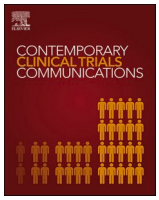
Contemporary Clinical Trials Communications 39 (2024) 101227

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



The IRIS clinic: A Protocol for a mixed-methods study evaluating the management of Hyperemesis Gravidarum

Eileen C. O'Brien [a,*], Jean Doherty [b], Sarah Louise Killeen [b], Melanie Bennett [b], Lillian Murtagh [b], Sinead Curran [b], Suzanne Murphy [b], Helen McHale [b], Lucille Sheehy [b]

[a] School of Biological, Health and Sports Science, Technological University Dublin, Dublin 7, Ireland
[b] The National Maternity Hospital, Holles Street, Dublin 2, Ireland

ARTICLE INFO

Keywords:
Hyperemesis Gravidarum
Nutrition
Women's experience
Pregnancy

ABSTRACT

Background: Hyperemesis Gravidarum (HG) is a severe form of nausea and vomiting in pregnancy that affects 0.3–3% of women and has profound nutritional, physical and psychological consequences. Research is lacking regarding the most effective management of the condition. In response to patient feedback, a multidisciplinary HG day-case service (IRIS Clinic) was launched in 2020 at The National Maternity Hospital, Ireland. The clinic provides routine, day-case care in a comfortable space with pre-booked appointments. The MDT involves midwives, dietitians, perinatal mental health, obstetrics and pharmacy, and the nature of the clinic enables peer-to-peer support. As this clinic is the first of its kind in Ireland, we aim to assess its effectiveness and feasibility, and suggest recommendations for improvement.

Methods: This is a sequential, mixed-methods study that commenced in August 2021. The prospective arm of the study is ongoing and involves enrolling women (n = 50) who are attending the IRIS clinic. Data are collected on first admission (pre-intervention) and approximately 8 weeks' later (post-intervention) relating to symptoms of HG, well-being, food tolerances, quality of life and nutritional intake. Qualitative, semi-structured interviews will be conducted to evaluate women's experiences of attending the clinic. The retrospective arm of the study will be a chart review (n = 200) of women diagnosed with HG to describe assessments, treatments and pregnancy and birth outcomes.

Conclusion: The IRIS clinic has the potential to improve pregnancy outcomes and nutritional status among women with HG. If found to be effective and feasible, the model for this clinic could be replicated elsewhere.

1. Introduction

Nausea and vomiting in pregnancy (NVP) is common with up to 70 % of women experiencing symptoms in the first trimester [1]. Hyperemesis Gravidarum (HG) however, is a severe and debilitating form of nausea and vomiting in pregnancy that has a prevalence of 0.3–3% [2,3]. There is no known single cause for HG, but genetic, endocrine and gastrointestinal causes are likely implicated. An increased risk exists among those with previous history of HG [4], a family history of HG and a positive association has been observed between HG and overexpression of the gene GDF15, which is associated with cachexia, reduced appetite and weight loss [5]. Recently, fetal production and maternal sensitivity to the hormone GDF15 have been linked to an increased risk of the condition [6]. Abnormal thyroid hormone levels [7], increased prevalence of *Helicobacter pylori* infection [8], a female fetus [9] and multiple pregnancies have also previously been associated with HG.

HG can result in greater number of hospital admissions and maternal morbidity, with women experiencing dehydration requiring IV fluids, electrolyte imbalances, >5 % weight loss, ketonuria, malnutrition and vitamin deficiencies, including Wernicke's encephalopathy caused by B1 vitamin deficiency. Inadequate weight gain, as a result of inadequate nutritional intake and excessive losses, affects approximately half (46 %) of women with HG [10]. The fetus may also be adversely affected by HG and has an increased risk of growth restriction, small for gestational age (SGA), low birth weight and premature birth [3,11–13]. Among women with HG and inadequate weight gain, SGA occurs in 16.7 % of infants, compared to 4.2 % of those with adequate weight gain [10]. Longer term consequences for offspring exposed to HG include increased risk for

