Promoter: Prof. Dr. Wilfried Gyselaers | Hasselt University

Co-promoters: Prof. dr. Lars Grieten | Hasselt University

dr. ir. Inge Thijs | Hasselt University

Jury members: Prof. dr. Marcel Ameloot (Chair) | Hasselt University

Prof. dr. Dominique Vandijck | Hasselt University

Prof. dr. ir. Ronald Thoelen | Hasselt University

Prof. Dr. Pieter Vandervoort | Hasselt University

Prof. Dr. Basky Thilaganathan | St. George's University of London

Prof. Dr. Kristien Roelens | Ghent Universty

Prof. dr. Inge Tency | Odisee

Prof. dr. Ignaas Devisch | Ghent University

dr. Patrick Luyten | KU Leuven

September 26, 2018

Dorien Lanssens was supported by the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk, Hasselt University, Ziekenhuis Oost-Limburg and Jessa Hospital.

Door de wetenschap bereikt men veel,

doch slechts de liefde voert tot volmaaktheid.

~ Rabindranath Tagore ~

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AT	Automatically transferred
BMI	Body mass index
BP	Blood pressure
CC	Conventional care
CG	Control group
CG	Control group
CINAHL	Cumulative index to nursing and allied health literature
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EH	Essential/chronic hypertension
EMBASE	Excerpta medica database
EPE	Early preeclampsia
FBS	Fasting blood sugar
GDM	Gestational diabetes mellitus
GH	Gestational hypertension
GHD	Gestational hypertensive disorders
HR	High risk
ICD	Implantable cardioverter defibrillator
ICSI	Intracytoplasmatic sperm injection
ISSHP	International Society for Studies of Hypertension in Pregnancy
IVF	In vitro fertilization
LIMPRON	Limburgs Pre-eclampsie Onderzoek
LPE	Late preeclampsia
LR	Low risk
MEDLINE	Medical literature analysis and retrieval system online
MESH	Medical subject headings
MIC	Maternal intensive care
MR	Medium risk
MRCT	Multicenter randomized controlled trial
MT	Manually transferred
N/A	Non applicable
NICU	Neonatal Intensive Care Unit
NS	Not significant

NSAID	Non steroid anti-inflammationary drug
OS	Observational study
PE	Preeclampsia
PREMOM	Pregnancy remote monitoring
QALY	Quality Adjusted Life Year
QS	Qualitative study
RCT	Randomized controlled trial
RM	Remote monitoring
RS	Retrospective study
SBP	Systolic blood pressure
SPE	Studiecenter perinatale epidemiologie
SRCT	Single randomized controlled trial
TM	Telemonitoring

GENERAL INTRODUCTION

GENERAL INTRODUCTION

With more than 6 billion mobile phone subscribers worldwide, it is estimated that 75% of the world's population has access to mobile communication. The number of devices with broadband capabilities has increased to more than 1 billion globally (1). More than 97,000 health-related mobile applications (apps) are available and approximately 1000 new apps are published every month (1). With the advent of mobile communications using smart mobile devices that support 3G and 4G mobile networks for data transport, mobile computing has been the main attraction of research and business communities. It offers numerous opportunities to create efficient mobile health (mHealth) solutions. mHealth is the new edge on healthcare innovation. It proposes to deliver healthcare anytime and anywhere, surpassing geographical, temporal and even organizational barriers. mHealth systems and its corresponding mobility functionalities have a strong impact on typical healthcare monitoring and alerting systems, clinical and administrative data collection, record maintenance, healthcare delivery programs, medical information awareness, detection and prevention systems, drug-counterfeiting, and theft. Typical mHealth services architectures use the Internet and Web services to provide an authentic pervasive interaction among doctors and patients (= telehealth or telemedicine). (2). Telemedicine is a relatively new approach (dating back to the early 1990s) that facilitates the management of patients at home (3). It can be broadly defined as the use of telecommunication technologies to assist in the transmission of medical information and services between healthcare providers and patients. The use of this two-way telecommunication technology, multimedia, and computer networks to deliver or enhance the delivery of healthcare is a growing trend internationally (4). It can potentially improve access to high-quality disease management. Remote monitoring (RM), a subclass of telemedicine, has developed rapidly over the last decade (5). There are several types of RM, ranging from simple to complex. In the simplest model, a patient receives support

from a healthcare professional over the telephone. The patient monitors his or her symptoms and reports them during a structured telephone call. Moving up the scale of complexity, patient-initiated electronic monitoring involves the transfer of physiological data and the reporting of symptoms by telephone or broadband Internet connection from the patient's home (home monitoring) to the healthcare professional. On reviewing these data, the healthcare professional can contact the patient to request further information before making a decision on disease management. At the next level of complexity, implanted monitoring devices transmit data wirelessly from the patient to a unit that is connected to a telephone or the Internet. Once again, if the data raise concerns, a healthcare professional will contact the patient to request further information before making a decision about care (5).

RM is frequently used in various domains of healthcare. RM can offer clinical benefits to patients diagnosed with chronic cardiovascular disease (CVD). All-cause mortality and hearth-related hospitalization are reduced in patients with CVD treated with RM compared with patients who receive usual care (6, 7). Even primary-care management programs for CVD can be enhanced by RM, improving patient outcomes and reducing health-related costs (8). Web-based RM for the management of type II diabetes mellitus is also a viable approach to healthcare delivery and enhances the patient's quality of life (9). Home RM in patients with chronic obstructive pulmonary disease (COPD) also effectively reduces respiratory distress and hospitalization and improves the patient's quality of life. Patients with COPD were generally satisfied with home RM and found that the system was useful in managing their disease and improved their healthcare provision (3). In fertility research, several articles have been published on the use of self-operated endovaginal RM of the ovarian stimulation phase during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). This technique allows the relevant clinical decisions to be made, generates significantly higher satisfaction among patients and their partners, induces a greater

feeling of empowerment, is discrete, allows more active partner participation, and tends to induce less stress than is experienced by traditionally monitored patients (10-12).

In obstetrics, little is known about the use of RM in prenatal follow-up programs for women at risk of gestational complications. Only a few trials have shown the effectiveness of RM in the obstetric care of both mother and child. When uterine activity is transmitted by telecommunication, significant prolonged pregnancy survivals were observed (13, 14). Greater feelings of self-efficacy and a reduction in (unscheduled) face-to-face visits (15-19) have been reported when RM is used in the prenatal follow-up of pregnant women with gestational diabetes mellitus (GDM) than in women treated with conventional care (CC). Elevated feelings of maternal satisfaction were also reported when RM was used in obstetric care (15, 19-21). Moreover, newborns had a higher gestational age at delivery (22) and were less likely display a low birth weight (13, 22) or be admitted to a neonatal intensive care unit (NICU) (13, 22) when an RM group was compared with a CC group.

Nothing is known about the effectiveness and added value of RM in prenatal care programs for women with gestational hypertensive disorders (GHD), although this is one of the commonest complications of pregnancy (23). Globally, 5%–8% of all pregnant women develop GHD. In Flanders and UZ Brussels, the prevalence of GHD was 4.6% in 2015 (24). Therefore, every year, ~3000 of the 64,000 pregnancies in Flanders are complicated with this disorder. Of these pregnancies, ~200 women (6.6%) deliver before the gestational age of 34 weeks as a result of GHD; 400 women (13.3%) deliver at 34–37 weeks; and 2400 women (80.1%) deliver after 37 weeks. Hypertension in pregnancy has important maternal consequences which include transient hypertension, a risk of cardiac arrest and stroke, and a risk of renal failure or liver failure, whereas the neonatal consequences include preterm birth, low birth weight, respiratory distress syndrome, and brain disorders. These children are also prone to various diseases in later life, including

diabetes, metabolic syndrome, and in the case of female offspring, pregnancies complicated with hypertension or fetal growth retardation. When untreated, hypertension in pregnancy can lead to perinatal or maternal death (25, 26).

There are three types of hypertension in pregnancy: essential/chronic hypertension (EH), gestational hypertension (GH), and pre-eclampsia (PE). According to the criteria revised by the International Society for Studies of Hypertension in Pregnancy (ISSHP), EH is defined as high blood pressure (BP) (> 140/90 mmHg) detected before conception or that develops in the first 20 weeks of gestation. GH is a condition in which BP is elevated above 140/90 mmHg, when measured twice within 6 h, after 20 weeks of gestation. Both conditions can develop into PE, in which hypertension is accompanied by protein loss (> 300 mg per 24 h) (27, 28). PE diagnosed before 34 weeks is defined as 'early pre-eclampsia' (EPE), and that diagnosed later is defined as 'late pre-eclampsia' (LPE) (28). EPE is commonly known as the 'placental' type, triggered by problems of trophoblast implantation and placentation, and is often associated with intrauterine grown restriction (IUGR, birth weight percentile ≤ 10) (23, 29, 30). LPE is the 'maternal' type of pre-eclampsia, which is triggered by preexisting maternal constitutional factors (obesity, age, diabetes, etc.), and generally has no effect on fetal growth (23).

Because there are gaps in our knowledge of the value that RM can add to prenatal follow-up programs for women with GHD, the Limburg Clinical Research Program (LCRP) initiated a RM program for women with or at risk for GHD in January 2015 at Ziekenhuis Oost-Limburg (Genk, Belgium).

AIMS

The aim of this doctoral thesis was to investigate the value added by an RM program included in the prenatal follow-up of women at risk of GHD. After a literature search to review the current RM technologies used in obstetrics (part I), the added value of RM was evaluated in four major domains: gestational physiology (part II), prenatal follow-up and gestational outcomes (part III), relationships to personal characteristics and perceptions of the caregivers and the pregnant women (part IV), and the costs to the healthcare system (part V).

This was achieved by examining the following topics:

Part I — Assesses whether TM adds any substantial benefits to the patient population with GHD and identifies research gaps in this area that might suggest goals for future research (Chapter 1).

Part II — Explores whether RM can be used to evaluate gestational physiology. Two case reports are presented of female patients who both participated in two RM programs: a cardiac RM program to monitor their implantable cardioverter defibrillator devices and an obstetric RM program for the early detection of hypertension in high-risk pregnancies (Chapters 2 and 3).

Part III — Investigates the value added by RM to the prenatal follow-ups and pregnancy outcomes. The data analyzed were collected from January 1, 2015 until December 31, 2015 (Chapter 4), and from January 1, 2015 until December 31, 2016 (Chapter 5).

Part IV — Explores the perceptions of recently delivered women, midwives, and

obstetricians who participated in a prenatal RM follow-up program (Chapter 6).

Part V Determines whether RM is a tool that can offer cost savings to the Belgium healthcare system (Chapter 7) and where those cost savings are distributed (Chapter 8).

GENERAL METHODOLOGY

In recent years, our research group has established in several phases a well-developed prenatal RM program for women at risk of GHD. First, the patient population to be included in this prenatal follow-up program was selected. Second, the devices to be used to transmit the patients' parameters to the healthcare worker at the hospital were chosen and an online platform developed on which the data could be controlled, evaluated, and stored. Following on this, a (para)medical caregiver, who would be the primary person evaluating the data available via the online dashboard or the app, and a network of cooperating hospitals were selected. Lastly, a protocol was prepared for the prenatal follow-up program.

PATIENTS INCLUDED IN THE RM PRENATAL FOLLOW-UP PROGRAM

At the start of our RM prenatal follow-up program, on January 1, 2015, women at both high and low risk of developing of GHD were included. The risk factors for developing GHD are: previous IUGR, systemic lupus erythematosus, nulliparity, maternal age > 35 years, previous stillbirth, chronic kidney disease, assisted reproductive technology, prepregnancy body mass index (BMI) of > 25, multifetal pregnancy, previous placental abruption, pregestational diabetes, and previous PE, EH, or antiphospholipid antibody syndrome (31).

During the first few months, 14 women with none of these risk factors for PE were included in the RM program. Three women (3/14, 21.43%) stopped measuring their vital parameters before they delivered because they saw no advantage of this program to themselves. 7 out of 14 women had a compliance rate for measuring their blood pressure on less than half the occasions as expected according to the protocol. Only 28.57% of the women displayed the demanded adherence to the RM program. After discussions within our research team about this compliance problem among women with low-risk profiles, it was decided that only women at risk of developing GHD should be included in the program.

DEVICES USED TO PERFORM RM

There are two ways to monitor BP with RM. First, the pregnant woman can buy or rent a BP monitor and manually enter the BP measurements into an online app, which will send those data automatically to the healthcare provider at the hospital. Second, the pregnant woman can buy or rent a BP monitor that is connected via Bluetooth to an app on her smartphone, which will send the data automatically to the healthcare provider. To eliminate the possibility of false BP values (caused by mistake or on purpose by the pregnant woman), our research team selected the latter option, in which the BP monitor is connected via Bluetooth to a smartphone.

At that time, the only available Bluetooth-enabled healthcare devices on the market were available from Withings (Issy-les-Moulineux, France). Our research team bought several Withings Wireless Blood Pressure Monitors, Withings Smart Body Analyzers, and Withings Pulse O^2, and commenced the RM program in January 2015. However, the Withings Blood Pressure Monitor generated some problems in the RM process. First, the cuff of the BP monitor was not adaptable to the thickness of the arm. Women with a high BMI were more likely to have false results because their upper arms were not correctly accommodated by the monitor. Second, the batteries of the BP monitors were not rechargeable and problems with patient compliance occurred when they needed to buy new batteries. Lastly, the BP measurements from the Withings BP monitors were usually higher than the measurements made at the hospital.

For these reasons, we looked for another connected BP monitor in mid 2015. After thoughtful consideration and a period of testing, we selected connected devices from iHealth (Paris, France). In August 2015, iHealth Feel Wireless Blood Pressure Monitors and iHealth Wave Activity Trackers were purchased to replace the Withings devices. No weight scales were bought for budgetary reasons. From this point onward, the women recorded their weights with an online app from iHealth.

The iHealth Feel was tested before it was used in the RM program. BP was measured twice in 153 pregnant women (from the Maternal Intensive Care Department [MIC] or prenatal consultations): the first time with the iHealth Feel and the second time with an Omron M2 Blood Pressure Monitor (Omron Healthcare Europe BV, Tienen, Belgium). The maximum time interval between the two measurements was 2 min. The Omron M2 BP monitor is the device used in the MICs and the prenatal wards of hospitals. No differences were detected in the diastolic BPs (DBPs) or systolic BPs (SBPs) recorded with the two BP monitoring devices (at a significance level of 95%). The differences in the means of the BP values were less than 5 mmHg, and the values were guaranteed with an A-score according to the British Hypertension Society (32). Therefore, there were no differences between the two devices and our research team decided to use the iHealth Feel in our research design for the subsequent 4 years.

THE ONLINE DASHBOARD

In cooperation with the Mobile Health Unit (UHasselt, Hasselt, Belgium), an online dashboard, called DHARMA, was developed in which to store the patient data. These data were automatically sent via Bluetooth and Wi-Fi from the patients' smartphones to the online dashboard. DHARMA aggregated and visualized the data in such a way that they could be consulted by the midwife and the (responsible) gynecologist. The BPs received from the patients were classified as followed:

- High risk: two successive measurements of ≥ 140/90 mmHg at an interval of at least 6 h; or DBP ≥ 100 mmHg. The responsible gynecologist was contacted; depending on the gynecologist's policy, an intervention begun.
- Medium risk: SBP of 130–140 mmHg or DBP of 80–90 mmHg. The midwife closely followed-up these measurements.
- Normal: BP < 130/80 mmHg. No action was required.

THE (PARA)MEDICAL CAREGIVER AND A NETWORK OF COOPERATING HOSPITALS

PREMOM was part of a larger study called the Limburgs Pre-eclampsie Onderzoek (LIMPRON). The LIMPRON investigations were performed at Hasselt University (Diepenbeek, Belgium) and in the Ziekenhuis Oost-Limburg (Genk, Belgium). This study is explained in detail in the doctoral dissertations of Sharona Vonck, Anneleen Staelens, and Kathleen Thomsin. In short, maternal cardiovascular changes were explored with safe, simple, noninvasive techniques to identify maternal cardiovascular maladaptations that could lead to hypertensive problems during pregnancy. Our research team used a trio of standardized and validated techniques to assess the maternal circulation: electrocardiography–Doppler ultrasonography for arteries and veins, impedance cardiography for heart function, and bioimpedance for body volume balance. When the cardiovascular studies identified a hypertensive problem, the pregnant woman was referred to the PREMOM program.

Three types of caregivers were involved in the PREMOM program:

- The referring gynecologist referred the patient at risk of GHD to the LIMPRON study, and remained the primary caregiver of the patient.
- The midwife included the pregnant woman in the RM program, explained the devices, and showed her how to use them and how an adequate BP measurement is made. The midwife also controlled and evaluated the data on the online dashboard and sent a weekly overview of the BPs to the referring and supervising gynecologists. When an alarming symptom occurred, the midwife contacted the responsible gynecologist and the supervising gynecologist. If an intervention was required, the midwife contacted the pregnant woman and monitored the effectiveness of the intervention (for example, if BP was reduced by an adjustment in the patient's antihypertensive medication).

- The supervising gynecologist performed the LIMPRON investigations and referred the patient to the PREMOM program when necessary. When an intervention was required, he/she suggested the most effective therapy, based on the LIMPRON results.

During the 4 years of this doctoral study, a network was set-up between all the hospitals in Limburg. The partners involved were: JESSA Ziekenhuis, Hasselt; Sint-Franciskusziekenhuis, Heusden-Zolder; Ziekenhuis Maas en Kempen, Bree; Mariaziekenhuis Noord-Limburg, Overpelt; Sint Trudo, Sint Truiden; and AZ Vesalius, Tongeren. Referrals from other hospitals also occurred during these years; among these were Imelda Ziekenhuis, Bonheiden; AZ Sint Lucas, Gent; Heilig Hart Ziekenhuis, Mol; AZ Turnhout, Turnhout; AZ Alma, Eeklo. The referring centers and the number of inclusions are presented in the figure below:

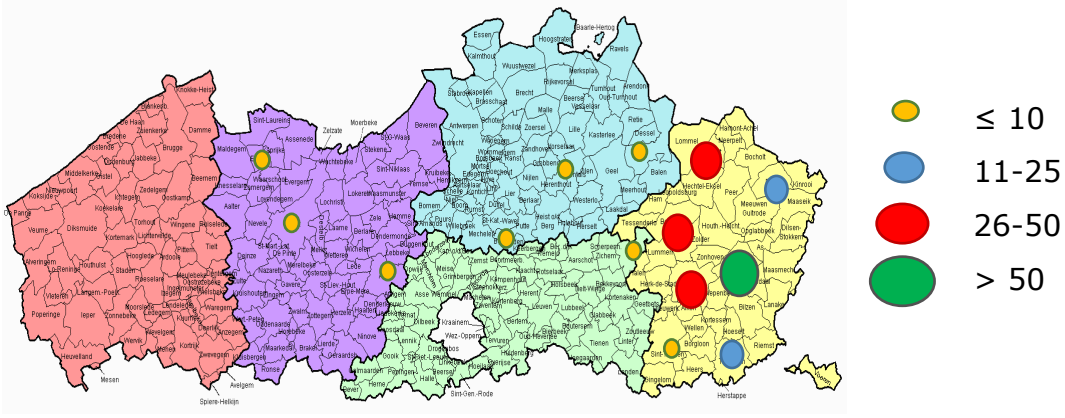

Figure 0.1: Referrals to the LIMPRON project

THE RM PROTOCOL

Women who consented to RM underwent obstetric surveillance with a Withings Wireless Blood Pressure Monitor, Withings Smart Body Analyzer, and Withings Pulse O² (Withings, Issy-les-Moulineux, France), or an iHealth Feel and iHealth Wave (iHealth, Paris, France). The pregnant women who participated in the prenatal RM follow-up program were asked

to make one BP measurement in the morning and one in the evening and one weight measurement a day, and to wear an activity tracker day and night until delivery or hospital admission.

The process followed is presented in Figure 0.2. The data from the monitoring devices were transmitted to an online dashboard developed by the Mobile Health Unit of the University of Hasselt. Predetermined alarm signals were set. One midwife remotely followed-up all the transformed data at the online dashboard. She distinguished normal and alarm signals for SBP (> 140 mmHg), DBP (> 90 mmHg), and weight gain (> 1 kg/day). When the trend line of the SBP crosses the value of 140 mmHg, and/or the trend line of the DBP crosses the value of 90 mmHg (like illustrated in Figure 0.3), this event was communicated to the obstetrician in charge and management options were discussed before the patient was contacted and instructed at home. The types of interventions used were: (1) expectant management; (2) ambulatory blood sampling and 24 h urine collection at home; (3) adjustment of antihypertensive therapy and/or physical activity; (4) admission to the antenatal ward; and (5) induction of labor. Therapeutic interventions were according to the local management strategies.

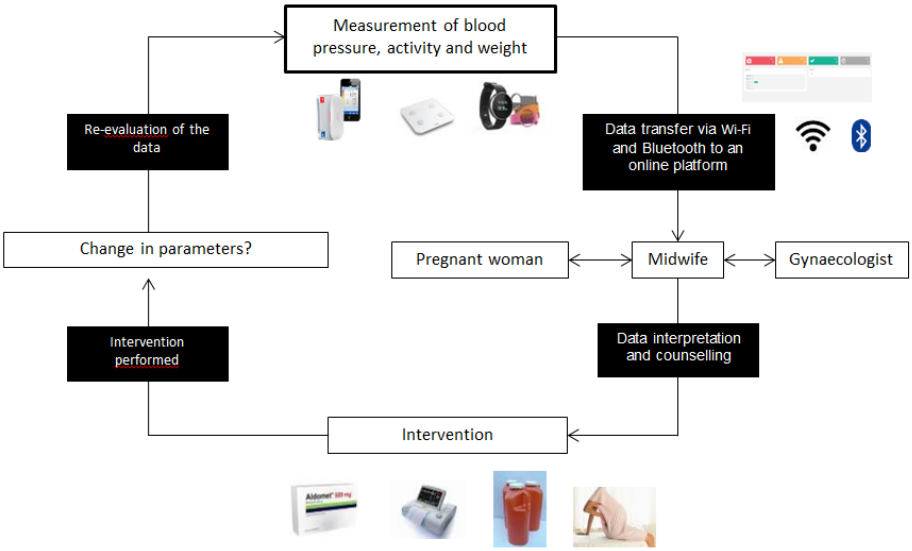

Figure 0.2: Remote monitoring process

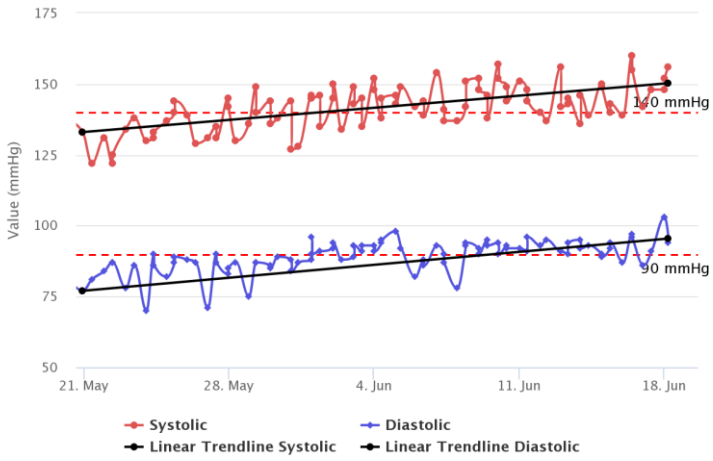

Figure 0.3: Trend lines for diastolic and systolic blood pressure

DATA USED IN THIS DOCTORAL THESIS

From the start of the PREMOM project, in January 2015, until May 2018, 504 patients were included in the RM program. Of these 504 patients, 64.23% (325/506) were referred from the Ziekenhuis Oost-Limburg (ZOL) and the other 35.77% (181/506) from other referring hospitals. A timeline of patient inclusion is presented in Figure 03.

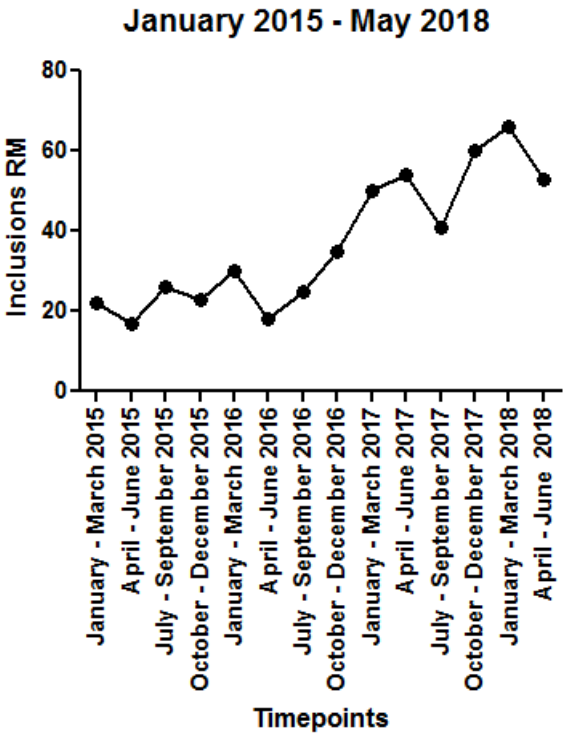

Figure 0.3: Inclusions in the RM program.

The data used for this doctoral dissertation were collected in 2015 and 2016, and include those for 86 patients who participated in the RM program. They are compared to the control group, which are patients with GHD who received conventional care (CC). The data of the CC group were retrospectively collected from the patient files in ZOL.

PART I

SCOPING REVIEW

CHAPTER 1

Effectiveness of remote monitoring in obstetrics: scoping review

Lanssens D, Vandenberk T, Thijs IM, Grieten L & Gyselaers W

J Med Internet Res. 2017 Sep 27; 19(9): e327

ABSTRACT

Background: Despite reported positive results of remote monitoring (RM) effectiveness in various health care domains, this new technology is rarely used in prenatal care. A few isolated investigations were performed in the past years but with conflicting results.

Objective: The aim of this review was to (1) assess whether RM adds any substantial benefit to this patient population and (2) identify research gaps in this area to suggest goals for future research.

Methods: This review includes studies exploring the effectiveness of RM interventions for pregnant women reported in the English language. Due to the paucity of research in this area, all reports including uncontrolled nonrandomized and randomized controlled studies were selected.

Results: Fourteen studies, which performed their data collection from 1988 to 2010, met the inclusion criteria and were published from 1995 to present; four of the 14 published papers were multicenter randomized controlled trials (RCTs), five papers were single-center RCTs, three papers were retrospective studies, one paper was an observational study, and one paper was a qualitative study. Of the 14 papers, nine were available for a risk of bias assessment: three papers were classified as "low risk," one as "medium risk," and five as "high risk." Furthermore, of those 14 papers, 13 focused on RM for maternal outcomes, and nine of the 14 papers focused on RM for fetal or neonatal outcomes. The studies reviewed report that RM can contribute to significant reductions in health care costs, (unscheduled) face-to-face visits, low neonatal birth weight, and admissions to the neonatal intensive care unit (NICU), as well as prolonged gestational age and improved feelings of maternal satisfaction when compared with a control group. When only studies with low risk of bias were taken into account, the added value of RM became less pronounced: the only added value of RM is for pregnant women who transmitted their

uterine activity by telecommunication. They had significant prolonged pregnancy survivals, and the newborns were less likely to be of low birth weight or to be admitted to the NICU. Following these results, RM can only be recommended by pregnant women at risk for preterm delivery. It is however important to consider that these studies were published in the mid-90s, which limits their direct applicability given the current technologies and practice.

Conclusions: This review shows that RM can be tentatively recommended for pregnant women at risk for preterm delivery. More recent RCTs with a blinded protocol are needed to strengthen the level of evidence around this topic and to have an insight in the added value of the technologies that are available nowadays. In addition, studies investigating patient satisfaction and economic effects in relation to RM are suggested for future research.

KEYWORDS: review; telemonitoring; obstetrics; maternal outcomes; fetal outcomes.

INTRODUCTION

With more than 6 billion mobile phone subscribers worldwide, it is estimated that 75% of the world population has access to mobile communication. The number of devices with broadband capabilities has increased to more than 1 billion worldwide (1). With more than 97,000 health-related mobile apps available and approximately 1000 new apps published every month, the potential to perform telemedicine exists (1). Telemedicine is a relatively new approach (dating back to the early 1990s), which facilitates patients' management at home (3). It can be broadly defined as the use of telecommunication technologies to assist in the transmission of medical information and services between health care providers and patients. The use of this two-way telecommunication technology, multimedia, and computer networks to deliver or enhance the delivery of health care is a growing trend internationally (4). It has the potential to improve access to high-quality disease management, and remote monitoring (RM), a subgroup of telemedicine, has developed rapidly over the past decade (5). There are several types of RM, ranging from simple to complex. In the simplest model, a patient receives support from a health care professional over the telephone. The patient monitors his or her symptoms and reports this during a structured telephone call. Moving up the scale of complexity is patient-initiated electronic monitoring with the transfer of physiologic data and record of symptoms by telephone or a broadband Internet connection from the patient's home (ie, home telemonitoring) to the health care professional. On reviewing the data, the health care professional can contact the patient to request further information before making a decision about disease management. Finally, implanted monitoring devices transmit data wirelessly from the patient to a unit that is connected to a telephone or the Internet. Once again, if the data raise concern, the health care professional can contact the patient to request further information before making a decision about care (5).

