Evaluation of antiemetic treatment of women hospitalised for *Hyperemesis gravidarum* at Muhimbili National Hospital, Dar es Salaam, Tanzania

Camilla Brox

Master thesis in Global Health - PEPER PROJECT

A collaboration between

Muhimbili National Hospital,
Muhimbili University of Health and Allied Sciences

And

Centre for International Health & Centre for Pharmacy

Faculty of Medicine

University of Bergen, Norway

May 2022

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Supervisors:

MUHAS: Professor Sheila Maregesi &
Professor Godeliver Kagashe

MNH: Dr. Peter J T Wangwe

UiB: Associate Professor, Dr. Lone Holst &
PhD-candidate Hilde Erdal

This thesis is submitted in partial fulfilment of the requirements for the degree of Master of Philosophy in Global Health at the University of Bergen.

May 2022

Acknowledgements

This master thesis is carried out and written in collaboration with Muhimbili National Hospital and Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania and Centre for Pharmacy, University of Bergen as a part of the Master´s programme in Global health at Centre for International Health, University of Bergen.

I wish to express my appreciation to my supervisors for all the help and support I have gotten this past year. Particularly I want to give a big thank you to Associate Professor Dr. Lone Holst for excellent guidance in planning this project and for support throughout the writing process. You have truly brought this project to life. I will equally thank my supervisor PhD-candidate Hilde Erdal for valuable advice and constructive criticism. I have been beyond fortunate to have support from you both, and your experience and knowledge in the field have been irreplaceable.

Several people played a decisive role in helping me adjust and to learn a substantial amount during my three months field work in Tanzania. I would like to extend my gratitude to Professor Sheila Maregesi & Professor Godeliver Kagashe at MUHAS and Dr. Peter J T Wangwe at MNH. You extended a great amount of assistance and helped me with all things necessary, big, or small for me to complete my data collection. A special thank you to Joel Junior Mkwizu, administrative officer at School of Pharmacy MUHAS, for arranging all things practical regarding my Tanzania stay.

Another very special person made completing this thesis as best as it could have been. I have gotten relentless support throughout the process from collecting the data in Tanzania to writing at all hours of the day in the lead up to deadline. You know who you are, thank you so much Marita Sandven. This project has truly brought me a new friendship.

Lastly, I will end this acknowledgement by thanking myself for completing my second master´s while juggling a full-time job. Actually, I would like to thank myself for even starting the Global Health Master´s degree. You never know where life will take you. Mine took me to Bergen, to Germany and to Tanzania over the past two years and I am beyond grateful for the experiences. They will last me a lifetime. To all my friends and family, I am forever grateful for your support.

Camilla Brox
University of Bergen, May 2022

Abstract

Background: Significant global efforts are required to achieve the United Nations Sustainable Development Goal (SDG) 3; “Ensure healthy lives and promote well-being for all at all ages”. In a limited resource setting, such as Tanzania, maximizing the benefits achieved with available resources is essential for optimal health outcomes.

Hyperemesis gravidarum (HG) is the most severe form of nausea and vomiting in pregnancy (NVP). A universally accepted definition of HG is lacking, but the condition entails intractable vomiting during pregnancy leading to complications including dehydration, weight loss, ketonuria, malnutrition, and/or electrolyte imbalance. Treatment options range from psychological care, emotional support, and dietary modifications to drug therapy (antiemetics, antacids), fluid management and total parental nutrition (TPN). Over the previous decade, management of HG have improved in large parts of the world, but most of the published treatment studies are from Europe and the United States. Very few studies are published from less-resources settings such as Asian and African countries. To the best of our knowledge, no published studies have assessed the hospital treatment and maternal demographics of HG patients in Tanzania. Furthermore, HG is the most common reason for hospitalization in early pregnancy and can result in maternal, fetal and/or child complications.

Aim: The aim of the study is to describe the treatment provided for women hospitalised for *Hyperemesis gravidarum* at Muhimbili National Hospital, Dar es Salaam, Tanzania.

Method: A retrospective cohort study of 163 women with HG admitted to Muhimbili National Hospital between 2004 and 2021.

Results: Most women (98,8%) received some type of antiemetic treatment during the hospital stay or when discharged and 95,7% got some type of fluid treatment during the hospital stay. The number of hospital admissions throughout the pregnancy for women with HG at MNH ranges from minimum 1 to maximum 5. The most used antiemetic medications were ondansetron (n = 81, 49,7%), doxylamine-pyridoxin (n = 80, 49,0%), and metoclopramide (n = 75, 46,0%). In accordance with international guidelines combinations of antiemetics were commonly used at MNH. Almost half of the woman presented with electrolyte disturbances. No prominent difference in treatment of insured and uninsured individuals were found regarding antiemetics, fluid, vitamins nor antacids.

Abbreviations

ANC	Antenatal care
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CHF	Community Health Fund
CI	Confidence interval
DNS	Dextrose Normal Saline
GDF15	Growth differentiation factor 15
GDP	Gross domestic product
H. pylori	Helicobacter Pylori
HCG	Human chorionic gonadotrophin
HELP	Hyper Emesis Level Prediction Score
HG	Hyperemesis Gravidarum
HRT	Hormone replacement therapy
ICU	Intensive care unit
IGRBP7	Insulin-like factor binding protein 7
IQR	Interquartile range
LMIC	Low and middle-income countries
MMR	Maternal mortality ratio
MNH	Muhimbili National Hospital
MOHSW	The Ministry of Health and Social Welfare
MUHAS	Muhimbili University of Health and Allied Sciences
NEMLIT	the National Essential Medicines List for mainland Tanzania
NHIF	National Health Insurance Fund
NL	Normal Saline
NVP	Nausea and vomiting in pregnancy
ORS	Oral rehydration solution
PPI	Proton pump inhibitor
PTSD	Post-traumatic stress disorder

PUQE	Pregnancy Unique Quantification of Emesis Score
RL	Ringer´s lactate
SD	Standard deviation
SDG	the United Nations Sustainable Development Goal
STG	Standard Treatment Guidelines
THHG	Transient hyperthyroidism of hyperemesis gravidarum
TPN	Total parental nutrition
TSH	Thyroid stimulating hormone
WHO	World Health Organization

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1 Introduction

1.1 Tanzania – country profile and health indicators

1.1.1 Country profile Tanzania

The United Republic of Tanzania (hereby called Tanzania) is an East African country, bordering Kenya and Uganda in the north, Rwanda, Burundi, Democratic Republic of Congo in the west and Zambia, Malawi and Mozambique in the south (African Development Bank, 2022). The largest and most populated city is Dar es Salaam while Dodoma is the capital city. Historically, Tanzania was formed in 1964 uniting Tanganyika (today known as mainland Tanzania) and Zanzibar (Bryceson, Ingham, Chiteji, & Mascarenhas, 2021).

The last Population and Housing Census, published in 2012, report a population of over 43 million people (National Bureau of Statistics Tanzania, 2013). However, data from 2020 by Centers for Disease Control and Prevention (CDC) present a significant population increase to approximately 59 million people (CDC, 2021). An updated 2022 census will be conducted but is not yet available.

Nearly half the population is under the age of 15 (MoHCDGEC, 2016). The population is mostly rural, with only 26% of the population living in urban areas. With regards to health care, there is a significant rural-urban division presented in access to and utilization of health care, specifically in maternal health care (Langa & Bhatta, 2020).

Regarding political governance, Tanzania has a stable history compared to neighboring countries. Tanzania is a republic and has one national government and a devolved government of Zanzibar. The first-mentioned having the authority regarding nationwide issues (African Development Bank, 2022). The incumbent president Samia Suluhu Hassan became president following the death of the former President John Magufuli in 2021. Samia Suluhu Hassan is the first female president in Tanzania.

Tanzania was previously classified by the World Bank as a low-income country, but in July 2020, five years ahead of the target year, Tanzania was declared a lower-middle income country when the GNI per capita increased to over $1,036 (The World Bank, 2021). Generally, the economic and social development is improving in Tanzania. However, the

economic growth is centralized in areas that only employ 20% of the Tanzanian population and might therefore not equally benefit the entire population (African Development Bank, 2022).

1.1.2 Health in Tanzania

Significant global efforts are required to achieve the United Nations Sustainable Development Goal (SDG) 3; “Ensure healthy lives and promote well-being for all at all ages” (World Health Organization, 2015). In a limited resource setting, such as Tanzania, maximizing the benefits achieved with available resources is essential for optimal health outcomes.

Many factors, including inadequate funding and the complexity of social and political dynamics in Tanzania have implications for health interventions to reach their goals. Another complicating factor is the lack of human resources needed to implement the variety of interventions. The Ministry of Health and Social Welfare (MOHSW) even declared a workforce crisis back in 2007 (World Health Organization, 2013). Specifically for Tanzania, research have found lack of staff supervision, low transportation possibilities, poor infrastructure and shortage of medical equipment and drugs to be the main challenges for the health care workers to provide safe and high quality services (Kwesigabo et al., 2012).

1.1.3 Health care system and financing

The Tanzanian health system can be roughly divided into 3 levels: National, Regional and District level, making up a pyramidal referral system, as illustrated in Figure 1-1 (Kwesigabo et al., 2012). The lower part of the pyramid represents the most easily accessible health care services. From there, moving up step by step on the figure, District, Regional, and lastly National level is reached. These can also be referred to as primary, secondary, and tertiary level of health care, respectively.

Another important health determinant is financing, including financing policy. In Tanzania, health financing is centralized (governmental). Access to primary health care for all citizens is the primary goal of the Tanzanian National Health Policy. Although the goal is to improve the system and to ensure equitable access to essential health services and health care

interventions, inadequate levels of funding are spent on health (WHO Regional Office for Africa, 2021).

Figure 1-1 Levels of health care delivery system of Tanzania showing health care level and service provided. Source: (Kwesigabo et al., 2012)

1.1.4 Health insurance in Tanzania

Tanzania has two health insurance models: the Community Health Fund (CHF) and the National Health Insurance Fund (NHIF). CHF and NHIF were launched in 1996 and 2001 respectively (Amani et al., 2021). The CHF is based on voluntary pre-payment scheme (member fee) and is meant for rural people in Tanzania while NHIF began solely as a mandatory insurance for government sector employees (Munishi, 2001). Although, today NHIF is expanded and can also cover the informal sector, then as a voluntary scheme (Amani et al., 2021).

Unfortunately, health insurance coverage is still low in Tanzania. As of 2021, about 31 % of the Tanzanian population have health insurance coverage, of which 24% under CHF, 6 % under the NHIF and 1% are members of private health insurance companies (Amani et al., 2021).

1.1.5 Sanitation and water

Just over half of the Tanzanian population (54%) have access to safe drinking water, while only 24% have access to quality sanitation facilities. In addition to the abovementioned differences in access and utilization of health care, the sanitation situation provides great disparities between urban and rural populations (World Health Organization, 2013).

1.1.6 Health indicators

A range of health indicators can be used to estimate the burden of disease and evaluate health in a country. A selected range of Tanzania´s health indicators compared to the world average are listed for in Table 1-1. Among other challenges, high maternal mortality, high prevalence of HIV/AIDS, child mortality, pneumonia, and malaria contribute to a serious health burden in Tanzania. In addition, the above world average under-5 mortality rate and below world average life expectancy paints a clear picture of challenges in health care and living standard.

Table 1-1 Health indicators of Tanzania compared to the World average

Health indicator	**Tanzania**	**World**
Under-5 mortality rate (per 1000 live births)	48.9 (2020)	36.6 (2020)
Neonatal mortality rate (per 1000 live births)	20.1 (2020)	17 (2020)
Life expectancy (years)	65 (2019)	72 (2020)
Fertility rate, total (births per woman)	4.8 (2019)	2.4 (2019)
Disability-Adjusted Life Years (DALYs) caused by communicable, maternal, neonatal, and nutritional diseases (per 100 000 population)	20 117 (2019)	9 483 (2019)
Maternal mortality ratio (per 100 000 live births)	524 (2017)	211 (2017)
Prevalence of HIV (% of population)	4.7% (2020)	0.7% (2020)
Percentage of pregnant women living with HIV receiving effective ARVs (% of population)	84 (2020)	85 (2020)

Source: (MoHCDGEC, 2016; Ourworldindata, 2021; The World bank, 2020; Unicef, 2020; Vollset et al., 2020)

1.1.7 Maternal health and Antenatal care in Tanzania

Over the past decades, the maternal mortality ratio (MMR, number of maternal deaths per 100,000 live births) has been decreasing substantially. The decrease from 2000 to 2017 was

38% (World Health Organization, 2019). Nevertheless, in Tanzania MMR is still high (524 in 2017). Actually, 99% or the global MMR is traced back to low and middle-income countries (LMICs). Tanzania´s Ministry of Health aimed the MMR to be 193 by the end of 2015 through the National Road Map Strategic Plan of 2008, but the country is still far from reaching the goal (RaCHS, 2008).

In Tanzania, most pregnant women (83%) receive antenatal care (ANC) from a skilled provider. In this case a skilled provider includes doctor, nurse, assistant nurse, clinical officer or others with medical training (National Bureau of Statistics, 2011) . Even though many women get ANC, just 1 in 4 have an appointment in the first trimester. Data of women seeing a doctor for ANC is unavailable. Furthermore, only half of the pregnant population got the recommended 4 or more ANC visits throughout their pregnancy (Unicef, 2020). Regarding delivery and postnatal care, around two out of three give birth in a health facility. The last one third of births take place at home. Within the last-mentioned group we find predominantly women with little to no education, those living in the poorest households and in rural areas (Ministry of Health and Social Welfare, 2008).

1.1.8 Consequences of the COVID-19 pandemic

In a time where the COVID-19 pandemic continues to challenge the global economy, allocating scarce health care recourses the best way possible is particularly important. Unfortunately, the pandemic has enlarged the differences between poor and rich and caused a significant setback in Sustainable Development all over the world (Benedek, Gemayel, Senhadji, & Tieman, 2021). Tanzania´s gross domestic product (GDP) growth rate slowed from 5.8 percent in 2019 to an estimated 2.0 percent in 2020 due to the pandemic-induced impact on tourism, which fell by 72%, manufacturing sector and related business services generating income (The World Bank, 2021). Health consequence of COVID-19 show health indicators that were previously improving, is now impaired or even reversed due to the pandemic. (Sachs, Kroll, Lafortune, Fuller, & Woelm, 2021).

1.2 Nausea and vomiting in pregnancy (NVP)

The physiological changes that occur during pregnancy widely affects the gastrointestinal tract (Gomes, Sousa, Lourenço, Martins, & Torres, 2018). One of multiple consequences is Nausea and vomiting in pregnancy (NVP). NVP is affecting approximately 70-80% of the

pregnant population (T. R. Einarson, Piwko, & Koren, 2013; Gadsby, Barnie-Adshead, & Jagger, 1993). The condition is usually self-limiting, peaks at around 9 weeks of gestation and diminish by approximately 20 weeks of gestation, although some women have symptoms throughout the pregnancy (Gadsby et al., 1993). Most women with NVP have normal vital signs (Lee & Saha, 2011).

NVP is commonly referred to as "morning sickness". The term "morning sickness" is fallacious, as only 1,8% of women report symptoms only in the morning and 80% report symptoms lasting throughout the day (Lacroix, Eason, & Melzack, 2000). Management of NVP consists mostly of lifestyle changes and dietary interventions. However, one third of the patients may require antiemetic treatment, fluid and/or vitamin supplementation (T. R. Einarson et al., 2013).

1.2.1 Global variation in NVP prevalence and management

A limited number of studies have been conducted to evaluate the association between race/ethnicity and NVP. Nevertheless, the incidence of NVP is found significantly lower in Blacks compared to White, Hispanic and Asian (Louik, Hernandez-Diaz, Werler, & Mitchell, 2006). A Canadian study supports the abovementioned finding by studying the reporting of NVP symptoms. The result of the study showed Caucasians reporting more symptoms of NVP during the 1st trimester than Asian women and Black women. Sociodemographic factors did not account for the racial/ethnic variation in disease prevalence, providing rationale for genetic and/or cultural factors contributing to NVP (Lacasse, Rey, Ferreira, Morin, & Bérard, 2009). On the other hand, an older study from 1988 shows the contrary; White women had less NVP than non-Whites (categorized as Hispanic and Black) (Weigel & Weigel, 1988).

Regarding management of NVP most of the published treatment studies are from Europe and the United States, and very few from less-resources settings such as Asian and African countries. Nevertheless, the basic principle of medical treatment is uniform across countries. Intravenous rehydration therapy, antiemetics and electrolyte substitution being essential components (Maslin & Dean, 2021; Wegrzyniak, Repke, & Ural, 2012). The complexity of the treatment (intravenous/infusion therapy), high cost, lack of relevant medications, and low access to specialist or hospital care may cause irregularities in access to treatment in some global settings (M. S. Fejzo, J. Trovik, et al., 2019).

1.3 Hyperemesis gravidarum: etiology, risk, consequences

1.3.1 Hyperemesis Gravidarum

The most severe form of NVP is hyperemesis gravidarum (HG). An universally accepted definition of HG has been lacking, but the condition entails intractable vomiting during pregnancy leading to complications including dehydration, weight loss, ketonuria, malnutrition, and/or electrolyte imbalance (T. R. Einarson et al., 2013). In 2021, a new windsor consensus definition of HG was published which consist of the following elements; Symptoms start in early pregnancy (before a gestational age of 16 weeks), characterized by severe nausea and vomiting, inability to eat and/or drink normally and strongly limits daily activities (Jansen et al., 2021).

The prevalence of HG varies largely. In a study from Norway the prevalence of HG was found to be 0,89% (Vikanes et al., 2010). Global findings differ between 0,3-3,6% (T. R. Einarson et al., 2013). The highest prevalence reported in Asia is 10,8% in a study from China and the highest ever reported is 44,9% in a study from Northeast Nigeria (Aminu, Alkali, Audu, Abdulrazak, & Bathna, 2020; J. Zhang & Cai, 1991). The wide variation may partly be caused by differing inclusion criteria due to the lack of a universal definition (T. Murphy Goodwin, 1998). Furthermore, unlike the other studies mentioned, the Chinese and Nigerian studies were not based on hospitalization for HG, but on clinical record of severe vomiting on care cards or women attending antenatal clinics. To our knowledge, prevalence studies of HG from Tanzania are not published. A cross-sectional study from Pemba (an island part of the Zanzibar Archipelago) on NVP found 49.4% of women reported nausea in the first trimester and 53.6% experiences vomiting, but the study does not mentioned HG specifically (Steinmetz, Abrams, & Young, 2012).

Commonly used definitions for hyperemesis gravidarum include criteria such as more than three episodes of vomiting per day accompanied by ketonuria and a weight loss of more than 3 kg or 5% of pre-pregnancy body weight (Golberg, Szilagyi, & Graves, 2007).

Furthermore, HG is the most common reason for hospitalization in early pregnancy and the second most common throughout the whole pregnancy, after preterm labour (Gazmararian et al., 2002). The symptoms of HG usually start early in pregnancy (around week 6), peak at 8-

13 weeks of gestation and usually decline during second trimester (M. S. Fejzo, J. Trovik, et al., 2019). However, 10% still experience symptoms after pregnancy week 22 (Lacroix et al., 2000). Serious maternal and fetal morbidity can occur for HG-patients, for example Wernicke encephalopathy, small babies for gestational age (fetal growth restriction) and even death for woman and/or child (Chiossi, Neri, Cavazzuti, Basso, & Facchinetti, 2006; Fairweather, 1968). More on maternal, fetal and child consequences in chapter 1.3.6.

It is important to underline differences between the common NVP and the serious disease HG which often needs hospital care. For clarifications see Table 1-2 below. As a matter of fact, women diagnosed with HG have a lower health related quality of life (Munch, Korst, Hernandez, Romero, & Goodwin, 2011). Not only does HG interfere with food and drink intake, the disease cause suffering and limit daily activities including self-care. The distinction between NVP and HG is a controversial topic. Some consider them as one disease with a broad spectrum. Table 2 represents a simplified scheme to help separate the two conditions.

Table 1-2 Comparing NVP and HG. A simplified overview of differences between the two conditions.

NVP	HG
Minimal to no weight loss	Weight loss (commonly >5%)
Sufficient food and drink intake most days	Inadequate food and drink intake for days, weeks or months
Nausea and vomiting experienced as unpleasant, but do not hinder essential activities	Nausea and vomiting causing suffering and misery. Often limit daily activities, such as self-care
Symptoms often manageable with dietary and lifestyle changes	Medical treatment needed
Symptoms ease by gestation week 14	Symptoms may persist until delivery, or ease late in pregnancy
Rarely require hospitalization	Often require hospitalization

Source: Hyperemesis Education and Research Foundation described in M. S. Fejzo, J. Trovik, et al. (2019)

1.3.2 Diagnosis

HG is a clinical diagnosis. However, tools such as the Pregnancy Unique Quantification of Emesis (PUQE) score is commonly used to evaluate the serious level of disease (Gideon Koren et al., 2002). A PUQE score is calculated using the number of hours of nausea per day, number of episodes of emesis per day and number of episodes of retching per day can be used to access the severity of symptoms (G. Koren et al., 2005). All of which is useful to identify and diagnose HG. It is also useful in the process of monitoring the women and for follow-up.

In a recent study, the newly developed measuring tool HyperEmesis Level Prediction (HELP Score) is described (MacGibbon, Kim, Mullin, & Fejzo, 2021). The HELP score generally measure higher severity than the PUQE score and will better identify patients in need of intervention. Historically, HG severity has been underestimated. The consequences are inadequate treatment with adverse outcomes for mother, child, or society.

Which measuring tools used in LMICs such as Tanzania, if any are used, is unpublished.

On the contrary to normal vital signs in NVP patients, clinical findings of dehydration, irregular serum electrolytes and inadequate nutrition can be found in HG patients. Furthermore, in serious cases, acidosis due to malnutrition or alkalosis due to loss of chloride and potassium can be found. In these cases the disease may be life threatening and immediate treatment must be initiated (Jueckstock, Kaestner, & Mylonas, 2010).

