Novel interventions for pregnant women: Pharmacist consultations and mobile applications in pregnancy

With focus on the management of nausea and vomiting during pregnancy

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To Khai, for your endless patience

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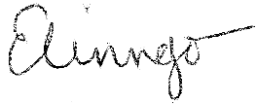

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SUMMARY IN ENGLISH

Background: Up to 80% of pregnant women experiences nausea and vomiting during pregnancy (NVP). Even mild NVP has shown a negative impact on pregnant women's quality of life, relationship with their partner, and social life and requires appropriate management to avoid development of more severe NVP. Sufficient information is essential to involve pregnant women in their health care and to help them make informed choices regarding NVP management. Digital decision support tools and pharmacist-led interventions have shown beneficial effects on patient involvement and enhanced medication use. However, there is still a lack in the literature on utilizing decision support tools and pharmacist consultations to inform about and involve pregnant women in the management of NVP.

Aim: The overall aim of this thesis was to examine the effect of different novel interventions on NVP severity and medication use, with focus of antiemetics, including the use of a mobile application and a pharmacist consultation. Specifically, **Study I** aimed to review the effects of decision support tools used during pregnancy and the common features of useful tools. **Study II** aimed to assess the effect of a mobile application on NVP severity, quality of life, and decisional conflict. Lastly, **Study III** investigated the impact of a pharmacist consultation on use of medications in general and antiemetics in specific.

Methods: Study I was a systematic literature review of existing decision support tools used to manage different conditions during pregnancy and included published studies up to January 18, 2019. **Study II** was a randomized controlled trial investigating the effect of using the MinSafeStart mobile application which utilized the Pregnancy-Unique Quantification of Emesis and Nausea score to track NVP severity, compared to standard care. The MinSafeStart mobile application also provided tailored advice based on the NVP severity. Pregnant women were recruited on social media. All data were self-reported by the women in online questionnaires. **Study III** was an intervention study with a pharmacist consultation as the intervention, compared to standard care. Pregnant women were recruited on social media and at pharmacies all over Norway.

Self-reported data on medication use was linked with filled prescriptions recorded in the Norwegian Prescription Database.

Results: Study I included 25 studies and illustrated that pregnant women found digital decision support tools useful, mainly when they could record their symptoms and receive tailored feedback. The use of decision support tools also increased pregnant women's knowledge, enhanced clinical measures, and was suggested to be beneficial in communication with health care providers. In total, 157/192 women in **Study II** experienced mild NVP at baseline. These women also had a poor quality of life (NVPQOL score: 146-149) and high decisional conflict (DCS: 40-43). Women who used the MinSafeStart mobile application to track their NVP severity did not show any difference in NVP severity (adjusted β: 0.6, 95% CI: −0.1, 1.2), quality of life (adjusted β: −5.3; 95% CI: −12.5, 1.9), or decisional conflict (adjusted β: −1.1, 95% CI: −6.2, 4.2), compared to standard care. Of the 229 women in **Study III**, 14-22% of women in the first trimester and 23-27% in the second trimester reported that they used antiemetic medications. **Study III** did not detect any impact of a pharmacist consultation in early pregnancy on pregnant women's use of medications.

Conclusion: The use of digital decision support tools during pregnancy was found useful and had potential in maternal care. However, the use of a mobile application did not demonstrate an enhanced NVP severity. An impact of a pharmacist consultation on medication use were not detected either. Future studies should still focus on a process evaluation to better understand how pregnant women use health mobile applications, and how they utilize them in communication with health care providers, such as pharmacists, during pregnancy. The role of pharmacist in maternity care should also be further explored.

SAMMENDRAG PÅ NORSK

Bakgrunn: Opptil 80% av gravide kvinner opplever svangerskapskvalme og dette er ofte første tegn på graviditet. I mange tilfeller oppstår svangerskapskvalme allerede før første svangerskapskontroll. Selv mild svangerskapskvalme har vist en negativ innvirkning på gravide kvinner, deres livskvalitet, forhold til partner og sosiale liv. Det er tidligere vist at svangerskapskvalme krever tidlig og riktig tilpasset behandling for å unngå utvikling av alvorlige symptomer. Likevel føler gravide kvinner at de ikke blir tatt alvorlig og ikke får optimal behandling. Gravide kvinner er ofte opptatt av og ønsker å bli mer involvert i sin egen helse. Optimal informasjon er et viktig element for å oppnå dette. Selv om bruk av digitale beslutningsstøtteverktøy og farmasøyt intervensjoner har vist gunstige effekter på informerte helsebeslutninger og riktig medisinbruk, er det likevel mangel på litteratur om bruk av beslutningsstøtteverktøy og farmasøytkonsultasjoner for å informere om og involvere gravide kvinner i behandling av svangerskapskvalme.

Hensikt: Den overordne hensikten med denne avhandlingen var å teste ut effekten av innovative intervensjoner på alvorligheten av svangerskapskvalme og bruk av legemidler, inkludert kvalmestillende. Dette inkluderer bruk av en mobil applikasjon for å logge svangerskapskvalme og en tilpasset farmasøytsamtale i første trimester. Mer spesifikt, var hensikten til **Studie I** å få en bedre forståelse av effekter og bruk av beslutningsstøtteverktøy under graviditeten. **Studie II** undersøkte effekten av en mobil applikasjon for å logge symptomer på svangerskapskvalme, livskvalitet og beslutningsevne. **Studie III** undersøkte effekten av en farmasøytsamtale på legemiddelbruk blant gravide, med fokus på bruk av legemidler generelt, og spesielt kvalmestillende.

Metode: Studie I var en systematisk litteraturgjennomgang av studier publisert frem til 18. januar 2019 for å gi en oversikt over effekter av eksisterende beslutningsstøtteverktøy for ulike tilstander blant gravide. **Studie II** var en randomisert kontrollert studie som undersøkte effekten av å logge kvalmesymptomer i MinSafeStart mobilapplikasjonen, basert på Svangerskaps Utløst Kvalme Kvantifisering Skår, sammenlignet med standard svangerskapsomsorg. MinSafeStart mobilapplikasjonen ga

tilpassede råd basert på alvorlighetsgraden av kvalmen. Gravide kvinner ble rekruttert via sosiale medier. All data var selvrapportert via elektroniske spørreskjemaer. **Studie III** var en intervensjonsstudie som tilbydde alle gravide kvinner i intervensjonsgruppen en individuell farmasøytsamtale i første trimester. Kontrollgruppen fulgte kun standard svangerskapsomsorg. Gravide kvinner ble rekruttert på sosiale medier og via apotek over hele Norge. Selvrapporterte data om medisinbruk ble koblet med data fra Reseptregisteret.

Resultater: Den systematiske litteraturgjennomgangen i **Studie I** inkluderte 25 studier og viste at gravide kvinner syntes digitale beslutningsstøtteverktøy var nyttige, spesielt når de kunne logge symptomer digitalt og få individuell tilbakemelding. Beslutningsstøtteverktøy hadde gunstige effekter på kliniske utfall, kunnskap blant kvinnene og kunne være fordelaktig i kommunikasjon med helsepersonell. I **Studie II** var det 157/192 kvinner som rapporterte mild svangerskapskvalme ved oppstart i studien. Kvinnene rapporterte også lav livskvalitet (NVPQOL skår: 146-149) og dårlig beslutningsevne (DCS: 40-43). Bruk av mobilapplikasjonen til å logge kvalmeskår viste ingen effekt på kvalmesymptomer (justert β: 0.6, 95% CI: −0.1, 1.2), livskvalitet (justert β: −5.3; 95% CI: −12.5, 1.9) eller beslutningsevne om behandling av svangerskapskvalme (juster β: −1.1, 95% CI: −6.2, 4.2). I **Studie III** (n=229) var det 14-22% av kvinner i første trimester og 23-27% av kvinner i andre trimester som rapporterte bruk av legemidler for behandling av svangerskapskvalme. Studien viste ingen effekt av farmasøytsamtalen sammenlignet med standard svangerskapsomsorg, verken på generell legemiddelbruk eller legemiddelbehandling for svangerskapskvalme.

Konklusjon: Intervensjonene viste ingen effekt på forbedring av kvalmesymptomer eller endring av generell legemiddelbruk eller bruk av kvalmestillende. Fremtidige studier bør fortsatt fokusere på hvordan gravide bruker beslutningsstøtteverktøy for å håndtere ulike svangerskapsrelaterte plager og i kommunikasjon med helsepersonell. Funnene i denne oppgaven kan likevel ha viktig klinisk betydning for svangerskapsomsorgen knyttet til bruk av digitale støtteverktøy og rollen som farmasøyt.

ABBREVIATIONS

aOR:	Adjusted odds ratio
CAM:	Complementary and alternative medicine
CI:	Confidence interval
DSC:	Decisional conflict scale
GP:	General practitioner
HG:	Hyperemesis Gravidarum
Mobile app:	Mobile application
MSS app:	MinSafeStart mobile application
NorPD:	Norwegian Prescription Database
NVP:	Nausea and vomiting during pregnancy
NVPQOL:	Nausea and vomiting of Pregnancy specific health-related Quality of Life
OR:	Odds ratio
OTC:	Over-the-counter
PUQE:	Pregnancy-Unique Quantification of Emesis and Nausea
Q1:	Baseline questionnaire
Q2:	Follow-up questionnaire
RCT:	Randomized controlled trial
SMS	Short Message Service
TSD:	Service for sensitive data
UiO:	University of Oslo
USIT:	University Center for Information Technology
WHO:	World Health Organization

1 INTRODUCTION

1.1 Why novel interventions for pregnant women?

Pregnancy is complex and can present many health challenges for pregnant women (1-3). It is therefore essential that each pregnant woman has access to health information tailored to her needs (2) in order to optimally manage her condition. Many pregnancy-related ailments occur during the first few weeks of gestation, *e.g.*, fatigue, nasal congestion, and, in particular, nausea and vomiting in pregnancy (NVP), also known as "*morning sickness*" (4, 5). NVP typically commences between gestational weeks 4-9 (6) and is associated with reduced quality of life (7-9), hospitalization (10), and sick leave days (11). This emphasizes the need for health care providers to recognize the impact of this common pregnancy ailment and be trained to provide optimal support and management related to NVP. As patient-centered care has become a focus and has known benefits (12), research must evaluate and validate novel interventions aiming to empower patients to actively take part in their own health care decisions. Yet, little is known about how novel interventions can contribute in the management of pregnancy-related ailments that occur in early pregnancy, especially NVP. This thesis is therefore focused on investigating the use of a mobile application (app) and a tailored pharmacist consultation to reduce common challenges related to NVP management.

1.2 The Norwegian prenatal care

Norway offers free prenatal care to all pregnant women residing within its borders (13). The overall aim of the prenatal care program is to promote a healthy lifestyle in pregnancy and to reduce morbidity and child and maternal mortality (13). In addition to prevent infectious diseases and detect pregnancy-related complications early. The basic program consists of nine consultations (**Table 1.1**). Extended care is offered based on individual assessment. All pregnant women in Norway can choose to be follow-up by their general practitioner (GP) and/or a midwife. The guidelines, updated in 2018, recommended that care begins in gestational week six and an early ultrasound in weeks 11-14 (13). Prenatal care is continuously evolving and successful interventions can be incorporated to expand the healthcare service for pregnant women.

Table 1.1: Overview of the basic Norwegian prenatal care program adapted from The National Guideline on Antenatal Care.

Gestational week	Recommended examinations and tests
6-12	Blood pressure, urine protein, hepatitis, HIV, syphilis, hemoglobin, serum ferritin, blood type and immunization, weight, and body mass index
11-14	Ultrasound
17-19	Ultrasound
24 28 32	Blood pressure, urine protein, weight, symphysis-fundus measurement, and fetal heartbeat
36 38 40	Blood pressure, urine protein, weight, symphysis-fundus measurement, fetal heartbeat, and fetal's position

1.3 Patient involvement

There is an increased awareness of the benefit of involving patients when decision about their health care is being made (14). Patient involvement is a concept with a multitude of meanings (14). It is frequently interpreted as the active participation of patients in their own health care, including decision making (15, 16). This can be achieved by providing information about the available options for management and treatment, intending to empower the patients and enable informed decision making (15). The approach has improved clinical outcomes in patients with diabetes, depression, rheumatic diseases, among others, and the patient's satisfaction with care (12, 17-20). More work is needed to investigate the effects of involving pregnant women in their health decisions.

Pregnant women search for pregnancy-related information on the internet, social media, and mobile apps to be more informed and involved in their health care (21-24). Primiparous women are more likely to use the internet (21, 25-27), especially when they feel that the information they received through prenatal care was not sufficient for their information needs (28). Adequate information is therefore essential for pregnant women to be empowered to have a useful discussion with their health care providers and to take an active role in managing (14). However, unclear and incomplete information are two known barriers to patient involvement (29). Investigating methods for providing pregnant women with adequate information is essential in order to achieve successful patient involvement in health care.

1.4 Pregnant women's need for health information

Pregnant women seek health information to feel more confident, involved, and comfortable when making decisions and communicating with health care providers (30, 31). To have sufficient health information has been shown to decreased stress and anxiety during pregnancy and reduced the risk for isolation (32). Pregnant women are more likely to search for information (22, 33) during the early stages of pregnancy (21). Women in a committed relationship or being pregnant for the first time are more likely to search for information compared to their counterparts (21). In a study of 404 pregnant women, women with higher education were more likely to search for information, compared to women with less than a high school education (34). Employed women (n=185) also search for information more frequently, compared to women who are unemployed (35). Through pregnant women primarily search for information online (36-39), up to 50% of women used pharmacies as their information source (34, 37, 40, 41). Women who used the internet, searched for information at least once a month and up to two times a week (21). The topics most frequently searched for are fetal development, nutrition, general pregnancy information, and labor and delivery (21, 39) and up to 40% search for information about topics previously discussed with their health care provider (42). A study reviewing an American NVP helpline reported that 86% called for information regarding NVP management (43). By the time the women called in, 95% were experiencing moderate/severe NVP based on the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score. This may contribute to the indication that pregnant women need more information about the management of NVP and they need the information earlier in the course of the development of NVP symptoms. A qualitative, Dutch study exploring women's recommendations for improving prenatal care emphasizes the importance of sufficient and tailored information with a personal approach (44). The highly requested information among pregnant women underscores the need to investigate information sources tailored to pregnancy in order to fulfill pregnant women's information needs.

1.5 Pregnant women's need for support

It is undisputed that pregnant women need support. A study (n=575) reported that social support from three or more people significantly decreased the risk of severe NVP in the third trimester in comparison to social support from one person (OR: 0.4, 95% CI: 0.2-0.4) (45). Similarly, *Elsenbruch et al.*, (n=896) found a significantly increased in the *Allgemeine Depressionsskala* (16.1 ± 8.1), indicating more significant depressive symptoms among women with low social support compared with women with medium (11.3 ± 6.8) and high social support (7.6 ± 5.8). Women with lower social support also had reduced quality of life (46). Other authors agree that social support from friends, family, and partners has a protective role in mental health, life satisfaction, well-being, NVP symptoms, and quality of life among pregnant women (45, 47, 48). Notably, mental health problems, low socioeconomic status, and being partnerless were decisive factors for not receiving social support during pregnancy (49). Social support is therefore highly recommended during the pregnancy period.

Support from health care providers has also been found to contribute to positive pregnancy-related outcomes. A randomized controlled trial (RCT) (n=79) concluded that providing a booklet with general information and lifestyle recommendations followed by emotional support from a health care worker via telephone was associated with decreased NVP severity after two and four weeks, compared to no additional support besides standard care (50). Women who received support from health care providers had improved perceived level of social support (51) and NVP severity, which positively impacted their quality of life (50, 52, 53). Health care providers are an essential part of pregnant women's support system during this delicate time of life.

The following sections will introduce how community pharmacist consultations and decision support tools as novel interventions can provide information to pregnant women and contribute to involving pregnant women in the managing of their health.

1.6 The Community Pharmacists' role

The pharmacists' role and profession have evolved over the course of the last decade, especially after the COVID-19 pandemic (54, 55). These changes have resulted in improved recognition of the pharmacists' ability to contribute to health care for all patient groups (56). The improved professional standing of pharmacists is providing pharmacists with new opportunities and a wider area of responsibility in providing patient care (57). For instance, Norwegian community pharmacies are now providing two pharmacist-led services, i.e., the inhalation technique service for patients using inhalations medications for asthma and chronic obstructive pulmonary disease (58), and the Medicine Start service for patients with a first-time prescription for a cardiovascular medicine (59). The services have been shown to be beneficial for correct inhalation technique and chronic cardiovascular medication adherence, respectively (58, 59). Starting 2018, the Norwegian pharmacists' scope of practice were also extended to include the administration of prescribed influenza vaccines. This service was later expanded to include both prescribing and administration of influenza vaccines (60). Pharmacists in Norway also contributed to the administration of the first round of COVID-19 vaccines due to a lack of health care providers to achieve rapid, mass vaccination throughout Norway (61). Norwegian pharmacists were allowed in 2020 to independently dispense sildenafil used for erectile dysfunction. Before dispensing sildenafil to a patient, pharmacists are required to ensure all criteria for use were met (62). This highlights that the Norwegian pharmacists' scope of practice also recently has been shifted towards patient care.

Though most medications are safe for use during pregnancy (63), pregnant women tend to overestimated the risk (64, 65). This overestimation of risk perception may lead to non-adherence. The role of a pharmacist in promoting maternal health has been an important focus (66, 67). Pharmacist-led interventions regarding medication adherence, health behavior, and treatment and management of diseases/illness have shown real potential in the last decades in several patient groups (68-74). A meta-analysis from 2021, by *Marcum et al.*, including 40 RCTs and 8822 patients, showed that pharmacist-led interventions had a significant effect in improving medication adherence among

patients (68). A systematic review by *Polly et al.*, have the same conclusion regarding the potential benefit of community pharmacists (75). Focusing on the pregnant population, involving pregnant women in their medication use by providing sufficient information through a consultation resulted in an increased knowledge level and adherence (76), and reduced pregnant women's risk perception (77). Earlier studies have also shown that pharmacist consultations provided in community pharmacies are feasible and highly appreciated by patients (78, 79). A review from 2019 by *Caulemans et al.*, included nine studies on pharmacist counselling of pregnant women suggested community pharmacists as an important role in primary care (66). However, the literature regarding pharmacist consultations for the pregnant population is still scarce.

1.6.1 Barriers to pharmacist consultations

Pharmacists can have an essential role in alleviating concerns regarding medication use during pregnancy (37, 80). Generally, pharmacists believe they have an important role in providing consultations for pregnant women and have sufficient knowledge about pregnant women`s health conditions (81-83). Even though studies have shown that the role of the pharmacist and the development of pharmacist-led interventions are driven in a confident direction, some pharmacists are still skeptical of a more advanced role in medication management beyond their standard practice (84). An interview study including 115 pharmacists in Canada found that community pharmacists viewed dispensing medications to the population and not patient-centered consultations as their primary task (85). In addition, there are multiple barriers that might hinder pharmacists from optimally communicating with their patients. Specifically, a patient's limited knowledge about and lack of understanding of their health can make it difficult for the pharmacist to identify the patient's needs (81, 86, 87). Other barriers have been described as the lack of time and funding (88), lack of support from and communication with other health care providers (88, 89), and lack of patient-centered communication skills training and educational programs, especially with respect to pregnancy (81, 82, 90). This enhances the importance of further training pharmacists for tailored consultations and make more evidence-based information available (66).

1.7 Decision support tools – the newest health information source?

Women started using the internet as a health information source starting in the early 1990s. What started with websites, forums, and chat rooms has now developed into social media and mobile apps (91-93). The term mHealth encompasses all mobile phone apps about health (94) and has driven our healthcare in a digital direction. The World Health Organization (WHO) defines mHealth as "*medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices*" (94). Given the revolution of technology and digitalization, it is a matter of course that healthcare system follows.

Good communication and personal care are crucial for optimal health decision making (95). A shared health-related decision between patient and health care provider is a highly recommended model (96). Individually tailored care consisting of unbiased information that includes options, outcomes, risks, and benefits in the context of the pregnant woman's needs is essential as a part of the women's prenatal care (97, 98). Decision support tools used during pregnancy can be practical, especially for this task. These tools have contributed to informed decision making by increasing confidence and knowledge level and suggesting beneficial in communication between women and health care providers (95, 99-102). Decision support tools are in addition useful for health care providers for information and shown to have potential to effectively assist health care providers in counselling pregnant women when challenging choices are to be made (103). A systematic review from 2022 by *Whybrow et al.*, included ten randomized controlled trials with data from 4028 women found that women who used a decision support tool had a decisional conflict score reduction by -3.7 points (CI: -5.9% to -1.6%) (99). The author suggested that decision support tools can effectively support personalized care. The main limitation of this review is the limited number of studies available. Prior studies have shown that such decision support tools are more beneficial for decision making regarding medication use when provided to pregnant women with pre-existing medical illness and who were more conflicted at baseline (99). Use of mobile apps in health care have improved the quality of care, increased access to information regarding diseases, ailments, management, treatment, and health

information in general, and promoted positive changes in the perception of health (104, 105), which may also lead to a more cost-effective management. A review by *Alayna et al.*, in 2022 suggests that digital support tools are low-cost and may be cost-effective. However, further research is needed to assess the cost-effectiveness of digital support tools in maternal health (106).

Wang et al., (n=535) reported that pregnant women mainly used mobile apps to follow the fetus' development (83%), for nutrition information (26.2%), and to get general information about prenatal care (23.9%) (107). Pregnant women using mobile apps (n=193) believe it is convenient (36%), still, 39% of women report a lack of credibility in the mobile apps (108). The opportunity to look up information on mobile devices was highly appreciated (92), including tailored information sent automatically based on the pregnancy period or situation and the child's development. However, such tools on clinical outcomes should be tested before recommending them or implementing them as a supplement in routine maternity care (109).

1.8 Nausea and vomiting during pregnancy

Nausea and vomiting in pregnancy is one of the most common pregnancy-related ailments, affecting up to 80% of pregnant women world-wide (110-113). NVP is often described as nausea, dry haves, retching, and/or vomiting (6) occurring in the first trimester, when other causes have been excluded (114). The symptoms typically begin in gestational week 4-9 and peaks between weeks 7-12. Symptoms of NVP usually decrease between weeks 12-16. Up to 15% of women experiencing NVP, however, will continue to have symptoms to weeks 20-22, with a small proportion experiencing symptoms until delivery (6). The pathophysiology of NVP is not fully understood, but it has been described to include genetic, endocrine, and gastrointestinal factors (115).

The symptoms of NVP range from mild, moderate to severe. The severity of NVP can be categorized based on the PUQE score (116). The PUQE score is described in detail in the methods section on page 30-31. In short, the PUQE consists of three questions yielding a total score of 3-15. A score between 3–6 points is defined as mild NVP, 7–12 points as moderate NVP, and scores ≥13 points as severe NVP. The most severe form of NVP is called Hyperemesis Gravidarum (HG), which affects up to 0.3-2% of pregnant women (110, 111, 117). There are no clear criteria to distinguish severe NVP and HG, and both terms have been used interchangeably in the literature (118). HG often occurs before week 20 and can last until delivery (119-121). There is no clear or specific diagnostic criteria of HG. HG usually refers to persistent and intractable NVP, >5% pre-pregnancy weight loss, dehydration, volume depletion, and for some severe cases, leads to ketonuria and/or ketonemia (122, 123). HG requires outpatient treatment or hospitalization for closer follow-up (119).

1.8.1 Acknowledgement of NVP

There is a variation in the treatment and management of pregnant women experiencing NVP due to a lack of understanding, women's risk perception, and restraint of medication use. Even though a significant proportion of pregnant women experience NVP, it is stated that only 10% of pregnant women experiencing NVP required treatment with antiemetic medications (124). There has seen an increased awareness of

NVP management coupled with a call for greater acknowledgment of NVP symptoms (125). Canadian and American NVP treatment guidelines recommend early treatment to prevent more severe symptoms and the associated cost of hospitalization and sick leave due to NVP (126). However, many pregnant women still frequently feel they are not taken seriously and trivialized when they presented the burden of NVP to their physician (127, 128). Even when the women pointed out that NVP had a negative impact on their daily quality of life, they were told that NVP was a normal part of pregnancy (128). Pregnant women felt that they were not sufficiently followed up, while GPs who participated in the same qualitative study emphasized that NVP is a normal state in pregnancy and something women must expect when pregnant. In another qualitative study by *van Vliet et al.,* women felt blamed for their condition (129). They did not feel they were taken seriously, not even when the women were experiencing severe NVP symptoms. Among 712 Norwegian women experiencing NVP, 70% of women with moderate NVP and 30% with severe NVP did not receive any pharmacological treatment (130). Pregnant women have also reported to feel that health care providers do not have adequate knowledge about HG to provide optimal care (129). Acknowledgement of the condition by health care providers is one of the first step towards an ideal management to avoid development of more severe NVP.

1.8.2 Management of NVP

NVP treatment is in direct response to the severity of the symptoms and is focused on managing symptoms, not on treating the illness. The PUQE score is a recommended approach for assessing the severity of NVP, including the impact of NVP on quality of life and ability to do daily tasks (119). The goal is to improve pregnant women's symptoms and minimize unwanted maternal and fetal outcomes (131). Treatment approaches often include lifestyle and dietary changes, over-the-counter (OTC) medications, prescribed medications, and complementary and alternative medicine (CAM) (**Figure 1.1**). Even though the prevalence of NVP is high (110-113), the proportion of pregnant women being treated with antiemetic have been found to range from around 2-42% (130). Canada is one of the country which has reported a high proportion of pharmacological treatment of NVP (130).

Dietary and lifestyle changes

Non-pharmacological treatments are common for NVP and are often recommended as first-line treatment for mild symptoms. This includes adequate rest, as fatigue is a common discomfort during pregnancy and has been shown by *Bai et al*. and *Chou et al*., to be associated with the worsening of NVP symptoms (53, 132). Recommendations for dietary and lifestyle changes often include eating small amounts of food every 1-2 hours, adding protein sources to each meal, avoiding caffeine, spicy and fatty food, and drinking two liters of liquid daily (133). Dietary and lifestyle changes are recommended even when treated with pharmacological treatment (119).

Complementary and alternative medicine

CAM as a treatment for NVP is receiving increasing amounts of attention (134). Ginger has a long history as treatment for NVP and is one of the most used herbs during pregnancy (134). Generally, 1 to 1.5 g of ginger orally over 24 hours is recommended (135). A blinded clinical trial of 77 women by *Sharifzadeh et al*., reported that ginger was more effective in treating mild to moderate NVP than a placebo. However, the Norwegian treatment guideline emphasize that ginger can promote dyspepsia and is therefore not recommended to women experiencing severe NVP or HG (119). There was no significant difference between ginger and pyridoxine (B6) (136). B6 has been shown to be effective in reducing nausea symptoms, but not vomiting (137, 138). A daily dose of 10 to 25 mg every 6-8 hours is recommended (139). Even though there have been studies reporting adverse effects related to neuropathy due to high doses of B6 or treatment over a longer period (>3 years) (140, 141), extensive studies over the years are still recommending B6 as a single agent or in combination with antihistamine for lower doses. Studies on stimulation of P6 point (Neiguan point) have conflicting results, but it is not associated with adverse effects and can safely be recommended for NVP management (142-144). Based on the Norwegian Obstetric Guideline for emesis and hyperemesis gravidarum, CAM are recommended for pregnant women experiencing moderate NVP, but pharmacological treatment should also be offered (119).

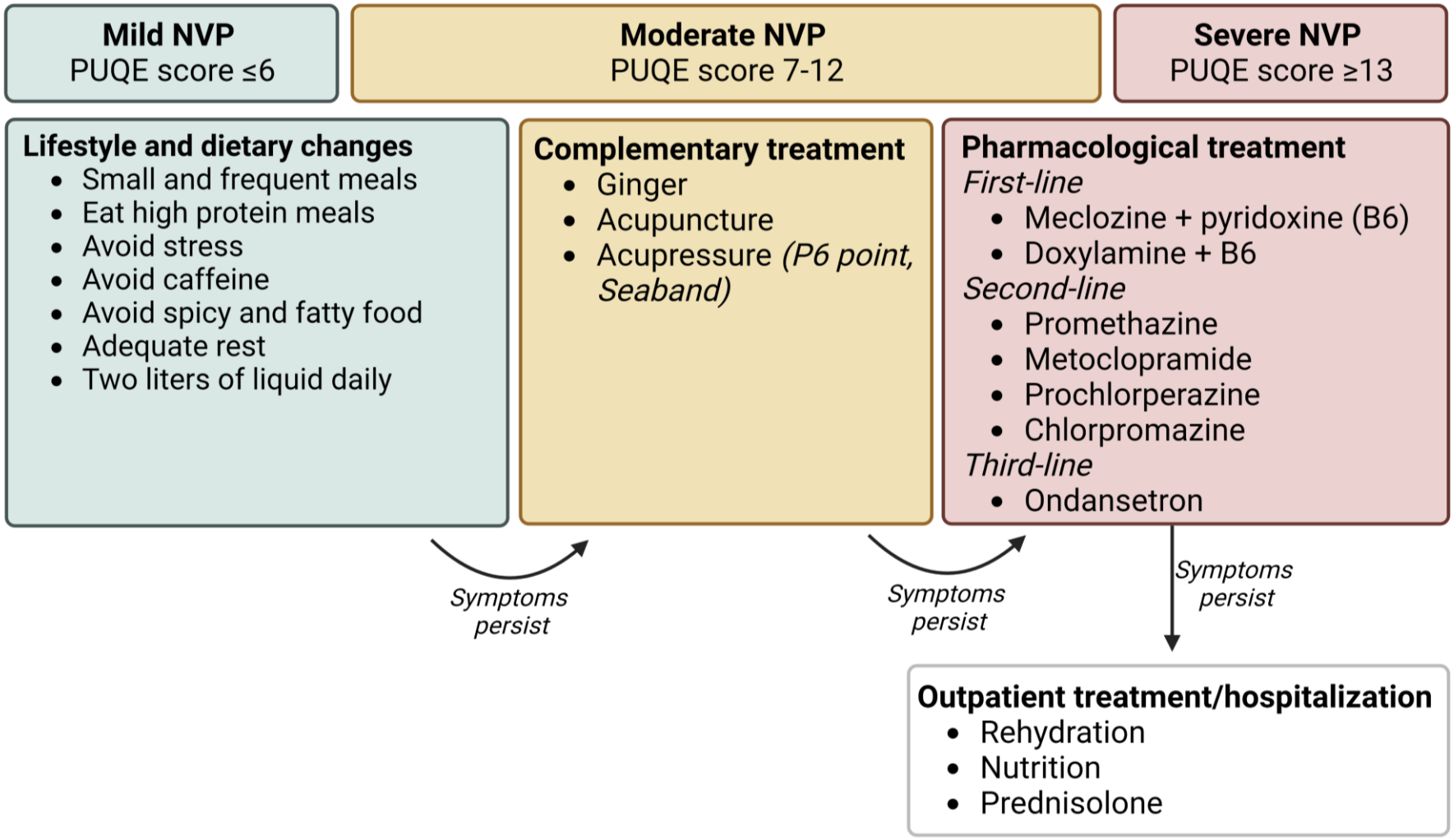

Figure 1.1: An overview of the treatment approaches for mild, moderate and severe NVP. Based on the Norwegian Obstetric Guideline for emesis and hyperemesis gravidarum.[1]
(Created with BioRender.com)

[1]Adapted from Torevik J, Nordeng H, et al., 2020. Emesis & Hyperemesis gravidarum. Den Norske legeforeningen.

Pharmacological treatment

The following sections feature a brief description of the safety of common medications recommended in the Norwegian Obstetric Guidelines for the treatment and management of NVP (119).

Antihistamines are considered safe in pregnancy and effective in treating NVP (145). There has not been shown any risk of major malformations when the antihistamines were taken in the first trimester (146, 147). Metoclopramide is often recommended as the second-line pharmacological treatment of NVP (148, 149). No increased risk for congenital anomalies in exposed infants compared to non-exposed infants has been found (150). A cohort study of 1.8 million pregnancies did not show any increased risk of congenital or cardiac malformations when exposed to ondansetron in early pregnancy (151). Other studies have found a small increase in cardiovascular malformations and cleft palate when exposed to ondansetron (151-154). Given the indecisive results regarding ondansetron exposure in early pregnancy, ondansetron is only suggested as treatment when other treatments have failed.

1.8.6 Impact of NVP

NVP can have a significant impact on the pregnant women themselves (155), the society and the unborn child. These consequences should be considered when interpreting the results of novel interventions to promote the management of NVP. The following sections will briefly describe the consequences of NVP and HG for society, women, and the unborn child.

Consequences for the pregnant women

A pregnant woman's quality of life is affected by NVP (7-9). More severe NVP is associated with lower quality of life (7). An earlier study by *Bai et al.*, which included 5,079 pregnant women enrolled before gestational week 18, showed lower quality of life among pregnant women experiencing nausea, vomiting, and/or fatigue daily compared to pregnant women not experiencing these symptoms (132). These results were significant in both physical and psychological domains and were in line with other

studies (9, 156). When comparing the health-related quality of life among women experiencing moderate to severe NVP (n=367) with other populations, it has been reported that their physical quality of life levels was close to women with breast cancer (8, 157, 158) and women who had experienced a heart attack (159). At the same time, women who experienced severe NVP had a quality of life comparable to women with postpartum depression (160). To summarize, all degrees of NVP has a negative impact on pregnant women's quality of life.

Women experiencing NVP frequently report feeling isolated and helpless (161). They also have a reduced ability to take care of other children, do daily activities, and attend social events (162-165), and willingness to become pregnant again (7). In addition, NVP impacts a pregnant woman's relationship with her partner (7). A Norwegian study (n=107) based on a structured interview and a questionnaire showed that HG significantly impacts pregnant women's daily activities. Two out of five women reported considering having a termination of the pregnancy due to HG (166). HG is, in western societies, one of the most common reason for hospitalization of pregnant women during the first trimester (166). NVP has a significant impact on pregnant women's life which should be taken into consideration when the ailments occur.

Socioeconomic consequences

Hospitalization results in significant costs to the health care system and society. HG was the second reason for hospitalization (9%) after preterm labor (24%) in *Gazmararian et al.* (n= 46,179) (10). A study of more than 8 million pregnancies reported that women hospitalized due to HG were more likely to have a C-section or premature birth (155). The annual increase in women being admitted to the hospital were due to NVP and the length of stay increased per admission (167). The overall cost of NVP treatment was $1827 on average for one woman and up to $1,778,473,782 in total. The cost increased with increased NVP severity (168, 169). In a Norwegian study including 2.918 women, 75% were on sick leave where NVP were one of the main reason (11). *Dørheim et al.* and *Backhausen et al*. also investigated sick leave among pregnant women and reported 23% and 34% of women were on sick leave due to NVP, in the respectively studies (11,

170). Women experiencing NVP were also more likely to be on sick leave in all three trimesters (11). For women experiencing HG, up to 93% (101/107) were on sick leave (166). Norwegian law entitles employees to 100% wage replacement, up to a fixed amount, when an employee is considered disabled and unable to work due to illness or injury. The employer pays the first 16 days; the rest is paid by The Norwegian Labour and Welfare Administration, usually known as NAV (171). The social economy is affected by the cost of NVP treatment and the high prevalence of hospitalization and sick leave, which implicates the importance of treatment and early recognition of NVP to prevent sick leave, hospitalization, and cost for society.

Fetal consequences

In contrast to consequences for society and women, mild NVP have been shown to yield favorable outcomes for the course of pregnancy, such as reduced rates for low birth weight and decreased risk for spontaneous abortion (172, 173) and preterm birth (174). These results were not comparable to pregnancy outcomes related to HG, which indicated that a fetus exposed to HG had a lower birth weight and smaller size for gestational age and preterm birth (155). A Norwegian study of 20.004 women diagnosed with HG suggested an association between HG and stillbirths (171). A different Norwegian study that utilized data from the Norwegian mother and child cohort concluded that there was no difference in birth weight among babies born to women who experienced or did not experience HG (175, 176). There are divergent results on fetal consequences, which may be influenced by the heterogeneity in the definition of HG.

1.9 The knowledge gap

NVP is a common pregnancy-related ailment and affects up to 80% of all pregnant women (110-113) and is often the first sign of pregnancy (177). To reduce symptoms of NVP and prevent the development of severe NVP, women and health care providers must intervene with appropriate management as soon as possible (133). Patient involvement has become a main factor in health care the recent years (14) and shown to be beneficial in managing different conditions and ailments (12, 17-19). Pregnant women are therefore no exceptions. Access to sufficient information is vital for pregnant women to be more engaged and involved in the management of their health (14, 29). All interventions to promote healthier pregnancies and reduce the economic burden for society are therefore highly warranted and prioritized. However, there are few studies and a lack in the literature regarding which type of interventions that could provide sufficient health information to pregnant women, to make them more informed regarding health decisions, and contribute to promote management of different conditions and ailments, such as NVP (**Figure 1.2**). Therefore, this thesis intended to fill this knowledge gap by examining how the use of a mobile app and a community pharmacist can provide health information and involve patient to optimal NVP management.