A number of systematic reviews have evaluated the effectiveness of RM interventions for patients diagnosed with chronic cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and diabetes (3, 6-9). These reviews show mainly positive results and suggest that there is tentative evidence that RM may offer clinical benefit in these three domains. All-cause mortality and heart-related hospitalizations are reduced for patients with CVD compared with patients who received usual care (6, 7). Even primary care management of CVD can be enhanced by improving patient outcomes and reducing health-related costs (8). Web-based remote monitoring for managing type 2 diabetes mellitus is also a viable approach for health care delivery and enhances patients' quality of life (9). Finally, home RM in patients with COPD appears to have a positive effect in reducing respiratory exacerbations and hospitalizations and in improving quality of life: patients with COPD were generally satisfied with home RM and found the systems useful to help them manage their disease and improve health care provision (3). With regard to fertility, a few papers on RM discussing self-operated endovaginal RM of the ovarian stimulation phase in in vitro fertilization or intracytoplasmic sperm injection are published. This technique leads to relevant clinical decisions; significantly higher satisfaction of patients and their partner; a higher feeling of empowerment, discretion, and more active partner participation; as well as a trend toward less stress versus a traditional monitored group (10-12). Despite the mainly positive results in the various health care domains and the ability to perform RM because of the improvement of technology, RM is rarely used in prenatal care. A few independent investigations were performed in the last years, but a systematic review has not yet been accomplished. For this reason, a systematic review of all clinical trials evaluating RM in high-risk pregnancies was performed. First, the characteristics of the study will be described, and then the maternal and neonatal outcomes in RM group versus control group (CG) will be reported. We aim to (1) assess

whether RM adds any substantial benefit in the pregnant women population and (2) identify research gaps in this area and thereby suggest topics for future research.

METHODS

SEARCH STRATEGY

The following databases were comprehensively searched in August 2016 by two independent researches: the Medical Literature Analysis and Retrieval System Online (MEDLINE), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), PubMed, Limo, and the Cochrane Library. The enumeration of selected relevant journals was manually screened, and the bibliographies of all retained papers were examined for relevant studies. A third reviewer resolved discrepancies in judgment and verified the completeness of the manuscript.

SEARCH ITEMS

The following terms were used in the search bar of the mentioned databases: "remote monitoring," "telemonitoring," "home monitoring," "telemedicine," "maternal health," "telehealth," "e-health," "pregnancy," "pregnancy-outcomes," "gynecology," "gravidity," and "obstetrics." Also medical subject headings (MeSH) thesaurus combined were used with the following terms: "blood pressure monitoring, ambulatory," "blood glucose self-monitoring," "pregnancy," 'pregnancy outcome," "gynecology," and "obstetrics."

A DEFINITION OF TELEMONITORING

In this review, we specified the definition of RM—as stated in the introduction—further to the following inclusion criteria: (1) require the patient to periodically measure physiological parameters (eg, blood pressure and weight) and/or record their symptoms or vital signs in a standardized format, (2) use telecommunication technologies (eg, mobile phone and Internet) that either manually or automatically transferred the patient's health status data from home to a health care service, and (3) lead to the automated or manual review of the patient's health status data.

INCLUSION AND EXCLUSION CRITERIA

To be included, studies had to examine the effectiveness of RM interventions for pregnant women as defined above. Scoping searches indicated a paucity of research in this area, and we therefore included uncontrolled and nonrandomized, as well as randomized controlled studies. All published studies reporting economic and/or clinically related outcomes (eg, hospital admission and preterm labor) were considered. Due to the scarce available publications, no time limitations were applied. All papers had to be written in English. Studies were excluded if health care professionals conducted the measurement of physiological signs at the patient's home. In addition, review papers, expert opinions, and single case or case series reports were excluded.

SELECTION PROCEDURE

A flowchart of the selection procedure is shown in Figure 1.1: Selection procedure. The database search identified 1437 papers. After the removal of duplicates, 1059 records were screened for relevant content. During title, abstract, and keyword screening, 969 papers were excluded because of the absence of the inclusion criteria. The full-text of the 90 potentially relevant papers was assessed, and 82 papers were excluded. Reasons for exclusion included (1) no clinical or economical relevance (n=32), (2) does not meet the definition of RM (n=21), (3) not written in English (n=8), (4) expert opinions (n=15), and (5) (systematic) reviews (n=6). Automatic updates from the databases and search for relevant papers within the bibliography of selected papers retrieved six papers, which were also included. In total, 14 papers were included.

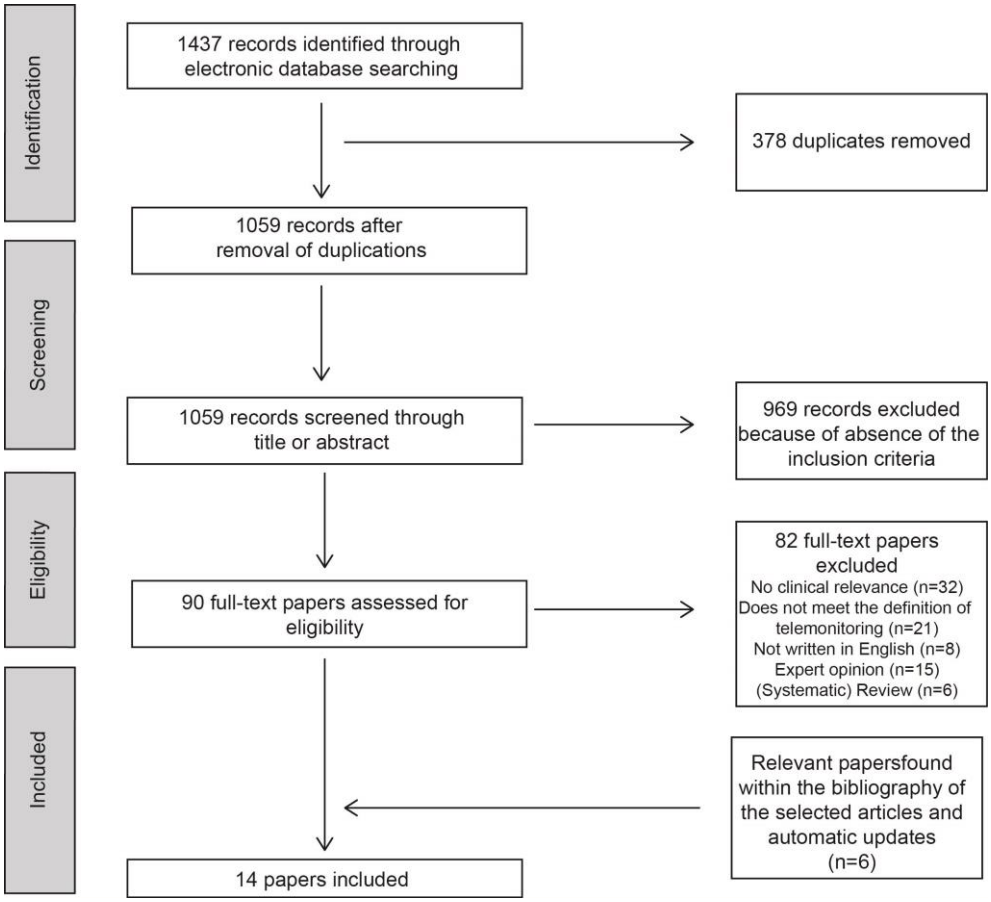

Figure 1.1: Selection procedure

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

A report on the methodological risk of bias of included studies (which had a randomized controlled design) in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (33) and the guidelines of the Cochrane Consumers and Communication Review Group was made. These guidelines recommend the explicit reporting of the following individual elements for randomized controlled trials (RCTs): random sequence generation, allocation sequence concealment, blinding (participants and personnel), blinding (outcome assessment), completeness of outcome data, and selective outcome reporting. Each item is judged as being at high, low, or unclear risk of bias as set out in

the criteria provided by Higgins et al (2011). Studies will be deemed to be at the highest risk of bias if they are scored as at high or unclear risk of bias for either the sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias (33).

DATA EXTRACTION

The following information was collected and tabulated from the included studies: description of patient population, sample size, whether any economic evaluation was performed, the nature of the intervention, and the outcomes reported.

RESULTS

STUDY CHARACTERISTICS

Fourteen studies were included, published from 1995 to present. An overview of these publication dates is presented in Figure 1.2.

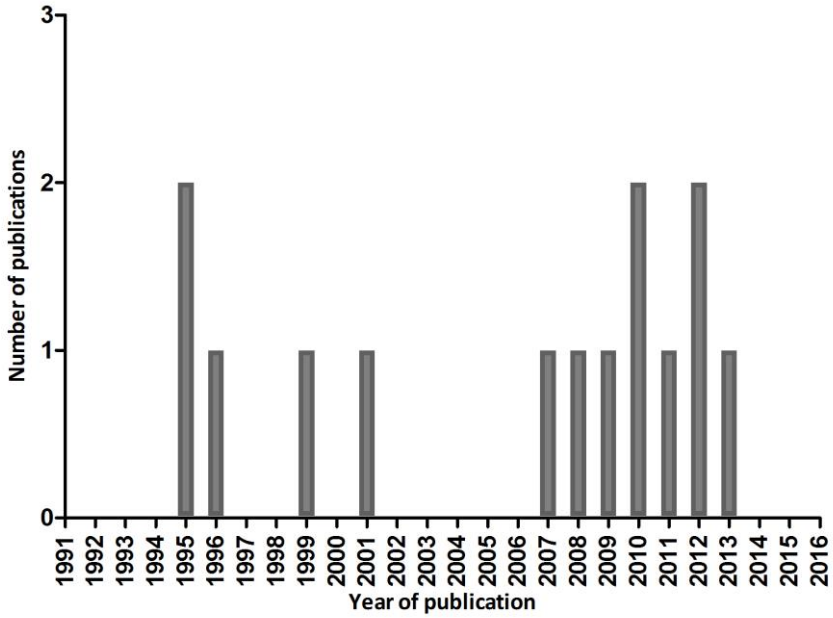

Figure 1.2: Number of publications during the last 25 years

Although the dates of the publications were from 1995 to present, the data collection was performed from 1988 to 2010.

Four of the 14 published papers were multicenter RCTs (13, 19, 34, 35), five papers were single-center RCTs (15-18, 36), three papers were retrospective studies (14, 22, 37), one paper was an observational study (20), and one paper was a qualitative study (21).

Tables 1.1 and 1.2 provide an overview of the characteristics of each study. All 14 papers report RM in obstetrics; 13 of the 14 papers focused on RM for maternal outcomes (13-22,

34, 36, 37), and nine of the 14 papers focused on RM for fetal or neonatal outcomes (13, 15-19, 34, 35). Samples included varied from 15 singleton pregnancies (21) to 1292 singleton pregnancies (34). Nine of the 14 papers were available for a risk of bias assessment: three papers were classified as "low risk" (13, 14, 34), one as "medium risk" (36), and five as "high risk" (15-19). Five of the 14 papers did not have an RCT design (20-22, 35, 37). For this reason, there was no risk of bias assessment made for them.

Table 1.1: summary table of included studies – maternal outcomes

Citation	Profile of included studies					Design of included studies						
	Nation-ality	Dates data collected	Study parti-cipants	Profes-sional feedback based on RM data	Data AT or MT	Design	Risk of bias	Size of experimental group	Size of control group	Study duration	Main types of data being transferred	Frequen-cy of data transmis sion
CHUMS Group (1995) (34)	United States of America	15/01/1991 – 27/05/1994	1292 singleton pregnancies at high risk for preterm labor	Yes	AT	MRCT	LR	N = 655	N = 637	From 24 – 32 weeks of gestation until 37 weeks of gestation or delivery	Uterine activity	Twice daily
Wapner et al. (1995) (14)	United States of America	02/1991 – 02/1993	218 singleton pregnancies at high risk for preterm labor or birth	Yes	AT	MRCT	LR	N = 107	N = 111	From 24 – 36 weeks of gestation until 37 weeks of gestation or delivery	Uterine activity	Twice daily
Corwin et al. (1996) (13)	United States of America	01/09/1988 – 31/08/1989	399 singleton pregnancies at high risk for preterm labor	Yes	AT	MRCT	LR	N = 174	N = 165	From 24 – 32 weeks of gestation until 37 weeks of gestation or	Uterine activity	Twice daily

										delivery		
Brown et al. (1999) (36)	United States of America	01/07/1991 – 01/01/1996	162 singleton pregnancies at high risk for preterm labor	Yes	AT	SRCT	MR	N = 82	N = 80	From 24 – 29 weeks of gestation until delivery	Uterine activity	Twice daily
Morrison et al. (2001) (22)	United States of America	01/1992 – 11/1994	100 singleton pregnancies diagnosed with preterm labor	Yes	AT	RS	/	N = 60	N = 40	N/A	Uterine activity	N/A
Homko et al. (2007) (15)	United States of America	09/2004 – 05/2006	57 singleton pregnancies with GDM	Yes	MT	SRCT	HR	N = 32	N = 25	Less than 33 weeks' of gestation until delivery	Blood glucose levels, fetal movement counting's, insulin doses, episodes of glycaemia	Three times a week
Buysse et al. (2008) (37)	Belgium	01/01/2005 – 01/06/2006	456 episodes originating from 415 patients (patients are not further defined)	No	N/A	RS	/	N = 456	N/A	N/A	Costs	N/A
Dalfrà et al. (2009) (19)	Italy	N/A	276 pregnant women of whom 240 diagnosed with GDM and 36 diagnosed with diabetes type 1	Yes	MT	MCRT	HRF	GDM N = 88 Diabetes type 1 N = 17	GDM N = 17 Diabets types 1 N = 15	GDM: a week after the diagnoses of GDM until delivery. Diabetes type 1: from first visit	Capillary glucose data	Once a week and more often is neces-sary

										after conception until delivery.		
Pérez-Ferre et al. (2010) (17)	Spain	06/2007 – 12/2007	97 singleton pregnancies diagnosed with GDM before 28 week of gestation	Yes	MT	SRCT	HR	N = 49	N = 48	From 24 – 32 weeks of gestation until delivery	Capillary glucose data	Once a week
Pérez-Ferre et al. (2010) (18)	Spain	06/2007 – 12/2007	97 singleton pregnancies diagnosed with GDM before 28 week of gestation	Yes	MT	SRCT	HR	N = 49	N = 48	From 24 – 32 weeks of gestation until delivery	Capillary glucose data	Once a week
Rauf et al. (2011) (20)	United Kingdom	01/01/2009 – 31/12/2010	70 women with healthy singleton pregnancies which had an induction of labour	Yes	AT	OS	/	N = 70	N/A	From 37 weeks of gestation until delivery	Uterine activity	Continuously monitoring from the moment of induction
Homko et al. (2012) (16)	United States of America	09/2007 – 11/2009	80 singleton pregnancies with GDM	Yes	MT	SRCT	HR	N = 40	N = 40	Less than 33 weeks' of gestation until delivery	Capillary glucose data	Four times a day
O'Brien et al. (2013) (21)	United Kingdom	N/A	15 singleton pregnancies which had an	N/A	AT	QS	/	N = 15	N/A	From 37 weeks of gestation	Uterine activity	Continuously monitorin

			induction of labour							until delivery		g from the moment of induction

AT = automatically transferred; MT = manually transferred; MRCT = multicenter randomized controlled trials ; SRCT = single randomized controlled trials ; RS = retrospective study; OS = observational study; QS = qualitative study; LR = low risk; MR = medium risk; HR = high risk. GDM = gestational diabetes mellitus; RM = remote monitoring group; CC: = control group. N/A = not applicable

Table 1.2: Summary table of included studies – neonatal outcomes

Citation	Profile of included studies					Design of included studies						
	Nationality	Dates data collected	Study participants	Professional feedback based on RM data	Data AT or MT	Des-ign	Risk of bias	Size of experimental group	Size of control group	Study duration	Main types of data being transferred	Frequency of data transmission
CHUMS Group (1995) (34)	United States of America	15/01/1991 – 27/05/1994	1292 singleton pregnancies at high risk for preterm labor	Yes	AT	MRCT	LR	N = 655	N = 637	From 24 – 32 weeks of gestation until 37 weeks of gestation or delivery	Uterine activity	Twice daily
Corwin et al. (1996) (13)	United States of America	01/09/1988 – 31/08/1989	399 singleton pregnancies at high risk for preterm labor	Yes	AT	MRCT	LR	N = 174	N = 165	From 24 – 32 weeks of gestation until 37 weeks of gestation or delivery	Uterine activity	Twice daily
Morrison et al. (2001) (22)	United States of America	01/1992 – 11/1994	100 singleton pregnancies diagnosed with preterm labor	Yes	AT	RS	/	N = 60	N = 40	N/A	Uterine activity	N/A
Homko et al. (2007)	United States	09/2004 – 05/2006	57 singleton pregnanci	Yes	MT	SRCT	HR	N = 32	N = 25	Less than 33 weeks' of	Blood glucose levels, fetal	Three times a week

(15)	of America		es with GDM							gestation until delivery	movement counting's, insulin doses, episodes of glycaemia	
Dalfrà et al. (2009) (19)	Italy	N/A	276 pregnant women of whom 240 diagnosed with GDM and 36 diagnosed with diabetes type 1	Yes	MT	MCRT	HR	GDM N = 88 Diabetes type 1 N = 17	GDM N = 17 Diabets types 1 N = 15	GDM: a week after the diagnoses of GDM until delivery. Diabetes type 1: from first visit after conception until delivery.	Capillary glucose data	Once a week and more often is neces-sary
Pérez-Ferre et al. (2010) (17)	Spain	06/2007 – 12/2007	97 singleton pregnancies diagnosed with GDM before 28 week of gestation	Yes	MT	SRCT	HR	N = 49	N = 48	From 24 – 32 weeks of gestation until delivery	Capillary glucose data	Once a week
Pérez-Ferre et al. (2010) (18)	Spain	06/2007 – 12/2007	97 singleton pregnancies	Yes	MT	SRCT	HR	N = 49	N = 48	From 24 – 32 weeks of gestation until	Capillary glucose data	Once a week

			diagnosed with GDM before 28 week of gestation							delivery		
Homko et al. (2012) (16)	United States of America	09/2007 – 11/2009	80 singleton pregnancies with GDM	Yes	MT	SRCT	HR	N = 40	N = 40	Less than 33 weeks' of gestation until delivery	Capillary glucose data	Four times a day
Kuleva et al. (2012) (35)	France	1999 - 2010	singleton pregnancies complicated by fetal gastroschisis	Yes	N/A	RS	/	N = 97	N/A	From 24 – 32 weeks of gestation until 37 weeks of gestation or delivery	Fetal heart rate	Daily

AT = automatically transferred; MT = manually transferred; MRCT = multicenter randomized controlled trials ; SRCT = single randomized controlled trials ; RS = retrospective study; OS = observational study; QS = qualitative study; LR = low risk; MR = medium risk; HR = high risk. GDM = gestational diabetes mellitus; RM = remote monitoring group; CC: = control group. N/A = not applicable

RM data were generally transmitted to a monitoring center on a regular basis. Patients' compliance with data transmission was assessed in three studies (14-16) and ranged from a mean of 21.8 (±16.9) sets of data (15) to a mean of 35.6 (±32.3) sets of data (16)depending on the physiological parameter measured. All the data were automatically transferred in the studies that investigated the added value of RM in pregnancies at high risk for preterm delivery or with an induction (13, 14, 20, 22, 34, 35, 37). The data of the studies which investigated the added value of RM in GDM was manually transferred (15-19). In almost all studies, patients' recordings outside predetermined values triggered an immediate action. Usual care included the same healthcare component as provided to the RM group, but without RM.

Maternal outcomes

Table 1 provides a summary of the twelve studies included focusing on RM for maternal outcomes: cervical dilatation/preterm labour, gestational diabetes mellitus, maternal satisfaction and health care related costs. These results will be further discussed below.

1. Cervical dilation/preterm labour

The use of RM in the monitoring of fetal heart rate and uterine activity dates back to the 1970s. The expected benefits lie in the prevention of perinatal mortality and morbidity (4). In five studies, women with singleton pregnancies at high risk for preterm birth were randomly assigned to a RM group and a control group. The results of these studies are presented in table 1.3.

Table 1.3: Cervical dilatation/preterm labour and RM

Citation	Risk of bias	Prolonged pregnancy survival	*p-value RM vs. CC*	Experience of a preterm delivery	*p-value RM vs. CC*
Brown et al. (1999) (36)	LR			-	0.73
Corwin et al. (1996) (13)	LR	+	0.02	-	0.04
CHUMS Group (1995) (34)	(LR			-	NS*
Wapner et al. (1995) (14)	LR	+	0.016		
Morrison et al. (2001) (22)	/			-	<0.001

+ = more experiences in RM group vs CC group; - = less experiences in RM group vs CC group. RM group = remote monitoring group; LR = low risk; MR = medium risk; HR = high risk; CC = control group; NS = not significant; * = no exact value is given

2. Gestational diabetes mellitus

The application of telemedicine in the management of GDM has primarily focused on the transfer of blood glucose values from the patient to the provider, thereby eliminating frequent clinical visits and adverse maternal and fetal/neonatal outcomes (4). Five studies did report these study-outcomes (table 1.4).

Table 1.4: Gestational Diabetes Mellitus and RM

Citation	Risk of bias	FBS	*p-value RM vs. CC*	HbA1c < 5.8%	*p-value RM vs. CC*	Insulin therapy	*p-value RM vs. CC*	Out-patient clinic visits	*p-value RM vs. CC*
Homko et al. (2007) (15)	HR	0	NS*			+	< 0.05		
Dalfrà et al. (2009) (19)	HR			0	NS*	0	NS*		
Homko et al. (2012) (16)	HR	0	0.26			+	*		
Pérez-Ferre et al. (2010) (17)	HR							-	<0.001
Pérez-Ferre et al. (2010) (18)	HR			0	NS*			-	<0.001

+ = more experiences in RM group vs CC group; - = less experiences in RM group vs CC group; 0 = no differences. RM group = remote monitoring group; LR = low risk; MR = medium risk; HR = high risk; CC = control group; FBS = fasting blood sugar; NS = not significant; * = no exact value is given

3. Maternal satisfaction

Because of the new aspect of RM, the maternal satisfaction of these domain is rarely investigated. Table 1.5 summarizes the major findings of five studies after adding RM to the obstetrical care.

Table 5: Maternal satisfaction and RM

Citation	Risk of bias	Result for women in RM group
Homko et al. (2007) (15)	HR	More feelings of self-efficacy in women with GDM
Dalfrà et al. (2009) (19)	HR	Women in RM showed lower levels of frustration and concerns about their GDM, and a better acceptance of their diabetic condition.
O'Brien et al. (2013) (21)	/	Better birth experiences resulting by induction of labour at home
Pérez-Ferre et al. (2010) (17)	HR	Higher patient satisfaction in women with GDM
Rauf et al. (2011) (20)	/	Labour induction at home is feasible and acceptable to women
RM group = remote monitoring group; LR = low risk; MR = medium risk; HR = high risk; GDM = gestational diabetes mellitus		

4. Health care related costs

The continuous strain on hospital bed occupancy puts clinicians under great pressure to discharge patients as soon as possible. It is assumed that RM can contribute to solve this problem. Two studies did compute these costs for a RM group in comparison with a CC group (table 1.6).

Table 1.6: Health care related costs and RM

Citation	Risk of bias	Result for women in RM group vs. women in CC group	
		Total cost saving	**Average cost saving per pregnancy**
Buysse et al. (2008) (37)	/	€145,822 for 415 pregnant women	€351.38
Morrison et al. (2001) (22)	/	$867,540 for 60 pregnant women	$14,459
RM group = remote monitoring group; LR = low risk; MR = medium risk; HR = high risk; CC = control group; € = euro; $ = United State dollars			

Fetal/neonatal outcomes

Table 2 provides a summary of the eight included studies focusing on RM for fetal/neonatal outcomes. In the next section will the influence of RM on the following fetal/neonatal outcomes, be presented: birth weight, gestational age and submission to the Neonatal Intensive Care.

1. Birth weight

Infants born small for gestational age (generally defined as less than 10^{th} percentile) or large for gestational age (generally defined greater than 90^{th} percentile) are at higher risk of short- and long term morbidities than appropriately grown for gestational age infants (38). A total of eight studies examined the impact of RM interventions on the birth weight of the neonate, which are presented in table 1.7.

Table 1.7: Birth weight and RM

Citation	Risk of bias	SGA (< 10th percentile)	*p-value RM vs. CC*	Mean birth weight	*p-value RM vs. CC*	LGA (> 90th percentile)	*p-value RM vs. CC*
CHUMS Group (1995) (34)	LR	-	NS*	+	NS*		
Corwin et al. (1996) (13)	LR	-	0.003				
Homko et al. (2007) (15)	HR					+	NS*
Dalfrà et al. 2009 (19)	HR			0	NS*	0	NS*
Homko et al. (2012) (16)	HR			0	0.30	+	0.70
Morrison et al. (2001) (22)	/	-	0.001	+	<0.001		
Pérez-Ferre et al. (2010) (17)	HR			0	NS*		
Pérez-Ferre et al. (2010) (18)	HR			0	0.39	-	NS*

+ = more experiences or higher mean in RM group vs CC group; - = less experiences or lower mean in RM group vs CC group; 0 = no differences. RM group = remote monitoring group; LR = low risk; MR = medium risk; HR = high risk ;CC = control group; NS = not significant; * = no exact value is given

2. Gestational age

We previously reported the influence of RM on cervical dilation/preterm labor. One of the consequences of preterm labor is a preterm delivery of the newborn. Only four studies reported gestational age of the newborn as a main outcome. In table 1.8, the rate of experiences of preterm births (for the gestational age of less than 37 weeks; less than 36 weeks; less than 35 weeks; less than 34 weeks; or less than 32 weeks) in RM group vs CC group is reported.

Table 1.8: Gestational age and RM

Citation	**Risk of bias**	**< 37 wks**	***p-value RM vs. CC***	**< 36 wks**	***p-value RM vs. CC***	**< 35 wks**	***p-value RM vs. CC***	**< 34 wks**	***p-value RM vs. CC***	**< 32 wks**	***p-value RM vs. CC***
CHUMS Group (1995) (34)	LR	+	NS*	-	NS*			-	NS*		
Homko et al. (2007) (15)	HR	0	NS*								
Morrison et al. (2001) (22)	/					-	<0.01			-	0.003
Kuleva et al. (2012) (35)	/			-	0.016						

+ = more experiences or higher mean in RM group vs CC group; - = less experiences or lower mean in RM group vs CC group; 0 = no differences. RM group = remote monitoring group; LR = low risk; MR = medium risk; HR = high risk; CC = control group; wks = weeks; NS = not significant; * = no exact value is given

3. Submission to Neonatal Intensive Care Unit (NICU)

Four studies have investigated the added value of RM and the submission to the NICU. These studies are presented in table 1.9.

Table 1.9: Submission to Neonatal Intensive Care Unit and RM

Citation	Risk of bias	Admission NICU	*p-value RM vs. CC*
CHUMS Group (1995) [20]	LR	-	NS*
Corwin et al. (1996) [14]	LR	-	0.01
Homko et al. (2007) [18]	HR	+	NS*
Morrison et al. (2001) [24]	/	-	< 0.001

+ = more experiences in RM group vs CC group; - = less experiences in RM group vs CC group. NICU = Neonatal Intensive Care Unit; RM group = telemonitoring group; LR = low risk; MR = medium risk; HR = high risk; CC = control group; NS = not significant; * = no exact value is given

DISCUSSION

The low level of evidence suggests a potential benefit of RM in the prenatal care This review provided a comprehensive description of the use of RM interventions in obstetrics. Nine of fourteen articles were published from 2007 to present, suggesting that RM interventions are a relatively new field in obstetrics research. The articles of RM which included cervical dilatation/preterm labour as a main outcome, demonstrated that transmitting uterine activity by telecommunication resulted in significant prolonged pregnancy survivals (13, 14). The articles of RM for GDM demonstrated lower levels of frustration and concerns about their diabetes, and a better acceptance of their diabetic condition (19), elated feelings of self-efficacy (15) and a reduction in (unscheduled) face-to-face visits (17, 18) in the RM group compared with the control group. On top, a cost reduction (22, 37) and elevated feelings of maternal satisfaction (15, 20, 21) were obtained when RM was used in obstetrical care. The newborns did have a higher gestational age at delivery (22) and were less likely to be of low birth weight (13, 22) or to be admitted to the NICU (13, 22) when a RM group was compared with a control group. Fetuses with abnormal versus normal fetal heart rate at home monitoring were more likely to have an earlier gestational age (35).

Despite the mainly positive results described above, a distinction between studies with low methodological risk of bias assessment and studies with high methodological risk of bias assessment has to be made. When only studies with low risk of bias assessment were taken into account, the added value of RM became less pronounced. Only pregnant women who transmitted their uterine activity by telecommunication would experience benefits of this technology. They had significant prolonged pregnancy survivals (13, 14), and the newborns were less likely to be of low birth weight (13) or to be admitted to the NICU (13). The study by the CHUMS group (1995) was rated low risk for bias, but didn't mention any significant results for these metrics. Based upon the low risk for bias criteria,

RM appears to be useful for reducing preterm delivery for pregnant women at risk, but caution should be used because only two high-quality studies reported these benefits were found. Also, these articles with a low risk for bias were published in the mid 90s. Their conclusions are questionable when we want to adapt them to current practice, due to rapid changes in technology.

RESEARCH GAPS AND SUGGESTIONS FOR FUTURE RESEARCH

Despite the positive results, which are reported above, further research needs to be done to define the added value of RM and advocate the use of this intervention as a patient management approach in clinical practice. Three main recommendations for future research are made, based on the research gaps elucidated through this review:

1. The level of evidence of the included articles is not high. When a methodological risk of bias is performed, four of these studies classified as 'high risk', one as 'medium risk' and three as 'low risk'. Information about randomization (random sequence generation and allocation of concealment) was often lacking, blinding of participants, personnel and outcomes wasn't performed in most studies and none of the used protocols in the intervention groups were available. The level of evidence of the other five studies (which were retrospective studies, a qualitative study and an observational study) was much lower. There is a need for new multicentric randomized controlled trials on different pregnancy conditions in which a blinding for both the patients and the caregivers as the outcomes is performed, but with well-considered decisions regarding the ethical aspects. This to (1) associate the potential of RM interventions with maternal and fetal outcomes, (2) verify the results which are become in the mentioned study, (3) investigate the added value of the new technologies nowadays and (4) improve the evidence on this topic with rigorous research designs.

2. Only four studies reported maternal satisfaction in relation with the use of RM during their pregnancy (two of them about the use of RM in pregnancies complicated with GDM; two in the context of labor induction at home). These studies have a relatively small patient population, ranging from 15 – 70 pregnant women. Patients' satisfaction with the use of RM systems should be further explored using more robust and validated instruments. Also an evaluation of satisfaction of RM when used in pregnancies with other pregnancy complications (like gestational hypertension, premature contractions etc.) and in a bigger patient populations is recommended. Alternatively, a thorough qualitative analysis can be conducted to enable an in-depth understanding of patients' satisfaction and the use of that information to improve future technology designs. This may help adjusting the interventions to the target population and can have a positive impact on various domains like patient compliance, birth experiences, etc.