* Corresponding author.School of Biological, Health and Sports Science, Technological University Dublin, Dublin 7, Ireland.
E-mail address: eileen.obrien@tudublin.ie (E.C. O'Brien).
@eileenobrienRD (E.C. O'Brien)

https://doi.org/10.1016/j.conctc.2023.101227
Received 24 March 2023; Received in revised form 21 October 2023; Accepted 4 November 2023
Available online 9 November 2023

anxiety disorders, sleep problems, autism and testicular cancer [14]. It has been hypothesised that it is likely malnutrition that drives poor intrauterine growth and several other adverse outcomes of HG. To date however, accurate nutritional intake among women with HG has been inadequately documented in the literature [15]. The limited evidence available suggests dietary intakes are poor among women affected by HG, with macro- and micro-nutrient intakes approximately 50 % or less of requirements [15]. Given these nutritional challenges, the approach to managing HG-associated malnutrition requires a multidisciplinary team consisting of midwives, obstetricians, pharmacists and dietitians who will manage the various aspects of the condition.

1.1. Day-case management

HG is one of the most common reasons for hospital admission in first trimester [16], causing significant personal, familial and economic disruption to the pregnant woman. Some hospital settings have day-case beds available for women with HG, and this has been demonstrated to have a positive impact on care. Day-case management is as effective as inpatient management in reducing the symptoms of HG, with comparable quality of life and pregnancy outcomes [17]. A number of studies have demonstrated that it also reduces total admission time in hospital, compared to inpatient management [17,18], making it a preferable choice for women and healthcare professionals from social and economic perspectives. Furthermore, an Irish study demonstrated that day-case management is less costly compared to inpatient management (€985 vs. €3837) [19]. A HG specific support intervention, which provided a HG information booklet and phone calls to women from a healthcare professional, demonstrated an improvement in severity of nausea and vomiting and the perceived level of symptom distress, compared to routine nursing care [20]. Despite no changes in body weight between the support and control groups, quality of life was significantly greater following the intervention, suggesting that individualised, attentive care is a beneficial aspect of HG management. A recent survey of members of the British Dietetic Association found that there was inconsistent use of referral criteria to dietetic services for HG and a lack of specific clinical guidelines and patient resources [21].

1.2. The IRIS clinic (intravenous fluids, rest, Insight and Support)

The IRIS clinic at The National Maternity Hospital, Dublin, Ireland, was created in response to qualitative research among women attending the service [22] and the above evidence. It has resulted in a bespoke HG day-case service, in a comfortable setting with peer support and a multidisciplinary team of healthcare professionals including midwives, dietitians, perinatal mental health professionals, obstetrians and pharmacists, who are experienced in the management of HG. The acronym for the clinic stands for Intravenous fluids, Rest, Insight and Support, and it is envisaged that this service provides holistic management and care for women with HG. Women are referred into the IRIS clinic by their healthcare professional at the NMH (obstetrician, midwife, dietitian) who they meet in the emergency department, the antenatal clinic or at a routine appointment. General practitioners do not refer women into the clinic. Assessment and diagnosis of HG is based on the Irish clinical practice guidelines [23]. In clinical practice, it is difficult to distinguish between 'severe nausea and vomiting' and HG. Regardless, in our institution, if a woman presents with a PUQE score in the moderate to severe range and their symptoms significantly impact hydration status, nutrition and/or daily activities, they will be offered a referral into the IRIS clinic.

1.3. The aims of this study are

1) To describe assessments and treatments of HG in the clinic as well as pregnancy and birth outcomes among a population of women with HG in Ireland.
2) To evaluate the impact of a specialist HG clinic (IRIS clinic) on symptoms of nausea and vomiting, well-being, ability to conduct daily activities, nutritional status, dietary intakes, food tolerance and anthropometry.
3) To qualitatively explore women's experiences of HG and attending a specialist HG clinic (IRIS clinic).

2. Methods

2.1. Study design

This is a mixed-methods study, taking place at the National Maternity Hospital, Dublin, Ireland, a tertiary maternity hospital with an average of 8000 birth/year. We use longitudinal sequential mixed-methods, with three studies embedded in the research: 1) Retrospective, cross sectional, review of medical charts of women previously exposed to HG; 2) Quasi-experimental study with pre-test and post-test design among women attending a specialist HG clinic (IRIS clinic); and 3) Qualitative study to explore women's experiences of HG and attending the specialist HG clinic (IRIS clinic) (Table 1).

