective case-control studies have found an association with oral cleft specifically (109-112). In contrast, several prospective cohort studies have failed to show an association between exposure to corticosteroids in pregnancy and any major malformations (70, 113-116). Motherisk conducted a meta-analysis including 5 cohort studies and 4 case controlled studies. Combining the cohort studies reporting on the total major malformations (390 exposed and 707 control pregnancies) the summary odds ratio was not significant (2.74; 95% CI: 0.96-7.82). However, the summary odds ratio for the case-control studies examining oral clefts specifically was significant (3.69; 95% CI: 2.15-6.32). Moreover, the cohort studies showed a clustering of cleft palate among the corticosteroid exposed group when compared to the controls (116).

Hence, while corticosteroids do not seem to represent a major teratogenic risk in humans, there may be a small risk for oral clefts. Since the palate is completely formed by week 12 of gestation, corticosteroid therapy appears to be safe to use thereafter without a risk for other major malformations.

2- Birth Weight:

Animal studies assessing the risk of exposure to antenatal hydrocortisone were limited primarily to the incidence of oral cleft. However, some of these studies also reported on other outcomes. One of the first studies on the fetal safety of hydrocortisone was performed in 1951 by Fraser and Fainstat (117), 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 (118), which were republished in 1998 (119). The group did not find any difference in mean gestational age. In another study in rabbits by Decosta et al (120), cortisone given IM produced IUGR in the pups. An increase in fetal and neonatal death was also observed.

Animal studies examining the impact of maternal antenatal glucocorticoids to promote fetal lung maturation have consistently observed a decrease in birth weight in the offspring. Jobe et al (121) found a 14% and 19% decrease in birth weight in fetal sheep exposed to a single dose and repeated doses of maternal betamethasone, respectively. Similar results were demonstrated by Newnham et al (122), with a 19% decrease in birth weight in fetal sheep. In a separate placebo controlled study by Jobe and colleagues in pregnant ewes (123), a dose-dependant relation was observed, with up to 26% reduction in birth weight after 1 dose of betamethasone and up to 30% reduction in birth weight after three doses of betamethasone. A similar study design carried out by Ikegami and colleagues also demonstrated a decrease in 15% after a single dose and 27% after three doses (124). Growth defects were also seen in rabbit and mice studies with exposure to maternal glucocorticoids (125,126). More growth effects were observed with increased doses and when exposed in later stages in pregnancy.

A prospective controlled trial by Gur and colleagues (127) followed 311 pregnancies with exposure to systemic corticosteroids, finding significant decrease in median birth weight (3080 grams in the treatment group vs. 3290 in the control group). There were also significant increases in rates of spontaneous abortions (11.5% in the treatment group vs. 7.0% in the control group) and preterm deliveries (22.7% in the treatment group vs. 10.8% in the control group). Studies done on safety of corticosteroids for treatment of maternal asthma have also been reported. A recent study by Schatz (128) on 297 women with asthma found a significant association between corticosteroid exposure (oral and topical) and low birth weight (6% 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). The Motherisk Program conducted a prospective observational study (116) on the use of systemic prednisone in pregnancy in 187 women. They reported a significant decrease in birth weight in the treatment group (3112 grams) vs. the control group (3428 grams). Prematurity was also significantly associated with antenatal corticosteroid use (17% vs. 6%). 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 (129).

Some authors have found an association between repeated doses of antenatal corticosteroids for lung maturation in humans and growth restriction. A retrospective study by Banks (130) found a slight decrease in birth weight in 710 infants whose mothers were treated with antenatal glucocorticoids between weeks 24 and 30 of gestation. Decrease of 39 grams and 80 grams were observed with doses greater than one course and greater than two courses of corticosteroids, respectively. Another

retrospective study by Thorp and colleagues (131) included over 8900 women who received antenatal corticosteroids. They found a decrease of 63 grams in birth weight (3.8%), after controlling for independent variables. Bloom and colleagues (132) found decreases of 161 grams and 80 grams at weeks 30-32 and 33-34 of gestation, respectively in a retrospective cohort study including 961 infants who received antenatal dexamethasone versus those who received none. French and colleagues (133) conducted a prospective observational study on 409 infants, in which there was a decrease of 122 grams (9%) in birth weight. All of the above studies examined the administration of betamethasone, dexamethasone or both.

Conversely, a few studies have contradicted the above findings. A retrospective study by Pratt et al examined 409 infants who had no difference in birth weight between one and two courses of maternal antenatal corticosteroids (134). Similar results were observed by Elimian, Abbassi and Shelton (135-137). All three were retrospective cohort studies and included 354, 713 and 152 participants respectively. However, similar to Pratt, the above three studies examined the difference between single versus multiple doses of antenatal corticosteroids. Negative controls comparing birth weight to that of the general population or a control group without antenatal corticosteroid exposure was not analysed in any of the four studies.

To summarize, literature on the adverse effect of hydrocortisone on birth weight is still highly controversial. Further studies are required to determine safety of hydrocortisone in pregnancy.

3- Other Findings

Recent animal data also seem to suggest that repeated use of antenatal corticosteroid is also associated with retarded brain and nervous system development (138-141). However, most of the human studies did not observe these effects (131,133). There is also some concern with adrenal gland suppression with repeated antenatal corticosteroid exposure (130,142) and a possible theoretical risk for developing hypertension, type 2 diabetes and coronary heart disease in later adulthood. However, these findings are still very controversial and further research is needed to confirm them.

Topical Corticosteroids

None of the above risks for malformations and adverse fetal effects have thus far been associated with the topical use of corticosteroids. Inhaled corticosteroids in pregnancy, such as beclomethasone and triamcinolone, have been examined in several studies (128, 143-153). None of the above studies observed any congenital defects (including oral cleft) in the neonates. Research investigating the possibility of IUGR with topical usage is still sparse.

Pharmacokinetics

The amount of hydrocortisone absorbed systemically via topical, local use is reported to be between 3-7% (153, 143). No pharmacokinetic studies on rectal absorption with the presence of hemorrhoids are presently available. Using an estimated absorption, with dosage of 2-3 applications of 1% Proctofoam-HC® per day, less than 1mg of hydrocortisone is thought to be systemically absorbed (154,155). Hydrocortisone crosses

the placenta (156-159). According to a few studies, the amount that crossed through the placenta is thought to be minimal (157,158). The syncytial trophoblastic cells in the placenta are rich with the enzyme 11β hydroxysteroid dehydrogenase 2 (160), which metabolizes active corticosteroids to the inactive 11 ketosteroids (corticosterone, 11-dehydroxycorticosterone) (161). However, this enzyme is not as effective with exogenous corticosteroids, and can be saturated with the presence of high levels of maternal cortisol (162, 163). One study measured the amount of hydrocortisone present in fetal cord blood after the mother received hydrocortisone IV and IM to prevent respiratory distress syndrome. A 3.8 fold increase over endogenous levels of hydrocortisone was observed (164).

2.7.4 Why is there concern?

Based on where the drug is applied anatomically, there may be significant differences in the amount of drug absorbed. The lower rectal region is drained by the inferior and middle rectal veins into the inferior vena cava and directly into the systemic circulation (165). 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 (165). Thus, drugs applied to the lower rectal region have the potential of entering the systemic circulation in higher concentrations. Rectal absorption of some drugs is higher than oral absorption, presumably because they bypass first-pass metabolism (165). One such example would be lidocaine, metabolized extensively in the liver, with an oral bioavailability of 35% (166). In a study in rats, rectal absorption of lidocaine was found to be 16% when applied 4 cm above the anus, 45% at 1

cm above the anus and as high as 72% when applied just above the anus (167). Similar results were found with rectal lidocaine application in humans, with an estimated rectal bioavailability between 63-71% (168). A few studies on rectal bioavailability of hydrocortisone have been conducted; however, large interindividual variability resulted in significant differences in estimates. Tromm and colleagues observed rectal bioavailability between 2.5% and 3.9% with rectal hydrocortisone acetate (169), while Barr *et al* reported systemic bioavailability between 0.4% and 9.8% (170). Petitjean and colleagues reported 30% bioavailability with rectal application of hydrocortisone acetate (171). Such variability could possibly be due to the difference in the positioning of rectal application, resulting in varying hepatic metabolism of the drug. Thus, absorption of hydrocortisone and pramoxine could be higher depending on the positioning of the application. Hence, there is a possibility that significant amounts of the drug may be entering the maternal systemic circulation. As seen with the literature above, systemic corticosteroid exposure in pregnancy has been shown to result in IUGR. IUGR is defined as a fetus whose estimated weight is below the 10th percentile for its gestational age. Infants with IUGR have high neonatal morbidity and mortality and are prone to hypoglycemia, necrotizing enterocolitis, thrombocytopenia, intraventricular hemorrhage, chronic lung disease and feeding difficulties (172).

Given the lack of data on the safety of pramoxine in pregnancy and the limited availability of information on the risk of IUGR with topical exposure of hydrocortisone, and considering potentially large amounts of the above can enter the maternal systemic circulation and possibly fetal circulation, a study to assess the fetal safety of the rectal use of both ingredients in pregnancy is strongly warranted.

2.8 Effectiveness of Proctofoam-HC® in Treating Hemorrhoids in Pregnancy

There are no studies that evaluate the efficacy of pramoxine hydrochloride in pregnancy. Data to support efficacy in the general population for local pain and pruritis is scarce as well. Some studies have shown the usefulness of pramoxine to treat itching associated with psoriasis and pruritus ani (173-175). A double-blind placebo controlled study conducted by Yosipovitch (175) showed a significant decrease in duration and magnitude of experimental histamine induced pruritus.

Similarly, no studies have evaluated the efficacy of hydrocortisone acetate to alleviate any hemorrhoidal symptoms in pregnancy. Hydrocortisone has been shown in a small number of studies in the general population to relive the itch associated with pruritus ani. One study showed a 68% decrease in anal itch compared with placebo with the use of topical 1% hydrocortisone (176). Hydrocortisone has also been shown to decrease other ano-rectal conditions in the general population, such as pain, bleeding and pruritus associated with anal fissures (177). There are limited data on the efficacy of hydrocortisone for treatment of hemorrhoids. One study compared two products containing hydrocortisone as one of their ingredients; both preparations were found to be efficacious (178). Despite the lack of controlled evidence to support its effectiveness in treating hemorrhoids, patients still appear to benefit with its use (179,180).

Additionally, studies on the efficacy of Proctofoam-HC® in general adult life is also scarce. Hitherto, there is limited data on the efficacy of most of the commonly used anti-hemorrhoidal treatments in pregnancy as well. Specifically, no data is available in the current literature to assess the efficacy and/or effectiveness of pramoxine hydrochloride

and hydrocortisone acetate, in conjunction, to treat pregnancy related hemorrhoids. Hence, a study to determine whether Proctofoam-HC® is, indeed, effective in treating pregnancy hemorrhoidal disease is necessary.