3. Only two studies did perform a cost-analysis of prenatal care including RM. Both were retrospective studies that were not assessed for risk of bias. Although these studies demonstrated the possibility of cost-reduction with the use of RM, there were visible shortcomings in the study designs Buysse et al. (2008) performed a retrospective study and didn't include variables like time-travel distance from home to hospital and the patient's actual clinical condition. In addition, the staffing costs and equipment costs (based on a reasonable estimate) weren't taken into account. Also, the data in the study of Morrison et al. (2001) was retrospectively collected and didn't included the actual clinical condition. In contrast to the previous mentioned study, they asked a fee to finance RM costs. It is challenging to examine the cost-benefit of RM when it's added to standard prenatal care and whether this is beneficial in both high- and low-risk pregnancies. We recently stated that new technologies can reduce the medicalization of prenatal care (39), but further studies with a prospective design and patient specific treatment(s) are needed

to substantiate or reject this hypothesis and to evaluate the cost-effectiveness and healthcare utilization of RM in obstetrical care.

LIMITATIONS

This review has several limitations that need to be acknowledged. First, the studies were restricted to the English language. Although records written in other languages were excluded, they could be relevant in the scope of this review. Secondly, a key limitation in the included articles is the heterogeneity of the interventions reported by the investigators. RM interventions are frequently multi-dimensional, containing a range of elements including the transmission of physiological data, coaching, telephone support, nurse interventions and web based communications (9). A few studies had a clearly stated aim for the RM intervention implemented but in general, the RM intervention is poorly described, especially in terms of the assessment of the data transferred and how this assessment leads to a service response or not. Thirdly, the rapid technological advancements that have been seen in the last decade may also impact the ability to compare older and newer studies using different technology. The oldest study dates from 1995, the most recent from 2012. Finally, there was almost no information concerning missing data or the compliance of the patients. The often missing information about compliance rates suggests that RM regimens may not be appropriate for all patients.

CONCLUSION

Overall, this review has shown the added value, for both mother and child, of RM used in a prenatal follow-up program in obstetrical care. However, most of the included studies have a high methodological risk of bias. When only studies with low risk of bias are taken into account, the added value of RM became less pronounced. Only the pregnant women who transmitted their uterine activity by telecommunication had significant benefits from this technology: they experienced prolonged pregnancy survivals and the newborns were less

likely to be of low birth weight or to be admitted to the NICU. Based upon the limited results of two high-quality studies conducted in the mid 90s, RM can be tentatively recommended for pregnant women at risk for preterm delivery. However, more recent randomized controlled trials with a blinded protocol and studies investigating patient satisfaction and economic effects in relation to RM are suggested for future research.

PART II

GESTATIONAL PHYSIOLOGY AND REMOTE MONITORING

CHAPTER 2

Detection of subclinical transient fluid accumulation during pregnancy in a patient with an implantable cardioverter defibrillator and Optivol® fluid monitoring algorithm

Smeets CJP, **Lanssens D**, Gyselaers W, Bertrand PB, Grieten L & Vandervoort P

Int J Cardiol. 2016 Juli 1; 214: 163-5

CASE PRESENTATION

The case of a 32-year-old female patient who developed an OptiVol 2.0 fluid index crossing at $7^{3/7}$ weeks of pregnancy, primigravida, is reported. An implantable cardioverter defibrillator (ICD, Protecta™ XT VR, Medtronic, Brussels, Belgium) with second generation fluid build-up detection algorithm, was implanted in 2011 after an episode of sudden cardiac death related to the Marfan syndrome with secondary heart failure (40, 41). In 2013, she underwent valve sparing aortic root replacement and mitral valve repair surgery because of aortic root dilation and severe mitral valve regurgitation (prolapse). She has been in routine follow-up since, with dilated left ventricular dimensions and borderline ejection fraction. The patient was included in the remote monitoring follow-up program of Ziekenhuis Oost-Limburg (Genk, Belgium) prior to conception by oocyte donation in April 2014.

In the early phase of pregnancy, at $7^{3/7}$ weeks, the patient developed an OptiVol 2.0 fluid index crossing (Event 1) (Figure 2.1). This crossing triggered an alert that was handled by specialized remote monitoring nurses. After thorough analysis of the alert and investigation of the other parameters, which seemed to be normal, the patient was contacted by phone interview to identify possible causes of this fluid buildup alert. The interview contained a structured questionnaire that can identify (early) signs of fluid retention, including shortness of breath and the presence of edema. The patient was asymptomatic, responded negative to all questions and consequently no further actions were undertaken. The OptiVol 2.0 fluid index crossing was closely monitored further.

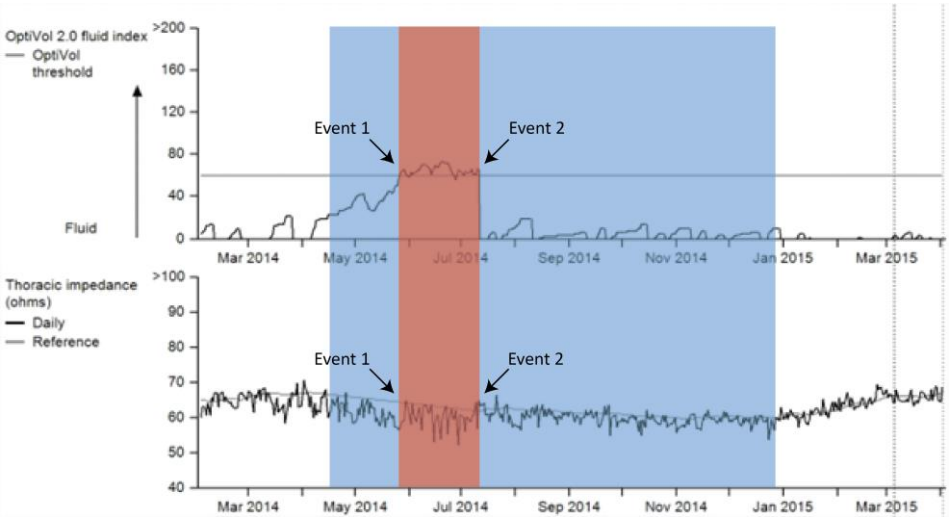

Figure 2.1: Overview of the OptiVol 2.0 information from an implantable cardioverter defibrillator. Blue box: gestation period; Red box: period of fluid index crossing; Red arrows: OptiVol crossing which triggers the fluid built up alert (Event 1); Green arrows: reset of the fluid index which corresponds to the end of the fluid built up alert (Event 2).

During the gestational period, thoracic impedance values kept decreasing (i.e. fluid accumulation). Significant difference in thoracic impedance values is found between the means before pregnancy vs. the second trimester of pregnancy ($p<0.01$) and second trimester of pregnancy vs. post-pregnancy ($p<0.01$). After delivery, thoracic impedance values recovered to pre-pregnancy values ($p=0.79$). (Figure 2.2)

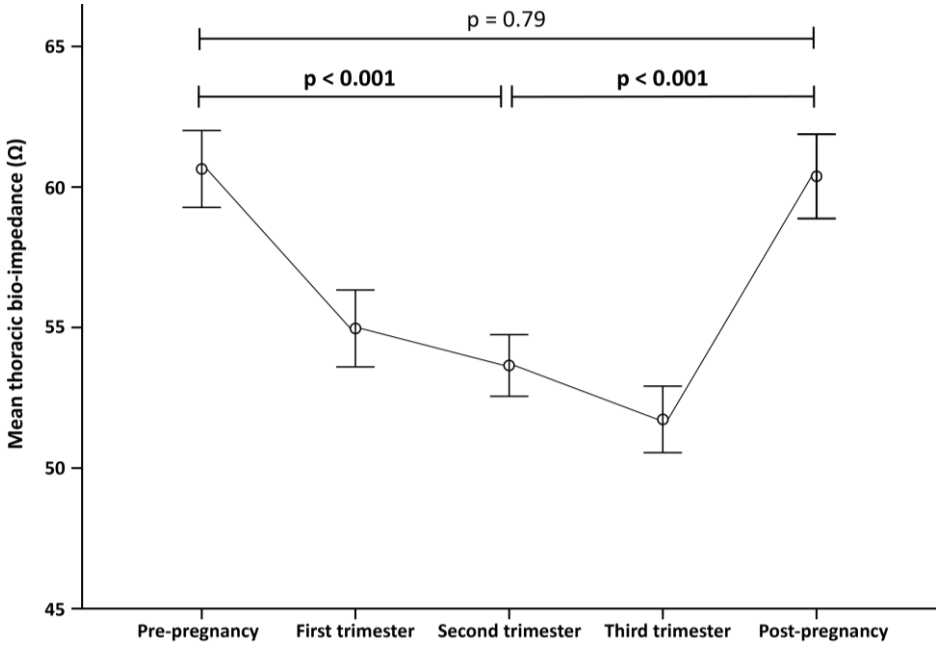

Figure 2.2: Mean thoracic bio-impedance values with 95% confidence intervals. p-values were calculated via independent t-test.

Interestingly, the OptiVol fluid index already recovered at week $13^{3/7}$ because of a crossing event between the daily thoracic impedance value and the reference signal (Event 2). No further OptiVol events were identified during the rest of the pregnancy (Figure 2.1). At 38 $^{4/7}$ weeks of gestation, a healthy boy of 3370g was delivered by C-section (breech presentation) with an Apgar score of 9 - 10 - 10. There were no obstetric complications for the mother, neither for the neonate.

DISCUSSION

The case of a pregnant woman, suffering from the Marfan syndrome, who received an OptiVol 2.0 fluid index crossing alarm through an implantable cardioverter defibrillator at $7^{3/7}$ weeks of pregnancy was presented. At pregnancy onset, thoracic impedance values decreased significantly. It is known that during pregnancy total fluid content, especially extracellular water, of the pregnant mother increases (42, 43). These results are well in line with our findings indicating that a possible explanation for the OptiVol crossing is due to fluid buildup during pregnancy and after delivery the total fluid content shifts back to normal values. Current findings indicate a significant decrease in thoracic impedance, indicating an increase in thoracic fluid content, at gestation onset. Based on the bioimpedance signal, the thoracic fluid content remained at a higher level during the whole pregnancy and started to recover to initial pre-pregnancy values immediately after delivery.

Importantly, the OptiVol crossing alert was only present from week $7^{3/7}$ and already disappeared at week $13^{3/7}$, although the raw bio-impedance remained at the same level and even slightly decreased further during pregnancy, indicating a further increase in thoracic fluid content. OptiVol is a fluid index measurement and indicates an accumulation of the difference between the daily impedance and dynamic reference impedance and is more an indication whether an event may occur in the near future or has occurred in the past. Since the fluid index takes into account a dynamic reference impedance value, it constantly adjusts for the new bio-impedance values. In fact, the reference impedance works as the patient's own control and the fluid index resets when the reference line is met. The thoracic impedance on the contrary gives a better estimation of thoracic fluid content since it plots the raw data measured from the right ventricular coil to the device can pathway and clearly represents the status of the patient's impedance or thoracic fluid status. Since the OptiVol alert is triggered only by the fluid index and not by the raw

bioimpedance data, it can give a false sense of security, the alert can disappear, although fluid has accumulated and may be still present or ongoing. This clearly demonstrates the importance on how a remote fluid accumulation alert is handled in daily practice. In this case, a pregnancy has a controlled change in thoracic fluid content, but in other pathologies such as congestive heart failure, these changes are causing disease worsening. It should be considered that OptiVol is only an alert indicator but not an indicator to monitor progression of fluid status since the index is not a quantified measure. Thus, for good clinical practice it is not only important to look at the fluid index, which triggers the alert, but more importantly, the raw BioZ data has to be considered, even when the alert disappears.

CONCLUSION

This case clearly demonstrated the presence of a significantly higher thoracic fluid content during the total gestational period, with a rapid recovery to initial pre-pregnancy values after delivery, measured with an implantable cardioverter defibrillator. It was demonstrated that fluid accumulation, which is subclinical and transient, already starts very early during pregnancy and stays present until delivery. In addition, it became clear that the way remote OptiVol fluid crossing alerts are currently evaluated in clinical practice needs to be handled with caution.

CHAPTER 3

Intrathoracic fluid changes from preconception to postpartum as measured by bio-impedance monitoring

Lanssens D, Smeets CJP, Vandervoort P, Grieten L & Gyselaers W

** *In press at J Matern Fetal Neonatal Med* **

ABSTRACT

Intrathoracic impedance was remotely monitored from preconception to postpartum in a woman with an implantable cardioverter defibrillator. At 6 and 20 weeks, 2 significant changes were recorded, suggestive for thoracic fluid accumulation. After normal outcome, postpartum intrathoracic impedance returned to preconception values. The obtained results from this case report show that these measurements can be obtained with an implanted device. Current devices for measuring cardiac output by impedance technique allow evaluating thoracic fluid changes non-invasively. As such, non-invasive impedance monitoring may be a potential new method for continuous monitoring of maternal vascular changes during any time window between preconception and postpartum, to be assessed in a large cross sectional observational study.

BACKGROUND

The case of a pregnant woman with an implantable cardioverter defibrillator (ICD, Evera™ XT DR, Medtronic, Brussels, Belgium) and second generation fluid build-up detection algorithm, implanted for the presence of the Long QT Syndrome, is presented. In contrast to first generation implantable electronic cardiac device, modern ICD devices also enable device-based diagnostic remote monitoring. The OptiVol® fluid status monitoring system continuously measures intrathoracic impedance which strongly relates to intrathoracic fluid content and allows for timely diagnosis of thoracic fluid retention. Using the broad concept of Ohm's law, intrathoracic impedance can be measured by delivering a small alternating current between the defibrillator's right ventricular coil and the device, meanwhile measuring the corresponding voltage drop and hence the electrical resistance. There is an inverse relation between intrathoracic impedance and thoracic fluid content (44). Important intrathoracic impedance changes are remotely signaled to clinicians by automated alerts. It is known that important cardiovascular adaptations occur during pregnancy to accommodate for fetal requirements (45). Vasodilatation has been observed within the first weeks after conception, before placentation is complete, and triggers a cascade of cardiovascular adaptive changes throughout pregnancy until postpartum (45). In addition, several research groups reported an early gestational increase of thoracic fluid content, especially the extracellular component (42, 43). However, these groups only performed bioimpedance measurements at specific moments during and after the gestational period. This is the first case report showing longitudinal and semi-continuous thoracic bioimpedance measurements before, during and after an uncomplicated pregnancy.

CASE PRESENTATION

The case of a 31-year-old female patient who experienced a thoracic impedance alert twice during gestation, is presented. This was observed via an implantable cardioverter defibrillator (ICD, Evera™ XT DR, Medtronic, Brussels, Belgium) with second generation fluid build-up detection algorithm (OptiVol® 2.0), implanted in 2003 after an episode of sudden cardiac arrest related to the Long QT Syndrome type intrathoracic impedance (46). She has been in routine follow-up since and was included in a cardiac remote monitoring follow-up program since February 2015, prior to conception. Five weeks before conception, the patient developed an OptiVol 2.0 fluid index crossing (Event 1) (Figure 3.1). This crossing triggered an alert that was handled by specialized cardiac remote monitoring nurses, who assessed technical aspects and other cardiovascular measurements associated with this event. Because these were all normal, the patient was contacted by phone to identify possible causes of the fluid buildup alert. An interview was taken, consisting of a structured questionnaire towards identification of (early) signs of fluid retention, including shortness of breath and the presence of edema. The patient mentioned having a flu since a couple of days, for which NSAIDs were taken. It is reported that infectious intrathoracic processes, such as pneumonia or a flu, can affect intrathoracic impedance measurements (44). The OptiVol 2.0 fluid index crossing recovered a few days later. In the early phase of gestation, at 6 $^{2/7}$ weeks, the patient developed a second OptiVol 2.0 fluid index crossing, the first one during pregnancy (Event 2) (Figure 3.1). The very first signs of this signal already started at 4 $^{4/7}$ weeks. She was again contacted by phone, but confirmed being asymptomatic and responded negative to all questions. At 20 $^{2/7}$ weeks of gestation, the patient developed a third OptiVol 2.0 fluid index crossing (Event 3) (Figure 3.1). Again, she was asymptomatic and responded negative to all questions. The alert disappeared at 28 $^{1/7}$ weeks of gestation, despite a continuing decrease of thoracic impedance (i.e. fluid accumulation) until delivery. Thoracic impedance values pre-

, per- and post- pregnancy were significantly different. At 40 $^{6/7}$ weeks of gestation, she delivered a girl of 3295 grams with normal Apgar score. There were no maternal or neonatal complications. At 6 weeks of age, the neonate was also diagnosed with Long QT Syndrome type II .

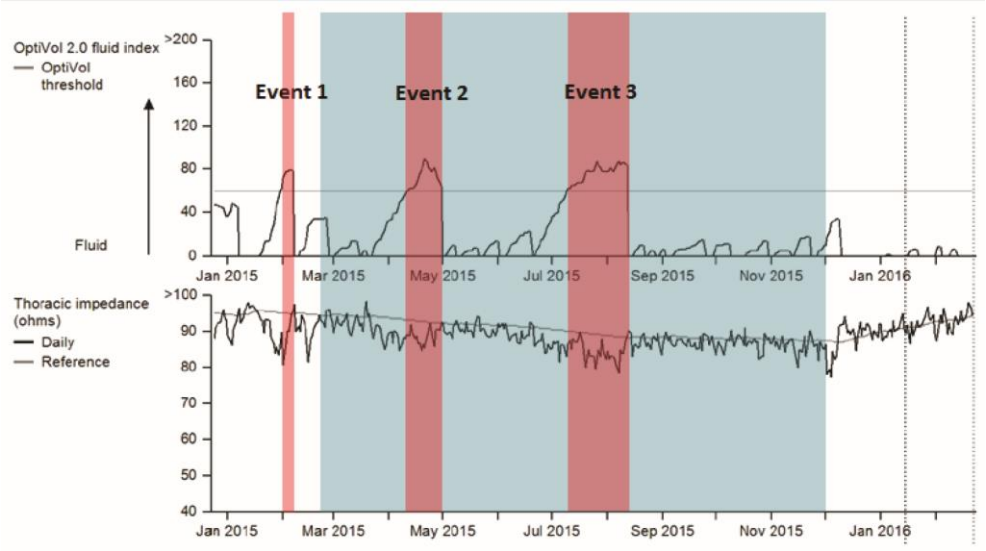

Figure 3.1: Overview of the OptiVol® 2.0 information from an implantable cardioverter defibrillator. Blue-marked areas: gestational period; Red-marked areas: period of fluid index crossing; Event 1: OptiVol crossing which triggered the fluid built up alert for the first time due to an episode of flu; Event 2: OptiVol crossing which triggered the fluid built up alert for the second time at 6 $^{2/7}$ weeks. Event 3: OptiVol crossing which triggered the fluid built up alert for the second time at 20 $^{2/7}$ weeks.

CONCLUSIONS

A decrease in thoracic impedance, indicating an increase in thoracic fluid content, started already shortly after fertilization (i.e. 4 $^{4/7}$ weeks of pregnancy). This increase in thoracic fluid content persisted during the course of pregnancy and immediately recovered to initial pre-pregnancy values after delivery. This clearly demonstrates the presence of a higher thoracic fluid content during pregnancy, which already starts at the early beginning of gestation (45). In our case, no severe cardiac events were recorded during pregnancy. Nevertheless, two events of OptiVol fluid index crossing were observed during gestation. Both crossing alerts can be explained by well-known physiological cardiovascular changes during the corresponding gestational stages. The event at 6 weeks is observed during the gestational window where maternal systemic vasodilation is reported which could result in a higher blood volume and lower intrathoracic impedance (45), one of the earliest observed changes in the body of the pregnant women. This vasodilatation causes a fall in systemic vascular resistance and triggers physiological changes in the cardiovascular and renal systems. In early pregnancy, osmoregulation is 'reset' at a lower osmolality around a new steady state which facilitates water retention (46). The second gestational OptiVol fluid index is observed around the moment previous research reported a maximum increase in cardiac output (47). This is associated with increased flow in the pulmonary circulation. Pulmonary vascular resistance is reduced and the increase in plasma volume is accompanied by a decrease in plasma colloid osmotic pressure of about 10-15%. Consequently, the colloid osmotic pressure/pulmonary capillary wedge pressure gradient falls by about 30%, increasing susceptibility to pulmonary edema in pregnant women (48). Since the patient was not experiencing any symptoms related to fluid overload, these events can be attributed to normal cardiovascular changes during pregnancy. From data received through the obstetric remote follow-up program, the maternal

cardiovascular profile at 27 weeks and the normal clinical outcome, we conclude that maternal hemodynamic changes in our case can be labeled as "normal".

This case report is the first one in which the earliest maternal cardiovascular changes are detected and registered longitudinally until full recovery in postpartum. Our observation illustrates the feasibility to use the bioimpedance technology for continuous monitoring of gestational cardiovascular changes. Our observations were made using the remote monitoring technique of an implanted cardioverter defibrillator. Today, innovative research is producing more and more devices to evaluate cardiovascular function by non-invasive mode, including external bioimpedance patches[7]. When these new devices would allow cardiovascular monitoring at similar quality, the way is open towards exploring periconceptional cardiovascular monitoring as a new tool to discriminate normal from abnormal maternal cardiovascular adaptations and identify pregnancies at risk for GHD already at the very first post-implantation stages.

PART III

THE INFLUENCE OF REMOTE MONITORING ON THE PRENATAL FOLLOW-UP AND THE GESTATIONAL OUTCOMES

CHAPTER 4

Remote Monitoring of Hypertension Diseases in Pregnancy: a Pilot Study

Lanssens D, Vandenberk T, Smeets CJP, De Cannière H, Molenberghs G, Van Moerbeke A, van den Hoogen A, Robijns T, Vonck S, Staelens A, Storms V, Thijs IM, Grieten L & Gyselaers W.

JMIR Mhealth UHealth. 2017 Mar 9; 5(3):e25

ABSTRACT

Background: Although remote monitoring has proven its added value in various healthcare domains, little is known about the remote follow-up of pregnant women diagnosed with a gestational hypertensive disorder (GHD).

Objective: to evaluate the added value of a remote follow-up program for pregnant women diagnosed with GHD.

Methods: A one year retrospective study was performed in the outpatient clinic of a 2nd level prenatal center where pregnant women with GHD received remote monitoring (RM) or conventional care (CC). Primary study endpoints include number of prenatal visits and admissions to the prenatal observation ward. Secondary outcomes include gestational outcome, mode of delivery, neonatal outcome and admission to neonatal intensive care (NIC). Differences in continuous and categorical variables in maternal demographics and characteristics were tested using Unpaired Student's two sampled *t*-test or Mann Whitney U-test and the χ^2 test. Both a univariate and multivariate analysis were performed for analyzing prenatal follow up and gestational outcomes. All statistical analyses are done at nominal level $\alpha = 0.05$.

Results: Of 166 patients diagnosed with GHD, 53 received RM and 113 CC. After excluding 5 patients in the RM group and 15 in de CC group because of missing data, 48 patients in RM group and 98 in CC group were taken into final analysis. The RM group had more women diagnosed with gestational hypertension but less with pre-eclampsia when compared with CC (81.25% versus 42.86% and 14.58% versus 43.87%). As compared to CC, univariate analysis in RM showed less inductions, more spontaneous labors, and less maternal and neonatal hospitalizations (48.98% versus 25.00%; 31.63% versus 60.42%; 74.49% versus 56.25%; and 27.55% versus 10.42%). This was also true in multivariate analysis, except for hospitalizations.

Conclusions: A RM follow – up of women with GHD is a promising tool in the prenatal care. It opens the perspectives to reverse the current evolution of antenatal interventions leading to more interventions and as such to ever increasing medicalized antenatal care.

INTRODUCTION

Gestational hypertensive disorders (GHD) remain one of the most significant & intriguing unsolved problems in obstetrics (49, 50). 5 – 10% of pregnancies is complicated with this disease, and it is one of the major causes of maternal and fetal morbidity and mortality (49, 51, 52). GHD is defined as new onset hypertension (diastolic blood pressure ≥ 90 mmHg and systolic blood pressure ≥ 140 mmHg), with or without proteinuria (≥ 300 mg in 24h urine collection) at or after 20 weeks of gestation (49). The most common management for GHD in Belgium is an admission to the prenatal observation unit for diagnostic and therapeutic follow-up before induction of labour or discharge at home. In severe cases, premature birth is indicated (49).

As part of the Hasselt University and the Limburg Clinical Research Program (LCRP), Ziekenhuis Oost-Limburg (Genk, Belgium) initiated in January 2015 a remote monitoring program for women with or at risk for GHD. Remote monitoring (RM) is an alternative approach in medical management (dating back to the early 1990s) facilitating patients' management at home (3). It is defined as the use of telecommunication technologies to assist the transmission of medical information and services between healthcare providers and patients. The use of this 2-way telecommunication technology, using multimedia and computer networks, to assist medical management, is a growing trend internationally (4).

In this paper, we report our first clinical results of remote monitoring in GHD, obtained retrospectively during the year of technical installation of remote communication between hospital doctors/midwives and pregnant women at home.

RELATED WORK

RM has already shown benefits in Cardiology and Pneumology (7, 53). Also in the prenatal care, RM has shown an added value to improve maternal and neonatal outcomes. Various studies reported a reduction in unscheduled patients visits, low neonatal birth weight and admissions to Neonatal Intensive Care for pregnant women who received RM compared with pregnant women who didn't receive these devices. Additionally, RM can contribute to significant reductions in healthcare costs. RM was also demonstrated to prolong gestational age and to improve feelings of self-efficacy, maternal satisfaction and gestational age at delivery when compared with a control group which didn't receive RM (13, 15, 17, 18, 22, 25, 34, 36). Unfortunately, some of the previous mentioned studies are dating back to 1995 and no more recent work is available. This is in contradiction with the rapid technological advancements that have been seen in the last decade. Further, no studies are published about the added value of RM in pregnant women with GHD. To our knowledge, this is the first publication about a prenatal follow-up program for pregnant women with GHD to date.

METHODS

SUBJECTS

All women diagnosed with GHD who delivered at the outpatient prenatal clinic of Ziekenhuis Oost-Limburg (Genk, Belgium) during 2015 were included. Women received RM on demand of the responsible obstetrician before admission or after discharge from the prenatal observation ward. The criteria to initiate RM was GHD at gestational age ≥ 20 weeks where an intensive follow-up until delivery was desirable. Women without a Smartphone, a gestational age less than 20 weeks, a fetus with congenital malformations and women who refused informed consent, were excluded and received conventional care (CC).

Between January 1st, 2015 and December 31, 2015, 2058 women had prenatal care and delivery at Ziekenhuis Oost-Limburg. 166 women were diagnosed with GHD, 53 of them received CC added with RM. The remaining 113 pregnant women with GHD didn't receive RM but only CC.

INTERVENTIONS IN THE REMOTE MONITORING GROUP

Women consenting for RM received obstetric surveillance by a Withings Wireless Blood Pressure Monitor, Withings Smart Body Analyzer and a Withings Pulse O² (Withings, Issy – les – Moulineux, France). Pregnant women participating in the prenatal remote follow-up program were asked to perform one blood pressure measurement in the morning and one in the evening, one weight measurement a day and wear an activity tracker day and night until delivery or hospital admission (see Figure 4.1).

Figure 4.1: The equipment used in the remote monitoring group.

The data from the monitor devices were transmitted to an online dashboard developed by the Mobile Health Unit of the University of Hasselt. Predetermined alarm signals were set; one midwife performed remote follow up of all transformed data at the online dashboard. She had to discriminate normal and alarm signals of systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg or weight gain > 1 kg/day. Alarm events were communicated with the obstetrician in charge to discuss management options before contacting and instructing patients at home. Type of interventions were (1) expectant management, (2) ambulatory blood sampling and 24 hours urine collection at home, (3) adjustment of the antihypertensive therapy and /or physical activity, (4) admission to the antenatal ward and (5) induction of labor. Therapeutic interventions were according to local management.

The hospital's Medical Ethics Committee approved the study.

MATERNAL DEMOGRAPHICS

Maternal demographics and characteristics of the patients in the RM group were collected at study entry. In the CC group, these data were obtained by manual search through the electronic medical records.

PRIMARY OUTCOME: PRENATAL FOLLOW-UP

Total numbers of prenatal consultations were collected from 10 weeks of gestation onwards: ultrasound scans, cardiotocographics (CTG), admission to the prenatal ward, total days of hospitalization and the number of admissions until delivery. These data were retrospectively collected from the electronic medical records after the delivery of the women in both the RM and CC group. These data were checked with the hospital administration and/or billing records.

SECONDARY OUTCOMES: DELIVERY OUTCOMES

Maternal parameters collected at birth were gestational age at delivery, and mode of delivery. Neonatal outcomes collected were birthweight, birthweight percent, length, Apgar at 1' and 5', and number of admissions to the Neonatal Intensive Care (NIC).

STATISTICAL ANALYSIS

Differences in continuous and categorical variables in maternal demographics and characteristics were tested using Unpaired Student's two sampled t-test or Mann Whitney U-test and the χ^2 test. Both univariate and multivariate analyses were performed for analyzing prenatal follow up and gestational outcomes. Beta coefficients and 95.0% confidence interval were calculated for multivariate analysis. All statistical analyses are done at nominal level $\alpha = 0.05$. Statistical analysis was performed with Statistical Package for Social Sciences release 22.0 (IBM® SPSS® Inc., Chicago, Illinois, USA).

RESULTS

PARTICIPANTS DEMOGRAPHICS

Of the 2058 deliveries in Ziekenhuis Oost – Limburg in 2015, 166 (8.06%) were diagnosed with GHD and had both prenatal care and birth in the same hospital. 53 (31.92%) of the GHD pregnancies had RM. Of these, 5 (3.01%) were excluded from analysis because of missing data (n = 4) and fetal loss (n = 1). A total of 48 (28.92%) RM women were eligible for analysis. The other 113 (68.08%) GHD pregnancies had CC. Of these, 15 (9.04%) women were excluded because of missing data, leaving 98 (59.04%) eligible for analysis. Figure 4.2 shows the study population in a flow chart.