Ethics were approved in 2021 from The National Maternity Hospital Research Ethics Committee (EC16.2021). This research is part-funded by the HSE Nursing and Midwifery Planning and Development Unit Dublin South, Kildare and Wicklow.

2.1.1. Patient involvement

The research team invited a woman with experience of HG at our institution to join the research team from the initial design phase of the study. This person will be involved throughout the data collection period, provide input on data analyses and will assist in dissemination of the findings to relevant stakeholders.

Furthermore, this study aligns with the research priorities of the HG community. The James Lind Alliance Priority Setting Partnership for HG is an international partnership comprised of patients, researchers and clinicians with an interest in HG, and includes Irish patient and clinician representatives [24]. In 2019, this partnership prioritised ten research questions for future research, of which four are related to this study.

- How can we most effectively manage hyperemesis gravidarum? What clinical support measure is most important to people who have had hyperemesis and what did they find most beneficial?
- What are the immediate and long-term effects of HG (including malnutrition and dehydration) on the developing fetus?

Table 1
Study aims and proposed study designs.

Study Aims	Proposed Study design
To describe assessments and treatments of HG in the clinic as well as pregnancy and birth outcomes among a population of women with HG in Ireland.	Retrospective, cross-sectional study (chart review)
To evaluate the impact of an IRIS clinic.	Quasi-experimental study (pre- and post-test)
To qualitatively explore women's experiences of HG and attending an IRIS clinic.	Qualitative study (interview)

- What are the immediate and long-term physical, mental and social consequences and complications of HG (including malnutrition and dehydration) on the pregnant person's body?
- What are the nutritional requirements of the 1st, 2nd and 3rd trimesters and how can people with HG achieve these goals?

2.2. Study population and inclusion criteria

Data collection began in August 2021 and is envisaged to continue until mid-2023.

1) Retrospective, cross sectional, review of medical charts
   - Inclusion criteria: Women who have been discharged from the HG service, since January 1, 2020, and who received a minimum of two encounters from staff, either through treatment in the hospital's emergency department, HG clinic attendance, phone consultations and/or overnight admission.
   - Exclusion criteria: Women discharged from the HG service before January 1, 2020. No other women will be excluded.
2) Quasi-experimental study with pre-test and post-test design among women attending a specialist HG clinic (IRIS clinic)
   - Inclusion criteria: Women who attend the specialist HG clinic (IRIS clinic) for treatment of HG at least twice, are over the age of 18 and have sufficient understanding of English to provide informed consent.
   - Exclusion criteria: Women who experience a miscarriage or abortion, women whose babies are diagnosed with a fetal abnormality, women who do not wish to participate and do not provide informed consent.
3) Qualitative study to explore women's experiences of HG and attending the specialist HG clinic (IRIS clinic).
   - Inclusion criteria: Women who attend the specialist HG clinic (IRIS clinic) for treatment of HG at least twice and are subsequently discharged from the service, are over the age of 18 and are fluent in English, in order to articulate their experience sufficiently.
     - Exclusion criteria: Women who experience a miscarriage, abortion, premature birth or perinatal death, women whose babies are diagnosed with a fetal abnormality, women who did not wish to participate.

2.3. Sampling and recruitment

1) Retrospective, cross sectional, review of medical charts

We aim to include 200 participants in this arm of the study. A list of patient referrals to the HG service will be used to select charts. Data will be collected from the charts in a sequential manner following the inclusion and exclusion criteria above. Fifty of the 200 charts will be from women included in the quasi-experimental study (below) in order to make comparisons between women who attended the clinic and women who did not.

2) Quasi-experimental study with pre-test and post-test design among women attending a specialist HG clinic (IRIS clinic)

Women in the IRIS clinic will be approached by a midwife working in the clinic (gate keeper), provided with information leaflets explaining the purpose of the study and the study questionnaire. Information will be given verbally by the midwife prior to completing the questionnaire. Participants will be provided with a consent form requesting the use of the data for research purposes, to gain access to medical records in order to collect further information to complement the questionnaire data, and whether or not they consent to a research midwife contacting them about participating in a one-to-one interview. The participants are provided with the opportunity to the option to consent to one or more of the above. We aim to include 50 participants with completed pre- and post-intervention questionnaires in this arm of the study.

3) Qualitative study to explore women's experiences of HG and attending the specialist HG clinic (IRIS clinic).