1.3.3 Differential Diagnosis

HG is not the only disease that can cause nausea and vomiting during pregnancy. In addition to using the abovementioned tools, HG must be distinguished from other conditions that can cause a similar clinical picture. Differential diagnosis for HG is listed in Table 1-3.

Table 1-3 Differential diagnosis for HG

Gastrointestinal disorders	Gastroenteritis
	Appendicitis
	Hepatitis
	Pancreatitis
	Biliary tract disease

	Gastroesophageal reflux disease
	Peptic ulcer disease
Genitourinary and renal disorders	Nephrolithiasis
	Pyelonephritis
	Uraemia
Metabolic disorders	Diabetic ketoacidosis
	Porphyria
	Addison's disease
	Hyperthyroidism
Psychiatric disorders	Substance use disorders
	Eating disorders
	Antidepressant discontinuation syndrome
Other	Medications—antiarrhythmic, antihypertensives, narcotics, anticonvulsants, antibiotics, iron supplementation, antiretroviral drugs (ARVs), antimalaria medication
	Cyclic vomiting syndrome
	Food poisoning
	Parasitic disease

Sources: J. R. M. D. Niebyl (2010), T. Murphy Goodwin (1998), Herrell (2014), Jueckstock et al. (2010) & Wegrzyniak et al. (2012)

1.3.4 Laboratory findings

To ensure the best possible disease management, laboratory findings are important. Women presenting with HG often have electrolyte abnormalities, poor nutritional status, ketonuria or hormone disturbances (J. R. M. D. Niebyl, 2010). Laboratory abnormalities may include high urinary ketones, increased blood urea nitrogen and hematocrit. Hyponatremia, hypokalemia, and hypochloremia is found in 15-25% of HG patients (T. Murphy Goodwin, 1998). Electrolyte abnormalities are corrected with intravenous fluid replacement. Pre-albumin levels may be depressed, reflecting the mother's lack of protein intake (Jain, Shah, Ransonet, Wise, & Bocchini, 1995).

1.3.5 Etiology and risk of HG

The etiology of HG is not fully understood, described, or researched. Many theories have been presented, each accumulating support and criticism. HG is referred to as a multifactorial disease, as one or more factors contribute to the disease mechanism (Jueckstock et al., 2010).

Contributory factors include biological, psychological, physiological and sociocultural factors (Gadsby et al., 1993).

Increased risk of HG is associated with many factors like carrying a multiple pregnancy, obesity, history of HG in previous pregnancy/pregnancies, hyperthyroidism, psychological disorders such as eating disorders, placental components, nulliparity, metabolic disturbances and HG in close family relation (Broussard & Richter, 1998; M. S. Fejzo, J. Trovik, et al., 2019; T. Murphy Goodwin, 2008; Y. Zhang et al., 2011). Although many theories are presented, no single theory seems to provide an adequate explanation for HG.

Genes

Evidence suggests a genetic predisposition to HG is present. For instance, women with a mother or a sister previously diagnosed with HG are at increased risk of getting HG themselves (Y. Zhang et al., 2011). Familial aggregation was found clearly present as women with a sister affected by HG have a 17-fold increased risk of getting HG and more than 80% of women who had HG in their first pregnancy experience severe nausea and vomiting in their next pregnancy. The risk of recurrent HG is 15-81%, depending on study settings, and the risk increases with increasing time interval between pregnancies (Nurmi, Rautava, Gissler, Vahlberg, & Polo-Kantola, 2018; Trogstad, Stoltenberg, Magnus, Skjaerven, & Irgens, 2005).

Research is ongoing to identifying the predisposing genes for better understanding of disease mechanisms. Gene sequencing of families with HG shows mutations in an intracellular calcium release channel gene, RYR2 and a thyroid hormone target gene (Marlena Schoenberg Fejzo et al., 2017). The RYR2 gene encodes for mechanisms involved in both vomiting and function as a thyroid target gene. More about thyroid and HG in section below. Another interesting part of RYR2 being associated with HG is that RYR2 is a drug target of propranolol (Marlena Schoenberg Fejzo et al., 2017; Wu, Dai, Zhang, & Gao, 2004).

Placental proteins

Relevant tissues in pregnancy are among others the ovaries and the placenta. The placenta as a part of the pathophysiology is supported by the observation that women with pregnancies without fetus (complete hydatidiform mole) also can experience clinical nausea and vomiting

(J. R. M. D. Niebyl, 2010). Over the past couple of years, placental proteins have been associated with genetic contribution to HG. Genotypes of growth differentiation factor 15 (GDF15) and insulin-like factor binding protein 7 (IGRBP7) are found to be risk factors for HG, both found in or around the locus of the placenta (Marlena S. Fejzo et al., 2018). The role of IGRBP7 in HG require further studies.

Furthermore, increased concentration of GDF15 in gestational week 15 is associated with nausea and vomiting in the second trimester and maternal antiemetic use. Women without nausea or vomiting were found to have lower GDF15 concentrations (Petry et al., 2018). Mechanism of action of GDF15 is in the chemoreceptor trigger zone of the brain, which leads to vomiting (Petry et al., 2018). Additionally, the GDF15 protein is a component in abnormal appetite regulation (M. S. Fejzo, P. A. Fasching, et al., 2019).

Hyperthyroidism

Thyroid function is altered during normal pregnancy through several mechanisms (Glinoer, 1997). Because thyroid function is altered by pregnancy alone it is difficult to interpret results regarding HG diagnosis. A specific mechanism of thyroid function alteration in pregnancy is through stimulation by human chorionic gonadotrophin (HCG). A specific type of hyperthyroidism, Transient hyperthyroidism of hyperemesis gravidarum (THHG) is found in HG patients, with increased HCG and T4 levels. The disease is self-limiting, meaning it does not require treatment. The similarities in chemical structure between HCG and thyroid stimulating hormone (TSH) resulting in HCG acting as TSH and binding to the TSH receptors (hyperstimulation) may cause this disease. Additionally, genetic variations of TSH receptors which are oversensitive towards stimulation from HCG is found in families affected by HG (Rodien et al., 2004).

Helicobacter pylori

Chronic Helicobacter Pylori (H. pylori) infection is found associated with an increased risk of HG (Ng et al., 2018). However, no study has shown eradication of infection before the women gets pregnant to significantly lower HG risk, so the association is controversial (M. S. Fejzo, J. Trovik, et al., 2019). A study from 1999 show a 91,5% seropositivity for H. Pylori in HG patients (Kocak et al., 1999). In a later histological study, H. Pylori was diagnosed in 19 out of 20 pregnant women (95%) compared to 50% in the control group (Bagis et al.,

2002). In addition, being pregnant might increase the susceptibility to H. Pylori infection due to altered gastric pH and immunity caused by changes in antibodies and fluid dynamic during pregnancy (Lanciers, Despinasse, Mehta, & Blecker, 1999). Although having a H. pylori infection might be associated with HG, it is not considered the only cause, but it should be taken into consideration as a contributing factor (Jueckstock et al., 2010).

Hormones

It is natural to suspect hormones as a cause of disease as a pregnancy causes multiple changes in the hormone system. Several hormones are found to be involved in HG pathophysiology and/or risk profile (M. S. Fejzo, J. Trovik, et al., 2019).

Reproductive hormones (HCG, estrogen and progesterone)

The incidence of HG is highest when HCG levels are most increased (around pregnancy week 9). Based on this HCG is suspected to be related to the pathophysiology of HG. In addition, increased HCG production is found in molar or multiple pregnancies which is associated with increased severity of HG symptoms (Thomas Murphy Goodwin, Hershman, & Cole, 1994; Sheehan, 2007). However, this hypothesis is disputed as woman suffer from HG symptoms also after the HCG levels decrease.

Estrogen and progesterone levels increase drastically during pregnancy and especially during first trimester (Kumar & Magon, 2012). Patients with HG are reported to have an increased level of estrogen compared to a control group. Further, conditions influenced by high estrogen such as low parity and obesity have been associated with increased incidence of HG (Depue, Bernstein, Ross, Judd, & Henderson, 1987).

Interestingly, the use of contraceptive pills and hormone replacement therapy (HRT) have nausea and vomiting as reported side effects (Bakken, Eggen, & Lund, 2004). These pills typically consist of estrogen and progesterone which have been relevant in the research on the involvement of these hormones in HG and NVP.

Additionally, together with estrogen or alone, progesterone decrease gastric smooth muscle contractility and may also cause gastric dysrhythmias (Walsh, Hasler, Nugent, & Owyang,

1996). These effects might promote and elicit nausea and vomiting. Even though the hormones have gastrointestinal effects, the role in HG remains unclear.

1.3.6 Maternal, fetal and child complications

Maternal complications

Simultaneously with improved treatment of HG, maternal complications are decreasing. Before intravenous fluid replacement therapy was offered, HG was a diagnosis with high maternal mortality (Ayyavoo, Derraik, Hofman, & Cutfield, 2014). Data on maternal mortality decreasing is based on studies from Europe and the USA and will most likely not reflect nor be accurate for the global situation. Gaps in the literature exist for data from low-middle income countries, including Tanzania.

Common maternal complications include dehydration, weight loss and nutritional deficiency (Fiaschi, Nelson-Piercy, Gibson, Szatkowski, & Tata, 2018). These conditions have complications like excessive vomiting leading to hematemesis and dehydration resulting in dizziness and syncope (Mullin, 2011)

Long-term maternal consequences remain unknown. Studies report increased rates of depression, post-traumatic stress disorder (PTSD), and various neurological disorders (T. Murphy Goodwin, 2008; N Mitchell-Jones et al., 2017). When symptoms last the entire pregnancy, HG causes PTSD in 18% of patients (Christodoulou-Smith et al., 2011). Another study found that 80% reported negative changes to socioeconomic factors (for example job loss), fear of future pregnancies and psychiatric issues (including depression and anxiety) (B. Poursharif et al., 2008). Furthermore, a systematic review by World Health Organization (WHO) concludes that women from low- and lower-middle-income countries have a higher risk of psychological disorders during pregnancy and post birth (Fisher et al., 2012).

Some women even terminate an otherwise wanted pregnancy and the likelihood of a future new pregnancy decreased (Nijsten et al., 2021). A study by Heitmann et al. found more than a quarter of the women with severe NVP considered terminating their pregnancy in addition to three out of four considered not to get pregnant again (Heitmann, Nordeng, Havnen, Solheimsnes, & Holst, 2017). It is also certain that increased knowledge among health care providers is important, as women reporting to have terminated a pregnancy due to HG were

three times as likely to state that their health care providers were uncaring or did not understand how sick they were (Borzouyeh Poursharif et al., 2007).

Regarding more severe complications those involve Mallory-Weiss tears, esophageal rupture, Wernicke's encephalopathy, central pontine myelinolysis, and peripheral neuropathy (T. Murphy Goodwin, 2008; Kuscu & Koyuncu, 2002). Some of the mentioned complications are caused by vitamin B6, B12 or B1 deficiency and can be prevented using vitamin supplements.

Fetal complications

In addition to adverse maternal outcomes, HG is associated with adverse fetal outcomes. One explanation of fetal complications may be that fetal development requires an adequate maternal supply of nutrients for fetal growth and organ development. Women with HG are having difficulties meeting the nutritional needs throughout gestation. In a study of deliveries by women with HG, the infants were more likely to be born small for gestational age, with low birth weight and delivered before 37 weeks of gestation (Dodds, Fell, Joseph, Allen, & Butler, 2006). Multiple studies support these finding (J. Zhang & Cai, 1991). Negative fetal outcomes were often accompanied by maternal weight loss >5% of pre pregnancy weight (Gross, Librach, & Cecutti, 1989). Low birth weight is more often seen in HG patients with multiple admissions to the hospital (Godsey & Newman, 1991). Lastly, preterm births are four times as common in pregnancies with HG that also had gestational hypertension, early symptoms, and antihistamine use (Marlena S Fejzo et al., 2013).

On the other hand, some studies have found no increased risk of adverse fetal outcome such as a study by Bashiri et al. In addition, the study reported women with HG had a lower incidence of spontaneous abortions (3.1%) compared with previously reported rates in the general population (15%) (Bashiri, Neumann, Maymon, & Katz, 1995).

Long-term child outcomes

A limited number of studies have been conducted regarding long-term outcomes for children born by a mother with HG. A study from 2013 showed adverse health outcomes for the child including 20% reduction in insulin sensitivity during the childhood (Ayyavoo et al., 2014). Another study showed an increase in psychological and behavioral disorders in adulthood.

On a positive note, incidence of depression, anxiety, bipolar disorders were not found higher in children born by mother with HG compared to mothers without HG (Mullin, 2011). Furthermore, neurodevelopmental delays such as learning delay, speech and language delay and increased risk of having a child diagnosed with autism is associated with HG (M. Fejzo, Kam, Laguna, MacGibbon, & Mullin, 2019; Marlena S Fejzo, Magtira, Schoenberg, Macgibbon, & Mullin, 2015).

1.3.7 Socioeconomic consequences

As previously mentioned, many women report socioeconomic consequences of HG such as job loss or job difficulties (Borzouyeh Poursharif et al., 2007). Although the disease is rare, it´s socioeconomic impact can be immense. The economic burden of HG is a combination of the personal economy of the affected individual and costs for the society, for example regarding hospital expenses and loss of working days. An Israeli study estimates the national economic burden due to HG per year to be 20 million NIS (equals approximately 5.2 million USD) (Konikoff, Avraham, Ophir, & Bornstein, 2016). Furthermore, a US study estimates total cost of HG in 2012 to be 185 million USD and a study from England reports a cost of 36.5 million GBP (approximately 53.3 USD) (Lee & Saha, 2011; Piwko, Koren, Babashov, Vicente, & Einarson, 2013).

1.4 Management of HG and treatment guidelines

There is lack of robust evidence about the efficacy of treatment for HG. Two systematic reviews have been conducted and have identified multiple treatment options, however both publications state the overall poor quality of the summarized studies (Boelig et al., 2018; McParlin et al., 2016). Data on predicting response to therapies are also lacking.

The goal when managing HG patients is to improve symptoms and simultaneously reduce risk to the pregnant woman and to the fetus. Tailored treatment for each individual is often necessary to attain sufficient treatment. Treatment options range from psychological care, emotional support, and dietary modifications to drug therapy (antiemetics, antacids) and total parental nutrition (TPN). In addition to supportive treatment to improve symptoms, correction treatment is given when dehydration or electrolyte disturbances are present.

In addition to antiemetics, fluid and nutritional treatment, thiamine replacement is important and indicated for HG patients to prevent the serious Wernicke's encephalopathy, a neurological disease, causing ataxia, confusion, and eye abnormalities (Sonkusare, 2011).

1.4.1 Thalidomide crisis

Overall, treating pregnant women with drugs has been highly restricted due to limited safety data during pregnancy. Furthermore, treating pregnant women with antiemetics is historically challenged due to the "thalidomide crisis". Thalidomide was a widely used drug in the late 1950s going into the early 1960s. The indication was nausea during pregnancy and the drug was supposedly safe. Unfortunately, it became apparent that thalidomide caused limb deformities in thousands of children (J. H. Kim & Scialli, 2011; Vargesson, 2015). "The thalidomide crisis" resulted in physicians being afraid of treating pregnant women, especially nausea management (Heitmann, Svendsen, Sporsheim, & Holst, 2016). On the other hand, "the thalidomide crisis" did result in updated and strict toxicity testing regulations for drugs to prevent future cases of serious drug side effects both in pregnancies and general toxicity (Junod, 2008).

Regarding HG treatment today, abundant data on safety of antiemetic drugs are published and treatment should therefore not be restricted based on teratogenicity concerns.

1.4.2 General treatment guidelines

The database UpToDate offers evidence-based and updated clinical advice for a range of diseases. The UpToDate literature review "Nausea and vomiting of pregnancy: Treatment and outcome" from February 2022 include recommended treatment for both NVP and HG (Smith, Fox, & Clark, 2022). HG is in this case defined as "Severe vomiting resulting in hypovolemia and weight loss".

The recommended treatment is prescription medicines, parenteral fluids and if persistent weight loss also enteral or parenteral nutrition. As optimal treatment is individual, UpToDate provides a stepwise recommendation where the choice is either to move stepwise or to add the next step to already given treatment. The recommendations for NVP are presented in Table 1-4.

Table 1-4 The UpToDate recommendations for NVP. The same guidelines are recommended for HG treatment, but with an additional fluid and/or nutritional treatment and thiamine.

First step	Pyridoxine (Vitamin B6)
Change to	Doxylamin-pyridoxin
Change to	First generation antihistamines: Dimenhydrinate, meclizine or diphenhydramine
Add/change to	Dopamin antagonists: Metoclopramide, promethazine, prochlorperazine or droperidol
Add/change to	Serotonin antagonists: Ondansetron, garnisetron or dolasetron
Adjunctive therapy	Acid-reducing agents: antacids, H2 blockers, proton pump inhibitors (PPIs)
For refractory cases	Short time use of glucocorticoids Or Chlorpromazine

Source: (Smith et al., 2022)

In case of HG, fluid therapy is recommended to be added. Sometimes nutritional treatment is needed. The review underlines the importance of monitoring electrolytes and to add vitamins to the therapy. Additionally, to prevent Wernicke's encephalopathy by not giving dextrose before thiamine (vitamin B1) supplementation has been given for a couple of days.

1.4.3 Treatment guidelines in Tanzania

The abovementioned treatment guideline by UpToDate is a general recommendation. However, most countries have their own guidelines based on treatment tradition and available medicines in the specific country.

The Tanzanian Standard Treatment Guidelines (STG) and the National Essential Medicines List for mainland Tanzania (NEMLIT) was first printed in 1991 with reviewed editions in 1997, 2007, 2013 and 2017. In Tanzania, HG was first mentioned in the 2007 STG and NEMLIT guideline, and the HG treatment have later been improved with the most recent update being from 2017 (Ministry Of Health, 2017). An observed transition from recommending dextrose together with promethazine or prochlorperazine to the additional vitamin B1 with a change of antiemetic to metoclopramide follows the available studies and other recommendations. The non-pharmacological treatments mentioned are reassurance,

emotional support, rest, lifestyle adjustments, ensure adequate hydration and frequent small carbohydrate meals. The pharmacological treatment guideline is illustrated in Figure 1-2.

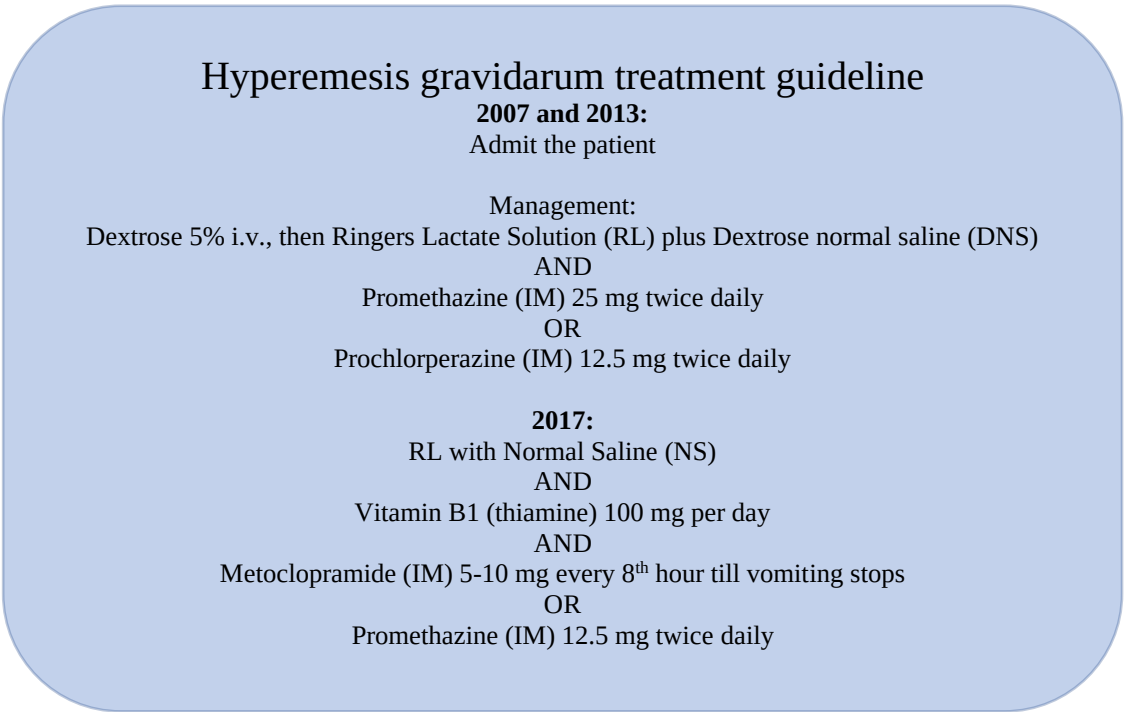

Figure 1-2 Treatment guideline HG in Tanzania. Source: STG and NEMLIT for mainland Tanzania

1.5 Nonpharmacological therapy of HG

1.5.1 Dietary and lifestyle interventions

Dietary and lifestyle interventions are recommended in NVP and HG treatment. General dietary advice to reduce nausea includes avoiding large meals in favor of small frequent meals throughout the day. Bland, low-fat foods are recommended as fatty foods further delay gastric emptying. Symptom relief is also reported by avoidance of spicy foods and inclusion of higher proportions of proteins and carbohydrates (Jednak et al., 1999; Latva-Pukkila, Isolauri, & Laitinen, 2010).

In addition, small volumes of salty liquids such as electrolyte-replacement fluids are suggested. If the smell of hot foods is noxious, a good option is to base food intake mostly on cold food (Jueckstock et al., 2010). Anecdotally, exacerbation of fatigue can be caused by nausea, and further strengthening the importance of dietary interventions and lifestyle changes to combat the symptoms (van Lier, Manteuffel, Dilorio, & Stalcup, 1993). An important lifestyle change is adequate rest to avoid fatigue. It must be said, most of the

studies on this topic are based on reporting of personal preferences and there is a general lack of RCTs.