CHAPTER 3: METHODS

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

3.1.1 Study Design

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

3.1.2 Subject Recruitment

Participants were recruited from six different sites between September 2006 and September 2008. The sites included Obstetrics and Gynaecology 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 final site of recruitment was the Motherisk Program in Toronto, Ontario.

3.1.3 Inclusion and Exclusion Criteria

To be included, women needed to satisfy the following criteria:

- Pregnant women in the third trimester of pregnancy (gestational age of 27 weeks onwards).
- Low risk pregnancy with evidence of no pregnancy complications.

- Primary anorectal conditions (not caused by a systemic disease such as portal hypertension) treated with Proctofoam-HC® prescribed by the woman's obstetrician.
- Consenting to participation in the study.

The following patients were excluded from the study:

- Women who were exposed to known teratogens during pregnancy evidenced either during the first interview (antenatal) or the second interview (postnatal)
- Mothers with insufficient English language skills to understand the questionnaires and assessment tools.
- Pregnant women younger than legal age of 18 years of age.
- Women who received during pregnancy other systemic corticosteroid medication.
- Women with the following conditions that constitute contraindications to Proctofoam-HC® treatment: anorectal abscess, fistula, tuberculosis, varicella, acute Herpes Simplex or fungal infection.
- History of reaction such as: local irritation, hypertrichosis or hypo pigmentation, to any of the product's components.
- Known intra uterine growth restriction (IUGR) or a chronic condition that may cause IUGR (systemic lupus erythematosus, placental insufficiency).
- Binge alcohol consumption.

3.1.4 Study Instruments

Questionnaires:

Two assessment questionnaires were developed for the purpose of this study. The first assessment, obtained antenatally, asked women to provide detailed medical and obstetric history as well as the time, indication, dose and duration of use of Proctofoam-HC®, information on the identity and doses of any other concomitant medications, smoking and alcohol usage. The second assessment was obtained postnatally. Here, the mother was questioned about the course of her pregnancy subsequent to the first interview. As well, information was collected on the duration and dose of Proctofoam-HC®, other medication use during gestation, maternal illnesses, possible perinatal and/or postnatal complications, gestational age at birth, birth weight (adjusted for gestational age), Apgar score and delivery methods. Appendices D and E document the Antenatal and Postnatal assessment forms, respectively.

Birth Weight for Gestational Age:

Raw birth weight of the neonates was adjusted for gestational age using the modified Birth Weight for Gestational Age Percentile Calculator (Sussman, 2006, Toronto, Canada). In a yet unpublished study (181), this calculator was found to provide nearly exact estimates when compared with traditional hand-plotting. On entering the neonate's gestational age, sex and birth weight into the program, the resultant output estimates the neonate's birth weight when born at 40 weeks gestation as well as the respective z-score and percentile. Gestational age was based on ultrasound or last menstrual period of the mother.

3.1.5 Study Procedure

Physicians specializing in obstetrics and gynecology (OB/GYN) were approached to collaborate in the study if they routinely prescribed Proctofoam-HC® to their pregnant patients. Collaborating physicians would prescribe Proctofoam-HC® as routine intervention to pregnant women with hemorrhoids in the third trimester of pregnancy. The physicians explained the study to the patient briefly. If the patient agreed to participate, the research co-ordinator (Sabina Vohra) telephoned the patient and obtained verbal consent (Appendix F). Once consent was obtained, participants were mailed a package containing a letter with all necessary contact information and details of the study (Appendix G). Further, women were also recruited through the Motherisk helpline. Motherisk callers in the third trimester of pregnancy who called between September 2006 and August 2008 and requested information regarding the use of Proctofoam-HC® in pregnancy were given verbal information on the exposure of the medication by the Motherisk counsellor. If eligible, the Motherisk counsellor would provide details of the study. At this point, the caller was asked if they might be interested in speaking with the study co-ordinator directly to obtain further information on the study. If the caller agreed, the study co-ordinator telephoned the caller and explained the study in detail. If the caller agreed to participate, verbal consent was obtained as above and a similar package containing the letter and study details was sent out. Women were offered complimentary samples of Proctofoam-HC®, either directly by their physician, or by contacting the research co-ordinator at Motherisk. The women did not receive any other form of payment or reimbursement.

Recruited women were asked to complete two 10 minute telephone interviews using the two specially designed questionnaires. Both interviews were conducted by the study co-ordinator. The first questionnaire was completed at the time of enrolment and prior to delivery. The second assessment 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 to corroborate the mother's information. Appendix H includes the letter sent to the child's primary care physician.

3.1.6 Outcome Measures

It was hypothesized that local (rectal) use of Proctofoam-HC® in the third trimester of pregnancy was safe for the fetus. To measure this, the primary endpoint of the study was birth-weight, which is a relative sensitive measure of fetal development in the third trimester. At 28 weeks the fetus 50^{th} percentile of weight is 1 kg, and ten weeks later it should gain an average additional 2.0 kg (182). A variety of fetal insults have been shown to adversely affect this rapid and dynamic process (example, cigarette smoking, and placental insufficiency) (183,184). Critical for this study, repeated oral doses of corticosteroids in pregnancy have been shown to cause a significant decrease in birth weight. The secondary outcomes include mode of delivery, labour complications, fetal distress and adverse events in the neonate.

3.1.7 Comparison Group

For analysis, a comparison group of women were included, which comprised of Motherisk callers who called to receive information on non-teratogenic drugs; such as

hair dye, cold medications, diclectin and occasional tea use; and who were not exposed to any teratogens during the course of the pregnancy. This was further limited to women who had not been exposed to Proctofoam-HC® and its components or any other topical corticosteroids or local anesthetics during the course of their pregnancy. None of the women in the comparison group suffered from hemorrhoids at the time of the call. Each control subject was matched for maternal age (+/- 2 years) and smoking status (+/- 2 cigarettes). As well, multigravid pregnancies were matched with controls carrying the same number of fetuses.

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 if the data were not normally distributed. The significance level was set at 0.05 for all tests.

SigmaStat (v 3.11.0 Systat Software Inc, Point Richmond, CA) was used to perform the above statistical analysis.

3.1.9 Sample Size

As the primary end point was IUGR secondary to rectal use of Proctofoam-HC®, the information available on smoking in pregnancy, which is a well known inducer of IUGR, was adopted. Exposure to tobacco in pregnancy has been shown to cause an average reduction of 200g in birth weight (185). Hence, to detect a clinically significant average decrease of 200g in birth weight with a power of 80% and alpha error of 5%, 200 women were required, each, in the treatment and control groups for a total of 400 subjects. During the study period, all eligible cases were recruited and the power of the available sample size is calculated in the Results section.

3.1.10 Ethical Considerations

The study protocol was approved by the research ethics board at the Hospital for Sick Children (Appendix I), North York General Hospital (Appendix K) and Sunnybrook Health Sciences Centre (Appendix K). 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.

3.2 Effectiveness of Proctofoam-HC® in Treating Hemorrhoids in Pregnancy

3.2.1 Study Design

This was a prospective, observational study.

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.

3.2.3 Study Instrument

Presently, there is no validated tool to measure effectiveness of any anti-hemorrhoidal treatment. To overcome this barrier, a new tool, the Hemorrhoids Effectiveness Measurement Scale (HEMS) (see appendix L) was developed. This scale is a short, 6 item questionnaire covering the six major symptoms of hemorrhoids: pain, itching, bleeding, swelling, discomfort and overall effect on well-being. Participants were asked to score each symptom on a scale from 0 to 10, where '0' indicates 'none' and '10' indicates 'maximum'. This questionnaire was completed twice, once prior to use of Proctofoam-HC® and once after treatment. Along with the completion of the second part, the participants were asked an additional single question regarding their total overall

improvement on Proctofoam-HC®, with '0' indicating 'no improvement' and '10' indicating 'maximum improvement'.

3.2.4 Study Procedure

Women who participated in the safety phase were asked to also participate in the effectiveness phase of the study. Subjects were asked questions pertaining to the effectiveness of the treatment twice, once during the baseline antenatal interview and again after using Proctofoam-HC® for a minimum of two weeks. At this point, women were asked to answer the questions to the best of their ability, whether the treatment was effective or not. If the subject was scheduled to deliver prior to two weeks, the second effectiveness questionnaire was completed during the routine postnatal interview.

3.2.5 Primary Outcome

Primary outcome measured was rectal pain. Pain is a common complaint in hemorrhoids sufferers. Any type of untreated pain can detrimentally affect all aspects of quality of life (186). Secondary outcomes include other hemorrhoidal symptoms such as pruritus ani, discomfort and anal swelling as well as improvement in well-being and global improvement scores.

3.2.6 Comparison Group

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

3.2.7 Data Analysis

Change in symptoms before and after treatment was analysed using a paired Student's T-test if the data were normally distributed or Wilcoxon Signed Rank test if the data were not normally distributed. The significance level 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.

3.2.8 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 (187). From a study employing a similar 11 point numerical scale (188), and with a power of 95% and an alpha error of 5%, 23 subjects would need to be recruited.

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.

3.3 Incidence of Hemorrhoids in Pregnancy

3.3.1 Research Design

The study was designed as a prospective, non-interventional questionnaire.

3.3.2 Subject Recruitment

Women in the third trimester of pregnancy (week 27 onwards) were recruited from the Obstetrics and Gynecology clinic at North York General Hospital in Toronto, Ontario, between November 2007 and August 2008.

3.3.3 Study Instrument

No questionnaire tool exists in literature to collect all necessary information on the incidence of hemorrhoids in pregnancy. For the purpose of this study, a survey was devised that included all pertinent information required, such as questions on medical and obstetric history, concomitant medication use and bowel habits. Finally, details on current or previous ano-rectal symptoms and treatment (where applicable) and diagnosis were also recorded (Appendix M). The instrument was not validated.

3.3.4 Study Procedure

The study was explained to every eligible patient seen at the Obstetrics and Gynaecology clinic by the research co-ordinator, Sabina Vohra. If the patient agreed to participate, verbal consent was obtained prior to enrolment (Appendix N). Once recruited, the participants were asked to complete the survey anonymously in a private room. The questionnaire was collected soon after completion. All results were calculated based on the self-questionnaire responses. Women were considered to have hemorrhoids if they answered 'yes' on the survey for having being diagnosed with an anal/rectal condition and following up with the word 'hemorrhoid' when asked for a description of

the anal/rectal condition. There was no proctologist/physician on board to diagnose or verify hemorrhoids and/or hemorrhoidal symptoms.