Figure 1.2: Sufficient information is the main factor for patient involvement, which has been essential in health care for optimal management. Yet, the literature is scarce on the type of intervention that can convey the information to pregnant women during a challenging and delicate time of their life.
(Created with BioRender.com)

2 AIMS

The overall goal of this thesis was to investigate novel interventions for NVP management. To achieve this, the two specific aims were 1) gain an extensive understanding of the efficacy and useful design elements of patient-centered decision support tools used during pregnancy, and 2) assess the effects of the use of a mobile app to track NVP symptoms on NVP severity and a pharmacist consultation in early pregnancy on medication use in general and antiemetics use in specific. **Figure 2.1** shows the overall goal, the specific aims for each study, and how the studies are connected.

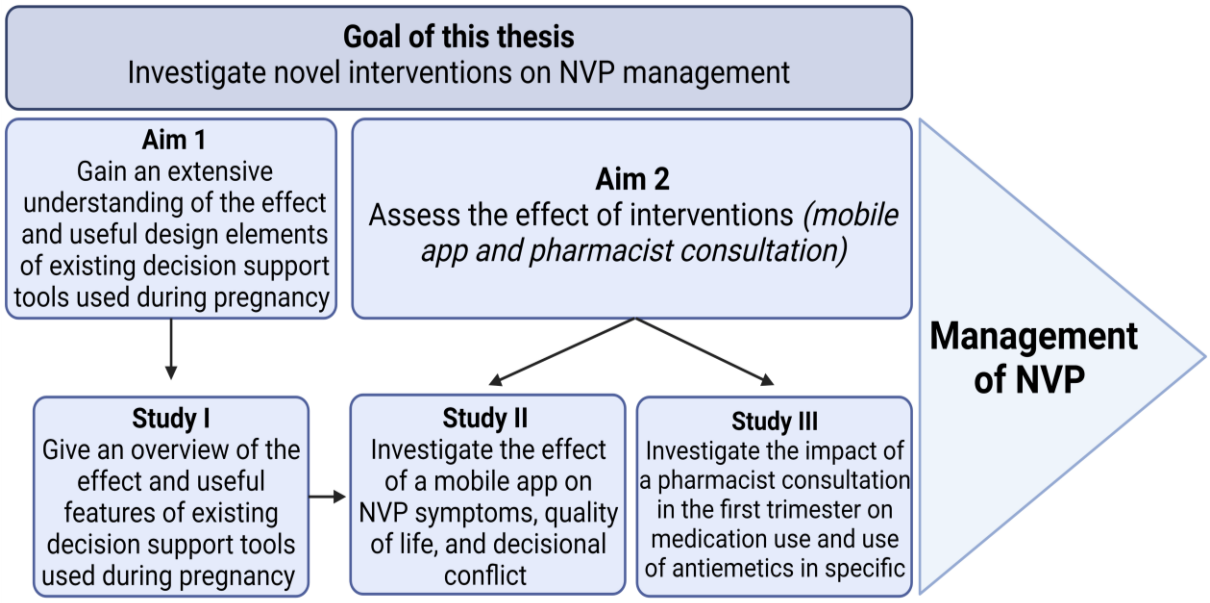

Figure 2.1: A schematic outline of the thesis' structure, and its underlying studies. The outline illustrates which studies assists in answering the different aims and how the different studies are connected.
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Study I: **Use of decision support tools to empower pregnant women: Systematic Review**

Aim: To identify studies evaluating the efficacy of patient-centered decision support tools for pregnant women and provide guidance for future research and the development of new efficient decision support tools.

Study II: **Impact of a mobile application for tracking nausea and vomiting during pregnancy (NVP) on NVP severity, quality of life, and decisional conflict regarding NVP treatments: MinSafeStart Randomized Controlled Trial**

Aim: To investigate whether the MinSafeStart mobile application could impact NVP severity, quality of life and/or improve their ability to make decisions regarding NVP treatment.

Study III: **Impact of a primary care pharmacist consultation on pregnant women's medication use: The SafeStart Intervention study**

Aim: To assess whether a community pharmacist consultation in the first trimester could impact the women's medication use, with a particular focus on antiemetic medications.

3 MATERIALS AND METHODS

The candidate conducted three studies (**Study I-III**) to investigate the overall goal of this thesis. **Study I** was a systematic review to explore the efficacy in decision support tools for pregnant women, in addition, to investigate the useful and practical design elements of such tools. **Study II** and **III** were interventional studies to assess the effect of a mobile app tracking NVP symptoms and a tailored community pharmacist consultation on NVP severity and medication use, respectively. **Table 3.1** summarizes the methodological aspect of the three studies included in this thesis.

Table 3.1: Overview of the methodological aspect of the three studies included in this thesis.

	Title	Design	Setting	Population	Data collection	Primary exposure	Outcome
Study I	Use of Decision Support Tools to Empower Pregnant Women	Systematic Review	-	Pregnant women (n=25 papers)	MEDLINE, EMBASE, Web of Science, PsycINFO, and Scopus	Digital or paper-based tools	Knowledge, satisfaction, decision making, quality of life, use experience, or clinical measures
Study II	MinSafeStart Randomized Controlled Trial	Quantitative, RCT	Mobile app use, Norway	Pregnant women experiencing NVP (n=192)	Mobile app and online questionnaire	Mobile app	NVP severity (PUQE score), quality of life (NVPQOL score), decisional conflict (DCS)
Study III	The SafeStart intervention study	Quantitative, intervention study	Community pharmacies, Norway	Pregnant women in the first trimester (n=229)	Online questionnaire and registry data (NorPD)	Pharmacist consultation in the first trimester	Medication use in the second trimester and use of antiemetics

NVP: Nausea and vomiting, **RCT**: Randomized Controlled Trial, **Mobile app**: Mobile application, **PUQE:** Pregnancy-Unique Quantification of Emesis and Nausea, **NVPQOL**: Nausea and Vomiting of Pregnancy specific health-related Quality of Life, **DCS**: Decisional Conflict Scale, **NorPD**: The Norwegian Prescription Database.

3.1 Literature review of decision support tools used during pregnancy (Study I)

For the systematic review (**Study I**), we searched MEDLINE, EMBASE, Web of Science, PsycINFO, and Scopus, from inception to December 1, 2019. All studies included were selected and structured according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2009 guidelines (178). **Table 3.2** shows an overview of the search structure presented according to the PICO framework (179).

Table 3.2: Overview of the PICO framework for the literature review (**Study I**).

Population (P)	Intervention (I)	Comparison (C)	Outcome (O)
Pregnant women	Digital or paper-based tools providing information	Standard prenatal care only or used a different decision support tool	Knowledge, satisfaction, decision making, quality of life, use experience, or clinical measures

The search strategy used for each database is described in detail in **Multimedia Appendix 1** in **Paper 1**. **Figure 3.1** presents the process for the inclusion and exclusion of studies for the systematic review. The duplicates were removed using EndNote X8.1 and the remaining process with screening of titles, abstract and full-text were performed in Rayyan. Rayyan is an online systematic review data management software (180). The candidate and another PhD student, hereby called MBTT, screened the title and abstract blindly and independently. Disagreements were discussed between the two researchers, and a third researcher was included when the discussion did not lead to an agreement. The data extraction followed a pre-defined extraction sheet including general information, study design, population, setting, recruitment methods, type of intervention, control group, and outcome measures with a description of the results of these outcomes. Only full-text of RCT, cohort, register-based, descriptive studies, and case-control studies in English, Norwegian, Swedish, and Danish which fulfilled our PICO framework were eligible for inclusion.

See a more detailed description of the study selection and data extraction for the literature search in **Paper I**.

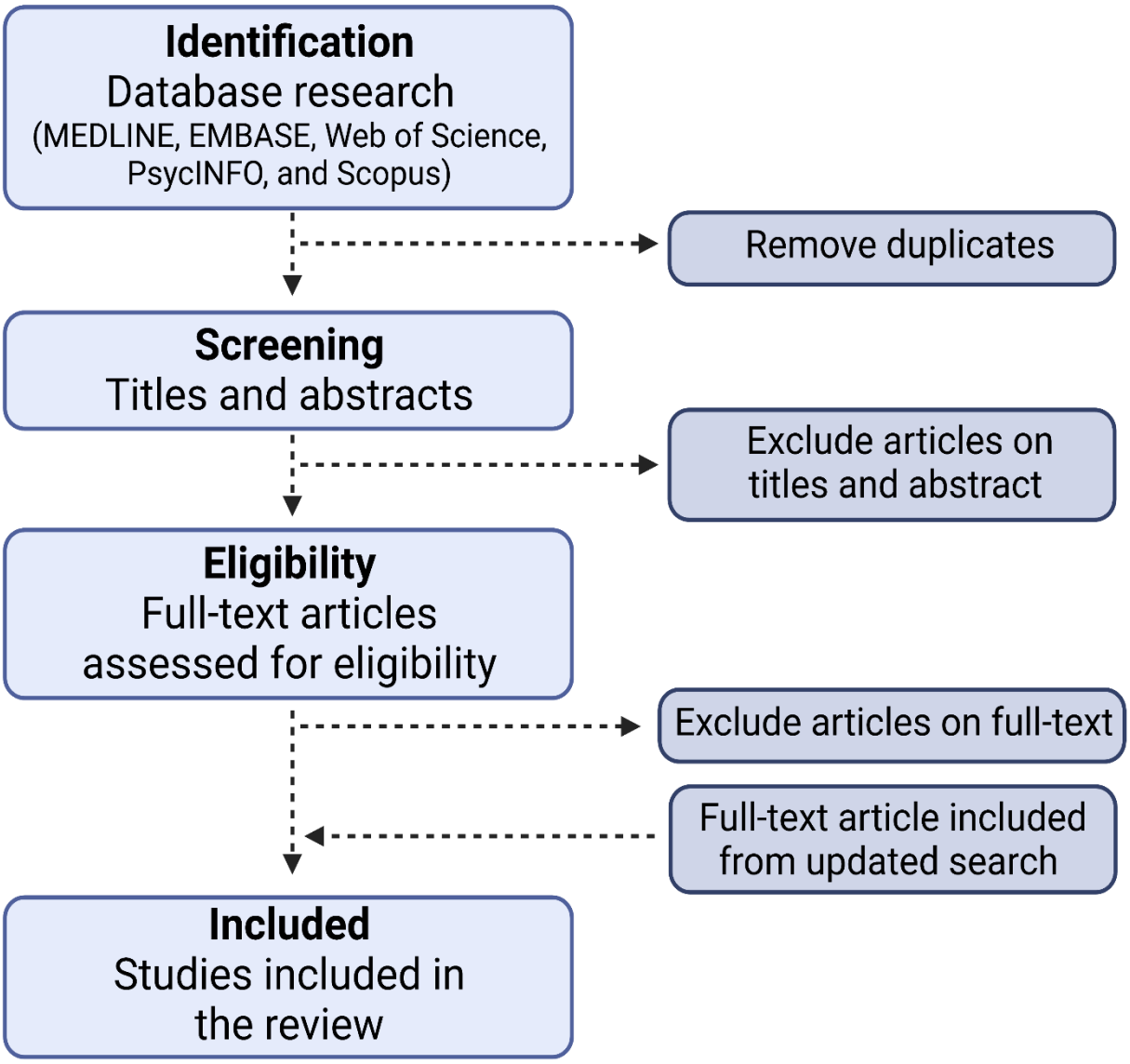

Figure 3.1: Flowchart of the process of identified, screened, excluded, and included studies in the systematic review (**Study I**).[2]
(Created with BioRender.com)

[2]Adapted from Ngo E, Truong MB, Nordeng H. Use of Decision Support Tools to Empower Pregnant Women: Systematic Review. J Med Internet Res 2020;22(9):e19436.

3.2 The SafeStart project

The SafeStart project is a large project including six studies, which so far have resulted in four master theses and two doctoral theses. **Figure 3.2** shows an overview of the SafeStart project and the studies included in the project. This thesis only includes **Study II** and **III** from the SafeStart project as they were performed and led by the candidate in this doctorial project. **Study II** and **III** were two independent intervention studies recruiting pregnant women all over Norway. Pregnant women experiencing NVP in **Study II** received the MinSafeStart mobile application (MSS app) as the intervention. Pregnant women in the first trimester in **Study III** received a pharmacist consultation as the intervention. A user-test of the MSS app was performed prior to **Study II**. For the SafeStart study, we firstly performed a feasibility study to test the feasibility of a pharmacist consultation in community pharmacies in early pregnancy (78). This was followed with a full-scale intervention study (79), which investigated the impact of a pharmacist consultation on pregnant women's quality of life and their satisfaction with the pharmacist consultation. Additionally, the full-scale study investigated the impact of a pharmacist consultation on medication use, antiemetics in specific, which is presented in **Study III**. A study to assess the pharmacists' experiences from the pharmacist consultations in the SafeStart intervention study were also performed by a master student.

The methodology of both **study II** and **III** are presented separately below in order to differentiate between the studies.

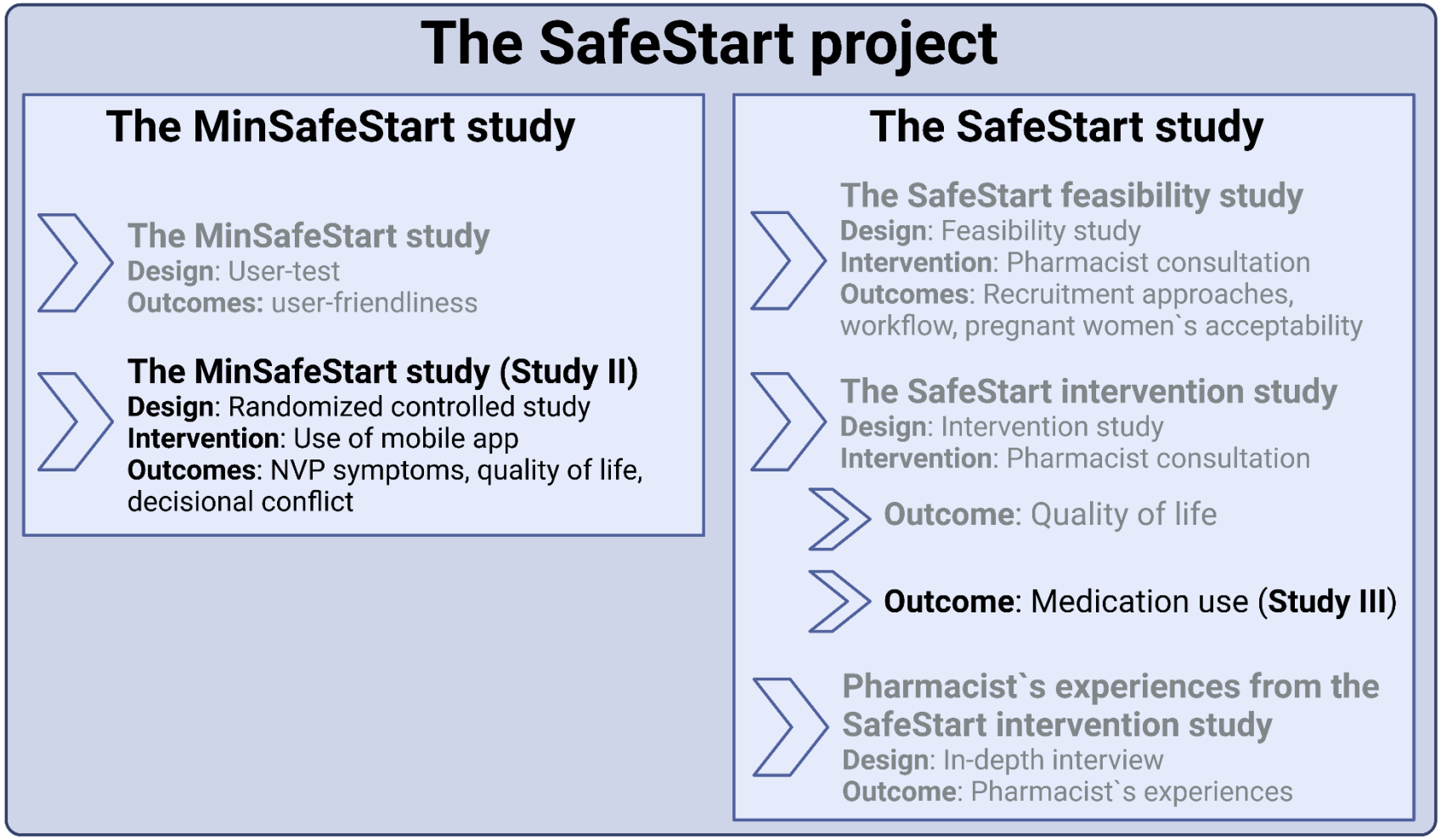

Figure 3.2: Overview of the SafeStart project and the studies included in the project. Only **study II** and **III** are included in this thesis as these two studies were performed and led by the candidate. The studies written in grey are a part of the SafeStart project but not included in this thesis. **Mobile app**: Mobile application, **NVP**: Nausea and vomiting during pregnancy.
(Created with BioRender.com)

3.3 MinSafeStart (Study II)

3.3.1 Study design and Setting

Study II was a randomized controlled trial conducted from September 2019 to June 2020 in Norway. All women over 18 years currently experiencing NVP, who could speak and understand Norwegian, and who had access to a smartphone were eligible to participate. Women randomized to the intervention group received an email with access to download the MSS app, which allowed them to log their NVP symptoms when convenient. The MSS app utilized the PUQE score to categorize the women's NVP severity.

3.3.2 Recruitment

Study II recruited women through social media, i.e., Facebook and pregnancy-related forums/webpages. Relevant posts about NVP and the MSS app were posted on the Facebook page of the study approximately four times a week. The Norwegian Hyperemesis Gravidarum Patient Organization's Facebook page also posted about the study with an invitation to attend a few times during the recruitment process. A banner (**Figure 3.3**) was posted on the webpage "*altformamma.no*" (all for mommy) regularly with an invitation to attend. All invitations led the women to the study webpage with further information and the consent form.

Figure 3.3: The banner posted on the "*altformamma.no*" (all for mommy) webpage.

Invitations to participate in the study was also posted by Helseoversikt on their app. Helseoversikt app is a digital platform used by healthcare centers in Norway. The app aims to collect all tools developed for pregnant women and partners in one place and provide relevant health information before, during, and after pregnancy.

3.3.3 Consent form

All women recruited to **Study II** were referred to an electronic consent form (**Appendix 1**). The consent form informed the women about the aim of the study, what participation involves, the protection of personal data, the risk and benefits of participating, and the possibility of withdrawing at any time. Only women who signed the consent form were eligible to participate and received additional information about the study via email. A two-step identification log-in was required to sign the consent form to identify the correct identity.

3.3.4 Allocation of study groups

Women given consent to participate in **Study II** were randomized to either the control or intervention groups by a bespoke software following the principle of simple randomization (flipping a coin). The software was developed in-house, especially for this study by University Center for Information Technology (USIT) at the University of Oslo (UiO), led by the candidate. The software additionally distributed emails with information about the study and intervention for the intervention arm, the groups they were allocated to, and the questionnaires at the predefined periods.

3.3.5 Study population

Pregnant women in all gestational weeks who were experiencing NVP, had access to a smartphone, and understood Norwegian were eligible for participation in **Study II**.

The intervention group

Women randomized to the intervention group had the opportunity to download and use the MSS app to log their daily PUQE score. The app was free of charge and protected by a personal password. Women were free to log their PUQE score whenever it was convenient. However, the app recommended logging their PUQE score every 24 hours. The purpose of the app was to give pregnant women experiencing NVP tailored advice based on the logged PUQE score and to see if this impacted their NVP severity, quality of life, and/or decisional conflict regarding NVP treatments. All women received lifestyle advice (e.g., adequate rest, eat small and frequent meals, avoid caffeine and strong seasonings in food, and stay hydrated). Women experiencing moderate or severe NVP received information regarding mediation use in addition. If they logged a PUQE score of ≥ 13 for more than three consecutive days, the app would alert the women to seek a physician for further consultation. The logged PUQE score was displayed as a graph over time, compared to the mean PUQE score of other pregnant women (**Figure 3.4**).

Figure 3.4: Overview of the women's logged PUQE score (purple graph) compared to the mean PUQE score of other pregnant women (blue graph) displayed as a graph. The illustration to the left is our sketch of the app, while the illustration to the right shows how the vision turned out after the app was developed.

The control group

Women randomized to the control group received standard prenatal care only.

3.3.6 The intervention

Development of the MinSafeStart mobile application

The MSS app was designed and developed by our research group in collaboration with interaction designers, programmers, and researchers from USIT, UiO. The MSS app is based on the PUQE score, which was originally in English, but translated and validated

in Norwegian in 2015 (181). The PUQE score included three questions. Each of the three first questions were ranged from 1-5 points. The total point score categorized NVP severity into three categories, mild (≤6 points), moderate (7-12 points), and severe (≥13 points). **Table 3.3** shows the three questions, answer options, and scores overview.

Table 3.3: The three questions in the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score including answer options and their respective points.

	5 points	**4 points**	**3 points**	**2 points**	**1 points**
On average in a day, for how long do you feel nauseated or sick to your stomach?	> 6 hours	4-6 hours	2-3 hours	≤ 1 hour	Not at all
On average in a day, how many times do you vomit or throw up?	≥ 7	5-6	3-4	1-2	None
On average in a day, how many times have you had retching or dry heaves without brining anything up?	≥ 7	5-6	3-4	1-2	None

User-test of the app

Two UiO Life Science summer students user-tested the app from July to August 2018 (182). The user-test included nine women. First, women participated in the user-test of usability, where they were instructed to use the app. Then a structured focus group interview explored their experiences of the app further. Women who participated in the user-test received a gift card valued at 200 NOK, and women who participated in the focus group received a gift card with 600 NOK. Women were provided structured questions before the user test to ensure they all tested the same features in the app. All participants were between 23-39 years, representing the pregnant population well. The results from the user-test of the usability and experiences with the app from the interviews were sorted into three categories; critical, moderate, and low. Problems categorized as critical are problems assessed by the two summer students as errors where women are unable to use the app for its full purpose. Moderate-level issues are the ones that should be changed before the app where utilized further, and the ones categorized as low are inputs that could be changed eventually. After the user-test was performed,

the candidate led the update of the app according to the issues discussed during the user-testing and the focus group interview, before it was utilized as the intervention in **Study II**.

3.3.7 Data collection

The questionnaires

Data were collected from four sets of electronic questionnaires sent to women by email by the software developed for the study (**Figure 3.5)**. **Study II** only includes data from the baseline questionnaire (Q1) and the follow-up questionnaire (Q2). The Q1 was sent to women by email right after enrollment and included questions about sociodemographic and lifestyle characteristics, NVP severity, quality of life, and decisional conflict. The Q2 was emailed to two weeks after enrollment and included questions about NVP severity, quality of life, and decisional conflict. These outcome measures are explained in more detail in section 3.3.8 Outcome measures.

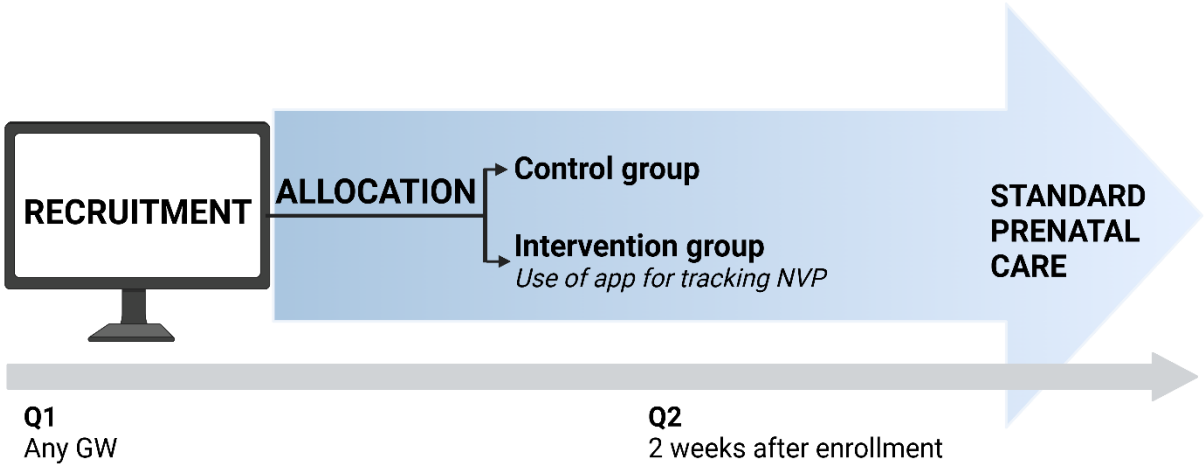

Figure 3.5: Overview of **Study II**. **Study II** included a baseline questionnaire (Q1) and a follow-up questionnaire (Q2). **Study II** recruited women in all gestational weeks (GW), given that they were experiencing NVP. Women allocated to the intervention group used the MinSafeStart mobile application (MSS app) to track nausea and vomiting (NVP) symptoms based on the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score. The Q2 was sent electronically to all women two weeks after enrollment.
(Created with BioRender.com)

The MinSafeStart mobile application

Every woman downloading the app for the first time was asked to fill in information regarding their gestational week, height, weight, and age. This information was used to customize the app for each woman by providing information on the development of the baby based on the women's gestational age, and alert the women if her weight has decreased based on the weight registration at baseline and the next weight registrations. The gestational week could be calculated from the first day of the last menstrual period or by the estimated delivery date, with the possibility to change in the app afterward. **Figures 3.6** and **3.7** show screenshots with the questions required to fill in the app upon registration.

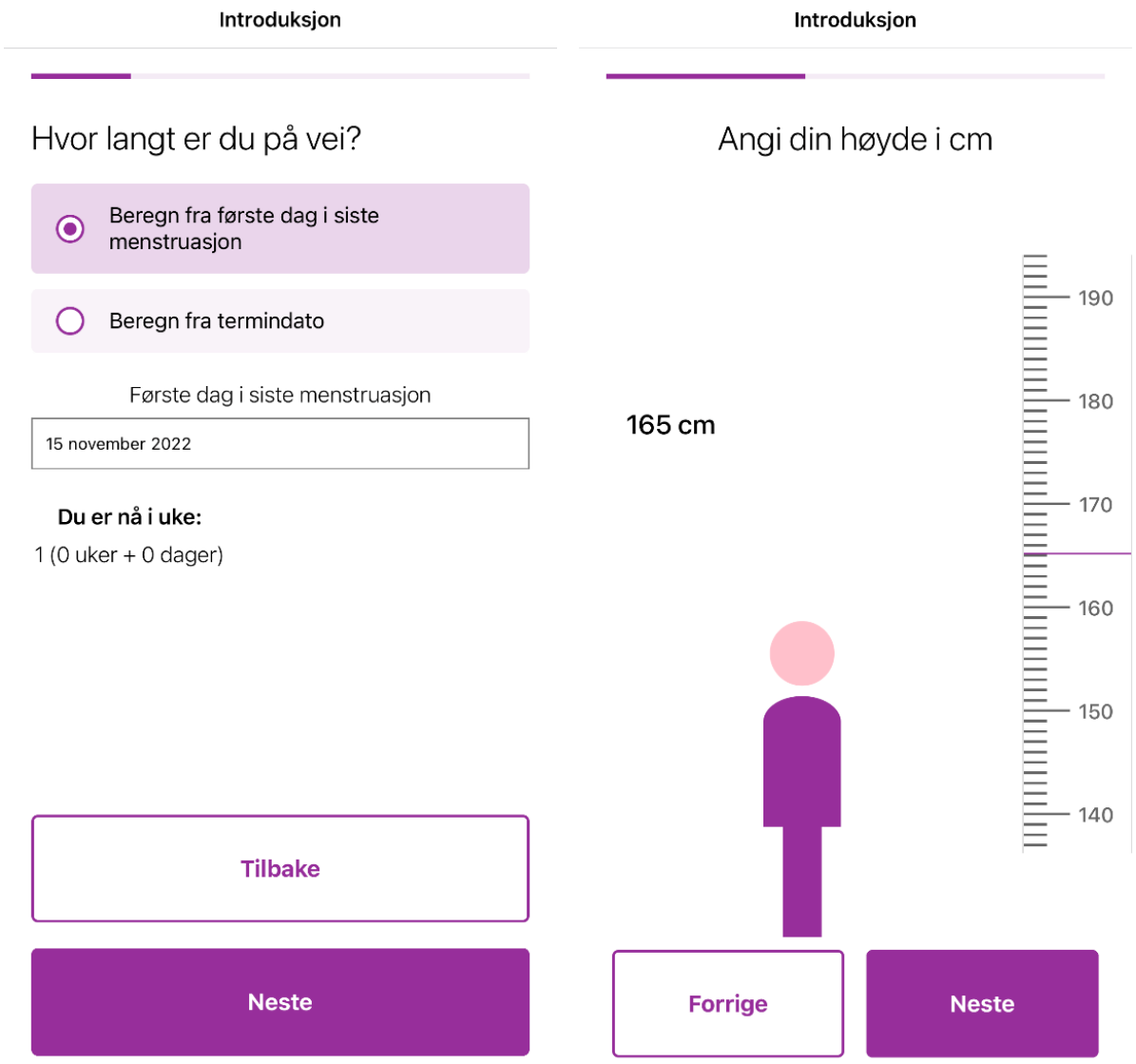

Figure 3.6: Screenshots of the questions regarding gestational week and height required in the app upon registration.

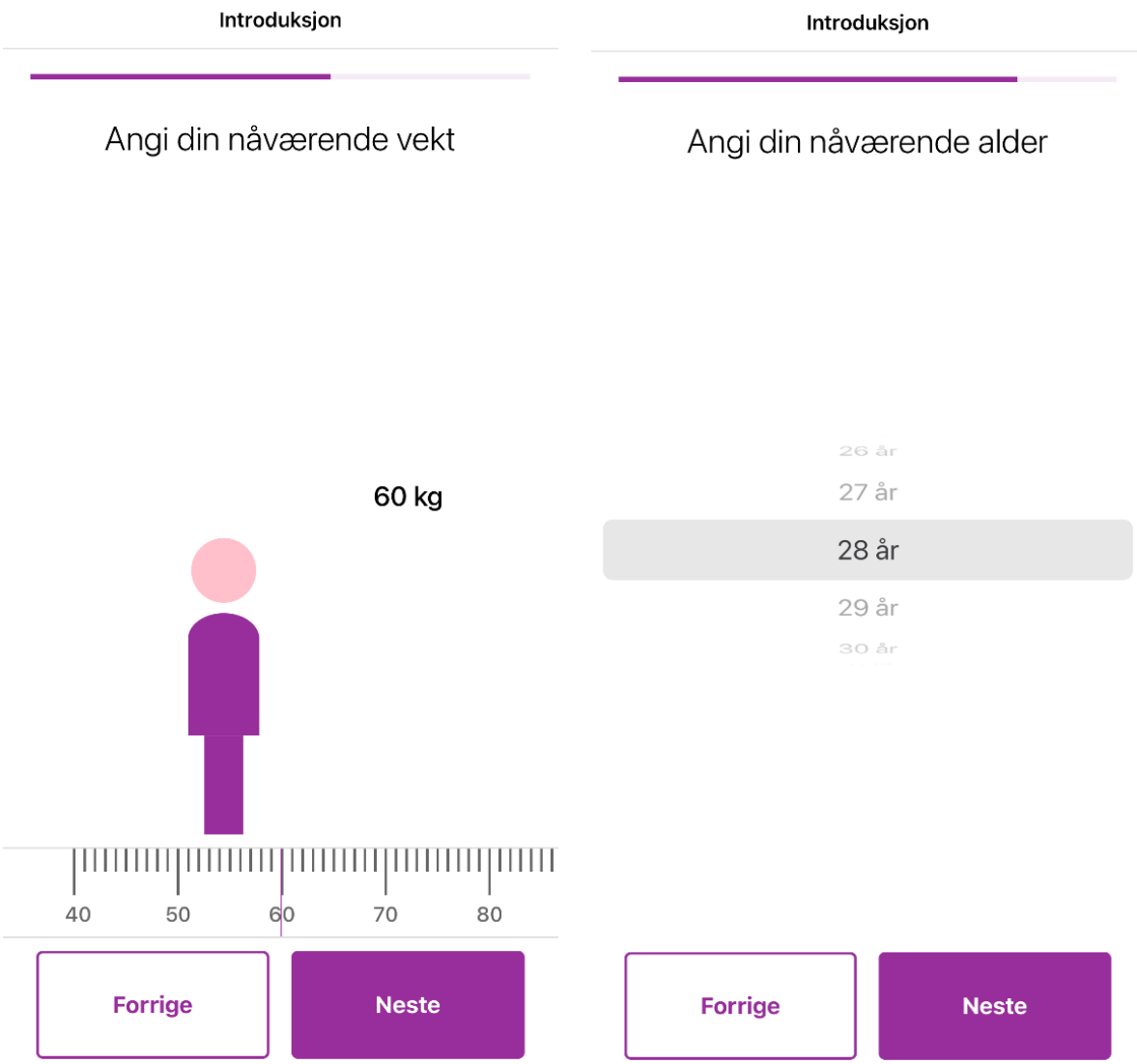

Figure 3.7: Screenshots of the questions regarding weight and age required in the app upon registration.

Women were free to log their PUQE score whenever it was convenient. The MSS app also asked about medication use for NVP by providing a list of medications related to NVP treatment, their food and liquid intake, sick leave, and hospitalization. These variables are not included in the analyzes in this thesis, as the MSS app was only used as the intervention in **Study II** without the intention of collecting data.

Nettskjema was utilized for all questionnaires. Nettskjema is a platform developed and operated by Service for Sensitive Data (TSD) at UiO, which students and employees can use to design and conduct electronic questionnaires (183). The platform extends

from basic forms to highly sensitive research questionnaires. Nettskjema was also used to collect data from the MSS app and electronic consent forms with identification login requirements. All data were immediately sent directly to TSD.

Reminders

An automated electronic reminder was sent to all non-responders on all four questionnaires 24 hours after the original mail with the link to the questionnaire was sent out. The app also sent out reminders regarding the logging of their PUQE score.

Drop out

The consent form informed all women that participation in the study was voluntary. If they, at any point, did not want to participate in the project anymore, they could drop out without providing any reason, but were given the opportunity to provide it. The study web page and every email sent to the women included information about dropout and a link to follow for dropout. The options they could choose for dropout were:

- The questionnaire took too much time to fill out
- I am no longer pregnant
- I was allocated to the control group
- I don't want to provide any reason
- Other reasons (free text)
- To women in the intervention group: The app was too difficult to use
- To women in the intervention group: The app was not useful

Data storage

All data collected from the electronic questionnaires, consent form and data from the MSS app were automatically encrypted and stored at TSD at UiO (184). TSD is a platform at UiO that enable storing and analyzing sensitive data. The platform is protected by a two-step password. Only registered project researchers within **Study II** had access to the data and the keys to decrypt the data. TSD meets all the requirements to maintain the Norwegian regulations regarding sensitive data and individual privacy for each participant.

3.3.8 Outcome measures

NVP severity

The primary outcome of **Study II** was the women's change of NVP severity, based on the PUQE score measured at baseline and after two weeks, compared to the control group. The PUQE score included three questions (**Table 3.3**) (116). Each of the three questions ranged from 1-5 points. The total point score ranged from 3 to 15 and categorized NVP severity into three categories, mild (≤6 points), moderate (7-12 points), and severe (≥13 points).

Quality of Life

The secondary outcome of **Study II** was the women's quality of life, based on Health-related Quality of Life for Nausea and Vomiting during Pregnancy (NVPQOL) score (185) after two weeks, compared to the control group. The NVPQOL score included 30 items covering physical symptoms and aggravating factors, fatigue, emotions, and limitations. The total score ranged from 30 to 210 points. A lower score indicated better quality of life and was categorized into five categories; much higher than average (30–50 points), higher than average (51–100 points), average (101–140 points), lower than average (141–190 points), and much lower than average (191–210 points) (186).

Decisional conflict

The Decisional Conflict Scale (DCS) measured the level of decisional conflict regarding NVP treatment at baseline and after two weeks, compared to the control group. DCS included 16 questions and covered the women's perception of uncertainty in choosing options, modifiable factors that contributed to uncertainty, and decision making effectiveness, regarding NVP treatment (187). The total score ranged from 0 to 100 points and was divided into three categories; low decision conflict (≤25 points), moderate decisional conflict (25-37.5), and high decisional conflict (≥37.5 points).

3.3.9 Sample size and Statistical Analyzes

Study II targeted 250 pregnant women, 125 women in each group (intervention and control groups) to detect a 3-point mean difference in the PUQE score with a two-tailed

hypothesis and 80% power. The 3-point difference was based on the clinical evidence that even mild NVP had a major impact on pregnant women's quality of life, daily function, and social life (7-9), and the mean PUQE score for a healthy group of women was 7 (SD: 5-8) (181). By reducing 3 points in PUQE score, the women will be closer to not experiencing NVP and assumed to be clinical significant. This targeted sample size also allowed a 25% dropout.

Descriptive statistics were used to summarize and present the women's maternal background and baseline characteristics. The Chi-square test was used to compare categorical variables and Student's t-test was used to compare continuous variables at baseline.