Ginger

Cases where symptoms of nausea and vomiting are not sufficiently treated with diet and lifestyle changes, another treatment option is ginger. It is commonly known ginger is a non-pharmacologic intervention recommended to treat symptoms of nausea. Ginger contains gingerols, which enhances gastrointestinal motility through acting on dopamine- and serotonin receptors (Yamahara, Huang, Li, Xu, & Fujimura, 1990). Through these effects ginger is believed to help improve NVP. Furthermore, three recent studies comparing ginger to placebo conclude with beneficial effects of ginger (Keating & Chez, 2002; Ozgoli, Goli, & Simbar, 2009; Vutyavanich, Kraisarin, & Ruangsri, 2001). On the other hand, a Cochrane review of 13 studies on ginger concludes the overall evidence is not consistent (Matthews, Haas, O'Mathúna, & Dowswell, 2015). Ginger is reported safe to use in the first trimester. However, data on doses above 1000 mg per day is not available and as for many plants or herbal medication a standardized dose is non-existing (M. S. Fejzo, J. Trovik, et al., 2019). Lastly, ginger extract is interestingly found to inhibit the growth of some strains of H. pylori suggesting a double effect in treating HG (Mahady, Pendland, Yun, Lu, & Stoia, 2003).

1.5.2 Other non-pharmacological treatment

Other types of non-pharmacological treatment used to treat HG and NVP are acupuncture, acupressure and electrical nerve stimulation of the P6 point (Neiguan point). All of these have shown varying results ranging from very effective to no symptom improvement (Matthews et al., 2015). A couple of studies have shown acupuncture treatment and acupressure treatment (using sea bands) effective in treating nausea in pregnancy (Aghadam & Mahfoozi, 2010; Norheim, Pedersen, Fønnebø, & Berge, 2001). Furthermore, acupressure of the Chinese acupuncture point P6 (Neiguan) can decrease nausea in patients with chemotherapy-induced nausea and additionally patients with postoperative nausea and vomiting. These results can additionally help in the research of HG treatment (Werntoft & Dykes, 2001).

1.6 Pharmacological treatment of HG

The pathophysiology of nausea and vomiting is poorly understood, but to develop a therapeutic antiemetic regime, it is key to understand the available information. Vomiting is a reflex. Physiologically speaking, the first step involves retrograde peristalsis moving gastrointestinal content towards the esophagus. From there an essential closing of the epiglottis occurs to protect the airways before contractions of the diaphragm, abdomen and esophagus result in ejection of gastric content (Denholm & Gallagher, 2018).

Two important structures in the brain control the vomiting reflex: the vomiting centre (the area postrema) and the chemoreceptor trigger zone (CTZ) located in the medulla oblongata. Signals to these parts of the brain goes through different mediators and receptors (Miller & Leslie, 1994). Some of the known mediators are 5-hydroxytriptamine (5-HT3, also called serotonin), dopamine (D2), histamine (H1) and agents acting on muscarinic receptors (M1) (Denholm & Gallagher, 2018). Stimulation of the receptors further induce a vomiting reflex (MacDougall & Sharma, 2021). Drugs acting on the abovementioned receptors are used in HG treatment and a variety of antiemetic treatment options are available. Some antiemetics have unknown mechanisms of action but have been proven in studies to be effective treatment for HG.

As previously mentioned, an abundance of data is available on safety of antiemetic drugs in pregnancy and treatment should therefore not be restricted based on teratogenicity concerns. Nevertheless, safety in pregnancy is a mentionable issue related to drug use and will therefore be mentioned when presenting the variety of pharmacological treatment options. There is no consensus on one predefined treatment of HG and the treatment need to include individual plans and associated adjustments.

1.6.1 Antiemetics

Pyridoxine-doxylamine

A slow-release tablet containing pyridoxine (vitamin B6) and doxylamine is the only drug available in the USA having NVP and HG as a licenced indication. The combination pyridoxine and doxylamine is widely used also outside of the US, and sometimes pyridoxin is given on its own. Even though pyridoxin is in use, no correlation is found between pyridoxin levels in the blood and NVP symptoms. However, multiple studies report decreased nausea

symptoms, less reporting of nausea and reduced number of episodes of vomiting using pyridoxin-doxylamine compared to placebo (J. R. Niebyl & Goodwin, 2002; Sahakian, Rouse, Sipes, Rose, & Niebyl, 1991). The reduction in nausea and vomiting when taking pyridoxin and doxylamine is comparable to ginger and acupuncture (Chittumma, Kaewkiattikun, & Wiriyasiriwach, 2007; Ensiyeh & Sakineh, 2009; Jamigorn & Phupong, 2007). The mechanism of therapeutic effect of pyridoxin is unclear. Doxylamine is a antihistamine, mentioned further in the next section.

The pyridoxine-doxylamine combination is found safe and with no risk of adverse effects for the fetus in a meta-analysis including 170,000 pregnancies (McKeigue, Lamm, Linn, & Kutcher, 1994). Furthermore, no adverse effects on children with mothers taking doxylamine and pyridoxin during pregnancy regarding cognitive development is observed (Abramowitz, Miller, & Wisner, 2017).

Antihistamines

Antihistamines are the recommended first line treatment of HG (Smith et al., 2022). Antihistamines easily pass through the blood brain barrier (BBB) and acts on the vestibular system resulting in decreased stimulation of the vomiting center (Badell, Ramin, & Smith, 2006). A variety of neurotransmitters are being inhibited by antihistamines. Most importantly regarding nausea treatment is histamine H_1 receptors, and then muscarine receptors and serotonin receptors. All of which reduce stimulation of the vomiting center and CTZ (Etwel, Faught, Rieder, & Koren, 2017).

The use of antihistamines is relatively common. In Sweden and the USA, approximately 1 in 6 pregnant women report the use of antihistamines throughout their pregnancy, most commonly during the first trimester (Stephansson et al., 2011; Werler, Mitchell, Hernandez-Diaz, & Honein, 2005). Randomized controlled trials are sparse, but among others meclizine and pheniramine are reported to reduce symptoms better than placebo (Boelig et al., 2018; Leathem, 1986).

Regarding safety, a meta-analysis found antihistamines having no increased teratogenetic risk either in cohort studies or case control studies. Furthermore, no increased risk of spontaneous abortions, low birth weight, stillbirth or prematurity were found (Etwel et al., 2017).

The antihistamine promethazine does also act as a weak dopamine antagonist. Promethazine is highly effective in relieving symptoms, but has some maternal side effects such as sedation and dystonia (Fitzgerald, 1955). No teratogenic effects were reported on promethazine use in one study, but another study report increased risk of congenital hip dislocation (Magee, Mazzotta, & Koren, 2002; Witter, King, & Blake, 1981).

Dopamine antagonists

Metoclopramide, droperidol, prochlorperazine and chlorperazine are antiemetics in the group dopamine antagonists. All of which have been used to treat HG (Bsat, Hoffman, & Seubert, 2003).

All dopamine antagonists have therapeutic effects by inhibiting dopamine signalling in the GI tract and CTZ reducing the stimulation on the vomiting centre (M. S. Fejzo, J. Trovik, et al., 2019). More specifically for metoclopramide, the mechanism of action is also through increasing gastric motility by lowering esophageal sphincter pressure and increasing gastric transit and correct gastric dysrhythmias . Increased well-being for the women and reduction of the number of vomiting episodes are found when using dopamine antagonists in HG treatment (Tan, Khine, Vallikkannu, & Omar, 2010). Adverse effects of metoclopramide involve dry mouth, sedation and dystonia (Pasricha, Pehlivanov, Sugumar, & Jankovic, 2006). Regarding safety data on dopamine antagonists, cohort studies have been performed and the results show no increase of the risk of foetal malformations (Matok et al., 2009; B Pasternak, Svanström, Mølgaard-Nielsen, Melbye, & Hviid, 2014)

In the group dopamine antagonists we also find the phenothiazines (chlorpromazine and prochlorperazine), both having central and peripheral dopamine antagonists effects and have been shown to reduce symptoms in HG (Leathem, 1986). Phenothiazine derivates may cause profound sedation for the women (M. S. Fejzo, J. Trovik, et al., 2019). Regarding safety data, an increased risk of birth defects using phenothiazines, particularly chlorpromazine, in first trimester is reported. However, it is important to underline confounding factors such as treatment duration and alcohol use was present in the study (Rumeau-Rouquette, Goujard, & Huel, 1977). Few studies are performed on safety data of these drugs, but the previously mentioned review concludes dopamine antagonists to have no or very low risk for fetal malformations (M. S. Fejzo, J. Trovik, et al., 2019).

Serotonin antagonists

Serotonin has been implicated as one of many causes/risks of HG, but the association is not related to an increase in serotonin secretion nor serum concentration. The most commonly prescribed serotonin antagonist used to treat HG is ondansetron and the use is rapidly increasing (Gideon Koren, 2014). Ondansetron acts as an antagonist in the small bowel, vagus nerve and the CTZ on serotonin HT_3-receptors (M. S. Fejzo, J. Trovik, et al., 2019). The use of ondansetron is varied. For example in the USA a large number (approximately 20%) of pregnant women use ondansetron off label, while in Norwegian guidelines ondansetron should only be used when the other antiemetics have not been reducing symptoms adequately (Trovik, Noreng, Tellum, & Lomsdal, 2020; Zambelli-Weiner, Via, Yuen, Weiner, & Kirby, 2019). The NorPD study found 1% of pregnant women in Norway getting ondansetron prescribed (Marleen & Nordeng, 2021).

Most studies report no association between ondansetron and birth defects. Safety data have been collected amongst others by a Danish study concluding with no increased risk of fetal malformations or adverse pregnancy outcomes (Björn Pasternak, Svanström, & Hviid, 2013). Another study confirm the findings comparing women exposed to ondansetron and unexposed controls (A. Einarson et al., 2004). However, an increased risk of cardiac septal defects and cleft palate have been described (Anderka et al., 2012; Danielsson, Wikner, & Källén, 2014). Side effects of ondansetron is headache and fatigue, and in some situations also QT prolongation and serotonin syndrome (Danielsson et al., 2014).

1.6.2 Glucocorticoids

Treatment guidelines may also provide glucocorticoids as an option for refractory cases of HG. Glucocorticoids are only recommended if other types of antiemetic have been tried unsuccessfully (Smith et al., 2022). There is a limited understanding of the mechanism of action of glucocorticoids on HG symptoms. However, the glucocorticoids have antiemetic effect through effects on the CTZ in the brainstem. Furthermore, HG can cause a hypothalamic-pituitary-adrenal axis unbalance providing a relative adrenal insufficiency which glucocorticoids are believed to correct (Safari, Alsulyman, Gherman, & Goodwin, 1998).

From the same study, women using glucocorticoids were found to have a lower re-hospitalization rate than the control group given promethazine (Safari et al., 1998). A more recent study reports the contrary. Women getting the additional parenteral and/or oral corticosteroids to their treatment of HG did not experience a reduction in the need for rehospitalization later in their pregnancy (Yost et al., 2003). A third finding is a reduction in re-admissions, but the same number of days in hospital in total (Matthews et al., 2015). Nevertheless, a systematic review including multiple randomized clinical trials found a benefit in glucocorticoids in patients with severe symptoms (McParlin et al., 2016).

If glucocorticoid use is indicated, short treatment duration is recommended as effectiveness and safety in pregnancy is not fully understood. Symptom relief caused by glucocorticoid treatment beyond 72 hours is uncommon and the medication should be discontinued if inadequate effect is observed after 2-3 days as effects occur quickly if the medication have effect on that individual (Smith et al., 2022). Another study show a sharp decline in the number of vomiting episodes during the first three days but if vomiting continued after three days intravenous antiemetics were reintroduced (Grooten, Vinke, Roseboom, & Painter, 2016).

Variable results are found regarding antiemetic effect and safety in pregnancy. A 3.4 fold increase in oral cleft incidence is reported in infants whose mothers used corticosteroids during the first trimester (Smith et al., 2022). Schaefer et al. recommends no use of glucocorticoids until after gestational week 10, as the palatum is not fully developed before that time (Schaefer, Peters, & Miller, 2014). Regarding pregnancy outcome, studies report a higher incidence of preterm birth and low birth weight when the mother was treated with glucocorticoids (Gur, Diav-Citrin, Shechtman, Arnon, & Ornoy, 2004).

1.6.3 Antacid treatment

Heartburn and reflux are common health challenges in pregnancy. More interestingly, heartburn and/or acid reflux are associated with increased severity of NVP and HG symptoms compared to women without heartburn or acid reflux (Simerpal Kaur Gill, Maltepe, Mastali, & Koren, 2009). Therefore, treatment with anti-acid medication might also reduce symptoms of HG. Another study documents that treatment of heartburn and/or acid reflux gives

improved PUQE score and increased quality of life (Simerpal Kaur Gill, Maltepe, & Koren, 2009).

Treatment options include first line treatment using antacids with aluminum or calcium, thereafter H_2 antagonists and lastly PPIs. All options are safe to use in pregnancy (Simerpal K Gill, O'brien, Einarson, & Koren, 2009; Simerpal Kaur Gill, O'Brien, & Koren, 2009).

1.6.4 Vitamin supplementation

Looking into the trends in HG treatment with vitamin supplementation, it ranges from 10% (in UK) to 33% (in USA). A study from 2008 presents that 67–90% of women with HG may have prolonged vitamin deficiencies (T Murphy Goodwin et al., 2008). An example of maternal undernutrition is vitamin K deficiency that may cause coagulopathy (Robinson, Banerjee, & Thiet, 1998).

Thiamine

Another well described nutritional deficiency secondary to HG is vitamin B1 (thiamine) deficiency and can cause the rare and serous Wernicke encephalopathy. Wernicke encephalopathy is associated with ocular problems with nystagmus, change of mental status (confusion) and ataxia. Even though vitamin B1 deficiency is preventable and a recommended supplement to reduce the risk of disease, an increase of incidence of Wernicke encephalopathy is reported (Oudman et al., 2019). Lastly, when providing fluid treatment, it is important to add thiamine 200-400 mg if dextrose solutions are used. Normal saline is therefore the preferred fluid initially (exceptions are starvation and diabetic ketoacidosis) (Lowe & Steinweg, 2022).

1.7 Fluid and nutritional treatment

Rehydration, electrolyte correction and/or parenteral nutrition or tube feeding is often essential treatment. It can be given as outpatient or inpatient treatment depending on the woman´s condition, medically and mentally, hospital practices or availability (McParlin et al., 2016; Mitchell-Jones, Farren, Tobias, Bourne, & Bottomley, 2017). More studies on efficacy of treatment and nutritional strategies are needed before a golden standard treatment is available.

As dehydration is common in HG, intravenous (IV) fluids are given to correct dehydration and electrolyte disturbance. Furthermore, even with no use of antiemetic, IV fluids have been shown to reduce vomiting in pregnancy (Ditto, Morgante, La Marca, & De Leo, 1999). Fluid is given until the reversal of signs of dehydration and electrolyte correction should be performed before further parenteral nutritional interventions are started. Consequences of electrolyte imbalances are for example pontine myelinolysis caused by severe hyponatremia (<120 mmol/L) and arrythmias such as Torsade de pointes from hypokalemia (Gowda, Khan, Mehta, Vasavada, & Sacchi, 2003; Sánchez-Ferrer, Prieto-Sánchez, Orozco-Fernández, Machado-Linde, & Nieto-Diaz, 2017). Hypokalemia is the most frequently reported electrolyte imbalance caused by dehydration. Not only can it cause maternal cardiac arrest, hypokalemia increase the risk of respiratory issues and refeeding syndrome (Walch, Duke, Auty, & Wong, 2018). Refeeding syndrome can be defined as changes in fluids and electrolytes that may occur in malnourished patients receiving total parenteral nutrition (TPN) (Solomon & Kirby, 1990). These fluid and electrolyte changes are potentially fatal.

Moreover, HG-patients often having a hard time getting enough nutritional intake. A Norwegian study documented 24-hour energy intake as a median of 990 kcal (Birkeland et al., 2015). Nutritional status in HG patients has been shown to be below 50% of the recommended dietary allowances for most nutrients (van Stuijvenberg, Schabort, Labadarios, & Nel, 1995). When antiemetics and fluids are not sufficient in reducing nausea and vomiting, further nutritional interventions are needed. Tube feeding is preferred over parenteral nutrition because it is less invasive and has fewer serious risks. TPN involves a central venous catheter can lead to thrombosis or even sepsis (Holmgren, Aagaard-Tillery, Silver, Porter, & Varner, 2008). Maternal morbidity was reduced after parenteral and enteral nutrition became available (Smith et al., 2022).

1.8 Muhimbili national hospital

Muhimbili National Hospital (MNH) in Dar es Salaam is the largest teaching and referral hospital in Tanzania. The city of Dar es Salaam is estimated to have about 7 million inhabitants and an annual growth rate of 5.6% (WorldPopulationReview, 2021). Based on the health care system pyramid illustrated in Figure 1, MNH is on the top level: a National Referral Hospital. MNH has a large bed capacity of 1,500 patients. In addition to treating in-

patients, 2,000 outpatients visit the hospital for health services every day. In total, 2800 employees work at MNH, among them doctors, pharmacists, nurses, health care workers and a variety of supporting staff (Muhimbili National Hospital, 2022b).

The eight directorates of the hospital are Medical services, Surgical Services, Nursing & Quality Services, Clinical Support Services, Human Resources, Finance and Planning, Technical Services, and Information & Communications Technology, further divided into 33 departments (Muhimbili National Hospital, 2022b). Patients are mostly referred from surrounding hospitals or larger regional hospitals. Some patients are also self-referrals coming directly from home.

The Department of obstetrics and gynecology and the Medical records department were essential for conducting the present study, and will be described in further detail below.

Department of Obstetrics and Gynaecology

The Department of Obstetrics and Gynecology has one building for gynecological patients and two maternity blocks. Within the two maternity blocks there it is a total of seven wards (labor ward, antenatal wards, and postnatal wards), each with a capacity of 50 patients. In the Gynecology building, the bed capacity is 80. The department also has an intensive care unit (ICU), treating critically ill patients with high morbidity, such as hyperemesis gravidarum (HG) and other medical and surgical condition.

Medical records department

The main responsibility of the medical records department is to store the patient´s medical records. This includes the responsibility to code and classify disease, store, and retrieve medical records, and collect and interpret data for research or administrative use. Patient records are currently partly physical files and partly electronic files. The electronic system Jeeva is used for creating and maintaining the medical records. The Medical records department currently has 78 employees (Muhimbili National Hospital, 2022a).

1.9 Significance of the study

To use medicines in a rational way is crucial to achieve optimal outcomes in healthcare through maximizing gain while minimize the harm and threats posed by inappropriate

treatment. Such threats can be illness due to under-prescribing, antimicrobial resistance, or major challenges due to polypharmacy.

Furthermore, standardized treatment guidelines (STG) may increase treatment quality and reduce irrational medication use. STGs help provide more consistent and correct diagnosis and establish recommended treatment pathways. This is especially important for LMICs, such as Tanzania, where irrational medicine use is more prominent than in higher-income settings (Wiedenmayer et al., 2021), and the health resources are limited.

1.10 Why study hyperemesis gravidarum in a hospital population in Tanzania

A list of top 26 ranked priorities in hyperemesis gravidarum research was preformed recently where point number two was “How can we most effectively manage HG? What clinical support measure is most important to people who have had hyperemesis and what did they find most beneficial? For example, medical management, pharmaceutical review, nutrition support, rehydration, psychological support” (Dean et al., 2021). This point is in the core of this research project, evaluating the treatment given to HG patients at a referral hospital in Tanzania.

Even though HG is one of the most common reasons for hospitalization during pregnancy, there is a knowledge gap in the treatment provided for women with HG in African settings, and no studies have been found evaluating treatment provided for hospitalized patients in Tanzania. Describing the treatment these women receive in a hospital setting may provide insight into areas of potential improvement, increase awareness of HG among health care workers, and knowledge base for policy change. Therefore, it is interesting to evaluate the treatment given to these women in a hospital population.

2 Aim of the study

The aim of the study is to describe the treatment provided for women hospitalised for *Hyperemesis gravidarum* at Muhimbili National Hospital, Dar es Salaam, Tanzania.

2.1 Problem statement

There is little knowledge about the prevalence and treatment of HG in Tanzania. As the condition is debilitating and can be life threatening if left untreated, it is important to know how it is treated in hospital.

2.2 Research questions

What demographic and gestational characteristics have women admitted to Muhimbili National Hospital for treatment of *Hyperemesis gravidarum*?

What kind of fluid, nutritional and/or pharmacological treatment is provided for the women admitted to Muhimbili National Hospital for treatment of HG?

Is the treatment in accordance with local and/or national guidelines?

3 Methods and materials

3.1 Study design

The study design of this master project is a retrospective cohort study of a hospital population. Data was collected from medical records of women admitted for treatment of HG at MNH, Dar es Salaam between January 1st 2004 and March 31st 2021.

Personal information, pregnancy data, admission details, and fluid-, nutritional-, and pharmacological management were collected in accordance with a standardized Data extraction Forms (Appendix 1 and 2). Data collection took place in the period 22nd of October to 10th of December 2021 and was aided by local research assistants.

3.2 Study population and sample size

The study population consists of all women admitted to MNH from year 2004 to year 2021 identified in Jeeva with a diagnosis of hyperemesis gravidarum and fulfilling the following criteria:

- ICD-10 diagnose code O21.0 or O21.1
- First admission before pregnancy week 20 (gestational age)
- Fulfilling two or more of the following criteria: dehydration, weight loss and ketonuria/electrolyte disturbances

3.3 Investigation tool, validity, and reliability issues

Data collection was preformed using a standardized Data Extraction Form (Appendix 1 and 2), adapted from a data extraction form developed in Bergen, Norway and used for data collection at Norwegian Hospitals (Bakkebø, 2020; Bryn, 2018; Kristiansen, 2016).

An in-study pilot of the first 15 patients was conducted to evaluate and adapt the study protocol and Data Extraction Form. The results from the pilot were discussed with local supervisors, including gynecologist Dr. Wangwe from Muhimbili, to ensure data quality and make local adaptations. As a result, the data extraction form was edited to fit the Tanzanian setting by including data on HIV-status, insurance, multiple pregnancy, and a variety of lab

results (serum electrolytes). Additionally, the data extraction form was simplified regarding type and duration of nutritional treatment.