3.3.5 Outcome Measures

The primary outcome for this study was the rate of developing hemorrhoids in pregnancy. The secondary outcomes measured were the risk of developing hemorrhoids with a) multiple pregnancies and b) previous record of hemorrhoids.

3.3.6 Data Analysis

Data was analysed using descriptive statistics. Rate of hemorrhoids in pregnancy was calculated using the formula:

$$\frac{\text{[Number of women with current hemorrhoids who completed the study]}}{\text{[Total number of women who completed the survey]}}$$

Odds ratio and 95% confidence intervals were used to calculate risk for developing hemorrhoids with a) previous pregnancies and b) previous record of hemorrhoids.

3.3.7 Sample Size

The annual average number of pregnant women in Canada is approximately 446,297 (Statistics Canada from 2000-2005, 189). Using this estimate, and an average response distribution of 23% taken from the three incidence studies (20,25,34) along with

a confidence level of 95% and an alpha error of 5%, 272 women would need to be recruited to this study.

3.3.8 Ethical Considerations

The study was approved by the research ethics board at North York General Hospital. Completion of the survey was completely voluntary. Participants were assured the survey would be kept completely confidential and no personal identifiers were attached to the completed questionnaire. Participants were assured that refusal to participate in the study would not affect the quality of health care they receive at Motherisk or at North York General Hospital.

CHAPTER 4: RESULTS

4.1 Safety of Proctofoam-HC® in the Third Trimester of Pregnancy

In total, 132 women were recruited into the treatment group. Four women moved and/or changed contact, 1 woman left the country, 2 women rescinded their consent and 8 women decided to not use any treatment after enrolment due to personal reasons. Of the 132 women, 90 completed the study in the treatment group. Figure 2 depicts study recruitment and patient disposition.

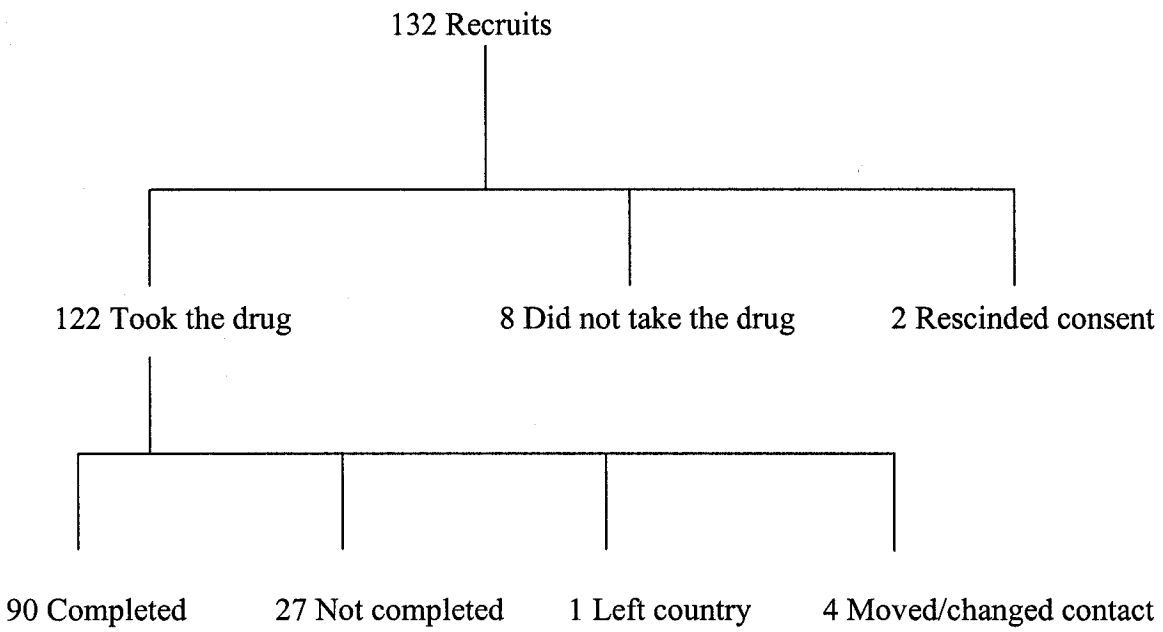

Figure 2: Flowchart of patient recruitment.

Altogether, 180 women completed the study, with 90 subjects each in the treatment and comparison group. Using the sample size of 180, effect size of 200 grams, standard deviation of 389 grams and alpha error of 5%, the power of the study was calculated to be 91.5%.

It was not possible to recruit one matching woman within two years of age. The woman in question was 47.6 years of age, and was matched with a woman aged 45. This slight difference is unlikely to skew the results of the study. Another exception was the inability to match a participant with a multifetal pregnancy (twins) with heavy tobacco exposure (a pack of cigarettes a day during the third trimester). This subject was matched to a comparison woman carrying twin pregnancy but without any exposure to tobacco in pregnancy.

Women treated with Proctofoam-HC® were compared to the matched, non-exposed group (table 1). The mean maternal age was similar in both groups (32.9 ± 4.5 vs. 32.9 ± 4.5, p=0.95). Seven (7.8%) and six (6.7%) women in the treatment and control groups were exposed to tobacco during pregnancy respectively (p=0.77). None of the women in either groups reported binge or heavy drinking, 5 (5.5%) and 8 (8.9%) consumed light quantities of alcohol in the treatment and control group respectively (p=0.56). The mean weight gain was similar in both groups as well (32.3 ± 10.7 vs. 32.3 ± 13.0, p=0.99).

Table 1: Maternal characteristics of patients in the treatment versus comparison group.

Characteristic	Treatment Group	Comparison Group	P-Value
Maternal Age			
N	90	90	P=0.95†
Mean (SD)	32.9 (4.5)	32.9 (4.5)	
Median (25-75% quartile)	32.9 (29.7-35.8)	33.0 (29.4 – 36.1)	
Gravida			
N	90	88	P=0.27‡
Median	2.0 (1.0-3.0)	2.0 (1.0-3.0)	
Parity			
N	90	89	P=0.74‡
Median	1.0 (0.0-1.0)	1.0 (0.0-1.0)	
Casual Alcohol Use			
Yes	5 (5.5%)	8 (8.9%)	P=0.56§
No	85 (94.4%)	82 (91.1%)	
Smoking			
Yes	7 (7.8%)	6 (6.7%)	P=0.77§
No	83 (9.2%)	84 (9.3%)	
Pregnancy weight gain (lb)			
N	85	59	P=0.99†
Mean (SD)	32.3 (10.7)	32.3 (13.0)	
Median (25-75% quartile)	32.4 (24.8 – 38.9)	30.0 (25.0-40.0)	

† Student's t-test ‡ Mann-Whitney Rank Sum test § Chi Square test

Table 2: Details on Proctofoam-HC® use in the treatment group.

	Mean (SD)	Median (25%-75% quartile)
Mean duration of treatment in pregnancy (weeks)	6.5 (5.0)	5.0 (3.0-8.8)
Frequency of treatment use per day	2.7 (0.8)	3.0 (2.0-3.0)
Total number of canisters used	2.2 (1.3)	2.0 (1.0 – 3.0)

Details on Proctofoam-HC® use in the treatment group are outlined in Table 2. The mean duration of treatment with Proctofoam-HC® was 6.5 weeks. Proctofoam-HC® was applied on average 2.7 times in a day in the treatment group. Just over 2 canisters of Proctofoam-HC®, on average, were used by each subject over the course of the treatment.

There were 93 live births in both groups, with 3 women delivering twins in each. The majority of the deliveries were vaginal, with 19.3% and 29.5% undergoing a caesarean section (p=0.15). The mean gestational age was not different between the groups (39.2 ± 1.4 vs. 39.3 ± 1.4, p = 0.57). There were 4 (4.3%) premature babies in the treatment group, compared with 5 (5.4%) in the control group (p=0.77) (Table 3).

Table 3: Pregnancy outcomes for patients exposed to Proctofoam-HC® versus comparison group.

Characteristic	Treatment Group	Comparison Group	P-Value
Method of Delivery			
Vaginal	75 (80.6%)	62 (70.4%)	P=0.15†
Caesarean section	18 (19.3%)	26 (29.5%)	
Gestational Age at Delivery (weeks)			
N	93	93	P=0.57‡
Mean (SD)	39.2 (1.4)	39.3 (1.4)	
Median (25-75% quartile)	39.4 (38.2 – 40.3)	40.0 (38.0 – 40.0)	
Prematurity			
Yes	4 (4.3%)	5 (5.4%)	P=0.73†
No	89 (95.7%)	88 (94.6%)	
Birth Weight (grams)			
N	93	93	P=0.71§
Mean (SD)	3483.1 (408.6)	3505.1 (389.0)	
Median (25-75% quartile)	3423.8 (3163.0 – 3730.0)	3464.8 (3246.0 – 3734.1)	
Low birth weight (<2500g)			
Yes	6 (6.4%)	4 (4.3%)	P=0.74†
No	87 (93.5%)	89 (95.7%)	
Malformation (minor)			
Yes	12	7	P=0.23†
No	82	86	
Fetal Distress			
Yes	14 (15%)	19 (20.4%)	P=0.34†
No	79 (84.9%)	74 (79.6%)	
Labour complications			
Yes	24	29	P=0.41†
No	66	61	
Neonatal health			
Yes	14	5	P=0.13†
No	79	64	

† Chi Square test ‡ Mann-Whitney Rank Sum test § Student's t-test

The primary outcome, birth weight, was corrected for gestational age. The corrected birth weight in the exposed group was not significantly different to that in the control (3483.1 ± 408.6 vs. 3505.1 ± 389.0, p=0.71). The rates of low birth weight babies (<2500g) in the two groups was compared. There were 6 (6.4%) and 4 (4.3%) low birth weight babies in the treatment and control group respectively. This difference was not statistically significant (p=0.74). Of the 6 low birth weight babies, 1 (17%) was exposed to prenatal tobacco, 1 (17%) was born off a twin fetus pregnancy and another 2 (33%) were born to a mother who was exposed to tobacco and carried a twin pregnancy.

No statistical differences in rates of major and minor malformations was found between the treatment and control groups (p=0.23). No major malformations were observed in either group. Table 4 lists the minor congenital malformations reported in the treatment group, along with details on their exposure to Proctofoam-HC®.

Table 4: Description of birth defect cases with duration of Proctofoam-HC® treatment.