Primary analyzes were performed by univariate and multivariate linear regressions to estimate the associations between the use of the MSS app (yes/no) and PUQE score, NVPQOL score, and DCS. The outcome measures were based on the difference in difference method. The mean score in the Q2 were subtracted with mean score in the Q1 for each study groups. This "*mean change*" were then compared between the intervention and control groups. See **Table 3.4** for the illustration of how the "*mean change*" were calculated.

Table 3.4: Illustration of the calculations of the "*mean change*" of Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score, Nausea and Vomiting of Pregnancy specific health-related Quality of Life (NVPQOL) score, and Decisional Conflict Scale (DCS) from baseline (Q1) to follow-up (Q2).

	Baseline (Q1)	**Exposure**	**Follow-up (Q2)**	***Mean change***
Intervention group	Q1 PUQE Q1 NVPQOL Q1 DCS	Use of the MSS app + standard care	Q2 PUQE Q2 NVPQOL Q2 DCS	Q2 PUQE – Q1 PUQE Q2 NVPQOL – Q1 NVPQOL Q2 DCS – Q1 DCS
Control group	Q1 PUQE Q1 NVPQOL Q1 DCS	Standard care	Q2 PUQE Q2 NVPQOL Q2 DCS	Q2 PUQE – Q1 PUQE Q2 NVPQOL – Q1 NVPQOL Q2 DCS – Q1 DCS

MSS app: MinSafeStart mobile application

All multivariable linear regressions were adjusted for baseline PUQE score, NVPQOL score, and DCS.

Stratified analyzes were performed according to the women's employment status (employed in healthcare sector/employed in other sectors) to determine whether the women included in the study found the app less useful based on their employment. The rationale for this was assumption of women employed in the healthcare sector are more exposed to health-related information compared to women working in other sectors. The stratified analyzes included the interaction term between the study groups (intervention and control) and employment status (employed in healthcare sector /employed in other sectors).

All results are presented as crude and adjusted beta-coefficients (β) with 95% confidence intervals (CI). All analyses were performed with Stata/MP v.16.1.

3.3.10 Ethical approval

Study II (Ref: 2018/2298) was approved by the Regional Committees for Medical and Health Research Ethics in Norway.

3.4 SafeStart (Study III)

3.4.1 Study design and Setting

Prior to **Study III,** a feasibility study was conducted from October to December 2017 (78). The purpose of the feasibility study was to investigate appropriate recruitment approaches, workflow, and pregnant women's acceptance of a pharmacist consultation. Furthermore, the SafeStart intervention study were performed from February 2018 to November 2019, investigating the impact of the pharmacist consultation on pregnant women's quality of life and their satisfaction with the consultation (79).

Data from **Study III** were based on the data from the SafeStart intervention study. In total, 14 community pharmacies all over Norway, the candidate and MBTT, performed the pharmacist consultations at the study pharmacies and over the phone. All women allocated to the intervention group had the opportunity to have a pharmacist consultation at a chosen study pharmacy or by phone.

3.4.2 Recruitment

Study III recruited women through social media, including Facebook and pregnancy-related forums/webpages. **Study III** also recruited women through flyers and posters in pharmacies all over Norway.

On social media

Information about pregnancy and the study were posted by the candidate and other project members 3-4 times a week on the study Facebook page. Ad with the invitation to participate in the study was also posted on relevant pregnancy forums and webpages, such as "*altformamma.no*" (all for mommy) and "*tryggmammamedisin.no*" (safe mother medicine). Women interested in the study were all sent from the post/ads to the study webpage, where the consent form could be signed if they chose to participate.

At pharmacies

Posters, flyers (**Figure 3.8**), and small cards promoting the study were displayed at 80% of pharmacies in Norway. Posters of size A1 were displayed on the walls, flyers of size A5 were available at the checkouts, and small visit cards were displayed at the checkouts and the shelves among pregnancy tests and folic acid.

3.4.3 Consent form

Women recruited to participate in **Study III** were sent to an electronic consent form (**Appendix 2**). After the consent form was signed, the women received an email with additional information about the study. Like **Study II**, a two-step identification log-in was required to sign the consent form.

3.4.4 Allocation of study groups

Women given consent to participate in **Study III** were allocated 1:1 in the control or intervention groups by a rented software developed for the study. The software also distributed emails to the women with information regarding the study, the groups they were allocated to, and the questionnaires. In addition, the software sent information on how to book a consultation to women in the intervention.

3.4.5 Study population

All Norwegian-speaking women in the first trimester were eligible for participation in **Study III**.

The intervention group

All women allocated to the intervention group had the opportunity to book a pharmacist consultation at one of the study pharmacies or over the phone. Women in the intervention group also followed standard prenatal care.

The control group

Women allocated to the control group followed standard prenatal care only.

Figure 3.8: The poster/flyer used to recruit pregnant women to participate in **Study III** at pharmacies all over Norway.

3.4.6 The Intervention

Recruitment of study pharmacies

The Norwegian Pharmacy Association and the headquarters of Apotek 1, Boots Apotek, Vitusapotek, and Sykehusapotekene were responsible for recruiting study pharmacies. In total, 14 pharmacies and 15 pharmacists volunteered to participate in the study to conduct the consultations.

The Pharmacist consultation

The planned pharmacist consultation was a structured consultation individualized to each woman. The purpose of the consultation was to answer the pregnant women's questions and concerns related to her health and pregnancy, including pregnancy-related ailments and medication use in pregnancy. Each consultation lasted up to 15 minutes. The study pharmacist conducting the consultation had access to the women's answers in the Q1. This information was used to prepare a structured, individualized consultation that addressed each woman's concerns and needs.

Preparing study pharmacists

All pharmacists were required to attend a program developed for the SafeStart study in order to participate as study pharmacists. The different parts of the training program are described in more detail below.

Practical training in communication

The practical training in clinical and risk communication was provided as a workshop. The workshop was a full-day event, at the University of Oslo. The training was based on presentations, discussions of scenarios, and role-play and was led by clinical pharmacists from the Regional Medicines Information and Pharmacovigilance Center (RELIS) and Ullevål Hospital.

Theoretical preparations

The theoretical preparations included three online courses, a compendium, and a study manual. The three online courses lasted 20-minute each with an introduction on advice

and treatment of allergies, asthma, diabetes, epilepsy, medication use during pregnancy in general, antibiotics during pregnancy, and medication use during breastfeeding. Each course was followed by a quiz, which the pharmacists were required to pass. Online courses of this type are familiar to pharmacists in Norway, as similar methods are currently used to provide new and updated information to all pharmacies in Norway. The compendium included information about treatment on common pregnancy-related ailments that generally can be treated with lifestyle advices and/or OTC medications, such as NVP, pain in general, headache, heartburn, constipation, stuffy nose, and the common cold. The compendium also included information about the use of the PUQE score. The study manual included general information about the study and other practical elements (i.e., how to see the Q1 answers, how to confirm a booking, and how to report the consultation). The manual also consisted of a detailed guide on how to perform the consultation with examples and methods, in addition to techniques for clinical and risk communication that were discussed in more detail at the workshop.

Booking of the consultation

Women who were allocated to the intervention group received an email with information about the pharmacist consultation and how to book a consultation. When booking the consultation, the women had to specify which study pharmacy or over the phone, date, and time. The study pharmacist confirmed the consultation by Short Message Service (SMS).

3.4.7 Data collection

The questionnaires

Study III consisted of a total of four electronic questionnaires (Q1-Q4). All four questionnaires were sent to women by email through the software rented for the study. Only the Q1 and the Q2 are included in the analyzes in **Study III** (**Figure 3.9**). Both questionnaires included questions about NVP severity, quality of life, chronic and acute illness, and medication use. Sociodemographic and lifestyle characteristics were only reported in the Q1. The Q1 was sent to women by email right after enrollment, while the Q2 was emailed to women 13 weeks after enrollment.

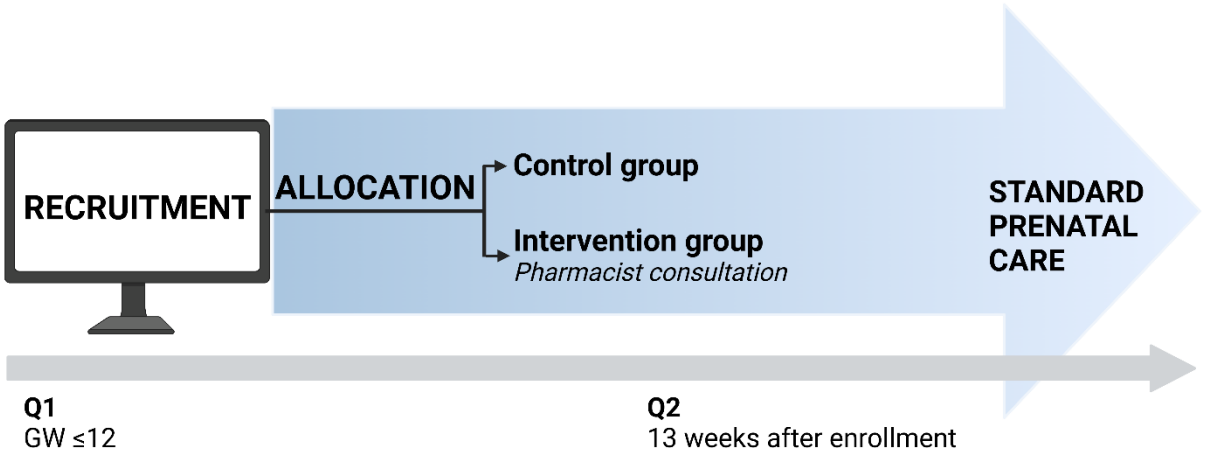

Figure 3.9: Overview of the **Study III**. **Study III** included a baseline questionnaire (Q1) and follow-up questionnaire (Q2). **Study III** recruited all pregnant women in the first trimester. Women allocated to the intervention group received a pharmacist consultation. The Q2 was sent electronically to all women 13 weeks after enrollment.
(Created with BioRender.com)

The consultation

After each consultation, the pharmacist was required to report the time used in the preparation, the setting, and the duration of the consultation. The report had to include a summary of the consultation, with topics discussed and information given to the women. This report was filled in a standard form developed for the study (**Appendix 3**).

Nettskjema was used in **Study III** for all questionnaires and the pharmacist notes (Nettskjema is described in more detail in section 3.3.7 Data collection, pages 34-35). Nettskjema also handled the electronic consent form with identification login requirements for **Study III**.

Registry data

Data from **Study III** was linked to the Norwegian Prescription Database (NorPD) by the women's social security numbers. NorPD includes all prescribed medications dispensed to individual patients from all pharmacies in Norway from January 2004 and contains information about the name of the medication, ATC code, defined daily dose, package size, and the dispense date. All data stored in NorPD is secured by pseudonymization. Pseudonymization is a data management and de-identification

procedure in which personally identifiable information is replaced by an identified number. This is to ensure we can connect the same prescriptions to the same identity without identifying the person.

Reminders

After 24 hours, the original mail with the link to the questionnaires was sent out, the software sent an electronic reminder to all women that did not respond to the questionnaires.

Drop out

The consent form included information that participation in the study was voluntary and that they, at any point, could drop out without providing any reason, but were given the opportunity to provide it. The study webpage and all emails sent to the women included information about the possibility of dropping out.

The options they could choose for dropout were:

- The questionnaire took too much time to fill out
- I am no longer pregnant
- I was allocated to the control group
- I don't want to provide any reason
- Other reasons (free text)
- The nearest pharmacy was too far away

Data storage

All data collected from the electronic questionnaires and consent forms were automatically encrypted and stored at TSD at UiO (TSD is described in more detail in section 3.3.7 Data collection, page 35). Only registered project researchers within **Study III** had access.

3.4.8 Outcome measure

The outcome measures for **Study III** were medication use in the second trimester after a pharmacist consultation for women in the intervention group, compared to women in

the control group. Medication use was measured by 1) numbers of women who self-reported medication use in the second trimester, 2) numbers of filled prescriptions on medications in general as registered in the NorPD, and 3) numbers of filled prescriptions on antiemetic medications as registered in the NorPD.

3.4.9 Sample size and Statistical Analyzes

All analyzes were performed as complete case analyzes. **Study III** included 229 women who responded to the Q1, the Q2 and completed the pharmacist consultation if they were allocated to the intervention group. Post hoc power analyzes demonstrated that this sample size was sufficient to detect a 19% difference in medication use among pregnant women with 80% power.

Statistical analyzes included in **Study III** included descriptive statistics to summarize and present the women's maternal background and baseline characteristics. The chi-square test and the Student's t-test were used to explore differences in categorical and continuous variables, respectively, in the baseline characteristics for the two study groups.

The primary analyzes were performed by logistic regression to estimate the association between pharmacist a consultation (yes/no) and medication use in the second trimester. The logistic regression analyzes were performed separately as 1) self-reported medication use in the second trimester, 2) filled prescriptions on medications in general as registered in the NorPD, and 3) filled prescriptions on antiemetics as registered in the NorPD. All analyzes were adjusted for medication use and employment status (chi-square test, p=0.03).

An additional logistic regression were performed and presented in this thesis to estimate the association between a pharmacist consultation (yes/no) and self-reported use of antiemetic medications. The analysis were also adjusted for medication use and employment status at baseline.

Stratified analysis were performed according to the pregnant women's employment status as employed in the healthcare sector or employed in other sectors. The rationale for this stratified analysis was to determine if women employed in the healthcare sector had a different impact on the pharmacist consultation compared to women employed in other sectors, as they may have better access to health-related information.

The results are presented as the crude and adjusted odds ratios (OR) with a 95% confidence interval (CI). All analyzes were performed with Stata/MP v.16.1.

3.4.10 Ethical approval

Study III (Reference: 2016/1686) was approved by the Regional Committees for Medical and Health Research Ethics in Norway.

4 MAIN FINDINGS

The main findings in this thesis are presented separately for each study below. **Figure 4.1** shows the overview of how each finding answers the overall goal and aims of this thesis.

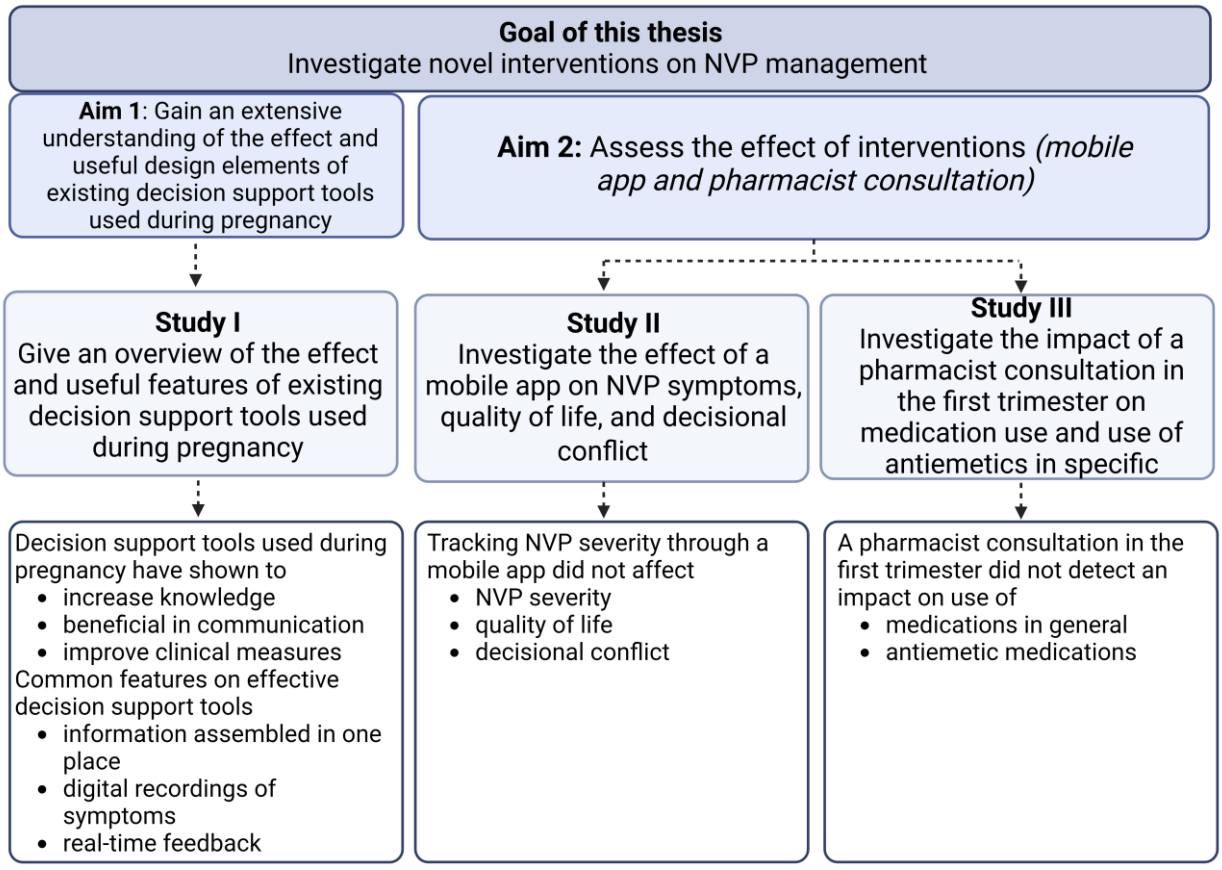

Figure 4.1: Overview of the main findings of each study (**Study I-III**) in relation to the overall goal and aims of this thesis. **NVP:** Nausea and vomiting during pregnancy, **Mobile app**: Mobile application.
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4.1 Study I: Literature review of decision support tools used during pregnancy

This systematic review included a total of 25 published studies (**Figure 4.2**). The studies assessed decisional support tools related to prenatal screening (n=10), gestational diabetes and weight gain (n=7), blood pressure and preeclampsia (n=2), lifestyle (n=3), depression (n=1), asthma (n=1), and physiological well-being (n=1). See a more detailed overview of the 25 studies included in the **Multimedia Appendix 3** in **Paper 1**.

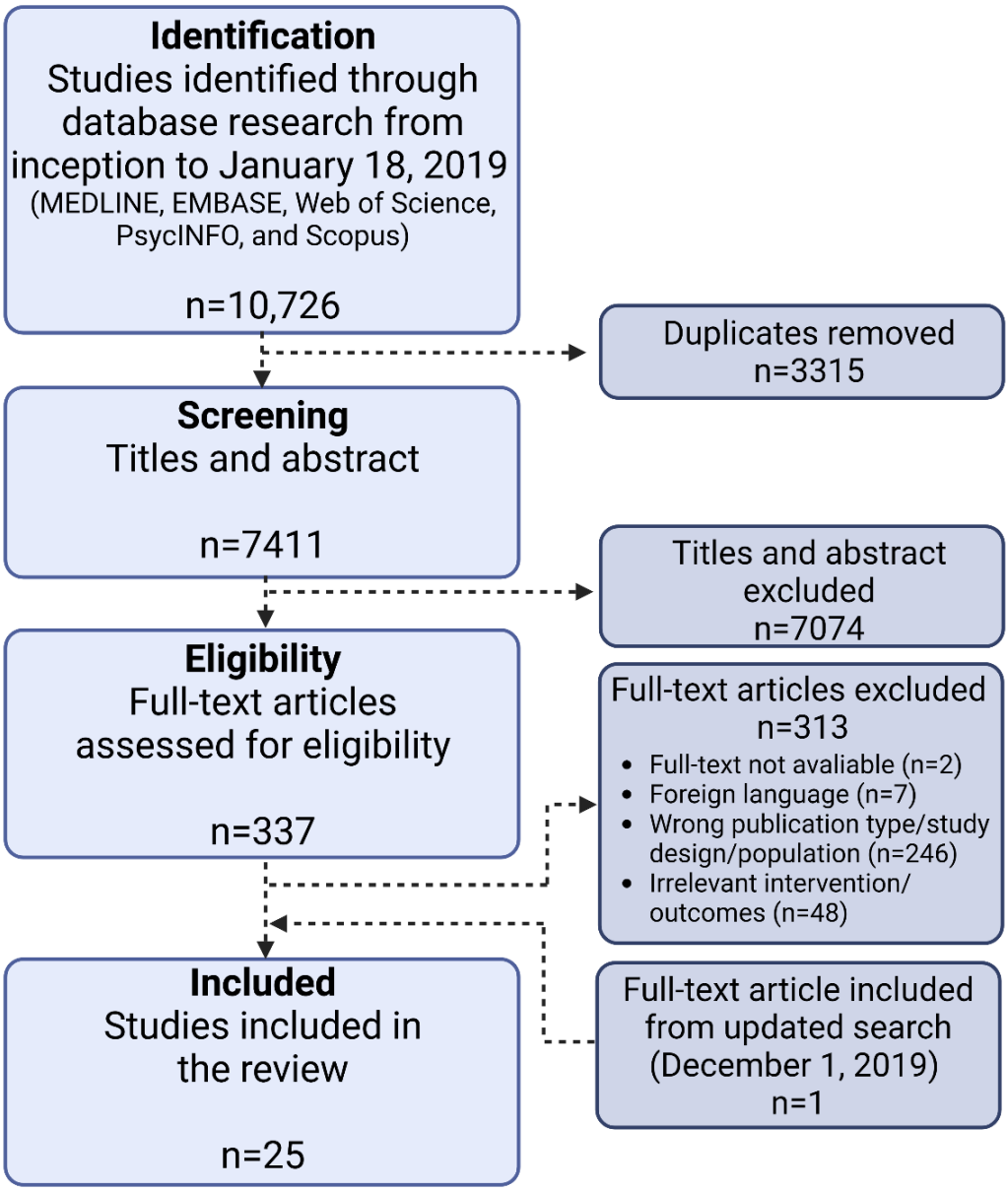

Figure 4.2: Flowchart of the identified, screened, excluded, and included studies in the systematic review (**Study I**).[3]

(Created with BioRender.com)

[3]Adapted from Ngo E, Truong MB, Nordeng H. Use of Decision Support Tools to Empower Pregnant Women: Systematic Review. J Med Internet Res 2020;22(9):e19436

The decision support tools included in this review were mostly digital, provided as a web page, mobile app, video, or SMS text messages. One decision support tool was provided as written material on paper. The majority of the decision support tools demonstrated a potential benefit for use during pregnancy, regarding knowledge, confidence in decision making, and communication between the pregnant women and their health care providers (**Figure 4.3**).

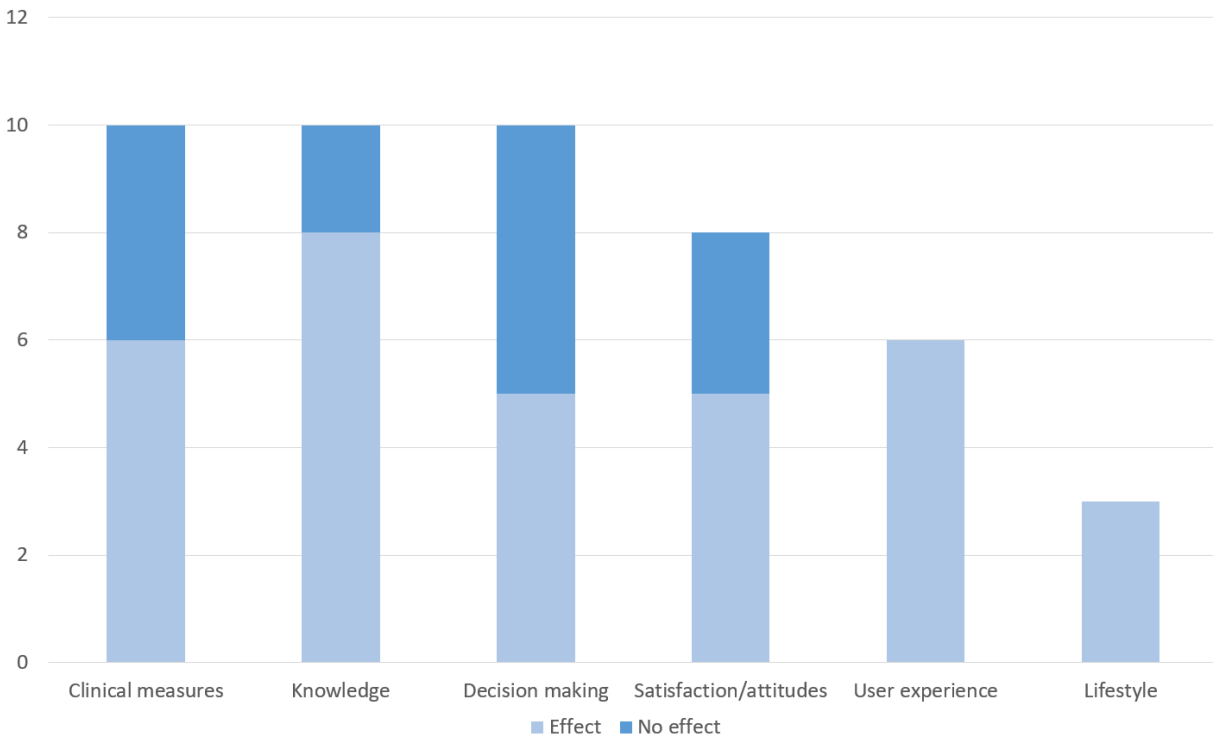

Figure 4.3: Overview of the effect of the decision support tools on different outcome measures. Several studies included multiple outcome measures.[4]

Pregnant women recorded their symptoms more frequently in digital decision support tools, compared to paper-based tools. The women also found it convenient when evidence based information was assembled in one tool and when they had the opportunity to record their symptoms and receive real-time feedback based on their recordings. Moreover, tools were suggested to be beneficial in communication with health care providers.

[4]Adapted from Ngo E, Truong MB, Nordeng H. Use of Decision Support Tools to Empower Pregnant Women: Systematic Review. J Med Internet Res 2020;22(9):e19436.

Study I highlighted that:

- Decision support tools can have a beneficial impact on patient involvement and potential in the management of pregnancy-related conditions.
- There is still a lack of decision support tools for managing acute pregnancy-related ailments, such as NVP.

4.2 Study II: The MinSafeStart randomized controlled trial

A total of 192 pregnant women experiencing NVP were included in this **Study II**, where 89 were randomized to the intervention group and 103 to the control group. Of 89 women, 88 downloaded the MSS app and logged their NVP severity based on the PUQE score. In total, 157/ 192 (82%) and 35/192 (18%) of women had mild and moderate NVP at baseline, respectively. The dropout rate was 34% in the intervention group and 24% for the control group, and the most common reason for dropout was "*lost to follow-up*" (**Figure 4.4**). The baseline characteristics of the study population (n=192) compared to the dropout population (n=55) are presented in **Appendix 4**.

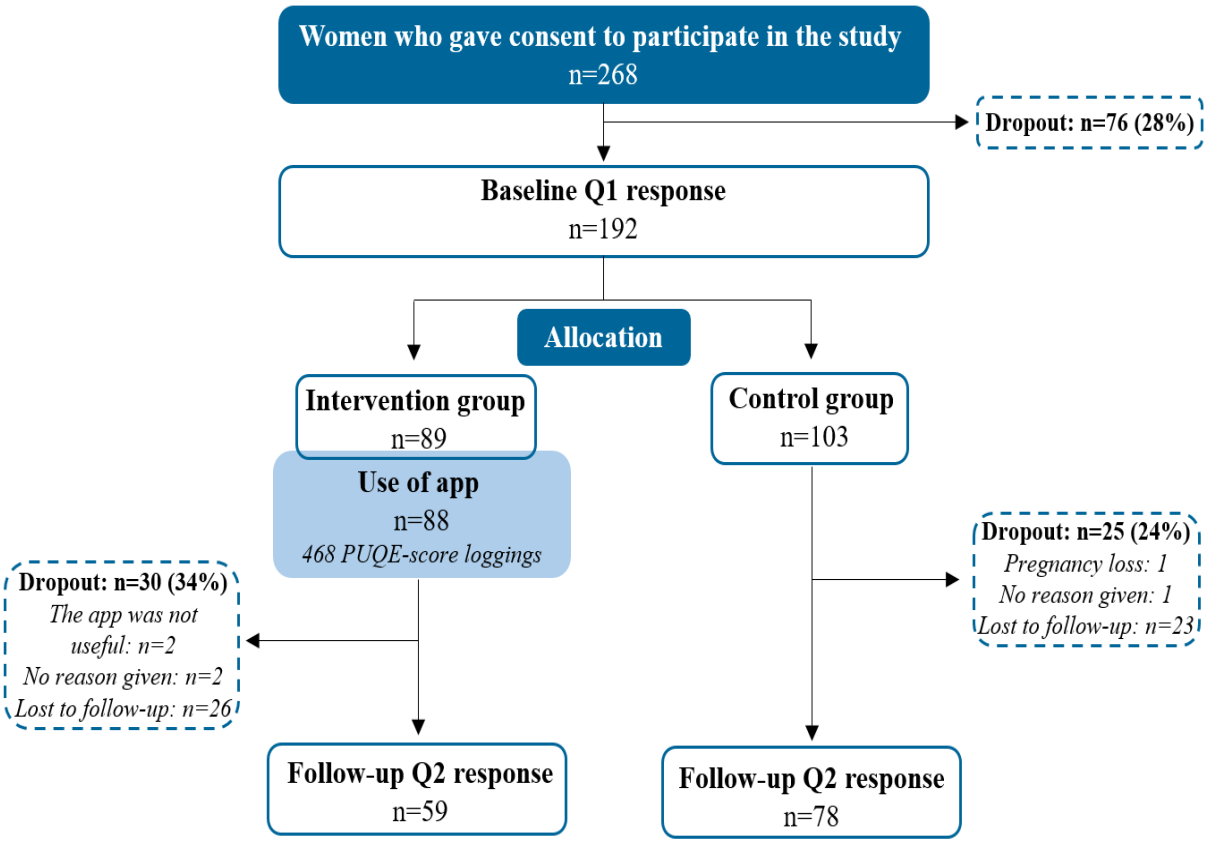

Figure 4.4: Flowchart shows the numbers of study participants in the enrolled group, randomized groups, and follow-up groups. **App:** MinSafeStart mobile application, **Q1**: Baseline questionnaire, **Q2:** Follow-up questionnaire.[5]

Figure 3 in the published manuscript of **Study II includes a typing error: The number of women who gave consent to participate in the study was 268 and not 222. The dropout was therefore n=76 (28%) and not n=30 (14%).*

[5]Adapted from Ngo E, Truong MB, Wright D, Nordeng H. Impact of a Mobile Application for Tracking Nausea and Vomiting During Pregnancy (NVP) on NVP Symptoms, Quality of Life, and Decisional Conflict Regarding NVP Treatments: MinSafeStart Randomized Controlled Trial JMIR Mhealth Uhealth 2022;10(7):e36226.

At enrollment, 15% was beyond the first trimester and 80% had experienced NVP in at least one previous pregnancy in both study groups. Over 95% were in a relationship, over 78% had higher education and over 83% were employed.

Women in both study groups had a high NVPQOL score (intervention group: 145.7, SD: 30.0 and control group: 148.5, SD: 28.8), which indicated quality of life lower than average at baseline. They were also highly conflicted at baseline regarding NVP treatments (DSC intervention group: 40.3, SD: 17.9 and control group: 42.5, SD: 20.9). As for NVP treatment approaches, women preferred either dietary and lifestyle changes alone or dietary and lifestyle changes with pharmacological treatment as a combination (**Table 4.1**).

Table 4.1: Preferred NVP treatment approaches among women in intervention and control groups reported in the Q1.

	Intervention group	**Control group**
Dietary and lifestyle changes	54/103 (52%)	43/88 (49%)
Pharmacological treatment	2/103 (2%)	1/88 (1%)
Dietary and lifestyle changes + pharmacological treatment	47/103 (46%)	44/88 (50%)

Pregnant women who used the MSS app to track their NVP severity did not show any change in NVP severity (adjusted β: 0.6, 95% CI: −0.1, 1.2), quality of life (adjusted β: −5.3; 95% CI: −12.5, 1.9), or decisional conflict score (adjusted β: −1.1, 95% CI: −6.2, 4.2), compared to standard care at follow-up. **Table 4.2** shows an overview of the association analyzes for the presented outcomes.

Table 4.2: Effect of the MinSafeStart mobile application on the Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score, Health-related Quality of Life for Nausea and Vomiting during Pregnancy (NVPQOL) score, and the Decisional Conflict Scale (DCS). None of the results were statistically significant.[6]

	Q1		**Q2**		**Change (Q2-Q1)**		
	PUQE[1]						
	n	Mean score (SD)	**n**	Mean score (SD)	Mean change (SD)	Crude difference in mean changes (β) (95% CI)	Adjusted difference in mean changes (β) (95% CI)
Intervention group	88	4.9 (2.0)	59	5.6 (1.8)	0.8 (2.0)	0.4 (−0.3,1.2)	0.6 (−0.1,1.2)[2]
Control group	103	4.7 (1.9)	78	4.9 (1.8)	0.4 (2.3)	*Reference*	*Reference*
	NVPQOL[3]						
Intervention group	88	145.7 (34.0)	59	143.8 (29.7)	−4.5 (22.4)	−4.2 (−11.9,3.5)	−5.3 (−12.5,1.9)[4]
Control group	103	148.5 (28.8)	78	151.6 (28.9)	−0.3 (22.9)	*Reference*	*Reference*
	DCS[5]						
Intervention group	88	40.3 (17.9)	59	36.2 (21.6)	−5.9 (16.4)	−0.7 (−6.1,4.7)	−1.1 (−6.2,4.2)[6]
Control group	103	42.5 (20.9)	78	38.1 (20.3)	−5.3 (15.5)	*Reference*	*Reference*

[1]PUQE score: Mild (≤6 points), moderate (7-12 points), and severe (≥13 points)

[2]Adjusted for the baseline PUQE score

[3]NVPQOL score: ranges from 30 to 210 points. Lower score indicated better quality of life.

[4]Adjusted for the baseline NVPQOL score

[5] DCS: Low (≤25 points), moderate (25-37.5), and high decisional conflict (≥37.5 points).

[6]Adjusted for the baseline DCS score

[6]Adapted from Ngo E, Truong MB, Wright D, Nordeng H. Impact of a Mobile Application for Tracking Nausea and Vomiting During Pregnancy (NVP) on NVP Symptoms, Quality of Life, and Decisional Conflict Regarding NVP Treatments: MinSafeStart Randomized Controlled Trial JMIR Mhealth Uhealth 2022;10(7):e36226.

Study II highlighted that:

- Even mild NVP has an impact on pregnant women's quality of life which supports the existing literature.
- Pregnant women experiencing NVP are highly conflicted when making decisions regarding NVP treatment approaches.
- The higher sociodemographic status among women included in the study may have impacted the effectiveness of the MSS app.
- Even though tracking NVP severity with tailored information did not show any effect on NVP severity, quality of life, or decisional conflict, future studies should include a process evaluation to better understand how pregnant women use health mobile apps, hence optimizing the mobile apps' utility during pregnancy.

4.3 Study III: The SafeStart intervention study

In **Study III**, 340 pregnant women in their first trimester responded to the Q1. Of these, 170 were allocated to the intervention group and 170 to the control group. Finally, 103 women in the intervention group and 126 women in the control group responded to the Q2 (**Figure 4.6**). The candidate performed 16 consultations, while MBTT performed 31 consultations. The dropout rate was 39% for the intervention group and 26% for the control group. The baseline characteristics of the study population (n=229) compared to the dropout population (n=111) are presented in **Appendix 5**.