3.4 Data collection method

Patients were identified using the integrated Hospital Management Information System (HMIS) application called Jeeva. The search was performed in the Jeeva system, module Medical Records (version 1.0.0.102), by searching for "date from" (01.01.2004) and "date to" (01.04.2021) and using the ICD-10 codes O21.1 and O21.0. After identification of the patients, the case file number (medical record number) was noted and given to the staff in the Department of Medical Records who retrieved the files from the archives. Delivery outcome was only available for women giving birth at MNH or if information of miscarriage or termination of pregnancy was documented in the woman's medical records.

Treatment data and personal data were retrieved from the medical record notes. The same patient was followed up in both the Maternity block and the Gynecology ward, but each woman had one single medical record. Additionally, medical records were searched looking for information on maternal and fetal outcome. HIV-status was cross-checked with the HIV registry.

All medical records used in this study were paper files from the hospital medical archives which were written in English.

3.5 Study setting

The study was conducted at MNH, department of Obstetrics and Gynecology which has approximately 18 000 deliveries annually. MNH is the largest referral hospital in the United Republic of Tanzania and is located in the city of Dar es Salaam. Additionally, MNH is a teaching hospital. Patient with HG before 28 weeks gestation are admitted at the Gynecological ward whereas women with gestational age above or equal to 28 weeks gestation are admitted at the Maternity block.

3.6 Ethical considerations

The study received ethical approval from MUHAS in Tanzania and the Regional Committee for Medical and Health Research Ethics in Norway (project ID 241381), including waiver of

consent, prior to data collection. Additionally, permission to conduct the study and waiver of individual informed consent was approved from the Executive Director at MNH (Appendix 3 & 4).

3.7 Data and statistical considerations

An overview of all the data that was collected in this project can be found in the data extraction form (Appendix 1 and 2). Selected variables will be described in detail below.

3.7.1 Demographics and maternal characteristics

Age

When birth year was the most detailed information provided, the date 01.07 was chosen based on the financial year in Tanzania. This is common practice for local projects. Age was calculated based as year of first admission minus birth year.

HG in earlier pregnancies

Registered as "No" if no previous pregnancy with HG diagnosis, "Yes" if previous pregnancy with HG diagnosis and blank if not mentioned in the patient file. Only relevant for the women with previous pregnancy/pregnancies (gravidity > 1).

Number of pregnancies with HG

Reported as number of previous pregnancies with HG diagnosis. The current pregnancy is excluded from this number.

Women with HG in > 1 pregnancy

In cases where one woman was admitted to MNH during more than 1 pregnancy with HG, all pregnancies were registered individually. Statistically, all pregnancies are considered as independent.

Ethnicity

All women reported African based on names, family history and help from local assistants with expertise on the women admitted to MNH.

Insurance

Insurance coverage was registered as covered or not covered based on papers from the finance department and information in the medical records. No distinctions were made between different types of insurances.

Last menstrual period

Information on last menstrual period of the woman was registered with the level of detail available in the files. If reported as month, year, the 1st was chosen as date. «Beginning» of a month reported as 1st , "Mid" reported as 15th, "Late" reported as 30th.

Gestational age

Gestational age at first admission was calculated based on time since last reported period (LMP).

Gravidity

Number of pregnancies, regardless of duration, including the present pregnancy.

Parity

Number of previous births.

Smoking

Categorized as not smoker, smoker or blank if not reported.

More than one baby (multiple pregnancy)

Recorded as "Yes" if more than one baby, "No" if singleton pregnancy.

Serum electrolytes

Electrolyte imbalance was registered if the value deviated from the reference levels used at MNH:Serum chloride [135-147 mmol/L], serum potassium [2,6-5,5 mmol/L] and serum sodium [135-147 mmol/L].

Readmission

All hospital admissions caused by HG throughout the pregnancy was registered. Women with admissions > 1 was considered as having readmission.

Dates

Date of admission and date of discharge was registered as date.month.year.

3.7.2 Data regarding the baby and pregnancy outcome

Expected date of birth

Calculated from last menstrual period or from information provided in the medical records.

Apgar score

International scoring scale on newborns general health situation right after birth. If not provided in the patient files, the field was left blank.

Abortion

Date of abortion, and if the abortion was spontaneous or induced.

3.7.3 Data regarding nutritional-, fluid- and pharmacological treatment while admitted

Antiemetics

All drugs with known antiemetic mechanism of action are included in the term antiemetics, including antihistamines. The antiemetics were registered as active substance, not trade name as this was not always mentioned and active substance is considered most

relevant. Every active substance used during hospital admission and prescribed when discharged were registered. For women with multiple admissions, data on medication use was analyzed as use during any hospital stay.

Medication regime

The medication regime was registered as "scheduled" or "on demand". Scheduled medicines are given regularly at predefined times during the day, while on demand medicines are given when needed.

Combinations

Use of more than one antiemetic on the same day was considered a combination.

Drugs at discharge

If doctors prescribed medication for a longer time than the women was admitted the drug was also reported as drugs at discharge.

Antacids, dalteparin, cortison, haloperidol and vitamins/minerals

The abovementioned drugs and vitamins were registered if given during the hospital stay. Both per oral and injectable vitamins/minerals is included. When "multivitamin" is reported it can be different combination of > 4 vitamins and minerals.

Vitamin as medication

Pyridoxin (B6) is given as pharmacological treatment/medication and is therefore in these cases registered as active substance of drugs and not as vitamin.

3.7.4 Data analysis

To describe the data material, descriptive statistics using frequency and percentages were used. Variables with distribution approximately normal distribution, were presented as mean and standard deviation (SD). Non-parametric data were presented as median and interquartile range (IQR). The statistical analyses were performed using Stata (Statistics and Data Science, version 17.0 SE-Standard Edition) and Microsoft Excel (version 16.60).

Non-parametric tests were used because for variables that were not normally distributed. Moreover, the small sample size makes non-parametric tests more suitable as validating the distribution of the data might not be feasible. Compared to parametric tests which makes assumptions about the population parameters and require data to meet a distribution (often normal distribution), non-parametric tests do not make assumptions about the underlying data. The significance level was set at 0,05. All tests were two-sided.

The Shapiro-Wilk test

The Shapiro-Wilk test is a test to test if the variables originate from a normal distribution, a test of normality.

Chi-square test

Chi-square test for independence is a hypothesis test comparing two variables in a contingency table (Zibran, 2007). The chi-square test was used to compare categorical variables. Fisher´s exact test was used if at least one of the table cells in the contingency table was below n = 5.

Mann-Whitney U test (Wilcoxon rank sum)

The Mann-Whitney U test is a non-parametric test to compare two independent groups. The Mann-Whitney U-test was used to test if there was a significant difference in median between different groups in the case of continuous variables.

The Newey–West estimator

The Newey–West variance estimator was used in linear regression of changes over time, accounting for first order autocorrelation. Reported as β (percentage change each year) and confidence interval (CI).

4 Results

4.1 Study population and sample size

A search of patients with the ICD-10 diagnoses O21.0 and O21.1 between 2007 and 2021 in the electronic system Jeeva at MNH yielded a total of 298 files, of which 163 women fulfilled the inclusion criteria, as illustrated in Figure 4-1 below.

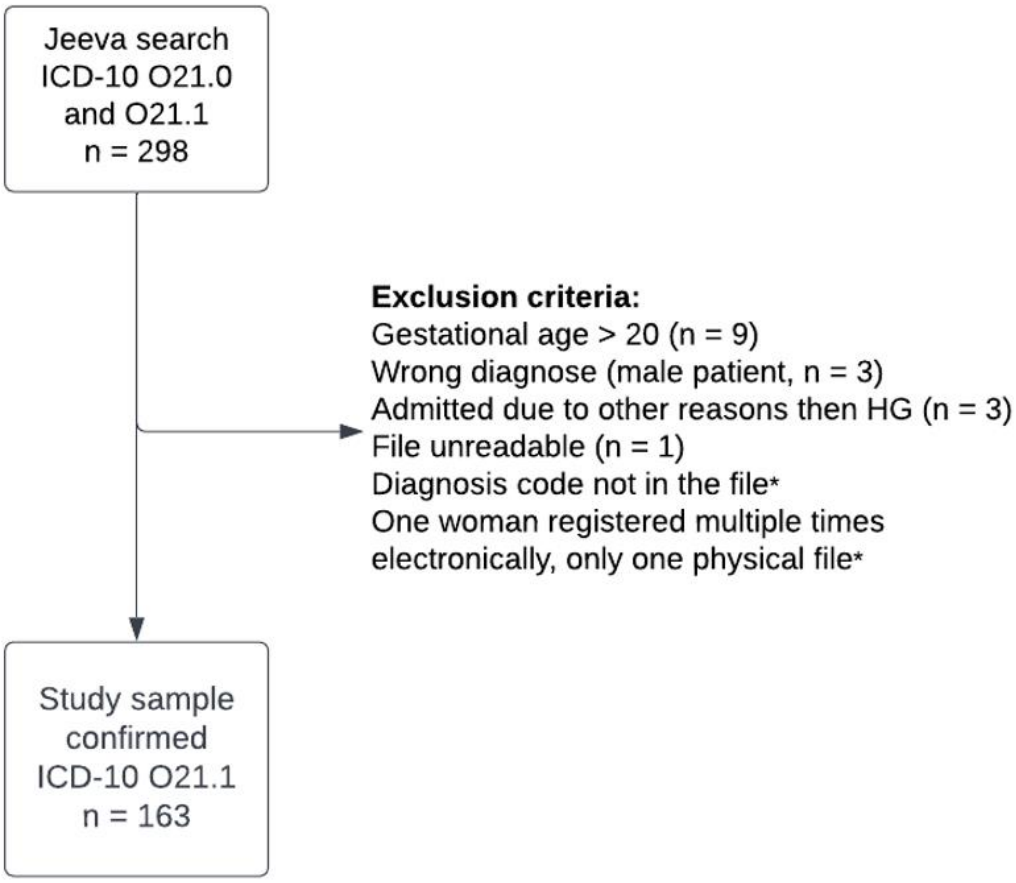

Figure 4-1 Flow chart of inclusion and exclusion of files found from search of ICD-10 O21.0 and O21.1 in electronic patient file system at Muhimbili National Hospital 2004-2021. Sample size in the present study and reasons for exclusion

The median age of the cohort was 29 years (25-33), ranging from 14 to 44 years. The number of hospital admissions throughout the pregnancy ranges from minimum 1 (n = 145, 89,0%) to maximum 5 (n = 1, 0,6%) and the median number of days admitted to hospital is 4 (3 - 8). Minimum number of total hospital days was 1 (n = 4, 2,5%) and the maximum 52 (n=1,

0,6%). Further characteristics of the study population are described in Table 4-1 and Table 4-2. Data on height and weight pre pregnancy were not systematically recorded in the files. Hight information was found for 12 women (7,4%) and weight pre pregnancy only reported for one woman (0,6%). In this study cohort one miscarriage is recorded, but no cases of termination of pregnancy.

No files were found from 2004 to 2007.

Table 4-1 Characteristics of women hospitalized for Hyperemesis Gravidarum at Muhimbili National Hospital between 2007 and 2021

Variable	Median (IQR[a])	Minimum - Maximum	Missing
Age (years) n = 162	29 (25 – 33)	14 - 44	n = 1
Gravity n = 144	2 (2 - 3)	0 - 6	n = 19
Parity n = 145	1 (0 – 2)	0 - 4	n = 18
Gestational age (in weeks) at first admission n = 163	11 (8 - 14)	3 - 20	-
Number of admissions n = 163	1 (1 – 1)	1 - 5	-
Number of total hospital days n = 163	4 (3 – 8)	1 – 52	-

[a]Interquartile range

Approximately 40% of the study population had health insurance, 2,5% were HIV positive and all (100%) included women were African. Furthermore, 8% had suffered from HG in previous pregnancies and 5,5% were pregnant with more than one fetus (multiple pregnancy), as summarized in Table 4-2.

Table 4-2 Binary variables characteristics of women hospitalised for hyperemesis gravidarum at Muhimbili National Hospital between 2007 and 2021

Variable	Distribution n (%)		
	Yes	No	Missing
Insurance coverage	63 (38,7%)	100 (61,3%)	-
HIV positive	4 (2,5%)	156 (95,7%)	3 (1,8%)
Multiple pregnancy	9 (5,5%)	108 (66,3%)	46 (28,2%)
Smoking	-	111 (100%)	-
African ethnicity	147 (100%)	-	16 (9,8%)
HG in earlier pregnancy	13 (8,0%)	110 (67,5%)	40 (24,5%)

4.2 Management of HG

Among the 163 women admitted for HG in the study period, 145 (89,0%) was admitted to hospital once, 15 (9,2%) was admitted twice, 2 (1.2%) was admitted three times and 1 (0,6%) was admitted 5 times. In other words, n = 18 (11,0%) of the women was readmitted to hospital during their pregnancy.

In cases with more than one admission, the median number days between admission number 1 and number 2 was 11 (8 – 21) days (n= 18). The median number of days between admission 2 and 3 was 18 (11 – 43) days (n = 4). Minimum days between admissions were 4 days (n = 1) and maximum were 219 (n = 1).

Most women (98,8%, n = 161) received some type of antiemetic treatment during the hospital stay or when discharged and 95,7% (n = 156) got some type of fluid treatment during the hospital stay. Regarding the two women who didn´t get antiemetic treatment (1,2%), one got intravenous fluid treatment and one did not get antiemetic treatment nor intravenous fluid treatment.

1.1.1 Antiemetic medications in use at MNH

The antiemetic medications used in treatment of HG at MNH were; Serotonin (5-HT3)-antagonist (ondansetron), antihistamines (doxylamine, meclizine, promethazine, hydroxyzine), dopamine antagonists (metoclopramide, prochlorperazine), glucocorticoid (dexamethasone), and anticholinergics (scopolamine, butylscopolamine).

The most used antiemetic medications were ondansetron (n = 81, 49,7%), doxylamine-pyridoxin (n = 80, 49,0%), and metoclopramide (n = 75, 46,0%), followed by promethazine (n = 41, 25,2%). The number of women receiving different antiemetic drugs by active substance either when hospitalised or when discharged is illustrated in Figure 4-2.

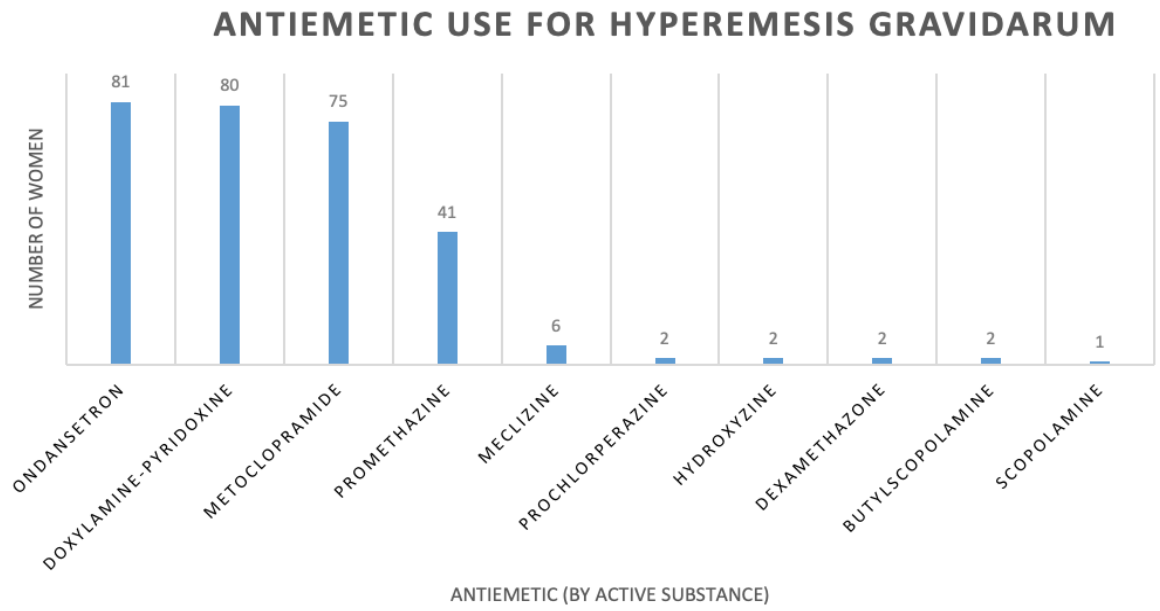

Figure 4-1 Number of women hospitalized at Muhimbili National Hospital for hyperemesis gravidarum 2007-2021 receiving different antiemetic drugs while at hospital or when discharged.

Of the women who received antiemetic treatment, 109 (67,7%) got two or more antiemetics. The maximum number of antiemetic medications given was 7 (n= 1, 0,6%). An overview of the number antiemetics used per women is shown in Figure 4-3 below.

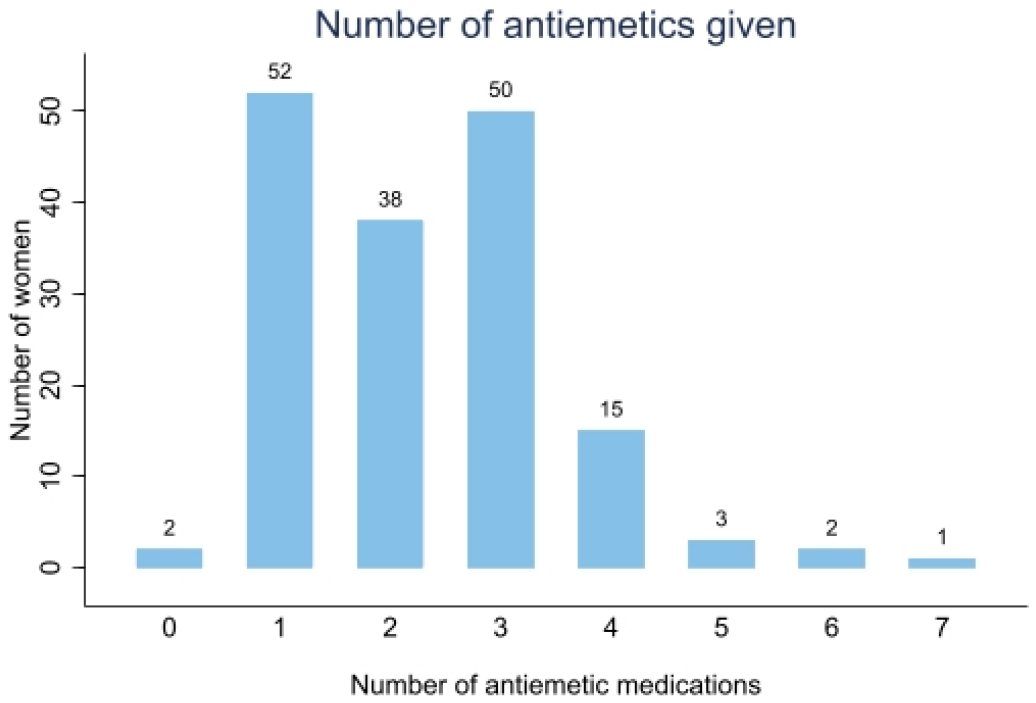

Figure 4-2 Number of different antiemetic medications used by each woman admitted for HG at MNH. The medications were given when admitted and/or prescribed when discharged.

Medications were mostly given as scheduled dosages (n =398, 94,3%). On demand regime was used in 5,7% (n = 24) of administrations.

1.1.2 Antiemetics during hospital admission

The distribution of antiemetics sorted by active substance is given in Figure 4-4. Compared to Figure 4-2 only drugs given while the women were admitted is included in this section. The most used antiemetics in hospital are ondansetron (n = 81, 49,7%), doxylamine-pyridoxin (n = 78, 47,9%) and metoclopramide (n = 73, 44,8%) followed by promethazine (n = 41, 25,2%).

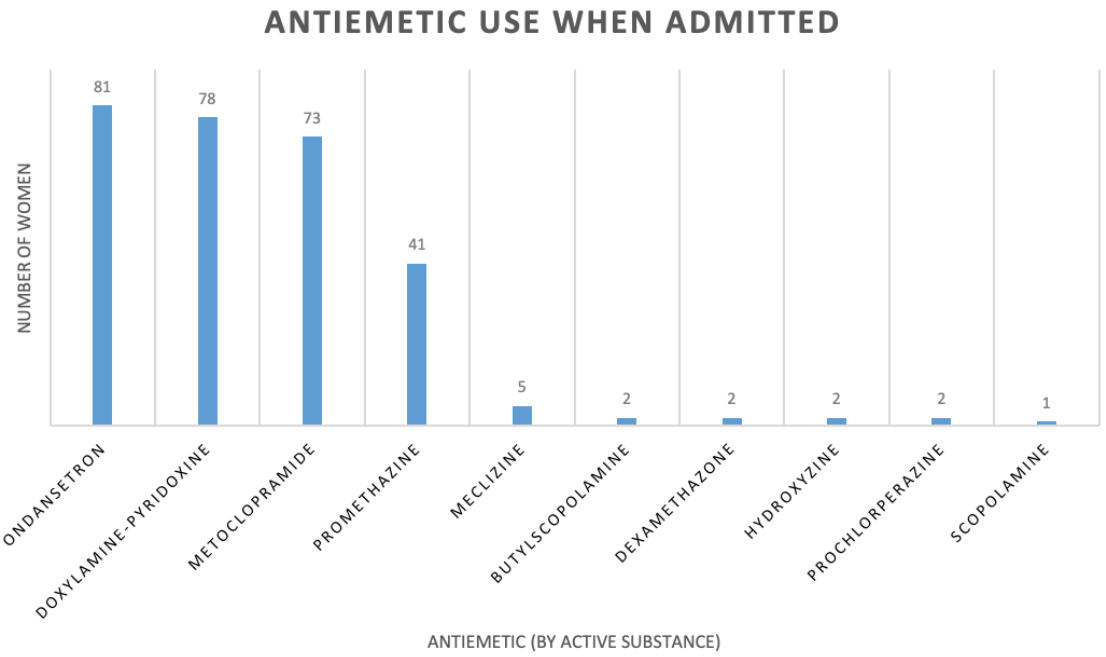

Figure 4-3 Distribution of antiemetic drugs used to treat HG at MNH between year 2007 and 2021. Each bar represents the number of women who got the respective drug during hospital admission.