Participant recruitment will be convenient and purposive. Initially, when the IRIS clinic was established, a number of women expressed interest in providing formal feedback. These women will be contacted and invited to participate in the current study. After that, participants of the broader study who complete questionnaires and consent forms, which include consent to be contacted for an interview, will be invited to participate. Each participant will receive an information leaflet, given time to ask questions and will sign a consent form for the interview to be audio recorded and the data to be used, pseudonymously, for the purposes of research. All participants are given the option of being interviewed in their home, online, or in a private room of the research site.

2.4. Intervention

Intervention is individualised, but typically includes intravenous fluids and vitamin infusion, medication review, dietetic support and perinatal mental health support as needed, delivered by staff with experience in managing HG. On admission, women are provided with a comfortable recliner chair and a snack-pack ordering sheet to select foods and drinks that they are willing to try during their stay. On the first admission to the clinic, women are also provided with an IRIS clinic comfort pack (tote bag, water bottle, ear plugs, hard-boiled sweets, eye mask) and educational leaflet about the condition. The nature of the clinic, with a number of recliners in the same room, facilitates informal peer-to-peer support among women with HG. Midwives assess HG severity and hydration status through the use of a PUQE score, subjective rating of well-being from 0 to 10, urine specific gravity and ketones, and body weight before and after fluids. Additional assessments are done as required, including blood tests (urea and electrolytes, anaemia screen and risk of refeeding syndrome). Dietetic support includes individual nutritional assessment, advice to increase food and fluid intake, advice to improve the nutritional content of the diet, advice regarding micronutrient supplementation, according to assessed priority with the aim to meet a greater percentage of dietary requirements on each subsequent review. Perinatal mental health services provide group-based interventions including meditation and strategies to improve maternal well-being, in addition to offering individualised care as needed. Follow-up appointments with the clinic are booked as required (typically on a weekly or bi-weekly basis), until an appropriate treatment plan is established and transfer can be completed to appropriate step-down measures.

2.5. Data collection

1) Retrospective, cross sectional, review of medical charts

The chart review will extract data on the following variables; demographic characteristics (maternal age, ethnicity, parity, gravida, employment status and support at home); medical and obstetric history as assessed at the initial antenatal outpatient appointment; HG related history (medications, past history of HG, gestation at first presentation and discharge, Pregnancy Unique Quantification of Emesis [PUQE] score, well-being, number and type of admissions); blood and urine tests at first presentation and most recent HG presentation (haemoglobin status, U&E, urine specific gravity, urine ketones); maternal weight, BMI and gestational weight gain; and birth outcomes (gestation, birth weight, birth type, gender).

2) Quasi-experimental study with pre-test and post-test design among women attending a specialist HG clinic (IRIS clinic)

At recruitment, women are invited to complete a pre-intervention questionnaire on first admission to the IRIS clinic. The post-

intervention questionnaire is completed approximately 8 weeks' later, on the day ward (if the woman is still attending the IRIS clinic); or via an online questionnaire to enable women who do not have an IRIS clinic appointment at that time or have been discharged from the service to complete the data collection. The pre- and post-intervention questionnaires collect details relating to maternal characteristics, gestation and number of times attended casualty and/or were admitted to the antenatal ward overnight for treatment of HG. Additionally, the following information is collected to gather a full picture of HG for each individual.

2.5.1. Symptom severity

A 24-h PUQE score [25] is calculated at the time of questionnaire. This gathers severity of nausea, vomiting and retching. The Pregnancy Symptoms Inventory [26] is also included. Women are asked to rate how often they experienced symptoms of pregnancy such as constipation, vivid dreams, fainting and dry skin. Options to choose from included never, rarely, sometimes and often.

Well-being and impact on Daily Living.

The 12-item short-form Health Survey - SF-12® [27] is a self-reported measure which assesses the impact of health on a person's daily life. This 12-question measure contains Likert scales and asks questions pertaining to a person's physical capabilities and emotional well-being. In addition, the WHO-5 Well-being Index [28] is included which is a self-reported measure of emotional well-being. This short measure has five questions, answered on a 5-point Likert scale from 'all of the time' to 'at no time'.