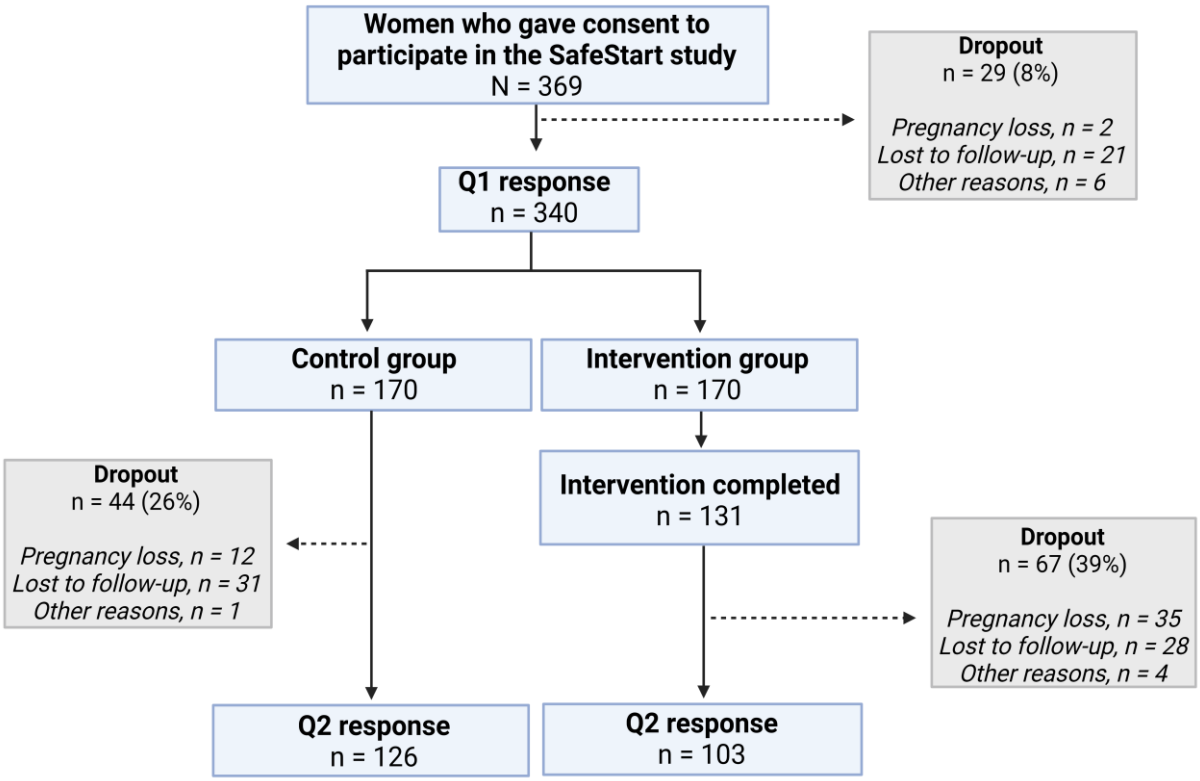

Figure 4.5: Flowchart of the study population of **Study III**. A total of 369 women gave consent to participate in the study. Of these, 103 women responded to the Q1, completed the consultation, and responded to the Q2 in the intervention group and 126 women responded to the Q1 and Q2 in the control group. All analyzes were performed as complete case analyzes (N=229). **Q1=** Baseline questionnaire, **Q2**= Second questionnaire.[7]
(Created with BioRender.com)

[7]Reprinted from Ngo E, Truong MBT, Nordeng H. Impact of a primary care pharmacist consultation on pregnant women's medication use: The SafeStart intervention study *(manuscript)*

At baseline, 97% were in a relationship, 85% had taken a higher education, and over 80% were employed. Over 60% in the intervention group and 48% in the control group were pregnant for the first time. Half of the women reported moderate/severe NVP at baseline. Advice and treatment of pregnancy-related ailments were most addressed during the consultations (59%), and NVP was the most common pregnancy-related ailments discussed (48%).

Meclizine, promethazine, and metoclopramide were the three most prescribed antiemetic medications and self-reported use (**Table 4.3** and **4.4**).

Table 4.3: Overview of filled prescription on antiemetic medications in the intervention (N=103) and control groups (N=126) as registered in the Norwegian Prescription Database (NorPD) in 1st (T1) and 2nd trimester (T2).[8]

Antiemetic medication	**Intervention group**	**Control group**	**Intervention group**	**Control group**
	T1 n *(%)*	**T1** n *(%)*	**T2** n *(%)*	**T2** n *(%)*
Meclizine	9 *(8.7)*	6 *(4.8)*	5 *(4.9)*	4 *(3.2)*
Promethazine	3 *(2.9)*	8 *(6.3)*	3 *(2.9)*	7 *(5.6)*
Metoclopramide	9 *(8.7)*	6 *(4.8)*	20 *(19.4)*	16 *(12.7)*
Total*	21 *(20.4)*	20 *(15.9)*	28 *(27.2)*	27 *(21.4)*

n=number of women

Table 4.4: Overview of self-reported use of antiemetic medications in the intervention (N=103) and control group (N=126) in 1st (T1) and 2nd trimester (T2).

Antiemetic medication	**Intervention group**	**Control group**	**Intervention group**	**Control group**
	T1 n *(%)*	**T1** n *(%)*	**T2** n *(%)*	**T2** n *(%)*
Meclizine	7 *(6.8)*	14 *(11.1)*	17 *(16.5)*	15 *(11.9)*
Promethazine	0 *(0)*	3 *(2.4)*	4 *(3.9)*	4 *(3.2)*
Metoclopramide	7 *(6.8)*	11 *(8.7)*	7 *(6.8)*	10 *(7.9)*
Total*	14 *(13.6)*	28 *(22.2)*	28 *(27.2)*	29 *(23.0)*

n=number of women

Women in both groups reported in the questionnaires that they used medications within ATC code A *(Alimentary tract and metabolism)*, N *(Nervous system)*, and R *(Respiratory system)* the most. Use of medications in ATC code A and N were more frequent in the second trimester (A: 20-25% and N: 45-47%) than in the first trimester (7-8% and N: 6-8%) for both study groups.

In total, 21/103 (20.4%) and 20/126 (15.9%) of women in the first trimester and 28/103 (27.2%) and 27/126 (21.4%) in the second trimester in the intervention and control group, respectively, had a filled prescription registered in the NorPD on antiemetic medications. Filled prescriptions within ATC code A, G *(Genito-urinary system and sex hormones)*, J *(Antiinfectives for systemic use)*, and R were most common among women in both groups. They were similar in all time periods (See a more detailed overview in **Supplementary file 3**, in **Paper 3**).

We did not detect a difference in medication use among women in the intervention group who received the pharmacist consultation compared to women in the control group for filled prescriptions (aOR: 0.7, 95% CI: 0.4, 1.2) or self-reported (aOR: 0.7, 95% CI: 0.4, 1.2). A difference in the use of antiemetic medications as reported in NorPD (aOR: 0.4, 95% CI: 0.1, 1.4) and self-reported (aOR: 0.2, 95% CI: -0.5, 1.1) was not detected either.

Study III highlighted that:

- NVP is a common ailment among pregnant women, and information about NVP management is highly requested. Available information should be easily accessed for pregnant women.
- Even though this study did not detect an impact of a pharmacist consultation on medication use in pregnancy, there is still a need to investigate if the role of pharmacists embedded within maternal care would benefit the communication between health care providers and pregnant women regarding medication use.

5 DISCUSSION

5.1 Summary of findings

This thesis gave new insight into the effect of decision support tools in pregnancy and how novel interventions can provide tailored information to pregnant women. More specifically, **Study I** highlighted the sparseness of studies on the effect of decision support tools in pregnancy. Prior studies showed decision support tools could increase pregnant women's knowledge about their conditions (asthma, depression, gestational diabetes, blood pressure, and preeclampsia) and suggested being useful in the communication between health care providers and the women. **Study II** and **III** did not demonstrate an effect of a mobile app and a pharmacist consultation on pregnant women's NVP severity and impact on medication use, respectively, compared to standard care. Moreover, the results gave insights into how to perform future research on novel interventions in pregnancy.

5.2 Discussion of findings

5.2.1 Decisional support tools developed for pregnant women

Though earlier studies (99, 188) and **Study I** support the effectiveness of using decision support tools during pregnancy to promote enhanced management of different conditions, most decision support tools were developed for pregnant women and target only chronic diseases and lifestyle factors (**Study I**). In other words, few decision support tools that manage acute pregnancy-related ailments have been developed.

To the best of our knowledge, **Study II** is the first study investigating the effect of a mobile app to track the severity of NVP as an RCT. A case report published in 2019 by *Korouri et al.,* (n=36) demonstrated, based on the women's and health care providers' perspectives, that the use of a mobile app to track NVP severity was accurate in defining symptoms, communication with health care providers, and improving HG care (189). In contrast, **Study II** showed no statistically significant results on NVP severity, quality of life, or decisional conflict for the pregnant study participants. In retrospect, the differences in study design and outcome make it difficult to directly compare the study by *Korouri et al.,* to **Study II**.

In line with other reviews (99, 103), findings from **Study I** indicate that decision support tools were found useful by the pregnant study participants. Some common features in the tools were found useful (**Study I**). These common features were that the tools were digital, could record symptoms, and provide feedback based on the symptoms recorded. These common features were included in the MSS app in **Study II** but did not provide any effect on pregnant women's NVP severity. However, the results from **Study I** and **II** may not be directly comparable, as the tools were designed for different purposes. The tools included in **Study I** aimed to reduce clinical symptoms of asthma, depression, gestational diabetes, blood pressure, and preeclampsia. None of the tools included in the review were targeted at managing pregnancy-related ailments, like NVP. Women with chronic diseases may be more likely to be closely monitored by their health care providers during their planning for pregnancy in comparison to women experiencing NVP. NVP is often trivialized (127, 128), and women experiencing NVP often feel a

lack of support and insufficient followed up (128). The different amount of follow-up based on the condition may have contributed to the diverse results of effect between the decision support tools in **Study I** and the MSS app in **Study II**. As reported in **Study I**, the use of decision support tools has been found to be more beneficial when patients use them with their health care providers, which may have led to more comprehensive treatment and management (190). While the MSS app in **Study II** was delivered outside of a consultation. More work is needed to assess the effect of the MSS app used with their health care providers in NVP management.

Moreover, 50% of the studies included in *Whybrow et al.,* aimed at decisions regarding the mode of birth (191-195), where women often have a clear opinion and express their desire for birth mode (196). Compared to NVP, which is mainly a subjective ailment. Effective decision support tools must be tailored to their situation, conditions, and ailments they target. Further research is needed to investigate how women experiencing NVP use this type of mobile app, especially in communication with health care providers, and how this impacts their NVP management.

5.2.2 Use of medications in pregnancy

Not surprisingly, similar to other national registry studies (197, 198), medications in ATC code A *(Alimentary tract and metabolism),* J (Antiinfectives for systemic use), N (*Nervous system),* and R (*Respiratory system)* were one of the most reported ATC codes with filled prescriptions in NorPD among women in **Study III**. When looking at the self-reported data, in a multinational study by *Lupattelli et al.* (n=9459), up to 70% of women reported the use of at least one medication and medication for heartburn, pain, and upper airways were most common (199). This is comparable to the self-reported medication use in **Study III**, where ATC codes A, N, and R were most reported. Further, the focus of this section will be on the use of antiemetic medications in pregnancy.

It has been reported that pharmacological treatment with antiemetic medications is necessary for 10% of pregnant women experiencing NVP (124). As around half of the women in **Study III** had moderate or severe NVP, our study supports that the proportion

of women who need pharmacological treatment is most likely higher than 10%. Even though our findings from **Study II** and **III** support previous findings that many pregnant women are experiencing NVP (110-113), only 14-22% of women in the first trimester and 23-27% in the second trimester reported using antiemetics (**Study III**). This prevalence was significantly higher than other pregnant women in Norway (8%) (200), yet lower than pregnant women in France, Sweden, Switzerland, and Canada (35-42%) (130). The high prevalence in Canada may be explained by explicit treatment guidelines (201) and Diclectin® (a combination of an antihistamine and vitamin B6), which has NVP as a specific indication (202). A reduction in hospitalizations due to NVP/HG has also been shown to correlate with an increase in sales of Diclectin® (203). This suggests the clinical importance of comprehensive national guidelines on NVP management and available medications for NVP management.

Meclizine, promethazine, and metoclopramide were the most used antiemetic medications in **Study III**. This is in line with *van Gelder et al.*, which reported that 62% of pregnant women (n=762 437) were dispensed metoclopramide, 28.2% meclizine, and 17.2% promethazine (200). *Heitmann et al.*, also reported meclizine and metoclopramide as one of the most commonly used antiemetics. These numbers are in accordance with the recommendations from the Norwegian Obstetric Guidelines for the treatment and management of NVP (119). For self-reported use of antiemetic medications, it was reported more use of meclizine (12-17%) compared to filled prescriptions as registered in the NorPD (3-5%) in the second trimester for both study groups. This may be explained by the fact that meclizine is sold OTC in Norway, and some women might have been recommended use without being provided a prescription. Moreover, more women were provided a filled prescription on metoclopramide in the second trimester, compared to meclizine which is the first-line treatment. These numbers may probably be explained that women were suffering from more severe NVP in the second trimester, which may not have been sufficiently managed in the first trimester. This underlines the importance of early recognition and management of NVP.

Even though half of the women in **Study III** experienced moderate/severe NVP, and requested advice and information about NVP management, the pharmacist usually does not have any OTC medications indicated for NVP to provide the women. Pharmacists have, in more than 60% of situations, recommended OTC medications where it has been available for the treatment of pain, common cold, runny nose, and fever (204-206), in addition to earlier dispensing experiences (60, 62). Meclizine is the first-line treatment for NVP and is sold as an OTC medication in Norway. However, it cannot be recommended for NVP management by pharmacists as it is only indicated for motion sickness (119). This is a possible barrier for pharmacists to provide optimal NVP management. Future studies investigating the potential role of the community pharmacist in dispensing meclizine, according to the PUQE score, are recommended. This approach may contribute to reducing the pressure on the health system, which is now tested for a range of medications in community pharmacies in New South Wales, Australia (207, 208). The suggestion of independently dispensing meclizine is also underlined by the pharmacists' earlier independent prescribing and dispensing experiences (60, 62).

5.2.3 Pregnant women's Quality of Life

Of 192 women in **Study II**, 157 and 35 reported mild and moderate NVP at baseline, respectively. These women also had a low quality of life, supporting that even mild NVP negatively impacts pregnant women's quality of life (7, 186). Early symptom management is therefore highly warranted to lower the risk of the development of more severe symptoms as well as decrease the incidence of hospitalization (126, 133). The study investigating the quality of life among 712 Norwegian women experiencing NVP (7) used the generic quality of life scale (209), while **Study II** used the NVPQOL score (185). This makes it difficult to compare the two populations. The same problem occurs when comparing the quality of life for women in **Study II** and **III**. An earlier SafeStart study, which investigated the impact of a pharmacist consultation on pregnant women's quality of life in the same study population as **Study III**, reported a score of 89 (range 42-112) for the intervention group and 91 (range 62-112) for the control group (79). The average score of the healthy population is about 90 (209) and about 81 for the pregnant

population (7). This indicates that the study population in **Study III** had a relatively good quality of life even though about half of the women had moderate/severe NVP. Compared to **Study II**, 157/192 (82%) had mild NVP but reported a *"lower than average"* (146–149 points) quality of life at baseline. Again, these differences may have been caused by the different quality of life scores used. The NVPQOL score might be more sensitive to detect a pregnancy-specific quality of life in the pregnant population, as it includes an emotions domain assessing the women's mental health. This is an important spectrum to include, as NVP has been linked to an increased risk of psychological distress (210, 211), and psychological distress in pregnant women significantly impacts their quality of life (212, 213).

5.2.4 The targeted population

NVP is often the first sign of pregnancy (177) and occurs before prenatal care has been established, which highlights the need for communication at an earlier pregnancy stage. This is, to the best of our knowledge, the first study to investigate the impact of a pharmacist consultation on medication use. There was not detect any difference in medication use in general or use of antiemetics in the second trimester after the pharmacist consultation (**Study III**). These results can be affected by many factors. Firstly, women in **Study III** in both study groups may have acquired information from pharmacists outside the study, as pharmacists are one of the primary sources of information (34, 40, 41) and are easy to access (214, 215). Women in **Study II** and **III** were also of high socioeconomic status. These women were resourceful, and most of them had a partner, which can indicate better support compared to those who are partnerless, as support has shown a beneficial effect on women's life satisfaction and well-being (45, 47, 48). These factors may plausibly have influenced the effect of the interventions. This raises the possibility that women with lower socioeconomic status and women without a partner, i.e., women who receive less support during pregnancy, may derive a greater benefit from this type of tailored interventions (49). Over 60% of women in **Study II** had been pregnant before, while over 60% of women in **Study III** were pregnant for the first time. Of the parous women, 80% had experienced NVP in earlier pregnancies (**Study II**) and may have already established an understanding of

NVP. In comparison, primiparous women are more likely to search for information online (21, 30), meaning they may also have a recently established understanding of NVP. Moreover, *Truong et al.*, reported that pregnant women suffering from moderate or severe NVP found a pharmacist consultation more beneficial compared to women with mild NVP (QOLS change: 3.6 vs. -1.9, p=0.048) (79). This highlights which subset, or subsets, of pregnant women to target in novel interventions.

As presented in section 5.1, the interventions investigated in this thesis did not affect the pregnant women's NVP severity or medication use. The remaining discussion will focus on the methodology of **Study I**, **II**, and **III** in order to understand the outcomes of the interventions and the direction of future research.

5.3 Methodological considerations

The results from this thesis must be interpreted in the context of the methodological strengths and limitations. The strengths and limitations of the three studies included in this thesis will be discussed separately for the systematic literature search (**Study I**) and the two intervention studies (**Study II** and **III**).

5.3.1 Study design

In **Study I**, we aimed to gain an extensive understanding of the effect of existing decision support tools used during pregnancy. Performing a systematic review is a suitable approach. Systematic reviews summarize the available studies on a specific research question based on given criteria and present reviewed and interpreted findings (216, 217). The strengths and limitations of the systematic review (**Study I**) are presented in more detail in section 5.3.2 Systematic literature review, pages 68-69.

In **Study II** and **III**, we aimed to assess two novel interventions. More specifically, to investigate the effects of using a mobile app and a pharmacist consultation on NVP severity and medication use, antiemetics in specific. RCTs are considered the most robust study design and the gold standard for evaluating the effect of interventions in evidence-based medicine (218, 219). This robust method is due to the random allocation of individuals, which ensures the intervention is comparable to the control groups by removing potential allocation bias (220).

5.3.2 Systematic literature review

The strengths of the systematic literature review (**Study I**) include its comprehensive search strategy developed with assistance from librarians at the University of Oslo. To ensure all the eligible studies were identified, the systematic search included several databases. All articles were screened independently by two blinded researchers, the candidate and MBTT. Limitations include the restrictions on the language the papers were published in, and only papers published in English, Norwegian, Danish, and Swedish were included. The outcome measures for the studies included were quite divergent, which made it difficult to compare the results between the studies. For

instance, twelve different scales were used to score the women's knowledge level. Overall, the literature provided a comprehensive overview of existing decision support tools used during pregnancy.

5.3.3 Intervention studies

The NorPD

Including data from the NorPD was advantageous for the results of **Study III**. NorPD contains all prescriptions dispensed to individuals in all pharmacies in Norway since 2004. For each prescription, NorPD contains the date of dispensing, the name of the drug, the ATC code, and the number of defined daily doses (221). When interpreting the results, it is important to bear in mind that registered prescriptions in NorPD do not indicate the consumption of the medication by the women, however, it illustrates physicians' rate of prescribing medications during pregnancy that are dispensed at the pharmacies. Merging data from **Study III** with NorPD data gave us a comprehensive overview of medication use among pregnant women.

Sample size and dropout

A significant limitation of **Study II** was that it did not reach the targeted sample size due to the high dropout rate. **Study II** targeted 250 pregnant women experiencing NVP, with a maximum dropout rate of 25%. Unfortunately, between providing informed consent and completing the Q1, the dropout reached 28%, and between completing the Q1 and Q2, the dropout rate was at 34 and 24% for the intervention and control groups, respectively. **Appendix 4** shows an overview of the baseline characteristics of the study population and the dropout population for **Study II.** The dropout proportion was higher in the intervention group and among women who had experienced NVP in earlier pregnancy/pregnancies. These women may not have found the information in the MSS app useful as it may not have provided them with additional information. For **Study III**, the dropout rate was 8% between consent and completing the Q1 and 39 and 26% between the Q1 and Q2 for the intervention and control groups, respectively. The differences between the groups were minor (**Appendix 5**), however, women in the dropout population were less educated. Women with less education often had higher

risk perceptions compared to women with higher education (222, 223). In retrospect, the women who drop out might find pharmacist consultations more beneficial and useful, and the dropout by these women may have affected the results in **Study III**. Of note, a larger proportion of women in the dropout population in **Study III** were employed in the health sector, which suggests these women found the pharmacist consultation less useful as they may have been fully informed and supported. Future interventions should assess the effect on women with lower sociodemographic status.

The pharmacist consultation

A total number of 131 pharmacist consultations were performed in **Study III**. The candidate and MBTT performed 36% of these consultations, i.e., 16 and 31 consultations, respectively. As the candidate and MBTT were involved in the design of the consultation, including the source document for collecting information on the content of the consultation, and knew how the consultations should be performed accurately and consistently in accordance with the protocol, this may not have had a significant impact on the results. From our own perspectives, this is seen as beneficial. The candidate and MBTT analyzed the data collected by the pharmacists during the consultations (for their respective articles), which topics were discussed, and information provided. This level of involvement made data management of the free text in the pharmacist consultation source documents easier. However, a process evaluation is still needed to be certain on the intervention's fidelity. Moreover, some may consider the researchers taking on the role of study pharmacist as a weakness, as the study aimed to specifically utilize community pharmacists as the intervention's primary provider, not researchers.

Previous comparisons of in-person consultations and telephone consultations demonstrated comparable levels of patient satisfaction, supporting the argument that, in some circumstances, a telephone consultation was suitable (224). In contrast to the latter, some clinicians feel that consultations over the phone were negative and loss of visual inspection of the patient (225). However, having the opportunity for phone consultations may reduce non-attendance, reduce costs and increase the efficiency of health care

(226). For pregnant women experiencing NVP, telephone consultations are considered an appropriate measure, as these women frequently struggle with daily tasks (7, 227), and visiting a pharmacy could plausibly also be a struggle. Counseling over the phone was not included in **Study III** before it was requested by the women in the feasibility study (78). As convenience has been recognized as an important factor for pregnant women to engage in clinical research (228), offering telephone consultations can increase the pharmacists' abilities to reach this specific target patient population.

Selection bias and Representativeness

Study II and **Study III** used multiple websites to target prospective study participants. Both studies recruited pregnant women through the studies' Facebook page and "*Altformamma.no*". **Study II** was also listed on "*Tryggmammamedisin.no*", while **Study III** was listed on "*Helseoversikt*". This recruitment approach may have influenced the representativeness of the participants in the two studies. One possibility is that only women with internet access who visited these websites were recruited. The suitability of this approach is underlined by 99% of women of childbearing age using the internet daily (229). It has also been shown that pregnant women frequently search for pregnancy-related information on the internet (21, 25-27), which makes recruitment through social media an appropriate method. In addition, studies comparing recruitment methods have reported that social media was more efficient and effective than offline methods and often six times faster (230-232). Especially paid-media advertisement (e.g., on Facebook) has been shown as a promising method for recruiting pregnant women (233, 234). On the other hand, women who habitually search for pregnancy-related information online tend to have a higher sociodemographic status than the general pregnant population in Norway (34) and are more likely to be primiparous (21, 30, 35), which can have influenced our results. Our study population for **Study II** and **III** represents a healthier part of the pregnant population in Norway, which may have resulted in a lower effect of the interventions. This contributed to lower representativeness to the general population of pregnant women. However, due to the large catchment area resulting from the use of online recruitment, the social media approach is an efficient and well suited approach for this specific target population.

Information bias and validity of collected data

Data on sociodemographic factors, lifestyle characteristics, and NVP severity in **Study II** and **III**, quality of life and decisional conflict in **Study II,** and medication use in **Study III** were self-reported by the participants through online questionnaires. NVP was self-diagnosed by the participants. As the experience of NVP is a subjective ailment, self-diagnosed NVP may therefore be accurate. Self-reported medication use may be closer to the actual amount of medications consumed as opposed to the prescribed amount. However, a study conducted by *Sundermann et al*. investigated pregnant women's recall (n=318) of medication use in the first trimester and reported that pregnant women had a better recall for medications used consistently than medications used intermittently (235). Other authors assessing the validity of maternal recall also confirm these findings (199, 236). In addition, the questionnaires regarding medication use in **Study III** were designed as a list of common chronic diseases, *e.g.*, allergy, asthma, depression/anxiety, and common acute illnesses, *e.g.*, NVP, heartburn, constipation, and headache. Only women who reported having one of these diseases or illnesses were prompted to report medication use specific to that illness. As a result, there might have been an underreporting since the women might not have remembered some medicines unless it was noted in the lists.

The randomization of study participants

Women in **Study II** were randomized by simple randomization, while women in **Study III** were allocated 1:1 to the intervention and control groups. All study groups were compared to explore differences in baseline variables before analyzes were performed. The comparison found a slight difference in medication use and employment at baseline between the two study groups in **Study III**. This imbalance might have been introduced due to the complete case analysis. However, as the imbalance could be adjusted for, we argue that complete case analysis is more suitable in this case, as it can contribute to the ideal situation and support the results on whether a pharmacist consultation in early pregnancy would have an impact on medication use or not (237). The measured baseline characteristics for **Study II** indicated sufficient allocations.

5.4 Clinical implications and future perspectives

The findings in this thesis have important clinical implications for maternal care related to the use of digital support tools and the role of pharmacists, and suggestions for future research regarding the management of NVP.

- Even though **Study III** did not detect an impact of the pharmacist consultation on medication use during pregnancy, it cannot be ruled out that a pharmacist consultation provided as part of standard prenatal care in collaboration with other health care providers, e.g., midwives and GP's, can be beneficial for pregnant women in regards of medication use. Future studies should further assess in which setting and format the pharmacist consultation can have the most impact on pregnant women.
- As even mild NVP impacts pregnant women's quality of life (**Study II**), an earlier and closer follow-up by health care providers is suggested for women experiencing NVP. Such follow-up should provide pregnant women with adequate information tailored to their situation, aiming to lower pregnant women's decisional conflict regarding NVP treatment seen in **Study II**.
- Since the updated National Guideline on Antenatal Care recommended that care should begin in gestational week six, this is an ideal possibility to assess pregnant women's NVP severity. The standard antenatal care program in Norway should therefore include an assessment of NVP in the first prenatal care visit, where using the PUQE score should be standard procedure. The National Guideline on Antenatal Care should also be updated and include guidelines of NVP management to direct health care providers in their choices in the management of NVP, together with pregnant women.
- NVP is a common ailment among pregnant women, and information about NVP management is highly requested (**Study III**). Women are also open to dietary and lifestyle advice (**Study II**). Clearly written information should be available, making it easier to comprehensible.
- The findings from **Study I** and **Study II** highlighted the need for further investigation on how to utilize decision support tools in NVP management.

- A critical approach to how women use the mobile app to track their NVP symptoms and how they utilize it in communication with health care providers (e.g., how pharmacists use digital tools as a part of pharmaceutical care) should be further assessed.
- Future studies should investigate the potential role of the community pharmacist in dispensing meclizine, according to the PUQE score, aiming to reduce GP's workload.
- **Study II** and **III** highlighted the need to explore other recruitment methods to reach women with lower sociodemographic status. Future interventions should also target pregnant women with low sociodemographic status in specific.

6 CONCLUSION

Research on novel interventions to involve pregnant women in their health care to promote management of different conditions and ailments, such as NVP, is highly warranted as this is lacking in the current literature. In conclusion, this thesis sought to contribute to filling this knowledge gap by investigating how the use of a mobile app and community pharmacist consultation can affect NVP severity and the use of medications, antiemetics in specific during pregnancy. Firstly, the review showed that decision support tools available for use during pregnancy were found useful and had potential in maternal care. However, studies on the use of decision support tools during pregnancy are scarce. Moreover, the use of the MSS app to track NVP severity with tailored information showed no effect on pregnant women's NVP severity. There was no detected impact of a pharmacist consultation on medication use compared to standard care. The findings in this thesis may have important clinical implications for maternal care related to the use of digital support tools and the role of pharmacists. Therefore, more work is needed to understand the use of mobile apps to track NVP symptoms and how such tools can be utilized together with health care providers. Novel interventions in the future should focus on pregnant women with low sociodemographic status.

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APPENDIX

Appendix 1: Consent form (**Study II**)

Appendix 2: Consent form (**Study III**)

Appendix 3: Consultation report (**Study III**)

Appendix 4: Baseline characteristics of the dropout population (**Study II**)

Appendix 5: Baseline characteristics of the dropout population (**Study III**)

Appendix 1

MinSafeStart

– Beslutningsverktøy for å fremme optimal behandling av kvalme og oppkast under graviditet

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Prosjektinformasjon og samtykkeerklæring

Professor Hedvig Nordeng

Ph. D. stipendiat Elin Ngo

Ph. D stipendiat Maria Bich-Thuy Truong

UiO : Universitetet i Oslo

Prosjektinformasjon og samtykke om deltagelse i forskningsprosjektet «MinSafeStart – Beslutningsverktøy for å fremme optimal behandling av kvalme og oppkast under graviditet».

Hensikt med prosjektet

Opptil 80% av gravide opplever svangerskapskvalme, og kvalme og oppkast er en av de hyppigste årsakene til sykefravær og sykehusinnleggelser under svangerskapet. Likevel vet vi at svangerskapskvalme er en av de mest feilhåndterte svangerskapsrelaterte plagene hos gravide. Med dette prosjektet ønsker vi å øke livskvaliteten hos gravide, øke kunnskapen om svangerskapskvalme og fremme optimal behandling av kvalme og oppkast under graviditeten. Vi inviterer alle gravide over 18 år som opplever svangerskapskvalme til å delta. For å delta trenger du en smarttelefon med telefonlås.

Hva innebærer prosjektet for deg?

Som deltager i prosjektet svarer du på to elektroniske spørreskjema som blir sendt til deg via mail i løpet av svangerskapet. Et spørreskjema vil bli sendt til deg ved påmelding til prosjektet og tre spørreskjemaer ved oppfølging 2 uker, 4 uker og 12 uker etter registrering. Informasjonen vi ønsker å innhente omhandler din helse, livskvalitet, dine holdninger til medisinbruk, om du har blitt sykemeldt eller sykehusinnlagt under svangerskapet og din kunnskap om svangerskapskvalme. Informasjonen du oppgir vil bli koblet sammen med data fra tre norske helseregistre; det Medisinske fødselsregistret, Reseptregistret og Pasientregisteret. Alle deltagere i prosjektet vil ved tilfeldig blir fordelt i en av to studiegrupper. Studiegruppene er beskrevet under.

Gruppe 1

Du vil motta en mail med informasjon om mobilapplikasjonen (app) MinSafeStart, inkludert hvordan appen lastes ned, og hvordan appen brukes. Du logger dine kvalmesymptomer i appen ved å svare på noen enkle spørsmål daglig om kvalme, oppkast, brekninger og væske- og matinntak. Målet med appen er å gi deg muligheten til å kartlegge dine kvalmesymptomer med hensikt å øke din forståelse, kunnskap og kommunikasjon med helsepersonell om svangerskapskvalme. Du følger standard

svangerskapsomsorg, i tillegg til å svare på fire spørreskjema totalt. Spørreskjemaene vil bli tilsendt til deg via mailen du oppgir ved påmelding til prosjektet.

Gruppe 2
Du følger standard svangerskapsomsorg, i tillegg til å svare på fire spørreskjema totalt. Spørreskjemaene vil bli tilsendt til deg via mailen du oppgir ved påmelding til prosjektet.

Hva skjer med informasjonen om deg?
Informasjonen om deg vil bli lagret i Universitetet i Oslo sin forskningsserver, Tjeneste for Sensitive Data (TSD). TSD oppfyller alle krav til lagring og prosessering av sensitiv data etter Helseforskningloven og Personopplysningsloven. Tilgang til din informasjon vil kun være tilgjengelig for registrerte prosjektmedarbeidere og vil kun bli brukt til formålet som beskrevet i dette informasjonsbrevet. Dersom du har spørsmål om behandlingen av dine personopplysninger i prosjektet, ta kontakt med Universitetet i Oslo's personvernombud ved e-postadresse: personvernombud@uio.no. Som deltaker har du rett til å klage på behandling av dine personopplysninger.

Behandlingsgrunnlaget hjemles i EUs personvernforordningen ved artikkel 6 nr. 1 bokstav e og artikkel 9 nr. 2 bokstav a.

Mulige fordeler og ulemper
Din deltagelse vil bidra til utviklingen av en mobilapplikasjon som kartlegger kvalmesymptomer hos gravide, for å fremme optimal behandling av svangerskapskvalme. Deltagelsen i dette prosjektet innebærer ingen ulemper for deg utenom tiden du bruker for å logge dine kvalmesymptomer og til å svare på fire spørreskjemaer som bli tilsendt via mail.

Frivillig deltagelse
Det er frivillig å delta i prosjektet. Dersom du ikke ønsker å delta i prosjektet, trenger du ikke å oppgi noen grunn, og det får ingen konsekvenser for deg.

Prosjektansvarlig/ mer informasjon

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Prosessen av samtykkeerklæringen

Jeg har lest prosjektinformasjonen om deltagelse i forskningsprosjektet «MinSafeStart –Beslutningsverktøy for å fremme optimal behandling av kvalme og oppkast under graviditet» og er kjent med at deltagelsen i «MinSafeStart»-prosjektet innebærer:

- At jeg fyller ut fire elektroniske spørreskjemaer under svangerskapet
- At opplysninger om meg hentes fra andre norske helseregistere (Medisinsk fødselsregister, Pasientregister og Reseptregisteret)
- At deltagelsen er frivillig og jeg kan når som helst rekke meg fra prosjektet uten grunn eller konsekvenser.

Jeg er over 18 år, gravid og plages av svangerskapskvalme.

JA **NEI**

Jeg samtykker å delta i MinSafeStart-prosjektet.

Beklager, da er du ikke i målgruppen for denne studien. Takk for din tid! For å komme ut av skjemaet, trykk på «Avslutt». Ha en fortsatt fin dag.

JA **NEI**

Du vil få tilsendt første spørreskjema via mail.

Beklager, da er du ikke i målgruppen for denne studien. Takk for din tid! For å komme ut av skjemaet, trykk på «Avslutt». Ha en fortsatt fin dag.

Appendix 2

«SafeStart – en intervensjonsstudie for å fremme trygg legemiddelbruk i svangerskapet»

Studieinformasjon & samtykkeerklæring

UiO : Universitetet i Oslo

Hensikt med prosjektet

Opptil 8 av 10 gravide bruker legemidler, og vi vet at mange har et stort behov for informasjon når det gjelder trygg og riktig legemiddelbehandling i svangerskapet. Vi vet også at vanlige svangerskapsrelaterte problemer, slik som kvalme og oppkast, kan ha en betydelig effekt på den gravides hverdag. I dette prosjektet ønsker vi å øke livskvaliteten og fremme trygg og riktig legemiddelbruk blant gravide ved å tilby en samtale om egenomsorg og legemidler tidlig i svangerskapet. Farmasøyter har god kompetanse om legemidler og vil kunne svare på spørsmål knyttet til legemiddelbruk i svangerskapet. Vi inviterer alle kvinner over 18 år og som er gravid i svangerskapsuke 1-12 til å delta.

Hva innebærer studien for deg?

Som deltager i prosjektet svarer du på fire elektroniske spørreskjema, to i løpet av svangerskapet, ett ved fødselen og ett etter fødselen. Informasjonen vi ønsker å innhente omhandler din helse og livsstil, om dine holdninger til legemidler, om du har vært sykemeldt eller sykehusinnlagt i løpet av svangerskapet, i tillegg til informasjon angående ditt barns helse ved fødsel. Informasjonen du oppgir i spørreskjemaene vil bli sammenstilt med data fra fire norske helseregistre.

Som deltager i prosjektet vil du ved loddtrekning (randomisering) bli plassert i en av to mulige studiegrupper:

<u>Gruppe 1:</u>

Du vil bli henvist til nærmeste studieapotek for en samtale om egenomsorg og legemidler tidlig i svangerskapet. Dersom du bor langt unna et studieapotek kan du få samtalen via telefon. Målet med samtalen er du at du skal få innsikt i, bli trygg på og oppnå best mulig effekt av din legemiddelbehandling. Samtalen vil ta utgangspunkt i dine behov og spørsmål du har. Samtidig vil samtalen bli strukturert ved at studie-farmasøyten tar opp faste punkter, som f. eks. bruk av kosttilskudd og reseptfrie legemidler. Du vil følge standard svangerskapsomsorg i tillegg. Vi vil også be deg om å svare på fire elektroniske spørreskjema slik som beskrevet over.

<u>Gruppe 2:</u>

Du følger standard svangerskapsomsorg, i tillegg til å svare på fire elektroniske spørreskjema som beskrevet over.

Halvparten av deltagere i hver gruppe vil i tillegg bli bedt om å laste ned en applikasjon (app) for å følge gravide opp.

Hva skjer med informasjon om deg?
Informasjonen du oppgir vil bli sammenstilt med informasjon fra Medisinsk fødselsregister, Reseptregister, Norsk pasientregister og Forløpsdatabasen Trygd. Alle opplysningene vil bli behandlet uten navn, adresse eller andre opplysninger som kan knyttes direkte til deg. En kode knytter deg til de innhentede opplysninger gjennom en navneliste. Denne navnelisten oppbevares adskilt fra dine opplysninger og det er kun prosjektmedarbeidere og farmasøyter tilknyttet prosjektet som har tilgang til navnelisten. Opplysningene vil slettes høsten 2022. Alle prosjektmedarbeidere og farmasøyter som er tilknyttet prosjektet har taushetsplikt i henhold til Forvaltningslovens § 13 og Helsepersonellovens § 21. Det vil ikke være mulig å identifisere deg i datamaterialet som forskerne bruker eller i en eventuell vitenskapelig artikkel dersom resultatene publiseres. Prosjektmedarbeiderne har konsesjon fra Datatilsynet, og Regional etisk komité har vurdert prosjektet.