Top three medications given as the first antiemetic were metoclopramide (n = 57, 35,4%), ondansetron (n = 46, 28,6%) and promethazine (n = 40, 24,8%).

Of the 81 women who got ondansetron treatment, 33 (40,7%) received ondansetron before gestational week 10. Two women were treated with dexamethasone, both during their first and only hospitalization.

The different routes of drug administration in use per woman are given in Figure 4-5. Half of the women (50,3%) got at least one drug administered intravenous, 41,3% got at least one medication per oral, 8,2% at least one intramuscular injection and lastly one was treated with suppositories. Use of transdermal antiemetics was not observed. Per oral antiemetics were given to 71 (61,7%) of those who got treated with at least one intravenous antiemetic, 20 (74%) of those who got treated at least once with intramuscular antiemetic and the woman who got suppositories also got per oral antiemetic treatment.

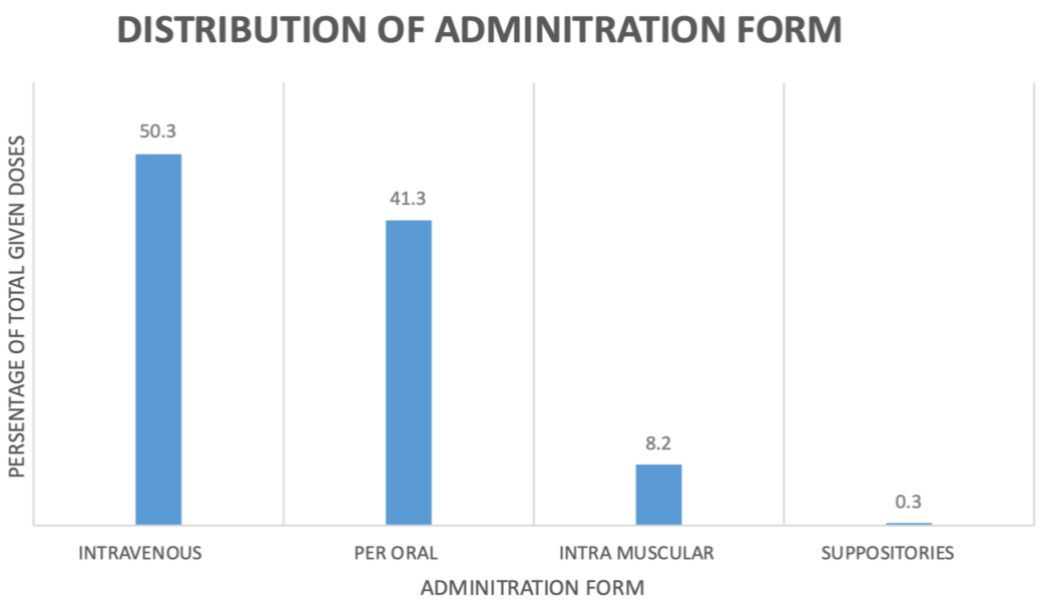

Figure 4-4 Distribution of the different route of administration of antiemetics given to women hospitalised for hyperemesis gravidarum at MNH between 2007 and 2021 while admitted to hospital. Peroral administration include oral solution, capsule, and tablets.

A summary of administration form and regimen for different antiemetic medications is displayed in Table 4-3. Medications were mostly given as scheduled dosages (n =339, 92,1%). On demand regime was only used in 7,9% (n = 29) of administrations during hospital admission and 83,3% (n = 20) of these are ondansetron and metoclopramide. The trend of using scheduled regimen over on demand regimen was applicable for all types of antiemetics. Most antiemetics were given as intravenous administration (n = 181, 48,1%), followed by per oral administration (n =152, 40,4%). Only once was an antiemetic given as suppository and this antiemetic was ondansetron (n = 1, 0,27%).

Table 4-3 Regimen and administration form of antiemetic drugs given in hospital to HG patients at MNH between 2007 and 2021

Antiemetic	Regimen[a]		Administration form[a]			
	Scheduled	On demand	Suppository	Per oral	Intravenous	Intramuscular
Ondansetron	109	10	1	24	94	0
Metoclopramide	90	10	0	30	64	5
Doxylamine-pyridoxin	80	3	0	80	1[b]	13[b]
Promethazine	46	3	0	10	20	20
Meclizine	5	0	0	5	0	0
Butylscopolamine	2	0	0	1	1	0
Dexamethasone	2	1	0	1	1	0
Hydroxyzine	2	2	0	0	0	2
Prochlorperazine	2	0	0	0	0	2
Scopolamine	1	0	0	1	0	0

[a] Regimen and administration form was registered per admission. Each woman may have received the same antiemetic medication during several admissions and in several administration forms
[b]When given intramuscular or intravenous, doxylamine succinate was given without pyridoxin

Antiemetics were given at the dosages listed below (Table 4-4). Some were given with standard dosages across admissions, but promethazine and ondansetron were given using a variety of different dosages. The antiemetic with the most dosages was ondansetron which was given with 13 different dosages.

Table 4-4 Dosages given to women hospitalize for HG at MNH between 2007 and 2021. Dosages given of each antiemetic drug.

Antiemetic	Dosage			
Meclizine Count (n)	**25 mg x 1** 4	**25 mg x 3** 1		
Promethazine Count (n)	**10 mg x 1** 2	**10 mg x 3** 2	**20 mg x 2** 2	**25 mg x 1** 16
	25 mg x 2 18	**25 mg x 3** 6	**50 mg x3** 1	
Ondansetron Count (n)	**2 mg x 1** 2	**4 mg x 1** 14	**4 mg x 2** 10	**4 mg x 3** 9
	6 mg x 3 1	**6 mg x 4** 1	**8 mg x 1** 30	**8 mg x 2** 19
	8 mg x 3 14	**10 mg x 1** 2	**10 mg x 3** 4	**12,5 mg x 1** 2
	16 mg x 2 1			
Prochlorperazine Count (n)	**12,5 x 1** 2			
Hydroxyzine	**25 mg x 1**			

Count (n)	2			
Doxylamine/ pyridoxin Count (n)	**10mg/10mg x 1** 31	**10mg/10mg x 2** 35	**10mg/10mg x 3** 10	
Dexamethasone Count (n)	**4 mg x 2** 1	**6 mg x2** 1		
Butylscopolamine Count (n)	**20 mg x 3** 1	**40 mg x 3** 1		
Scopolamine Count (n)	**1,25 mg x 1** 1			

1.1.3 Combinations of antiemetic drugs

At least one combination of antiemetic drugs was given to 41.5% (n= 68) of the women. Maximum number of different combinations were 3 (n = 3, 1,8%) as illustrated in Figure 4-6.

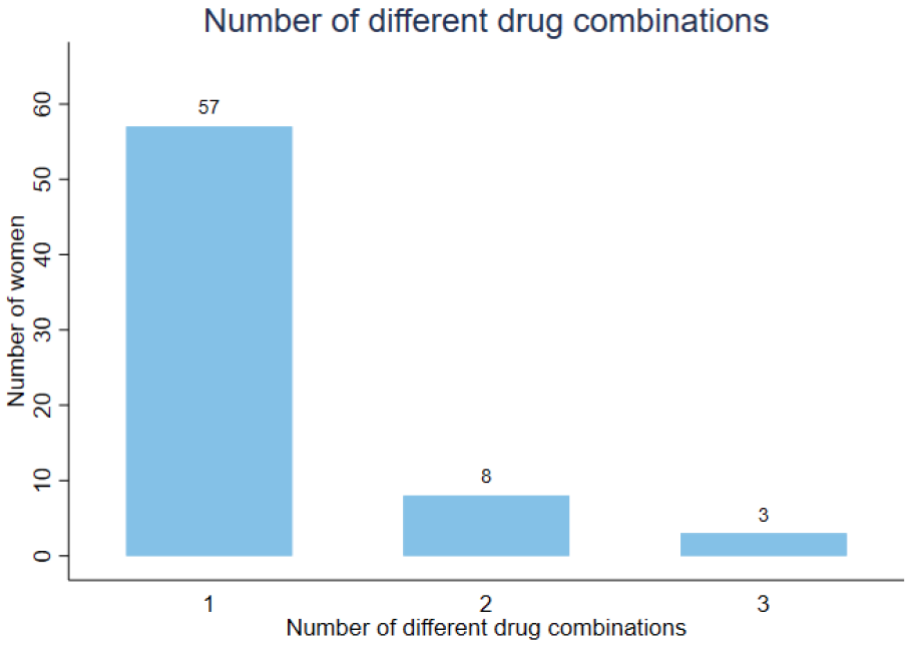

Figure 4-5 Bar plot of the number of combinations of antiemetic drugs per woman admitted for HG at MNH between 2007 and 2021

Where Figure 4-6 shows the number of different combinations in use, Table 4-5 shows which combinations were given. The most common combination was "metoclopramide + doxylamine + pyridoxin" (n = 16, 9,8%). Thereafter, "ondansetron + doxylamine + pyridoxin" (n = 14, 8,6%). Regarding combination of two antiemetics, "metoclopramide + ondansetron" (n = 6, 3,7%) was most used. The combinations consist mostly of drugs from different groups of antiemetics. The exception is antihistamines which is combined in five combinations (27,8%), as two or three antihistamines used together.

Table 4-5 List of different combinations of antiemetic drugs given to women at MNH between 2007 and 2021

Combinations of antiemetica	Number of women getting the combination treatment (% of total study population n = 163)
Two antiemetics combined	
Metoclopramide + ondansetron	n = 6 (3,7%)
Prochlorperazine + ondansetron	n = 5 (3,1%)
Promethazine + ondansetron	n = 5 (3,1%)
Promethazine + metoclopramide	n = 1 (0,6%)
Metoclopramide + dexamethasone	n = 1 (0,6%)
Butylscopolamine + metoclopramide	n = 1 (0,6%)
Three antiemetics combined	
Metoclopramide + doxylamine + pyridoxin	n = 16 (9,8%)
Ondansetron + doxylamine + pyridoxin	n = 14 (8,6%)
Promethazine + doxylamine + pyridoxin	n =13 (8,0%)
Meclizine + doxylamine + pyridoxin	n = 2 (1,2%)
Promethazine + metoclopramide + ondansetron	n = 2 (1,2%)
Four antiemetics combined	
Metoclopramide + ondansetron + doxylamine + pyridoxin	n = 7 (4,3%)
Promethazine + ondansetron + doxylamine + pyridoxin	n = 2 (1,2%)
Prochlorperazine + scopolamine + doxylamine + pyridoxin	n = 1 (0,6%)
Butylscopolamine + metoclopramide + doxylamine + pyridoxin	n = 1 (0,6%)
Promethazine + metoclopramide + doxylamine + pyridoxin	n = 1 (0,6%)
Five antiemetics combined	
Promethazine + metoclopramide + meclizine + doxylamine + pyridoxin	n = 1 (0,6%)
Promethazine + metoclopramide + ondansetron + doxylamine + pyridoxin	n = 1 (0,6%)

1.1.4 Vitamin supplements

The majority (n = 112, 68,7%) got vitamin supplements, as illustrated in Figure 4-7. The most given vitamin supplement was folic acid (n = 66, 40,0%) followed by combinations of B-vitamins (n = 56, 34.4%). A general multivitamin supplement was given to 29 of the women (17,8%). Thiamine was provided for 56 women (34,4%) while iron supplement was given to 46 women (28,2%). One woman was treated solely with vitamin supplement and did not receive antiemetics nor fluid treatment.

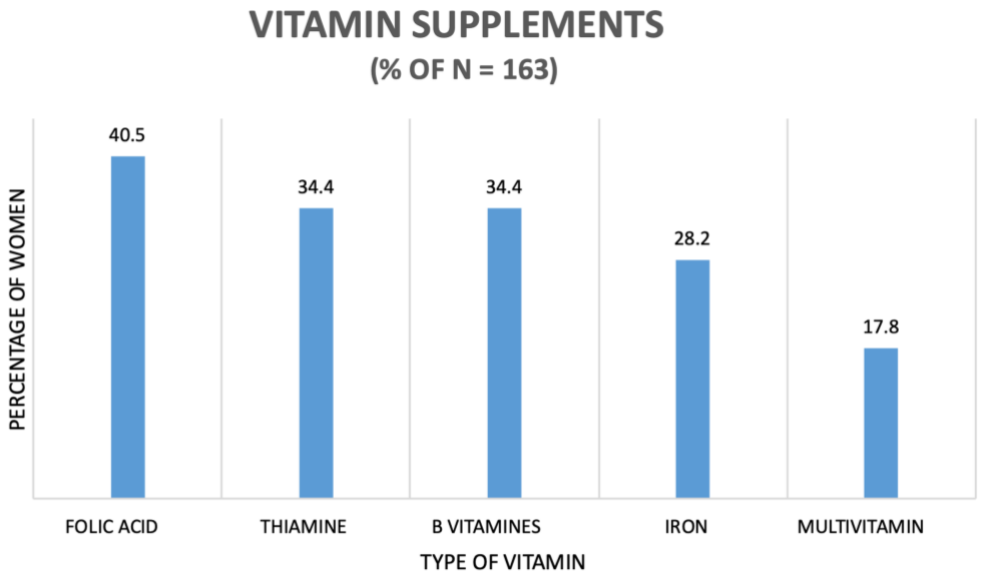

Figure 4-6 Distribution of vitamin treatment used on HG patients at MNH between year 2007 and 2021. Each bar represents the number of women who got the respective vitamin during hospital admission.

The use of folic acid and thiamin over the study period (2007-2021) is illustrated in Figure 4-7. Thiamin use fluctuated over time, with no significant increase over the study period as a whole. The yearly increase is 1,7% (95% CI: -1,2 to 4,7, p=0,229). However, looking at the years up until 2018 a significant yearly increase (4,2%) in thiamine use is found (95% CI: 2,7 to 5,8, p < 0,05). No significant yearly change was observed in use of folic acid (ß = 0,525, 95% CI: -1,6-2,7, p = 0,61), as illustrated in Figure 4-8. It is important to underline there are fluctuations in the percentage of women who get these vitamins each year.

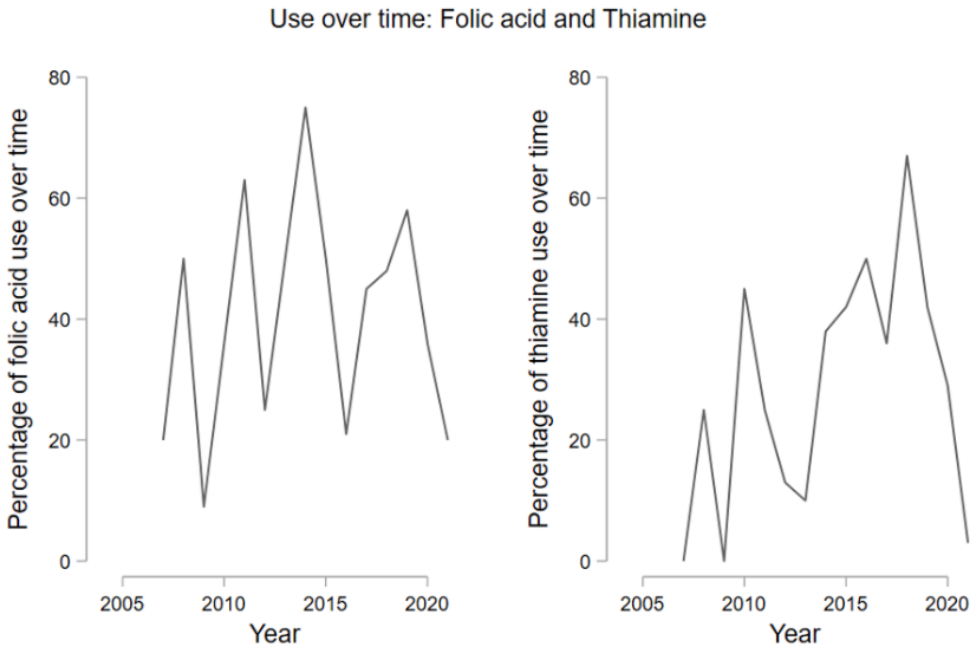

Figure 4-7 ***Folic acid and thiamine management over time from 2007 to 2021*** *Left: Folic acid use over time, indicating a stable use of folic acid. Right: Use of thiamine, especially important for HG patient. The use has increased over the years, but have had a drastic drop the last three years.*

1.1.5 Antacid treatment

Antacids (stomach acid neutralizing medication) was given to 67 women (41,1%). The most used antacid was pantoprazole which 51 women (31.1%) got treated with. Thereafter, the second most used anti-acid medications are Relcer gel® (containing aluminum hydroxide/magnesium/simethicone) and omeprazole. Both given to 18 women (11,0%).

Of those who got treated with antacids, 35,8% (n = 24, of 67) were treated with a combination of different antacids. Double PPI treatment as given to 8 women (4,9%). Triple PPI was given to 1 woman (0,6%). The distribution of antacids (by active substance) is illustrated in Figure 4-8.

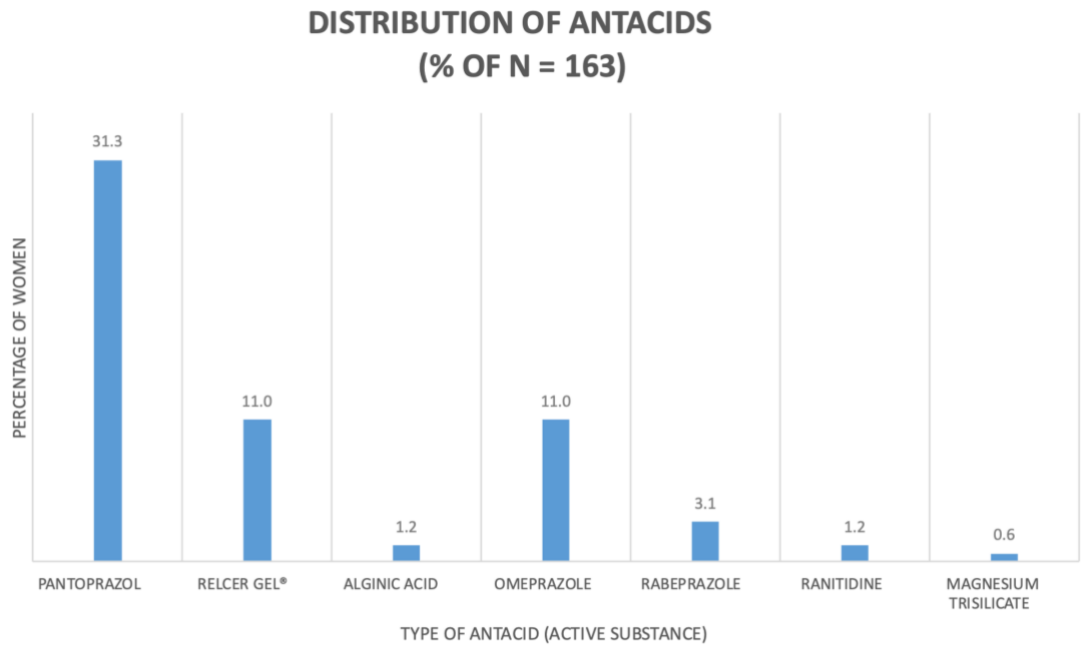

Figure 4-8 Distribution of antacids (by active substance) given to women admitted to MNH for hyperemesis gravidarum between 2007-2021. Relcer gel contains aluminum hydroxide/magnesium/simethicone.

4.3 Fluid management

Figure 4-10 shows the distribution of different fluids used to treat dehydration caused by HG during hospital stay. Fluid treatments were given to 156 women (95,7%). Four different fluids were given: normal saline (NS), Ringer´s lactate (RL), Dextrose & normal saline (DNS) and Oral rehydration solution (ORS) where NS, RL and DNS are intravenous treatment and ORS is a solution given orally.

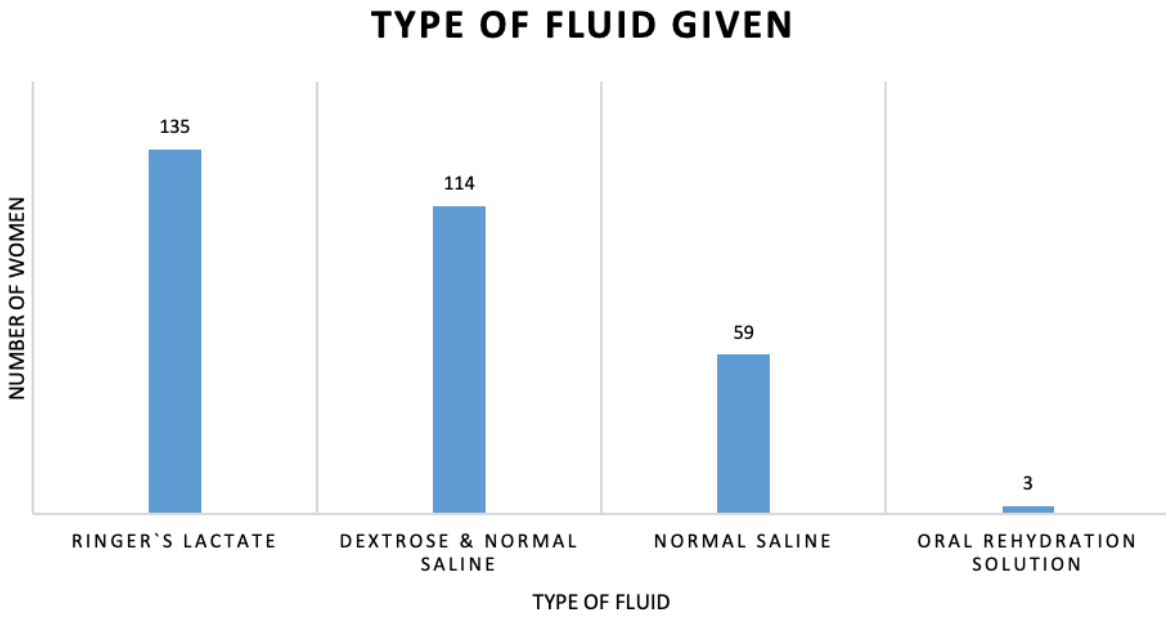

Figure 4-9 Distribution of fluid treatment used on HG patients at MNH between year 2007 and 2021. Each bar represents the number of women who got the respective fluid during hospital admission.