2.5.2. Dietary intakes

The questionnaire includes a 24-h food and fluid diary that is self-completed by the woman if the questionnaire is paper-based, or by phone with a trained research midwife if the women completes the questionnaire online. Written instructions are provided outlining how to complete the diary. Women are instructed to be as clear as possible on what they ate and to exclude food that was not eaten (i.e. leftovers). Examples of how to report on portion sizes are included (e.g. "1 medium potato, 1 large portion of lasagne, 150 g of Salmon, dessertspoon of mayonnaise"). Other suggestions on how to report portion size are to indicate how much of the plate was covered, or to use handfuls or cup measurements. The women are also instructed to write down how the food was cooked.

Information is also collected on the type and dose of all micronutrient supplements taken, and the number of days per week that the supplement was tolerated and not vomited. Women are also asked whether and how HG impacted on the ability to take supplements.

2.5.3. Food tolerance

Changes in food tolerance to food groups (e.g. savoury snacks, meat, fruit and vegetables) and food characteristics (e.g. smooth, cold, crunchy foods) are examined using a questionnaire created for the purposes of this study by the research team as there is a dearth of previously published literature in this area. Women are asked to choose less than usual, about the same and more than usual tolerance.

3) Qualitative study to explore women's experiences of HG and attending the specialist HG clinic (IRIS clinic).

This arm of the study consists of audio recorded semi-structured interviews of women who attended the IRIS clinic. The interviews will be conducted by JD, a midwife with personal experience of pregnancy, but not HG. Audio recordings will be transcribed by the interviewer, with consent. Data collection and analysis will be conducted simultaneously. Data collection will be ended once the research team recognise that sufficient information power had been reached in order to answer the research question [29].

2.6. Outcome variables (quantitative data)

The primary outcome is change in severity of HG as assessed by the patient reported PUQE score (evaluating frequency of nausea, vomiting and retching) from pre-to post-intervention among women attending the IRIS clinic. Secondary outcomes include, but are not limited to change in maternal subjective well-being, quality of life, gestational weight gain, dietary intakes and infant birthweight.

2.7. Sample size

The primary outcome of the IRIS clinic evaluation is change in PUQE score pre-to post-intervention. A small-scale study (not published) at the NMH demonstrated a reduction in moderate/severe PUQE score category from 94 % pre-intervention to 61 % post-intervention, and the correlation between the two categories was 0.23. Assuming that 94 % and 61 % of the pairs have a moderate/severe PUQE score at the pre- and post-intervention questionnaire, respectively, the correlation between paired observation is 23 % and after applying continuity correction, the study would require a sample size of 26 pairs to achieve a power of 80 % and a two sided significance of 5 % for detecting a difference of −0.33 between marginal proportions [30].

The aim of the chart review data collection is to provide descriptive statistics regarding outcomes among women with HG. We therefore aim to collect details on a pragmatic sample given the low prevalence of the condition. Data collected in from the research site in 2021 demonstrated that 2.5 % of mothers who delivered at the research site were referred to the dietetic department for HG, equating to approximately 200 women [31]. Based on this data the research team felt that including 200 women in the chart review would be feasible.

2.8. Data handling and analyses

Information is gathered from the hand written and electronic questionnaires. Hand written questionnaires are stored in a locked cabinet in the NMH. This information is entered into a password protected Microsoft Excel, version 16.66.1 sheet. To uphold confidentiality, each participant is given a unique questionnaire number independent of any hospital number that could identify the participant.

The food diaries are analysed using Nutritics software version 5.82. Any decisions on portion sizes, specific food items and recipes are documented to ensure all diaries are analysed systematically (e.g. "bread with butter" will be recorded as one slice of white bread (30 g) with 7 g of salted butter). If portion sizes are not specified in the food and fluid diary an average portion size will be chosen using Nutritics software.

1) Retrospective, cross sectional, review of medical charts

Statistical analysis will be conducted using the software SPSS, version 28. Statistical significance will be considered $P < 0.05$. Descriptive and inferential statistics will be used in the analysis and description of the chart review data through the use of univariate and bivariate statistics. Descriptive statistics (frequencies, frequency percentages, measures of tendency and measures of variability) will be used to summarise results. Repeated measures *t*-tests will be undertaken to compare lab test results over time.