Mulige fordeler og ulemper
Ved å delta i prosjektet vil du bidra til å skreddersy en tjeneste som kan øke livskvaliteten til gravide kvinner og fremme trygg og optimal legemiddelbruk i svangerskapet. Deltakelse i dette prosjektet innebærer ingen ulemper annet enn tiden du bruker i forbindelse med å svare på fire elektroniske spørreskjema, og eventuelt en samtale i apotek. Vi vil trekke ut flere gavekort i løpet av studieperioden.

Du bestemmer selv
Det er frivillig å delta i studien. Dersom du ikke ønsker å delta i studien, trenger du ikke å oppgi noen grunn, og det får ingen konsekvenser for deg. Om du nå sier ja til å delta ved å klikke på «Ja» samtykkeerklæringen, kan du senere trekke tilbake ditt samtykke uten at det medfører ulemper for deg.

Studieansvarlig/ mer informasjon
Dersom du har spørsmål om prosjektet eller trenger mer informasjon, kan du kontakte:
Stipendiat Bich Thuy Truong
Farmasøytisk institutt, Universitet i Oslo
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Tlf: 22 85 55 71
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Professor Hedvig Nordeng
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Email: h.m.e.nordeng@farmasi.uio.no

SAMTYKKEERKLÆRING

1. Jeg har lest studieinformasjonen om «SafeStart – en intervensjonsstudie for å fremme trygg legemiddelbruk i svangerskapet» og er kjent med at opplysningene jeg gir vil bli behandlet strengt fortrolig. Jeg er kjent med at deltagelse i «SafeStart»-studien innebærer følgende:

- At jeg fyller ut fire elektroniske spørreskjemaer, under og etter svangerskapet.
- At opplysninger om meg og mitt barn kan hentes fra andre kilder, slik som Medisinsk fødselsregister, Reseptregister, Norsk pasientregister og Forløpsdatabasen Trygd.
- At jeg når som helst kan trekke meg fra studien ved å kontakte prosjektansvarlig. I tillegg kan jeg be om at alle opplysninger om meg blir slettet uten å oppgi grunn.

Jeg samtykker til å delta i «SafeStart»-studien:

□ Nei

□ Ja

(Hvis nei) Beklager, da er du ikke i målgruppen for denne studien. Takk for din tid!

For å komme ut av skjemaet, trykk på «Avslutt». Ha en fortsatt fin dag.

2. Jeg er over 18 år og gravid i svangerskapsuke 1-12?

□ Nei

□ Ja

(Hvis nei) Beklager, da er du ikke i målgruppen for denne studien. Takk for din tid!

For å komme ut av skjemaet, trykk på «Avslutt». Ha en fortsatt fin dag.

(Hvis ”ja”) Du vil nå bli dirigert til første spørreskjema i studien.

Appendix 3

Samtalenotat, studieapotek:

SUKK – SKÅR:

Har du vært kvalm/uvel/uggen hittil i svangerskapet? ☐ Ja ☐ Nei **Hvis «*Ja*»:** I løpet av de siste 24 timene:

1. Hvor mange klokketimer har du følt deg kvalm eller uvel i magen?	Over 6 timer ☐	4-6 timer ☐	2-3 timer ☐	≤1 time ☐	Ikke i det hele tatt ☐
2. Hvor mange ganger har du kastet opp?	Over 7 ganger ☐	5-6 ganger ☐	3-4 ganger ☐	1-2 ganger ☐	Ikke i det hele tatt ☐
3. Hvor mange ganger har du hatt brekninger (uten at noe er blitt kastet opp)?	Over 7 ganger ☐	5-6 ganger ☐	3-4 ganger ☐	1-2 ganger ☐	Ikke i det hele tatt ☐
Poeng	*5 poeng*	*4 poeng*	*3 poeng*	*2 poeng*	*1 poeng*

Poengskår (summer poengene fra spørsmål 1, 2 og 3): _____ ☐ Mild: 3-6 poeng ☐ Moderat: 7-12 poeng ☐ Alvorlig: 13-15 poeng

Hvis «*Ja*»: Har du prøvd behandling/gjort noen tiltak for å behandle kvalmen? ☐ Nei, ingen behandling/tiltak er prøvd

Spesifiser behandling/tiltak:

☐ Kvalmedagbok utlevert

Farmasøyt anbefaler oppfølgning:	☐ Nei, ingen oppfølgning nødvendig	☐ Kvinnen ønsker ikke oppfølgning
☐ På apotek ☐ Via telefon Angående: Dato:_____kl:_____ Tlf:_____		☐ Farmasøyt anbefaler at kvinnen kontakter **legen** angående:
Oppfølgning med farmasøyt gjennomført:	☐ På apotek ☐ Via telefon	☐ Avtalt men ikke gjennomført

..Fortsetter fra forrige side

Legemiddel og styrke	**Bruksområde**	**Dosering**	**Fast vs. Ved behov**

Spørsmål/problemstilling fra deltager:	**LRP**	**Svar/råd fra farmasøyt:**

Appendix 4

Table A5: Baseline characteristics of the study population (n=192) and the dropout population (n=55) for **Study II**.

	Study population (n=192)	**Dropout population** (n=55)
CHARACTERISTICS	**Value**	**Value**
Gestational week at enrollment, *mean (SD, range)*	8 (5.7, 4-39)	9 (5.0, 4-39)
Age (years), *mean (SD, range)*	32 (4.2, 21-43)	32 (4.8, 21-42)
Relationship status		
Married/co-habitation, n (%)	185 (96.4)	53 (96.4)
Other[a], n (%)	7 (3.6)	2 (3.6)
Higher education		
Yes, n (%)	154 (80.2)	41 (74.5)
No, n (%)	38 (19.8)	14 (25.5)
Working situation		
Employed, n (%)	115 (59.9)	32 (58.2)
Employed in the health sector, n (%)	50 (26.0)	13 (23.6)
Other[b], n (%)	27 (14.1)	10 (18.2)
PUQE score, *mean (SD, range)*	5 (1.9, 1-11)	5 (1.9, 2-11)
NVPQOL score, *mean (SD, range)*	147 (31.3, 36-203)	147 (35.6, 36-193)
DCS, *mean (SD, range)*	41 (19.6, 0-90)	38 (19.8, 0-89)
Primigravida		
Yes, n (%)	51 (26.6)	11 (20.0)
No, n (%)	141 (73.4)	44 (80.0)
NVP during previous pregnancy/pregnancies		
Yes, n (%)	113 (58.9)	37 (67.3)
No, n (%)	28 (41.1)	8 (32.7)

SD: Standard deviation, **PUQE score**: Pregnancy Unique Quantification of Emesis score, **NVPQOL**: Health-Related Quality of Life for Nausea and Vomiting during Pregnancy scale, **DCS**: Decisional conflict scale, **NVP** = nausea and vomiting during pregnancy

Values are expressed as mean (SD, range) or percentage as indicated

[a]*Other* includes single/unmarried and divorced/separated women

[b]*Other* includes students and unemployed women

Appendix 5

Table A6: Baseline characteristics of the study population (n=229) and the dropout population (n=111) for **Study III**.

	Study population (n=229)	**Dropout population** (n=111)
CHARACTERISTICS	**Value**	**Value**
Gestational week at enrollment, *mean (SD, range)*	7 (2.2, 3-13)	7 (2.5, 3-13)
Age (years), *mean (SD, range)*	31 (4.3, 18-44)	31 (4.2, (22-41)
Relationship status		
Married/co-habitation, n (%)	221 (96.5)	109 (98.2)
Other[a], n (%)	8 (3.5)	2 (1.8)
Higher education		
Yes, n (%)	194 (84.7)	84 (75.7)
No, n (%)	35 (15.3)	27 (24.3)
Working situation		
Employed, n (%)	134 (58.5)	52 (46.8)
Employed in the health sector, n (%)	62 (27.1)	42 (37.8)
Other[b], n (%)	33 (14.4)	17 (15.4)
PUQE score, *mean (SD, range)*	6 (2.7, 3-15)	6 (2.5, 3-14)
Primigravida		
Yes, n (%)	125 (54.6)	55 (49.5)
No, n (%)	104 (45.4)	56 (50.5)

SD: Standard deviation, **PUQE score**: Pregnancy Unique Quantification of Emesis score
Values are expressed as mean (SD, range) or percentage as indicated
[a]*Other* includes single/unmarried and divorced/separated women
[b]*Other* includes students and unemployed women

STUDY I

Use of Decision Support Tools to Empower Pregnant Women: Systematic Review

I

Elin Ngo, Maria Bich-Thuy Truong, Hedvig Nordeng
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Review

Use of Decision Support Tools to Empower Pregnant Women: Systematic Review

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Abstract

Background: Women face many health-related decisions during pregnancy. Digitalization, new technology, and a greater focus on empowering patients have driven the development of patient-centered decision support tools.

Objective: This systematic review provides an overview of studies investigating the effect of patient-centered decision support tools for pregnant women.

Methods: We searched 5 online databases, MEDLINE, EMBASE, Web of Science, PsycINFO, and Scopus, from inception to December 1, 2019. Two independent researchers screened titles, abstracts, and full-texts against the inclusion criteria. All studies investigating the effect of patient-centered decision support tools for health-related issues among pregnant women were included. Study characteristics and results were extracted using the review management tool Rayyan and analyzed according to topic, type of decision support tools, control group, outcome measurements, and results.

Results: The 25 eligible studies covered a range of health topics, including prenatal screening (n=10), gestational diabetes and weight gain (n=7), lifestyle (n=3), blood pressure and preeclampsia (n=2), depression (n=1), asthma (n=1), and psychological well-being (n=1). In general, the use of decision support tools increased women's knowledge, and recording symptoms enhanced satisfaction with maternity care.

Conclusions: The opportunities created by digitalization and technology should be used to develop innovative patient-centered decision support tools tailored to support pregnant women. Effect on clinical outcomes should be documented.

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KEYWORDS

decision support tools; pregnancy; mobile application; empowerment

Introduction

Background

Patient-centered decision support tools are developed to involve patients in their own health-related decisions by (1) clearly stating the decisions that need to be made, (2) providing information about the options, outcomes, risks, and benefits, and (3) clarifying personal values. Decision support tools aim to complement, not replace, counseling from health care providers. The goal is to empower patients to make the decisions that are best for themselves and improve communication with their care providers [1,2].

Patient involvement in decision making varies among patient groups but is especially common among young women [3], coinciding with the time in life at which they become pregnant and, for many women, face completely new health-related decisions. In particular, decisions about medication use in pregnancy may be challenging, as it requires handling the unique task of weighing the benefits and risks of treatment for themselves against the benefits and risks for their unborn child.

These situations are not uncommon, as over 60% of pregnant women use medications at least once during pregnancy [4-6].

Prior studies [7] have shown that pregnant women actively seek information to enable them to make decisions about medication use in pregnancy. First time pregnant women are more likely to seek information about medications and health-related problems during pregnancy than women who have previously had children [8-10]. Despite the frequent use of the internet, pregnant women tend not to discuss the information they have retrieved online with their health care providers [11]. Provision of tailored and credible information though a decision support tool may have the potential to empower and improve informed decision making among pregnant women [12].

The last literature review [13] on patient-centered tools to support women's decisions during pregnancy was published in 2012. Since then, there has been an increased focus on digitalization and novel tools to empower patients. An updated literature review could help identify knowledge gaps concerning patient-centered decision support tools for pregnant women [14,15].

Objective

The aim of this systematic review was to identify studies evaluating the efficacy of patient-centered decision support tools for pregnant women and provide guidance for future research and the development of new, efficient tools.

Methods

Literature Search Strategy

The following online databases were searched from inception to January 18, 2019: MEDLINE, EMBASE, Web of Science, PsycINFO, and Scopus. An updated search was conducted December 1, 2019. Each database was searched using a customized search strategy (Multimedia Appendix 1). The following keywords or MeSH terms (Medical Subject Headings) were used for the database search: *pregnancy*, *parturition*, *prenatal care*, *antenatal care*, *mobile application*, *mobile health*, *decision support techniques*, *choice behavior*, *patient education*, *decision making*, *satisfaction*, *quality of life*, and *knowledge*.

Selection of Studies

The studies were selected in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [16].

Type of Study

Randomized controlled trials, cohort studies, register-based studies, and case-control studies were eligible for inclusion. Reviews, nonoriginal studies, Delphi studies, editorials, commentaries, letters to the editor, animal studies, and conference papers or abstracts were excluded. Full-texts in English were included in this review. Moreover, full texts in Norwegian, Swedish, or Danish were included, as the authors could fluently read papers in these languages.

Type of Participants

All studies focusing on women who used one or several patient-centered decision support tools during pregnancy regarding health- or pregnancy-related issues were included in this review. Studies evaluating decision support tools for use in the prepregnancy period, postpartum period, or delivery-related (eg, support during birth, cesarean delivery, mode of birth after cesarean section, or breech position) were excluded.

Type of Intervention

All types of tools (digital or paper-based) developed to support women's health-related decisions by providing tailored information to her situation or recordings in pregnancy were included.

Type of Control Group

Participants in the control group were pregnant women who received standard prenatal care or used a different decision support tool than the participants in the intervention group. A control group was not required in descriptive studies.

Types of Outcome Measures

Outcome measures that assessed the women's knowledge, satisfaction, decision making, quality of life, use experience, behaviors, or control of clinical measures in pregnancy were included.

Study Selection and Data Extraction

All studies identified from the 5 databases were saved in reference management software (EndNote X8.1). Duplicates were removed, and the remaining studies were uploaded to free online systematic review data management software (Rayyan) [17]. First, the 2 researchers (EN and MT) independently screened titles and abstracts against the inclusion criteria, and disagreements were discussed until consensus was reached. The full-texts included from the previous round were then independently screened and categorized by the same researchers using EndNote and Excel (Microsoft Inc). At this step, excluded studies were categorized as (1) full-text not available, (2) foreign language, (3) wrong publication type, (4) wrong study design, (5) the study did not investigate the use of a decision support tool, or (6) the study did not include pregnant women or irrelevant outcome (eg, delivery, cesarean section, and economic analyses).

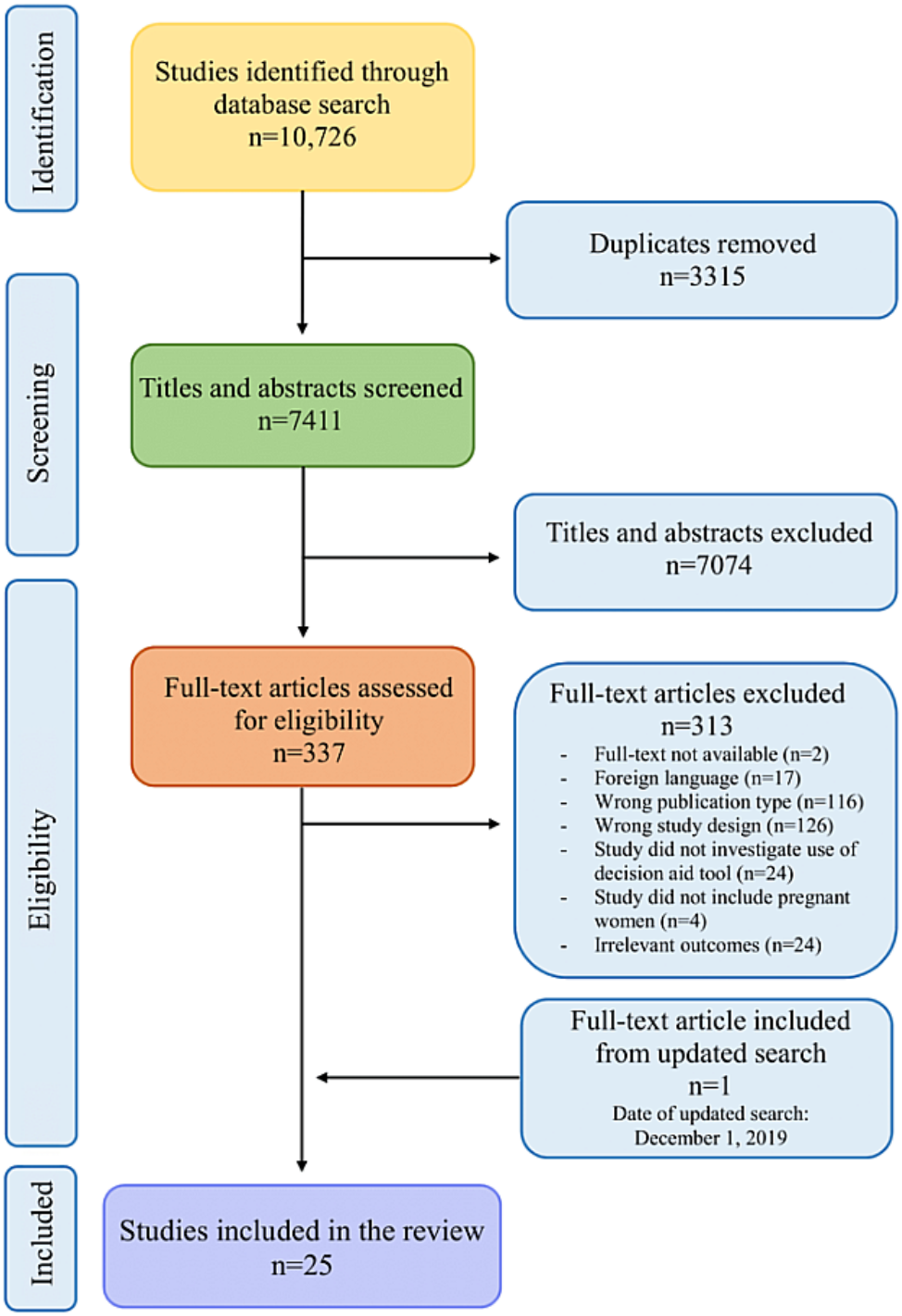
The studies included after the full-text screening were analyzed using a data extraction form (Multimedia Appendix 2). Information extracted from the studies included information about the study design, population, setting, method of recruitment, type of intervention or decision support tool, control group, outcomes measure, and results. Findings were grouped into major topics such as prenatal screening, gestational diabetes and weight gain, lifestyle, blood pressure and preeclampsia, depression, asthma, and physiological well-being.

Results

Search Findings

A total of 10,726 studies were initially identified in the first search (January 18, 2019) from the 5 online databases, with 7411 remaining after the deletion of duplicates. Of these, 7074 studies were excluded based on titles and abstracts, and 337 full-texts were screened for eligibility (Figure 1). The most common reason for exclusion was wrong study design (n=126).

Figure 1. Flowchart of the identification and selection of evaluated studies.



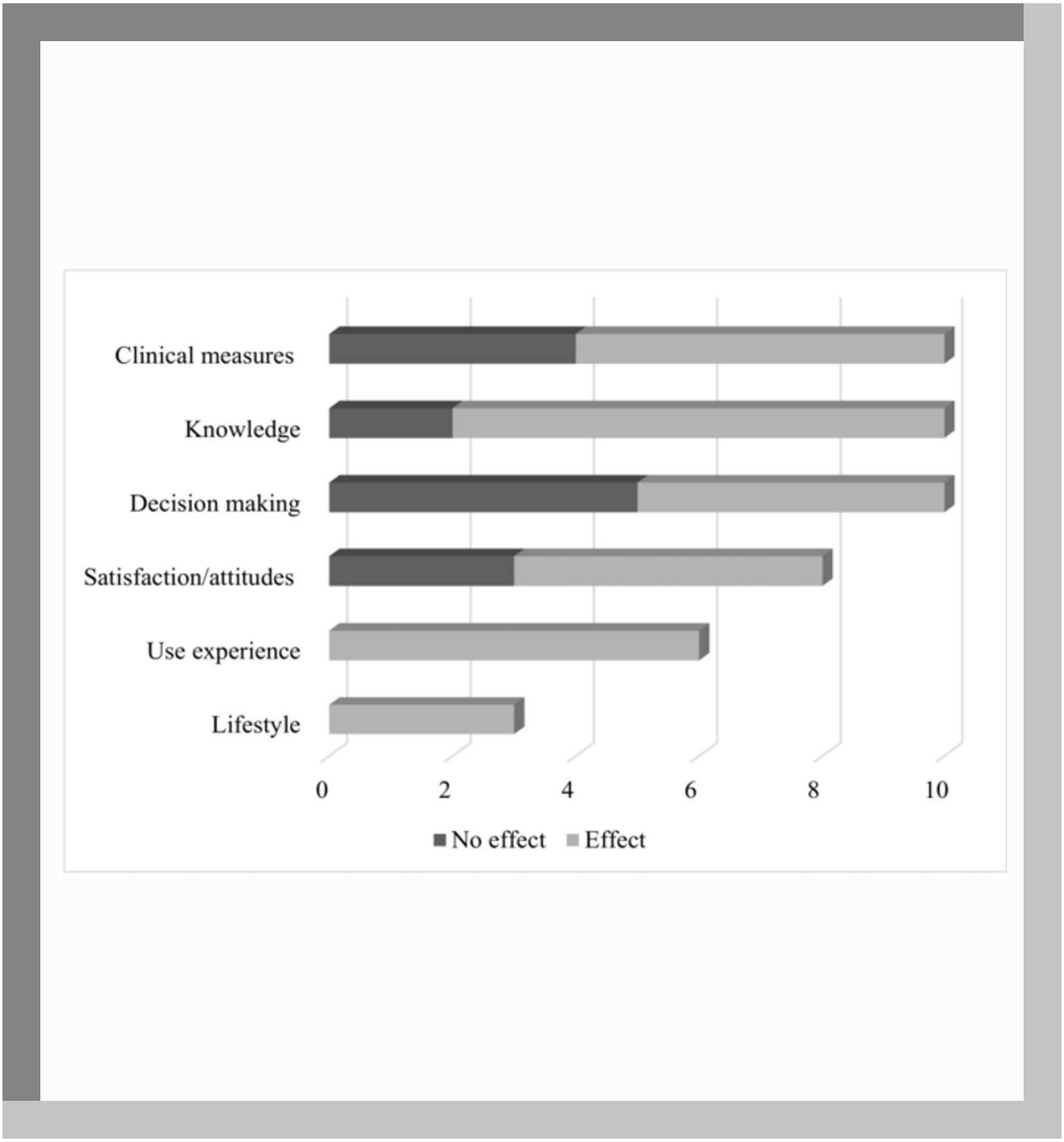
The updated search (December 1, 2019) identified 1221 new studies from the same databases as the first search. Of these, only 1 study was eligible for inclusion in this review after the screening process.

Included Studies

A total of 25 studies were included in this review, all in English. The studies covered 7 major topics: prenatal screening, gestational diabetes and weight gain, blood pressure and preeclampsia, lifestyle, depression, asthma, and physiological well-being (Multimedia Appendix 3). The decision support

tools were provided either as digital tools (webpage, mobile app, video, SMS text messages, n=24) or as written educational material (n=1). Outcome measures included in the digital decision support tools were clinical measures (n=10), knowledge level (n=10), decision making (n=10), satisfaction or attitudes (n=8), use experience (n=6), and lifestyle (n=3). One paper-based decision support tool investigated the effect on knowledge (n=1), attitudes (n=1), decision making (n=1), and clinical measures (n=2) (Figure 2). Several studies used multiple instruments for measuring the same outcome. The total number of outcome measures may thus exceed the number of studies included.

Figure 2. Effect of digital decision support tools.



Effect of Patient-Centered Decision Support as Interventions

Prenatal Screening

Ten studies [18-27] evaluated the effect of a patient-centered decision support tool on women's decisions about performing prenatal screening for genetic disorders and birth defects. Pregnant women at ≤26 gestational weeks were included in these studies. One study [24] did not have a cut-off on gestational weeks. Nine decision support tools were digital and one was provided as written material. The outcomes measured in these studies were knowledge (n=9), decision making (n=11), satisfaction or attitudes (n=6), clinical measures (n=3), and use experience (n=1).

Overall, women who used a decision support tool had higher knowledge scores than the control group and knew about the risks and benefits of genetic screening in pregnancy (Multimedia Appendix 3). Independent of the type of decision support tool, the results show decreased decisional conflict for women in the intervention group compared to those in standard care. This indicated that women using decision support tools felt more informed and were more aware of the risk and expected outcome of each option when compared to their counterparts [19-21,23,27]. Women using decision support tools also had better knowledge scores [19,21-23,25-27], except for in 2 studies [20,24] which showed no effect on knowledge. Both digital and paper-based decision support tools showed no difference in attitudes and frequency of completing screening (digital: 32%; paper-based: 15%; P=.087) [19,23,25,27].

Gestational Diabetes and Weight Gain

Seven studies [28-33] investigated the effect of using decision support tools on blood glucose level control for pregnant women with gestational diabetes. Two studies [28,34] evaluated the effect on gestational weight gain in general and among women with gestational diabetes. The evaluated decision support tools were apps (n=4), web-based tools (n=2), and SMS text message–based (n=1). Outcome measures were knowledge level (n=1), satisfaction (n=2), use experience (n=2), blood glucose level control (n=3), and weight control (n=2).

Women using an app to record blood glucose level readings daily, in addition to receiving SMS text messages from their doctor with advice when readings were abnormal, reported more blood glucose level readings than women who recorded their blood glucose level readings in a paper diary (app: 3.8; paper diary: 2.6 recordings per day) [30]. The vast majority of women with diabetes using the apps felt more satisfied with the care they received [29]. Women receiving tailored advice online (about blood glucose) from their care provider also had a better understanding of the risks related to gestational weight gain for themselves (tailored advice: 34%; control: 21%; P=.044) and the fetus (tailored advice: 62%; control: 38%; P=.001) [31].

Women using apps as decision support tool showed no difference or improvements in in blood glucose level control [28,30]. However, women who used a web-chat with direct contact and feedback from their health care providers had significant lower fasting blood glucose level (web-chat and feedback: 4.3; control: 5.3; P<.001) and 2-hour postprandial blood glucose (web-chat and feedback: 5.8; control: 6.9; P<.001) [33]. They also felt they had more control of their symptoms and a better overview of their blood glucose when using a decision support tool as a supplement to standard care [32].

Lifestyle

Three studies [35-37] investigated the effect of decision support tools on alcohol consumption and smoking cessation during pregnancy. The tools were an app [35], a web-based tool [36], and an SMS text message–based tool [37].

A computer-tailored letter providing information about the risk of alcohol use in pregnancy had no effect on women's refrainment from alcohol use after 3 months when compared to standard care. They did, however, refrain from alcohol to a larger extent after 6 months (computer-tailored letter: 78%; standard care: 55%, P=.04) [36]. Providing SMS text messages with general pregnancy information also resulted in a decreased alcohol consumption in pregnancy compared to maternity care alone (SMS text messages: 3.5%; standard maternity care: 1.1%; P<.098) [37].

Blood Pressure and Preeclampsia

Two studies [38,39] investigated the effect of an app on blood pressure readings and knowledge about preeclampsia. Women using the app recorded their blood pressure and shared the information with their care provider more frequently [38]. They also had significantly higher knowledge scores than women not using the app (app user: 78.1; control: 15.8; P<.001) [39].

Depression

A recently published study [40] investigated the effect of a mood tracking and alert app among pregnant women with depression on mood and depressive symptoms measured by the Patient Health Questionnaire 9 [41]. The app also provided information about mental health and physical activity and alerted prenatal providers when depressive symptoms were worsening. All women in the study also had access to a patient portal that provided an overview of upcoming appointments and clinical results and which could be used to request prescription refills. Women in the intervention group recorded depressive symptoms an average 5.3 days per week. Their health care providers were more likely to mention mental health at check-ups (P=.02), and women using the app had a higher rate of referral to a mental health specialist (P=.03) [40].

Asthma

One study [42] investigated the effect of an app on asthma symptoms during pregnancy. In that study, 58% of the women had moderate to severe asthma. Women in the intervention group received a chronic obstructive pulmonary disease measurement device (COPD - 6) in addition to an app for recording symptoms and medication use weekly, as well as with weekly feedback. Women in the intervention groups had better control of symptoms (Asthma Control Questionnaire: –0.30 vs. 0.06, P=.02), and quality of life (Asthma Quality-of-life Questionnaire score: 0.51 vs. –0.22, P=.002) after 6 months [42].

Psychological Well-Being

One study [43] investigated the use of a decision support tool and its effect on psychological well-being. Women received SMS text messages with information tailored to their gestational week, 2 times per week from gestational week 28 onward. Women receiving these SMS text messages had lower anxiety scores (2.8 vs. 4.9, P=.002) and higher confidence scores (8.9 vs. 7.8, P=.001) than women receiving standard care only [43].

Discussion

Main Findings

This systematic review provides an updated overview of current knowledge regarding patient-centered decision support tools

for women during pregnancy. The 25 studies included more than 5000 women covering a broad range of health conditions in pregnancy. The majority of studies investigated the effect of a decision support tool in relation to prenatal screening (10/25, 40%) or gestational diabetes and weight gain during pregnancy (7/25, 28%). In general, the decision support tools were found to increase the women's knowledge and enhance communication with health care providers. Digital decision support tools also seemed to be more convenient and led to more recorded clinical data than what was recorded by paper-based tools.

Interestingly, almost all decision support tools, both digital and written material, increased the women's knowledge compared to knowledge received through standard care [19,21-27,31]. However, the majority of women participating in the studies were highly educated, and had been pregnant before; thus, they may not be representative of the general pregnant population. In addition, knowledge scores were most commonly measured immediately after the intervention was given or within 6 weeks. Therefore, whether gained knowledge lasted over time is unknown. One study [20] found no difference in knowledge between women receiving genetic counseling about prenatal screening with and without a supplementary app. The fact that both groups received a high-standard intervention such as genetic counseling could possibly explain why there was no additional benefit of the app on knowledge scores. Taken together, these results indicate that decision support during pregnancy, regardless of whether it is written or digital, may be a useful complement to standard antenatal care when specialized counseling is less available. It is still important to bear in mind that women receiving a consultation in advance may have been influenced to read more, which may have affected the results.

The studies included in this review show the potential of a patient-centered decision support tool to promote communication between health care providers and women. Women who frequently used digital support tools were more likely to bring their recordings to their health care provider. They were also more satisfied with the care they received and discussed their concerns with the health care provider to a greater extent than their counterparts did [27,29,31,38,40]. This indicates that women are more likely to discuss their problems with their health care providers when they are knowledgeable about the topic [44-46]. It should be noted that many of the studies included samples of women of higher sociodemographic status than that of the general population of pregnant women. This may have caused a selection bias of potentially more resourceful or motivated women, limiting the generalizability of the findings to all pregnant women.

Interpretation in Light of Other Evidence

The use of decision support tools, in general, improves patient knowledge, make them better informed, and makes their choices and options clearer [47,48]. This review shows that this also applies to pregnant women. Mobile apps and decision support tools are increasingly used for self-management in many different chronic diseases that women of reproductive age have, such as migraine and diabetes, but high-quality decision support tools developed specifically for pregnancy are, to a large degree, still lacking. Moreover, there is clear potential for developing decision support tools to support decisions about medications in pregnancy. Nausea and vomiting in pregnancy, pain and self-managed conditions such as heartburn and constipation are examples where digital treatment algorithms may yet prove to be useful.

Our findings expand on and support earlier reviews that reported the potential benefits of decision support tools for decisions related to pregnancy. Both Say et al [49] and Dugas et al [13] advocated the potential for decision support tools to improve obstetric care. Our review included more studies that were recent (since 2012), even though our inclusion criteria were focused on decision support tools used only by women during pregnancy. More decision support tools after 2012 are electronic, as apps and web-based. The opportunities created by digitalization and technology should be used to develop innovative patient-centered decision support tools tailored to support pregnant women. Furthermore, the studies in our review covered a wider range of topics during pregnancy, but coverage of the most common topics regarding women's health during pregnancy was still lacking (eg, decision support tools for nausea and vomiting in pregnancy).

What Makes a Good Decision Support Tool for Pregnant Women?

The most effective decision support tools for pregnant women shared some common features. First, digital decision support tools seem more convenient if evidenced-based and if relevant information from different sources can be assembled in one app. This will avoid multiple or conflicting information sources, which has previously been an important concern among pregnancy women [50].

Second, digital tools that enable pregnant women to share recordings with their health care providers and get real-time feedback seem to be the most useful [18,29,32]. Such tools enable individually tailored information and improve communication during pregnancy. This is in line with previous findings on weight gain in pregnancy showing that specific and tailored information is more effective than general information [34].

Lastly, digital decision support tools were more convenient for recording symptoms than spiral notebooks. Women using digital support tools recorded their symptoms more frequently [38]. An earlier study [51] comparing the use of digital tools and spiral notebooks in general also reported that digital tools are potentially more accurate. This indicates that future development of decision support tools should focus and invest in digital tools.

A Supplement, Not a Replacement

Even with increased technology, there is still a gap in the development of patient-centered decision support tools for pregnancy-related conditions. Given that women have high information needs and the potential that decision support tools have in empowering them, we expect this can be a valuable supplement for both women and their health care providers during prenatal care. Given that women were more satisfied with and were more likely to discuss their health problems with their care providers [30,31,38,40], it seems plausible that

patient-centered decision support tools may promote healthier pregnancies and reduce the burden on health care services, with little extra cost after development. Decision support tools do not replace health care providers but provide additional relevant clinical information, supporting women to make better decisions together with their health care providers.

The sparseness of studies evaluating the effect of decision support tools, especially on clinical outcomes, stands in great contrast to the number of apps targeting pregnant women. This highlights the importance of developing and testing decision support tools for pregnant women. Only tools that are of high quality and that are efficient should be promoted.

Limitations

This literature review has some limitations that should be taken into consideration when interpreting the results. First, there were few patient-centered decision support tools within each topic, and the diversity of outcome measures made it challenging to draw overall conclusions. Second, the individual studies overrepresented women with higher sociodemographic status, and the majority of pregnant women included in the studies were of a white ethnic background. Third, a number of studies had a low number of participants, and the women who consented to the studies may have been motivated to participate, which can cause a selection bias and give more positive results than what would be achieved in the typical target population.

Studies including decision support tools used by health care providers, decision support tools regarding childbirth, maternal and fetal health outcomes, and decision tools used in the postpartum period were excluded. An expanded review including these outcomes and topics should be assessed in future studies and may provide greater insight into the field.

Conclusion

Despite the technological possibilities, the focus on patient involvement, and documented information needs, few heterogeneous studies have been performed on the effect of decision support tools in pregnancy. These few studies, however, have demonstrated the potential benefit to knowledge, perception, confidence in decision making, and communication between the women and their health care providers. More decision support tools should be developed and tailored to meet the needs of pregnant patients. The effect of such tools on clinical outcomes should be tested before recommending them or implementing them as a supplement in routine maternity care.