More than half of the women (n = 88, 56,4%) got two different types of fluid during their hospital stay. 7 women (4,5%) did not get fluids while admitted and the maximum number of fluid combinations were 3 (n = 33, 21,2%). Figure 4-11 provides a bar plot of number of fluids given per woman. Among women who got discharge medications most were not readmitted to hospital (80%) and 20% were readmitted ($p < 0,05$, chi square test).

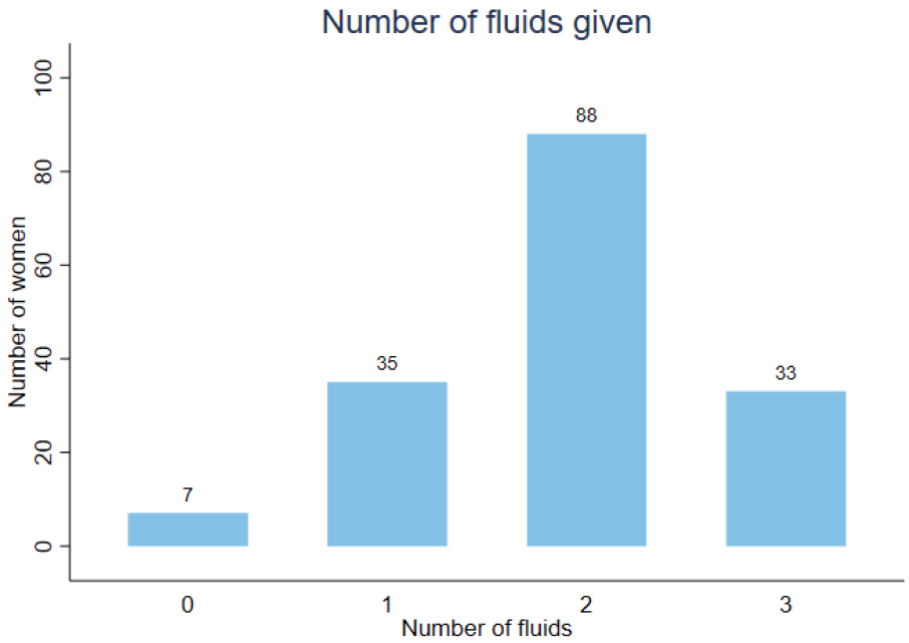

Figure 4-10 Bar plot of the number of fluids per woman admitted for HG at MNH. The fluids were given while the women were admitted to hospital.

Moreover, intravenous fluids were frequently used in management of HG, but no use of feeding tube (enteral nutrition) or total parenteral nutrition (TPN) were recorded in the present sample population.

Serum electrolytes in relation to fluid treatment

Electrolyte imbalances were recorded in 74 (45,4%) of the women. Firstly, 33 women (20,2%) had at least one deviant serum value of serum chloride (ref. 135-147 mmol/L). Further, 51 (31,3%) and 73 women (44,8%) had at least one deviant serum value of serum potassium (ref. 2,6-5,5 mmol/L) or serum sodium (ref. 135-147 mmol/L), respectively.

For serum chloride, all deviant measurements were below reference. Regarding serum potassium most (n = 50, 98,0%) measurements were below reference. Lastly, serum sodium imbalance was equally divided between above (n = 39, 23,9%) and below (n = 40, 24,5%) reference. Six women had serum sodium values both below and above reference. The serum electrolyte data are given in Table 4-6 below.

Table 4-6 Electrolyte imbalances and normal value distribution in HG patients admitted to MNH between 2007 and 2021. One woman is represented multiple times if serum electrolyte measurements of different type deviated.

Serum electrolyte level	Chloride	Potassium	Sodium	Frequency
Below reference	33 (20,2%)	50 (30,7%)	40 (24,5%)	123
Normal	130 (79,8%)	112 (68,7%)	90 (55,2%)	332
Above reference	0	1 (0,6%)	39 (23,9%)	40

Over half the women (n = 24, 60%) with hyponatremia got corrective fluid treatment with NL while as much as 90% (n = 45) of women with potassium deficiency got corrective fluid treatment with RL either alone or using fluid combination. Additionally, many women got advice on eating potassium rich foods. DNS was given to 32 (80%) of the women with hyponatremia.

Table 4-7 gives an overview of which intravenous fluid were given separated into two groups: women with normal electrolyte measurements and women with electrolyte imbalance. A significantly higher percentage of women who got NL had electrolyte imbalance ($p < 0,05$).

Table 4-7 Intravenous fluid given to women hospitalised for HG at MNH between 2007 and 2021 separated into two groups: normal electrolyte measurements and electrolyte imbalance

Type of intravenous fluid	Normal electrolyte measurements n =89	Electrolyte imbalance n = 74	Chi square test p-value
NL	20 (33,9%)	39 (66,1%)	**<0,05**
RL	69 (51,1%)	66 (48,9%)	0,059
DNS	60 (52,6%)	54 (47,4%)	0,441

4.4 Treatment of HG and insurance status

Table 4-8 include maternal og hospital characteristics of two groups, women admitted to hospital who have insurance compared to women without insurance. There is no significant difference between the two groups regarding gravida, prevalence of HG in previous pregnancy, readmission rate nor electrolyte disturbances. In both groups approximately one in ten got readmitted to hospital at least once. However, it is observed a significant higher percentage of multiparous women not having insurance versus having insurance ($p < 0,05$).

Table 4-8 Maternal and hospital characteristics of women hospitalised for HG at MNH between 2007 and 2021 divided into two groups: insured and uninsured

Variable	Insured n = 63	Uninsured n = 100	p-value (Chi-square test of independence)
Gravida	n = 54	n = 90	
Primigravida 1, n = 36	17 (47,2%)	19 (52,8%)	0,164
Multigravida > 1, n =108	37 (34,3%)	71 (65,74%)	
Para	n = 54	n = 91	
0, n = 48	24 (50,0%)	24 (50,0%)	< **0,05**
1 or >1, n = 97	30 (30,9%)	67 (69,1%)	
HG in previous pregnancy	n = 44	n = 78	
Yes, n = 110	6 (50,0%)	6 (50,0%)	0,290
No, n =2	38 (34,6%)	72 (65,5%)	
Readmitted to hospital (≥ 2)			
Yes, n = 18	8 (39,3%)	10 (55,6%)	0,592
No, n = 145	55 (37,9%)	90 (62,1%)	
Electrolyte disturbance			
Yes, n = 74	28 (37,8%)	46 (62,2%)	0,846
No, n = 89	35 (55,6%)	54 (60,7%)	

Table 4-9 provides an overview of hospital treatment comparing insured individuals to uninsured individuals. There is no significant difference between groups regarding antiemetic treatment, antacid treatment, and fluid treatment. There is a significant difference in total number of days in hospital ($p < 0,05$). Uninsured individuals spend more days in hospital than insured individuals.

Table 4-9 Antiemetics, antacids, fluid treatment received by women hospitalised for HG at MNH between 2007 and 2021 divided in the groups insured and uninsured

Variable	Total n = 163	Insured n = 63	Uninsured n = 100	p-value (Chi-square test of independence)
Antiemetic				
Ondansetron	81 (49,7%)	34 (42,0%)	47 (58,0%)	0,386
Doxylamine-pyridoxin	78 (47,9%)	30 (38,5%)	48 (61,5%)	0,962
Meclizine	5 (3,1%)	1 (20%)	4 80%)	0,650[b]
Promethazine	41 (25,2%)	12 (29,3%)	29 (70,7%)	0,154
Hydroxyzine	2 (1,2%)	1 (50%)	1 (50%)	1,000[b]
Metoclopramide	75 (46%)	27 (36,0%)	48 (64%)	0,521
Prochlorperazine	2 (1,2%)	0	2 (100%)	0,523[b]
Dexamethasone	2 (1,2%)	0	2 (100%)	0,523[b]
Scopolamine	1 (0,6%)	0	1 (100%)	1,000[b]
Butylscopolamine	2 (1,2%)	0	2 (100%)	0,523[b]
Antacids				
Yes, n = 67		25 (37,3%)	42 (62,7%)	0,770
No, n = 96		38 (39,6%)	58 (60,4%)	
Vitamin supplement				
Yes, n = 112		39 (34,8%)	73 (65,2%)	0,137
No, n = 51		24 (47,1%)	27 (52,9%)	
Fluid treatment				
No, n = 7		4 (57,1%)	3 (42,9%)	0,101[b]
1 type of fluid, n = 35		18 (51,4%)	17 (48,6%)	
2 or more fluids, n = 121		41 (33,9%)	80 (66,1%)	
		Median / 95% IQR[a]	Median / 95% IQR[a]	
Total hospital days		3 / 2 – 6	5 / 3 - 8	**<0,05[c]**
Number of antiemetic given		2 / 1 - 3	2 / 1 - 3	0,422[c]

[a] Interquartile range

[b] Fisher´s exact test

[c] Mann-Whitney U test (Wilcoxon rank sum)

4.5 Antiemetic medications prescribed when discharged

As Figure 4-12 illustrates, the antiemetic drugs meclizine, promethazine, metoclopramide, ondansetron and doxylamine-pyridoxin were prescribed when the women were discharged. In total 55 women (33,7%) got prescribed antiemetics when discharged. An unspecified number of files lacked information on discharge and therefore also on prescribed medications.

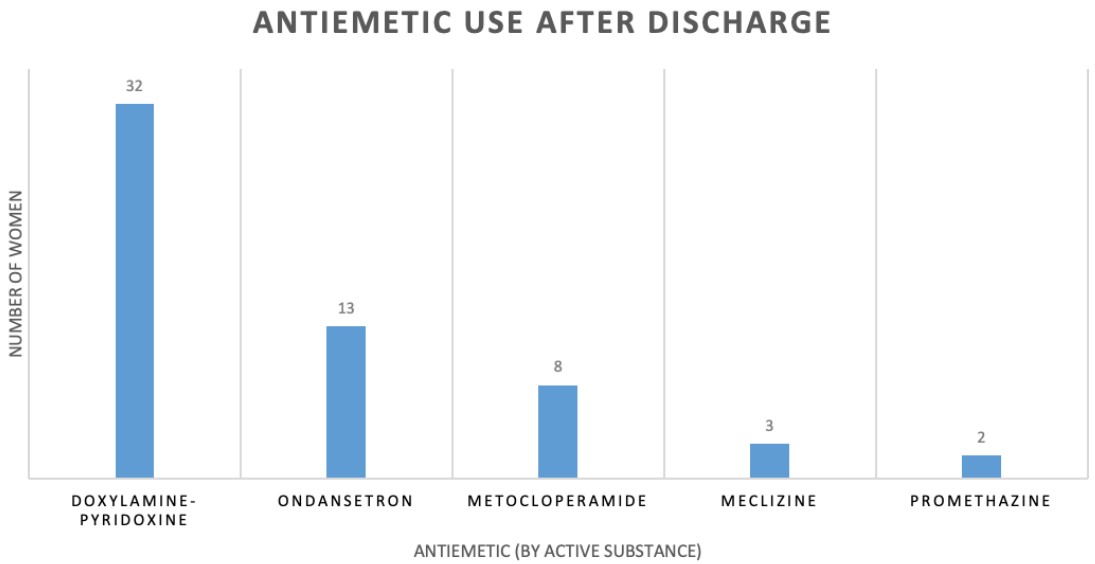

Figure 4-11 Distribution of antiemetic drugs prescribed for HG patients after discharge from MNH between year 2007 and 2021. Each bar represents the number of women who got prescribed the respective drug when discharged.

Among the women who got prescribed antiemetics when discharged, 58% got doxylamine-pyridoxin, 23,6% ondansetron and 14,5% metoclopramide. Table 4-10 provides an overview of discharge medications by active substance. All discharge medications (n = 55, 100%) were prescribed as scheduled regimen. The two women who did not get antiemetic treatment in hospital did not get any antiemetic medication prescribed after discharge either.

Table 4-10 Number of women who got prescription on antiemetic medication when discharged from MNH between 2007 and 2021

Antiemetic medication	Antiemetic medication prescribed when discharged, n = 55 (% of the women who got medication prescribed)
Doxylamine-pyridoxine	32 (58,2%)
Ondansetron	13 (23,6%)
Metoclopramide	8 (14,5%)
Meclizine	3 (5,5%)
Promethazine	2 (3,6%)

4.6 Hospital use of antiemetics over time

Figure 4-12 shows the change over time in use of different specific antiemetic drugs among the women admitted the respective year. The use of promethazine has significantly decreased while ondansetron and metoclopramide have had significant increase in use over the years. However, ondansetron use did decrease around year 2013 and in 2021. Doxylamine-pyridoxin combination have had a more stable use over time with fluctuations between 2008 and 2010. Scopolamine, butylscopolamine and hydroxyzine were only used sporadically.

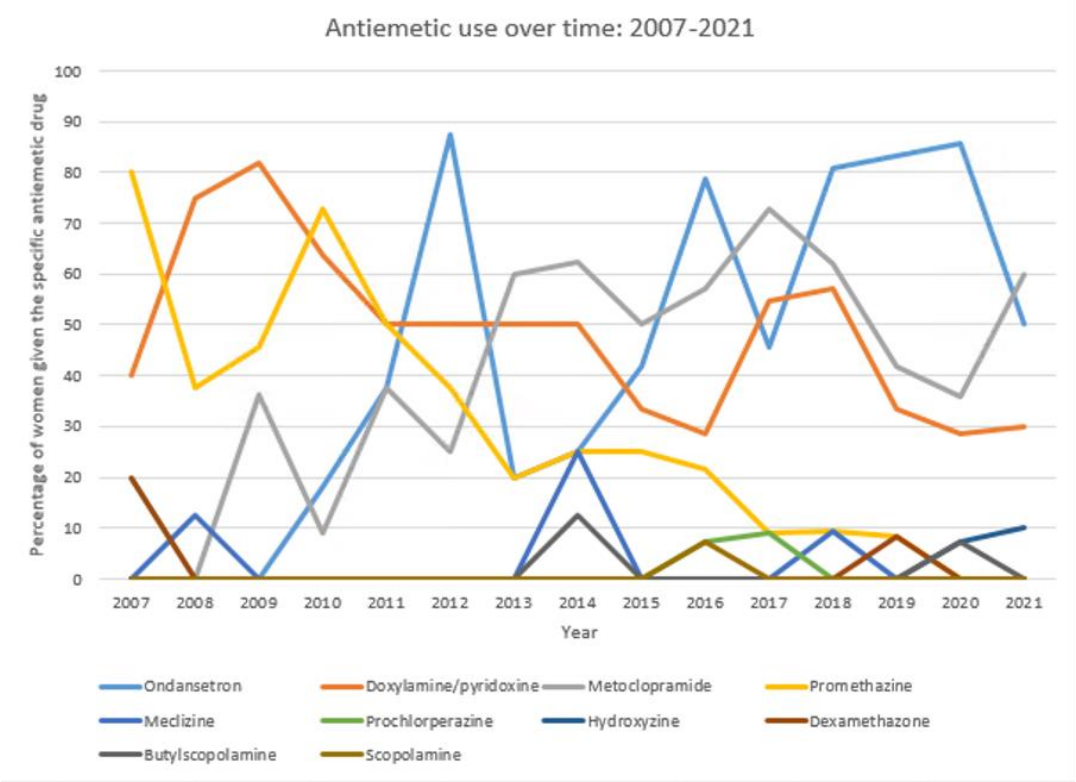

Figure 4-12 Use of antiemetics over time, from 2007 to 2021 presented for individual drugs. Each line represents a specific drug and numbers are given as percentages of women getting the drug that year. Between year 2007 and 2007 no record of women admitted with HG was found.

The use of promethazine, doxylamine-pyridoxin, metoclopramide and ondansetron during the time period is accentuated in Figure 4-14 and Figure 4-15. A significant yearly decrease (-2,4%) in use of doxylamine-pyridoxine is observed (95% CI: -4,4 to -0,4, $p < 0,05$). Fluctuations in promethazine use is observed, although no significant change in use ($\beta = -2,9$, 95% CI: -6,1 to 0,3, $p = 0,07$). Furthermore, metoclopramide and ondansetron show significant yearly increase in use. Metoclopramide had a yearly increase of 3,2% (95% CI: 1,0 to 5,4, $p < 0,05$) and ondansetron had a yearly increase of 5,6% (95% CI: 3,1 to 8,0, $p < 0,05$).

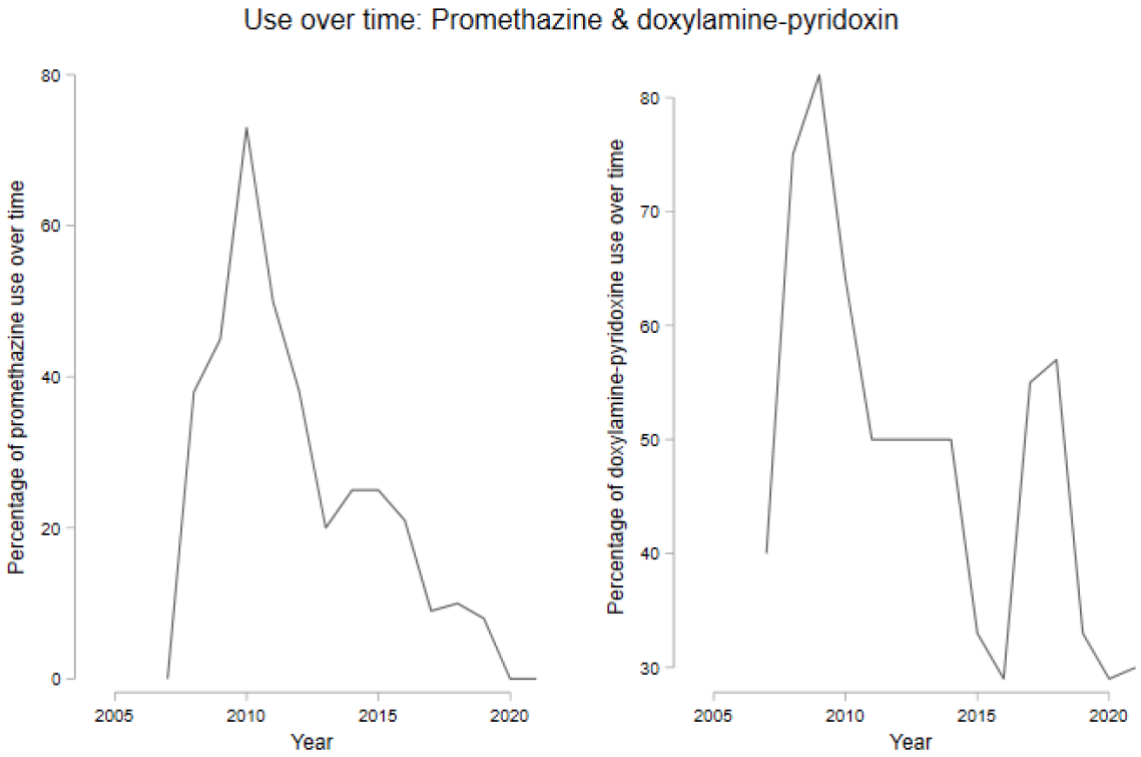

Figure 4-13 ***Use of promethazine and doxylamine-pyridoxin over time, from 2007 and 2021.*** *Promethazine use over time show fluctuations while a significant decrease in the use of doxylamine-pyridoxin is found (p<0,05)*

WHO changed the metoclopramide recommendations in 2013. Looking at the increase in use up until 2013 it shows a significant yearly increase of 6,1% (96% CI: 1,0 to 11,3, p < 0,05), but after the change in recommendations the increase in metoclopramide use have ceased (ß = -1,75, 95% CI: -5,3 to 1,8, p = 0,273).

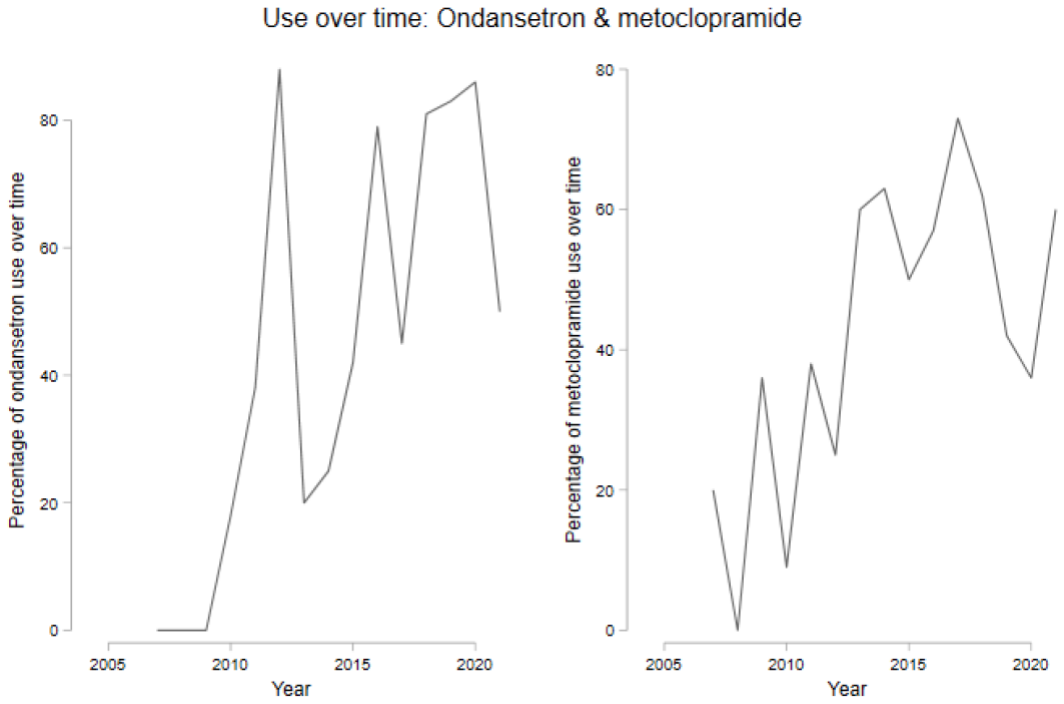

Figure 4-15 Use of promethazine, metoclopramide, and ondansetron over time between 2007 and 2021. Both antiemetics have had a significant yearly increase in use (p<0,05).