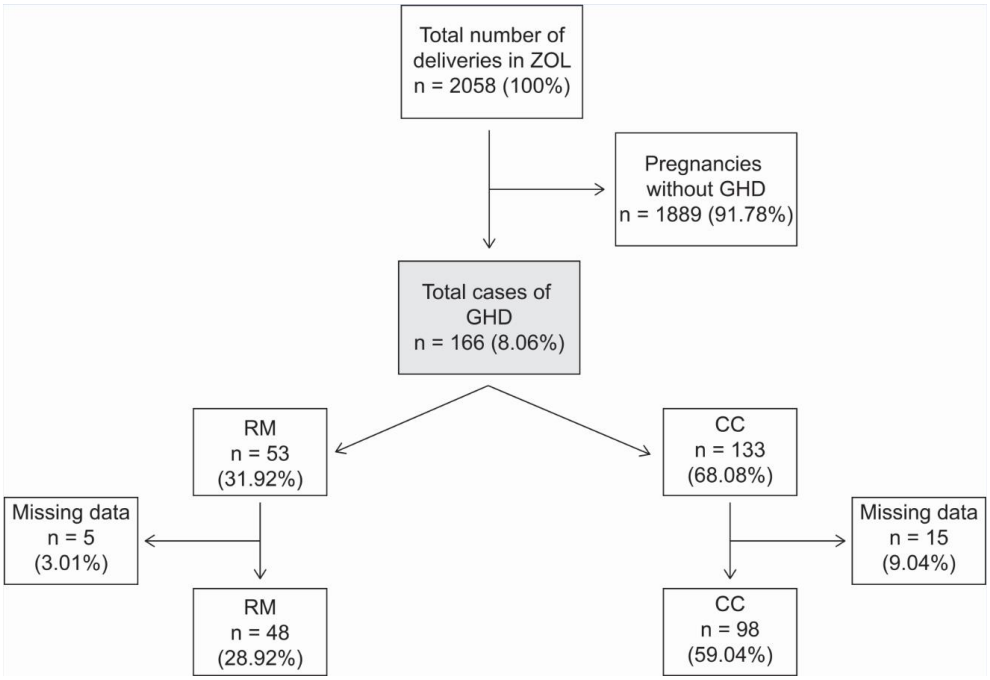

Figure 4.2: The study population

Table 4.1 shows the maternal demographics and characteristics of the women diagnosed with GHD. In CC, there were more primigravidas and smokers than in RM: 65/98

(66.32%) versus 20/48 (41.66%) and 10/98 (10.20%) versus 0/48 (0.00%) respectively.

Table 4.1: maternal demographics and characteristics

Variable	*RM Group (n = 48)*	*CC Group (n = 98)*	*Statistical significance (2 – tailed)*
Maternal age (year)	31.69 (± 4.25)	31.94 (± 4.77)	*P* = 0.73
Pre pregnancy weight (kg)	72.00 (± 17.99)	76.80 (± 19.74)	*P* = 0.11
Height (cm)	166.00 (± 6.94)	167.08 (± 6.86)	*P* = 0.38
BMI (kg/m²)	25.54 (±5.58)	27.08 (± 6.92)	*P* = 0.32
Primigravidity (%)	41.66% (n = 20)	66.32% (n = 65)	***P* = 0.005**
Concomitant diseases (%)			
- Cardiovascular disorders (%)	0% (n = 0)	1.02% (n = 1)	*P* = 0.48
- Blood coagulation disorder (%)	2.08% (n = 1)	1.02% (n = 1)	*P* = 0.61
- Endocrine disorders (%)	4.16% (n = 2)	5.10% (n = 5)	*P* = 0.81
- Immunological disorders (%)	2.08% (n = 1)	2.04% (n = 2)	*P* = 0.99
Smoking (%)	0% (n = 0)	10.20% (n = 10)	***P* = 0.02**
GA first visit (week)	10.10 (± 5.36)	11.21 (± 7.60)	*P* = 0.66

RM = remote monitoring, CC = conventional care, GA = gestational age; Data are mean (± SD) or percentage (number).

PRENATAL FOLLOW-UP: COMPARISON BETWEEN RM AND CC

Data on prenatal follow-up balance are shown in table 4.2. The number of prenatal hospital admissions and admissions until delivery were lower in RM than in CC when a univariate analysis is performed: 27/48 (56.25%) versus 73.98 (74.49%) and 13/48 (27.08%) versus 61/97 (62.24%). This wasn't significant in multivariate analysis. For both uni- and multivariate analysis was the prevalence of gestational hypertension higher in RM than in CC (81.25% versus 42.86% and β = 6.62), but the prevalence of pre-eclampsia was lower (14.85% versus 43.87% and β = 0.24).

Table 4.2: Prenatal follow-up

Variable	*Univariate analysis*			*Multivariate analysis*		
	RM group (n = 48)	*CC group (n = 98)*	*p-value*	*RM vs. no RM (Beta)*	*95.0% CI for Beta*	*p-value*
Total number prenatal visits (no.)	8.77 (± 4.12)	8.86 (± 3.51)	*P* = 0.90	-0.56	-1.74 – 9.14	*P* = 0.54
CTG's (no.)	2.23 (± 2.05)	1.89 (± 1.70)	*P* = 0.46	-0.08	-1.12 – 0.53	*P* = 0.48
Echo's (no.)	3.95 (± 2.00)	3.67 (± 2.12)	*P* = 0.08	0.07	-0.56 – 1.19	*P* = 0.48
Prenatal admission (%)	56.25% (n = 27)	74.49% (n = 73)	***P* = 0.03**	0.46	0.18 – 1.45	*P* = 0.09
Days hospitalized (no.)	5.74 (± 8.98)	4.73 (± 5.69)	*P* = 0.57	0.10	-1.62 – 4.81	*P* = 0.32
Prenatal admission until delivery (%)	27.08% (n = 13)	62.24% (n = 61)	***P* < 0.001**	0.38	0.12 – 1.22	*P* = 0.11
Gestational outcome (%):						
- Essential hypertension	2.08% (n = 1)	9.18% (n = 9)	*P* = 0.11			
- Gestational hypertension	81.25% (n = 39)	42.86% (n = 42)	***P* < 0.001**	6.62	2.40 – 18.27	***P* <0.001**
- Pre-eclampsia	14.58% (n = 7)	43.87% (n = 43)	***P* < 0.001**	0.24	0.08 – 0.71	***P* = 0.01**
- HELLP	2.08% (n = 1)	4.08% (n = 4)	*P* = 0.53			

CI = Confidence interval, RM = remote monitoring, CC = conventional care, HELLP = Hemolysis Elevated Liver enzymes and Low Platelets.
Univariate analysis: Data are mean (± SD) or percentage (number).

In order to investigate the influence of the maternal demographics and characteristics on the prenatal follow-up, a multiple linear regression analysis and a multivariate logistic regression analysis is performed. A detailed overview of these data is proved in Supplementary file 1 in the Supplementary Appendices.

DELIVERY OUTCOMES: COMPARISON BETWEEN RM AND CC

Delivery outcomes are shown in table 4.3. For both uni- and multivariate analyses, in the RM group, the number of spontaneous start of the birth process were higher as compared to CC group: 29/48 (60.42%) versus 31/98 (31.63%) and $\beta = 3.25$. Also the number of inductions were lower in RM group as compared to CC group: 12/48 (25.00%) versus 48/98 (48.98%) and $\beta = 0.36$. Neonates in RM group did have a shorter length compared to the CC group when performed a multivariate analysis ($\beta = 0.23$). Finally, neonates in the RM group, compared with CC group, were less likely to be admitted to the NIC department when performed an univariate analyses (5/48 (10.42%) versus 27/98 (27.55%)) but not in multivariate analyses ($\beta = 0.34$). Despite the significant differences in the start of the birth process, there are no differences in the mode of delivery between the two groups.

Table 4.3: delivery outcomes

Variable	*Univariate analysis*			*Multivariate analysis*		
	RM group (n = 48)	*CC group (n = 98)*	*p-value*	*RM vs. no RM (Beta)*	*95.0% CI for Beta*	*p-value*
GA delivery (week)	37.49 (± 2.52)	37.20 (± 3.20)	*P* = 0.94	-0.21	-1.29 – 0.06	*P* = 0.85
Start birth process (%):						
- Spontaneous	60.42% (n = 29)	31.63% (n = 31)	***P* = 0.001**	3.25	1.36 – 7.78	***P* < 0.001**
- Induction	25.00% (n = 12)	48.98% (n = 48)	***P* = 0.006**	0.36	0.14 – 0.89	***P* = 0.03**
- Primary cesarean section	14.54% (n = 7)	19.39% (n = 19)	*P* = 0.48	0.67	0.21 – 2.18	*P* =0.51
Mode of delivery (%):						
- Vaginal	66.67% (n = 32)	59.18% (n = 58)	*P* = 0.38	1.06	0.4 4 – 2.54	*P* =0.90
- Instrumental	8.33% (n = 4)	8.16% (n = 8)	*P* = 0.97	2.34	0.47 – 11.64	*P* =0.30
- Primary cesarean section	14.54% (n = 7)	19.39% (n = 19)	*P* = 0.48	0.67	0.21 – 2.18	*P* =0.51
- Secondary cesarean section	10.42% (n = 5)	13.27% (n = 13)	*P* = 0.63	0.49	0.11 – 2.10	*P* =0.33
Birthweight (g)	3058.54 (± 692.60)	2953.09 (±8 74.80)	*P* = 0.36	0.11	-162.71 – 535.33	*P* =0.29
Length (cm)	49.53 (± 2.85)	48.33 (± 3.52)	*P* = 0.07	0.23	0.02 – 3.45	***P* =0.05**
Apgar 1′	8.11 (± 1.20)	7.91 (± 1.63)	*P* = 0.86	0.08	-0.38 – 0.88	*P* =0.43
Apgar 5′	9.13 (± 0.80)	9.03 (± 1.27)	*P* = 1.00	0.06	-0.37 – 0.65	*P* =0.59
Admission NIC (%)	10.42% (n = 5)	27.55% (n = 27)	***P* = 0.02**	0.34	0.10 – 1.14	*P* =0.08

CI = Confidence interval, RM = remote monitoring, CC = conventional care, GA = gestational age, NIC = Neonatal Intensive Care. Univariate analysis: Data are mean (± SD) or percentage (number).

In order to investigate the influence of the maternal demographics and characteristic's on the delivery outcomes, a multiple linear regression analysis and multivariate logistic regression analysis is performed. A detailed overview of these data is provided in Supplementary File in the Supplementary Appendices.

DISCUSSION

PRINCIPAL RESULTS

We sought to determine whether RM was an added value to facilitate the prenatal follow-up and to improve the delivery outcomes in patients diagnosed with GHD. To our knowledge, this is the first publication about a prenatal follow-up program for pregnant women with GHD.

The findings show us a reduced appearance of preeclampsia, but an increased appearance of gestational hypertension in the group of women who received a prenatal RM program when compared to women who received CC. Women in the RM group, when compared with CC group, had a lower number of prenatal hospitalizations, prenatal hospitalizations until delivery and their neonates were less likely to be admitted to the NIC department in univariate but not in multivariate analysis. In both analysis, spontaneous deliveries were more likely and inductions less likely to occur in the RM group when compared with CC group.

STRENGTHS AND LIMITATIONS

Despite the potential benefits, the use of RM in obstetrical care is still very limited and is not integrated into healthcare systems. The Commission of the European Communities has in 2012 written an eHealth Action Plan (54) in which they foster a spirit of innovation in eHealth in Europe as the way forward to ensure better health. Our study is one of the first studies in the obstetrical care for women at risk for GHD which meets this requirement. Additionally, one of the strengths of this study is the fact that all patients had antenatal care and delivery in the same hospital with electronic medical records in line with administration files. Also, all patients had antenatal care according to uniform local management protocols. Finally, the percentage of missing data for RM group and CC group is 3.01% and 9.04% respectively, which is a low value.

Our study has three main limitations. First, the data collection was done retrospectively so selection bias cannot be excluded. Second, in CC group were more primigravida and women who smoked during their pregnancy when compared to RM group. Although, our multivariate analysis didn't show any influence of these parameters on our principal findings, nulliparous women are known to have a higher risk for the development of preeclampsia superimposed on chronic hypertension (25, 49) and smoking during pregnancy carries adverse outcomes, however a reduced risk of developing GHD in women who smoke is shown by many studies (49, 51). The last limitation is the interference from family doctors or community midwives which cannot be excluded.

COMPARISONS WITH PREVIOUS TRIALS

To our knowledge, this is the first publication about a prenatal follow-up program for pregnant women with GHD to date. There are a few publications about a RM program during prenatal follow up in the management for pregnant women at risk for preterm labor or with the diagnosis of gestational diabetes mellitus. When looking at their maternal outcomes, the results of these studies are not in line with our findings. Compared with the usual care, these studies report no significant difference in prenatal hospitalizations (36) and mode of delivery (17, 18) in RM group. When looking at the neonatal outcomes, some contradictions were found: the study of Corwin et al. (13) and Morrison et al. (22) states that infants born to monitored women were less likely to be admitted to a NIC compared with women without a RM follow – up program, which are in line with our findings. The Collaborative Home Uterine Monitoring Study Group (34) and Homko et al. (15) did not find any difference between the two groups in neonatal hospitalization to the NIC. A side note which has to made is that some of the mentioned studies are dating back to 1995, which is in contradiction with the rapid technological advancements that have been made in the last decade.

POSSIBLE EXPLANATIONS

A possible hypothesis of the differences in admission to the prenatal observational ward, admission to the NIC and the gestational outcomes is the hypothesis that preeclampsia possibly a result is of gestational hypertension or essential hypertension (55, 56). This may be due to the possibility to start or adjust an antihypertensive drugs therapy to reduce a high systolic and/or diastolic blood pressure which can be picked up by RM. There are some studies who mentioned a reduced risk of developing severe hypertension and preeclampsia associated with the use of antihypertensive drugs (57-60). However, these results are in contradiction with the review of Duley (61), which states that antihypertensive drugs may be effective at reducing the risk of severe hypertension, but not of preeclampsia. Further examination of the influence of antihypertension drugs therapy on the development of severe hypertension or preeclampsia when moderate hypertension is diagnosed, is necessary to obtain clarification herein.

When women are diagnosed with preeclampsia, an induction of labour is often necessary the prevent for further complications (62, 63). The explanation of more inductions in CC could be the higher number of women diagnosed with preeclampsia in this group. Gestational hypertension isn't often a requirement to induce women, and a spontaneous onset of their labour is preferred. This can be the cause of the higher number of spontaneous start of labour in RM.

Additional shows our study that there are no differences in prenatal consults between RM and CC. These findings are in contradiction with the statement that medicalization of childbirth has gone too far, which arises from different angles (64-69). Our study showed that adding RM devices to standard prenatal care doesn't mean an increase of total amount of echo's, CTG's or other prenatal consultations. In addition, RM opens the perspective to timely initiative and monitor antihypertensive treatments for gestational

hypertension. Like stated in the review of Gyselaers et al. (39), offering RM to a high risk group allows timely identification of most cases of alarm events without increasing ambulatory or in-hospital interventions. This also opens perspectives to reverse the current evolution of antenatal interventions leading to more interventions and as such to ever increasing medicalized antenatal care.

RECOMMENDATIONS FOR FURTHER RESEARCH

Although women in the RM group were invited for an extra prenatal consult to evaluate fetal and maternal wellbeing when events occurred, no statistical significant difference is present in prenatal consultations (total number of consultations, total number of CTG's and total number of echo's) in the RM group versus the CC group. This indicates that RM doesn't cause extra prenatal consultations but, when further implemented, can ensure an reduction in this number when obstetricians and gynecologists are more familiar with this system. A study to evaluate the cost-effectiveness of a RM follow-up program needs to be performed in the further. Additionally, early detection of GHD in the monitoring group demonstrated the value of objective measurements of increase in blood pressure by a remote blood pressure monitoring device. The patients not receiving these devices relied on standard prenatal care, where a GHD mostly will be discovered by chance or when the patient comes to the hospital with self-reported complaints, e.g. headache or blurred vision. In these cases, the degree of the GHD is often severe and an active management is necessary (49). Recent resources showed that providing information about GHD enables women to spot signs and symptoms of these diseases. This leads to earlier diagnoses and management, and reduces morbidity and mortality rates (70). It is possible that combining patient education and a remote prenatal follow-up program could make morbidity and mortality rates further decrease, but this requires further. Lastly, more research should be done to the influence of antihypertension drugs therapy on the development of severe hypertension or preeclampsia when moderate hypertension is

diagnosed. When the effect of the medication is clarified, the added value of RM in the prenatal care of women diagnosed with GHD will be more apparent.

CONCLUSION

Prenatal RM follow-up is linked with an increased prevalence of a spontaneous start of the birth process, when compared with CC. This may relate to a trend for less maternal and neonatal hospitalizations in RM group as compared to CC group. This study illustrates that RM opens perspectives to timely initiate and monitor antihypertensive treatments for gestational hypertension, and early identifications of alarm events without increasing ambulatory or in-hospital interventions. To our knowledge, this is the first publication about a prenatal follow-up program for pregnant women with GHD to date. Further examinations about the effect of an prenatal RM follow-up program for women at risk for the development of GHD needs to be done in a randomized controlled trial to confirm these results.

CHAPTER 5

The Impact of a Remote Monitoring Program on the Prenatal Follow-up of Women with Gestational Hypertensive Disorders

Lanssens D, Vonck S, Storms V, Thijs IM, Grieten L & Gyselaers W

Eur J Obstet Gynecol Reprod Biol. 2018 Apr; 223:72-78

ABSTRACT

Objectives: In 2015, we showed the value of a remote monitoring (RM) follow-up program for women diagnosed with gestational hypertensive disorders (GHDs) compared with women who received conventional care (CC). We want to confirm or refute the conclusions drawn in 2015, by including data from 2016.

Study design: A two year retrospective study in which all women diagnosed with GHD, who underwent prenatal follow-up at the outpatients prenatal clinic of Ziekenhuis Oost-Limburg (Genk, Belgium) during 2015 and 2016, were included. Of the 320 women diagnosed with GHD, ninety (28.13%) were monitored with RM. The other 230 (71.88%) GHD pregnancies were monitored with CC. Differences in continuous and categorical variables in maternal demographics and characteristics were tested using Unpaired Student's two sampled t-test or Mann Whitney U-test and the χ^2 test. Both a univariate and multivariate analysis were performed for analyzing prenatal follow up and gestational outcomes. All statistical analyses are done at nominal level $\alpha = 0.05$.

Results: The RM group had more women diagnosed with gestational hypertension but less with pre-eclampsia when compared to the CC group (69.77% versus 42.79% and 19.77% versus 44.19% respectively). In both uni- and multivariate analyses, the RM group had, when compared to the CC group, less prenatal admission (51.62% versus 71.63%), less prenatal admissions until the moment of the delivery (31.40% versus 57.67%), less induced starts of the birth process (43.00% versus 32.09%), more spontaneous starts of the birth process (32.86% versus 46.51%), more births after 37 weeks of gestational age in pregnancies complicated with gestational hypertension (91.67% versus 53.33%) and pregnancies complicated with pre-eclampsia (58.82% versus 53.33%). In multivariate analysis, a reduction in total number of prenatal visits was visible in the RM group when compared to the CC group ($\beta = -1.76$; CI = -2.74 –

0.77). Only in the univariate analysis was the mean gestational age at delivery between 34 and 37 weeks of gestation in pregnancies complicated with gestational hypertension higher in the CC group versus the RM group (35w 4/7 (±0.49) versus 34w 6/7 (± 0.00).These conclusions were almost the same as in the analyses of 2015, except (1) there wasn't a difference anymore in NICU admissions between the RM and CC group in the analyses of 2015 - 2016 and (2) a significant decrease in total number of visits is reported in the RM group in the dataset of 2015 - 2016, which wasn't visible in the dataset of 2015.

Conclusions: This study demonstrates that RM provides opportunities to offer timely interventions to pregnant women who require them.

INTRODUCTION

Gestational hypertensive disorders (GHDs), including gestational hypertension and pre-eclampsia, are some of the leading causes of maternal morbidity and mortality (50, 71). Gestational hypertension is characterized by the new onset of hypertension (≥ 140/90 mmHg systolic blood pressure or ≥ 100 mmHg diastolic blood pressure) after 20 weeks of gestation. When this hypertension is combined with proteinuria (spot urine protein/creatinine ratio ≥ 30 mg/mmol or ≥ 300 mg/day or at least 1 g/L on dipstick testing), a diagnosis of pre-eclampsia is made (72). The commonest management strategy for GHD in Belgium is admission to a prenatal observation unit for diagnostic and therapeutic follow-up before the induction of labor or discharge. In severe cases, premature birth is indicated (49).

As part of the Hasselt University and Limburg Clinical Research Program (LCRP), Ziekenhuis Oost-Limburg (Genk, Belgium) initiated a remote monitoring (RM) program in January, 2015 for women at risk of GHD. RM is a relatively new approach (dating back to the early 1990s), which facilitates patient management at home (3). It can be broadly defined as the use of telecommunication technologies to facilitate the transmission of medical information and services between health-care providers and patients. The use of this two-way telecommunication technology, multimedia, and computer networks to deliver or enhance the delivery of health care is a growing trend internationally (4).

The first clinical results of RM in GHD, obtained retrospectively during the year in which remote communication between hospital doctors or midwives and pregnant women at home was technically installed, were published in 2016 (73). A second pilot project was performed in which more patients were included in both the prenatal RM follow-up program and in the conventional care (CC) program during a study period of 2 years. In

this paper, we report the results of this RM program to confirm or refute the conclusions of the analysis published in 2016.

MATERIAL AND METHODS

SUBJECTS

All women diagnosed with GHD who underwent prenatal follow-up at the outpatients prenatal clinic of Ziekenhuis Oost-Limburg (Genk, Belgium) during 2015 and 2016 were included. Women received RM at the behest of the responsible obstetrician because of their high-risk status or after discharge from the prenatal observation ward. The criterion to initiate RM was GHD at a gestational age of ≥ 10 weeks when intensive follow-up until delivery was desirable. Women at a gestational age of < 10 weeks, or women who did not give their informed consent received CC.

Between January 1, 2015 and December 31, 2016, 4142 women underwent (at least a part of) their prenatal care and/or delivery at Ziekenhuis Oost-Limburg: 320 (7.73%) were diagnosed with GDH, 90 (28.13%) of whom received CC together with RM, and the remaining 230 (71.86%) women with GHD did not receive RM, but only CC.

INTERVENTIONS IN THE RM GROUP

Women consenting to RM received obstetric surveillance via a wireless blood-pressure monitor, weight scale, and activity tracker. Pregnant women participating in the prenatal RM follow-up program were asked to make one blood-pressure measurement in the morning and one in the evening and one weight measurement weekly, and to wear the activity tracker day and night until delivery or hospital admission. The bloodpressure monitors which were used are CE-approved and comply with the European regulations. These devices were clinically validated in ZOL before given them to the women who used them at home.

The data from the monitoring devices were transmitted to an online dashboard developed by the Mobile Health Unit of the University of Hasselt. Predetermined alarm signals were set. One midwife was responsible for remote follow-up of all the transmitted data at the

online dashboard, by distinguishing normal and alarm signals for systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, and weight gain > 1 kg/day. Alarm events were communicated to the obstetrician-in-charge to discuss management options before the patient at home was contacted and instructed. The types of interventions were: (1) expectant management; (2) ambulatory blood sampling and 24 h urine collection at home; (3) adjustment of antihypertensive therapy and/or physical activity; (4) admission to the prenatal ward; and (5) induction of labor. The therapeutic interventions were based on local management strategies.

The Ziekenhuis Oost-Limburg Medical Ethics Committee approved the study.

MATERNAL DEMOGRAPHIC FACTORS

The maternal demographic factors and characteristics of the patients in the RM group were collected at study entry. In the CC group, these data were obtained by manual searches through the electronic medical records.

PRIMARY OUTCOME: PRENATAL FOLLOW-UP

The total number of prenatal consultations was measured from the start of the pregnancy: ultrasound scans, cardiotocography, admission to the prenatal ward, total days of hospitalization, and the number of admissions until delivery. These data were collected retrospectively from the electronic medical records after the delivery of the women in both the RM and CC groups. These data were checked with the hospital administration and/or billing records.

SECONDARY OUTCOME: DELIVERY OUTCOMES

The maternal parameters collected at birth were gestational age at delivery, intended mode of delivery, and mode of delivery. The neonatal outcomes collected were birth weight, Apgar score at 1 min and 5 min, and number of admissions to the NICU.

STATISTICAL ANALYSIS

Differences in continuous and categorical variables in the maternal demographic factors and characteristics were tested with unpaired Student's two-sample *t* test or the Mann–Whitney *U* test and a χ^2 test. Both univariate and multivariate analyses were performed to analyze the prenatal follow-up and gestational outcomes. Beta coefficients and 95.0% confidence intervals were calculated for the multivariate analysis. All statistical analyses are performed with a nominal level of $\alpha = 0.05$. The statistical analyses were performed with SPSS release 24.0 (IBM® SPSS® Inc., Chicago, Illinois, USA).

RESULTS

PARTICIPANT DEMOGRAPHICS

Of the 4142 women who delivered in Ziekenhuis Oost-Limburg in 2015 and 2016, 320 (7.73%) of them were diagnosed with GHD and had prenatal care and/or gave birth at this hospital. Ninety (28.13%) of the GHD pregnancies were monitored with RM. Of these, four (1.25%) were excluded from the analysis because of missing data, so 86 (26.86%) were eligible for analysis. The other 230 (71.88%) GHD pregnancies were monitored with CC. Of these, 15 (4.69%) women were excluded because of missing data, so 215 (67.19%) were eligible for analysis. Figure 5.11 shows the study population in a flow chart.

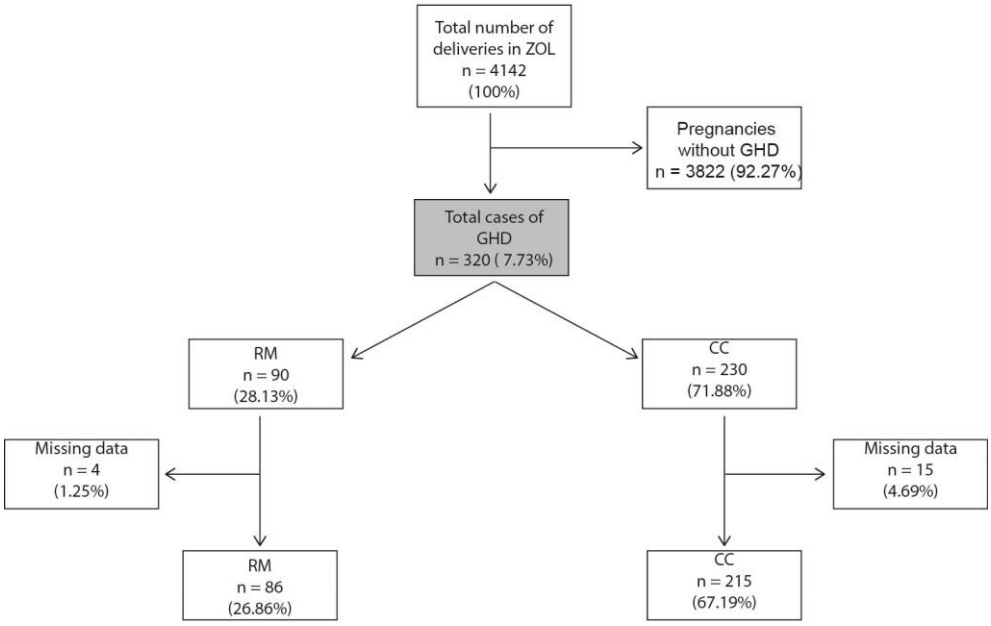

Figure 5.1: Flowchart of the study population

Table 5.1 shows the maternal demographic factors and characteristics of the women with GHD. In the RM group, there were more women with immunological disorders (2/86

[2.30%] versus 2/215 [0.90%], respectively) and fewer smokers than in the CC group (2/86 [2.30%] versus 23/215 [10.70%], respectively).

Table 5.1: Maternal demographic factors and characteristics

Variable	*RM group (n = 86)*	*CC groups (n = 215)*	*Statistical significance (2 – tailed)*
Maternal age (years)	30.97 (± 5.61)	30.53 (± 5.17)	*P* = 0.25
Pre-pregnancy weight (kg)	73.76 (± 15.88)	77.57 (± 18.87)	*P* = 0.08
Height (cm)	165.54 (± 6.46)	165.60 (± 13.70)	*P* = 0.24
BMI (kg/m²)	26.79 (± 53.36)	28.38 (± 6.67)	*P* = 0.05
Primigravida (%)	52 (60.47%)	142 (66.05%)	*P* = 0.33
Concomitant diseases (%)			
- Cardiovascular disorders (%)	1 (1.16%)	4 (1.86%)	*P* = 0.67
- Blood coagulation disorder (%)	2 (2.32%)	2 (0.93%)	*P* = 0.34
- Endocrine disorders (%)	2 (2.32%)	14 (6.51%)	*P* = 0.82
- Immunological disorders (%)	2 (2.32%)	2 (0.93%)	***P* = 0.04**
Smoking (%)	2 (2.32%)	23 (10.70%)	***P* = 0.02**
GA first visit (week)	10.51 (± 6.11)	10.60 (± 5.52)	*P* = 0.58

RM = remote monitoring, CC = conventional care, GA = gestational age; data are means (± SD) or percentages (numbers).

PRENATAL FOLLOW-UP: COMPARISON OF RM AND CC

Data on the prenatal follow-up are shown in Table 5.2. In the multivariate analysis, the total number of prenatal visits was lower in the RM group than in the CC group (β = –1.76). The number of prenatal admissions (44/86 [51.16%] versus 154/215 [71.63%], respectively, β = –1.23) and prenatal admissions until delivery (27/86 [31.40%] versus 124/215 [57.67%], respectively, β = –1.24) were lower in the RM group than in the CC group in both the uni- and multivariate analyses. In both the uni- and multivariate analysis, the prevalence of gestational hypertension was higher in the RM group than in the CC group (60/86 [69.77%] versus 92/215 [42.79%], β = 0.24), but the prevalence of

pre-eclampsia was lower in the RM group (17/86 [19.77%] versus 95/215 (44.19%], β = –0.23).