2) Quasi-experimental study with pre-test and post-test design among women attending a specialist HG clinic (IRIS clinic)

Statistical analysis will be conducted using the software SPSS, version 28. Descriptive and inferential statistics will be used in the analysis and description of the chart review data through the use of univariate and bivariate statistics. Statistical significance will be considered $P < 0.05$. Descriptive statistics (frequencies, frequency

percentages, measures of tendency and measures of variability) will be used to summarise results. Pre- and post-test comparisons will be analysed to determine the impact of the IRIS clinic, using paired samples *t*-tests and Wilcoxon Signed rank tests.

3) Qualitative study to explore women's experiences of HG and attending the specialist HG clinic (IRIS clinic).

Reflexive thematic analysis will be used for the analyses of the transcribed audio recordings of the interviews [32]. In order to increase validity, the same researcher (JD) who conducts the interviews will transcribe the audio data and conduct the data analysis. The researcher, with extensive qualitative data collection and analysis experience, will familiarise herself with the data and spend time absorbing the meaning of the participants words and the significance in terms of answering the research question. A second researcher (EOB), with clinical experience of dietetic management of HG, but no personal experience of HG, will assist with analysis. Codes will be attached to relevant excerpts of the data and initial themes will be generated from these developed codes. Further review and development of themes will be conducted throughout this process, in order to truly capture women's experiences of living with HG and of attending a dedicated HG clinic.

2.9. Dissemination

Results will be reported as research papers and submitted to relevant medical, midwifery and nutrition journals for publication. Authors will present the research at relevant professional conferences and symposia. Relevant outcomes will be shared directly with HG patient advocacy groups, such as Hyperemesis Ireland and Pregnancy Sickness Support (UK).

3. Discussion/conclusion

This mixed-methods study aims to provide evidence regarding the implementation and evaluation of a dedicated day-case service for women with HG. It is hoped that the involvement of a wide range of multidisciplinary healthcare professionals and a patient representative in the design of the study will lead to meaningful findings for both women affected by the condition and those who provide HG care. This is one of the few studies examining nutritional intake before and after a HG specific intervention and will therefore add significantly to the literature base.

Funding statement

This study was funded by Health Services Exectutive Nursing and Midwifery Planning and Development Unit, South Dublin, Kildare & Wicklow.