Table 4-11 presents antiemetic use divided into two time periods: 2007-2014 and 2015-2021. As no data on women hospitalized for HG from the first three years of the study period (2004-2007) is available the first group starts at 2007.

A significant difference is observed in use of ondansetron ($p < 0,05$), promethazine ($p < 0,05$) and metoclopramide ($p < 0,05$) between the two time periods. Ondansetron and metoclopramide are both significantly more used in 2015-2021 compared to 2007-2014. On the other hand, promethazine is significantly more used in 2007-2014 compared to 2015-2021. The use of antacids and multivitamins are significantly higher in the later time period (2015-2021) compared to 2007-2014 ($p < 0,05$). Furthermore, comparing use of fluid treatment, more women are treated with more fluids in the recent time period (2015-2021) ($p < 0,05$).

Table 4-11 Antiemetic use for woman hospitalised for HG at MNH separated into two time periods (2007-2014 & 2015-2021)

Variable	2007-2014 n = 69 n (%)	2015-2021 n = 94 n (%)	p-value (Chi square test)
Antiemetic given in hospital			
Ondansetron n = 81	16 (19,8%)	65 (80,2%)	< **0,05**
Meclizine n = 5	3 (60,0%)	2 (40,0)	0,651[a]
Promethazine n = 41	31 (75,6%)	10 (24,4%)	< **0,05**
Metoclopramide n = 73	22 (30,1%)	51 (69,9%)	< **0,05**
Prochlorperazine n = 2	0 (0%)	2 (100%)	0,509[a]
Hydroxyzine n = 2	0 (0%)	2 (100%)	0,509[a]
Dexamethasone n =2	1 (50,0%)	1 (50,0%)	1,00[a]
Doxylamine-pyridoxin n = 78	41 (52,6%)	37 (46,4%)	0,011
Scopolamine n = 1	0 (0%)	1 (100%)	1,00[a]
Butylscopolamine n = 2	1 (50,0%)	1 (50,0%)	1,00[a]
Got antiemetics after discharge			
Yes n =55	24 (43,6%)	31 (56,4%)	0,810
No n = 108	45 (41,7%)	63 (58,3%)	
Antacids			
Yes, n = 67	15 (22,4%)	52 (77,6%)	**<0,05**
No, n = 96	54 (56,3%)	42 (43,7%)	
Vitamin supplement			
Yes, n = 112	37 (33,0%)	75 (67,0%)	**<0,05**
No, n = 51	32 (62,7%)	19 (37,3%)	
Fluid treatment			
No, n = 7	6 (85,7%)	1 (14,3%)	**<0,05**[a]
1 type of fluid, n = 35	21 (60,0%)	14 (40,0%)	
2 or more fluids, n = 121	42 (34,7%)	79 (65,3%)	

[a] Fisher´s exact test

5 Discussion

Methodological considerations

The present study is a retrospective cohort study of women hospitalized for Hyperemesis Gravidarum at Muhimbili National Hospital between 2004 and 2021. All files including ICD-10 diagnosis code O21.0 (mild hyperemesis gravidarum) and O21.1 (hyperemesis gravidarum with metabolic disturbance) were evaluated and included if all inclusion criteria were met.

The inclusion criteria were chosen to eliminate milder cases of NVP in pregnancy, and to include as HG-patients with metabolic complications. All women admitted in the given time period fulfilling the criteria where included, limiting selection bias.

MNH is a referral hospital. Hospitalization length provided in this study is not necessarily the total length of hospital stay. The woman might have been admitted to other hospitals first and then transferred to Muhimbili for further treatment, as this information was not available from the patient's file. Thus, an unknown element is where the woman got referred from, which can be directly from home, another hospital, a health care center, or a private institution. The present study is therefore a descriptive study on how HG is treated while at MNH, and not necessarily representative of the treatment provided at other levels in the health care system in Tanzania.

5.1 Study design

A cohort study design has huge advantages for examining rare diseases as the study population is selected by exposure status (Song & Chung, 2010). The retrospective nature of the study includes a series of associated strengths and limitations. All data were collected in hindsight of the patient´s hospital admissions by reading though the patient file and extracting the relevant information. A strength by retrospectively looking at information from medical files and not doing interviews, is that one avoids recall bias. Recall bias is for example people not remembering or remembering the wrong information. Other methods of retrospective studies, such as interviews might have recall bias as a major limitation. Another strength with the present study design is it does not include observation of hospital workers and therefore health care professionals did not act/perform differently when knowing they are being studied.

The primary disadvantage of this study is related to the retrospective nature and use of medical records is missing data. Data might be completely missing, incomplete, fragmented, or inaccurate and the investigator has limited control over data collection, all of which can influence the results of the study. The included data must be documented in the medical record and in this study no opportunity to verify the written information nor obtain information which is not written exist.

5.2 Study setting

The availability of medicines in Tanzania is unstable leading to problems regarding treatment scheme and standardized treatment. Medicines shortages at Medical Stores Department, the national supplier for all public health care facilities, does occur. The degree of medicine shortage at MNH is unknown, and therefore the results regarding compliance to treatment guidelines might be affected by the availability of medicines.

Regarding reliability of data: In Tanzania not everyone remembers their birth year accurately. If a patient does not remember the year, the doctor can write an approximate year and regarding the date of birth, the Governmental New Year (01.07) is often used. Therefore, the age of the patients is not completely reliable, but more an estimate. The records do not always have reliable height or weight data either, often height is put to 160 cm for women and weight 70 kg. The consequence for these data limitations is that body mass index (BMI) is not possible to calculate and use to control the diagnosis criteria weight loss. A lot of trust is therefore in the doctor treating the patients that they did a proper evaluation before diagnosing hyperemesis gravidarum. However, inclusion criteria were controlled.

The official languages in Tanzania are Swahili and English. All medical records were written in English, meaning no translation step was necessary, further, limiting the possible sources of data collection error substantially.

The major strength of this analysis is the comprehensive search with predefined criteria from a single referral centre dealing with women presenting with hyperemesis gravidarum in Tanzania. To our knowledge, this is the first time Hyperemesis Gravidarum management is described in Tanzania.

5.3 Study population and sample size

During the data collection period it was noticed that medical files were removed from the Medical Records Department into storage if the woman had not been admitted to MNH for eight years. This can party explain the difference between available files in the electronic system (298) and the number of hard copies found (163). However, we did get hard copies of files back to 2007, indicating an unsystematic removal of files. Furthermore, a significant number of the electronic findings were duplicates or multiple registrations due to readmissions for HG. A limitation to our study is that we do not know how many files were removed in the time period included in our study. Therefore, the number of women included in this study does not necessarily reflect all women admitted to MNH for HG in the same period.

The study was unable to investigate birth weight and gestational age at birth. For investigating the outcome of the babies, the study limits findings of data to 2014, as the hospital does not have more data on births before that time. Additionally, it is not common to give birth at a tertiary hospital in Tanzania, and therefore measurements of outcome of the babies are not included in the thesis.

A sample size should be chosen to reflect the study population. Intended sample size was 400 women, but due to the number of patients and available information the sample size is 164. The low population size might hinder the clinical relevance of the study and weaken the validity. The data material will likely not attain sufficient power to test statistically significant differences in outcomes by the collected variables. However, the study will give valuable insights into current treatment compared to guidelines and might provide basis for improvement of pregnancy care for women with NVP and HG.

5.4 Data collection method

The two-step method of data collection was necessary for practical reasons and because of time management. Amongst other reasons, access to computer, internet and power was uncertain before the study began, limiting the possibility of direct transfer of data from the file to the statistical data program. We are aware a two-step transfer might result in more

errors than a direct transfer method would have, but most likely these errors will not have been systematic and therefore not alter the results to a significant extent.

Extracting data from paper files provides a higher risk of error than extracting data from digital medical records. Some sources of errors are deciphering handwriting, finding the location of information and interpret medical terms. Regarding deciphering handwriting, mostly the files were perfectly readable, but some files were difficult to read. Errors can be made in the process of extracting information. Furthermore, the pilot study consisted of 15 medical files. These files lack some information we later learned where was written. Unfortunately, we did not access these files again to collect the missing data. It is possible that the files we collected at the beginning of the project are more deficient as you eventually learn where to find the information.

A well-known limitation with cohort studies is the limited control over data collection. One of the disadvantages in the present study is the change of terminology from 2004 to 2021. When doing the analysis, it was observed that the terminology used in the files change from the oldest files to the most recent regarding ultrasound routines and gestational age determination. This change in terminology increases the risk of not uniformly reporting for all subjects.

In some files daily notes were not found. Sometimes a few days were missing, a week missing, or half the paper file lost. Almost no file included complete information. In cases where one day of information was missing the data was extrapolated using information from the day before and the day after. Where one week or a bigger part of the file were missing, data on treatment of that week is not included in the study. Therefore, reported duration of medication use (in days) might be influenced and the study report a shorter duration than what was given to the patient.

Sometimes in the files doctors and pharmacists write on top of each other's writing to indicate the number of ampules given. For example, if 8 mg ondansetron was given, the pharmacist could write 2 x 4mg ampules on top. This resulted in an intricate file, and increased the potential errors when extracting data as the data collector might write 4 mg on the data extraction form instead of 8 mg.

Three data collectors were involved in retrieving data from the medical files in the present project. This increases the errors as people think differently. Even though training was given, and everyone were sitting in the same room and available for discussions, having three data collectors is a limitation to the study.

Additionally, the present study involves data on in-patient care only. However, out-patient care was often recommended to the woman when discharged. The out-patient treatment is not included in the study as this treatment provided was not recorded in the woman´s medical file. The women will often visit antenatal clinic for follow up as well.

Results discussion

5.5 Maternal characteristics

The fertility rate in Tanzania is 4.8 (2019). The number of pregnancies (gravidity, median 2) and deliveries (parity, median 1) was lower than expected based on fertility rates in Tanzania. This might be a result of the HG diagnosis because many women are not willing to get pregnant again due to HG (Trogstad et al., 2005). Women who have experienced HG in previous pregnancies are scared and restraint towards being pregnant again because they are afraid to experience the same symptoms over again. As much as 8% of the study population in the present study have had previous HG. Together with the low fertility related observations, supports that HG can impact family planning and result in less pregnancies and deliveries.

Some patients had information on gestational age from ultrasound, but not all women, therefore time since last reported period (LMI) is used in this study. Optimal calculations would be routine ultrasounds or ultrasounds at time of first admission, but that data was not available.

Termination of pregnancy has been observed as a consequence of HG. In a cohort study of over 800 women, 15,2% had at least one termination and 6,1% had multiple terminations due to HG (Borzouyeh Poursharif et al., 2007). Termination of pregnancy was not observed in our study, likely because of restrictive abortion laws in Tanzania, with the penal code chapter 16 stating many years in prison for performing, helping or procure miscarriage of a women (Tanzania, 2019). Abortion is however legally permitted if it is performed to save the

woman´s life. Based on our findings, the low parity compared to the population average can therefore not be explained by women with HG in Tanzania terminating the pregnancy.

In Tanzania, the prevalence of HIV is 4,7% and the percent of pregnant women living with HIV receiving effective ARVs are 84%. Results from the present study found a HIV prevalence of 2,5%. As all pregnant women are screened for HIV at MNH and HIV data were cross-checked in the HIV registry, we can be sure that our study population had a lower prevalence of HIV compared to the general population.

5.5.1 Study setting and the view on use of antiemetics in pregnancy

MNH is a referral hospital and data presented in the study is based solely on the treatment given at MNH. Prior to admission at MNH women have either been treated at other hospitals/health care facilities or they have been referred from home. For women who have been admitted to other hospitals first, one can assume those who gets referred to MNH are severely ill and in need of specialized care. Therefore, the treatment given at MNH will likely represents many of the most severe cases of HG in Tanzania.

Furthermore, previous studies performed in Norway have investigated the use of antiemetics before hospital admission. Antiemetic treatment can be initiated at a lower level in the health care system to treat NVP/HG before admission to hospital is necessary. A study by Kristiansen et al. asks the question, “too little too late?” regarding antiemetic treatment for HG patients where the importance of antiemetic use prior to hospitalization is emphasized. A staggeringly high number of the hospitalized women in Norway (54%) had not received antiemetic treatment prior to hospital admission (Kristiansen, Heitmann, Holst, & Trovik, 2016). Based on knowledge of skepticism in treating nausea in pregnancy it would have been interesting to include this data in the present study, unfortunately due to lack of this information in the medical files this was not possible.

Reassuringly, in-patient antiemetic treatment was given to 98,8% of the women while at MNH. One can question why not all women got antiemetic treatment, as the disease profile for these women is so severe it is requiring hospitalization. One explanation might be the reluctance of prescribing antiemetics to pregnant women. As previously mentioned, we do not have data on the medication use of these women prior to hospitalization nor if the women themselves by choice declined using antiemetic medicines. Studies from Norway present a

high skepticism around medication use in pregnant women in general and for NVP/HG affected women, showing that the woman's perspective and attitude towards medications had impact on the treatment of NVP/HG (Heitmann, Solheimsnes, Havnen, Nordeng, & Holst, 2016; Nordeng, Koren, & Einarson, 2010). The findings show that women´s perspective and attitude towards medications impacted the NVP/HG treatment.

Furthermore, less educated women has been shown to believe medications in general were harmful compared to women with higher education (Nordeng et al., 2010). This might be relevant in the study setting of Tanzania where even though they achieved nearly universal access to primary education in 2007, almost 70% of children between 14 and 17 are not enrolled in secondary school (Unicef, 2022). A general lower education level might lead to a larger skepticism in medication use during pregnancy compared to other countries.

5.6 Management of HG

5.6.1 Type of antiemetic

The most used antiemetics while in hospital were ondansetron (49,7%), doxylamine-pyridoxin (47,9%) and metoclopramide (44,8%) followed by promethazine (25,2%). The national treatment guidelines (STG) in Tanzania recommend the use of metoclopramide or promethazine. It is therefore not surprising that both metoclopramide and promethazine are among the top four antiemetics given to women admitted at MNH. Even though doxylamine-pyridoxin is not mentioned in the Tanzanian STG, it is well known as HG treatment and a safe first line option (McKeigue et al., 1994; Smith et al., 2022). The high use of doxylamine-pyridoxin is in line with treatment guidelines from UpToDate which recommends beginning with pyridoxine alone before changing to doxylamine-pyridoxin as step number two. The pyridoxine-doxylamine combination is found safe and with no risk of adverse effects for the fetus in a meta-analysis which including 170,000 pregnancies (McKeigue et al., 1994). A surprising finding is that ondansetron is the most used antiemetic in hospital as ondansetron is not mentioned in the national guidelines and are mentioned at step number five in the UpToDate guidelines after antihistamines and dopamine antagonists. Other alternatives of antiemetics are recommended to try before using ondansetron.

Even though ondansetron should only be used on women where other antiemetics (antihistamines and dopamine antagonists) did not give sufficient symptomatic relief it is the

most used antiemetic for HG at MNH. The high use of ondansetron is however supported by research comparing metoclopramide to ondansetron. A similar score was reported on reduction of nausea, but ondansetron had a more substantial effect on reducing vomiting (Kashifard, Basirat, Golsorkhtabar-Amiri, & Moghaddamnia, 2013). One can also think about how the high use of ondansetron found in the present study illustrates the severity of symptoms in these women. When hospitalization is required, ondansetron is often indicated. The knowledge among doctors, available medicines and what is preferred by the women might all influence the antiemetic treatment.

Ondansetron use in pregnancy have previously been shown to give an increased risk of cardiac septal defects and cleft palate (Anderka et al., 2012; Danielsson et al., 2014). The chances of such teratogenic effects are generally low, but the most vulnerable period is up until week 10 of gestation. Nevertheless, of the 81 women who got ondansetron treatment at MNH in this cohort study, 33 women (40,7%) got ondansetron at admissions before gestation week 10. This also supports the hypothesis that these women present such a severe clinical picture that the doctors do a thorough evaluation of treatment, and that ondansetron is indicated also before week 10. It is considered positive the doctors do not exclusively prescribe medications based on a high focus on risk and teratogenicity.

Furthermore, the corticosteroid dexamethasone was used by two women in the present study. The corticosteroid used at MNH was dexamethasone. Both times dexamethasone was given during the first hospital stay at MNH and was not used if the woman was readmitted. Glucocorticoids is recommended as a last resort treatment for women with intractable symptoms (Smith et al., 2022) and might reflect women referred from other hospitals. It is important to underline this is a hypothesis, as referral information was not included in the study. More studies on HG are needed to be more certain what type of corticosteroid is most effective and for which patients.

Promethazine, metoclopramide, domperidone, and ondansetron are the four antiemetics listed on the essential medicine list, meaning that they are generally the most available antiemetics in Tanzania (Ministry Of Health, 2017). Apart from domperidone, these are commonly used to treat HG patients. There are different reasons why domperidone is not used in pregnancy. Previous reproductive toxicity studies have shown teratogenicity and historically a limited number of studies have been available. Therefore, domperidone have been contraindicated

for use in pregnancy. However, a very recent study from 2021 on domperidone exposure during the first trimester concludes that domperidone was not associated with increased risk of substantial malformations so the guidelines might change in the future (Hishinuma et al., 2021).

5.6.2 Dosages and drug administration

Medications were mostly given as scheduled dosages (n =341, 93,4%). By scheduled dosages we mean consistent doses given at the same frequency every day. On demand regime was only used in 6,6% (n = 24) of administrations during hospital admission. On demand regime is also called pro re nata, and is medication provided to the woman when needed. The trend of using scheduled regimen was applicable for all types of antiemetics of the present study. Scheduled dosages is recommended to more easily control symptoms of HG (Maltepe, 2014). For a different type of nausea and vomiting, induced by chemotherapy, using a combination of scheduled and on demand antiemetics were most effective (Rha, Sohn, Kim, Kim, & Lee, 2018). However, this is not necessarily applicable for HG patients, but these studies can support the use of combination regimen.

Some antiemetics were given using standard dosages. However, ondansetron was recorded with 13 different dosages. One reason might be that ondansetron was often given as intravenous administration and the drug used have 2 mg/ml concentration allowing more changes in dosage than set dosages in tablets or intramuscular injections do.

Regarding routes of administration, most antiemetics were given as intravenous administration (48,9%, n = 184), followed by per oral administration (39,9%, n =150). Only once was an antiemetic given as suppository and this antiemetic was ondansetron (0,3%, n = 1). Going back to the essential medicines list all antiemetics listed are either tablets or injections which explain the high percentages of these administration routes found in the study. When treating HG, oral medications might be difficult for the patients due to the frequency of vomiting and level of nausea. The nature of the disease makes i.v. treatment a good option. Patients admitted to MNH are also, as previously mentioned, likely to represent the most severe cases of HG which explains the high use of i.v. treatment.

5.6.3 Combination treatment

Combination treatment was given to 41,5% of the women in the study. Use of more than one antiemetic on the same day was considered a combination. Not necessarily at the same time or in the same tablet/infusion/injection. A limitation in this variable is when one drug is being stopped and another drug is being started on the same day, in this case the drugs will be included as combination.

Mostly, the combinations consisted of antiemetics from different groups of medicines. However, antihistamines were often combined with other antihistamines (27,8% of combinations given). Using two or more drugs from the same pharmacological group might act against its purpose as it increases the risk of side effects and do not necessarily provide a corresponding increase in effect against symptoms. Simultaneous use of different types of antiemetics are found to increase the symptom relief in HG patients (Badell et al., 2006). Combination treatment is recommended in international treatment guidelines by adding on different types of antiemetics until the symptoms are controlled (Smith et al., 2022).

5.6.4 Vitamin supplements

Most women (68,7%) got vitamin supplement of some sort. Folic acid and vitamin B combinations where the most common followed by iron and multivitamin.

We are aware that the present study underestimates the use of folic acid, and possibly also other supplements, as most women get folic acid for free from other levels or health care services. If the women bring their own supplements when admitted, the doctors do not systematically document use in the medical files (Dr. Peter Wangwe, personal communication, 01 October 2021). We find that 40% of the women were given folic acid in hospital, but strongly suspect that the observed frequency of use of folic acid and other supplements is underestimated.

Especially important in this patient group is supplementing thiamine (B_1). At MNH, thiamine was provided for 34,4% of the women. Thiamine replacement is important and indicated for HG patients to prevent the serious Wernicke's encephalopathy, a neurological disease, causing ataxia, confusion, and eye abnormalities (Sonkusare, 2011). Thiamine was not used for this patient group in 2007 but has since increased and reached the highest percentage

(66,7%) in 2018. Thiamin use fluctuated over time, with no significant increase over the study period seen as a whole. However, looking at the years up until 2018 a significant yearly increase (4,2%) in thiamine use is found (95% CI: 2,7 to 5,8, $p < 0,05$). The last three years, use of thiamine has decreased. If this reflects actual provided treatment, this is concerning, as Wernicke's Encephalopathy is a potentially fatal complication of untreated thiamine deficiency in HG. We are not aware of changes in routine reporting of thiamine use in the patient files during this period, but as vitamin supplementation is not routinely documented, the actual use of thiamine might be higher than we find.

Pyridoxin (B_6) use is recorded as antiemetic medications in the present study as the use of pyridoxin alone was rarely seen, and the vitamin was mostly given in combination with doxylamine as the antiemetic drug Nosic®. Two slow-release tablets containing pyridoxine (vitamin B6) and doxylamine (Bonjesta® & Diclegis®) is available in the USA and is the only medication with HG as licensed indication (Gideon Koren, 2019). Furthermore, an increased focus on doxylamine pyridoxin combination is given in the most recent American guidelines (Bulletins-Obstetrics, 2018). Compared to slow-release tablet given in the USA, the medication given at MNH was a normal tablet. The treatment is in line with UpToDate guidelines where antihistamines and pyridoxin are first line treatment (Smith et al., 2022). Therefore, the recorded 49% getting doxylamine pyridoxin combination indicates treatment in accordance with guidelines.