Acknowledgments

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Authors' Contributions

EN, MT, and HN designed the study. EN and MT performed the systematic search and conducted the main analysis. EN drafted the first version of the manuscript. EN, MT, and HN contributed to the interpretation of results and critical appraisal of the manuscript. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search strategy.
[DOCX File , 41 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Extraction sheet.
[DOCX File , 25 KB-Multimedia Appendix 2]

Multimedia Appendix 3

The characteristics of studies included in this review.
[DOCX File , 39 KB-Multimedia Appendix 3]

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MULTIMEDIA APPENDIX 1

Search strategy: MEDLINE

Patient	Exposure	Outcome
MeSH terms		
Pregnancy Pregnant Women Parturition Prenatal Care	Decision Support Techniques Mobile Applications Smartphone Decision Support Systems	Choice Behavior Pregnancy Outcome Patient Education as Topic Decision Making Personal Satisfaction Patient Satisfaction Quality Of Life Patient Medical Knowledge Patient Participation Health Education Clinical Decision Making
All fields		
Pregnan* Parturition Childbirth Birth* "Prenatal care" Antenatal care"	Mobile health Decision support* App* Decision aid Decision tool	Choice behavior "pregnancy outcome" Education "decision making" Satisfaction "Quality of life" Knowledge

MeSH: Medical Subject Headings

Empowering pregnant women through use of decision support tools: a systematic review
Appendix S1. Search Strategy

Search January 18th in PubMed/MEDLINE

#	search	Results
1	exp Pregnancy/	**851535**
2	exp Pregnant Women/	**7161**
3	exp Parturition/	**15285**
4	exp Prenatal Care/	**25129**
5	Pregnan*.mp.	**951429**
6	Parturition.mp.	**113007**
7	Childbirth.mp.	**43816**
8	Birth*.mp.	**352951**
9	"Prenatal care".mp.	**30293**
10	"Antenatal care".mp.	**7862**
11	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10	**1172761**
12	exp Decision Support Techniques/	**72548**
13	exp Mobile Applications/	**3674**
14	exp Smartphone/	**2518**
15	exp Decision Support Systems/	**7013**

16	Mobile health.mp.	**51020**
17	Decision support*.mp.	**33643**
18	App*.mp.	**23489**
19	Decision aid.mp.	**85529**
20	Decision tool.mp.	**16996**
21	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20	**182660**
22	exp Choice Behavior/	**51941**
23	exp Pregnancy Outcome/	**68580**
24	exp Patient Education as Topic/	**81298**
25	exp Decision Making/	**183398**
26	exp Personal Satisfaction/	**16575**
27	exp Patient Satisfaction/	**81975**
28	exp Quality Of Life/	**170736**
29	exp Patient Medical Knowledge/	**140**
30	exp Patient Participation/	**23327**
31	exp Heath Education/	**229616**

32	exp Clinical Decision Making/	**4737**
33	Choice Behavior.mp.	**70120**
34	"Pregnancy putcome".mp.	**51778**
35	education.mp.	**1360091**
36	"Decision Making".mp.	**185932**
37	Satisfaction.mp.	**184173**
38	"Quality of life".mp.	**291509**
39	Knowledge.mp.	**681905**
40	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39	**2557054**
41	11 AND 21 AND 40	**2225**

Search strategy: EMBASE

Patient	Exposure	Outcome
Emtree		
Pregnancy Pregnant Women Birth Prenatal Care Childbirth	Decision Support System Mobile Applications Smartphone	Choice Behavior Pregnancy Outcome Patient Education as Topic Decision Making Personal Satisfaction Patient Satisfaction Quality Of Life Patient Medical Knowledge Patient Participation Health Education Clinical Decision Making
Keywords		
Pregnan* Parturition “Prenatal care” Childbirth “Antenatal care”	Decision Support Techniques Mobile Application Smartphone* Decision Support System Health Tool Aid App	Choice behavior “pregnancy outcome” Education “decision making” Satisfaction “Quality of life” Knowledge

Empowering pregnant women through use of decision support tools: a systematic review
Appendix S1. Search Strategy

Search January 18th in EMBASE

#	search	Results
1	exp Pregnancy/	**762703**
2	exp Pregnant Women/	**74071**
3	exp Birth /	**28370**
4	exp Prenatal Care/	**145609**
5	exp Childbirth/	**60170**
6	Pregnan*.mp.	**1026330**
7	Parturition.mp.	**18182**
8	"Prenatal care".mp.	**40735**
9	Childbirth.mp.	**33477**
10	"Antenatal care".mp.	**10304**
11	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10	**1118623**
12	exp Decision Support System/	**21973**
13	exp Mobile Applications/	**7446**
14	exp Smartphone/	**7329**
15	Decision.mp.	**544262**

16	Support.mp.	**1217546**
17	15 AND 16	**77691**
18	Tool.mp.	**601376**
19	Aid.mp.	**236666**
20	15 AND 18	**28490**
21	15 AND 19	**13481**
22	Techniques.mp.	**2416332**
23	15 AND 16 AND 22	**6098**
24	Mobile.mp.	**128926**
25	Application.mp.	**918265**
26	24 AND 25	**17727**
27	Smartphone*.mp.	**1896**
28	System*.mp.	**6693570**
29	15 AND 16 AND 28	**41144**
30	Health.mp.	**3731382**
31	24 AND 30	**25190**

32	App.mp.	29532
33	12 OR 13 OR 14 OR 17 OR 20 OR 21 OR 23 OR 26 OR 27 OR 29 OR 31 OR 33	**173207**
34	exp Medical Decision Making/	**82430**
35	exp Education/	**1397469**
36	exp Health Education/	**306258**
37	exp Pregnancy Outcome/	**52030**
38	exp Patient Education/	**106784**
39	exp Decision Making/	**340106**
40	exp Patient Satisfaction/	**125286**
41	exp Satisfaction/	**213759**
42	exp Knowledge/	**153535**
43	exp Quality Of Life/	**447634**
44	exp Patient Participation/	**24713**
45	Choice.mp.	**393350**
46	Behavior.mp.	**1403207**
47	45 AND 46	**29974**

48	"Pregnancy outcome".mp.	**63587**
49	"Decision making".mp.	**391759**
50	"Quality of life".mp.	**517707**
51	"Patient participation".mp.	**26195**
52	Education.mp.	**1124943**
53	Knowledge.mp.	**808589**
54	Satisfaction.mp.	**256423**
55	34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54	**3247837**
56	11 AND 33 AND 55	**3918**

Search strategy: PsycInfo

Patient	Exposure	Outcome
Thesaurus		
Pregnancy Birth Prenatal care	Decision Support System Mobile Deceives	Satisfaction Choice Behavior Pregnancy Outcome Client Education Decision Making Quality Of Life Health Education Health Knowledge
Keywords		
Pregnan* Parturition Childbirth "Prenatal care" "Antenatal care"	Decision Support* Aid Tool App "Smart phone*"	"Pregnancy outcome*" Choice Behavior Education Decision Making Satisfaction "Quality of life" Education Knowledge

Search January 18th in PsycInfo

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Appendix S1. Search Strategy

#	search	Results
1	exp Pregnancy/	**23515**
2	exp Birth/	**12786**
3	exp Prenatal Care/	**1933**
4	Pregnan.mp.	**46933**
5	Parturition.mp.	**1267**
6	Childbirth.mp.	**5643**
7	“Prenatal care”.mp.	**2970**
8	“Antenatal care”.mp.	**840**
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8	**59547**
10	exp Decision Support System/	**3044**
11	exp Mobile Devices/	**6057**
12	Decision.mp.	**157468**
13	Support*.mp.	**450138**
14	Aid.mp.	**36648**
15	Tool.mp.	**86673**
16	12 AND 13	**32792**
17	12 AND 14	**2804**
18	12 AND 15	**5210**

19	App.mp.	**5040**
20	“Smart phone*”.mp.	**483**
21	10 OR 11 OR 16 OR 17 OR 18 OR 19 OR 20	**41464**
22	exp Satisfaction/	**56244**
23	exp Choice Behavior/	**26379**
24	exp Pregnancy outcome/	**16628**
25	exp Client Education/	**3734**
26	exp Decision Making/	**98126**
27	exp Quality Of Life/	**39218**
28	exp Health Education/	**17592**
29	exp Health Knowledge/	**7239**
30	“Pregnancy outcome*”.mp.	**1958**
31	Choice.mp.	**119474**
32	Behavior.mp.	**863323**
33	31 AND 32	**41278**
34	Education.mp.	**442108**
35	Making.mp.	**249621**
36	12 AND 35	**114317**
37	Satisfaction.mp.	**116647**

38	"Quality of life".mp.	**70535**
39	Education.mp.	**442108**
40	Knowledge.mp.	**290045**
41	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 33 OR 34 OR 36 OR 37 OR 38 OR 39 OR 40	**957297**
42	9 AND 21 AND 41	**629**

Empowering pregnant women through use of decision support tools: a systematic review
Appendix S1. Search Strategy

Search strategy: Scopus

Patient	Exposure	Outcome
All fileds		
Parturition	"Decision support"	Choice behavior
Pregnan*	Mobile application*	"Pregnancy outcome*"
Birth*	Smartphone*	"Decision making"
Childbirth*	App	Satisfaction
Prenatal care	Decision aid	"Quality of life"
Antenatal care	Decision tool	Knowledge
		Patient participation
		Education

Empowering pregnant women through use of decision support tools: a systematic review
Appendix S1. Search Strategy

Search January 18th in Scopus

#	search	Results
1	TITLE-ABS-KEY (Parturition)	**26262**
2	TITLE-ABS-KEY (Pregnan*)	**1072681**
3	TITLE-ABS-KEY (Birth*)	**491181**
4	TITLE-ABS-KEY (Child AND birth*)	**126747**
5	TITLE-ABS-KEY (Prenatal AND care)	**63492**
6	TITLE-ABS-KEY (Antenatal AND care)	**20146**
7	(TITLE-ABS-KEY (Parturition) OR (TITLE-ABS-KEY (Pregnan*) OR (TITLE-ABS-KEY (Birth*) OR (TITLE-ABS-KEY (Child AND birth*) OR (TITLE-ABS-KEY (Prenatal AND care) OR (TITLE-ABS-KEY (Antenatal AND care)	**1401082**
8	TITLE-ABS-KEY (“Decision support”)	**107322**
9	TITLE-ABS-KEY (Mobile application*)	**166573**
10	TITLE-ABS-KEY (Smartphone*)	**47303**
11	TITLE-ABS-KEY (app)	**42270**
12	TITLE-ABS-KEY (Decision aid)	**29415**
13	TITLE-ABS-KEY (Decision tool)	**133877**
14	(TITLE-ABS-KEY (“Decision support”)) OR (TITLE-ABS-KEY (Mobile application*)) OR (TITLE-ABS-KEY (Smartphone*)) OR (TITLE-ABS-KEY (app	

	)) OR (TITLE-ABS-KEY (Decision aid)) OR (TITLE-ABS-KEY (Decision tool))	**466857**
15	TITLE-ABS-KEY (Choice behavior)	**127044**
16	TITLE-ABS-KEY (“Pregnancy outcome*”)	**69719**
17	TITLE-ABS-KEY (“Decision making”)	**690386**
18	TITLE-ABS-KEY (satisfaction)	**412006**
19	TITLE-ABS-KEY (“Quality of life”)	**446306**
20	TITLE-ABS-KEY (knowledge)	**1827128**
21	TITLE-ABS-KEY (Patient participation)	**79066**
22	TITLE-ABS-KEY (Education)	**185670**
23	(TITLE-ABS-KEY (Choice behavior)) OR (TITLE-ABS-KEY (“Pregnancy outcome*”)) OR (TITLE-ABS-KEY (“Decision making”)) OR (TITLE-ABS-KEY (satisfaction)) OR (TITLE-ABS-KEY (“Quality of life”)) OR (TITLE-ABS-KEY (Knowledge)) OR (TITLE-ABS-KEY (Patient participation)) OR (TITLE-ABS-KEY (Education))	**8452184**
24	((TITLE-ABS-KEY (Parturition) OR (TITLE-ABS-KEY (Pregnan*) OR (TITLE-ABS-KEY (Birth*) OR (TITLE-ABS-KEY (Child AND birth*) OR (TITLE-ABS-KEY (Prenatal AND care) OR (TITLE-ABS-KEY (Antenatal AND care)) AND ((TITLE-ABS-KEY (“Decision support”)) OR (TITLE-ABS-KEY (Mobile application*)) OR (TITLE-ABS-KEY (Smartphone*)) OR (TITLE-ABS-	

KEY (app)) OR (TITLE-ABS-KEY (Decision aid)) OR (TITLE-ABS-KEY (Decision tool))) AND ((TITLE-ABS-KEY (Choice behavior)) OR (TITLE-ABS-KEY (“Pregnancy outcome*”)) OR (TITLE-ABS-KEY (“Decision making”)) OR (TITLE-ABS-KEY (satisfaction)) OR (TITLE-ABS-KEY (“Quality of life”)) OR (TITLE-ABS-KEY (Knowledge)) OR (TITLE-ABS-KEY (Patient participation)) OR (TITLE-ABS-KEY (Education))) **2154**

25 ((TITLE-ABS-KEY (Parturition) OR (TITLE-ABS-KEY (Pregnan*) OR (TITLE-ABS-KEY (Birth*) OR (TITLE-ABS-KEY (Child AND birth*) OR (TITLE-ABS-KEY (Prenatal AND care) OR (TITLE-ABS-KEY (Antenatal AND care)) AND ((TITLE-ABS-KEY (“Decision support”)) OR (TITLE-ABS-KEY (Mobile application*)) OR (TITLE-ABS-KEY (Smartphone*)) OR (TITLE-ABS-KEY (app)) OR (TITLE-ABS-KEY (Decision aid)) OR (TITLE-ABS-KEY (Decision tool))) AND ((TITLE-ABS-KEY (Choice behavior)) OR (TITLE-ABS-KEY (“Pregnancy outcome*”)) OR (TITLE-ABS-KEY (“Decision making”)) OR (TITLE-ABS-KEY (satisfaction)) OR (TITLE-ABS-KEY (“Quality of life”)) OR (TITLE-ABS-KEY (Knowledge)) OR (TITLE-ABS-KEY (Patient participation)) OR (TITLE-ABS-KEY (Education))) ANDDOCTYPE (le) AND DOCTYPE (cp)

1959

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Appendix S1. Search Strategy

Search strategy for search in Web of Science

Patient	Exposure	Outcome
All fields		
Pregnan*	"Decision support*"	Choice behavior
Parturition*	Mobile application*	"Pregnancy outcome*"
Prenatal care*	Mobile health	"Decision making"
Childbirth*	App	Satisfaction
Birth*	Decision aid	"Quality of life"
	Decision tool	Knowledge
		Patient participation
		Education

Empowering pregnant women through use of decision support tools: a systematic review
Appendix S1. Search Strategy

Search January 18th in Web of Science

#	search	Results
1	ALL FIELDS: (Pregnan*)	**483361**
2	ALL FIELDS: (Parturition*)	**18008**
3	ALL FIELDS: (Prenatal care*)	**19892**
4	ALL FIELDS: (Antenatal care*)	**13233**
5	ALL FIELDS: (Childbirth*)	**99857**
6	ALL FIELDS: (Birth*)	**394723**
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	**799153**
8	ALL FIELDS: (“Decision support*”)	**60290**
9	ALL FIELDS: (Mobile application*)	**116105**
10	ALL FIELDS: (Smartphone*)	**10424**
11	ALL FIELDS: (Mobile health)	**35204**
12	ALL FIELDS: (App)	**66096**
13	ALL FIELDS: (Decision aid)	**46968**
14	ALL FIELDS: (Decision tool)	**103506**
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	**391720**
16	ALL FIELDS: (Choice behavior)	**94107**
17	ALL FIELDS: (“Pregnancy outcome*”)	**25106**
18	ALL FIELDS: (“Decision making”)	**324096**

19	ALL FIELDS: (Satisfaction)	**203924**
20	ALL FIELDS: (“Quality of life”)	**343338**
21	ALL FIELDS: (Knowledge)	**1397807**
22	ALL FIELDS: (Patient participation)	**46053**
23	ALL FIELDS: (Education)	**3205945**
24	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23	**5153670**
25	#7 AND #15 AND #24	**1995**

MULTIMEDIA APPENDIX 2

EXTRACTION SHEET - Use of Decision Support Tools to Empower Pregnant Women: Systematic Review

General information

Reference number:

First author:

Year of data collection:

Year of publication:

Country:

Theme:

Study design

☐ Analytical study AND ☐ Randomized controlled study (RTC) ☐ Register-based study ☐ Other:_____

☐ Descriptive study ☐ Cohort study ☐ Case controlled study

Population

☐ Pregnant women Population size: _____ Other comments: _____

Setting

☐ Primary care ☐ Secondary care ☐ At home ☐ Other: _____

Method of recruitment

☐ By midwifes ☐ By physicians ☐ Internet/social media Other ☐ Other: _____

Intervention

☐ Decision support tool as an app/on mobile ☐ Decision support tool on computer ☐ Decision support tool on paper

☐ Other: _____ Size of intervention group: _____ Other comments: _____

Control

Type of control group: _____ Size of control group: _____ Other comments: _____

☐ No control group

Outcome

☐ Satisfaction ☐ Quality of life ☐ Knowledge ☐ Education

☐ Pregnancy outcome ☐ Choice behavior ☐ Decision making ☐ Other: _____

Describe outcome:

☐ **Included** ☐ **Excluded, reason:**_____

MULTIMEDIA APPENDIX 3

Use of Decision Support Tools to Empower Pregnant Women: Systematic Review
Multimedia appendix 3: The characteristics of studies included in this review

Reference	Country	Study design	Population	DST intervention	Control	Outcome	Main results*
Prenatal screening							
Carlson et al., 2019 [20]	USA	RCT	Pregnant women, <22 weeks of gestation I: n=92 C: n=105	App as a DST and genetic counseling	Genetic counseling and standard care	Knowledge, 0-12 point scale (Higher score indicates higher level of knowledge)	No difference in knowledge (10.9 vs. 10.6, *P*=.306) between the groups
						Decisional conflict, DCS, 10-item, 0-100 point scale (Lower score indicates less decisional conflict)	Decisional conflict was reduced among women using an app as a DST and women receiving genetic counseling (0.2 vs. 1.7, *P*=.003)
Rothwell et al., 2019 [25]	USA	RCT	Pregnant women, < 15 weeks of gestation I: n=40 C: n=39	Game-based decision tool	Brochure about prenatal screening, standard care	Knowledge, PSK survey, 23-item (Higher score indicates higher level of knowledge)	Higher knowledge score among women using the DST (21.4 vs. 19.6, *P*=.004)
						Attitudes	More positive attitudes towards prenatal screening (no data reported)
						Screening frequency (%)	Similar in frequency of completing screening between the groups (32% vs. 15%, *P*=.087).
Ahman et al., 2016 [18]	Sweden	Descrip-tive study	Pregnant women in second trimester after routine screening n=11	Web-based decision tool	No control group	Women`s perception of a web-based decision tool	Enhanced awareness in prenatal screening. The information was more attractive, easier to access, and reliable cause it was selected.
Beulen et al., 2016 [19]	Nether-lands	RCT	Pregnant women with asthma, < 22 weeks of gestation I: n=157 C: n=157	Web-based decision tool	Standard care	Decisional conflict, DCS, 16-item, 0-100 point scale (Lower score indicates less decisional conflict)	Women using DST had lower decisional conflict (18.4 vs. 25.7, *P*=.002)
						Decisional regret, DRS, 5-item, 0-100 point scale (Lower score indicates less decisional regret)	No difference in decisional regret between women using DST and standard care (14.0 vs. 14.5, *P*=.809)
						Anxiety, STAI, 20-item, 0-80 point scale (Higher score indicates greater anxiety level)	No difference in anxiety between women using DST and standard care (10.2 vs. 10.3, *P*=.890)
						Attitudes, MMIC, an attitude scale with five bipolar adjective pairs, scored as response towards having the procedures performed, midpoint of the scale equals neutral attitude Scores above mid: positive attitude Score below mid: negative attitude	No significant difference in attitudes between the two groups (15.6 vs. 16.5, *P*=.186)

					Knowledge, 19 statements (true/false/do not know), scored as number of correct responses ≥12: sufficient knowledge	Higher sufficient knowledge in the group using DST (14.9 vs. 12.8, *P*<.001)
					Informed choice, MMIC, a combination of sufficient knowledge and choice value-consistent	Higher informed choice among women using DST (82.3% vs. 66.4%, *P*=.004)
Kupperma nn et al., 2014 [22]	USA	RCT	Pregnant women, < 20 weeks of gestation I: n=375 C: n=369	Computerized decision support tool	Standard care	Knowledge, MSSKQ, 0-15 point scale (Higher score indicates higher level of knowledge)	Women using DST had higher knowledge score (9.4 vs. 8.6, *P*<.010)
						Decisional conflict, DCS, 16-item, 0-100 point scale (Lower score indicates less decisional conflict)	No significant difference in decisional conflict between the groups (12.9 vs. 14.1, *P*=.470)
						Decisional regret, DRS, 5-item, 0-100 point scale (Lower score indicates less decisional regret)	No difference on decisional regret between the groups (8.3 vs. 6.8, *P*=.120)
Skjoth et al., 2015 [24]	Denmark	RCT	Pregnant women I: n=577 C: n=578	Computer-based decision tool, videos, and chat forum	Standard care	Knowledge, MMIC, 10-item, 0-10 point scale (Higher score indicates higher level of knowledge)	No difference in knowledge between the groups (8.3 vs. 8.2, *P*=.406)
						Attitude, MMIC, 6-item survey, 0-36 point scale	No difference in attitude between the groups (33.7 vs. 33.5, *P*=0.433)
						Informed choice, MMIC, measured by a combination of good knowledge, positive attitude and uptake of screening OR good knowledge, negative attitude, and no uptake of screening	No difference in making informed choice between the groups (91.8% vs. 93%, *P*=.588)
Yee et al., 2014 [26]	USA	RCT	Pregnant women, 6-26 weeks of gestation I: n=75 C: n=75	Computer-based education tool	Standard care	Knowledge, 23-item, 18 false/true and 3 open-ended questions, scored as the % of the items answered correctly	Women using DST had more correct answers (69.4% vs. 46%. *P*<.001)
Bjorklund et al., 2012 [27]	Sweden	RCT	Pregnant women, <11 weeks of gestation I: n=236 C: n=247	25-minute film	Standard care	Knowledge, MMIC, 9-item, 0-9 point scale, scored as number of correct answers 5-9: sufficient knowledge	Women who watched the film had higher knowledge (6.9 vs. 6.4, *P*=.005
						Attitudes, MMIC, 6-item survey, 0-36 point scale	No difference in attitudes about screening between the groups (25.7 vs. 26.8, *P*=.275)
						Informed choice, MMIC, a combination of good knowledge, positive attitude and uptake of screening OR good knowledge, negative attitude, and no uptake of screening	Women who watched the film made more informed choice about screening (71.5% vs. 62.4%, *P*=.062)

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Kupperma nn et al., 2009 [21]	USA	RCT	Pregnant women, <20 weeks of gestation I: n=244 C: n=252	Computerized decision tool	Education booklet	Knowledge, 10-item (Higher score indicates higher level of knowledge)	Significant higher knowledge among women using DST (77.6% vs. 65.5%, *P*<.001)
						Satisfaction, 0-10 points scale	Women using DST had higher satisfaction (8.1 vs. 7.5, *P*>.001)
						Decisional conflict, DCS, 16 questions, 0-100 points scale	Women using DST had lower decisional conflict compared to women receiving an education booklet (19.1 vs. 20.9, *P*=.21)
Nagle et al., 2008 [23]	Australia	Cluster RCT	Pregnant women, <12 weeks of gestation I: n=218 C: n=221	24-page booklet	Standard care	Knowledge, MMIC, 8-item, 0-8 point scale >4: Good knowledge ≤4: Poor knowledge	More women receiving an education booklet had "good" level of knowledge compared to women following standard care (88% vs. 72%)
						Informed choice, MMIC, measured by a combination of good knowledge, positive attitude and uptake of screening OR good knowledge, negative attitude, and no uptake of screening	More women receiving an education booklet made an informed choice (76% vs. 65%)
						Decisional conflict, DCS, 16-item score, 0-100 point scale (Lower score indicates less decisional conflict)	No differences in level of decisional conflict. Mean score was low in both groups (1.7 vs. 1.7)
						Attitudes, MMIC, 5-25 points score	No differences in attitude towards prenatal testing between the groups (86% vs. 81% had positive attitudes)
						Anxiety, STAI, 6-item, 0-80 point scale (Higher score indicates greater anxiety level)	No differences in anxiety between the groups (36.2 vs. 37.4)
						Depression, EPDS, 0-30 point score ≥13: clinically depressed	No differences in depression between the groups (≥13: 11.6% vs. 11.2%)
Gestational diabetes and weight gain							
Guo et al., 2018 [28]	China	RCT	Pregnant women with gestational diabetes , 24-28 weeks of gestation I: n=64 C: n=60	App to record BG, provide information and notice when BG record was abnormal	Conventional outpatient treatment regimen	BG, FBG and PBG (mmol/L)	No significant improvement in BG among women using DST (*FBG*: 4.2 vs. 4.3,*P*=.602, *PBG*: 7.0 vs. 7.1, *P*=.683)
						Weight gain (kg)	Less weight gain in the group using DST (3.2kg vs. 4.8kg, *P*<.001)
Mackillop et al., 2018 [30]	UK	Single center RCT	Pregnant women diagnosed with gestational diabetes, < 35	App to record, tag, and review BG readings, and SMS (Short Message	Standard care with a paper diary to record BG	Rate of BG change (mmol/L) and HbA_{1c} rise (%)	No significant difference in rate of BG change (-0.16 vs. -0.14, *P*=.78) and HbA_{1c} rise (0.02% vs. 0.03%)

			weeks of gestation I: n=103 C: n=103	Service) with advice and encouragement		Satisfaction, OMDTSQ, 9-item, 0-54 point scale (Higher score indicates higher satisfaction)	Women from both group reported high satisfaction with the care they received (43.0 vs. 44.5, *P*=.049)
Skar et al., 2018 [32]	Norway	Descriptive	Women in the postpartum period who used the *Pregnancy*+ app during pregnancy n=17	App to record, tag, and review BG readings	No control group	Experience	Easily accessible and trustworthy information, overview of BG increased feeling of control of symptoms, conflicting feedback between the app and HCP
						Self-management	The app may have potential for assisting women in self-managing BG.
Yang et al., 2018 [33]	China	RCT	Pregnant women with gestational diabetes I: n=57 C: n=50	We-chat platform	Standard care	BG, FBG and PBG (mmol/L)	Significantly lower FBG and PBG among women using We-chat (*FBG*: 4.3 vs.5.3,*P*<.001, *PBG*: 5.8 vs. 6.9, *P*<.001)
McDonald et al., 2015 [31]	Canada	Cohort study	Pregnant women, < 20 weeks of gestation I: n=131 C: n=310	Web-based decision tool	Standard care	Knowledge of risk assessments	Women using DST discussed GWG-related topics with their health care provider more often (60.5% vs. 29.2%, *P*<.001). They also had higher knowledge about risk assessments: *Risk in gaining excess GWG to themselves*: 79% vs. 50%, *P*=.014 *Risk in gaining excess GWG to their infants:* 64% vs. 56%, *P*=.295 *Risk in gaining inadequate GWG to themselves:* 34% vs. 21%, *P*=.044 *Risk in gaining inadequate GWG to their infants:* 62% vs. 38%, *P*=.001
Hirst et al., 2014 [29]	UK	Descrip-tive study	Pregnant women with gestational diabetes, < 34 weeks of gestation	App to record BG and receive calls from doctor	Standard paper-based recording of BG	Satisfaction, OMDTSQ, 9-item -3: strongly disagree +3: strongly agree	The majority of women agreed or strongly agreed that the app was convenient and reliable
Pollak et at., 2014 [34]	USA	RCT	Overweight or obese pregnant women I: n=23 C: n=12	SMS 3 times/week with advice/ encouragements. Women received feedback based on their loggings	SMS three times/ week with general pregnancy information	Weight gain (kg)	Mean weight gain was 2.7kg less in the group receiving SMS with advice/encouragements

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Lifestyle							
Dotson et al., 2017 [35]	USA	Descrip-tive	Pregnant women n=210	App with health education	No control group	Comprehension	Apps and other electric health education methods are useful and have potential for promoting tobacco cessation efforts in clinical setting.
van der Wulp et al., 2014 [36]	Nether-lands	Cluster 3-arm RCT	Pregnant women I1: n=116 I2: n=135 C: n= 142	I1: Computer-tailored letter of feedback after usual counseling from midwife I2: Health counseling from midwife according to a given health counseling protocol	Standard care	Refrained from alcohol use, QFV-questionnaire	3 months follow up: 65% of health counseling responders (vs. standard care, *P*=.790), 70% computer-tailored responders (vs. standard care, *P*=.150), and 45.4% standard care responders (vs. computer-tailored, *P*=.230) refrained from alcohol. These results were not significant. 6 months follow up: computer-tailored feedback can be effective to stop alcohol use during pregnancy, compared to standard care (78% vs. 55%, *P*=.04). Health counseling did not have an effect compared to standard care (72% vs. 55%, *P*=.26).
Evans et al., 2012 [37]	USA	RCT and descriptiv e	Pregnant women n=123	SMS with pregnancy information and tips	Standard care	Smoking	Women who reported smoking in the last 30 days decreased from 5.8% to 1.2%
						Alcohol use	Women who reported consuming alcohol after they found out they were pregnant decreased from 3.5% to 1.1% (*P*<0.098)
Blood pressure and preeclampsia							
Ledford et al., 2017 [38]	USA	RCT	Pregnant women I: n=120 C: n=121	App with education material and recordings of BP	Spiral book with education material and BP recordings	Use of app	Women using the app recorded BP and shared the recordings with their health care providers more frequently (*P*<.001)
Parsa et al., 2019 [39]	Iran	Two groups	Pregnant women I: n=54 C: n=54	App with information and education material	Standard care	Knowledge, 32-item (Higher score indicates higher level of knowledge)	Significantly higher knowledge score among women after use of DST (78.1 vs. 15.8, *P*<.001)
Depression							
Hantsoo et al., 2018 [41]	USA	RCT	Pregnant women with depressive symptoms, <32 weeks of gestation I: n=48 C: n=24	Mood tracking and alert (MTA) mobile app + patient "portal" app	Patient portal app	Patient engagement and care satisfaction, 6-item, Likert-scale from "very poor" to "excellent" OR "Completely agree" to completely disagree"	41% of women in the MTA groups received a phone call from their providers, and had a higher rate of referral to a mental health specialist (*P*=.03). Their providers were also more likely to mention mental health (*P*=.02). No difference in confidence of managing their own health between the groups (6.1 vs. 6.1, *P*=.87)

Use of Decision Support Tools to Empower Pregnant Women: Systematic Review
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Asthma							
Zairina et al., 2016 [42]	Australia	Pro-spective multi-center single-blinded RCT	Pregnant women with asthma and < 20 weeks of gestation I: n=36 C: n=36	COPD-6 to measure lung function. App to record asthma symptoms and give automated feedback message	Standard care	Change of symptoms after 3 and 6 months ACQ, 7-item, 0-6 point scale 0: totally controlled 6: severe uncontrolled	Women using DST did not have better control of symptoms 3 months after baseline (-0.01 vs. 0.16, *P*=.260), however they did have better control of symptoms 6 months after baseline (-0.30 vs. 0.06, *P*=.020)
						Change in lung function after 3 and 6 months, measured by FEV_1/FEV_6	No difference between the groups after 3 and 6 months (*3 months*: 3.43 vs. 0.14, *P*=.05, *6 months*: 1.53 vs. -0.56, *P*=.16)
						Change in quality of life after 3 and 6 months, mAQLQ, 15-item, 0-7 point scale (Higher score indicates better quality of life)	No difference between the groups after 3 months (0.09 vs. -0-17, *P*=.15). The intervention group had a higher change in QOL after 6 months (0.51 vs. -0.22, *P*=.002)
Psychological well-being							
Jareethum et al., 2008 [43]	Thailand	RCT	Pregnant women < 28 weeks of gestation I: n=32 C: n=20	SMS 2 times/week and a phone call at gestational week 32	Standard care	Satisfaction, questionnaire, 1-10 points scale (Higher score indicates higher satisfaction)	Women receiving SMS had a higher satisfaction score than women following standard care (9.3 vs. 8, *P*<.001)
						Confidence, questionnaire, 1-10 points scale (Higher score indicates more confidence)	The group receiving SMS 2 times a week was significant more confidence (8.9 vs. 7.8, *P*=.001)
						Anxiety, questionnaire, 1-10 points scale (Higher score indicates greater anxiety)	Women receiving SMS had lower anxiety score than women who did not receive SMS (2.8 vs. 4.9, *P*=.002)

RCT=randomized controlled trial, **I**=intervention group, **C**=control group, **vs.**=versus, **DST**=decision support tool, **App**=mobile application, **p**=p-value, **DCS**=decision conflict scale, **PSK**=prenatal screening knowledge, **DRS**=decision regret scale, **STAI**=Speilberger State Trait Anxiety Inventory, **MMIC**=multidimensional measure of informed choice, **MSSKQ**=Maternal Serum Screening Knowledge Questionnaire, **EPDS**=Edinburgh Postnatal Depression Scale, **GWG**=gestational weight gain, **BG**=blood glucose, **FBG**=Fasting blood glucose, **PBG**=2-hour postprandial blood glucose, **OMDTSQ**=Oxford Maternity Diabetes Treatment Satisfaction Questionnaire, **SMS=**Short Message Service, **HCP**=Health care personnel, **HEI**=Healthy Eating Index, **QFV**=Dutch Quantity-Frequency-Variability, **BP**=blood pressure, **PP**=patient portal, **CORD**=chronic obstructive pulmonary disease measurement device, **FEV1/FEV6**=Forced expiratory volume in 1/6 s, **ACQ-7**=7-item Asthma Control Questionnaire, **mAQLQ**=Juniper`s mini-Asthma Quality-of-life Questionnaire score

**All main results is presented as mean scores.*

STUDY II

Impact of a Mobile Application for Tracking Nausea and Vomiting During Pregnancy (NVP) on NVP Symptoms, Quality of Life, and Decisional Conflict Regarding NVP Treatments: MinSafeStart Randomized Controlled Trial

Elin Ngo, Maria Bich-Thuy Truong, David Wright, Hedvig Nordeng
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II

Original Paper

Impact of a Mobile Application for Tracking Nausea and Vomiting During Pregnancy (NVP) on NVP Symptoms, Quality of Life, and Decisional Conflict Regarding NVP Treatments: MinSafeStart Randomized Controlled Trial

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Related Article:
This is a corrected version. See correction statement in: https://mhealth.jmir.org/2022/9/e41927

Abstract

Background: Pregnant women are active users of mobile apps for health purposes. These apps may improve self-management of health-related conditions. Up to 70% of pregnant women experience nausea and vomiting (NVP). Even mild NVP can significantly reduce quality of life (QoL), and it can become an economic burden for both the woman and society. NVP often occurs before the first maternal care visit; therefore, apps can potentially play an important role in empowering pregnant women to recognize, manage, and seek appropriate treatment for NVP, when required.

Objective: This study investigated whether the MinSafeStart (MSS) mobile app could impact NVP-related symptoms, QoL, and decisional conflict regarding NVP treatment.

Methods: This randomized controlled trial enrolled 268 pregnant women with NVP in Norway from 2019 to 2020. The intervention group had access to the MSS app, which could be used to track NVP symptoms and access tailored advice. NVP severity was rated with the Pregnancy Unique Quantification of Emesis (PUQE) score. The control group followed standard maternal care. We collected data on maternal baseline characteristics, NVP severity, QoL, and decisional conflict using 2 sets of online questionnaires. One set of questionnaires was completed at enrollment, and the other was completed after 2 weeks. We performed linear regression analyses to explore whether the use of the MSS app was associated with NVP severity, QoL, or decisional conflict.

Results: Among the 268 women enrolled in the study, 192 (86.5%) completed the baseline questionnaires and were randomized to either the intervention (n=89) or control group (n=103). In the intervention group, 88 women downloaded the app, and 468 logs were recorded. In both groups, women were enrolled at a median of 8 gestational weeks. At baseline, the average PUQE scores were 4.9 and 4.7; the average QoL scores were 146 and 149; and the average DCS scores were 40 and 43 in the intervention and control groups, respectively. The app had no impact on NVP severity (aβ 0.6, 95% Cl −0.1 to 1.2), QoL (aβ −5.3, 95% Cl −12.5 to 1.9), or decisional conflict regarding NVP treatment (aβ −1.1, 95% Cl −6.2 to 4.2), compared with standard care.

Conclusions: Tracking NVP symptoms with the MSS app was not associated with improvements in NVP symptoms, QoL, or decisional conflict after 2 weeks, compared with standard care. Future studies should include a process evaluation to improve our understanding of how pregnant women use the app and how to optimize its utility within maternity care. Specifically, studies

should focus on how digital tools might facilitate counseling and communication between pregnant women and health care providers regarding NVP management during pregnancy.

Trial Registration: ClinicalTrails.gov (NCT04719286): https://www.clinicaltrials.gov/ct2/show/NCT04719286

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KEYWORDS

eHealth; mHealth; decision support tool; nausea and vomiting; pregnancy; RCT

Introduction

Background

Pregnant women and women of reproductive age are active users of mobile apps for health purposes [1]. Available apps are designed for promoting self-management of chronic diseases, such as migraine and diabetes; tracking gestational weeks, weight, and belly measurements during pregnancy; and keeping track of pregnancy development in general [1,2]. These apps are often used to supplement routine care, because women tend to search for health-related information early in pregnancy, before and after health consultations, and when making decisions [1,3-5]. Often, the primary motivation for using apps is the need for easily accessible health information [6]. Our recent systematic review on decision support tools in pregnancy revealed that few studies had investigated the effect of digital tools on the course of pregnancy and pregnancy-related ailments. However, available studies have shown that apps could have a positive impact on the knowledge level of pregnant women, when integrated as part of patient care. Pregnant women also seemed to appreciate and were satisfied with digital tools [7].

Nausea and vomiting in pregnancy (NVP) is one of the most common pregnancy-related conditions. NVP affects up to 70% of pregnant women worldwide [8,9]. NVP symptoms often occur during the first few weeks of pregnancy, on average, at around gestational week 4 [10]. The etiology of NVP is not clearly understood, but it is thought to be multifactorial and complex [10]. The severity of NVP can range from mildly uncomfortable to hyperemesis gravidarum (HG), which is the most severe form of NVP. HG affects 1%-3% of all pregnant women, and it is the most common reason for hospitalization in early pregnancy [8]. Although HG is a relatively rare condition, it is essential to recognize the burden of NVP in general. Previous studies have shown that even mild NVP symptoms significantly reduce quality of life (QoL) of pregnant women and their willingness to become pregnant again [11,12]. Moreover, as the severity of NVP increases, the costs for society increase due to increased hospital and emergency room admissions, health care visits, prescribed medications, and income loss for both the woman and her partner [13].

NVP treatment guidelines recommend early recognition and treatment to prevent or reduce more severe symptoms. The first-line management of mild symptoms consists of nonpharmacologic measures, including lifestyle and dietary changes (Multimedia Appendix 1). Pharmacological treatment is indicated when NVP symptoms are moderate to severe or when symptoms significantly impact the women's daily activities [14,15]. The first NVP symptoms typically occur early in pregnancy and, often, before the first maternal care visit. Therefore, it is important to empower pregnant women to ensure that they can optimally manage NVP symptoms [15,16].