Table 5.2: Prenatal follow-up

Variable	*Univariate analysis*			*Multivariate analysis*		
	RM group (n = 86)	*CC group (n = 215)*	*p-value*	*RM vs. no RM (Beta)*	*95.0% CI for Beta*	*p-value*
Total number prenatal visits (no.)	6.93 (± 3.86)	7.62 (± 3.33)	*P* = 0.12	-1.76	-2.74 – 0.77	***P* < 0.01**
CTG's (no.)	2.23 (± 1.96)	1.75 (± 1.64)	*P* = 0.08	0.42	-0.13 – 0.96	*P* = 0.13
Echo's (no.)	3.67 (± 1.84)	3.49 (± 1.76)	*P* = 0.16	0.01	-0.53 – 0.56	*P* = 0.96
Prenatal admission (%)	44 (51.16%)	154 (71.63%)	***P* < 0.01**	-1.23	0.16 – 0.54	***P* <0.01**
Days hospitalized (no.)	5.14 (± 7.41)	4.05 (± 4.49)	*P* = 0.88	1.18	-1.06 – 3.43	*P* = 0.30
Prenatal admission until delivery (%)	27 (31.40%)	124 (57.67%)	***P* < 0.01**	-1.24	0.16 – 0.53	***P* < 0.01**
Gestational outcome (%):						
- Essential hypertension	8 (9.30%)	19 (8.84%)	*P = 0.90*	0.005	-0.08 – 0.07	*P = 0.90*
- Gestational hypertension	60 (69.77%)	92 (42.79%)	***P* <0.01**	0.24	0.15 – 0.39	***P* <0.01**
- Pre-eclampsia	17 (19.77%)	95 (44.19%)	***P* <0.01**	-0.23	-0.36 - -0.12	***P* <0.01**
- HELLP	1 (1.16%)	9 (4.19%)	*P* = 0.19	-0.08	-0.08 – 0.02	*P* = 0.19

CI = confidence interval, RM = remote monitoring, CC = conventional care, HELLP = hemolysis elevated liver enzymes and low platelets.
Univariate analysis; data are means (± SD) or percentages (numbers).

To investigate the influence of the maternal demographic factors and characteristics on the prenatal follow-up, a multiple linear regression analysis and multivariate logistic

regression analysis were performed. A detailed overview of these data is given in Supplementary File I in the Supplementary Appendices.

DELIVERY OUTCOMES: COMPARISON OF RM AND CC

The delivery outcomes are shown in Table 5.3, 5.4 and 5.5. In both the uni- and multivariable analyses in Table 5.3, the RM group showed a higher number of spontaneous births than the CC group (43/86 [50.00%] versus 69/215 [32.09%], respectively, $\beta = 0.86$). The number of inductions was also lower in the RM group than in the CC group (28/86 [32.56%] versus 100/215 [46.51%], respectively, $\beta = -0.66$).

Table 5.3: Delivery outcomes

Variable	*Univariate analysis*			*Multivariate analysis*		
	RM group (n = 86)	*CC group (n = 215)*	*p-value*	*RM vs. no RM (Beta)*	*95.0% CI for Beta*	*p-value*
GA delivery (week)	37.53 (± 2.77)	36.77 (± 3.64)	*P* = 0.18	0.24	-0.64 – 1.13	*P* = 0.59
Start birth process (%):						
- Spontaneous	43 (50.00%)	69 (32.09%)	***P* < 0.01**	0.86	1.31 – 4.23	***P* < 0.01**
- Induction	28 (32.56%)	100 (46.51%)	***P* < 0.01**	-0.66	0.28 – 0.92	***P* < 0.01**
- Primary cesarean section	15 (17.44%)	46 (21.40%)	*P* = 0.44	-0.18	0.40 – 1.75	*P* = 0.63
Mode of delivery (%):						
- Vaginal	55 (63.95%)	121 (56.28%)	*P* = 0.22	0.17	0.66 – 2.13	*P* = 0.57
- Instrumental	4 (4.65%)	12 (5.58%)	*P* = 0.75	0.001	0.27 – 3.75	*P* = 0.99
- Primary cesarean section	15 (17.44%)	46 (21.40%)	*P* = 0.44	-0.18	0.40 – 1.75	*P* = 0.63
- Secondary cesarean section	10 (11.63%)	32 (14.88%)	*P* = 0.46	-0.14	0.69 – 2.07	*P* = 0.76
Birthweight (g)	2988.62 (± 745.97)	2843.67 (± 919.44)	*P* = 0.34	43.901	-191.97 – 279.77	*P* = 0.71
Apgar 1′	8.22 (± 1.29)	8.05 (± 1.36)	*P* = 0.19	0.21	-0.17 – 0.59	*P* = 0.27
Apgar 5′	9.14 (± 0.94)	9.10 (± 0.90)	*P* = 0.57	0.01	-0.24 – 0.27	*P* = 0.93
Admission NIC (%)	8 (9.30%)	36 (16.74%)	*P* = 0.43	-0.23	0.41 – 1.54	*P* = 0.49

CI = confidence interval, RM = remote monitoring, CC = conventional care, GA = gestational age, NIC = neonatal intensive care.

Univariate analysis; data are means (± SD) or percentages (numbers).

In table 5.4, both the uni- and multivariable analyses showed in the RM group, versus CC group, more births after 37 weeks of gestational age in pregnancies complicated with gestational hypertension (91.67% [55/60] versus 53.33% [61/83], β = 0.26) and pregnancies complicated with pre-eclampsia (58.82% [10/17] versus 53.33% [40/75], β = 0.22).

Table 5.4: Prevalence of gestational age by gestational hypertensive disorder

Variable	*Univariate analysis*			*Multivariable analysis*		
	Remote monitoring group	*Conventional Care*	*Statistical significance (2 – tailed)*	*RM vs. no RM (Beta)*	*95.0% CI for Beta*	*P-value*
Essential hypertension	*(n = 8)*	*(n = 17)*				
- < 34 weeks GA	0 (0.00%)	2 (11.76%)	*P = 0.44*	*-0.07*	*-0.12 – 0.26*	*P = 0.45*
- 34 weeks – 37 weeks GA	1 (12.50%)	3 (17.65%)	*P = 0.50*	*-0.09*	*-0.35 – 0.18*	*P = 0.52*
- > 37 weeks GA	7 (87.50%)	12 (70.59%)	*P = 0.88*	*0.01*	*0.08 – 0.09*	*P = 0.88*
Gestational hypertension	(n = 60)	(n = 83)				
- < 34 weeks GA	3 (5.00%)	6 (7.23%)	*P = 0.36*	*-0.16*	*-0.52 – 0.20*	*P = 0.37*
- 34 weeks – 37 weeks GA	2 (3.33%)	16 (19.28%)	*P = 0.65*	*-0.10*	*-0.35 – 0.55*	*P = 0.11*
- > 37 weeks GA	55 (91.67%)	61 (73.49%)	**P < 0.01**	*0.26*	*-0.40 - 0.12*	**P < 0.01**
Pre-eclampsia	*(n = 17)*	*(n = 75)*				
- < 34 weeks GA	4 (23.53%)	18 (24.00%)	*P = 0.47*	*-0.14*	*-0.26 – 0.54*	*P = 0.48*
- 34 weeks – 37 weeks GA	3 (17.65%)	17 (22.67%)	*P = 0.85*	*-0.04*	*-0.50 – 0.41*	*P = 0.86*
- > 37 weeks GA	10 (58.82%)	40 (53.33%)	**P = 0.01**	*0.22*	*0.10 – 0.35*	**P <0.01**
HELLP	*(n = 1)*	*(n = 7)*				
- < 34 weeks GA	1 (100.00%)	2 (28.57%)	*P = 0.63*	*0.05*	*-0.29 – 0.18*	*P = 0.64*
- 34 weeks – 37 weeks GA	0 (0.00%)	1 (14.29%)	*P = 0.68*	*-0.03*	*-0.11 – 0.16*	*P = 0.69*
- > 37 weeks GA	0 (0.00%)	4 (57.14%)	*P = 0.14*	*-0.03*	*-0.01 – 0.07*	*P = 0.14*

GA = gestational age, HELLP = Hemolysis Elevated Liver enzymes and Low Platelets.

Data are mean (± SD) or percentage (number).

Only in the univariate analysis was the mean gestational age at delivery between 34 and 37 weeks of gestation in pregnancies complicated with gestational hypertension higher in the CC group versus the RM group (35w 4/7 (±0.49) versus 34w 6/7 (± 0.00); p = 0.008) (Table 5.5)

Table 5.5: Gestational age by gestational hypertensive disorder

Variable	*Univariate analysis*			*Multivariable analysis*		
	Remote monitoring group	*Conventional Care*	*Statistical significance (2 – tailed)*	*RM vs. no RM (Beta)*	*95.0% CI for Beta*	*P-value*
Essential hypertension	*(n = 8)*	*(n = 17)*				
- < 34 weeks GA	/	31w 1/7 (± 7.07)	/	/	/	/
- 34 weeks – 37 weeks GA	/	36w 3/7 (± 1.15)	/	/	/	/
- > 37 weeks GA	38w 6/7 (±1.07)	38w 4/7 (± 1.18)	*P = 0.89*	0.53	-1.04 – 1.19	*P = 0.89*
Gestational hypertension	*(n = 60)*	*(n = 83)*				
- < 34 weeks GA	31w 3/7 (± 2.08)	30w 6/7 (± 2.28)	*P = 0.84*	0.33	-3.39 – 4.05	*P = 0.84*
- 34 weeks – 37 weeks GA	34w 6/7 (± 0.00)	35w 4/7 (± 0.49)	**P = 0.008**	-0.36	-1.57 – 0.14	*P = 0.08*
- > 37 weeks GA	38w 6/7 (± 1.09)	38w 6/7 (± 1.07)	*P = 0.46*	-0.14	-0.54 – 0.25	*P = 0.46*
Pre-eclampsia	*(n = 17)*	*(n = 75)*				
- < 34 weeks GA	30w 4/7 (± 3.30)	30w 1/7 (± 2.88)	*P = 0.75*	0.52	-2.87 – 3.93	*P = 0.07*
- 34 weeks – 37 weeks GA	34w 6/7 (± 1.00)	36w 2/7 (± 1.62)	*P = 0.18*	-1.35	-3.41 – 0.70	*P = 0.18*
- > 37 weeks GA	38w 1/7 (±1.31)	38w 4/7 (± 1.20)	*P = 0.36*	-0.41	-1.26 – 0.44	*P = 0.34*
HELLP	*(n = 1)*	*(n = 7)*				
- < 34 weeks GA	/	33w 6/7 (1.41)	/	/	/	/
- 34 weeks – 37 weeks GA	/	/	/	/	/	/
- > 37 weeks GA	/	37w 4/7 (±1.00)	/	/	/	/

GA = gestational age, HELLP = Hemolysis Elevated Liver enzymes and Low Platelets.
Data are mean (± SD) or percentage (number).

To investigate the influence of the maternal demographic factors and characteristics on the prenatal follow-up, a multiple linear regression analysis and multivariate logistic regression analysis were performed. A detailed overview of these data is given in Supplementary File II in the Supplementary Appendices.

COMMENT

PRINCIPAL RESULTS

We sought to confirm or refute the conclusions of a retrospective analysis of data from 2015. The findings of the present study include a lower incidence of pre-eclampsia but an increased incidence of gestational hypertension in the group of women on the prenatal RM program than in the women who received CC. Compared with the CC group, the women in the RM group had fewer admissions to the prenatal ward and fewer hospitalizations until the moment of delivery, more births after 37 weeks of gestational age in pregnancies complicated with gestational hypertension and pregnancies complicated with pre-eclampsia in both uni- and multivariate analyses. The women in the RM group also had fewer prenatal visits than the women in the CC group, but only in the multivariate analysis. In both analyses, spontaneous deliveries were more likely and inductions less likely in the RM group than in the CC group. Only in the univariate analysis was the mean gestational age at delivery between 34 and 37 weeks of gestation in pregnancies complicated with gestational hypertension higher in the CC group versus the RM group.

Our conclusions are basically the same as the conclusions drawn from the dataset of 2015. Only two distinctions can be made: (1) the newborns of the women who received RM during their pregnancies in 2015 were less likely to be admitted to the NICU than the newborns of the women who received CC, and this discrepancy is not evident in the 2015–2016 analysis; and (2) there was no difference in the total number of prenatal visits between the women of the RM and CC groups in 2015. In contrast, in the present analysis, the women on the RM program had fewer prenatal visits than the women who received CC.

STRENGTHS AND LIMITATIONS

One of the major strengths of this study is its design: data were collected over a study period of 2 years, and a retrospective design was used. Many data were collected during this time on a prenatal RM program for the follow-up of GHD, one of the commonest pregnancy complications, although its prevalence is only 10% (50). It is hard to undertake a prospective investigation of this topic because the prevalence of the disorder is often unpredictable. A retrospective design may not be the first choice for a study, but it was the best way to collect data on this topic over a period of 2 years. Another strength of our study is that ours is the only hospital in the province of Limburg (Flanders, Belgium) with its own prenatal ward. Pregnant women with an elevated risk of developing GHD, or who develop this disorder unexpectedly during their pregnancy, are referred to our hospital for further follow-up. In this way, we have a lot of information about prenatal follow-up in this patient population and our hospital has close associations with the other hospitals in Limburg, so it is easy to exchange missing data. Therefore, all the patients received antenatal care in accordance with uniform local management protocols and we had an almost complete dataset.

Our study also had three main limitations. First, by collecting data retrospectively, we could not exclude selection bias. Second, there were small differences in the maternal demographic factors and characteristics. More women smoked during their pregnancy and fewer women had immunological disorders in the CC group than in the RM group. Although a multivariate analysis showed that these parameters did not influence our principal findings, smoking during pregnancy has adverse outcomes, although a reduced risk of developing of GHD in women who smoke has been demonstrated in many studies (49, 51). There is insufficient or conflicting evidence suggesting that immunological diseases influence the development of GHD (74-77). The last limitation is that interference by family doctors or community midwives cannot be excluded.

COMPARISONS WITH PREVIOUS TRIALS

The retrospective study of an RM prenatal follow-up program for women with GHD, published in 2016, was to our knowledge the first study to report the value of this technology in obstetrics. Since the appearance of that publication, no new articles have been published about the value of an RM prenatal follow-up program for women with GHD. However, Marko et al. (2016) reported a feasibility study of the use of a mobile phone app and connected digital devices (weight scale and blood-pressure monitor) for women at risk for adverse pregnancy outcomes. They concluded that this system is feasible for prenatal care (77). Several studies of RM programs that assist nonpregnant patients with hypertension to control their blood pressure have been reported. All of these have concluded that home monitoring of blood pressure is a reliable and promising method that can potentially contribute to blood pressure reduction (78-82). Based on this literature, RM has already proven its utility for the management of hypertensive disorders outside pregnancy. In our study, we have demonstrated that RM also has value for hypertensive disorders during pregnancy.

POSSIBLE EXPLANATIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

A possible explanation of the differences in admission to the prenatal observational ward and gestational outcomes observed in this study is that pre-eclampsia can result from gestational hypertension or essential hypertension (55, 56, 83). RM makes it possible for caregivers to see abnormal events in pregnant women in their home contexts and to offer an intervention when necessary to prevent the worsening of the disease. Several studies have suggested that starting or adjusting an antihypertensive therapy can reduce the risk of developing severe hypertension or pre-eclampsia (58-60, 84). However, this is refuted by the study of Duley (2011), who demonstrated that an antihypertensive therapy can reduce the risk of severe hypertension, but not of pre-eclampsia (61). Further

investigation of the value of an antihypertensive therapy in preventing the exacerbation of GHD is recommended.

When pre-eclampsia is diagnosed, the only treatment that can be used to prevent further complications is the induction of labor (62, 63). More women were diagnosed with pre-eclampsia in the CC group, than in the RM group. This could explain the higher rate of inductions in the CC group. Gestational hypertension is not usually a reason to induce labor, and expectant management until a spontaneous labor is advised. This may explain the higher number of spontaneous births in the RM group.

Fewer prenatal visits were also observed in the RM group than in the CC group. Women with GHD who participated in the RM prenatal follow-up program were no longer required to visit the hospital in the prenatal period to monitor their blood pressure. Blood pressure can be monitored at home, under the remote supervision of a responsible caregiver. This new type of management can be a useful tool for caregivers in that it allows them to spend their time on pregnant women who really require their attention. However, caregivers will require time to get used to this type of management, which may explain why there was a reduction in the total number of prenatal visits in 2016, but not in 2015. Additionally, it would be interesting and valuable to perform a cost-effectiveness study. When RM has a positive cost-effectiveness rating, less-expensive care will improve gestational outcomes.

To conclude, a qualitative investigation of maternal satisfaction with the use of RM is recommended. A thorough qualitative analysis will allow a comprehensive understanding of patient satisfaction, and this information could be used to improve future technological designs. This may allow interventions to be adjusted to the target population and have positive effects on various domains, including patient compliance and birth experience.

PART IV

PERCEPTIONS OF THE CAREGIVERS AND THE PREGNANT WOMEN

CHAPTER 6

The Perceptions of Midwives, Obstetricians and recently delivered Mothers to Remote Monitoring for Prenatal Care

Lanssens D, Vandenberk T, Lodewijckx J, Peeters T, Storms V, Thijs IM, Grieten L & Gyselaers W.

** *Submitted at JMIR* **

ABSTRACT

Background: There have been few studies on remote monitoring (RM) in midwifery. These studies were mostly performed several decades ago, and no recent studies have investigated the perceptions to or experiences of new technologies. The Pregnancy Remote Monitoring (PREMOM) study, which started in January 2015 in Ziekenhuis Oost-Limburg (Genk, Belgium), enrolled pregnant women at increased risk of developing gestational hypertensive disorders (GHD). Women enrolled in PREMOM underwent conventional prenatal follow-up, which was complemented with RM. We sought to investigate the perceptions and experiences of mothers, midwives, and obstetricians to the RM approach used in the PREMOM study.

Methods*:* We developed specific questionnaires for the mothers, midwives, and obstetricians. The questionnaires comprised five domains: 'prior knowledge and experience of RM', 'reactions to abnormal values', 'privacy', 'quality and patient safety', and 'financial aspects'. The caregivers were also questioned about which issues they consider important when implementing RM. A five-point Likert scale was used to provide objective scores.

Results: Ninety-one participants completed the questionnaires, including 47/92 (51.08%) mothers, 35/52 (67.30%) midwives, and 9/14 (64.29%) obstetricians. The mothers, midwives, and obstetricians reported positive experiences and perceptions to RM. Overall, 29/35 (82.85%) midwives and 7/9 (77.78%) obstetricians had no or little prior experience with this technology. After working for 1 year with RM, 28/35 (80.00%) midwives and 6/9 (66.67%) obstetricians felt that this technology is an important component in the prenatal monitoring of high-risk pregnancies and that it had a positive contribution to the care of pregnant women. They support a further roll-out of RM in Belgium, but caregivers need additional training on RM devices and the pathological aspects of GHD. Nearly three-

quarters of the mothers who participated in the PREMOM study (34/47, 72.34%) did not report any problems with taking the measurements at the required times. Almost half of the mothers (19/47, 40.43%) wanted to be contacted within 3–12 hours after abnormal values, preferably by telephone. Nearly all of the mothers (41/47, 87.24%) did not have any problems with regularly sharing their health data with their gynaecologist. Finally, most of the mothers (39/47, 82.97%) reported that RM gave them a feeling of security throughout their pregnancy.

Conclusions: Although the majority of midwives and obstetricians had no or very little experience with RM before enrolling in the PREMOM study after one year, they reported that RM is an important component in the follow-up of high-risk pregnancies and would recommend it to their colleagues and pregnant patients.

INTRODUCTION

Due to demographic changes and rapid improvements in medical technologies, the healthcare sector is confronted with major challenges and with great opportunities. One challenge in healthcare includes pregnant women. The number of high-risk pregnancies is elevated due to the changing lifestyles of pregnant women that have occurred over the last few decades (85-87). Therefore, there is an increasing need to intensively follow-up these pregnancies. Telemedicine represents an opportunity for the follow-up of such women.

Defined as the use of information and communication technologies for supporting health and health-related activities (88), telemedicine is not simply an addition to conventional care, but rather is implemented in current private and public healthcare approaches. Remote monitoring (RM) represents a type of telemedicine that has a broad definition. It is useful for conducting medical practice from a distance and has been used in a wide variety of electronic healthcare applications (89). RM can be performed either by live monitoring or asynchronously, whereby data obtained in the patient's home environment are sent to the caregiver and stored in the patient's electronic medical records (88). Although very few studies to date have investigated the use of RM in prenatal care, these studies concluded that RM could have a major role in the improvement of obstetric care, especially in improving maternal satisfaction (18) and reducing adverse neonatal outcomes (13, 22). However, most of the publications are over 10 years old and did not evaluate the newer RM technologies.

The Pregnancy Remote Monitoring (PREMOM) study, which started in January 2015 in a tertiary centre Ziekenhuis Oost-Limburg (Genk, Belgium), involved RM of pregnant women at high risk of gestational hypertensive diseases (GHD). The PREMOM study design, data collection method and first promising results are described in detail elsewhere

(73, 90) Briefly, the PREMOM study is performed in the outpatient clinic of a 2nd lever prenatal center where pregnant women with GHD received RM or conventional care (CC). Women consenting for RM received obstetric surveillance using a BP monitor, activity tracker and weight scale. The participating women were asked to measure blood pressure twice daily, measure their weight once daily, and to wear an activity tracker during the 24 hours/day. These data were automatically sent by Wi-Fi or Bluetooth to an online platform which is developed by the Mobile Health Unit (UHasselt), and a midwife reviewed the parameters every workday. Predetermed alarm signals were set (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg or weight gain > 1 kg/day) and were automatically generated based on an evidence-based triage system. Alarm events were by the midwife communicated with the obstetrician in charge to discuss management options before contacting and instructing patients at home. Therapeutic interventions were according to local management. Two pilot studies demonstrated that women with RM did have less inductions, more spontaneous labors, and less maternal and neonatal hospitalizations when compared with conventional care (73, 91). Also a cost-analyses of the hospital bills of women with GHD who received RM versus the women who received CC showed a cost-effective effect for the healthcare system in RM (90). Because no research has been done to investigate the perceptions to or expectations of a prenatal RM follow-up program, we performed quantitative surveys of recently delivered women and caregivers involved in these technologies to elucidate their perceptions and expectations. Here, we describe the main outcomes, which covered the following domains: 'prior knowledge and experience of RM', 'reactions to abnormal values', 'privacy', 'quality and patient safety' and 'financial aspects'. Caregivers were also asked about important aspects to consider when implementing RM.

METHODS

QUESTIONNAIRES

Three anonymous questionnaires were designed by the research group of the Mobile Health Unit (University of Hasselt, Hasselt, Belgium). The questionnaires were designed for women who were followed-up with RM during their last pregnancy, the midwives working at the Ziekenhuis Oost-Limburg (Genk, Belgium) (ZOL) who are involved in the use of RM, and the consulting obstetricians working at several hospitals in Limburg. The questionnaires assessed five issues to elucidate the perceptions and experiences of the participants in PREMOM to RM, and were based on the six building blocks established by the Mobile Health working group of VOKA Health Community (Brussels, Belgium): (1) protection of data, privacy, and the use of big data; (2) national/international regulations and responsibility; (3) quality, accessibility, and patient safety; (4) technology and interoperability; (5) financing and business models; and (6) supportive policy frameworks in telemedicine. The results of the descriptive PREMOM questionnaires on the domains 'prior knowledge and experience of RM', 'reactions to abnormal values', 'privacy', 'quality and patient safety', and 'financial aspects', which are important to caregivers for further implementation of RM, are discussed in this manuscript. We also recorded the demographic data for all participants. The questionnaires were drafted in April 2016 using Survey Monkey (Survey Monkey, 2016), and were to be completed online. All questions were assessed using five-point Likert scales to obtain objective scores.

PARTICIPANTS

The questionnaires were sent in April 2016 to the women, midwives working at ZOL, and obstetricians (from several hospitals in Limburg) who participated in the PREMOM study in 2015. Student midwives and doctors in training were excluded from the present study.

DATA COLLECTION

The study participants received an e-mail from the research team with a link to the online survey. E-mail reminders were sent to all participants at 9 and 23 days after the first invitation.

ANALYSIS

Mean scores and ranks were assessed for each question using descriptive analytical methods. The number of participants included in the analyses of individual questions differed from the total number of analysed questionnaires because some mothers, midwives, and obstetricians did not complete all of the questions. Statistical analysis was performed with Statistical Package for Social Sciences release 24.0 (IBM SPSS Inc).

ETHICAL CONSIDERATIONS

To maintain anonymity, the participants were sent a generic link to the survey. A bulk e-mail was sent with the subjects' e-mail addresses included as a BCC to ensure there were no recognisable personal elements in the e-mail. The e-mail was addressed with 'Dear Madam', or 'Dear Colleague', to confirm there were no personal items in the invitation to participate in this study. In addition, the participants were not asked to report an ID when completing the questionnaires. The Medical Ethics Committee of Ziekenhuis Oost-Limburg approved this study (nr. 14/078U).

RESULTS

A study population of 158 people consist out: 92 mothers (58.23%), 52 midwives (32.91%), and 14 obstetricians (8.86%). The total number of involved pregnant women in the PREMOM study n = 119, so 77.31% (92/119) of the participants was contacted after their delivery. The missing 27 women didn't answer their phone, didn't have an e-mail address or there was language barrier. One gynaecologist was excluded from final analyses because less than 50% of the questionnaire was completed. Therefore, the total response rate was 57.59%. An overview of the questions to the midwives, obstetricians and recently delivered mothers, and their answers, are submitted in Appendix 1. The characteristics of the participants are listed in Table 6.1.

Table 6.1: Characteristics of participants

Characteristics of women who have involved with RM during their last pregnancy (n = 47)	**Response categories**	**Results**	
		N	**%**
Age	< 20 year	0	0
	20 – 25 years	5	10.64
	26 – 30 years	16	34.04
	31 – 35 years	21	44.68
	36 – 40 years	4	8.51
	> 40 year	1	2.13
Primigravidity	Primipara	21	44.68
	Multipara	26	55.32
History of GHA	Yes	17	36.17
	No	10	21.28
	N/A	20	42.55
Level of education	Lower secondary school	4	8.51
	Higher secondary school	12	25.53
	High school	20	42.55
	University	11	23.40
Characteristics of the midwives (n = 35)	**Response categories**	**Results**	
		N	**%**
Age	20 – 25 years	3	8.57
	26 – 30 years	8	22.86
	31 – 35 years	7	20.00
	36 – 40 years	3	8.57
	> 40 year	14	40.00
Years of experience	< 5 year	4	11.43
	5 – 15 years	15	42.86

	16 – 25 years	8	22.86
	> 25 year	8	22.86
Main activity on nurse unit	Delivery unit	11	31.43
	Maternity	8	22.86
	MIC	10	28.57
	Prenatal visits	6	17.14
Characteristics of the gynecologists (n = 9)	**Response categories**	**Results**	
		N	**%**
Years of experience	< 5 year	1	11.11
	5 – 15 years	6	66.66
	16 – 25 years	0	0.00
	> 25 year	2	22.22
Main activity on their specialism	Delivery unit	4	44.44
	Gynaecologist	4	44.44
	Oncology	1	11.11

Table 1: Characteristics of respondents

N/A = not applicable; MIC = maternal intensive care

PRIOR KNOWLEDGE AND EXPERIENCE OF RM

The first part of the questionnaire examined the midwife's and gynaecologist's prior knowledge or experience of RM. Overall, 29/35 midwives (82.85%) and 7/9 (77.78%) obstetricians reported little or no experience of RM (Figure 6.1).

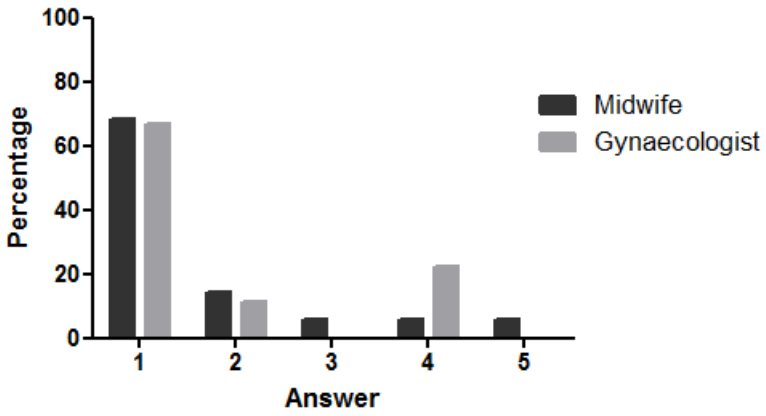

Figure 6.1: Summary of responses from the midwives and obstetricians on the question 'Please indicate with a score from 1 (strongly disagree) to 5 (strongly agree): I had already experience with RM before this study.'

The midwives were also asked about their experience of RM as a threat to their daily work. The majority (29/35, 82.85%) of midwives felt that they did not perceive RM as a threat to their work.

TIMING AND METHOD OF COMMUNICATION IN CASE OF AN EVENT

Nearly three-quarters (34/47, 72.34%) of the participating mothers reported that they had no problems with performing the measurements at the requested times. Of the 7 mothers (14.89%) who reported difficulty with the recommended measurements, 4 (57.14%) were 36–40 years old, 2 (28.57%) between 26-30 years and 1 (14.29%) between 31-35 years.

Participants were also asked about the acceptable time limit for being contacted by their caregiver in case of an unexpected event. Of 47 women who completed the questionnaire,

13 (27.66%) preferred to be contacted within 3 hours of the event, and 19 (40.43%) agreed to be contacted between 3–12 hours, and 15 (31.91%) complied with being contacted > 12 hours after the event (Figure 6.2).