Birth Defect Cases	Duration of treatment in pregnancy (gestation age in weeks)	Frequency of treatment use per day	Total number of canisters used
Syndactyly	34-35	3-4	2
Single umbilical artery	36-38	3-4	4
Syndactyly	36-40	1 -2	1
Ankyloglossia	37-39	4-5	3
Ankyloglossia, dacryostenosis	27-40	3	6
Talipes equinovarus	29-37	Once every 2 days	1
Small atrial septal defect, small umbilical hernia	26-38	2	3
Undescended testicle	32-40	3	3
Dacryostenosis	35-40	3	2
Coarctation of the aorta	30-36	4	3

There were no statistical differences in the rates of fetal distress and labour complications between the two groups (p=0.34, p=0.41). Some of the causes for fetal distress included momentary decreases in heart rate and umbilical cord wrapped around head. Labour complications included breech presentation, failure to progress and high blood pressure resulting in caesarean section and hemorrhaging. Furthermore, there were no significant differences in neonatal health post delivery between both groups (p=0.13). However, 25 controls were not asked details of neonatal health, and another 25 were not asked specific questions on the health of the newborn. Table 5 presents the breakdown of neonatal health problems observed in the treatment and comparison groups.

Table 5: List of neonatal health concerns in the treatment group exposed to Proctofoam-HC® and comparison group

Neonatal Health	Treatment (%)	Comparison (%)	P-value
Mild jaundice	8 (8.6%)	1 (1.1%)	P=0.08†
Heart murmur	2 (2.1%)	2 (2.1%)	P=1.00†
High white blood cell count	1 (1.1%)	0	P=1.00†
Conjunctivitis	1 (1.1%)	0	P=1.00†
Pulmonary aspiration	1 (1.1%)	0	P=1.00†
Colic	0	1 (1.1%)	P=0.42†
Tachypnea	0	1 (1.1%)	P=0.42†

† Fisher's Exact test

These results support the hypothesis that rectal (local) use of Proctofoam-HC® in the third trimester of pregnancy does not cause any decreases in birth weight in the infants. Further, no other adverse fetal events were observed following fetal exposure to Proctofoam-HC®.

4.2 Effectiveness of Proctofoam-HC® in Treating Hemorrhoids in Pregnancy

A total of 88 women completed the effectiveness study. No additional recruiting was necessary for this phase of the study, and since most participants in the safety study were eager to share and discuss their symptoms following treatment, the study co-ordinator elected to include all the safety study participants into the effectiveness phase. The general characteristics of the subjects were described in Table 1. At baseline, almost all of the participants complained of hemorrhoid swelling (99%) and anal discomfort (98%). Anal/rectal pain was noted by 90% of the women, while rectal bleeding was

present in half the participants (53%). Almost all of the women (97%) reported that hemorrhoids negatively affected their well-being.

Table 6: Details on the changes in ano-rectal scores following local treatment with Proctofoam-HC®.

Symptom	N	Before Treatment (SD)	After Treatment (SD)	Mean Decrease in Score (SD)	% decrease	Significance (p)
Pain	79	6.4 (2.4)	1.7 (2.1)	4.3 (2.6)	73.4	P<0.001*
Itching	66	4.9 (2.2)	1.3 (1.9)	3.3 (2.3)	73.5	P<0.001*
Swelling	87	6.8 (2.4)	2.7 (2.7)	3.8 (2.9)	60.3	P<0.001*
Bleeding	47	3.9 (3.0)	1.0 (1.4)	2.9 (2.7)	74.4	P<0.001*
Discomfort	86	6.9 (2.6)	1.6 (2.2)	5.1 (3.0)	76.8	P<0.001*
Well-being	85	6.5 (2.6)	1.7 (2.1)	4.5 (3.0)	73.8	P<0.001*

Scores rated on an 11 point numerical scale where '0' indicates 'no pain' and '10' indicates 'maximum pain'. * Wilcoxon Signed Rank test

Table 6 presents the change in symptoms with the use of Proctofoam-HC®. Significant decrease in the primary outcome, pain, was reported (73%, p<0.001). A 4.3 point decrease in pain score was reported. A decrease of a minimum of 2 points on an 11 point numerical pain scale is considered meaningful clinical improvement. Thus a greater than two fold clinical improvement in pain scores was found with the use of Proctofoam-HC®. Significant decreases in the secondary outcomes: itching (73%, p<0.001), swelling (60%, p<0.001), bleeding (74%, p<0.001) and discomfort (77%, p<0.001) was

also noted following treatment. Participants also reported significant improvement in their overall well-being (74%, $p<0.001$) (Figure 3). The mean global improvement with treatment was rated at 7.6 ± 2.3 (range: 0 – 10, median: 8). Only one participant reported no improvement with treatment (score of 0), and another 2 experienced minimal improvement (score of 1, and 2 respectively). Two-thirds of the participants (62%) rated improvement as '8' or greater and 29% (n=26) reported maximum improvement possible (score of 10).

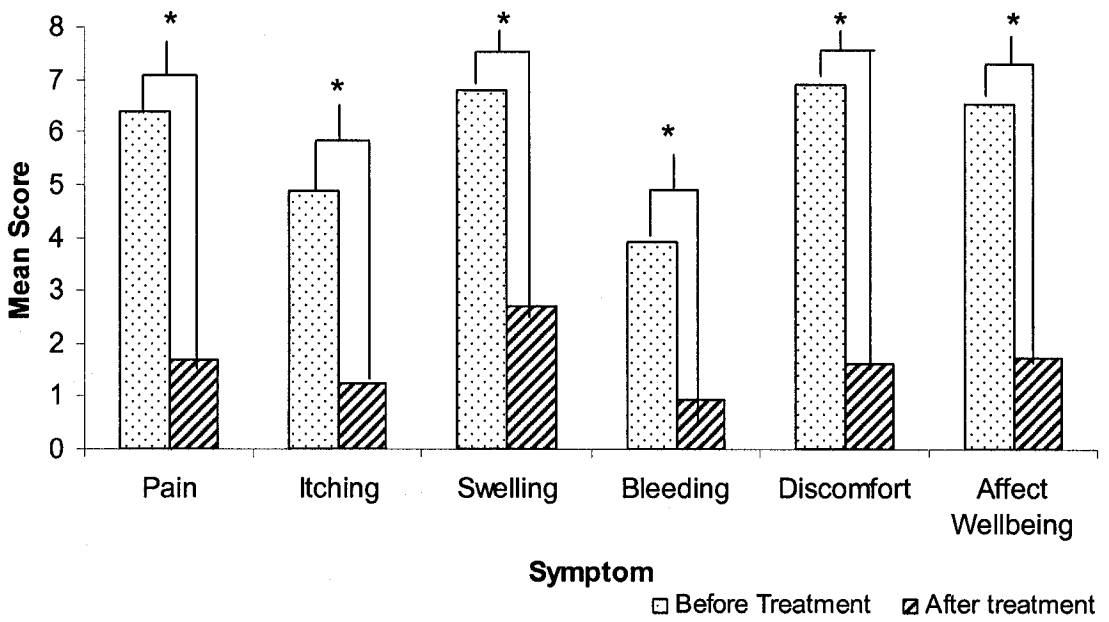

Figure 3: Graphical representation of the changes in symptom score, *p=<0.001

The above results agree with the hypothesis that treatment of hemorrhoids in pregnancy with topical Proctofoam-HC® alleviates all symptoms of hemorrhoids. Significant decreases in pain, swelling, pruritis, bleeding and discomfort were observed. Further, treatment with Proctofoam-HC® increased well-being and resulted in global improvement of symptoms.

4.3 Incidence of Developing Hemorrhoids in Pregnancy

One hundred and forty six women were recruited to participate in the questionnaire study. With the available sample size, the power of the study was calculated to be 77.9%. Margin of error was determined to be 6.83%. The mean gestational age of the women at the time of completion of the survey was 32.9 weeks. General characteristics of the participants are shown in Table 7.

Table 7: Demographic data of the 146 participants who completed the incidence survey.

Characteristics	Mean (+/- SD)	Median
Gestational Age (weeks)	32.9 (4.0)	33
Gravida	2.6 (1.7)	2
Parity	0.8 (0.9)	1
Spontaneous Abortions	0.6 (0.9)	0
Therapeutic Abortions	0.3 (0.7)	0

Of the 146 women, 15 (10.3%) suffered from rectal bleeding, while 23 (15.8%) experienced pruritus, and 27 (18.5%) complained of anal pain. Constipation was reported in 32 (21.9%) cases and 30 women (20.9%) reported difficulties in passing stool (Table 8).

Table 8: Details on ano-rectal conditions of the 146 participants in the incidence study

N=146	Hemorrhoids	Bleeding	Difficulty passing stool	Itching	Pain
Yes	12	15	31	23	27
Possible	10	0	0	0	0
Total	22 (15.1%)	15 (10.3%)	31 (20.9%)	23 (15.8%)	27 (18.5%)

One third of the women reported suffering from at least one of the above ano-rectal symptom. 16% and 9% of women suffered from at least two and three ano-rectal symptoms respectively, while 3.4% suffered from all four symptoms (Table 9).

Table 9: Current ano-rectal symptoms of the 146 participants in the incidence study.

Ano-rectal symptoms	Number
At least one symptom	48 (33%)
At least two symptoms	16 (20%)
At least three symptoms	9 (9.6%)
All four symptoms	5 (3.4%)

Of the 146 participants, 15.1% reported on hemorrhoids. Out of those, 12 were formally diagnosed and another 10 believed they had hemorrhoids without formal diagnosis (Table 8). Thirty-four women suffered from hemorrhoids in the past, of which 15 were in previous pregnancies and 19 at anytime in their adult life (Table 10). Two-thirds of the above women suffered from hemorrhoids again in the current pregnancy. There was a significant increased risk to develop hemorrhoids in the current pregnancy with a history of hemorrhoids [OR=9.1, 95% CI= 3.4-24.5] (Table 11).

Table 10: History of hemorrhoids of the 146 participants in the incidence study

N=146	Yes (%)
History of hemorrhoids in pregnancy	15 (10.3)
History of hemorrhoids anytime	19 (13.0)
Total history	34 (23.3)

Table 11: Present and previous record of hemorrhoids in the study population (n=146).

	Hemorrhoids during last pregnancy	No hemorrhoids during last pregnancy	Total
Hemorrhoids this pregnancy	14 (9.6%)	8 (5.5%)	22 (15.1%)
No hemorrhoids this pregnancy	20 (13.7%)	104 (71.2%)	124 (84.9%)
Totals	34 (23.3%)	112 (76.7%)	146 (100%)

Seventeen out of 78 women (22%) with more than one full term pregnancy, suffered from hemorrhoids. Conversely, only 5 out of 68 women (7.3%) suffered from hemorrhoids in their first pregnancy (Table 12). Essentially, 17 women (77%) with hemorrhoids in the subject sample were carrying their second or more pregnancy. Subsequently, women experiencing their second pregnancy or more were found to have a significantly increased risk for developing hemorrhoids [OR=3.5, 95% CI=1.2-10.1].