CRediT author statement

Eileen C O'Brien: Conceptualization, Methodology, Formal analysis, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition, Jean Doherty: Methodology, Investigation, Formal analysis, Resources, Data Curation, Writing - Review & Editing, Project administration, Sarah Louise Killeen: Investigation, Resources, Data Curation, Writing - Review & Editing, Melanie Bennett: Investigation, Resources, Data Curation, Writing - Review & Editing, Lillian Murtagh: Conceptualization, Methodology, Writing - Review & Editing, Sinead Curran: Conceptualization, Methodology, Resources, Writing - Review & Editing, Supervision, Funding acquisition, Suzanne Murphy: Patient representative, Helen McHale: Conceptualization, Methodology, Writing - Review & Editing, Lucille Sheehy: Conceptualization, Methodology, Resources, Writing - Review & Editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] T. Einarson, C. Piwko, G. Koren, Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis - PubMed, J Popul Ther Clin Pharmacol 20 (2) (2013) e171–e183.
[2] ACOG, ACOG practice bulletin No. 189: nausea and vomiting of pregnancy, Obstet. Gynecol. 131 (Issue 1) (2018), https://doi.org/10.1097/AOG.0000000000002456.
[3] M.S. Fejzo, J. Trovik, I.J. Grooten, K. Sridharan, T.J. Roseboom, Å. Vikanes, R. C. Painter, P.M. Mullin, Nausea and vomiting of pregnancy and hyperemesis gravidarum, Nat. Rev. Dis. Prim. 5 (1) (2019) 62, https://doi.org/10.1038/s41572-019-0110-3.
[4] L.I. Trogstad, C. Stoltenberg, P. Magnus, R. Skjaerven, L.M. Irgens, Recurrence risk in hyperemesis gravidarum, BJOG 112 (12) (2005) 1641–1645, https://doi.org/10.1111/j.1471-0528.2005.00765.x.
[5] M.S. Fejzo, D. Arzy, R. Tian, K.W. Macgibbon, P.M. Mullin, Evidence GDF15 plays a role in familial and recurrent hyperemesis gravidarum, Geburtshilfe Frauenheilkd 78 (9) (2018) 866–870, https://doi.org/10.1055/a-0661-0287.
[6] M. Fejzo, N. Rocha, I. Cimino, et al., GDF15 linked to maternal risk of nausea and vomiting during pregnancy, Nature (2023). https://doi.org/10.1038/s41586-023-06921-9.
[7] S. Sun, X. Qiu, J. Zhou, Clinical analysis of 65 cases of hyperemesis gravidarum with gestational transient thyrotoxicosis, J. Obstet. Gynaecol. Res. 40 (6) (2014) 1567–1572, https://doi.org/10.1111/JOG.12372.
[8] M.N. Niemeijer, I.J. Grooten, N. Vos, J.M.J. Bais, J.A. Van Der Post, B.W. Mol, T. J. Roseboom, M.M.G. Leeflang, R.C. Painter, Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis, Am. J. Obstet. Gynecol. 211 (2) (2014) 150.e1–150.e15, https://doi.org/10.1016/j.ajog.2014.02.012.
[9] M. Rashid, M.H. Rashid, F. Malik, R.P. Herath, Hyperemesis gravidarum and fetal gender: a retrospective study, J. Obstet. Gynaecol. 32 (5) (2012) 475–478, https://doi.org/10.3109/01443615.2012.666580.
[10] T. Meinich, J. Trovik, Early maternal weight gain as a risk factor for SGA in pregnancies with hyperemesis gravidarum: a 15-year hospital cohort study, BMC Pregnancy Childbirth 20 (1) (2020) 255, https://doi.org/10.1186/s12884-020-02947-3.
[11] L. Fiaschi, C. Nelson-Piercy, J. Gibson, L. Szatkowski, L.J. Tata, Adverse maternal and birth outcomes in women admitted to hospital for hyperemesis gravidarum: a population-based cohort study, Paediatr. Perinat. Epidemiol. 32 (1) (2018) 40–51, https://doi.org/10.1111/PPE.12416.
[12] C.J. Petry, K.K. Ong, K. Beardsall, I.A. Hughes, C.L. Acerini, D.B. Dunger, Vomiting in pregnancy is associated with a higher risk of low birth weight: a cohort study 18 (1) (2018) 1–8, https://doi.org/10.1186/S12884-018-1786-1.
[13] M.V.E. Veenendaal, A.F.M. Van Abeelen, R.C. Painter, J.A.M. Van Der Post, T. Roseboom, Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis, BJOG An Int. J. Obstet. Gynaecol. 118 (Issue 11) (2011) 1302–1313, https://doi.org/10.1111/j.1471-0528.2011.03023.x. BJOG.
[14] K. Nijsten, L.A.W. Jansen, J. Limpens, M.J.J. Finken, M.H. Koot, I.J. Grooten, T. J. Roseboom, R.C. Painter, Long-term health outcomes of children born to mothers with hyperemesis gravidarum: a systematic review and meta-analysis, Am. J. Obstet. Gynecol. (2022), https://doi.org/10.1016/J.AJOG.2022.03.052.
[15] K. Maslin, V. Shaw, A. Brown, C. Dean, J. Shawe, What is known about the nutritional intake of women with Hyperemesis Gravidarum?: a scoping review, Eur. J. Obstet. Gynecol. Reprod. Biol. 257 (2021) 76–83, https://doi.org/10.1016/j.ejogrb.2020.12.003.
[16] J.A. Gazmararian, R. Petersen, D.J. Jamieson, L. Schild, M.M. Adams, A. D. Deshpande, A.L. Franks, Hospitalizations during pregnancy among managed care enrollees, Obstet. Gynecol. 100 (1) (2002) 94–100, https://doi.org/10.1016/S0029-7844(02)02024-0.
[17] C. McParlin, D. Carrick-Sen, I.N. Steen, S.C. Robson, Hyperemesis in Pregnancy Study: a pilot randomised controlled trial of midwife-led outpatient care, Eur. J. Obstet. Gynecol. Reprod. Biol. 200 (2016) 6–10, https://doi.org/10.1016/J.EJOGRB.2016.02.016.
[18] F.P. McCarthy, A. Murphy, A.S. Khashan, B. McElroy, N. Spillane, Z. Marchocki, R. Sarkar, J.R. Higgins, Day care compared with inpatient management of nausea and vomiting of pregnancy: a randomized controlled trial, Obstet. Gynecol. 124 (4) (2014) 743–748, https://doi.org/10.1097/AOG.0000000000000449.
[19] A. Murphy, F.P. McCarthy, B. McElroy, A.S. Khashan, N. Spillane, Z. Marchocki, R. K. Sarkar, J.R. Higgins, Day care versus inpatient management of nausea and vomiting of pregnancy: cost utility analysis of a randomised controlled trial, Eur. J. Obstet. Gynecol. Reprod. Biol. 197 (2016) 78–82, https://doi.org/10.1016/j.ejogrb.2015.10.022.
[20] M.C. Liu, S.H. Kuo, C.P. Lin, Y.M. Yang, F.H. Chou, Y.H. Yang, Effects of professional support on nausea, vomiting, and quality of life during early pregnancy, Biol. Res. Nurs. 16 (4) (2014) 378–386, https://doi.org/10.1177/1099800413506036.
[21] K. Maslin, H.A. Billson, C.R. Dean, J. Abayomi, The contribution of registered dietitians in the management of hyperemesis gravidarum in the United Kingdom, Nutrients 13 (6) (2021), https://doi.org/10.3390/nu13061964.