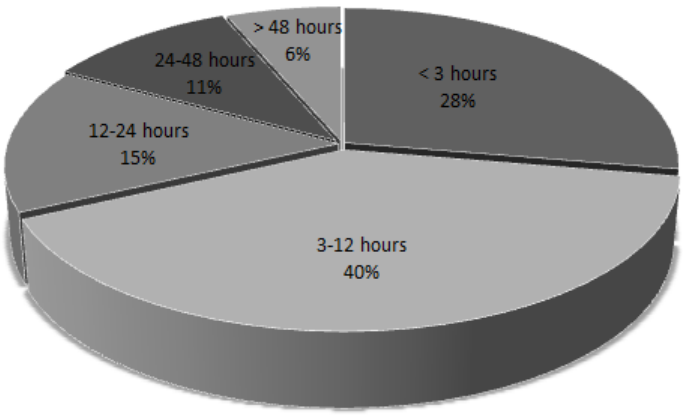

Figure 6.2: Summary of responses to the question 'Within how much time do you want to be contacted about events?'

Interestingly, 4/5 mothers (80.00%) aged < 25 years asked to be contacted within 3 hours of an event. The participants were also asked how to be contact following an event. The participants' first preference was to be contacted by telephone (weighted average 4.55/5), while prenatal consultation (weighted average 3.94/5) and text messages (weighted average 3.17/5) were the second and third preferences, respectively. In the final question in this section, we asked the participants to state who should contact the women in case of an event. The mothers and midwives stated that the gynaecologist should be the first to contact the pregnant woman after an abnormal event. However, the obstetricians reported that their representing researcher should be the first caregiver to contact the pregnant woman in case of an event.

PRIVACY

The mothers were asked if they felt that regularly sharing their health data was a threat to their privacy. Most (41/47, 87.24%) of the mothers reported that they did not have any

negative concerns about privacy. Three mothers reported a threat to their privacy, and they were aged 36–40 years.

QUALITY AND PATIENT SAFETY

The mothers were asked about the importance of RM in the follow-up of their pregnancy. Most (42/47, 89.36%) of the mothers had a positive response to this question. Meanwhile, 28/35 (80.00%) midwives reported that RM provided added value to pregnant women and 27/35 (77.14%) midwives felt that RM improved the care of pregnant women at increased risk of gestational complications. This percentage is slightly higher than that of obstetricians; 6/9 (66.67%) of whom felt that RM provided added value to their patients (Figure 6.3).

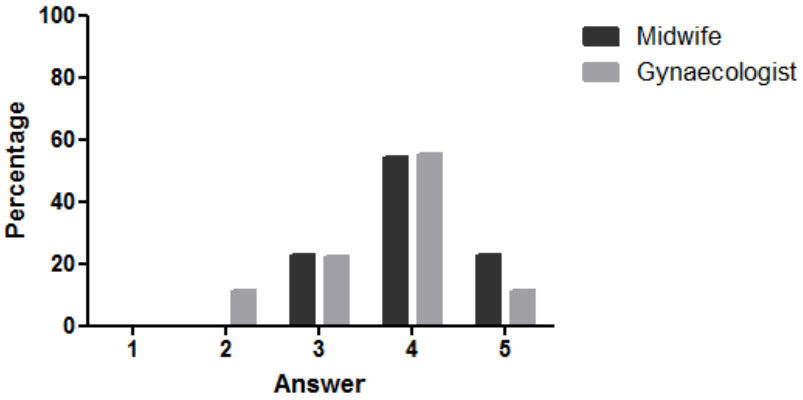

Figure 6.3: Summary of responses from the midwives and obstetricians to the question "Do you believe that RM improves the care for pregnant women with an increased risk of gestational complications? Please indicate with a score from 1 (strongly disagree) to 5 (strongly agree).

Moreover, 8/9 (88.89%) obstetricians responded, based on their experience of the PREMOM study, that the pregnant women did not request additional prenatal consultations for the purpose of viewing their own vital parameters. Finally, 39/47 (82.97%) mothers reported that RM gave them a feeling of safety.

FINANCIAL

An important element in new healthcare practices is their financial cost. Therefore, the relative and absolute costs of each component in telemonitoring programmes need to be evaluated. All three groups of participants reported that the cost of RM should be as low as possible, and about half of the mothers expected RM to be free (25/47, 53.19%). It is also important to obtain information on any potential payer of RM. The mothers expected the hospital to be the main payer, followed by health insurance (company), whereas midwives and obstetricians felt that the pregnant women should contribute to the cost of RM.

FURTHER IMPLEMENTATION OF RM

The midwives and obstetricians were asked about important factors to support the implementation of RM into daily practice. Most of the midwives (31/35, 88.57%) felt that it is important to receive additional training on "the information that must be given to pregnant women about GHD and the added value of RM in this monitoring this disease". A lower proportion of obstetricians (7/9, 77.78%) considered this necessary. More obstetricians (8/9, 88.89%) felt that training on the technical handling of the devices (e.g. installation and common problems) was the most important factor. About three-quarters of midwives (27/35, 77.14%) had the same response to this question. In terms of the final evaluation of the project, the obstetricians were asked whether they would recommend RM to pregnant women and their colleagues. Overall, 6/9 (66.67%) obstetricians supported this service and would recommend it to their patients while 7/9 (77.78%) obstetricians would recommend RM to their colleagues. Finally, 6/9 (66.67%) obstetricians recommended that this follow-up should be expanded to all pregnant women in Belgium who are at increased risk of GHD.

DISCUSSION

PRINCIPAL FINDINGS

To our knowledge, this is the first quantitative survey of an RM program for prenatal care. The results show that the majority of midwives and obstetricians had no or very little experience of RM before they participated in the PREMOM study. After taking part in the PREMOM study and the survey, the midwives reported that RM is not a threat to their daily work. The majority of mothers who were followed up by RM during their last pregnancy did not experience any problems with taking the required measurements at the specified times. Most of the mothers thought that it is acceptable to be contacted within 3–12 hours after an abnormal value, and they preferred to be contacted by telephone. The mothers did not have concerns with sharing their health data with their gynaecologist, and reported that RM gave them a feeling of security throughout their pregnancy.

The mothers, midwives, and obstetricians included in the study reported that RM is an important aspect of the follow-up of (high risk) pregnancies. The obstetricians stated that they would recommend RM to colleagues and other pregnant women. Most of the obstetricians proposed extending RM to all women with high-risk pregnancies in Belgium. The obstetricians and midwives also reported that all users need additional training to support the implementation of RM.

STRENGTHS AND LIMITATIONS OF THE STUDY

Despite the increased implementation of RM in healthcare, its use is still limited in obstetrics. Ours was the first study to investigate the perceptions of obstetricians, midwives, and recently delivered mothers to the use of RM for preterm follow-up of pregnancies at risk for GHD. Another strength of this study is that it included stakeholders involved in the use of RM, including caregivers and actual users. The questionnaire also included additional space allowing the participants to explain their responses to each

question, allowing us to obtain supplementary information. Furthermore, the participants could complete the questionnaire anonymously, an important strength of this study. Finally, a relatively high percentage of participants in PREMOM study completed the questionnaires.

This study also has some weaknesses to mention. First, because the questionnaire was completed anonymously, it was not possible to write to the individual participants to request additional information. Second, the questionnaire was completed in uncontrolled conditions, and it is unclear whether the participants were exposed to external influences when they completed the questionnaire. Additionally, the three groups in this study had small sample sizes, which could affect external validity. Third, this study is performed in a local hospital with a rather low number of participants. Finally, the study included obstetricians who worked at several hospitals in Limburg, but the midwives and mothers were enrolled only from a single center (Ziekenhuis Oost-Limburg).

COMPARISON WITH THE LITERATURE AND POSSIBLE EXPLANATIONS

Although very few studies have examined the use of RM for the prenatal follow-up of pregnant women, the results of these studies were positive. Previous research concluded that pregnant women with gestational diabetes mellitus had an increased sense of self-regulation when they used RM to send their blood glucose levels to their midwives (15, 17). Meanwhile, other research showed that pregnant women had heightened feelings of maternal satisfaction when using RM as additional care with their labour induction (20, 21).

The PREMOM pilot study demonstrated the importance of properly performing the required data sampling in order for RM to succeed (92). Measuring blood pressure, body weight, and activity every day is a prerequisite to ensure adequate monitoring of pregnant women. Although this may appear burdensome to many pregnant women, the mothers

surveyed in this study did not experience this obstacle. 'Privacy' is a critical aspect of healthcare and RM (93). In the PREMOM study, it was necessary to ensure that the clinical data were measured, transmitted, and stored safely and securely. The clinical data were uploaded to an online database through the website of the commercial partner (Withings, Issy-les-Moulineux, France). A midwife reviewed all the data. Some risk-averse participants might be unwilling to share their clinical data with a commercial partner. However, none of the participants reported any privacy breaches using RM. In addition, the quality of care experienced by pregnant women with (increased risk of) GHD was enhanced by RM, as reported by the surveyed mothers and caregivers, and supported by the results of the prior pilot study (73, 91).

Finally, a common argument against RM is the perception that it may place extra burden on healthcare services because pregnant women with concern about their health may wish to consult their own data. This perception was assessed in the questionnaires, but it was not expressed by the obstetricians participating in this survey. This conclusion is consistent with the results of studies of pregnant women with gestational diabetes mellitus supported by RM (17, 18).

RECOMMENDATIONS FOR FURTHER RESEARCH

Both the mothers and the midwives felt that the gynaecologist should be responsible for contacting the patient after an abnormal event, while the obstetricians suggested that their reporting researcher is responsible for this task. This may relate to the organisation of prenatal care in Belgium, where midwives nearly act as obstetric nurses instead of independent midwives and the prenatal care for pregnant women mostly is performed by an obstetrician, nevertheless if a pregnant women has a high or a low risk pregnancy. It is remarkable that none of these three groups felt that this could be a task of the patient's midwife, although the researcher in this study is certified as a midwife. Still, the allocation

of RM – coordination to the responsibilities of the midwives seem logic, as they act as an intermediary between the pregnant woman and the gynaecologist. Clearly, further research is needed to understand the factors underlying this opinion and how it could be changed.

Additionally, both the mothers as the healthcare workers stated that RM should be offered for free or they want to pay as less as possible for the RM services. Although a cost-effectiveness study is executed and it has proven that RM makes a cost saving possible for the healthcare system (90), a willingness to pay study isn't performed yet. This would have an additional value to set a price for the RM services when the healthcare society or the hospital asks for it.

Further, although 66% of the obstetricians would recommend RM to their patients and 77% to their colleagues, the obstetricians who wouldn't recommend it didn't give any reason for this. A following qualitative questionnaire which investigates the underlying reasons for this should be helpful the further implement RM in the standard prenatal care for women at risk for GHD.

Interestingly, the mothers preferred to be contacted between 3 and 12 hours after an abnormal clinical measurement. This implicates that the clinical data should be monitored 24/7 in order to evaluate and interpret the vital parameters of pregnant women, and permit an intervention if necessary. We therefore recommend developing a system of care aimed at providing these services. Like we showed in our previous studies, the prenatal ward will be less burdened by women with GHD due to our RM prenatal follow-up (73, 91). Leading from the reductions in prenatal hospitalisations, the work package of the midwife working on the prenatal ward be redefined and there will be some additional space for the RM follow-up, performed by the midwives. Finally, although the mothers with abnormal events were invited to additional prenatal consultations to assess the fetal

and maternal wellbeing, none of the patients or the participating obstetricians believed that this was needed and as such was no treat for overloading the healthcare system. These findings may contradict the statement that the medicalization of childbirth has gone too far and too much medical interventions are performed in pregnancies, which has arisen from a variety of sources (64-69).

CONCLUSIONS

Although most midwives and obstetricians had no or very little experience of RM before they participated in the PREMOM study, they felt that it is an important aspect of the follow-up of pregnancies at risk for GHD. Most of the mothers who were followed-up by RM during their last pregnancy thought that it was acceptable to be contacted within 3–12 hours after an abnormal value, and they preferred to be contacted by telephone. The majority of women had no concerns about regularly sharing their clinical data with their gynaecologist, and they reported that RM gave them a feeling of security throughout their pregnancy. To our knowledge, this is the first quantitative survey of mothers, midwives, and obstetricians involved in an RM program in prenatal care. Further studies are needed to understand the underlying opinions of mothers, midwives, and obstetricians to RM. Based on our findings, we propose developing a care system with 24/7 surveillance by RM for mothers at high risk of GHD.

PART V

COSTS FOR THE HEALTHCARE SYSTEM

CHAPTER 7

Prenatal Monitoring of Women with Gestational Hypertensive Diseases: Cost Analyses

Lanssens D, Vandenberk T, Smeets CJ, De Cannière H, Vonck S, Claessens J, Heyrman Y, Vandijck D, Storms V, Thijs IM, Grieten L & Gyselaers W

J Med Internet Res. 2018 Mar 2016;20(3)e102

INTRODUCTION

Remote monitoring (RM) in obstetrics is a relatively new field of research, only a few trials shown the effectiveness of RM in obstetrical care for both mother and child. When uterine activity is transmitted by telecommunication, significant prolonged pregnancy survivals are observed (13, 14). Higher feelings of self-efficacy and a reduction in (unscheduled) face-to-face visits (15, 17-19) is reported when RM is used in the prenatal follow up of pregnant women with gestational diabetes mellitus in comparison to conventional care (CC). On top, elevated feelings of maternal satisfaction were obtained when RM was used in obstetrical care (15, 19-21). Finally, the newborns did have a higher gestational age at delivery (22) and were less likely to be of low birth weight (13, 22) or to be admitted to the Neonatal Intensive Care Unit (13, 22, 73) when a RM group was compared to a CC group. In an earlier publication, we reported that RM in pregnant women with gestational hypertensive diseases (GHD) reduces the number of inductions and maternal prenatal admissions (73). However, up to the present, few studies have evaluated the economic impact of RM compared to CC (22, 37), and no study is known concerning the cost effectiveness of a RM prenatal follow-up program for women diagnosed with GHD.

The Pregnancy Remote Monitoring (PREMOM) study was designed for women diagnosed with GHD who had their prenatal follow-up in Ziekenhuis Oost-Limburg (Genk, Belgium). According to the Flanders' register of perinatal outcomes (SPE, 2015), the prevalence of hypertensive disorders in pregnancy is 4.6%: 0.3% deliver before <34 weeks; 0.6% deliver between 34 – 37 weeks and 3.7% deliver > 37 weeks (94). As continuation on this trial, a study was designed with the objective of quantifying the costs of both RM and CC from the perspectives of the Belgium global healthcare system (HCS), which combines costs for the National Institution for Insurance of Disease and Disability (RIZIV) and costs for individual patients. The calculations were made for four major domains: prenatal follow-up, prenatal admission to the hospital, maternal and neonatal care at and after

delivery, and total amount of costs. A simulation exercise was made when an additional fee of €100/month/patient for RM was charged. We hypothesized the addition of RM to a prenatal follow-up program for pregnant women with GHD to be cost-effective, when compared to CC. This paper reports on the results for the Belgium situation.

MATERIAL AND METHODS

DATA

Data collected from the PREMOM study was used for this cost-analysis. The PREMOM study design and data collection method are described in detail elsewhere (73). Briefly, the PREMOM study was a 1 year retrospective study, performed in the outpatient clinic of a 2nd level prenatal center where pregnant women with GHD received RM or CC. From the first of January 2015 to the 31st December 2015, 166 pregnant women were diagnosed with GHD: 53 of them received RM and 113 CC. After excluding 5 patients in the RM group and 15 in the CC group because of missing data, 48 patients in the RM group and 98 in the CC group were taken into the final analysis. Women consenting for RM received obstetric surveillance using a Withings Wireless Blood Pressure Monitor, Withings Smart Body Analyzer, and a Withings Pulse O² (Withings, Issy-les-Moulineux, France). Pregnant women participating in the prenatal remote follow-up program were asked to perform one blood pressure measurement in the morning and one in the evening, one weight measurement a day, and to wear an activity tracker day and night until delivery or hospital admission. The data from the monitor devices were transmitted to a Web-based dashboard developed by the Mobile Health Unit of Hasselt University. Predetermed alarm signals were set, alarm events were communicated with the obstetrician in charge to discuss management options before contacting and instructing patients at home. Therapeutic interventions were according to local management. The clinical goal of routine prenatal outpatient care is to timely detect abnormal course of maternal and/or fetal health. The study protocol was approved by the local ethics committees responsible for the site. The investigation conformed to the principles outlined in the Declaration of Helsinki. All patients gave written informed consent, and data were treated confidentially.

STUDY DESIGN

The objective of the study was to quantify the costs of RM vs CC from the perspectives of the HCS, the RIZIV and the patients. The costs of the HCS is a total amount of costs which have to be payed to cover the care which has been provided. These HCS costs can be divided into two subgroups who have to pay their part of the costs: 1) RIZIV, which is the national institutional social security in Belgium. It ensures every insured individual, regardless of his financial situation, to have access to necessary qualitative medical care which are in accordance with the tariff agreements between caregivers and government (95); and 2) the patients who have to pay their part of care from their own financial resources. The HCS costs are estimated by using the national tariffs applied for these services. The costs for the RIZIV were calculated using the Belgium national reimbursement tariffs (95). The costs for the patients were the HCS costs minus the RIZIV costs.

Below are the four major domains in which the costs are divided presented with its subcategories. A detailed overview of the included costs are presented in the Supplementary file 1 in the Appendix.

Cost analysis: prenatal follow-up

All costs related to urgent and nonurgent in-office visits were used in the prenatal follow-up cost analysis: (1) costs of prenatal consultations, (2) costs of ultrasounds and (3) costs of cardiotocographics (CTG).

Cost analysis: prenatal admission to the hospital

In order to evaluate the economic impact of RM on the three major stakeholders, the following data points were collected when the pregnant women were admitted to the prenatal ward: (1) costs related to the labs of the mother; (2) costs of the medicines; and (3) costs related to the admission.

Cost analysis: maternal and neonatal care at and after delivery

For both groups, the following costs were included for this topic: (1) costs of the delivery; (2) costs necessary for the care of the neonate; and (3) other costs.

Cost analysis: total amount of costs

After analyzing the previous mentioned data, a cost analysis of the total amount of costs is made. This includes (1) costs of the prenatal follow-up; (2) costs of the prenatal admission to the prenatal ward; and (3) costs of the maternal and neonatal care at and after delivery.

Simulation exercise

A simulation exercise is made in which the amount that can be demanded to RIZIV for funding the RM service is calculated. This charge is calculated by dividing the cost savings in RIZIV (by subtracting the total costs from the RM group with those from the CC group) by the mean time of prenatal RM follow-up/pregnant woman. This charge can be used to finance the costs which are needed to perform RM in the prenatal follow op of women at risk for GHD, like the need of midwives to accompany the pregnant women in their RM follow-up and to interpret the (alarm) signals, the need of obstetrics to refer and supervise the pregnant women at risk and the need of technical staff in order to maintain the platform, to give technical support, etc.

STATISTICAL ANALYSIS

For the baseline characteristics are continuous data summarized as mean ± SD. Categorical data are summarized as count and percentage and were compared using the χ^2 test or Fisher exact test, when appropriate. Costs were reported as means, standard deviations, medians and inter-quartile ranges. Cost data are typically highly skewed (96) since a few patients incur particularly high costs, therefore the Mann – Whitney U test was

used to compare costs across groups. Both univariate and multivariate analyses were performed for analyzing the costs for the three domains.

The nominal level $\alpha < 0.05$ was considered significant. All statistical analyses were performed with Statistical Package for Social Sciences release 24.0 (IBM SPSS Inc).

RESULTS

BASELINE CHARACTERISTICS

The baseline characteristics of the patients are summarized in Table 7.1. Of the 48 patients participating in the RM study, 5 (5/48, 10.46%) were excluded due to missing data. In the CC group was 1 participant excluded due to missing data (1/98, 1.02%). Finally, the RM group comprised 43 (30.81%) patients; and the CC group 97 (69.29%). The baseline clinical characteristics of the population enrolled were almost homogeneous, without differences between the two groups except for primigravida (44.19% in RM group vs. 66.33% in CC group; p = 0.02) and smoking (0.00% in RM group vs. 10.20% in CC group; p = 0.03).

Table 7.1: Baseline clinical characteristics

	RM group (n = 43)	*CC group (n = 97)*	*Statistical significance (2 – tailed)*
Age (years)	31.72 (± 4.44)	31.95 (± 4.77)	0.77
Pre pregnancy weight (kg)	70.12 (± 16.26)	76.80 (± 19.75)	0.05
Height (cm)	165.65 (± 6.89)	167.08 (± 6.86)	0.18
BMI (kg/m²)	25.23 (±5.03)	27.01 (± 6.94)	0.32
Primigravida (%)	19 (44.19%)	65 (66.33%)	**0.02**
Cardiovascular disorders (%)	0 (0.00%)	1 (1.02%)	0.99
Coagulation disorders (%)	1 (2.33%)	1 (1.02)	0.52
Endocrine disorders (%)	2 (4.66%)	5 (5.10%)	0.99
Immunology disorders (%)	1 (2.33%)	2 (2.04)	0.99
Smoker (%)	0 (0.00%)	10 (10.20%)	**0.03**

Values are mean (± SD) or numbers (percentages).

RM = remote monitoring; CC = conventional care.

HEALTHCARE COSTS

The healthcare costs are presented in Table 7.2. The results are discussed in detail below.

Table 7.2: Healthcare costs

		Study group		Cost saving in the RM group		Statistical significan-ce (2 – tailed)
		RM group (n = 43)	*CC group (n = 97)*	*€*	*%*	
Prenatal follow-up						
Prenatal visits						
- HCS costs (€)	Mean	184.26 (± 79.10)	183.31 (± 71.79)	-0.95	-0.52	0.71
	Median	205.80 (144.06 – 226.38)	185.22 (144.06 – 226.38)			
- RIZIV costs (€)	Mean	110.58 (±47.83)	110.00 (± 43.08)	-0.58	-0.52	0.71
	Median	123.50 (86.45 – 135.85)	111.15 (86.45 – 135.85)			
- Patients costs (€)	Mean	73.69 (± 31.87)	73.31 (± 28.71)	-0.38	-0.52	0.71
	Median	82.30 (57.61 – 90.53)	74.07 (57.61 – 90.53)			
Ultrasounds						
- HCS costs (€)	Mean	89.66 (± 58.61)	96.49 (± 57.23)	6.83	7.08	0.96
	Median	79.77 (79.77 – 106.36)	79.77 (79.77 – 106.36)			

- RIZIV costs (€)	Mean	81.30 (± 53.14)	87.49 (± 51.89)	6.19	7.08	0.96
	Median	72.33 (72.33 – 96.44)	72.33 (72.33 – 96.44)			
- Patients costs (€)	Mean	8.36 (± 5.47)	9.00 (± 5.34)	0.64	7.08	0.96
	Median	7.44 (7.44 – 9.92)	7.44 (7.44 – 9.92)			
Cardiotocographics						
- HCS costs (€)	Mean	127.58 (± 130.45)	93.19 (± 105.37)	-34.39	-36.90	0.15
	Median	124.68 (0.00 – 187.02)	62.34 (0.00 – 124.68)			
- RIZIV costs (€)	Mean	63.79 (± 65.22)	46.59 (± 52.68)	-17.20	-36.90	0.15
	Median	62.34 (0.00 – 93.1)	31.17 (0.00 – 62.34)			
- Patients costs (€)	Mean	63.79 (± 65.22)	46.59 (± 52.68)	-17.20	-36.90	0.15
	Median	62.34 (0.00 – 93.51)	31.17 (31.17 – 62.34)			
Prenatal admission						
Labs						
- HCS costs (€)	Mean	25.07 (± 55.34)	38.28 (± 44.08)	13.21	34.51	**<0.01**
	Median	0.00 (0.00 – 19.58)	27.86 (5.13 – 56.74)			
- RIZIV costs (€)	Mean	21.09 (± 27.94)	36.19 (± 41.36)	15.10	41.72	**<0.01**
	Median	0.00 (0.00 – 19.07)	25.74 (5.13 – 50.53)			
- Patients costs (€)	Mean	3.98 (± 14.06)	2.09 (± 8.78)	-1.89	-90.43	0.78

	Median	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)			
Prenatal admission						
- HCS costs (€)	Mean	1423.57 (± 1184.78)	1336.40 (± 670.99)	-87.17	-6.52	0.73
	Median	1166.62 (1013.25 -1407.54)	1172.61 (950.68 – 1450.04)			
- RIZIV costs (€)	Mean	798.47 (± 596.93)	783.44 (± 372.81)	-15.03	-1.92	0.63
	Median	663.30 (600.25 – 786.59)	714.96 (501.09 – 922.33)			
- Patients costs (€)	Mean	625.10 (± 606.57)	552.96 (± 372.50)	-72.14	-13.05	0.41
	Median	497.67 (394.29 – 617.61)	477.88 (324.57 – 663.41)			
Medicaments						
- HCS costs (€)	Mean	209.22 (± 141.86)	213.32 (± 67.09)	4.10	1.92	**0.02**
	Median	168.73 (155.71 – 206.18)	204.65 (168.99 – 233.79)			
- RIZIV costs (€)	Mean	122.60 (± 92.02)	121.76 (± 20.77)	-0.84	-0.69	**<0.01**
	Median	106.03 (99.61 – 111.77)	114.81 (108.02 – 130.01)			
- Patients costs (€)	Mean	86.61 (± 68.81)	91.56 (± 20.77)	4.95	5.41	0.14
	Median	63.71 (47.69 – 97.87)	79.13 (55.67 – 108.43)			
Maternal and neonatal care						
Delivery						
- HCS costs (€)	Mean	1157.66 (± 469.34)	1076.61 (± 485.14)	-81.05	-7.53	0.15

	Median	1298.10 (670.34 – 1329.38)	998.94 (670.34 – 1298.10)			
- RIZIV costs (€)	Mean	700.48 (± 186.41)	712.87 (± 196.03)	12.39	1.74	0.79
	Median	670.34 (370.34 – 685.98)	670.34 (663.34 – 755.66)			
- Patients costs (€)	Mean	457.17 (± 344.53)	363.73 (± 404.17)	-93.44	-25.69	0.15
	Median	627.76 (0.00 – 643.40)	424.11 (0.00 – 628.86)			
Neonatal Care						
- HCS costs (€)	Mean	989.66 (± 3020.22)	1872.92 (± 5058.31)	883.26	47.16	**<0.01**
	Median	146.32 (102.67 – 374.19)	290.78 (147.69 – 625.23)			
- RIZIV costs (€)	Mean	872.97 (± 2761.64)	1684.86 (± 4702.20)	811.89	48.19	**<0.01**
	Median	98.48 (85.49 – 279.14)	230.45 (104.81 – 519.38)			
- Patients costs (€)	Mean	116.69 (± 263.74)	188.06 (± 413.95)	71.37	37.95	0.10
	Median	48.22 (13.01 – 95.05)	61.68 (23.69 – 120.19)			
Other						
- HCS costs (€)	Mean	26.63 (± 11.83)	63.19 (± 158.23)	36.56	57.86	**0.04**
	Median	25.73 (25.73 – 25.73)	25.73 (25.73 – 25.73)			
- RIZIV costs (€)	Mean	26.14 (± 19.86)	63.19 (± 158.23)	37.05	58.63	**<0.01**
	Median	25.73 (21.10 – 25.73)	25.73 (25.73 – 25.73)			
- Patients costs (€)	Mean	0.49 (± 20.99)	0.00 (± 0.00)	-0.49	-0.77	**0.01**

	Median	0.00 (0.00 – 0.00)	25.73 (25.73 – 25.73)		

Values are means ± SD and median with inter-quartile in euros (€); costs savings are calculated in euros (€) and percentages (%).

RM = remote monitoring; CC = conventional care; HCS = health care system; RIZIV = national healthcare insurances

In order to investigate the influence of the maternal demographics and characteristics on the healthcare costs, a multiple linear regression analysis and a multivariate logistic regression analysis is performed. A detailed overview of these data is proved in Supplementary file 2 in the Supplementary Appendices. No important influences of the maternal demographics and characteristics is found in the healthcare costs.

Cost analysis: prenatal follow-up

No differences were found in costs for prenatal follow-up (prenatal visits, ultrasounds and CTG's): not in the costs for the HCS, the RIZIV or the patients.

Cost analysis: prenatal admission to the hospital

Patients admitted to the RM group did have 34.51% less HCS- and 41.72% les RIZIV costs for labs when compared to CC group (RM: €25.07 ± €55.34 vs. CC: €38.28 ± €44.08 (P < 0.01) and RM: €21.09 ± €27.94 vs. CC: €36.19 ± €41.36 (P < 0.01) respectively). Also the HCS cost for the medicaments were 1.92% lower in RM group when compared to CC group (€209.22 ± €141.86 vs. €213.32 ± €67.09; P = 0.02) but the RIZIV costs were 0.69% higher in RM group compared to CC group (€122.60 ± €92.02 vs. €121.76 ± €20.77; P < 0.01).

Cost analysis: maternal and neonatal care at and after delivery

No differences were found in costs for delivery in RM group vs. CC group. A reduction of 47.16% in HCS cost, and 48.19% in RIZIV costs for neonatal care was become in RM group when compared to CC group (RM: €989.66 ± €3020.22 vs. CC: €1872.92 ± €5058.31 (P < 0.01); and RM: €872.97 ± €2761.64 vs. CC: €1684.86 ± €4702.20 (P < 0.01) respectively). Other costs were for the HCS 57.86% and RIZIV 58.63% lower in RM versus CC (RM: €26.63 ± €11.83 vs. CC €63.19 ± €158.23 (P = 0.04); and RM: €26.14 ± €19.86 vs. CC: €63.19 ± €158.23 (P < 0.01)), but 0.77% higher for the patients in RM versus CC (€0.49 ± €20.99 vs. €0.00 ± €0.00; P = 0.01)).