Table 12: Hemorrhoids with gravida in the incidence study participants.

	Presence of hemorrhoids	Absence of hemorrhoids	Total
>1 term pregnancy	17 (11.6%)	61 (41.8%)	78 (53.4%)
< 1 term pregnancy	5 (3.4%)	63 (43.1%)	68 (46.6%)
Totals	22 (15.1%)	124 (84.9%)	146 (100%)

These results appear to support the hypothesis that there exists an increased risk for developing hemorrhoids in pregnancies with a history of hemorrhoids. Additionally, the above results agree with the hypothesis that having more than one pregnancy in the past is a risk factor for developing hemorrhoids in subsequent pregnancies. Finally, the results report a 15.1% rate of hemorrhoids in the third trimester of pregnancy.

CHAPTER 5: DISCUSSION

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

This pilot was the primary objective of my thesis. No previous study has ever studied the fetal safety of any topically used anti-hemorrhoidal preparations in pregnancy. Altogether, 180 women were recruited to this phase of the study, with 90 each in the treatment and comparison group. Post hoc analysis on the power of the study with this sample size was determined to be 91.5%. This was surprising, as the initial necessary sample size to achieve 80% power was determined to be 400 subjects. Standard deviation used to calculate post hoc statistical power was 389 grams (which was obtained from the comparison group in this study). Using the above value, 122 subjects would need to be recruited in order to detect a 200 gram decrease in birth weight with a power of 80% and an alpha error of 5%. Thus, it would appear that with the above measurements of standard deviation, the sample size achieved thus far in the study was more than adequate to detect a 200 gram decrease in birth weight. Further, since majority of the subjects who took the medication completed the study, recall bias in the study was very minimal.

Upon comparing the treatment and comparison group, no significant differences were apparent in any of the endpoints analysed. All pregnancies lead to a live birth in both groups (n=93) and the primary endpoint, IUGR, was identical.

The mean gestational age at delivery was not different between the two groups. There were 11 and 7 malformations in the exposed and control group respectively. No major malformations were reported in either group. However, at 27 weeks gestation, the fetus is considered to be completely developed (190), and since treatment with Proctofoam-HC® was limited to the third trimester of pregnancy, one cannot expect to see any malformations associated with its use.

There was no different in fetal distress or labour complications between the exposed and non-exposed groups. There were no statistical differences in neonatal health between the two groups. In total, only 4 cases of neonatal health problems post delivery were reported in the control group, compared to the 14 in the treatment group. This can be attributed to the incomplete documentation of neonatal health in the comparison group. Majority of the controls were not asked specific questions on the child's health, and the responses were not corroborated with a pediatrician. Follow-up forms for the exposed group were more detailed, and asked specific questions regarding the health of the newborn. Further, results were verified by the child's neonatal assessment forms, which would catch any details left out in the verbal interview with the subject. As such, in this study, 8 cases of neonatal jaundice in the exposed group were reported versus an unrealistic single case in the comparison group. Jaundice in neonates is fairly common, with an incidence of 6.1% and up to 32.7% in certain populations (191 -193). The numbers observed in the treatment group are consistent with that reported in literature. Based on the above information, it seems apparent that neonatal health concerns were underreported in the comparison group. Extrapolating that, it is not believed that the use of Proctofoam-HC® in late pregnancy increases the risk of neonatal health problems.

After correcting for gestational age, birth weight in the exposed group was similar to the comparison group. There were similar percentages of low birth weight babies in the two groups, showing similar proportion, and in most of them an objective etiology was identified (multiple birth, smoking). Both, multiple pregnancies, as well as tobacco exposure in pregnancy, has been associated with low birth weight in babies (194, 195). In essence, rectal use of Proctofoam-HC® in pregnancy does not appear to produce any changes in birth weight. The birth weight in the treatment group was also consistent with the expected birth weight of full term babies in Canada, which is estimated to be 3394 grams (Statistics Canada, years 2000-2007) (196). Based on the preliminary results, the minimal quantity of hydrocortisone absorbed rectally is not expected to induce any significant detrimental effects on birth weight.

One study by Schatz (128) found a significant association between corticosteroid (oral and topical) exposure and low birth weight (6% in the treatment group vs. 3.3% in the control group) in women with asthma. However, when the authors further analysed the risk by regrouping exposure to oral and topical, no significant decrease in birth weight was observed in the subgroup of women exposed to topical corticosteroids. Similar results were observed by Mygind (152), who noted no differences in birth weight with topical use of corticosteroids. Studies in the literature that observed a decrease in birth weight used higher potency corticosteroids and all exposures were to repeated oral doses (40-43). One should also take into consideration that the decrease in birth weight noted in most of these studies was very small. Banks quoted a decrease in just 39g (130), while Thorp noted a decrease of 63g (131) in the subjects receiving antenatal corticosteroids. To observe such small decreases in birth weight, a sample size of 2500

participants would be required in each group. Obtaining such a large group would not be feasible, considering the issues of recruitment. Further, the clinical significance of such small reductions in birth weight is questionable.

While this study adds to the limited literature on this topic, there are issues that warrant further investigation. The pilot sample size, although providing adequate power, is smaller than what we initially set out to achieve. Motherisk plans to continue the study and obtain the predetermined sample size that will have a much higher power to detect even smaller decreases in birth weight. That said, the fact that the first recruited half does not show any differences in birth weight strongly suggests the full cohort will not document any difference between the Proctofoam-HC® treated and comparison group. As a potential challenge, the percentage of women who applied Proctofoam-HC® internally, and moreover, at what section in the anal canal was unknown. It is possible that majority of the women used the medication externally or in the upper rectal region only. As addressed previously, there is a substantial difference in the absorption of any ingredient if administered in the lower rectal region versus the upper rectal region; however the difference in absorption has not been quantified as yet. If none of the subjects used the drug in the lower rectal region, these results might not be a good indicator of the complete fetal safety of the medication. There is also much need for pharmacokinetic studies to examine what percentage of hydrocortisone enters the systemic circulation following internal rectal application in different sections of the anal canal. Further, little is known on the long-term neurodevelopment outcomes of *in utero* hydrocortisone exposure, thus to establish complete safety of Proctofoam-HC® follow-up studies for at least the next 3 years of life should be undertaken.

5.2 Effectiveness of Proctofoam-HC® in Treating Hemorrhoids in Pregnancy

To detect a clinically significant decrease in the primary outcome, pain, 23 patients were required. However, during antenatal and postnatal assessments, majority of the patients were eager to share their current hemorrhoidal symptoms, as well as any improvement or worsening of symptoms. Administering the HEMS took no more than 3 minutes. Due to this, the study co-ordinator elected to include every subject from the study phase to the effectiveness phase, for a total recruitment of 88 subjects. This additional sample size, though unnecessary, improved the power of the study and decreased the margin of errors.

To date, there is no validated tool to measure the effectiveness of any anti-hemorrhoidal treatment. Several efficacy studies on oral and local preparations for the treatment of symptomatic hemorrhoids used a 4 point scoring scale (197-200), 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 worse than before (201-203) and a few used a combination of the two (204,205). However, neither of these two scales was felt to be sufficiently detailed to measure the continuity of given symptoms quantitatively and qualitatively. Most of these scales did not include all major symptoms of hemorrhoidal disease either. The scale used in this study (HEMS) was an 11 point scale, which was thought to be better suited to detect the smallest changes in symptoms. This scale included all major symptoms of hemorrhoids: pain, swelling, bleeding, itching and discomfort. To better understand changes in the patient's

quality of life, the scale also included questions on any changes in well-being. Finally, global improvement scores were included in the scale questionnaire. Being detailed, the HEMS might be more likely to detect effectiveness of treatment where there is one. However, this scale is not yet fully validated, and this process is under way.

In the present study, local treatment with Proctofoam-HC® was found to be very effective in reducing all symptoms related to hemorrhoids. A significant decrease in the primary outcome, pain, was noted. From previous studies, a decrease in 2 points from baseline on the 11-point pain intensity numerical rating scale is considered to be clinically significant (187). With the above results, the decrease in pain was twice as much, falling 4.3 points from baseline. One study found that patients only considered a 50% improvement in pain as a 'treatment success' (206). Thus, a 73.4% decrease in pain, as observed in this study, was highly successful in treating pregnancy hemorrhoids in the subjects.

A significant decrease in itching, swelling, discomfort and bleeding was also noted post treatment. The magnitude of effectiveness was substantial, with 73-77% decrease in symptoms of itching, bleeding and discomfort. Swelling decreased by 60%, which, while considerable, was not as high as the rest of the parameters. This can be accounted by the well-known fact that hemorrhoids, defined as the swelling of veins, will not generally completely resolve until post delivery when the weight of the fetus is lifted and hormone levels are back to non-pregnancy levels. In fact, there was a marked decrease in swelling, given the nature of hemorrhoids in pregnancy. Such an effect size is quite reassuring, especially given that the effectiveness of any commonly used topical anti-hemorrhoidal preparations have not been studied in pregnancy. Subjects also

reported a 74% increase in overall well-being after treatment with Proctofoam-HC®. The primary basis of finding effective antihemorrhoidal treatment in pregnancy is to improve well-being, and thus quality of life, which, is believed to have been demonstrated by these results.

At the end of the questionnaire, women were asked a sole question regarding the magnitude of improvement with the treatment. The mean response by the participants to that query was 7.6 ± 2.3 (range 0 – 10), with a median response of 8. Previous epidemiological studies have reported that around 10-20% of patients have persistent symptomatic hemorrhoids; requiring surgery (207). Based on that, it was expected that 9 to 18 women in the study sample may have persistent hemorrhoids that would not heal. The numbers observed in the study appeared to be on the lower end of that spectrum, which is reassuring.

One of the limitations of this study was the lack of a placebo group. Since hemorrhoids in pregnancy are chronic in nature, the chance of spontaneous improvement appears to be slim; suggesting that the effect size that observed in this study was probably the true measure of effectiveness, devoid of a significant placebo effect. Nonetheless, it is important to estimate the outcome if there was, indeed, a placebo effect. To that extent, literature on interventional antihemorrhoidal trials with a placebo group was systemically reviewed. A total of 11 studies were available (197-205,208,209). Out of those, only 2 included pregnant women (202,205). The duration of the 9 non-pregnant studies extended from at least 7 days up to two months. It is well established that adult-life hemorrhoids

are self-limiting and can heal without medication (210). In one study (199), mean healing time without any treatment was 5.6 and 6.5 days for anal bleeding and pain, respectively. Other studies have shown 7 to 24 days for remission of severely thrombosed hemorrhoids (4,16). Given the possibility of spontaneous remission prior to the completion of the study, it is quite possible that the above studies in non-pregnant patients experienced a high placebo effect. Secondly, one does not expect hemorrhoids to resolve spontaneously without treatment in pregnancy, hence a placebo effect, if any, would not be similar to those observed in adult-life hemorrhoids.