Digitalization, eHealth initiatives, and the wide use of the internet have opened up new possibilities for using digital tools in maternal care [17]. Mobile apps can enable pregnant women to take a more active role in self-care and disease management during pregnancy. Moreover, these apps can provide large amounts of patient-generated data during pregnancy for research purposes [17,18]. The Pregnancy Unique Quantification of Emesis (PUQE) score is an internationally validated tool for categorizing the severity of NVP based on 3 questions regarding vomiting, nausea, and retching symptoms [19,20]. In the latest (2009) version of the PUQE score, women are asked to rate the severity of symptoms that occurred in the last 24 hours [19]. A translated and validated Norwegian version of the PUQE score became available in 2015 [21]. Incorporating the PUQE score into an app could potentially empower women by improving their management of NVP. The app could allow women to track symptoms over time and record responses to interventions. Because 99%-100% of women of reproductive age use smartphones [22] and most women use health-related apps [23,24], digital tools should be particularly suitable for maternal care.

A recent review pointed out that, although there is a growing number of apps available for monitoring and managing health-related issues, the majority are never tested nor clinically validated [25]. That finding implied that it remains largely unknown whether available apps are beneficial or whether they even have an effect on clinical outcomes. A prior study showed that integrating apps into professional clinical services could potentially improve the effectiveness of health care [26]. Our previous review concluded that the innovative use of eHealth initiatives and digitalization could potentially empower pregnant patients and improve maternal care [7]. However, at the same time, a more scientific approach is needed for testing and evaluating these apps and other digital tools. Indeed, health care providers should encourage patients to use only tools that are beneficial and effective as a supplement to routine maternity care.

Objective

The primary aim of this study was to investigate whether the MinSafeStart (MSS) mobile app could impact NVP severity in pregnant women. The secondary aims were to assess whether the MSS app could affect the QoL of pregnant women and improve their ability to make decisions regarding NVP treatment.

Specifically, the primary research question was: Will women who use the MSS app for 2 weeks have different NVP symptoms, based on PUQE scores, compared with women who follow standard maternal care without the MSS app?

The specific secondary research questions were: (1) Will women who use the MSS app for 2 weeks have different QoL, based on Health-related Quality of Life for Nausea and Vomiting during Pregnancy (NVPQOL) scores, compared with women who follow standard maternal care without the MSS app? (2) Will women who use the MSS app for 2 weeks have different decisional conflict scale (DCS) scores regarding NVP treatment, compared with women who follow standard maternal care without the MSS app? (3) Will the use of the MSS app modify the association between the PUQE score and the NVPQOL score (ie, is the MSS app an effect modifier)?

Methods

Study Design, Study Population, Recruitment, and Sample Size

The MinSafeStart study was a randomized controlled trial. We recruited pregnant women in Norway between September 2019 and June 2020. All pregnant women over 18 years old who were currently experiencing NVP, owned a smartphone (iOS or Android), and could speak and understand Norwegian were eligible for inclusion.

Participants were primarily recruited through social media advertisements. Invitations to participate in the study were available on the study Facebook page, the Norwegian Hyperemesis Gravidarum Patient Organization's Facebook page, and other pregnancy-related web pages or forums, such as "altformamma.no" (all for mommy) and "tryggmammamedisin.no" (safe mother medications). Invitations were additionally accessible through the Helseoversikt app. Helseoversikt is a digital platform used by health care centers all over Norway that provides relevant health information to pregnant women and parents.

All invitations to participate contained a link to the online consent form. When the women signed the consent form and responded to the baseline questionnaire, they were automatically randomized to either the intervention or control group. Both groups received emails with information about the study group to which they were assigned. The intervention group also received an email with instructions on how to download and use the app.

Results from the power analysis suggested that we would need a total of 250 pregnant women (n=125 in each group, 2-tailed hypothesis) to detect a mean difference of 3 points in the PUQE score between the groups, with a power of 80% (Cohen d=0.5). This total sample size included a 25% dropout rate.

Randomization

An automated software program was specifically developed for the project. The software automatically managed participant enrollment, randomization to study groups, and email distributions of electronic information and online questionnaires to the study participants. This software was developed for the project by the University Center for Information Technology (USIT) at the University of Oslo.

Development of the MinSafeStart Mobile Application

The MSS app was a patient-centered app for women with NVP. Our research group developed the MSS app in collaboration with interaction designers, programmers, and researchers from USIT. The app utilized the daily PUQE score (Multimedia Appendix 2) to categorize NVP severity (ie, mild, moderate, or severe), and it displayed the fluctuations over time in a graph (Figures 1 and 2). The aim of the app was to assist pregnant women in identifying and managing NVP. The app tracked their NVP symptoms every day and provided tailored advice according to the severity of their symptoms. All women with NVP symptoms received lifestyle and dietary advice (eg, stay hydrated, eat small meals frequently, and get some rest). Women that experienced severe NVP also received information about medical treatments. The app alerted the woman to seek appropriate treatment when she logged PUQE scores >13 for more than 3 consecutive days. The app was user tested in July 2018. The user test included 9 women who completed a structured interview with a set of tasks and questions regarding the app. Of these 9 women, 5 also participated in a focus group to discuss and share their experiences and opinions about the app. The user test results showed that the app was user-friendly and had the potential to empower women who experienced NVP to improve their management skills and treatment decisions. Nevertheless, some minor issues were mentioned in the user test and focus group that could be improved (ie, explanations of terminologies, an opportunity to change the due date, links to external information, an overview of previously logged scores, and the layout and design). These suggestions were incorporated into the app to make it as user-friendly as possible before it was launched for iOS and Android smartphones.

Figure 1. Front page of the MinSafeStart application (in Norwegian) for pregnant women to track nausea and vomiting, showing the user's gestational week at the top, text in the center (“How do you feel? Use the button below to log your NVP symptoms”), and button to log nausea and vomiting in pregnancy (NVP) symptoms.

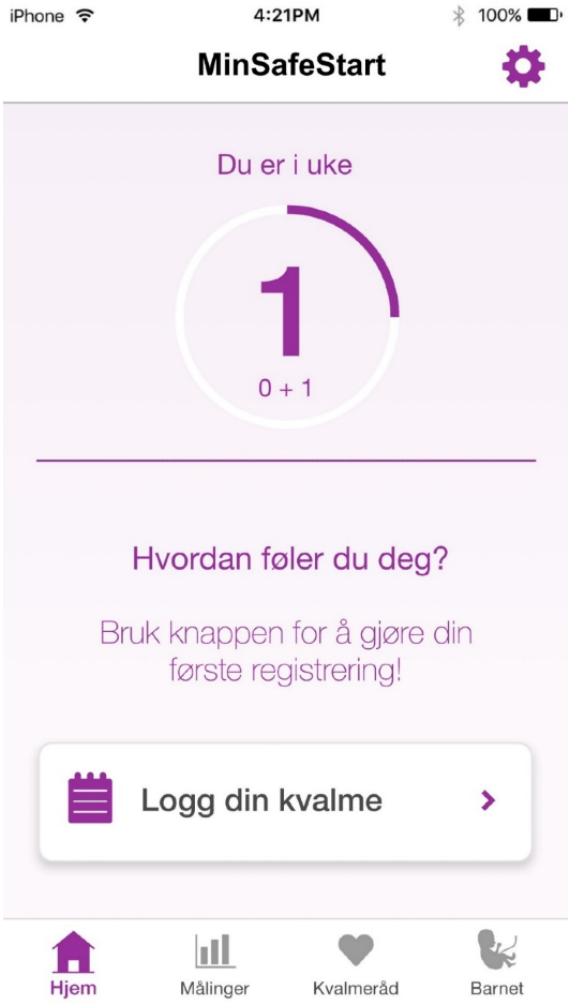
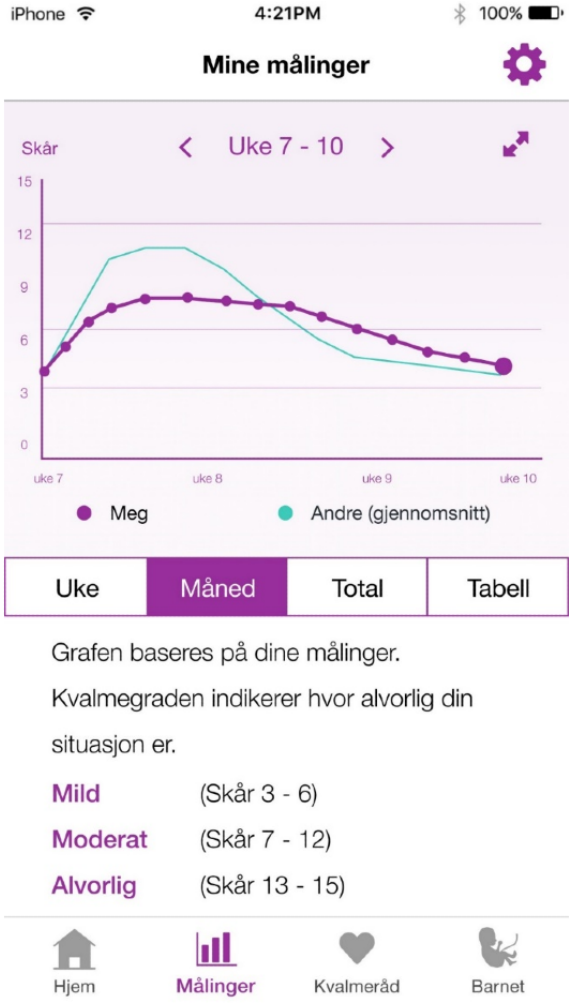


Figure 2. The MinSafeStart app (in Norwegian) for pregnant women with nausea and vomiting (NVP) shows the women's NVP loggings (Mine Malinger) as the user's NVP scores (purple) as a graph over time (week [Uke], month [Måned], for all data recorded in the app [Total]), compared with the mean Pregnancy Unique Quantification of Emesis (PUQE) score of other pregnant women (blue line), or as a table (Tabell). The bottom section shows the numeric rating scale for NVP symptoms. Alvorlig: severe; Moderat: moderate; Skår: Score.



Data Collection

In this MinSafeStart study, we collected data from the MSS app and from 4 sets of questionnaires (Q1-Q4) that were completed electronically. Q1 was administered to participants at enrollment (baseline), and Q2 was administered 2 weeks later. Q3 and Q4 were additional follow-up questionnaires administered at 4 weeks and 6 weeks after baseline, respectively. All questionnaires were sent to participants by email with the automated software developed for the study. This study only analyzed data from the Q1 and Q2 sets of questionnaires. We selected a 2-week follow-up for this study because we considered that 2 weeks were sufficient to become familiar with the app.

All data collected from the app and questionnaires were automatically encrypted and stored at the Service for Sensitive Data at the University of Oslo (TSD). The TSD platform is available to collect, store, and analyze sensitive data [27]. The platform is protected by a 2-step password system and meets all the necessary requirements to maintain compliance with Norwegian regulations regarding individual privacy. The data are not accessible outside of the TSD. Only registered researchers within the project had access to the data and the encryption key.

The study is reported in accordance with the CONSORT-EHEALTH checklist (Multimedia Appendix 3).

Intervention Group

All women in the intervention group were given access to the MSS app in addition to standard maternal care. They were free to log their NVP symptoms into the app whenever convenient. Standard maternity care in Norway is free of charge. It includes 9 routine checkups with a midwife or physician and 1 ultrasound scan at gestational week 18 [28].

The app recommended logging symptoms every 24 hours because the PUQE score was calculated based on NVP symptoms over the past 24 hours. Users could also compare their symptoms to the expected population average NVP score. Thus, women received individual treatment advice based on their PUQE scores (Multimedia Appendix 1). Women also received general dietary and lifestyle advice (eg, get some rest, stay hydrated, eat small meals frequently, and avoid fatty and spicy foods [29]) independent of their PUQE score. Women with moderate or severe symptoms received additional advice about antiemetic medications. When a woman scored ≥13 points

(ie, severe NVP) for more than 3 consecutive days, she would see a pop-up message that encouraged her to see the doctor.

Control Group

The control group received only standard maternal care.

Outcome Measures

NVP Severity

The PUQE score was internationally validated for rating the severity of NVP symptoms over the past 24 hours (Multimedia Appendix 2) [19,21]. The scale consists of 3 questions. Each question is rated from 1 to 5. The total score ranges from 3 to 15 points, where ≤6 points indicate mild NVP, 7-12 points indicate moderate NVP, and 13 or more points indicate severe NVP. This study utilized the translated and validated Norwegian version of the PUQE [21]. We evaluated the change in PUQE scores from Q1 to Q2 (ie, after 2 weeks).

Quality of Life

The NVPQOL was used to rate QoL [30] over the past week (Multimedia Appendix 2). The score includes 30 items covering 4 general domains: physical symptoms and aggravating factors, fatigue, emotions, and limitations. Each item is rated on a Likert scale that ranges from 1 (never) to 7 (all the time). The total score ranges from 30 to 210 points, and lower scores indicate a better QoL. The NVPQOL score is significantly associated with the SF-12 health-related QoL questionnaire [30]. We evaluated the change in NVPQOL scores from Q1 to Q2.

Decisional Conflict

Decisional conflict was measured with the decisional conflict scale (DCS). The DCS measures the individual's perception of uncertainty in choosing options, modifiable factors that contributed to uncertainty, and decision-making effectiveness [31,32] (Multimedia Appendix 2). The DCS has been widely used in previous studies among pregnant women to evaluate their decision-making abilities regarding the use of antidepressants and the choice between vaginal birth or cesarean section [33,34]. The DCS consists of 16 items and 5 response categories (strongly agree, agree, neither agree nor disagree, disagree, and strongly disagree). The total score ranges from 0 to 100 points. Scores below 25 points indicate low decisional conflict, scores of 25 to 37.5 points indicate moderate decisional conflict, and scores above 37.5 points indicate high decisional conflict. We evaluated the change in DCS scores from Q1 to Q2.

Statistical Analyses

Descriptive Analysis

Categorical variables (ie, relationship status, education level, work situation, parity, and prior NVP symptoms) are presented as percentages for each group (intervention and control groups). Continuous variables are presented as the median and range (eg, gestational week) or the mean and SD (eg, maternal age). We performed a Pearson Chi-squared test to compare categorical variables, except when the expected cell count was less than 5; in those cases, we performed a Fisher exact test. We performed a Student *t* test to compare continuous variables. All analyses were performed with Stata/MP v.16.1. *P* values <.05 were considered statistically significant.

Primary and Secondary Analyses

We performed univariate and multivariable linear regression analyses to estimate associations between the use of the MSS app and (1) NVP severity, (2) QoL, and (3) decisional conflict. All results are presented as the crude and adjusted beta-coefficients (β) with 95% CIs. We adjusted the multivariable linear regression model with predefined covariates (ie, baseline PUQE score, baseline NVPQOL score, and baseline DCS) [35].

Subanalyses

We performed a prespecified stratified analysis to assess whether employment in the health sector modified the association between the use of the MSS app and the PUQE score. We reasoned that women employed in the health sector might have better access to information and advice regarding NVP management, and thus, they may have less need for an app to track their NVP symptoms, compared with women employed in other settings. Alternatively, they may have received more support or information from co-workers in the field that allowed them to capitalize on the information provided by the app, compared with women employed in other settings.

Ethical Approval

This study was approved by the Regional Committees for Medical and Health Research Ethics in Norway (Ref: 2018/2298). Informed consent to participate in the study was obtained from all participants.

Results

Study Population

Overall, 268 women consented to participate in the study (Figure 3). Of these, 192 (86.5%) responded to the baseline questionnaires (Q1) and were randomized to either the intervention group (n=89) or the control group (n=103). In total, 137 women responded to the follow-up questionnaires 2 weeks later (Q2). The dropout rates were 34% (30/89) for the intervention group and 24.3% (25/103) for the control group. The main reason for dropout was "lack of response."

At enrollment, the median stage of pregnancy was the same in both groups: 8 (range 4-36) gestational weeks in the intervention group and 8 (range 4-39) gestational weeks in the control group. These groups had the same mean age at enrollment: 32 (SD 4.6) years and 32 (SD 3.9) years, respectively. Most women had been pregnant previously (65/89, 73%, and 76/103, 73.8%, respectively). In both groups, 80% (52/89 and 61/103, respectively) had experienced NVP in at least one previous pregnancy. None of the women reported severe NVP (ie, PUQE score ≥13) at baseline. A comparison of baseline characteristics using the Student *t* test, Chi-squared test, or Fisher exact test indicated no statistical difference (all *P*<.05) between the 2 study groups (Table 1).

Figure 3. Flowchart of the study participants in the enrolled group, allocation groups, and follow-up groups. app: MinSafeStart mobile app; PUQE: Pregnancy Unique Quantification of Emesis; Q1: Questionnaire 1.

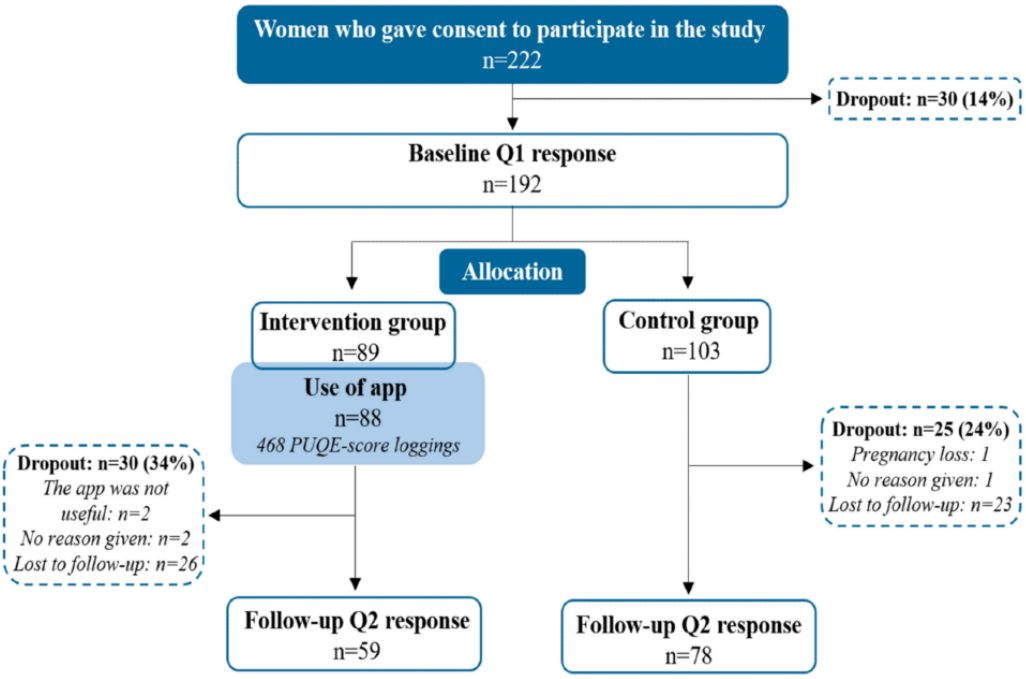


Table 1. Baseline characteristics of the study population (n=192), stratified by whether they used the MinSafeStart (MSS) app (intervention) or received standard maternity care (control).

Characteristics	Intervention group (n=89)	Control group (n=103)
Gestational week at enrollment, median (range)	8 (4-36)	8 (4-39)
Age (years), mean (SD)	32 (4.6)	32 (3.9)
Relationship status, n (%)		
Married/cohabitation	85 (95.5)	100 (97.1)
Other[a]	4 (4.5)	3 (2.9)
Higher education, n (%)		
Yes	69 (77.5)	85 (82.5)
No	20 (22.5)	18 (17.5)
Working situation, n (%)		
Employed	55 (61.8)	60 (58.2)
Employed in the health sector	19 (21.4)	31 (30.1)
Other[b]	15 (16.8)	12 (11.7)
Primigravida, n (%)		
Yes	24 (27.0)	27 (26.2)
No	65 (73.0)	76 (73.8)
NVP[c] during previous pregnancy/pregnancies, n (%)		
Yes	52 (80.0)	61 (80.3)
No	13 (20.0)	15 (19.7)

[a]Includes single/unmarried and divorced/separated women.

[b]Includes students and unemployed women.

[c]NVP: nausea and vomiting during pregnancy.

The Intervention

Of the 89 women randomized to the intervention group, 88 downloaded the MSS app. These women performed a total of 468 logs. Because they were not satisfied with the app, 2 women dropped out of the study. They reported no benefit in using the MSS app.

Impact on NVP Severity

The groups showed no differences in the change in PUQE scores between Q1 and Q2 (adjusted β 0.6, 95% Cl −0.1 to 1.2). Among women employed in the health sector, those who used the MSS app had a significantly higher PUQE score (adjusted β 2.1, 95% Cl 0.9 to 3.2) after 2 weeks than those who did not use the app. However, among women employed in other sectors, the PUQE scores were not significantly different between the intervention and control groups (Table 2).

Table 2. Associations between the use of the MinSafeStart (MSS) app and the Pregnancy Unique Quantification of Emesis (PUQE) score.

Analysis	Baseline (Q1) PUQE score[a], mean (SD)	Follow-up (Q2) PUQE score, mean (SD)	Change in PUQE score (Q2-Q1)		
			Mean change (SD)	Crude difference in mean changes, β (95% CI)	Adjusted difference in mean changes[b], β (95% CI)
Primary analysis					
Intervention group (n=88)	4.9 (2.0)	5.6 (1.8)[c]	0.8 (2.0)	0.4 (−0.3 to 1.2)	0.6 (−0.1 to 1.2)
Control group (n=103)	4.7 (1.9)	4.9 (1.8)[d]	0.4 (2.3)	Reference	Reference
Subanalyses by employment: women employed in the health sector					
Intervention group (n=19)	4.6 (1.9)	6.6 (1.7)[e]	1.8 (2.5)	2.1 (0.3 to 3.9)	2.1 (0.9 to 3.2)
Control group (n=31)	4.5 (1.9)	4.6 (1.6)[f]	−0.3 (2.7)	Reference	Reference
Subanalyses by employment: women employed in other sectors					
Intervention group (n=55)	4.9 (2.1)	5.2 (1.7)[g]	0.4 (1.7)	−0.1 (−0.8 to 0.7)	0.0 (−0.7 to 0.7)
Control group (n=60)	4.7 (1.9)	5.1 (1.8)[h]	0.5 (1.9)	Reference	Reference

[a]This score ranges from 3 to 15 points, and symptoms are rated as follows: mild: ≤6 points; moderate: 7-12 points; severe ≥13 points.

[b]Adjusted for the baseline PUQE score.

[c]n=59.

[d]n=78.

[e]n=14.

[f]n=23.

[g]n=38.

[h]n=45.

Impact on Quality of Life

The adjusted primary analysis showed that the changes in NVPQOL scores from baseline to Q2 were not significantly different between the intervention and control groups (adjusted β −5.3, 95% Cl −12.5 to 1.9; Table 3).

Table 3. Association between the use of the MinSafeStart (MSS) app and quality of life.

Group	Baseline (Q1) NVPQOL[a,b] score, mean (SD)	Follow-up (Q2) NVPQOL score, mean (SD)	Change in NVPQOL score (Q2-Q1)		
			Mean change (SD)	Crude difference in mean changes, β (95% CI)	Adjusted difference in mean changes[c], β (95% CI)
Intervention group (n=88)	145.7 (34.0)	143.8 (29.7)[d]	−4.5 (22.4)	−4.2 (−11.9 to 3.5)	−5.3 (−12.5 to 1.9)
Control group (n=103)	148.5 (28.8)	151.6 (28.9)[e]	−0.3 (22.9)	Reference	Reference

[a]NVPQOL: Health-Related Quality of Life for Nausea and Vomiting during Pregnancy scale.

[b]This score ranges from 30 to 210 points, and lower scores indicate better quality of life.

[c]Adjusted for the baseline NVPQOL score.

[d]n=59.

[e]n=78.

Impact on Decisional Conflict Scale Score

The mean changes in the DCS between Q1 and Q2 were −5.9 (SD 16.4) for the intervention group and −5.3 (SD 15.5) for the control group (Table 4). The changes in DCS were not significantly different between the women in the intervention group and the women in the control group (adjusted β −1.1, 95% Cl −6.2 to 4.2).

Table 4. Association between the use of the MinSafeStart (MSS) app and the decisional conflict scale (DCS).

Group	Baseline (Q1) DCS, mean (SD)		Follow-up (Q2) DCS, mean (SD)	Change in DCS[a] (Q2-Q1)		
				Mean change (SD)	Crude difference in mean changes, β (95% CI)	Adjusted difference in mean changes[b], β (95% CI)
Intervention group (n=88)	88	40.3 (17.9)	36.2 (21.6)[c]	−5.9 (16.4)	−0.7 (−6.1 to 4.7)	−1.1 (−6.2 to 4.2)
Control group (n=103)	103	42.5 (20.9)	38.1 (20.3)[d]	−5.3 (15.5)	Reference	Reference

[a]This score ranges from 0 points (no decisional conflict) to 100 points (extremely high decisional conflict).

[b]Adjusted for the baseline decisional conflict score.

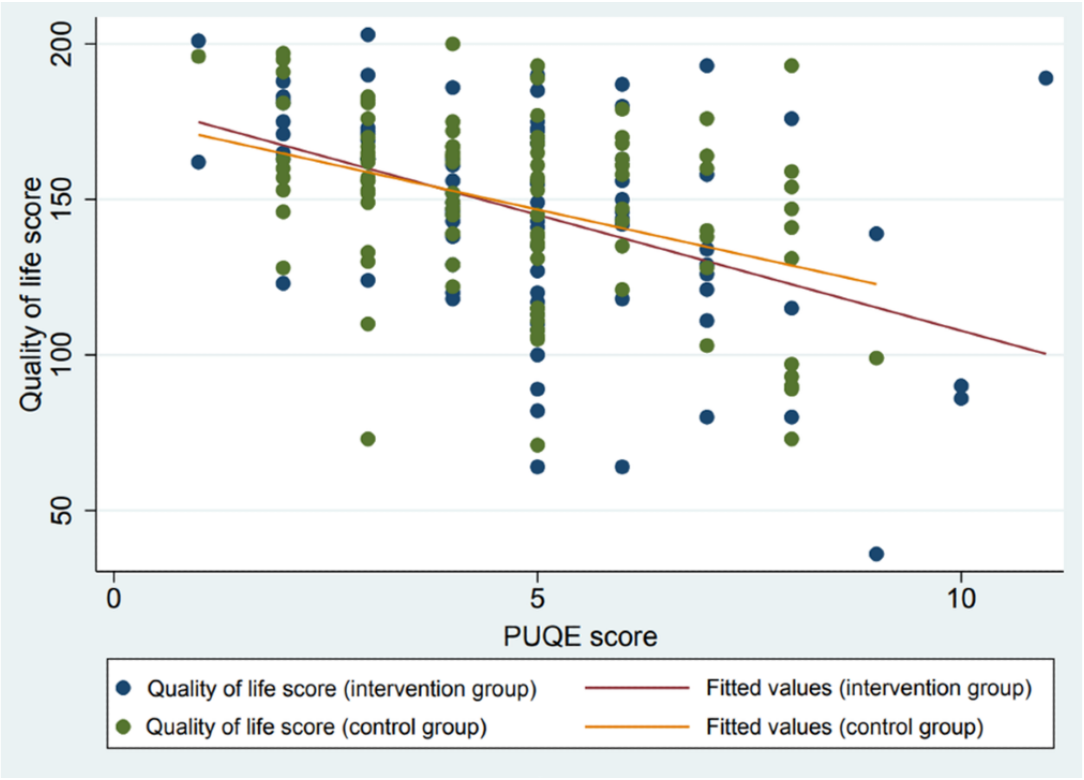
[c]n=59.

[d]n=78.

Association Between NVP Severity and Quality of Life

Women with more severe NVP (higher PUQE scores) had lower NVPQOL scores than women with less severe NVP (lower PUQE scores; Figure 4).

Figure 4. Association between the Health-Related Quality of Life for Nausea and Vomiting during Pregnancy score (NVPQOL) score and the Pregnancy Unique Quantification of Emesis (PUQE) score. MSS app: MinSafeStart mobile application.



Discussion

Main Findings

The MinSafeStart trial was the first to investigate the effectiveness of a patient-centered mobile app that was designed to empower pregnant women to optimally manage their NVP symptoms. We found no significant associations between the use of the MSS app and the severity of NVP symptoms, QoL, or decisional conflict, compared with standard maternal care. These results should be interpreted with caution because the study was slightly underpowered, due to a higher dropout rate than expected.

Earlier studies have shown that the majority of the pregnant population owns a smartphone and over 50% use apps related to pregnancy [36]. Studies that have investigated the use of health-related apps have shown that the apps could improve the knowledge levels of pregnant women and the apps were perceived as tools during pregnancy [7,24]. Except for user satisfaction, our results were not consistent with those from previous studies. We found no associations between the use of the MSS app and NVP symptoms at 2 weeks after baseline. This may be explained by several factors related to our study population and study design. First, we included women at any gestational stage in pregnancy. In fact, 15% of the women included were beyond the first trimester, which is the most relevant time window for NVP. On average, NVP occurs during gestational week 4 [10] and peaks during gestational weeks 10-16 [37,38]. However, our intervention group had completed a median of 8 gestational weeks at enrollment, with a range of 4-36 weeks. Therefore, in many cases, it may have been too late for women to benefit from the app. Moreover, we included women with mild NVP, and this group may not derive the most benefit from the app. Second, a 2-week follow-up may not have been optimal for evaluating the effect of the intervention. The rationale for choosing a 2-week follow-up was based on earlier studies that showed that PUQE scores decreased by 4.7 points when treated within 1 week [39]. We could not exclude the possibility that natural fluctuations in NVP severity could have affected the results or that a shorter follow-up time before the app assessment might have been a better choice. In fact, there might not be a particular time that is optimal for measuring the effects of the app. Indeed, NVP severity varies from morning to evening and from day to day. Therefore, selecting a specific time point for follow-up and reporting the PUQE score in Q2 may not have fully captured the changes in NVP severity over time. Future studies should consider these elements when designing a trial to evaluate the effect of using a digital tool during pregnancy.

Another factor that may have affected the results was that the study included a high proportion of parous women with a prior NVP history. Moreover, most were in a relationship with a partner, which may have provided emotional support. Therefore, these women may have already been informed about optimal NVP management and treatment, and consequently, they may not have felt they needed more information from an NVP tool. Many earlier studies have shown that women with a higher sociodemographic status and women who are pregnant for the first time are more likely to search for information online [40-42]. In their first pregnancy, women often search for information about concerns and symptoms related to the first period of pregnancy [6,40,43-45]. Therefore, our study may not have targeted the appropriate subgroup of pregnant women.

Strengths and Limitations

The main strength of this study was that very few studies have been conducted to assess the effectiveness of mobile apps for disease management among pregnant women. This study provided new insights in this regard. An important strength of this study was the use of the randomized controlled trial study design, which is considered the gold standard in evidence-based medicine [46]. Another strength of this study included our use of the internet for recruitment and electronic data collection. The main benefit of social media recruiting is that it is convenient for sampling. Indeed, pregnant women in their first trimester are not given any routine care, and there is no ideal place to reach out to this group, outside of social media. This approach facilitated the participation of pregnant women all over Norway, which may have increased the representativeness of the study sample and, thus, the generalizability of the results. In addition, the NVPQOL may have provided an advantage over other QoL scales because the NVPQOL is more specific [40].

The major limitation of this study was that we did not reach our targeted number of participants, which was 250 women, including a 25% dropout rate. Furthermore, as in all studies based on voluntary patient recruitment, there might have been a self-selection bias, where more motivated and resourceful women are included in the study compared with the general population. Participants who were parous women with higher sociodemographic status than the general birthing population in Norway might also have contributed to a selection bias. Because these women might have been more informed about optimal NVP management, they might have had less use for the app. We could not exclude the possibility that this selection bias might explain why we did not find any significant beneficial effect of the app on NVP severity in this study.

Last, 15% of the women in the intervention group were beyond the first trimester when the app was introduced. It may have been too late for many of these women to take advantage of the app because NVP often occurs in week 4 [10] and it peaks around weeks 10-16 [37,38].

Future Research

Digitalization and eHealth have provided opportunities to develop innovative apps that support pregnant women. These mobile applications must be tested in clinical studies to establish evidence for health efficacy before they can be included in the health care system or recommended by health care personnel [47]. Our review from 2020, consistent with previous studies [48], demonstrated that decision support tools could potentially provide benefit to pregnant women. However, the tools were mainly useful when relevant information was assembled into one digital tool and when the woman could share her recordings with her health care provider [7]. Based on the results of this study, future research should focus on how to design trials to determine the effect of digital tools on the pregnancy outcomes that are most important to pregnant patients. Future studies should also investigate whether digital tools and apps might be more effective when developed as part of a more extensive health intervention. Specific focus should be placed on how digital tools might facilitate counseling and communication between pregnant women and health care providers regarding NVP management in pregnancy.

Conclusion

This study showed that tracking NVP symptoms with a mobile application was not associated with reduced NVP symptoms, less decisional conflict, or improved QoL after 2 weeks of use. These findings may have been influenced by study design–related factors, such as the gestational week of enrollment, women's parity, time to follow-up, and sample size. Future studies should include a process evaluation to improve our understanding of how pregnant women use the app and how to optimize its utility within maternity care.

Acknowledgments

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Authors' Contributions

EN, MBTT, and HN designed the study. EN conducted the main analysis. EN drafted the first version of the manuscript. EN, MBTT, DW, and HN contributed to the interpretation of the results and the critical appraisal of the manuscript. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Management of nausea and vomiting in pregnancy (NVP), according to treatment guidelines. PUQE= Pregnancy Unique Quantification of Emesis score; this score ranges from 3 to 15 points.
[DOCX File , 104 KB-Multimedia Appendix 1]

Multimedia Appendix 2

The questions in the PUQE score, NVPQOL scale, and the decisional conflict scale. PUQE= Pregnancy Unique Quantification of Emesis; NVPQOL=.
[DOCX File , 16 KB-Multimedia Appendix 2]

Multimedia Appendix 3

CONSORT-eHEALTH checklist (V 1.6.1)
[PDF File (Adobe PDF File), 1164 KB-Multimedia Appendix 3]

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Abbreviations

DCS: decisional conflict scale
HG: hyperemesis gravidarum
MSS: MinSafeStart
NVP: nausea and vomiting in pregnancy
NVPQOL: Health-Related Quality of Life for Nausea and Vomiting during Pregnancy scale
PUQE: Pregnancy Unique Quantification of Emesis
Q1: Questionnaire 1
Q2: Questionnaire 2
Q3: Questionnaire 3
Q4: Questionnaire 4
QoL: quality of life
TSD: Service for Sensitive Data at the University of Oslo
USIT: University Center for Information Technology

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MULTIMEDIA APPENDIX 1

Multimedia appendix 1: Management of nausea and vomiting in pregnancy (NVP), according to treatment guidelines. PUQE= Pregnancy Unique Quantification of Emesis score; this score ranges from 3 to 15 points**.**

MULTIMEDIA APPENDIX 2

Multimedia appendix 2: The questions in the PUQE score, NVPQOL scale, and the Decisional conflict scale.

Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score

Answer the option that suits the best for your situation for the last 24 hours.

1	On average in a day, for how long do you feel nauseated or sick to your stomach?				
Answer option	> 6 hours	4-6 hours	2-3 hours	≤ 1 hour	Not at all
2	On average in a day, how many times do you vomit or throw up?				
Answer option	> 6 hours	4-6 hours	2-3 hours	≤ 1 hour	Not at all
3	On average in a day, how many times have you had retching or dry heaves without brining anything up?				
Answer option	> 6 hours	4-6 hours	2-3 hours	≤ 1 hour	Not at all
4	On a scale of 0 to 10, how would you rate your well-being: _____ 0 (worst possible) 10 (as good as you felt before pregnancy)				

Nausea and vomiting in pregnancy Quality of life (NVPQOL)

Over the past week, from 1 (none of the time) to 7 (all of the time) how much have you been experiencing…

1. Nausea
2. Feeling sick to your stomach
3. Vomiting
4. Dry-heaves (vomiting without bringing anything up)
5. Poor Appetite
6. Symptoms being worse in the evening
7. Not eating for longer than you would like
8. Feeling worse when exposed to certain smells
9. Feeling worse when exposed to certain foods
10. Fatigue
11. Feeling worn-out and loss of energy
12. Feeling exhausted
13. Feeling tired
14. Feeling emotional
15. Being less interested in sex
16. Feeling downhearted, blue, sad, unhappy, depressed, gloomy
17. Feeling frustrated
18. Feeling fed up with being sick
19. Not feeling that your symptoms are all part of normal pregnancy
20. Feeling that you can`t enjoy your pregnancy
21. That everything is an effort
22. Feeling like you have accomplished less than you would like
23. That it takes longer to get things done that usual
24. Difficultly performing your work and activities
25. Difficultly maintaining your normal social activities
26. Relying on your partner for doing things that you would normally do
27. Difficulty looking after your home
28. Difficulty shopping for food
29. Difficulty preparing or cooking meals
30. Cutting down on amount of time you spend at work or other activities

Decisional Conflict Scale (DCS)

Which treatment option do you prefer for nausea and vomiting during pregnancy? Please check one.