TOTAL AMOUNT OF COSTS

An overview of the total amount of costs is presented in Figure 7.1 and in the Supplementary file 3 in the Appendix. There were no significant differences between RM and CC in total amount of costs for HCS (RM: €4233.31 ± €3463.31 vs. CC: €4973.69 ± €5219.00 (*P* = 0.82)), the RIZIV (RM: €2797.42 ± €2905.18 vs. CC: €3646.40 ± 4878.47 (*P* = 0.19)) or the patients (RM: €1435.89 ± €829.09 vs. CC: €1327.30 ± €753.94 (*P* = 0.38)). But a cost reduction of €740.38 pp (14.89%) was made for HCS and a cost reduction of €848.97 (23.18%) was made for RIZIV in RM compared with CC. Patients costs were slightly higher (€108.59; 8.18%) for RM than for CC.

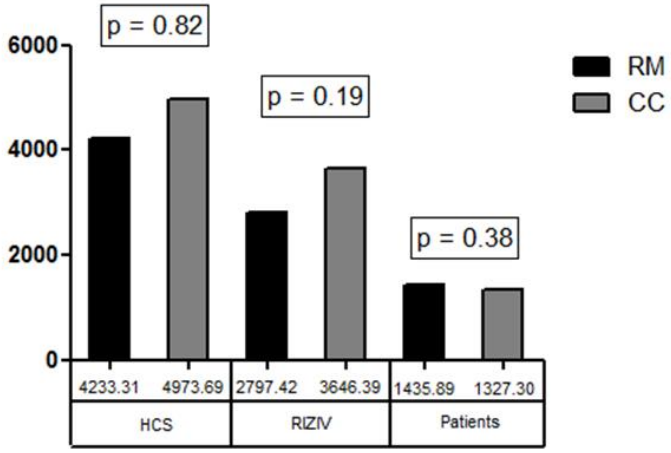

Figure 7.1: Total amount of costs

SIMULATION EXERCISE

A simulation exercise is made in which is calculated how much can be demanded to RIZIV for funding the RM service. For this study, 43 pregnant women were included in the analysis with a range of 1 day of participation until 145 days of participation in the PREMOM project. The mean time of participation to this project is 44.42 days, or 1.41 month (Supplementary file 4 in the Appendix). By dividing €740.35/1.41 month, a funding

of €525.07/month/pregnant woman can be asked. Because of the difference of almost €1000 pp in costs for the RIZIV, it is reasonable to charge the supplementary costs to RIZIV. As a result, there is a significant difference in costs for HCS by having a reduction of €2.11 pp in RM vs. CC (RM: €4971.58 ± 3479.69 vs CC: 4973.69 ± 5219.00 (*P* = 0.01)) and in RIZIV costs by also having a reduction of €110.70 pp in RM vs. CC (RM: 3535.69 ± 2931.90 vs. CC: 3646.39 ± 4878.47, *P* = 0.005). The patients still doesn't have to pay more for their prenatal care (RM: €1435.89 ± €829.09 vs. CC: €1327.30 ± €753.94 (*P* = 0.38)). An overview of the costs is shown in in the supplementary file 4 in the Appendix and in Figure 7.2.

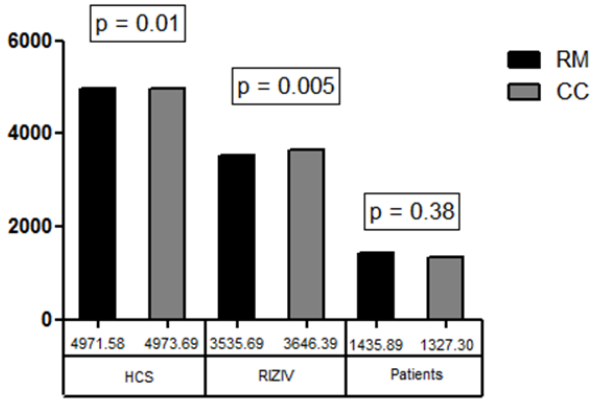

Figure 7.2: Total amount of costs + remote monitoring

DISCUSSION

PRINCIPAL FINDINGS

The main finding of this study is that a RM prenatal follow-up for pregnant women at risk for GHD reduces the total amount of costs for a national health care in comparison to a standard follow-up strategy. This cost reduction is due to a marked reduction in the consumption of health care services, including the labs which were taken, medication use, maternal and neonatal admissions. When an additional fee of €525.07/month/pregnant woman for funding RM costs is asked, RM is still acceptable in their costs for HCS, RIZIV and individual patients.

STRENGTHS AND LIMITATIONS

The use of 'real-life' data from the hospital bills is the main strength of this study. By using these data, the actual situation of pregnancies complicated with GDH is simulated and these results are generalizable for settings with similar economics and social characteristics. Also the requested fee of €525.07/month/pregnant woman is a strength of this study, because of the applicability and thoughtfulness of this item. It is very likely that this price will actually cover the costs of a RM prenatal follow-up program. Finally, by adding this supplement to the RIZIV costs, there will be no increase in costs between the RM group and CC group in the three domains, but the prenatal follow-up and gestational outcomes will be improved for the RM group as we reported before (73)

The main limitation of this study is its retrospective structure and the fact that the patients from the PREMOM study were not randomized. Nevertheless, the populations in the two arms were almost homogeneous when regarding the baseline clinical characteristics. Second, the PREMOM study and this financial analysis, provides a picture of 'real-life' practice in Belgium; we did receive the data from the patient files and the hospital bills, but we don't have information of patients act of hospital and medical consumption, our the

patients social costs (like transportation- and travel costs and the cost of lost employment income for the time spent for inhospital visits). Our results could also differ in different HCSs and different economic and social settings such as, for example, in other countries. Additionally, this study is limited to six weeks after the delivery. It is generally known that neonates which needed intensive care at the moment of their delivery will have a higher impact on healthcare costs then neonates who did not need this care. These costs are mostly due to rehospitalizations, acute care visits or further intensive care for the rest of the infant's life (97-101). Further, we didn't investigate the quality adjusted life years (QALYs), which can be used as a generic measure of effectiveness. QALYs are a generic measure of disease burden, including both the quality and the quality of the life lived and it assess the value for money of medical interventions. To conclude, we evaluated only one type of RM monitoring follow-up program, which does not allow our results to be transferred to other proprietary technologies with varying transmission frequencies and methods of alert notifications.

COMPARISONS WITH PREVIOUS TRIALS

Only two studies are known who performed a cost-analysis of a RM follow-up program in women with high risk pregnancies. Morrison et al. (2001) performed a cost-effectiveness evaluation of RM in patients diagnosed with preterm labour. An average reduced cost of $14,459 per pregnancy using RM services was obtained when compared to usual care. This cost reduction was due to a reduced costs in antepartum hospitalization and intensive care nursery (22). The conclusions of this manuscript are in line with our main findings. Also the study of Buysse et al. (2007) matches our principal findings. They obtained a cost-reduction of €145,882 per year for high risk pregnancies. But unlike our study, these researchers did not use 'real-life' data from patients in a RM program: they made a simulation exercise for all the high-risk pregnancies which may qualify for home monitoring (37).

POSSIBLE EXPLANATIONS

The main objective of our study was to compare direct costs of a prenatal follow-up program for women diagnosed with GHD between RM and CC in-hospital visits for a single-center population based on the initial assumption that RM technologies were provided with no additional costs. Early detection of clinical and device-related critical events provided by RM may have a positive impact on complication rates like the development of severe hypertension, the need of inductions, prenatal hospitalizations and neonatal hospitalizations. . In our previous mentioned study, we reported a reduction in the prevalence of preeclampsia, hospitalization of the mother and the neonate and inductions of labor (73). In summary: by adding RM to the prenatal care tract of women at risk of these disorders, the risk of the development of a severe hypertensive disorder is reduced and large potential benefits in terms of social and hospital expenditure restraint. These results can be read in Supplementary file 5 in the Appendix. In line with these benefits, which are obtained with RM, the costs necessary for the medical care of the previous mentioned complications are reduced and/or avoided in the RM group and not in the CC group. The slightly higher costs of the medications for the patients of the RM group, when compared to CC group, can be explained by the higher need of medication for those patients. During the RM process, it is easy to make some changes in the antihypertensive treatment because their daily parameters are constantly at hand (73). Women in the CC group will have less medication changes due to the lack of daily follow-up of their bloodpressure.

The suggested €525.07/month/pregnant woman fee for funding RM allows it for HCS to not be elevated. By showing that there is no significant difference in costs between the RM group and CC group, a door is opened for policy makers charged with deciding how limited health care resources should be allocated in the era of exploding needs. This study, together with our previous report, states that better prenatal follow-up and gestational

outcomes for the same cost as conventional care are possible by adding RM to the care of pregnant women with GHD.

RECOMMENDATIONS FOR FURTHER RESEARCH

Firstly, it would also be useful to investigate the QALYs for both the mother and the neonate who received RM. This to make further recommendations about this topic. This study is also shortened to the postnatal follow-up until six weeks after the delivery. It would be interesting to monitor the neonates in both groups RM and CC group for longer than six weeks postpartum to get insights into the long-term cost-benefits. Lastly, because the social costs (like transportation- and travel costs and the cost of lost employment income for the time spent for inhospital visits) are not taken into account, it would be interesting to make additional analyses with these type of costs included. It is plausible that the differences in costs will be further apart, when the previous mentioned items will be taken into account.

CONCLUSIONS

The results of this study show that a RM prenatal follow-up of women with GHD will not increase the costs for the HCS, RIZIV or patient in comparison with conventional care. Furthermore, a RIZIV fee of €525.07/month/pregnant woman, allows the implementation of RM without increasing the healthcare costs for the RM group. These results are useful for policy makers charged with deciding how limited health care resources should be allocated in the era of exploding need. Further research of the long-term cost effectiveness of RM, the QALYs and social costs is recommended.

CHAPTER 8

A Prenatal Remote Monitoring Program in Pregnancies complicated with Gestational Hypertensive Disorders: What are the Contributors to the Cost Savings?

Lanssens D, Vonck S, Vandenberk T, Schraepen C, Storms V, Thijs IM, Grieten L & Gyselaers W

** *In press at Telemedicine and eHealth* **

ABSTRACT

Background: In 2015, we performed a cost analysis of a prenatal remote monitoring (RM) program compared with conventional care (CC) for women diagnosed with gestational hypertensive disorders (GHD).

Introduction: We investigated where the cost savings were distributed by dividing our patient population into three subgroups, according to the gestational age (GA) at the time of delivery: 1) < 34 weeks; 2) 34–37 weeks; and 3) > 37 weeks of GA.

Material and methods: Healthcare costs were calculated from patient-specific hospital bills at Ziekenhuis Oost Limburg (Genk, Belgium) in 2015–2016. Cost comparisons were made from the perspectives of the Belgium national health care system (HCS), the National Institution for Insurance of Disease and Disability (RIZIV), and the costs to individual patients.

Results: A total of 256 pregnant women were included, 80 (31.25%) of whom received RM and 176 (68.75%) CC. The greatest difference in costs between RM and CC was in the group that delivered before 34 weeks of GA, followed by the group who delivered after 37 weeks of GA, and then the group of women who delivered at 34–37 weeks of GA. Most of the cost savings were in neonatal care, for both the three separate study subgroups and the total study group.

Discussion and conclusion: Our data showed that RM is more cost- saving than CC for pregnant women with GHD. Further investigation of the effects of RM on the long-term economic and social costs is recommended, together with an analysis of the price that should be asked for RM services.

INTRODUCTION

Gestational hypertensive disorders (GHD) are one of the commonest complaints during pregnancy. According to the Flemish Study Center of Perinatal Epidemiology (SPE), 4.9% of all pregnancies are complicated by these disorders: of the 64,323 deliveries in 2016, 3152 were complicated by GHD (24). GHD is defined as a systolic blood pressure (BP) > 140 mmHg and a diastolic BP > 90 mmHg. It refers to any of the following four conditions: a) preexisting hypertension; b) gestational hypertension; c) pre-eclampsia; and d) unclassifiable hypertension (83). GHD is a major cause of maternal, fetal, and newborn morbidity and mortality (83, 102). The assessment of women with pregnancies complicated with GHD includes a clinical follow-up, serological investigation, and fetal ultrasound evaluation. The type and frequency of follow-up depends on the kind and severity of the hypertensive disorder (83). The goal of treatment is to prevent significant cerebrovascular and cardiovascular events in the mother, without compromising fetal well-being (103).

Recently, new techniques for medical monitoring have been developed, such as remote monitoring (RM), which can be broadly defined as the use of telecommunication technologies to facilitate the transmission of medical information and services between healthcare providers and patients (4). RM is a relatively new approach (dating back to the early 1990s) that allows patient management at home (3). As part of the Hasselt University and Limburg Clinical Research Program (LCRP), Ziekenhuis Oost-Limburg (Genk, Belgium) added RM to its prenatal care for women with GHD in the Pregnancy Remote Monitoring (PREMOM) Study. The initial results were promising (73, 91), and other feasibility studies, within and outside pregnancy, have also successfully tested the possibility of sending data such as BP and/or body weight from the patient's home (104, 105). However, until now, few studies have evaluated the economic impact of RM compared with that of conventional care (CC) (22, 37, 106, 107). Our research team

performed the first economic analysis to assess the costs of RM versus CC and we concluded that the RM prenatal follow-up of women with GHD is cost saving for the global healthcare system (90). A second cost analysis was performed in which data were collected in 2015 and 2016. In this study, in which we divided our patient population into three subgroups according to the gestational age (GA) at the time of delivery, we analyzed the cost savings made with RM and identified where these savings were made.

MATERIAL AND METHODS

DATA

Data collected from the PREMOM Study, extending from 1 January 2015 to 31 December 2016, were used for this cost analysis. The PREMOM Study design and data collection method are described in detail elsewhere (73, 91). Briefly, the PREMOM Study was a 2-year retrospective study, performed at the outpatient clinic of a secondary prenatal center, where pregnant women at risk for GHD received either RM or CC. In 2015 and 2016, 320 pregnant women were diagnosed with GHD: 90 (28.13%) received RM and 230 (71.88%) received CC. Women consenting to RM underwent obstetric surveillance with a BP monitor, an activity tracker, and a weight scale. Pregnant women in the prenatal remote follow-up program were asked to make one BP measurement in the morning and one in the evening, to make one weight measurement once a week, and to wear an activity tracker day and night until delivery or hospital admission. The data from the monitoring devices were transmitted to a Web-based dashboard developed by the Mobile Health Unit of Hasselt University. Predetermed alarm signals were set based on international guidelines was decided to generate an alarm signal when the diastolic blood pressure was greater than or equal to 90 mmHg and/or the systolic blood pressure was greater than or equal to 140 mmHg (108, 109). When appropriate, individual alarm signals were set (e.g. when they started with an antihypertensive therapy, on demand of the obstetrician, etc). All alarm events were communicated to the obstetrician in charge to discuss management options before the patient was contacted and instructed at home. Therapeutic interventions were in accordance with local management strategies.

This study protocol was approved by the local ethics committees responsible for the site. The study conformed to the principles outlined in the Declaration of Helsinki. All patients gave their written informed consent, and all data were treated confidentially.

STUDY DESIGN

The objective of the study was to determine where the main cost savings were distributed, or which aspect of the pre-, peri-, or postnatal care involved an increase in costs, when RM was used instead of CC. The study population was divided into three subgroups: 1) delivery before 34 weeks of GA (which is the cut-off value to determinate whether a pregnant women suffers from early or late pre-eclampsia); 2) delivery at 34–37 weeks of GA (which is the intermediate measure); and 3) delivery after 37 weeks of GA (which is the cut-off value to determinate whether a pregnant women delivers preterm or term).The data were examined from three different perspectives, based on the current organization of Belgian healthcare: 1) the Belgium global healthcare system (HCS), which combines the costs for the National Institution for Insurance of Disease and Disability (RIZIV) and for individual patients; 2) the RIZIV, which is the national institutional social security system in Belgium, which ensures that every insured individual, regardless of his/her financial situation, has access to necessary quality medical care, in accordance with the tariff agreements between caregivers and the government (95); and 3) the patient, who must pay for part of their care from their own financial resources. The HCS costs were estimated from the national tariffs applied for these services. The costs to RIZIV were calculated from the Belgium national reimbursement tariffs (95). The costs to the patients were calculated as the HCS cost minus the RIZIV cost.

The calculations were made for three major domains and the total costs, presented below. A detailed overview of the included costs is presented in Supplementary file 1 in the Appendix.

Cost analysis: prenatal follow-up

All costs related to urgent and nonurgent in-office visits were used in the prenatal follow-up cost analysis: (1) cost of prenatal consultations; (2) cost of ultrasound examinations; and (3) cost of cardiotocographic readings.

Cost analysis: prenatal admission to the hospital

To evaluate the economic impact of RM on the three major stakeholders, the following data points were collected when a pregnant woman was admitted to the prenatal ward: (1) costs related to the laboratory tests of the mother; (2) costs of medicines; and (3) costs related to admission.

Cost analysis: maternal and neonatal care at and after delivery

For both the CC group and the RM group, the following costs were included: (1) cost of the delivery; (2) necessary costs for the care of the neonate; and (3) other costs.

Cost analysis: total costs

After analyzing these data, a cost analysis of the total costs was made. This included (1) the costs of the prenatal follow-up; (2) the costs of admission to the prenatal ward; and (3) the costs of maternal and neonatal care at and after delivery.

STATISTICAL ANALYSIS

Because the baseline characteristics were continuous data, they are summarized as means ± SD. Categorical data are summarized as counts and percentages and were compared with the χ^2 test or Fisher's exact test, where appropriate. Costs are reported as means and standard deviations or medians and interquartile ranges, depending if they were normal or abnormal distributed. Differences in costs were calculated with the Mann–Whitney *U* test, because the cost data were typically highly skewed (96) in that a few patients incurred particularly high costs. Nominal level $\alpha < 0.05$ was considered significant.

All statistical analyses were performed with SPSS release 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

RESULTS

PREGNANCY-RELATED OUTCOMES

The pregnancy-related outcomes of the patients are summarized in Table 8.1. Of the 90 patients who participated in the RM study, 10 (11.12%) were excluded because they received (part of) their prenatal follow-up at another prenatal center and the financial bills for those services were not available. In the CC group, 54 (23.48%) patients were excluded for the same reasons. Finally, the RM group comprised 80 patients (31.25%) and the CC group 176 patients (68.75%). The pregnancy-related outcomes of the populations enrolled were almost homogeneous, with no differences between the groups, except in the prevalence of gestational hypertension (80.00% in RM vs 50.56% in CC, $p < 0.001$) and pre-eclampsia (18.75% in RM vs 41.48%, $p < 0.001$) in the total study group and in the group with GA > 37 weeks (86.15% in RM vs 56.06% in CC [$p < 0.001$] and 12.31% in RM vs 35.61% in CC [$p = 0.001$], respectively).

Table 8.1: Pregnancy-related outcomes

	RM group (n = 80)	*CC group (n = 176)*	*Statistical significance (two-tailed)*
Total group			
GA at delivery	38w 1/7 (± 2.65)	37w 5/7 (± 3.22)	0.31
GHD:			
EH	1 (1.25%)	9 (5.11%)	0.14
GH	64 (80.00%)	89 (50.56%)	**<0.001**
PE	15 (18.75%)	73 (41.48%)	**<0.001**
HELLP	0 (0.00%)	5 (2.84%)	0.13
	RM group (n = 7)	*CC group (n = 20)*	
GA < 34 weeks			
GA at delivery	31w 3/7 (± 2.63)	30w 1/7 (± 0.59)	0.30
GHD:			
EH	0 (0.00%)	0 (0.00%)	–
GH	3 (42.85%)	6 (30.00%)	0.54
PE	4 (57.14%)	13 (65.00%)	0.71
HELLP	0 (0.00%)	1 (5.00%)	0.55
	RM group (n = 8)	*CC group (n = 24)*	
GA 34–37 weeks			
GA at delivery	35w 4/7 (± 0.94)	35w 5/7 (± 0.85)	0.61
GHD:			
EH	0 (0.00%)	1 (4.17%)	0.56
GH	5 (62.50%)	9 (37.50%)	0.22
PE	3 (37.50%)	13 (54.17%)	0.41
HELLP	0 (0.00%)	1 (4.17%)	0.56
	RM group (n = 65)	*CC group (n = 132)*	
GA > 37 weeks			
GA at delivery	39w 1/7 (± 0.14)	39w 1/7 (± 0.10)	0.84
GHD:			
EH	1 (1.54%)	8 (6.06%)	0.15
GH	56 (86.15%)	74 (56.06%)	**<0.001**
PE	8 (12.31%)	47 (35.61%)	**0.001**
HELLP	0 (0.00%)	3 (2.27%)	0.22

Values are means (± SD) or numbers (percentages).
RM = remote monitoring; CC = conventional care; GA = gestational age; GHD = gestational hypertensive disorder; EH = essential hypertension; GH = gestational hypertension; PE = pre-eclampsia; HELLP = hemolysis, elevated liver enzymes, and low platelets

TOTAL COSTS

An overview of the total costs per study group is presented in Supplementary file 2a–d in the Appendix and in Figure 8.1. There were no significant differences in the three study subgroups (< 34 weeks of GA, 34–37 weeks of GA, and > 37 weeks of GA), or when all three subgroups were combined, between RM and CC in the total costs for HCS, RIZIV, or

patient costs. There was a reduction of 50.52% (€9125.17) in the HCS costs for women who delivered before 34 weeks of GA, 1.16% (€35.94) for women who delivered after 37 weeks of GA, and 25.00% (€1293.86) for the total study group when RM was compared with CC. There was an increase in the total HCS cost of 3.90% (€227.12) for the RM group women who delivered at 34–37 weeks of GA. Among women who delivered before 34 weeks of GA, there were reductions of 56.23% (€8929.77) in the RIZIV costs and 8.95% (€195.18) in the patient costs when the women were treated with RM rather than with CC. Women treated with RM who delivered at 34–37 weeks of GA had a reduction in RIZIV costs of 21.03% (€652.13) and an increase in the patient costs of 67.04% (€863.79) compared with the CC women. Among the women who delivered after 37 weeks of GA, the RIZIV costs were 5.09% (€102.42) lower in the RM group than in the CC group, but the patient costs were 6.08% (€66.49) higher in the RM group than in the CC group. In summary, the total cost for RIZIV was 35.17% (€1383.72) lower in women treated with RM than in women treated with CC, but the patient costs were 7.07% (87.89) higher for the women in the RM group than for those in the CC group.

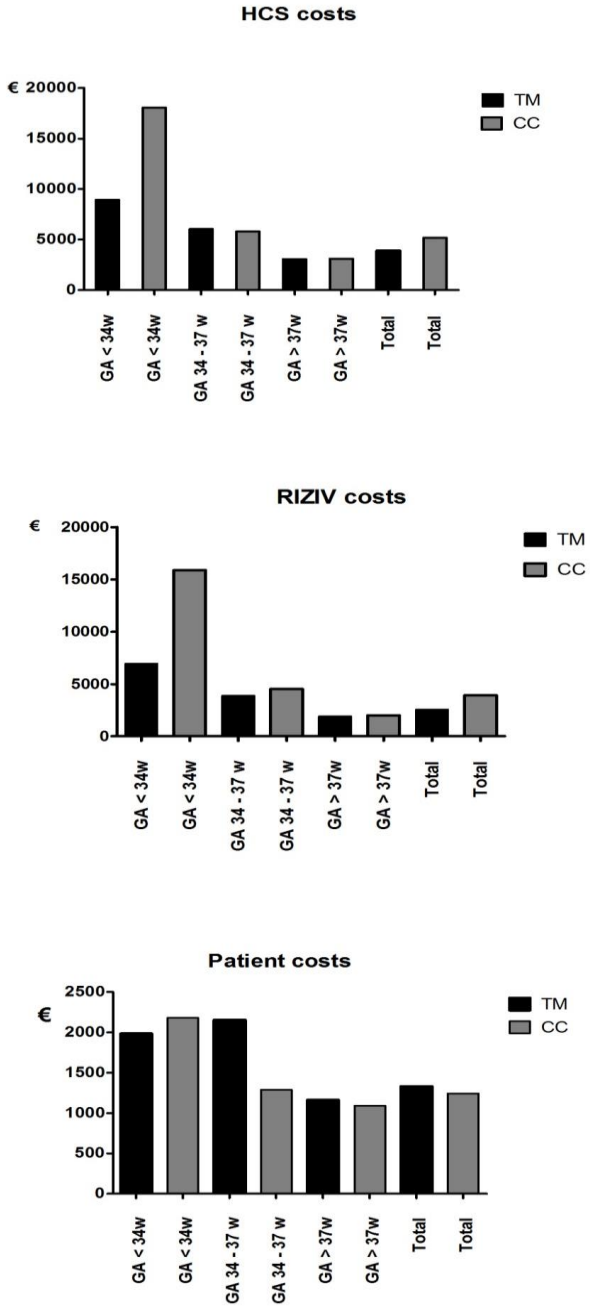

Figure 8.1: Total costs per study group

DISTRIBUTION OF COST SAVINGS

The healthcare costs for the three major domains, according to study group, are presented in Supplementary file IIIa–d in the Appendix. In women who gave birth before 34 weeks of GA, 91.96% of the cost savings were in maternal and neonatal care at and after delivery (they were all located in the neonatal care), and less than 10% of the costs savings were located in the prenatal follow-up (0.34%) and the prenatal admission to the hospital (7.70%) (which could be further divided in prenatal visits (0.18%), ultrasound (0.16%), prenatal admission (7.58%), and medications (0.12%)). In women who gave birth at 34–37 weeks of GA, 79.11% of the cost reductions were located in maternal and neonatal care at and after delivery (which all are located in the neonatal care), followed by the prenatal admission until to the hospital (medications (12.16%), laboratory tests (5.44%)) and 3.29% for the prenatal follow-up (an reduction in the prenatal visits of 3.29%). In women who delivered after 37 weeks of GA, 76.27% of the cost reductions were located in maternal and neonatal care at and after delivery (of which 59.60% is located in the neonatal care and 16.67% in other), 17.92% in the prenatal follow up (14.91% in prenatal visits and 3.01% in the ultrasounds) and 5.81% in the prenatal admission to the hospital (which are located in the laboratory tests).

DISCUSSION

PRINCIPAL FINDINGS

We investigated where the main cost savings in a RM prenatal follow-up program were distributed by dividing the patient population into three subgroups according to the GA at the time of delivery.

The findings of this study, performed on a dataset collected over 2 years, showed the greatest differences in costs between RM and CC were in the group who delivered before 34 weeks of GA (50.52% in HCS costs, 56.23% in RIZIV costs, and 8.95% in patient costs), followed by the group who delivered after 37 weeks of GA (1.16% in HCS costs, 5.09% in RIZIV costs, and –6.08% in patient costs), and was least in the group of women who delivered at 34–37 weeks of GA (–3.90% in HCS costs, 21.03% in RIZIV costs, and –67.04% in patient costs). In the total RM group, the reductions were 25.00% in HCS costs, 35.17% in RIZIV costs, and –7.07% in patient costs.

Most of the cost savings were in neonatal care for all three study subgroups (birth < 34 weeks GA, birth 34–37 weeks GA, and birth > 37 weeks GA) and when all three study subgroups were analyzed together. Obviously, the higher the GA at the time of delivery, the lower the cost for neonatal care. In the RM women who delivered after 34 weeks of GA, reductions were observed in the costs of prenatal visits (3.29% with birth at 34–37 weeks of GA and 14.91% with birth at > 37 weeks of GA), ultrasound (3.01% with birth at > 37 weeks of GA), laboratory tests (approximately 5% in both groups), medications (12.16% with birth at 34–37 weeks of GA), and other costs (16.67% with birth at > 37 weeks of GA) compared with the CC group. When the study subgroups were analyzed together, more than 95% of the cost savings with RM were in neonatal care.

STRENGTHS AND LIMITATIONS

The use of 'real-life' data from hospital bills and from the SPE was the main strength of this study. By using these data, the actual situation of pregnancies complicated with GHD (in Flanders) was analyzed and the results are generalizable to settings with similar economic and social characteristics. It is nearly impossible to give all pregnant women with GHD this type of prenatal care, but it is clear that for each woman who received this type of care, the HCS cost was reduced.

The main limitation of this study was that the patients from the PREMOM Study were not randomized. Nevertheless, the PREMOM Study and this financial analysis provide a picture of the 'real-life' situation in Belgium. We obtained the data from patient files and hospital bills, although we had no information on patients act of hospital and medical consumption, the patients' social costs (such as transportation and travel costs and the loss of employment income during hospital stays). These results may differ in different HCSs and different economic and social settings, such as in other countries. This study was also limited to 6 weeks after delivery. It is clear that neonates who need intensive care at the moment of delivery will have higher healthcare costs than neonates who do not need this care. These costs usually arise from rehospitalizations, acute care visits, or further intensive care for the rest of the infant's life. Finally, the costs for organizing RM are not taken into account, which are: the RM devices, the midwife who supervised the data, and the technical support. To obtain a complete picture of the cost of and cost savings attributable to this technology, further research is required that takes these data into account.

COMPARISONS WITH PREVIOUS TRIALS

A cost analysis of a RM prenatal follow-up program for women with GHD, for which the data analysis was performed in 2015, was, to the best of our knowledge, the first study to report that RM is less expensive for a global healthcare system, mainly through savings to the insurance institution RIZIV. Since that analysis was completed, no new studies have been published on the financial impact of an RM prenatal follow-up program for women with GHD.

POSSIBLE EXPLANATIONS

This study demonstrated that neonatal care is one of the largest costs in the care of mothers and babies. However, this is not new information. Neonatal care is characterized by its intensive character and is known as one of the most expensive services in hospitals (110). It is recognized that most neonatal morbidity associated with GHD is attributable to the complications of prematurity and that the cost of neonatal care correlates with the severity of prematurity (111). Our research team has shown that the neonates in the RM group who were born before 34 weeks of GA were approximately 10 days older than the corresponding neonates in the CC group. RM makes it possible for caregivers to see abnormal events in pregnant women and to offer an intervention when necessary to prevent the worsening of the disease. It may not always be possible to prevent a premature delivery, but RM makes it possible to delay a premature delivery by up to 10 days. These 10 days will have a significant impact on the health of the neonate and reduce the costs to the HCS and RIZIV by more than 50%. The lower prevalence of premature births in the RM group compared with the CC group can be similarly explained. The literature indicates that a premature birth at 28–36 weeks of GA is 2.30 times more expensive than a birth after 36 weeks of GA, and that births before 28 weeks of GA are 12.47 times more expensive (111). Because fewer premature neonates were born in the RM group than in the CC group, the cost savings will increase when RM is extended to all

pregnant women in Flanders. This can explain the cost savings that will be reached when we extrapolate this over a large number of women with GHD.