Hence, to target the special population in this study, only the two remaining trials focusing on pregnant women were included. Both studies randomized pregnant women to receive oral rutosides and observed women twice, at 2 weeks and again at 4 weeks. The first study (205) 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 (4, 16). 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 grade 3 and possibly a few grade 4, hemorrhoids. Hence, the first placebo study in pregnancy did not estimate the placebo effect appropriately for the subject population in the effectiveness study. The second study, by Wijayanegara and colleagues (202), observed a 12% and 14% improvement of their placebo-treated patients at week 2 and week 4 respectively. Most of the women included in the study had grade 2 or 3 hemorrhoids. Extrapolating

this observed placebo effect, the results of the effectiveness study were reanalysed 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. Upon analysis with the Wilcoxon Signed Rank Test, a highly significant decrease in all hemorrhoidal symptoms (p=<0.001) was still observed (Figure 4).

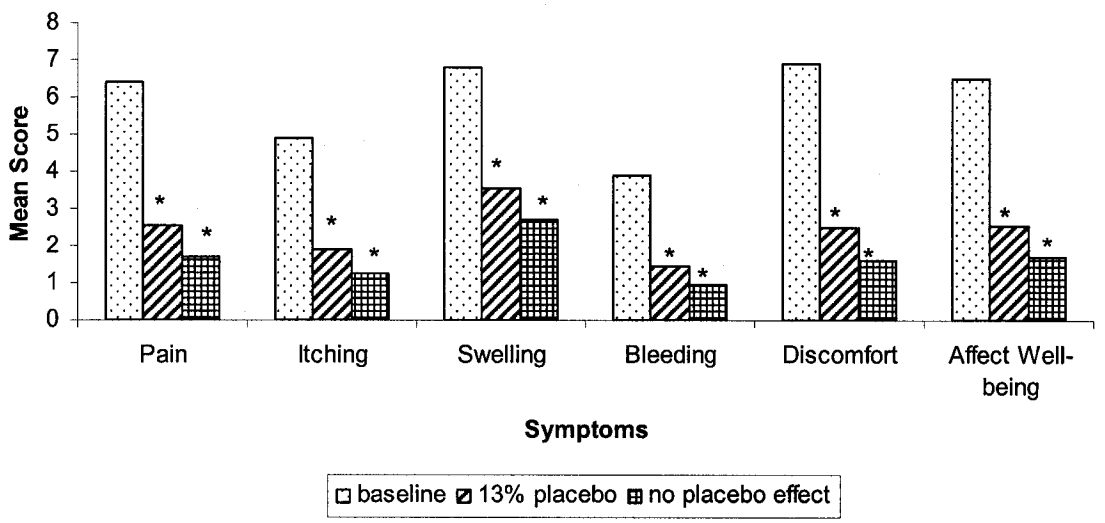

Figure 4: Graphic tabulation of the change in symptom score upon treatment with Proctofoam-HC®, with and without a suggested 13% placebo effect. *p=<0.001

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. Demonstrating the effectiveness of a commonly used anti-hemorrhoidal preparation to treat piles in pregnancy will serve to aid thousands of pregnant women world-wide.

5.3 Incidence of Developing Hemorrhoids in Pregnancy

All 146 women who were approached to complete the questionnaire did so willingly. It was surprising to observe such enthusiasm towards participation in the study exhibited by the pregnant women. Since all third trimester women who visited the clinic were captured, the 100% response helped to avoid any potential systematic bias in the survey. Further, being a general community-based obstetric practice, this absolute participation allows for generalization of the data. The recruitment for this study did not reach the target sample size. Post-hoc analysis determined the power of the study at 77.9%. Although the results did not reach necessary power, the margin of error was only slightly increased. Further recruiting would be necessary to achieve adequate power.

This study was one of the first on Canadian women, with an estimated incidence of 15.1% for hemorrhoids in pregnancy. However, in this estimate, women with "possible" hemorrhoids were included as well because of two reasons: they complained of protrusions (prolapse) or have had hemorrhoids diagnosed in the past and hence were able to relate current symptoms to the previous diagnosis. The incidence of hemorrhoids could potentially be much higher if the women complaining of pruritus and anal pain have also had grade 1 or 2 internal hemorrhoids, which are typically presented with these ano-rectal symptoms. The lack of an on-site proctologist was a definite limitation of this study, as it would have confirmed the "possible" cases of hemorrhoids, as well as any additional cases missed due to vague or mild symptoms.

The incidence recorded by this study was much lower than that published by Simmons (25), who noted that 26 (38%) women out of 68 had problems with hemorrhoids. However, Simmons distributed a postnatal questionnaire with only a single question asking women if they had any trouble with piles (hemorrhoids) in pregnancy or labour. Firstly, labour in itself can instigate development of hemorrhoids, so a good percentage of the women might have developed piles post delivery, which would not be a good indicator of the incidence of hemorrhoids in pregnancy. Secondly, the authors did not include scoring of objective ano-rectal symptoms, thus it is quite possible that women might mistakenly assume that any single ano-rectal complaint might be piles, when in fact, it could just as well be unremarkable pruritus ani. Pradel and colleagues (34) published a 24% incidence of hemorrhoids in the antenatal period. However, over 35% of the study population was lost to follow-up, which could grossly overestimate the true incidence. Additionally, Canadian women might also differ form their counterparts around the world in terms of lifestyle, diet, exercise and genetics, all of which can contribute to the development of hemorrhoids (as explained earlier). Further studies analysing individual risk factors would be necessary to distinguish the incidence of hemorrhoids in Canadian women from those around the world.

This study was one of the first of its kind to assess previous record of hemorrhoids as a risk factor to develop hemorrhoids in pregnancy. A significantly higher risk was found for developing hemorrhoids in current pregnancy with a medical history of hemorrhoids. Almost 64% of the women with hemorrhoids in this pregnancy had suffered from hemorrhoids in the past. This further strengthens the claim that

hemorrhoids are partially caused due to the deterioration of supporting connective tissue (15). Weakening the anchoring system, due to recurrent hemorrhoids, would explain why a woman would have a higher tendency to have repeated episodes of hemorrhoidal disease. These results most certainly warrant further investigation of possible structural damage behind the etiology of hemorrhoidal disease.

These results also concur with previous literature that suggests carrying more than one pregnancy to term might increase the risk of developing hemorrhoids in subsequent pregnancies (31,35). Almost 22% of women with 1 or more full term pregnancies suffered from hemorrhoids. Conversely, just over 7% of women with their first pregnancy suffered from hemorrhoids. Seventeen of the 22 women (77%) with hemorrhoids in the current pregnancy had more than one full term baby in the past. These values are consistent with those observed by two other studies, one reporting 70% (31) and the second reporting 85% (35) of their pregnant population with hemorrhoids were carrying their second or third pregnancy. It would be interesting to analyse what percentage of the women in the above studies also suffered from hemorrhoids in the past, and determine if the two (previous record of hemorrhoids and greater than one term pregnancy) together might act synergistically to increase the risk of developing hemorrhoids in pregnancy.

An advantage in this study was the anonymity of the questionnaires. Hemorrhoids can pose an embarrassment to some women; hence individuals would be less likely to discuss such issues with a health care professional. Providing anonymity can overcome

the embarrassment that is typically associated with most ano-rectal conditions. As outlined by the above results, a large proportion of women suffered from ano-rectal nuisances. Almost 19% of women were affected by anal pain, and another 10% with rectal bleeding. Especially, with one third of the study sample suffering from at least one ano-rectal symptom, it was surprising that very few brought them to the attention of the attending obstetric-gynaecologist. This further demonstrates the stigma surrounding private parts, especially the anus, which is often represented as 'dirty' and 'shameful' (211). Raising awareness in this area is imperative, considering the vast number of women who may be suffering silently through their pregnancy from conditions that may be easily, and safely, treatable.

5.4 Overall Study Limitations

Some of the limitations this study encountered are as follows:

- Results of the effectiveness study were limited by the unverified validity of the study instrument (HEMS).
- Extent of the effectiveness was hindered by the lack of a placebo group.
- Conclusions on incidence of hemorrhoids in pregnancy were temporarily limited by the sample size
- Unavailability of an on-site proctologist to diagnose possible and potential hemorrhoids.

CHAPTER 6: CONCLUSIONS

6.1 Conclusions and Significance

Hemorrhoids are a common concern in pregnancy, affecting up to 15% of Canadian women. Majority of women suffer from one or more ano-rectal symptoms in the third trimester. Exposure to Proctofoam-HC® does not appear to cause any adverse fetal effects. Further, Proctofoam-HC® appears to be highly effective in treating all ano-rectal symptoms of hemorrhoidal disease in pregnancy. Proctofoam-HC® might, indeed, provide a feasible option that enables women to have a more comfortable pregnancy, thereby increasing their quality of life.

This is the first study to examine fetal safety of any local anti-hemorrhoidal preparation. Raising awareness in this area of health care will help women overcome stigma and seek medical advice. By demonstrating its safety and effectiveness, women need not suffer silently through this common ailment. Beyond the importance of the results with respect to Proctofoam-HC®, this study sets a new standard for testing fetal safety of anti-hemorrhoidals, a step never taken before. The same standard should be expected from any other commonly used anti-hemorrhoidal medication.

6.2 Future Directions

The pilot safety study will continue until the target sample size is achieved. With a larger than required sample size, very small differences in birth weight can be detected that may not have been apparent at this time. Completion of missing information of the comparison group should be undertaken, and specific questions on the presence of minor neonatal health concerns should be addressed and noted where possible. A further addition to the safety study 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. Further, validation of the HEMS scale would not only aid in confirming the results in this study, but would be beneficial to any other study assessing efficacy of oral, topical and surgical anti-hemorrhoidal treatments. Finally, recruitment of the survey study should continue to achieve adequate numbers to determine an accurate estimate of the incidence of hemorrhoids in pregnancy.

6.3 Conflict of Interest

The Motherisk Program is supported by grants from Duchesnay Inc., producer of Proctofoam-HC®. To eliminate any potential bias, Duchesnay Inc is kept at an arm's length from any research 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 Sabina Vohra, the study coordinator at the Motherisk Program. All data collected is property of The Motherisk Program. The Motherisk Program is solely responsible for any current and future publications using the acquired data.