1) Self-care
2) Antiemetic drugs
3) Self-care and antiemetic drugs

Considering the option you prefer (strongly agree, agree, neither agree or disagree, disagree, strongly disagree), please answer the following questions:

Statement
I know which options are available to me.
I know the benefits of each option.
I know the risk and side effects of each option.
I am clear about which benefits matter most to me.
I am clear about which risks and side effects matter most.
I am clear about which is more important to me (the benefits or the risks and side effects).
I have enough support from others to make a choice.
I am choosing without pressure from others.
I have enough advice to make a choice.
I am clear about the best choice from me.
I feel sure about what to choose.
This decision is easy for me to make.
I feel I have made an informed choice.
My decision shows what is important to me.
I expect to stick with my decision.
I am satisfied with my decision.

STUDY III

Impact of a primary care pharmacist consultation on pregnant women's medication use: The SafeStart intervention study linked to a national prescription database

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In press (Accepted for publication March 14, 2023)

III

Impact of primary care pharmacist consultations on pregnant women's medication use: The SafeStart intervention study linked to a national prescription database

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Keywords: pregnancy, prescription database, medication, pharmacist counseling, prenatal care, pharmaceutical care, NVP, intervention, community pharmacy, NorPD, SafeStart

ABSTRACT

Background

Prior studies show that pharmacist consultations are highly appreciated by pregnant women and feasible in community pharmacies. However, it is unknown whether such counseling has an impact on medication use during pregnancy.

Aim

This study aimed to assess whether a pharmacist consultation in early pregnancy was associated with pregnant women's medication use, with a focus on antiemetic medications.

Method

The SafeStart study recruited Norwegian pregnant women in the first trimester between February 2018 and February 2019. Women in the intervention group received a pharmacist consultation in a community pharmacy or by phone. An follow-up questionnaire was completed 13 weeks after enrollment. Data from the SafeStart study were linked to the Norwegian Prescription Database. Logistic regression was used to assess the association between the pharmacist intervention and medication use in the second trimester.

Results

The study included 103 women in the intervention group and 126 in the control group. Overall prescription fills in the first and second trimesters were 55% and 45% (intervention group) and 49% and 52% (control group), respectively. In total, 16-20% of women in the first trimester and 21-27% of women in the second trimester had a prescription for antiemetics. The pharmacist intervention was not associated with women's medication use in the second trimester.

Conclusion

This study did not detect an impact of a pharmacist consultation on pregnant women's use of medications. In the future, pharmacist consultations should focus on other outcome factors, such as risk perception, knowledge level, and the use of other health care services.

Trial registration

The SafeStart study is registered with ClinicalTrials.gov (identifier: NCT04182750, registration date: December 2, 2019).

Impact statement

- Information about advice for and treatment of pregnancy-related conditions are highly requested. Available information should be easily accessed by pregnant women.
- Although a pharmacist consultation did not impact medication use during pregnancy, it is still unknown whether the role of pharmacists in maternity care may benefit pregnant women's medication use.
- Intervention studies among pregnant women need to take into account women of high socioeconomic status when estimating the effect of an intervention.

INTRODUCTION

Up to 90% of pregnant women use medications during pregnancy [1, 2]. The use of prescribed and over-the-counter medications in the first trimester has increased by more than 60% in the last three decades [3]. Despite widespread use, pregnant women still report a lack of information from their health care providers regarding safe medication use during pregnancy [4], including for the treatment of nausea and vomiting in pregnancy (NVP) [5].

NVP affects up to 80% of pregnant women and often starts around gestational weeks 4-9 [6-8]. Although safe pharmacological treatments for NVP are available [9-12], the combination of trivializing NVP, lack of knowledge about the use of antiemetic medications during pregnancy, and fears of fetal harm often lead to late recognition and undertreatment of NVP [13, 14].

Moreover, up to 77% of pregnant and postpartum women report the need for information regarding the use of medications during pregnancy [15]. Even though pregnant women frequently use the internet to search for information about medication use [16, 17], they prefer to receive this information from their health care providers, such as GPs, midwives, and pharmacists [4].

Pharmacists are an important information source for pregnant women with respect to OTC medications and the management of minor ailments during pregnancy [18]. Patient-centered consultations have led to increased knowledge, compliance and enhanced health outcomes among pregnant women [19]. We previously found that a pharmacist consultation for pregnant women in the first trimester was feasible and highly appreciated by the women [20]. Women found it most useful when the information they received was tailored to their needs and when

the consultations could be performed over the phone [20, 21]. However, these studies did not explore the impact of pharmacist consultations on medication use during pregnancy.

ETHICAL APPROVAL

The SafeStart project was approved by the Regional Committees for Medical and Health Research Ethics in Norway on November 23, 2016 (Reference: 2016/1686).

AIM

We hypothesized that a pharmacist consultation in the first trimester of pregnancy could impact the extent and type of medications used in the second trimester. Therefore, the aim of this study was to assess whether a community pharmacist consultation in early pregnancy is associated with women's medication use in the second trimester, with a particular focus on antiemetic medications.

METHODS

The SafeStart study

This study was a part of the SafeStart interventional trial [20, 21]. Norwegian-speaking pregnant women in their first trimester were eligible for participation. The SafeStart interventional trial included a total of 229 women who responded to the baseline questionnaire (Q1) and follow-up questionnaire (Q2). These women were included in the analyzes of this study. Of the 229 women, 103 were allocated to the intervention group and 126 were allocated to the control group. The SafeStart study was conducted according to the CONSORT guidelines [22].

Recruitment

For the SafeStart interventional trial, pregnant women were recruited between February 2018 and February 2019 through Facebook (i.e., our own Facebook page for the study), pregnancy-related webpages/forums (e.g., "*altformamma.no*", and "*tryggmammamedisin.no*), and flyers in pharmacies throughout Norway.

Sample size

Power analysis performed in the SafeStart interventional trial estimated that a sample size of 385 pregnant women would be needed to detect a medium effect size (Cohen's d=0.5) based on a two-sided α of 0.05, a power of 80%, and a dropout rate of 30%. We then performed a post hoc power analysis to determine our actual study power. Post hoc power analysis showed that a sample size of 229 (complete cases) from the SafeStart interventional trial was sufficient to detect a 19% difference in medication use with 80% power.

Allocation

All women who consented to participate were assigned (1:1) to either the intervention group or the control group by software developed specifically for this project. The software automatically handled the women's enrollment, group allocation, and distribution of informational emails and online questionnaires.

The intervention group

The women in the intervention group received a tailored pharmacist consultation at one of the 14 pharmacies that voluntarily participated in the study or over the phone. The consultation lasted up to 15 minutes. The pharmacist conducting the consultation had access to the women's

answers to Q1 in advance. This information was used to prepare a structured, individualized consultation that addressed each woman's concerns and needs.

The control group

Women assigned to the control group received only standard Norwegian prenatal care. Prenatal care in Norway is offered to all Norwegian pregnant women, and the basic program consists of nine consultations in total, with the first consultation recommended in gestational weeks 6-12. Prenatal care is free of charge [23].

Data collection

SafeStart survey data

The SafeStart interventional trial included four sets of questionnaires (Q1-Q4). In this study, we analyzed data from Q1, Q2, and the study pharmacists' notes from the consultation. Q1 was completed at enrollment in the first trimester, and Q2 was distributed 13 weeks after enrollment and completed in the second trimester (Figure 1).

SafeStart survey data – Q1

Q1 included questions about the women's sociodemographic and lifestyle characteristics, chronic conditions and NVP severity. Q1 also included a list of health conditions (e.g., allergies, general pain, heartburn, NVP, constipation) and related medication use.

SafeStart survey data – Q2

The follow-up questionnaire, Q2, was distributed 13 weeks after enrollment and aimed to identify medication use in the second trimester, defined as gestational weeks 14-26. Q2

included the repeated list of medical conditions and related medication use from Q1. The English versions of Q1 and Q2 are provided in Supplementary file 1.

SafeStart survey data - Pharmacist notes

Pharmacist notes provided information about the consultation, such as the setting and duration, in addition to the topics discussed and pregnancy-related conditions addressed during the consultation.

Prescription registry data

The SafeStart survey data were linked to the NorPD data by the women's unique social security numbers. NorPD is a national registry covering all prescribed medications dispensed at pharmacies to individual patients in Norway. NorPD data include the medication name, ATC code, defined daily dose, package size, and dispense date for the participant. The completion date of Q1 and the reported gestational week reported in Q1 were used to calculate the pregnancy start date. The three months before the start of pregnancy was defined by the pregnancy start date minus 90 days. The trimesters were defined as follows: first trimester: 1-90 days after the pregnancy start date; second trimester: 91-180 days after the pregnancy start date; and third trimester: 180 days after the pregnancy start date and until delivery. Three months postpartum was defined as the estimated date of delivery plus 90 days. The time point of medication exposure during the pregnancy period, which included the three months before the pregnancy start date and three months postpartum, was identified by utilizing the dispensing date as registered in the NorPD.

Data storage

All collected data were stored and analyzed at the Service for Sensitive Data at the University of Oslo (TSD) [24]. The TSD is protected by two-factor authentication and designed for storing and postprocessing sensitive data in compliance with the Norwegian *"Personal Data Act"*, *"Health Research Act", and* regulations regarding an individual's privacy.

The datasets used in this study are from a third party and are not publicly available due to ethical and legal restrictions. Please contact the corresponding author for further information regarding the questionnaires and the data.

Outcome measures: Medication use

The outcome measure was medication use in the second trimester. The outcome was assessed by evaluating the differences in medication use in the second trimester among women in the intervention and control groups.

All medications were classified in the anatomical/pharmacological group by the Anatomical Therapeutic Chemical (ATC) classification system (ATC 1st level) [25]. Antiemetics were classified at the substance level (ATC 5th level).

Statistical methods

Descriptive analyzes

All analyzes were performed as complete case analyzes. Complete case analyzes was chosen because it reflects the ideal situation of the impact of a pharmacist consultation on medication use during pregnancy.

We compared the baseline characteristics of the intervention and control groups to evaluate whether the allocation process produced balanced groups. This was also done to evaluate covariate balance, as complete case analyzes put the randomization process at risk. The chi-squared test was used to compare categorical variables, i.e., relationship status, education level, work situation, folic acid supplementation, parity, pregnancy-related conditions, and chronic conditions, which are presented as medians and ranges. Student's test was used to compare continuous variables, i.e., gestational week, maternal age, and Pregnancy Unique Quantification of Emesis (PUQE) score, which are presented as counts and percentages. Proportions of filled prescriptions of medications and their ATC codes with at least 20 women in the defined time periods as registered in the NorPD were calculated for the five pregnancy periods: three months before pregnancy, the first, second, and third trimesters, and three months postpartum. Filled prescriptions for antiemetic medications were considered for the first and second trimesters only.

Association analyzes

Logistic regression was performed to estimate the association between pharmacist consultations (intervention vs. control groups) and second trimester medication use. Separate models were computed for self-reported medication use and filled prescriptions, including medications in general and antiemetic medications specifically. The results are presented as crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). The adjusted ORs were adjusted for medication use in the first trimester and employment status at baseline, as these variables were unbalanced between the intervention and control groups at baseline.

Sensitivity analysis

We performed a predefined stratified analysis according to employment status to assess effect modification by being employed as a health care worker. We hypothesized that the intervention would have a different impact on medication use among pregnant women working as health care workers compared to those working elsewhere, as we assumed that health care workers would have a higher knowledge level regarding health care and medication use.

RESULTS

Study population

In total, 103 pregnant women were allocated to the intervention group and 126 to the control group (Figure 2). The median gestational week at enrollment was week 7 (intervention group range: 3-12 weeks; control group range: 3-13 weeks). The mean PUQE score for both groups was 6 points (range: 3-14 and 3-15) at baseline, and half of the pregnant women scored >6 points. There was a significant difference in employment status between the two study groups (chi-square test, *p=0.03)*. The study population baseline characteristics are presented in Table 1.

The intervention

Of 103 pharmacist consultations, 37 (36%) were performed at the study pharmacies and 66 (64%) were performed over the phone. All consultations were performed between gestational weeks 4-14. One woman received the consultation in week 17, but still prior to the completion of Q2. The most frequent topics addressed during the consultations were *advice and treatment of pregnancy-related conditions* (61/103, 59%). NVP was the pregnancy-related condition that was most frequently addressed during pharmacist consultations (49/103, 48%) (Supplementary file 2).

Medication use

Self-reported medication use (SafeStart study data)

Women in the intervention and control groups most frequently self-reported having used medications with ATC codes A *(alimentary tract and metabolism*), N (*nervous system),* and R *(respiratory system)*. Both groups reported having used medications with ATC codes A and N more frequently in the second trimester (ATC code A: 20-25% and N: 45-47%) than in the first trimester (ATC code A: 7-8% and N: 6-8%, Table 2).

Filled prescriptions (prescription registry data)

The most commonly filled prescriptions for both groups were for medications with ATC codes A, G (*genito-urinary system and sex hormones),* J (*anti-infectives for systemic use),* and R. The rates of filled prescriptions with each ATC code were similar in all periods for both study groups (Table 2 and Supplementary file 3).

Associations between the pharmacist intervention and medication use in the second trimester

Self-reported medication use (SafeStart study data)

There were not detected any differences in self-reported medication use in the second trimester between the intervention and control groups for ATC codes A (adjusted OR (aOR): 0.8, 95% CI: 0.4, 1.5), N (aOR: 1.0, 95% CI: 0.6, 1.7) or R (aOR: 0.8, 95% CI: 0.4, 1.5). The analyses are presented in Table 2.

Filled prescriptions (prescription registry data)

There was no difference between the intervention and control groups in filled prescriptions during the second trimester, except for medications with ATC code G, where women in the

intervention group had lower odds of filling prescriptions after the pharmacist consultation (aOR: 0.4, 95% CI: 0.2, 0.8, Table 2).

Prescribed antiemetic medications (Prescription registry data)

A total of 28 women in the intervention group and 27 women in the control group had filled a prescription for an antiemetic medication in the second trimester (Table 3). However, there was a lower, but not significant, difference in the number of filled prescriptions for antiemetic medications in the second trimester between the two study groups (aOR: 0.4, 95% CI: 0.1, 1.4).

In the analysis stratified by employment status, we found lower odds of filled prescriptions for antiemetic medications among women who were employed in the health care sector than among women employed in other sectors (aOR: 0.3, 95% CI: 0.2, 0.5).

DISCUSSION

Main results

To our knowledge, this study is the first to assess the impact of a pharmacist consultation in the first trimester on medication use during pregnancy. This study showed no association between pharmacist consultations and the use of medications in the second trimester of pregnancy.

In comparison to an earlier multinational study [2] and similar to a Swedish register-based study [26], in our study, pregnant women also filled medications with ATC codes A, J, N, and R as the most frequently used medications. In line with other Scandinavian studies, medications with ATC code J were the most frequently prescribed medications for pregnant women [26-28]. In the second trimester, 27% of the women in the intervention group and 21% in the control group had filled prescriptions for antiemetics. This is considerably higher than the rate in a previous

Norwegian registry study (2005-2017) that showed that 8% of pregnant women filled at least one prescription for antiemetics during pregnancy [29]. Given that approximately half of the women in the SafeStart study received a score over the cutoff value for moderate NVP (≥6 points) and that 48% of the women in the intervention group discussed NVP during the consultation, the higher number of prescribed antiemetic medications is therefore reasonable. The Norwegian registry study reported meclizine, promethazine, and metoclopramide as the most commonly prescribed antiemetic medications [29], which aligns well with our study.

The lack of association between pharmacist consultations and medication use during pregnancy may be due to several reasons. Our study population was a more resourceful group of women with higher education than the general birthing population in Norway (Supplementary file 4). Over half of the women in the study were primiparous and were more likely to actively seek medical information online [16, 17, 30, 31]. It is possible that well-informed groups of women benefit less from pharmacist consultations than less resourceful groups of women. Other studies have shown that pregnant women trust pharmacists to provide them with information about medications [15, 16, 32]. We cannot exclude the possibility that women in the control group became aware of the type of information available and contacted other pharmacies outside of their study participation.

Strengths and limitations

The main strength of this study was that we were able to recruit women from all parts of Norway, consequently increasing the generalizability of our results beyond one study site. Another strength of this study was the linking of self-reported data regarding medication use to filled prescriptions as recorded in the NorPD.

Limitations to take into consideration are selection bias and recall bias. Our study included a resourceful group of women with higher educational status. As in other studies based on the recruitment of women, there is always an inherent risk of selection bias toward more interested and motivated individuals. Moreover, the data on medication use collected in Q1 and Q2 was self-reported, which may introduce recall bias; for example, women in the intervention group may have provided more accurate reports than those in the control group. This bias, however, would not be present in the analyses based on data from the prescription registry, as registry data were recorded independent of the intervention. Another limitation to consider is that Q1 and Q2 did not include identical lists of medical conditions and related medications. Therefore, self-reported medication use may not be directly comparable to illnesses but only to medication use in general.

Future research

Future work should focus on the role of pharmacies within maternity care. The most frequent pregnancy-related condition addressed during the consultations was NVP. This indicates that the role of pharmacists may be beneficial for women with pregnancy-related symptoms that occur in early pregnancy, often prior to their first prenatal care visit [8, 33]. Moreover, future studies should investigate the impact of a pharmacist consultation on other outcomes that are equally important for women's daily lives, such as knowledge about medication use, risk perception, and the utilization of health care services.

Moreover, digitalization and m- and eHealth have all been shown to be beneficial as a part of patient care. In particular, mobile applications, websites, and other digital programs for improving health and medication use in pregnant women have been shown to be beneficial [34-37]. There has been a call for digital technologies to promote self-care and improve

communication between pregnant women and health care providers [38, 39]. Future studies should therefore explore how pharmacists use digital tools as a part of pharmaceutical care.

CONCLUSION

In this study, we did not detect an impact of an early pharmacist consultation on medication use in general or the use of antiemetic medications during pregnancy. The results may have been affected by the study population, which included a large proportion of women with high socioeconomic status. Future studies should focus on the impact of pharmacist consultations on other outcome factors and the role of pharmacists in maternity care.

STATEMENTS AND DECLARATIONS

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Competing interests

The authors have no conflicts of interest to declare.

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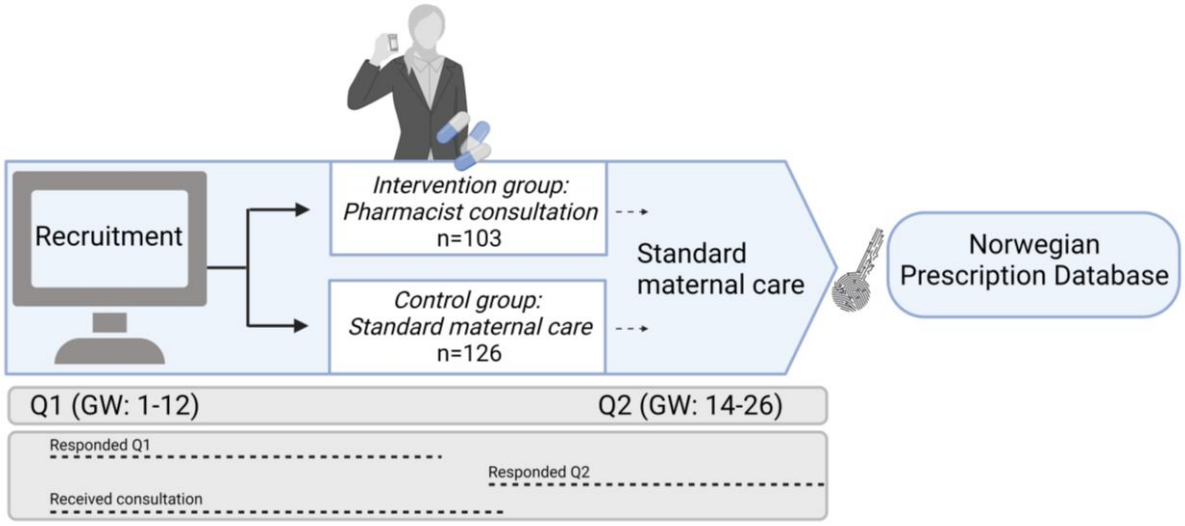

Figure 1: Overview of the SafeStart study design. Pregnant women were mainly recruited through social media and allocated to either the intervention or control groups. Women in the intervention group were offered a tailored pharmacist consultation. All women received standard maternal care. The women responded to Q1 and Q2 between GW 3-13 and GW 14-26, respectively. The pharmacist consultations were performed from GW 4-14 for women in the intervention group. One woman received the intervention in GW 17. Self-reported data from the SafeStart questionnaires (Q1 and Q2) were linked to data from the Norwegian Prescription Database (NorPD) by using the women's unique social security numbers. **GW**= gestational week, **Q1=** baseline questionnaire, **Q2**= follow-up questionnaire.
(Created with BioRender.com)

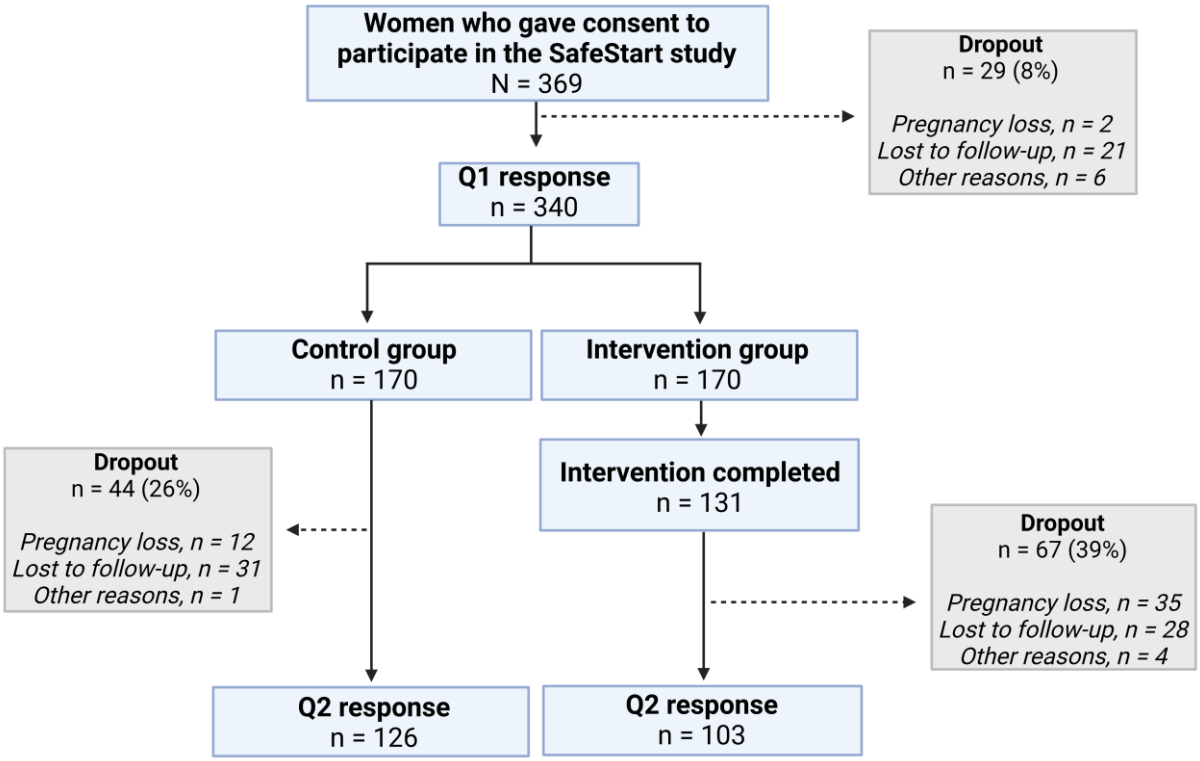

Figure 2: Flowchart of the SafeStart inclusion and exclusion criteria to determine the final study population. A total of 369 women gave consent to participate in the study, which resulted in 103 women in the intervention group and 126 women in the control group. All analyzes were performed as complete case analyzes (N=229). **Q1=** Baseline questionnaire. **Q2**= Follow-up questionnaire.
(Created with BioRender.com)

Table 1: Baseline characteristics of the study population according to the study groups (intervention group, N=103 and control group, N=126) compared to the general birthing population in Norway.

CHARACTERISTICS	n	Intervention group (n=103) Value (Median, range or %)	n	Control group (n=126) Value (Median, range or %)	Balance of covariates *(p value)**
Gestational week at enrollment		7 (3-12)		7 (3-13)	*0.65*
Maternal age (years)		31 (21-40)		31 (21-41)	*0.65*
Relationship status					*0.48*
Married/cohabitating	100	97.1	121	96.1	
Single	3	2.9	5	3.9	
Higher education					*0.42*
Yes	89	86.4	105	83.3	
No	14	13.6	21	16.7	
Employment status					*0.02*
Employed	71	68.9	63	50.0	
Employed in the health sector	23	22.3	39	30.9	
Other	9	8.8	24	19.1	
Primigravida					*0.22*
Yes	64	62.1	61	48.4	
No	39	37.9	65	51.6	
Folic acid supplementation before/during pregnancy					*0.23*
Yes	102	99.1	124	98.4	
No	1	0.9	2	1.6	
PUQE score		6 (3-14)		6 (3-15)	*0.40*
Chronic conditions					
Asthma	9	8.7	15	11.9	*0.44*
Allergies	20	19.4	32	25.4	*0.28*
Hypothyroidism	4	3.9	6	4.8	*0.75*
Depression/anxiety	7	6.8	9	7.1	*0.92*
*Other***	19	18.4	26	20.6	*0.50*

n= number of women, **SD**= standard deviation, **PUQE score:** Pregnancy Unique Quantification of Emesis score

*Chi-squared tests were used to compare categorical variables, and Student's t tests were used to compare continuous variables.

****Other*** chronic conditions include ADHD, cardiovascular disease, chronic fatigue syndrome, Crohn's disease, eczema, endometrioses, epilepsy, fibromyalgia, high cholesterol, hyperthyroidism, irritable bowel syndrome, mental disorders, migraine, multiple sclerosis, polycystic ovary syndrome, psoriasis, rheumatic diseases, sarcoidosis, and ulcerative colitis.

Table 2: Overview of self-reported medication use in the baseline (Q1) and follow-up questionnaires (Q2) and the number of women with filled prescriptions as registered in the Norwegian Prescription Database (NorPD). The impact of a pharmacist consultation on medication use in the second trimester in the intervention (N=103) and control groups (N=126) are presented as crude ORs and adjusted ORs.

	Intervention group **Medication use in the 1st trimester** n *(%)*	**Control group** **Medication use in the 1st trimester** n *(%)*	**Intervention group** **Medication use in the 2nd trimester** n *(%)*	**Control group** **Medication use in the 2nd trimester** n *(%)*	**Impact of a pharmacist consultation on medication use in the 2nd trimester** Crude OR (95% CI)	Adjusted OR* (95% CI)
Filled prescriptions as registered in the NorPD****						
A - *Alimentary tract and metabolism*	29 *(28.2)*	37 *(29.4)*	24 *(23.3)*	34 *(26.9)*	0.8 (0.4, 1.5)	0.7 (0.3, 1.7)
B - *Blood and blood forming organs*	15 *(14.6)*	21 *(16.7)*	16 *(15.5)*	26 *(20.6)*	0.7 (0.4, 1.4)	0.6 (0.2, 1.9)
G - *Genito-urinary system and sex hormones*	37 *(35.9)*	51 *(40.5)*	23 *(22.3)*	48 *(38.1)*	0.5 (0.2, 0.8)	0.4 (0.2, 0.8)
H - *Systemic hormonal preparations*	16 *(15.5)*	28 *(22.2)*	13 *(12.6)*	26 *(20.6)*	0.6 (0.3, 1.1)	0.6 (0.2, 1.9)
J - *Anti-infectives for systemic use*	41 *(39.8)*	41 *(32.5)*	36 *(34.9)*	47 *(37.3)*	0.9 (0.5, 1.6)	0.7 (0.3, 1.3)
N - *Nervous system*	18 *(17.5)*	35 *(27.8)*	14 *(13.6)*	31 *(24.6)*	0.5 (0.2, 0.9)	0.6 (0.2, 1.6)
R - *Respiratory system*	36 *(34.9)*	39 *(30.9)*	32 *(31.1)*	39 *(30.9)*	1.0 (0.6, 1.8)	0.8 (0.4, 1.7)
Total***	**57** ***(55.3)***	**62** ***(49.2)***	**46** ***(44.7)***	**65** ***(51.6)***	**0.8 (0.4, 1.3)**	**0.7 (0.4, 1.2)**
	Intervention group **Medication use in the 1st trimester** n *(%)*	**Control group** **Medication use in the 1st trimester** n *(%)*	**Intervention group** **Medication use in the 2nd trimester** n *(%)*	**Control group** **Medication use in the 2nd trimester** n *(%)*	**Impact of a pharmacist consultation on medication use in the 2nd trimester** Crude OR (95% CI)	Adjusted OR* (95% CI)
Self-reported medication use**						
A - *Alimentary tract and metabolism*	7 *(6.8)*	10 *(7.9)*	21 *(20.4)*	32 *(25.4)*	0.8 (0.4, 1.4)	0.8 (0.4, 1.5)
N - *Nervous system*	6 *(5.8)*	10 *(7.9)*	46 *(44.6)*	59 *(46.8)*	0.9 (0.5, 1.5)	1.0 (0.6, 1.7)
R - *Respiratory system*	25 *(24.3)*	34 *(26.9)*	28 *(27.2)*	40 *(31.7)*	0.8 (0.5, 1.4)	0.8 (0.4, 1.5)
Total****	***36 (34.9)***	**45** ***(35.7)***	***59 (57.3)***	**83** ***(65.9)***	**0.7 (0.4, 1.2)**	**0.7 (0.4, 1.2)**

NorPD: Norwegian Prescription Database, **n=** Number of women

*Adjusted for medication use and employment status at baseline.

**ATC codes S (sensory system) and M (*musculoskeletal system) are not included in this table because the number of women who reported them was below 10.*

***Total number of women who reported at least one medication/ had at least one filled prescription registered in the NorPD.

*****ATC codes C (cardiovascular system), D (dermatologicals), L (antineoplastic and immunomodulating agents), M (musculoskeletal system), P (antiparasitic products, insecticides and repellents), S (sensory system), and V (various) were not included in this table as the number of women who reported them was below 10.*

Table 3: Overview of filled prescriptions for antiemetic medications in the intervention (N=103) and control groups (N=126) as registered in the Norwegian Prescription Database (NorPD) in the 1st (T1) and 2nd trimester (T2). The impact of an early pharmacist consultation on the use of antiemetic medications in the second trimester in the intervention and control groups is presented as crude ORs and adjusted ORs.

Antiemetic medication	**Intervention group**	**Control group**	**Intervention group**	**Control group**	**Use of antiemetic medications during the 2nd trimester**	
	T1 n *(%)*	**T1** n *(%)*	**T2** n *(%)*	**T2** n *(%)*	Crude OR (95% CI)	Adjusted OR* (95% CI)
Meclizine	9 *(8.7)*	6 *(4.8)*	5 *(4.9)*	4 *(3.2)*	-	-
Promethazine	3 *(2.9)*	8 *(6.3)*	3 *(2.9)*	7 *(5.6)*	-	-
Metoclopramide	9 *(8.7)*	6 *(4.8)*	20 *(19.4)*	16 *(12.7)*	-	-
Total*	21 *(20.4)*	20 *(15.9)*	28 *(27.2)*	27 *(21.4)*	0.6 (0.3, 1.2)	0.4 (0.1, 1.4)

T1= First trimester, **T2**= Second trimester, **n**= number of women
*Adjusted for medication use and employment status at baseline.

SUPPLEMENTARY FILE 1

Supplementary file 1: Baseline characteristics of the study population compared to the general birthing population in Norway.

CHARACTERISTICS	n	Study population (n=229) Value (Median, range or %)	General birthing population in Norway Value (Median, range or %)
Maternal age (years)		31 (21-41)	31**
Relationship status			
Married/co-habitant	221	96.5	93.6**
Higher education			
Yes	194	84.7	51.5***
Employment status			
Employed	196	85.6	86.4****
Primigravida			
Yes	125	54.6	42.4**
Folic acid supplement before/during pregnancy			
Yes	226	98.7	33.8**

SD= standard deviation, **PUQE score**= Pregnancy Unique Quantification of Emesis score

***Other** chronic conditions includes ADHD, cardiovascular disease, Chronic fatigue syndrome, crohn`s disease, eczema, endometrioses, epilepsy, fibromyalgia, high cholesterol, hyperthyroidism, irritable bowel syndrome, mental disorders, migraine, multiple sclerosis, polycystic ovary syndrome, psoriasis, rheumatic diseases, sarcoidosis, and ulcerative colitis.

**Data from the Norwegian Medical Birth Registry for 2018

***Data from Statistics Norway, women aged 20–39 in 2018

****Data from Statistics Norway, women aged 25–39 in 2018

SUPPLEMENTARY FILE 2

Supplementary file 2: Overview of conducted pharmacist consultations, topics and pregnancy-related conditions addressed during the consultation.

	Value Mean (range) or n	*%*
Pregnancy week when receiving the pharmacist consultation	9 (4-17)	
Number of pharmacist consultations		
At the pharmacies	37	*35.9*
On the phone	66	*64.1*
Topics addressed during the consultation*		
General information about medications	32	*31.1*
Advice and treatment of pregnancy-related conditions	61	*59.2*
Need of medications	9	*8.7*
Negative attitudes and anxiousness about medication use	9	*8.7*
*Other topics related to medication use***	18	*14.5*
Need of referral to her GP	2	*1.9*
No topics addressed	12	*11.7*
Pregnancy related conditions addressed during the consultation*		
Nausea and vomiting	49	*47.6*
Constipation	24	*23.3*
Heartburn	17	*16.5*
Cold/stuffy nose	21	*20.4*
Headache	14	*13.6*
Pain in general	11	*10.7*
*Other pregnancy related conditions****	10	*9.7*

n= Number of women

*One women can address serval topics and pregnancy related conditions

**Other topics related to medication use as anxious about the effect of the medication on the child and low adherence to regular medication

****Other pregnancy related conditions with below 10 cases includes sleeping problems, dizziness, and fatigue*

SUPPLEMENTARY FILE 3

Supplementary file 3: Overview of women with filled prescriptions as registered in the Norwegian Prescription Database, categorized after ATC-codes for, three months before pregnancy, 1st, 2nd, 3rd trimester, and three months post-partum.

ATC-code*	Three months before pregnancy n *(%)*	1st trimester n *(%)*	2nd trimester n *(%)*	3rd trimester n *(%)*	Three months post-partum n *(%)*
A - *Alimentary tract and metabolism*					
I	21 *(20.4)*	29 *(28.2)*	24 *(23.3)*	22 *(21.4)*	17 *(16.5)*
C	29 *(23.0)*	37 *(29.4)*	34 *(26.9)*	35 *(27.8)*	38 *(30.2)*
B - *Blood and blood forming organs*					
I	13 *(12.6)*	15 *(14.6)*	16 *(15.5)*	12 *(11.7)*	7 *(6.8)*
C	18 *(14.3)*	21 *(16.7)*	26 *(20.6)*	24 *(19.0)*	23 *(18.3)*
G - *Genito-urinary system and sex hormones*					
I	32 *(31.1)*	37 *(35.9)*	23 *(22.3)*	26 *(25.2)*	31 *(30.1)*
C	44 *(34.9)*	51 *(40.5)*	48 *(38.1)*	45 *(35.7)*	58 *(46.0)*
H - *Systemic hormonal preparations*					
I	15 *(14.6)*	16 *(15.5)*	13 *(12.6)*	10 *(9.7)*	15 *(14.6)*
C	24 *(19.0)*	28 *(22.2)*	26 *(20.6)*	26 *(20.6)*	27 *(21.4)*
J - *Antiinfectives for systemic use*					
I	36 *(34.9)*	41 *(39.8)*	36 *(34.9)*	29 *(28.2)*	35 *(33.9)*
C	36 *(28.6)*	41 *(32.5)*	47 *(37.3)*	39 *(30.9)*	48 *(38.1)*
N - *Nervous system*					
I	18 *(17.5)*	18 *(17.5)*	14 *(13.6)*	16 *(15.5)*	15 *(14.6)*
C	28 *(22.2)*	35 *(27.8)*	31 *(24.6)*	32 *(25.4)*	30 *(23.8)*
R - *Respiratory system*					
I	37 *(35.9)*	36 *(34.9)*	32 *(31.1)*	32 *(31.1)*	30 *(29.1)*
C	35 *(27.8)*	39 *(30.9)*	39 *(39.9)*	38 *(30.2)*	37 *(29.4)*
Total					
I	48 *(46.6)*	58 *(56.3)*	46 *(44.7)*	41 *(39.8)*	50 *(48.5)*
C	57 *(45.2)*	62 *(49.2)*	65 *(51.6)*	60 *(47.6)*	69 *(54.8)*

ATC-code= Anatomical Therapeutic Chemical Classification System, **n**= number of women, **I**= intervention group, **C**= control group

**ATC-code P (Antiparasitic products, insecticides and repellents), S (Sensory organs), and V (Various) is not included in this table as numbers of prescriptions in total were below 20 in the defined time period.*