5.6.5 Antacid treatment

67 women (41,1%) were treated with antacids, the most used acid neutralizing drug being pantoprazole (n = 51, 31.1%). Thereafter, the second most used antacid is Relcer gel® (containing aluminum hydroxide/magnesium/simethicone) and omeprazole. Both given to 18 women (11,0%). The high number of patients getting anti acid treatment is reassuring as heartburn and/or acid reflux are associated with increased severity of HG symptoms compared to women without heartburn or acid reflux (Simerpal Kaur Gill, Caroline Maltepe, & Gideon Koren, 2009). Therefore, addressing symptoms of acid reflux indicate better management of HG.

On the other side we registered the use of double (n = 8, 11,9%) and triple (n=1, 1,4%) PPI treatment. Among others, a meta-analysis from 2009 has shown PPI safe in pregnancy so the

use of PPI in standard dosages are fine (Simerpal K Gill et al., 2009). However, combining drugs with the same pharmacological effects is rarely effective. Mostly it results in increased risk of side effects and limited additional effects on symptoms and therefore works against its purpose. Combinations of PPIs have not been researched and therefore the use of combination lacks scientific support. Other measures to improve acid neutralizing treatment can be to increasing the frequency of dosage from single dose to twice daily. Furthermore, three-times daily PPIs are found to have similar effect as twice-daily PPIs (Graham & Tansel, 2018). Based on the available data double and triple use of PPIs is not recommended.

5.7 Intravenous fluid treatment

Electrolyte disturbances caused by dehydration is common in HG patients and can be corrected with intravenous replacement fluids. Fluid treatment was given to 156 women (95,7%) in this study. Four different fluids were given: NS, RL, DNS and ORS. ORS being oral solution. The fluid treatment is mostly in accordance with the Tanzanian STG (Ministry Of Health, 2017). From 2007 to 2017 the guideline recommended Dextrose 5% i.v, then RL plus DNS and in 2017 the recommendation changed to RL with NL.

Electrolyte imbalances were recorded in 74 (45,4%) of the women. Hyponatremia was corrected using NL (in 60% of the cases) and 90% of potassium deficiency were corrected using RL. A concerning finding was that dextrose (DNS) was given to 32 (80%) of the women with hyponatremia. From the literature, dextrose infusions are not appropriate unless the woman has normal serum sodium levels as dextrose can cause an additional unfortunate lowering of sodium levels (Aylwin, Burst, Peri, Runkle, & Thatcher, 2015). Hyponatremia is associated with increased morbidity and mortality and must be taken seriously (Corona et al., 2013).

5.7.1 Nutritional treatment

No use of TPN or enteral nutrition was found in the present study. In resource-poor environments, such as Tanzania, the loss of nutrition and calories due to nausea and vomiting could greatly impact maternal energy intake, possible in a higher degree than in high income settings (Steinmetz et al., 2012). Nutritional conditions for pregnant woman in Tanzania may already be impacted by the limited access to the plentiful and varied food available during pregnancy one may find in high income settings. It is therefore surprising that no use of

nutritional support was found especially since maternal morbidity was reduced after parenteral and enteral nutrition became available (Smith et al., 2022).

5.8 Discharge prescribing

One in three women got one or more antiemetic prescribed when discharged. It is important to underline that most likely more women got antiemetics, but the discharge form was not always attached and possible to retrieve from the medical record file. If doctors prescribed medication for a longer time than the women were admitted, the drug was also reported as drugs at discharge. There are uncertainties around the fact if the women did get the drug at the discharge or a prescription.

Mostly tablets in scheduled dosages were prescribed. Even though the antiemetics were prescribed the present study do not have data on the use and access of these medications after discharge. Access to medicines is among other things challenged by individual economy and availability in the pharmacies.

Among women who got discharge medications, significantly more were not readmitted to hospital (80% vs 20%) ($p < 0,05$, chi square test). This supports that use of antiemetic treatment after discharge from hospital can reduce the need for readmissions in this patient group.

5.9 Adherence to treatment guidelines

One approach to achieve optimal health goals is through responsible prescribing and to adhere to standard treatment guidelines (STG). For LMICs irrational use of medicines are more widespread than in higher income settings (Irunde, Minzi, & Moshiro, 2017; Kruk et al., 2018). Therefore, it is important to investigate if treatment of hyperemesis gravidarum is in accordance with guidelines.

Tanzania published an essential medicines list in the 1970s, even before the WHO essential medicine list program was enrolled (Laing, Waning, Gray, Ford, & Hoen, 2003). The STG and National Essential Drugs List in Tanzania was first printed in 1991, followed by 2007, 2013 and 2017. One study from 2021 investigated how prescribers used and what they knew

about the STGs in Dodoma region, Tanzania. The results from this study reviled a suboptimal adherence to the STGs (Wiedenmayer et al., 2021).

One aim of this study is to compare the treatment given at MNH to local and national guidelines. Any relevant local guidelines from the hospital have not been found. The comparison is therefore based on the national guidelines in Tanzania, available online (Ministry Of Health, 2017). However, how the guidelines are updated or what evidence they are based on is not stated. A study conducted in 2014 found the foundation of decision making when reviewing the STG and NEMLIT in Tanzania to be safety, efficacy, availability, and affordability. Committees of experts are largely involved in the decision making, but are found to base the choices on "experience and discretionary judgement" (Mori, Kaale, Ngalesoni, Norheim, & Robberstad, 2014).

The most used antiemetics at MNH are ondansetron (n = 81, 49,7%), doxylamine-pyridoxin (n = 78, 47,9%) and metoclopramide (n = 73, 44,8%) followed by promethazine (n = 41, 25,2%). Of these, both metoclopramide and promethazine are listed in the current national guidelines indicating a systematic and responsible prescribing of medications. Since limited information is available regarding decisions and the essential medicine list the adherence to treatment guidelines will be considered in accordance with national and international guideline (UpToDate).

Beside of the two women who did not get any antiemetics in hospital nor when discharged, HG patients are supported by general advice, antiemetic medication, antacid treatment, vitamin supplements and fluid treatment when admitted to MNH. A general review of the treatment given at MNH is that treatment choices indicate that the doctors have a thorough understanding of the disease, the burden of the disease and that the treatment offered is in line with national or international guidelines for treatment of HG.

5.10 Treatment given to insured compared to uninsured individuals

Health insurance coverage is still low in Tanzania. As of 2019, 32% of Tanzanians had health insurance coverage (Amani et al., 2021). In this study approximately 40% had health insurance, which is somewhat higher than the general population. This can be explained by

many of the patients coming from urban areas where the socioeconomic status is generally higher than in rural areas.

Regarding maternal and hospital characteristics of insured compared to uninsured individuals, there were no significant differencse between the two groups regarding gravidity, parity, prevalence of HG in previous pregnancy, readmission rate nor electrolyte disturbances found in this study. However, it is a vague trend (not significant) towards more insured individuals being primigravida and nulliparous compared to the uninsured group.

No differences between the two groups were found regarding use of different antiemetic drugs, antacids, vitamin supplements nor fluid treatment. A somewhat surprising finding was that uninsured individuals spent a significantly longer time in hospital compared to the insured individuals ($p < 0,05$). The insured spent a median of 3 (2 – 6) days compared to 5 (3 – 8) days for the uninsured group. The reason behind the difference is unknown, as one would think insurance coverage resulted in longer hospitals stays as the patients might have more economic power. However, even when insured, high levels of out of pocket spending is still common in Tanzania.

5.11 Treatment of HG over time

Due to variations in excess of medicines, NEMLIT changes and increased research on antiemetic in pregnancy the use of antiemetic medications have changed a lot over time.

Looking specifically at metoclopramide, the metoclopramide recommendations from European Medicines Agency (EMA) got updated with reduced maximum treatment length in 2013 (EMA, 2013). Looking at the increase in use in metoclopramide at MNH up until 2013 it shows a significant yearly increase of 6,1% (96% CI: 1,0 to 11,3, $p < 0,05$), but after the change in recommendations the increase in metoclopramide use have ceased (ß = -1,75, 95% CI: -5,3 to 1,8, $p = 0,273$). These numbers give us a sign that MNH adhere to updated studies and recommendations from global sources and have reduced the use of metoclopramide recent years. The increased use of ondansetron is discussed in chapter 5.6.1.

Dividing the study period in two halves, a significant difference is observed in use of ondansetron ($p < 0,05$), promethazine ($p < 0,05$) and metoclopramide ($p < 0,05$) between the

two time periods. Ondansetron and metoclopramide are both significantly more used in 2015-2021 compared to 2007-2014. On the other hand, promethazine is significantly more used in 2007-2014 compared to 2015-2021. The increase in use of ondansetron can be explained by more safety studies on the drugs being available recent years.

The use of antacids and multivitamins are significantly higher in the later time period (2015-2021) compared to 2007-2014 ($p < 0,05$). Furthermore, comparing use of fluid treatment, more women are treated with more fluids in the recent time period (2015-2021) ($p < 0,05$).

5.12 Non measurable information

Ambulant treatment / outpatient treatment is common practice for HG patient, but this data is not possible to obtain as it is not recorded in the medical records at MNH. Data on child outcome is not included as most women give birth at other places than MNH. PUQE score (or similar) was not used in diagnosis setting at MNH, unsystematic data on weight and height made calculating body mass index (BMI) not possible and weight gain/weight drop was not possible to extract from this data material. PUQE score is a tool that is used and recommended in many places in the world, but it does not appear to be in clinical use at MNH for diagnosing HG, monitoring the women´s symptoms nor measure the effectiveness of treatment.

Patient groups found to be prioritized for health care in a region in Tanzania are the sickest patients, those living near a facility and those who could afford long journeys and frequent visits (Johansson, Miljeteig, Kigwangalla, & Norheim, 2011). Information about whether, and eventually where the admitted women were treated before admission to MNH would be interesting, including any pre-hospital antiemetic treatment.

The study did unfortunately not manage to include the updates household cencus, being conducted in August 2022.

6 Future perspectives

Many aspects of pregnancy need more studies and focus. Research on mechanisms behind diseases such as hyperemesis gravidarum is needed and long-awaited. The importance of understanding the mechanisms of a disease (pathophysiology) can be underlined by the fact that finding mechanisms also means finding potential drug targets to increase the drug treatment. General research on medication usage in pregnancy, both qualitative and quantitative research is needed. Despite the severity of HG, a paucity of research is available.

A structural approach to evaluate and describe the treatment given to HG patients in hospitals in more parts of the world could portray the potential differences between countries and may support the start of a more uniform understanding of HG treatment. Additionally, lack of knowledge among health care workers and practitioners is a major issue. Studies on knowledge and awareness is proposed, including teaching, and learning interventions as these results can be used to improve care and treatment of HG patients.

To investigate treatment differences between multiple pregnancies and singleton pregnancies would be interesting for future research. A bit over 5% of the included woman were pregnant with multiple pregnancy (more than one fetus). Previously published reports showed that multiple pregnancies are a risk factor of HG (H. Y. Kim et al., 2020). At MNH the gynecologist Dr. Wangwe had personal experience with more severe clinical picture and symptoms in women with multiple pregnancies compared to singleton pregnancies (Dr. Peter Wangwe, personal communication, 28 September, 2021). As the sample size of this study is small, no statistical analysis was suitable for investigating any possible associations.

Prior to admission at MNH women have either been treated at other hospitals/health care facilities or they have been referred from home. For future research, it would be preferred to include information on referral in the study. For women who have been admitted to other hospitals first, one can assume the treatment given at MNH will likely represents many of the most severe cases of HG in Tanzania. To evaluate differences, if any, in HG treatment between referral groups would add a deeper understanding of how treatment prior to hospitalization at MNH influence the treatment given at MNH.

Research on interventions which might reduce the risk of evolving HG is needed and when in the pregnancy these interventions would be most suitable. In the future, progress in knowledge and understanding of etiology, diagnosis and treatment may improve maternal quality of life and limit the adverse outcomes associated with HG.

7 Conclusion

Most women (98,8%) admitted to MNH for HG received some type of antiemetic treatment during the hospital stay or when discharged and 95,7% got some type of fluid treatment during the hospital stay. The number of hospital admissions throughout the pregnancy for women with HG at MNH ranges from minimum 1 to maximum 5 and the median number of days admitted to hospital is 4 (3 - 8).

The most used antiemetic medications were ondansetron (n = 81, 49,7%), doxylamine-pyridoxin (n = 80, 49,0%), and metoclopramide (n = 75, 46,0%). However, a significant yearly decrease in use of doxylamine-pyridoxine is observed together with a significant increase in use of metoclopramide and ondansetron. In accordance with international guidelines combinations of antiemetics were commonly used at MNH.

Almost half of the woman presented with electrolyte disturbances. However, more than half the women (60%) with hyponatremia got corrective fluid treatment with NL while as much as 90% of women with potassium deficiency got corrective fluid treatment with RL either alone or using fluid combinations.

A significant yearly increase (4,2%) in thiamine use until 2018 is recorded, with a prominent decrease the past years which needs to be further investigated. No prominent difference in treatment of insured and uninsured individuals were found regarding antiemetics, fluid, vitamins nor antacids.

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9 Appendix

Appendix 1:

Registration of drug- and nutritional treatment of women with HG

ID:	Date of birth	Height:	Pre-pregnancy weight:	HG in earlier pregnancies: yes / no	Number of pregnancies with HG:	Ethnicity:	Insurance:
Study ID:	Last period:	Gestation length: ____w + ____d	Gravida:	Para:	Smoking:	More than one baby (multiple pregnancy)? yes / no	HIV positive: yes / no

1st admission								
Date in:	Weight in:	Ketonuria in:	PUQE in:	Prealbumin in:	Prealbumin min:	Serum chloride in:	Serum potassium in:	Serum sodium in:
Date nadir:	Weight nadir:							
Date out:	Weight out:	Ketonuria out:	PUQE out:	Prealbumin out:	Ketonuri max:	Serum chloride out:	Serum potassium out:	Serum sodium out:

Birth						
Expected:	Date:	Weight child 1:	Apgar child 1:	Gender child 1:	Placenta weight:	
	Weight mother:	Weight child 2:	Apgar child 2:	Gender child 2:	Complications?	
Evt date of abortion:	Induced: Yes/no					

ID												
Date 1st admission												
Date of discharge												
Antiemetics drug treatment	**Dose**	**Adm**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
Meclizine		p.o.										
		i.v.										
Prometazine		p.o.										
		i.v.										
Metoclopramide		p.o.										
		i.v.										
Prochloroperazine		p.o.										
		i.m.										
Chlorpromazine		p.o.										
Ondansetron		p.o.										
		i.v.										
		Supp.										
Other antiemetic drug: API:												
API:												

Registration of drug- and nutritional treatment of women with HG

Other drug treatment												
1st admission	**Dose**	**Adm**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
Haloperidol												
Cortison												
Antacids												
Fragmin												
Other treatments offered for HG (herbal etc)												
Side-effects of drugs:												

Fluids and nutritional treatment:

1st admission	**Fluid/nutrition type**	**Fluid/nutrition volume/dose**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
i.v. fluids												
i.v. nutrition												
Enteral nutrition												
Vitamins												
Other treatments offered												
Complications of CVC or gastric tube.					**Type of tube:**							
Weight pre Nutrition/fluid		**Weight post Nutrition/fluid**			**Total number of days with fluid:** **Total number of days with nutrition:**							

Appendix 2:

Registration of drug- and nutritional treatment of women with HG

ID:	Date of birth	Height:	Pre-pregnancy weight:	HG in earlier pregnancies: yes / no	Number of pregnancies with HG:	Ethnicity:	Insurance:
Study ID:	Last period:	Gestation length: ____w +_____d	Gravida:	Para:	Smoking:	More than one baby (multiple pregnancy)? yes / no	HIV positive: yes / no

1st admission	Date in: Date nadir:	Weight in: Weight nadir:	Ketonuria in:	PUQE in:	Prealbumin in:	Prealbumin min:	Serum chloride in:	Serum potassium in:	Serum sodium in:
	Date out:	Weight out:	Ketonuria out:	PUQE out:	Prealbumin out:	Ketonuri max:	Serum chloride out:	Serum potassium out:	Serum sodium out:

2nd admission	Date in: Date nadir:	Weight in: Weight nadir:	Ketonuria in:	PUQE in:	Prealbumin in:	Prealbumin min:	Serum chloride in:	Serum potassium in:	Serum sodium in:
	Date out:	Weight out:	Ketonuria out:	PUQE out:	Prealbumin out:	Ketonuri max:	Serum chloride out:	Serum potassium out:	Serum sodium out:

Birth

Expected:	Date:	Weight child 1:	Apgar child 1:	Gender child 1:	Placenta weight:
	Weight mother:	Weight child 2:	Apgar child 2:	Gender child 2:	Complications?
Evt date of abortion:	Induced: Yes/no				

ID												
Date 1st admission												
Date of discharge												
Antiemetics drug treatment	**Dose**	**Adm**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
Meclizine		p.o.										
		i.v.										
Prometazine		p.o.										
		i.v.										
Metoclopramide		p.o.										
		i.v.										
Prochloroperazine		p.o.										
		i.m.										
Chlorpromazine		p.o.										
Ondansetron		p.o.										
		i.v.										
		Supp.										
Other antiemetic drug: API:												
API:												

Other drug treatment												
1st admission	**Dose**	**Adm**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
Haloperidol												
Cortison												
Antacids												
Fragmin												
Other treatments offered for HG (herbal etc)												
Side-effects of drugs:												

Fluids and nutritional treatment:

1st admission	**Fluid/nutrition type**	**Fluid/nutrition volume/dose**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
i.v. fluids												
i.v. nutrition												
Enteral nutrition												
Vitamins												
Other treatments offered												
Complications of CVC or gastric tube.					**Type of tube:**							
Weight pre Nutrition/fluid		**Weight post Nutrition/fluid**			**Total number of days with fluid:** **Total number of days with nutrition:**							

ID												
Date 2nd admission												
Date of discharge												
Antiemetics drug treatment	**Dose**	**Adm**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
Meclizin		p.o.										
		i.v.										
Prometazin		p.o.										
		i.v.										
Methoclopramide		p.o.										
		i.v.										
Prochloroperazin		p.o.										
		i.m.										
Chlorpromazin		p.o.										
Ondansetron		p.o.										
		i.v.										
		Supp.										
Other antiemetic drug: API:												
API:												

Other drug treatment												
2nd admission	**Dose**	**Adm**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
Haloperidol												
Cortison												
Antacids												
Fragmin												
Other treatments offered for HG (herbal etc)												
Side-effects of drugs:												

Fluids and nutritional treatment:

2nd admission	**Fluid/nutrition type**	**Fluid/nutrition volume/dose**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Discharge**
i.v. fluids												
i.v. nutrition												
Enteral nutrition												
Vitamins												
Other treatments offered												
Complications of CVC or gastric tube.					**Type of tube:**							
Weight pre Nutrition/fluid		**Weight post Nutrition/fluid**			**Total number of days with fluid:** **Total number of days with nutrition:**							

Appendix 3:

THE UNITED REPUBLIC OF TANZANI

MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY AND CHILDREN

MUHIMBILI NATIONAL HOSPITAL

In reply please quote;

Ref. No.: MNH/TRCU/Perm/2021/126 Date: 05th October, 2021

Head of Department
Obstetrics and Gynaecology
Muhimbili National Hospital

RE: PERMISSION TO COLLECT DATA AT MNH.

Name of Student	**Camilla Brox**
Title	**"Evaluation of Antiemetic Treatment of Women Hospitalised for Hyperemesis Gravidarum in Muhimbili National Hospital, Dar es Salaam Tanzania".**
Institution	Muhimbili University of Health and Allied Sciences
Supervisors	Prof. Sheila Maregesi Prof. Godeliver Kagashe Dr. Perer J. T. Wangwe
Period	04th October 2021, to 05th March, 2022

Permission has been granted to the named above principal Investigator.

The names below have been approved to collect data for this study.

No	Name	Institution
1	Daniel John	MUHAS
2	Edius Mukuras	MUHAS

Kindly ensure that they abide to the ethical principal and other conditions of the Research Approval.

Sincerely,

Reid B. Mchome
Coordinator - TRCU
For: Head of Teaching, Research and Consultancy Unit

HEAD, TEACHING, RESEARCH & CONSULTANCY UNIT
P. O. Box 65000
DAR-ES-SALAAM
MUHIMBILI NATIONAL HOSPITAL

c.c DSS
c.c Camilla **Brox**
c.c Edius Mukuras
c.c Daniel John

Upanga West, Kalenga Street, Plot No. 10480/3, P.O. BOX 65000, Dar es Salaam, Tanzania.
Telephone: +255-22-2151367-9, Telephone: +255-22-2151351-2
Email: info@mnh.or.tz, Website: www.mnh.or.tz

Appendix 4

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR OF RESEARCH AND PUBLICATIONS

P.O. Box 65001
DAR ES SALAAM
TANZANIA
Web: www.muhas.ac.tz

Tel G/Line: +255-22-2150302/6
Ext: 1016
Direct Line: +255-22-2152489
Telefax: +255-22-2152489
E-mail: drp@muhas.ac.tz

Ref. No.DA.282/298/01.C/ Date: 21/07/2021

MUHAS-REC-07-2021-767
Camilla Brox
Elective student from University of Bergen, under School of Pharmacy - MUHAS
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: Evaluation of antiemetic treatment of women hospitalised for Hyperemesis gravidarum in Muhimbili National Hospital, Dar es Salaam, Tanzania

Reference is made to the above heading.

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 21/07/2021
EXPIRATION DATE OF APPROVAL: 20/07/2022

STUDY DESCRIPTION:
Purpose:
The purpose of this retrospective cohort study is to describe and evaluate the antiemetic treatment of women hospitalised for Hyperemesis gravidarum in Muhimbili National Hospital. Additionally the study will evaluate if the treatment is in accordance with local or national guidelines.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:
https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%20774.pdf and in the MUHAS archives.

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain data transfer agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain data transfer agreement (DTA) from NIMR if data will be transferred to a foreign country.
8. Apply for and obtain material transfer agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country,
9. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
10. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
11. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.

Dr. Bruno Sunguya
Chairman, MUHAS Research and Ethics Committee