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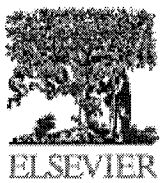

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Appendix B: Literature review on the safety of commonly used anti-hemorrhoidal preparations.

The safety of commonly used anti-hemorrhoidal preparations in pregnancy

Vohra S[1,2], Koren G[1,2,3]
[1]Motherisk Program, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Canada, [2]Department of Pharmaceutical Sciences, University of Toronto, Toronto, Canada, [3]Ivery 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.

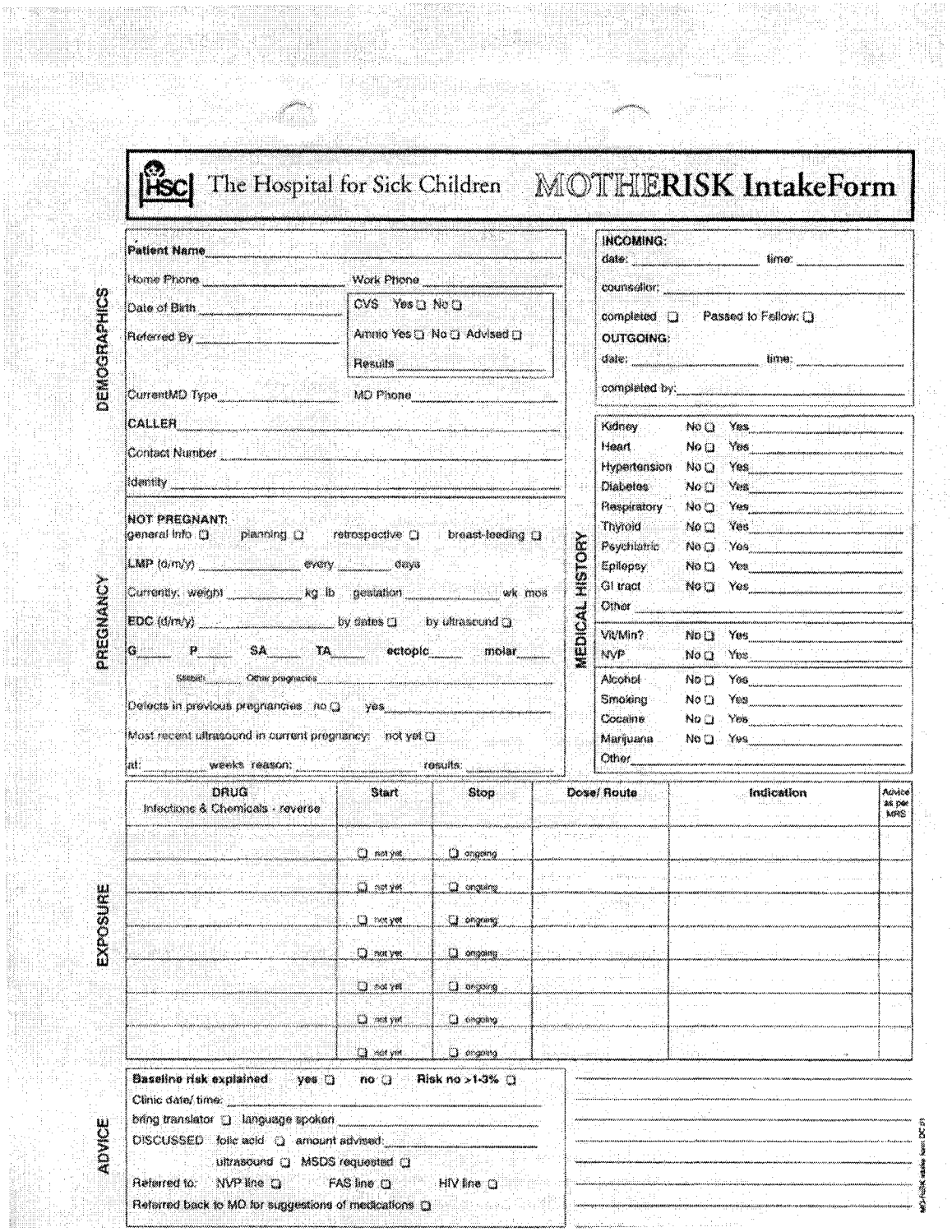
Conclusions: Hemorrhoids are a common concern during pregnancy and can potentially affect quality of life. No evaluation of the maternal and fetal safety of currently used local antihemorrhoidal treatments is available. It is critical to study the safety and efficacy of antihemorrhoidal treatments used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

Keywords: *hemorrhoids, pregnancy*

Appendix C: Ingredients present in the 8 most commonly used local antihemorrhoidal preparations in pregnancy by Motherisk callers

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

Appendix D: Antenatal questionnaire used in the safety study.



The Hospital for Sick Children MOTHERISK IntakeForm

DEMOGRAPHICS

Patient Name
Home Phone Work Phone
Date of Birth
Referred By
CVS Yes ☐ No ☐
Amnio Yes ☐ No ☐ Advised ☐
Results
CurrentMD Type MD Phone
CALLER
Contact Number
Identity

INCOMING:
date: time:
counsellor:
completed ☐ Passed to Fellow: ☐
OUTGOING:
date: time:
completed by:

PREGNANCY

NOT PREGNANT:
general info ☐ planning ☐ retrospective ☐ breast-feeding ☐
LMP (d/m/y) every days
Currently: weight kg lb gestation wk mos
EDC (d/m/y) by dates ☐ by ultrasound ☐
G P SA TA ectopic molar
Stillbirth Other pregnancies
Defects in previous pregnancies no ☐ yes
Most recent ultrasound in current pregnancy: not yet ☐
at: weeks reason: results:

MEDICAL HISTORY

Kidney	No ☐	Yes
Heart	No ☐	Yes
Hypertension	No ☐	Yes
Diabetes	No ☐	Yes
Respiratory	No ☐	Yes
Thyroid	No ☐	Yes
Psychiatric	No ☐	Yes
Epilepsy	No ☐	Yes
GI tract	No ☐	Yes
Other		
Vit/Min?	No ☐	Yes
NVP	No ☐	Yes
Alcohol	No ☐	Yes
Smoking	No ☐	Yes
Cocaine	No ☐	Yes
Marijuana	No ☐	Yes
Other		

EXPOSURE

DRUG Infections & Chemicals - reverse	Start	Stop	Dose/ Route	Indication	Advice as per MRS
	☐ not yet	☐ ongoing			
	☐ not yet	☐ ongoing			
	☐ not yet	☐ ongoing			
	☐ not yet	☐ ongoing			
	☐ not yet	☐ ongoing			
	☐ not yet	☐ ongoing			
	☐ not yet	☐ ongoing			

ADVICE

Baseline risk explained yes ☐ no ☐ Risk no >1-3% ☐
Clinic date/ time:
bring translator ☐ language spoken
DISCUSSED folic acid ☐ amount advised:
ultrasound ☐ MSDS requested ☐
Referred to: NVP line ☐ FAS line ☐ HIV line ☐
Referred back to MO for suggestions of medications ☐

MOTHERISK

TREATING THE MOTHER - PROTECTING THE UNBORN

Antenatal Questionnaire

our date of birth: _____
/hat is the current gestational age? ____ (weeks) ____ (days), or _____ (months).
/hen was the **first day** of your last menstrual period? _____
/hat is your Due date? _____

lease mark

THNICITY	LIVING ARRANGEMENTS	EDUCATION	OCCUPATION
Caucasian	☐Single	☐ Public school	☐ Unemployed
Black	☐Married	☐ High school	☐ Homemaker
Native American	☐ Living with partner	☐ College	☐ Student
South Asian	☐ Separated	☐ University	☐ Employed ☐ Full ☐ Part ☐
Hispanic	☐ Divorced	☐ Post-graduate	☐ Self-employed ☐ FT ☐ PT
Oriental	☐ Widowed		
Other _____			

/hat is your job? _____

REGNANCY HISTORY:

low many times (including this one) have you been pregnant? _____
low many children do you have? _____
/hat was the mode of delivery in the past pregnancies?
- section (how many)?_____
lormal vaginal delivery? How many? _____
id you ever have a miscarriage, and how many times? _____
id you ever have an abortion, and how many times? _____
low many children live with you at home? _____

Did you ever suffer any of the following medical conditions:

☐ Heart ☐ Liver ☐ Kidney	☐ Infectious Diseases (specify) _____	☐ Diabetes
☐Hypothyroid ☐Hyperthyroid	☐Hypertension ☐Hypotension	☐ Anemia
☐Crohn's ☐Ulcerative colitis ☐Peptic/duodenal ulcer ☐ Reflux ☐Irritable colon ☐ Irritable bowel ☐Celiac Disease ☐ Other_____	☐ Previous surgery/ hospitalizations	☐ Depression ☐Bipolar ☐ Anxiety ☐ 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 to you have bowel movements? _____/day_____/ week Any recent change in bowel habits?_____
Is there any blood? _____
Any difficulty passing stool?_____
Any anal itching? _____
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 E: Postnatal questionnaire used in the safety study.

MOTHERISK

TREATING THE MOTHER – PROTECTING THE UNBORN

POSTNATAL QUESTIONNAIRE: The Safety of Proctofoam-HC® In the Third Trimester of Pregnancy	FOLLOW-UP Date:

PREGNANCY OUTCOME:

Due Date:	Tel: (H) (W) Address:	Live Birth ☐ Miscarriage (<20wks) ☐ Fetal Death (>=20wks) ☐ Elective Abortion ☐

If miscarriage, fetal death or elective abortion:

At 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

Amniotic Fluid Alter'n	Y / N	Infectious Diseases	Y / N	
Cardiovascular	Y / N	Gastro-Intestinal	Y / N	
Central Nervous Syst	Y / N	Genito-Intestinal	Y / N	
Dermatology	Y / N	Hematology	Y / N	
Diabetes	Y / N	Musculo-Skeletal	Y / N	
Ears,Eyes,Nose,Throat	Y / N	IUGR/Growth Problems	Y / N	
Endocrine	Y / N	Respiratory	Y / N	
Psychiatric Disorders	Y / N			

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

THERAPY	INDICATION	START	STOP	DOSE/FREQ	SIDE EFFECTS

USE

Please record use of following:

	START	STOP	DOSE/ FREQ	DECREASE
ALCOHOL				
TOBACCO				
COCAINE				
MARIJUANA				

VITAMIN USE

Please record vitamin use

VITAMIN	START	STOP	DOSE/ FREQ	SIDE EFFECTS

TESTS DURING PREGNANCY

Triple screening	☐No ☐Yes	wks	Reason:	Result:
Amniocentesis	☐No ☐Yes	wks	Reason:	Result:
Glucose Tolerance Test	☐No ☐Yes	wks	Reason:	Result:
Ultrasound	☐No ☐Yes	wks	Reason:	Result:
		wks	Reason:	Result:
Chorionic villus sampling	☐No ☐Yes	wks	Reason:	Result:
Other	☐No ☐Yes	wks	Reason:	Result:

DELIVERY INFORMATION

MATERNAL

Pre-pregnancy weight: _____lb _____kg

Weight at delivery: _____lb _____kg

Total lenght of labour: _____hours

Premature Rupture of Membranes?