[22] E.R. Beirne, L.B. Andrews, L.P. Murtagh, S. Browne, S.B. Curran, E.C. O'Brien, The far-reaching burden of Hyperemesis Gravidarum - an exploration of women's experiences and perceptions of healthcare support, Women Health 63 (7) (2023) 485–494, https://doi.org/10.1080/03630242.2023.2219749.
[23] RCPI & HSE, Hyperemesis and nausea/vomiting in pregnancy. 2015. https://www.hyperemesis.ie/documents/Guidelines-Ireland-HyperemesisNauseaVomitinginPregnancy.pdf. (Accessed 14 April 2023).
[24] James Lind Alliance Priority Setting Partnership, Hyperemesis Gravidarum Top 10, 2019. https://www.jla.nihr.ac.uk/priority-setting-partnerships/hyperem-%0Aesis-gravidarum. (Accessed 14 October 2023).
[25] G. Koren, C. Piwko, E. Ahn, R. Boskovic, C. Maltepe, A. Einarson, Y. Navioz, W. Ungar, Validation studies of the Pregnancy Unique-Quantification of Emesis (PUQE) scores 25 (3) (2009) 241–244, https://doi.org/10.1080/01443610500060651, 10.1080/01443610500060651.
[26] K.F. Foxcroft, L.K. Callaway, N.M. Byrne, J. Webster, Development and validation of a pregnancy symptoms inventory, BMC Pregnancy Childbirth 13 (1) (2013) 1–9, https://doi.org/10.1186/1471-2393-13-3/TABLES/2.
[27] B. Gandek, J.E. Ware, N.K. Aaronson, G. Apolone, J.B. Bjorner, J.E. Brazier, M. Bullinger, S. Kaasa, A. Leplege, L. Prieto, M. Sullivan, Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project, J. Clin. Epidemiol. 51 (11) (1998) 1171–1178, https://doi.org/10.1016/S0895-4356(98)00109-7.
[28] C.W. Topp, S.D. Østergaard, S. Søndergaard, P. Bech, T. Cw, Ø. Sd, S. S, B. P, The WHO-5 well-being index: a systematic review of the literature, Psychother. Psychosom. 84 (3) (2015) 167–176, https://doi.org/10.1159/000376585.
[29] K. Malterud, V.D. Siersma, A.D. Guassora, Sample size in qualitative interview studies: guided by information power, Qual. Health Res. 26 (13) (2016) 1753–1760, https://doi.org/10.1177/1049732315617444.
[30] N.K. Dhand, M.S. Khatkar, Statulator: an Online Statistical Calculator. Sample Size Calculator for Comparing Two Paired Proportions, 2014. http://statulator.com/SampleSize/ss2PP.html.
[31] National Maternity Hospital, Annual Report - 2021, 2022.
[32] V. Braun, V. Clarke, Reflecting on reflexive thematic analysis, Qualitative Research in Sport, Exercise and Health 11 (4) (2019) 589–597, https://doi.org/10.1080/2159676X.2019.1628806.