☐No ☐Yes: _____hours before onset of labour

Method: ☐vaginal, vertex ☐C.S emergency
☐vaginal, breech ☐C.S scheduled
☐C.S repeat

Assistance: ☐vacuum ☐forceps

Hemorrhage? ☐No ☐Yes

Transfusion? ☐No ☐Yes

Pain relief? Anaesthetics ☐No ☐Yes
Epidural ☐No ☐Yes
Analgesic ☐No ☐Yes
Specify: _____

NEONATAL

Hospital City:

Gestational age at birth: _____ weeks _____days

1oz=28.4 grams

Birth Weight: _____ *lb* _____ *oz (* _____ *grams)*

Apgar scores: 1 minute_____ 5 minute_____

Appearance Pulse Grimace Activity Respiration

Fetal Monitoring: ☐No ☐Yes external [ ] internal [ ]

Explain:

Fetal distress: ☐No ☐Yes

Explain:

Meconium: ☐No ☐Yes

Explain:

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: _____

Refused 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			
	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 conditions overall? _____

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 F: Oral consent form to participate in the safety study.

SickKids

MOTHERISK
TREATING THE MOTHER – PROTECTING THE UNBORN

Introduction

"Hi, I am Sabina Vohra, 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.

_____

Sabina Vohra, HBSc (Study co-ordinator)

_____

Dr. Gideon Koren, MD (Study Principal Investigator)

Appendix G: Information letter mailed to the participant.

MOTHERISK

TREATING THE MOTHER –
PROTECTING THE UNBORN

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, Sabina Vohra, at (416)813-7283 (mailbox 5) or e-mail at: sabina.vohra@utoronto.ca

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

Sincerely,

Sabina Vohra
Motherisk Program
Division of Clinical Pharmacology and Toxicology
Hospital for Sick Children
(416) 813-7283; mailbox 5
sabina.vohra@utoronto.ca

Appendix H: Letter sent to the child's primary care physician.

MOTHERISK

sent by fax to:

Antenatal Clinic for Drug/ Chemical Risk Counselling

The Division of Clinical Pharmacology

Direct line: 416-813-6780
Fax: 416-813-7562
Email: momrisk@sickkids.ca

Director of Motherisk
Gideon Koren, MD, FACMT, FRCPC
The Ivey Chair in Molecular Toxicology,
The University of Western Ontario

Monica Bologa, MD, ABCP
Teratogen Information Specialist

Lee Dupuis, MSc Pharm
Drug Information Centre

Adrienne Einarson, RN
Assistant Director

Thomas R. Einarson, PhD
Faculty of Pharmacy

Dan Farine, MD, FRCPC
Mount Sinai Hospital

Shital Ghandi, MD
Mount Sinai Hospital

Director; Division of Clinical Pharmacology
Shinya Ito, MD, ABCP

Bhushan Kapur, PhD
Analytical Toxicology

Julia Klein, MSc
Director, Fetal Toxicology Lab

Myla Moretti, MSc
Assistant Director

Associate Director
Irena Nulman, MD
Alcohol & Drugs in Pregnancy

Joanne Rovet, PhD
Department of Psychology

Peter Selby, MBBS, CCFP
Addiction Research Foundation

Neil H. Shear, MD, FRCPC
Sunnybrook Medical Health Centre

Wee Shian Chan, MD, FRCPC
Maternal Medicine,
Women's College Hospital

Cheryl Shuman, MSc
Department of Genetics

Rosanna Weksberg, MD, PhD, FRCPC
Department of Genetics

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

Sabina Vohra

(416)813-7283 [Mailbox 5]
sabina.vohra@utoronto.ca
Motherisk Program
Division of Clinical Pharmacology and Toxicology
Hospital for sick Children

Follow Up Report
MOTHERISK PROGRAM

ID #: Clinic or ID Number
Attention: Sabina Vohra
Physician: Physician's Name
Mother: Mother's Name

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: _____

Appendix I: Ethics approval from the Hospital for Sick Children.

SickKids
THE HOSPITAL FOR SICK CHILDREN

RESEARCH ETHICS BOARD

February 08, 2008

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

Dear Dr. Koren:

Your study "The Safety of Proctofoam-HC in the Third Trimester of Pregnancy"

REB File No.: 1000008482

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 2E. 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,

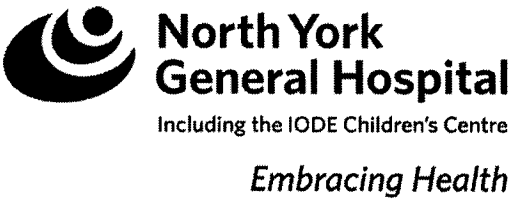
Richard Sugarman
Chair, Research Ethics Board

Co-Investigator(s): Alon Shrim

555 University Ave
Toronto, Ontario
Canada M5G 1X8

www.sickkids.ca

Appendix J: Ethics approval from North York General Hospital.



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

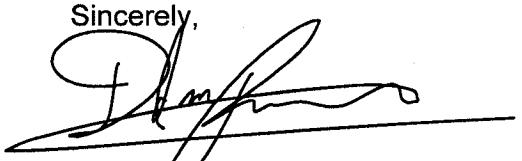
The above-named protocol and the consent form were reviewed at a meeting of the North York General Hospital Research Ethics Board. At the time of the meeting, members of the Research Ethics Board requested additional information. The information requested has been received and reviewed. This submission 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

Appendix K: Ethics approval from Sunnybrook Health Sciences Centre.

Sunnybrook
HEALTH SCIENCES CENTRE

Research Ethics Board, Room C819
2075 Bayview Avenue
Toronto, ON
Canada M4N 3M5
t: 416-480-4276
www.sunnybrook.ca

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.

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. Hébert, MD PhD FCFPC
Chair, Research Ethics Board
/cap

Hemorrhoid Survey Scale

Please answer the following survey to the best of your knowledge. The first set of questions asks you about your health **PRIOR** to using Proctofoam-HC® for the treatment of your hemorrhoids. The second set of questions asks you about your health **AFTER** the use of Proctofoam-HC®. We would like to assess whether Proctofoam-HC® provided any relief for your pregnancy related hemorrhoidal symptoms.

Please answer each question with 0 being 'none' and 10 being 'maximum'.

Prior to treatment with Proctofoam-HC®:

How do you rate the pain you experienced?

0 1 2 3 4 5 6 7 8 9 10

How much itching did you have?

0 1 2 3 4 5 6 7 8 9 10

How much swelling was present?

0 1 2 3 4 5 6 7 8 9 10

How much bleeding did you experience?

0 1 2 3 4 5 6 7 8 9 10

How much discomfort did you experience?

0 1 2 3 4 5 6 7 8 9 10

How much did your hemorrhoids affect your well-being?

0 1 2 3 4 5 6 7 8 9 10

Post Treatment (with Proctofoam-HC®):

How do you rate the pain you experienced?

0 1 2 3 4 5 6 7 8 9 10

How much itching did you have?

0 1 2 3 4 5 6 7 8 9 10

How much swelling was present?

0 1 2 3 4 5 6 7 8 9 10

How much bleeding did you experience?

0 1 2 3 4 5 6 7 8 9 10

How much discomfort did you experience?

0 1 2 3 4 5 6 7 8 9 10

How much did your hemorrhoids affect your well-being?

0 1 2 3 4 5 6 7 8 9 10

How would you rate the overall improvement? With 0 being 'no improvement' and 10 being 'maximum improvement'.

0 1 2 3 4 5 6 7 8 9 10

Appendix M: Questionnaire used in the incidence study.

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

Motherisk 20 years with you and your baby

Survey to Assess Rectal Problems in Pregnancy

This survey is being conducted to access the frequency and intensity of anorectal symptoms in pregnancy. You may fill this form anonymously. All information will be kept confidential. Please only complete this survey **ONCE**, unless you are now experiencing anorectal symptoms and were not when you first completed the form.

If you are experiencing hemorrhoids, please speak to Dr. N. Pairaudeau. You may be asked to fill out another survey later during your pregnancy to assess your symptoms.

Gestational age: ____ (weeks) ____ (days), or _____ (months).

First day of Last Menstrual Period: _____

Due date: _____

Number of pregnancies (including this one): _____

Number of children: _____

Number of miscarriages: _____

Number of terminations: _____

Mode of delivery in past pregnancies: _____ Vaginal _____ C-Section

Any other medical conditions: _____

Are you currently taking any medications (Please specify): _____

Do you have regular bowel movement habits? Yes / No

How often? _____/day_____/ week Any recent changes:_____

Anal Conditions:

Is there any blood? Yes / No

Any difficulty passing stool: Yes / No Explain: _____

Any anal itching: Yes / No

Any pain: Yes / No Is the pain: Mild Moderate Severe

If yes to any of the above symptoms:

When did your symptoms begin: _____

Were you diagnosed with any anal/rectal condition? (Hemorrhoids, piles, anal fissure, other...): Yes / No If yes, what? _____

Did you receive any treatment (rectal cream/ointment): Yes / No If yes, specify name: _____

Did the treatment help? Yes / No

Previous History:

Have you ever (**in the past-** prior to this pregnancy) felt anal itching/pain? And when? _____

Were you ever **in the past** diagnosed with any anal/rectal condition? (Hemorrhoids, piles, anal fissure, other...): Yes / No If yes, what? _____
When? _____

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

Appendix N: Verbal consent used in the incidence study.

Hello. My name is Sabina Vohra and I am a graduate student at the Motherisk Program at the Hospital for Sick Children. We are conducting a study to assess the incidence of hemorrhoids in the third trimester of pregnancy. This is a joint study by Dr. Nicholas Pairaudeau at North York General Hospital and Dr. Gideon Koren at the Hospital for Sick Children.

This survey is completely anonymous and voluntary. All information will be kept in secured location and will be kept absolutely confidential. If you choose not to participate, it will not affect the quality of health care you receive at North York General Hospital, Motherisk Program or at the Hospital for Sick Children.

If you have any questions, please feel free to ask me.

Verbal Consent to Participate: YES NO