The increase in patient costs for the study group who delivered at 34–37 weeks of GA mainly occurred in the categories 'prenatal admission', 'neonatal admission', and 'delivery' (39.88%, 41.20%, and 14.98%, respectively). Further analysis of these data showed that the pregnant women in the RM group were more likely to choose a single room for their hospitalization than a room shared with other patients. Therefore, the patient costs were higher in the RM group. Moreover, more insurance was reimbursed to the women in the CC group whose child was hospitalized after delivery than to the corresponding women in the RM group. This may explain the large difference in the costs incurred by the two groups.

To conclude, of the women who gave birth at > 37 weeks GA, significantly more patients were diagnosed with pre-eclampsia and fewer with gestational hypertension in the CC group than in the RM group. Although these diseases require different treatments, which entail different costs, the GA at which these women gave birth partly explains the slight discrepancy in costs. Women who gave birth at > 37 weeks of GA who were considered at risk for or had pre-eclampsia were less likely to be hospitalized due to the GA, but had more frequent prenatal visits and laboratory tests to monitor their vital parameters. This difference in costs is clear in this study, but it did not affect the total costs as strongly as the difference in the cost of neonatal care in the group who gave birth at < 34 weeks of GA.

RECOMMENDATIONS FOR FURTHER RESEARCH

This study was restricted to a postnatal follow-up period of 6 weeks after delivery. It would be interesting to monitor the neonates in both the RM and CC groups for more than 6 weeks postpartum to allow a long-term cost–benefit analysis. Because the social costs

(such as transportation and travel costs and the cost of lost employment income for the time spent in hospital) were not taken into account in this study, it would be interesting to include this type of cost in a future study. It is possible that the differences in costs will be even greater when these factors are also considered. It would also be interesting to know how much pregnant women are prepared to pay each month to fund the RM service. In this way, it would be possible to fund RM through both RIZIV and patient contributions. The costs required to provide RM were not taken into account in this analysis, but should be included in follow-up studies. To conclude, for future RM programs, it would be interesting to implement screening tools towards the identification of pregnancies at high risk for hypertensive and/or fetal growth. Some screenings programs already exist (e.g. for pre-eclampsia, gestational diabetes mellitus, etc) but most of them are troubled with poor performance both in terms of sensitivity and/or specificity, in particularly for late pre-eclampsia, gestational hypertension or isolated fetal growth restriction. A prenatal screening tool with a high sensitivity and specificity rate would allow including only high risk pregnancies in RM programs. This is necessary to prevent an unwanted rise of costs of RM offered to all pregnant women.

CONCLUSIONS

When a RM program was included in the prenatal care of women at risk of GHD, the greatest differences in costs between RM and CC were observed in the women who gave birth before 34 weeks of GA, followed by the group who delivered after 37 weeks of GA, and were least in the group of women who delivered at 34–37 weeks GA. In the total study group, saving in both the HCS and RIZIV costs were observed. Most of the cost savings were in neonatal care, both in the three individual RM study subgroups and in the combined RM group. Our data show that RM is more cost-effective than standard care for pregnant women with GHD. We recommend further investigation into the effect of RM on long-term and social costs, and into the price that can be asked for the provision of RM services.

GENERAL DISCUSSION
AND
SUMMARY

GENERAL DISCUSSION

The aim of this doctoral thesis was to investigate the added value of a remote monitoring (RM) prenatal follow-up in pregnancies complicated with gestational hypertensive disorders (GHD). I start with a scoping review, in which an overview of the RM techniques used in obstetrics is given. The value added by these techniques is evaluated in four major domains: (1) gestational physiology; (2) clinical outcomes; (3) personal characteristics and perceptions; and (4) the costs to the healthcare system. The major findings of the scoping review in these four domains are summarized, and the strengths and limitations of the study, and the future perspectives and future directions are discussed.

MAJOR FINDINGS OF THIS DOCTORAL DISSERTATION

PART I – SCOPING REVIEW

During the literature search performed at the start of this PhD project (Chapter 1), it became clear that RM can only be recommended for pregnant women at risk of premature deliveries. However, it is important to recognize that most of these studies were published in the mid 1990s, so the technologies used differed from more recent technologies. Therefore, current randomized controlled trials with a blinded protocol are required to strengthen the level of evidence around this topic and to gain insight into the added values of the technologies that are available today. Studies that investigate patient satisfaction with and the economic benefits of RM are warranted. No reports of the value of RM programs for women at risk of GHD have been published.

PART II - GESTATIONAL PHYSIOLOGY AND REMOTE MONITORING

In the next part of this thesis, I present the cases of two female patients implanted with a cardioverter (ICD, Protecta™ XT VR, Medtronic, Brussels, Belgium) with a second-generation fluid build-up detection algorithm, to monitor the effects of Marfan syndrome (Chapter 2) and long QT syndrome (Chapter 3). Both women were included in two RM follow-up programs: a cardiac RM program for the ICD device and the PREMOM program for the early detection of hypertension in pregnancy.

These two case studies demonstrated the presence of a significantly higher thoracic fluid content during the total gestational period, with a rapid recovery to the initial prepregnancy value after delivery. The observation of increased thoracic fluid can be explained by well-known physiological cardiovascular changes during the gestation. Maternal hemodynamics research is currently a hot topic in the obstetric world, as GHD are a result of a maladapted cardiovascular system (109). Recent data of our research group illustrate already significant cardiovascular differences in the first trimester between

all types of GHD (unpublished data). Our case observations illustrate the feasibility to use the bioimpedance technology for continuous monitoring of a cardiovascular parameter (thoracic fluid) during the complete pregnancy, but this one parameter has unfortunately not enough power to discriminate between a normal or abnormal pregnancy. A large cross sectional observational study with the combination of blood pressure monitoring with fluid monitoring is needed to estimate the exact discrimination potential. Today, innovative research is producing more specified methods to evaluate the complete maternal cardiovascular function by non-invasive mode, including external bioimpedance patches (112, 113), but also echocardiography or Doppler ultrasound is generally used (114-119). However, these devices still require a single, in-hospital measurement and generate an exhaustive list of cardiovascular parameters (heart, veins, arteries and/or fluid). When these devices would allow continuous cardiovascular monitoring at home, like, and in addition to, remote blood pressure monitoring, the way is open towards exploring periconceptional cardiovascular monitoring as a new tool to discriminate normal from abnormal maternal cardiovascular adaptations during the pregnancy ,and thus identify pregnancies at risk for GHD already at the very first post-implantation stages. Research covering these mobile devices is still rather poor and unknown. My telemonitoring project could act as a fundament of a future step, where the main cardiovascular parameters could be included in order to use this device as easy applicable and non-invasive home screening tool during pregnancy. But we should keep in mind not to frighten the pregnant women with too many devices.

PART III – THE PRENATAL FOLLOW-UP AND THE GESTATIONAL OUTCOMES

In part III, the added value of an RM program during the prenatal follow-up and in the gestational outcomes of women at risk of GHD were investigated. In Chapter 4, the study population included only patients at risk of GHD in 2015. In Chapter 5, women at risk of

GHD in both 2015 and 2016 were included, because a larger study population allowed more reliable conclusions to be drawn.

Both studies showed reductions in prenatal admissions and prenatal admissions before delivery, and reductions in the prevalence of pre-eclampsia and the total number of inductions when women received RM prenatal follow-up rather than conventional care (CC). Women in the RM group had a significantly higher risk of gestational hypertension and spontaneous birth than those in the CC group. In the 2015 study, the number of neonatal hospitalizations in the neonatal intensive care (NIC) unit was lower in the RM group than in the CC group, although this was not observed in the 2015–2016 study. However, in the 2015–2016 study, the women with GHD in the RM group made fewer prenatal visits than those in the CC group. This difference was not observed in 2015.

These two studies demonstrate that RM can reduce healthcare consumption without compromising maternal or neonatal outcomes. Moreover, the women who received RM and their neonates were more likely to have better perinatal outcomes than the women and neonates who received CC. No other studies of the effects of an RM program in the prenatal follow-up of women with GHD have been published since our manuscripts were presented, although increasing numbers of feasibility studies of the use of mobile phone apps and connected digital devices for women at risk of adverse pregnancy outcomes have been undertaken (77). Several studies of RM programs that assist nonpregnant hypertensive patients to control their blood pressure have reported that monitoring blood pressure at home is a reliable and promising method of reducing blood pressure (78-82). Two recent studies compared CC with RM in the management of postpartum hypertension. Both concluded that RM is more successful than CC in closely managing and monitoring blood pressure and detecting the warning signs of worsening disease (105,

120). Therefore, we believe that RM is an important and promising tool to guide women at risk of GHD through their prenatal period and to minimize the risk of complications.

PART IV – PERCEPTIONS OF PREGNANT WOMEN AND THEIR CAREGIVERS TO REMOTE MONITORING FOR PRENATAL CARE

Chapter 6 discusses the perceptions of midwives, obstetricians, and recently delivered mothers of a prenatal RM program. Although the majority of caregivers had no or very little experience of RM before they participated on the PREMOM project, after 1 year working with this program, they considered RM an important factor in the follow-up of (high-risk) pregnancies. They would recommend it to their colleagues and pregnant women, and they proposed extending RM to all women with high-risk pregnancies in Belgium. However, they wanted additional training on the technical aspects of the devices used and the counseling of patients. Most of the mothers were also satisfied with the RM prenatal follow-up. They reported a feeling of security throughout their pregnancy and were not concerned about sharing their health data with the caregiver. Most of the mothers wanted to be contacted within 3–12 hours of an abnormal value, preferably by phone. This implies the need for 24/7 surveillance of the vital parameters of pregnant women at risk of GHD.

PART V – THE COSTS FOR THE HEALTHCARE SYSTEM

During our investigation of the prenatal follow-up of women with an RM program and their comparison with women on a CC program (Chapters 4–5), we speculated whether the reduced number of prenatal visits and hospitalizations observed in the RM group might entail cost savings to the healthcare system.

In Chapter 7, we investigated the possible cost reduction to the healthcare system (HCS) with the addition of RM to the prenatal follow-up program of women with GHD. We compared the hospital bills of the RM and CC groups, from the beginning of pregnancy

until the discharge from hospital of both the mother and child after delivery. A mean cost saving for the HCS of €740.38 (14.89%) per person who followed the RM program was made relative to the cost of CC. The major cost savings were made by the National Institution for Insurance of Disease and Disability (RIZIV), with a difference in costs between RM and CC of €848.97 (23.18%) per person. This cost reduction arose from the marked reduction in the consumption of healthcare services, including laboratory tests, medications, and maternal and neonatal admissions. In Chapter 8, we identified the domain in which most cost savings occurred. We analyzed the women's hospital bills in 2015 and 2016, with the method described above, by dividing all the participants into one of three groups: delivery at < 34 weeks of gestation; at 34–37 weeks of gestation; or at > 37 weeks of gestation. It became clear that the greatest cost savings occurred in the group who delivered at < 34 weeks of gestation (reductions of 50.52% in HCS costs, 56.23% in RIZIV costs, and 8.95% in patient costs), followed by the group who delivered after 37 weeks of gestation (reductions of 1.16% in HCS costs, 5.09% in RIZIV costs, and –6.08% in patient costs), and were least in the group of women who delivered at 34–37 weeks of gestation (–3.90% in HCS costs, 21.03% in RIZIV costs, and –67.04% in patient costs). Most cost savings were made in neonatal care in each of the three study groups (delivery at < 34 weeks of GA, 34–37 weeks GA, and > 37 weeks of GA) and when all the study groups were combined. This study made it clear that neonatal care is one of the largest costs in the care for mothers and neonates. However, this is not new information: neonatal care is characterized by its intensive character and is known as one of the most expensive services in hospitals (110). It is well recognized that most neonatal morbidity associated with GHD is attributable to complications of prematurity and that the severity of prematurity correlates with the cost of neonatal care (111). Our research team showed that the neonates of women the RM group, who were born before 34 weeks of GA, were approximately 10 days older at birth than the neonates of the CC group. These 10 days

will greatly affect the health of the neonate and reduced the costs to HCS and RIZIV by more than 50%.

Since our publication of the cost analysis for 2015, no other study of the cost-effectiveness of an RM program in women at risk of GHD has been published. Studies of this topic in hypertensive patients who are not pregnant are also rare.

STRENGTHS AND LIMITATIONS

The four domains investigated in this doctoral thesis are still rarely investigated in the obstetric field: RM and (1) gestational physiology; (2) prenatal follow-up and gestational outcomes; (3) personal characteristics and perceptions of caregivers; and (4) costs. No new studies have examined these topics since our manuscripts were published. One of the strengths of our study design was that all the patients included in our analyses received their antenatal care and delivered at the same hospital, so that their electronic medical records were in line with their administrative files. Furthermore, the antenatal care of all patients was according to the uniform local management protocols (of the Ziekenhuis Oost-Limburg, Genk, Belgium). The use of 'real-life' data from hospital bills in the cost-effectiveness study was another strength of our studies.

However, these studies also had some major limitations. First, the data were collected retrospectively and the patients were not randomized in either study, so the possibility of selection bias cannot be excluded. The studies were performed at a single center, although the evidence of multicenter studies has more power, and it would be interesting to investigate the added value of RM in other prenatal programs for women at risk of GHD using protocols other than the Ziekenhuis Oost-Limburg protocol. Finally, the exact mechanisms contributing to these improved outcomes are unknown. The actions of the participants were not precisely noted and no conclusions can be drawn about the added value of RM in the care process.

FUTURE PERSPECTIVES

Like we stated before, we live in a world in which mobile technologies are ubiquitous. Policy makers could not have anticipated that this mobile technology would change healthcare; however, its evolution has several advantages. In our previous papers, we have reported the potential improvements in the outcomes of pregnant women at risk of GHD and their neonates, from the clinical, psychological, and economic perspectives (73, 90, 91, 121). It is expected that RM will allow the evolution of a healthcare system with personalized management, in which individuals can participate actively; that focuses more on prevention than on cure; and is less expensive (122, 123).

In the following paragraphs, we speculate on some future aspects of RM in medical care: (1) the organization of RM in the national healthcare system; (2) new opportunities and challenges for midwives in RM-assisted prenatal care; and (3) the psychosocial aspects for women from a socio-economic perspective.

ORGANIZATION OF RM IN THE NATIONAL HEALTHCARE SYSTEM

RM in other aspects of prenatal care

In the previous chapters, we have shown that RM can be implemented in the standard prenatal care for women at risk of GHD. A research team at the University of London (St George's University Hospitals NHS Foundation Trust) is also investigating the use of RM in the prenatal care of women with GHD. In conjunction with the Health Foundation (London, UK), they have developed HaMpton, a smartphone app for monitoring hypertension in pregnancy. This app allows patients to monitor their blood pressure, urine, and symptoms at home. In that study, the patients manually entered their parameters into the app, from where they were sent to the caregivers at the hospital. They have also shown that in hypertensive pregnancies, RM can potentially reduce the number of hospital visits required by patients and reduce costs compared with traditional monitoring, without compromising

the maternal and pregnancy outcomes (124, 125). RM has also been investigated in other domains of prenatal health. Recent publications by other researchers have shown that remote monitoring of blood glucose in women with gestational diabetes mellitus (GDM) is safe, and that the women preferred this model of care over standard prenatal care (126). RM also offers opportunities to develop new technologies for prenatal care. The use of a sensor developed to detect fetal movements and (premature) contractions is currently being explored by a research team at Ziekenhuis Oost-Limburg (Genk, Belgium) and Bloom Technologies (San Francisco, USA) (127, 128). A few accelerometer-based systems have been developed in the past few years to allow remote self-monitoring of fetal movements during pregnancy. Although fetal movement is routinely used as a proxy for fetal well-being, it is challenging to obtain noninvasive, long-term monitoring of fetal movement that is accurate. Another technology combines electrohysterography and maternal heart rate data to detect (preterm) labor, which could be useful in providing timely and correct care without unnecessary antenatal visits (127, 128). Our research team is also investigating the possible use of an activity tracker in pregnant women. The main aim is to ensure that pregnant women undertake sufficient physical activity, by providing them with an activity tracker (iHealth, Paris) together with regular feedback on their daily activity. This telecoaching model is consistent with the research of Hurkmans et al. (2018), who used a combination of conventional and mobile programs in overweight adults. The results of their study showed that a conventional weight-loss program can be partially completed with an RM program without compromising its effectiveness (129). This knowledge will also be used in the INTER-ACT project by a research team in Leuven (Belgium) in developing interpregnancy lifestyle interventions to prevent pregnancy complications (130).

Action Point19: Mobile Health

The Belgian Government has accepted that RM technologies are changing healthcare. Therefore, mid 2016, the Minister of Healthcare (Maggie De Block) launched 'Action Point 19: Mobile Health'. The aim of this initiative was to evaluate RM pilot projects in a medical context for a period of 6 months, as a first step in the further evaluation of all steps for eventual reimbursement. PREMOM was selected as one of the 24 pilot projects that participated in this initiative, and was the only project involving prenatal care. The study period extended from May 2017 until October 2017, and the final decisions of the Government are expected in the summer of 2018.

During this 6 month period, 105 new patients were included in the UHasselt RM program, seven (6.67%) of whom dropped out for various reasons (psychological reasons, n = 2; incompatible with normal life activities, n = 4; technological failure, n = 1). Between 65 and 75 patients were simultaneously monitored on a daily basis, and 85 women gave birth during this period. A compliance rate of 89.17% was achieved for blood pressure measurements in the morning and 89.00% for blood pressure measurements in the evening. The compliance rates for weight measurements and wearing the activity trackers were lower, at 53.67% and 50.67%, respectively. The outcomes at the prenatal follow-up and the gestational outcomes were reported in our previous papers (73, 91).

Our manuscript entitled 'A prenatal telemonitoring program in pregnancies complicated with gestational hypertensive disorders: where are the cost savings located?' showed that a larger proportion of neonates were born after gestational age (GA) of 37 weeks in the RM group than in the conventional care (CC) group (81.25% vs 75.00%, respectively). From the data presented in that manuscript, the following calculations can be made:

Table 9.1: Cost savings for RIZIV in 2015–2016

	Study group		Cost savings	Numbers of patients in the RM group	Total cost savings for this group
	RM group (n = 80)	*CC group (n = 176)*	*€*		*€*
GA < 34 weeks	6951.59 (± 5894.59)	15881.69 (± 14972.48)	8930.10	7	62511.00
GA 34–37 weeks	3878.95 (± 2828.58)	4531.08 (± 4720.36)	652.13	8	5217.00
GA > 37 weeks	1912.77 (± 381.50)	2015.19 (± 626.51)	102.42	65	6657.00
Values are numbers (percentages). RM = remote monitoring; CC = conventional care; GA = gestational age					

For the period 2015–2016, a total of €74,385 in cost savings for RIZIV was made in patients in the RM group relative to the cost in the CC group. When this number was divided by 575 RM months (the total number of months in which the women participated in the RM program in 2015–2016), a cost saving of €129.40/month in RIZIV was made, excluding the long-term health outcomes and related costs.

However, the costs of RM itself must also be taken into account. By analyzing the bills for the devices, the information and communication (ICT) platform, and the personal and technical support teams, the following costs were calculated:

Table 9.2: Cost of RM for 2015–2016

Variable	Costs	Duration	Total costs
	€		€
Blood pressure monitors + activity trackers	11,740 (in total)	2 years	11,740
Midwives	45.29/hour	638u/575 RM months	28,895
ICT support	20/month	575 RM months	11,500
RM = remote monitoring; ICT = information and communication platform			

To implement RM in the Belgian healthcare system, additional costs, on top of certain prenatal care costs, are required to ensure 24/7 follow-up for these women. These costs include a 24h permanence and administration costs for the midwives responsible for the RM, a compensation for the responsible gynecologist and a fee for the referring gynecologist:

Table 9.3: Costs of RM that must be considered in 2015–2016

Variable	Costs	Duration	Total costs
	€		€
24 h permanence + administration costs	20/month	575 RM months	11,500
Coordinating gynecologist	15/month	575 RM months	8625
Referring gynecologist	10/month	575 RM months	5750
RM = remote monitoring			

The balance of savings and costs is summarized in Figure 9.1. For a total of 80 women involved in RM for 2 years, the costs and expeditions are in balance.

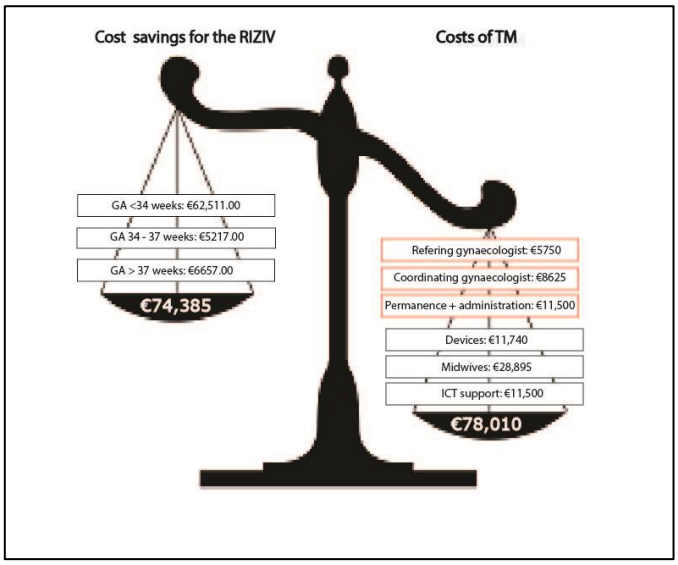

Figure 9.1: Balance of savings and costs

RM structures that can be implemented

In the RM model used in the prenatal care of women with GHD, ZOL functions as a center of expertise. Pregnant women at high risk are monitored under the supervision of one gynecologist specialized in maternal and fetal medicine, in collaboration with external gynecologists. This organization provides one example of organized RM care, as presented in Figure 9.2

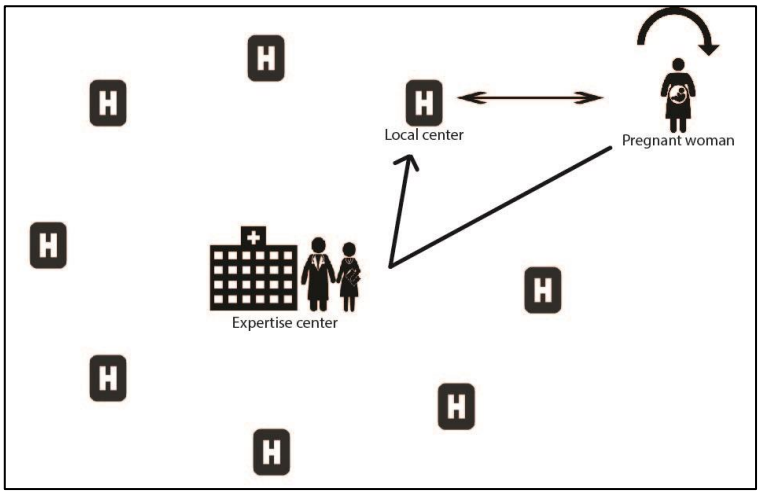

Figure 9.2: Organization of RM

RM structures can be organized in three different ways, depending on the purpose of the RM program and the health risk associated with the gestational complications:

(1) Individual care: The patient can monitor her parameters automatically and their feedback is app-assisted, without any interaction with a medical or paramedical supervisor. An example of this is the prenatal follow-up of daily physical activity and sleep patterns with a remote activity tracker. This informs the patient of her physical condition, her steps/day, sleep pattern, etc. The app, which is coupled to the activity tracker, gives preprogrammed feedback on those parameters. There is no risk to the health of the pregnant women or her fetus if this information is neglected by the patient.

(2) Linked centers: In the second structure, a healthcare worker is involved in the prenatal care of the woman. This healthcare worker may be someone of the first or secondary line, but specialists are not involved (yet). Some disorders can be kept stable when the pregnant woman is sufficiently empowered and collaborates closely with her healthcare worker. The woman can measure her parameters and

send them to the healthcare worker, who will review them. When alarm signals are triggered, the healthcare worker can contact the pregnant women and recommend an intervention. However, for most of the time, the healthcare worker simply has a coaching role. An example of this is the prenatal follow-up of GDM. This complication of pregnancy is not a major risk for the pregnant women or her fetus when the woman adheres strictly to her diet and/or takes her medication as prescribed. Prenatal hospitalization is rarely needed, but the close monitoring of blood glucose is necessary.

(3) Expert centers: The PREMOM project exemplifies the third structure. Pregnant women in this program have a high risk of complications, regardless of their compliance with therapy. A close collaboration between the healthcare worker in the tertiary line (= expertise center), the healthcare workers in secondary/primary care, and the pregnant woman is necessary to ensure the best possible perinatal outcome. The pregnant woman measures her parameters and sends them to the healthcare worker in the expertise center. When an alarm signal is triggered, he/she will contact the healthcare workers at the secondary/primary center to undertake the necessary intervention.

The three types of structures can be summarized as follows:

Table 9.4: Structures of RM

	Individual care	**Linked centers**	**Expert center**
Collaboration: person(s) with access to information in the monitoring app	Only the pregnant woman	Pregnant woman and healthcare workers at primary/secondary care centers	Pregnant woman, healthcare workers at primary/secondary care center, and healthcare workers at the expert center
Risk to health (of both fetus and pregnant woman)	Very low risk	Low risk	High risk
Role of RM	Informing pregnant woman	Coaching and prevention	Diagnostic and therapeutic interventions and monitoring
Example	Sleep and physical activity	Gestational diabetes mellitus	Gestational hypertensive disorders

Conclusion

Belgian politicians must very soon decide whether to fully implement and finance (fully, partially, or not at all) RM for prenatal care. The results of our research show that the use of RM in patients at risk of GHD has potential advantages for the clinical, social, and economic outcomes, in both the short and long term. By reimbursing RM, this service will become accessible to all strata of the population and every pregnant woman, regardless of her financial situation, would receive the best care possible. Decisions about the organization and implementation of RM structures in the Belgian healthcare system must also be made.

NEW OPPORTUNITIES AND CHALLENGES FOR THE MIDWIFE IN A POLICY WITH RM*

**This part is partly translated from a publication in the 'Tijdschrift voor Vroedvrouwen'(131)*

If RM is further implemented in the Belgian healthcare system, new opportunities and challenges will arise for midwives working in hospitals. In this process, the midwife will first admit the pregnant woman (and her partner), and explain what RM means and how the pregnant woman can participate in this care process. The midwife evaluates the vital parameters of the pregnant woman, and consults with the responsible gynecologist if the values are abnormal. The midwife is the first to contact the second-line caregivers or the pregnant woman when interventions are required, such as adjustment of an antihypertensive therapy. However, above all, she is the primary contact person at the first level for the pregnant woman, answering questions, addressing insecurities and worries, filtering the (alarm) signals through to the gynecologist, and communicating information to the pregnant woman. It is clear that the midwife will regain her place in the prenatal care of women experiencing a high-risk pregnancy, under the supervision of and in collaboration with medical staff. Indeed, the Belgian law reserves a place for the midwife in the follow-up of a high-risk pregnancy in collaboration with the primary- and secondary-level caregivers (132, 133). In clinical practice, a Belgian woman with a high-risk profile receives her prenatal follow-up only at the secondary-care level (134). This trend can be reversed to conform to the model prescribed by the *Federale Raad van de Vroedvrouwen* (14), in which both midwives and gynecologists actively participate in the prenatal follow-up.

RM is often insufficiently respected for fear of the overmedicalization of prenatal care. The accusation that the medicalization of childbirth has gone too far comes from many quarters (64-69). The results of our PREMOM studies demonstrate that this fear is unfounded. The total numbers of prenatal visits, inductions, and prenatal hospitalizations were reduced by adding RM to the prenatal care process (73, 91). Furthermore, only women at risk of developing GHD will be cared for with these technologies, not women with normal pregnancies and low risk profiles. It is important to make this distinction, and

once again, the midwife has an important role in this. By adequately collecting an anamnesis and specifically identifying the risk factors for GHD at the first prenatal visit, it is possible to determine whether a pregnancy is high risk in an early stage of that pregnancy (31). Based on this risk profile, a further follow-up can be arranged in which the midwife plays the most important role (in the case of low-risk pregnancies), or in which a collaboration is established between the midwife and a secondary-care center (in the case of high-risk pregnancies).

As previously mentioned, the number of prenatal hospitalizations was reduced in women at risk of GHD who received RM in their prenatal follow-up (73, 91). It was also clear that RM had an greater effect on this process than was initially anticipated. As shown in Figure 9.3, the number of prenatal observations made when GHD was suspected, but the diagnosis was negative, was reduced by 29.23% between 2014 (the reference year in which no RM was performed) and 2016. However, the total number of prenatal hospitalizations for suspected or confirmed GHD increased by 25.00% in these years. Two conclusions can be drawn: 1) the total number of 'unnecessary' hospitalizations decreased when pregnant women participated in the RM program. When GHD is suspected but the situation does not seem to be acute, an RM prenatal follow-up will often be commenced or, when the pregnant woman is already participating in an RM prenatal follow-up, her blood pressure will be received via RM and checked. The hospitalization of such women in the prenatal ward will be less often based on conjecture and more often based on objective data retrieved in the home environment. 2) Pregnant women who are hospitalized with GHD have serious pathologies, which require intensive treatment. The total number of hospitalizations for pre-eclampsia increased by 20.83% between 2014 and 2016, which indicates that this pathology is picked up by RM. There were also more referrals from other centers because of the growing confidence in the RM technology. However, the total number of days in the prenatal ward did not increase. In 2014, there

were 600 days of hospitalizations due to (suspected) pre-eclampsia, which decreased to 490 days (–18.34%) of hospitalizations due to (suspected) pre-eclampsia in 2016. For the midwives who work in the prenatal ward, this was a paradox. The reduction in (the duration of) prenatal hospitalization reduces the workload, so it is possible to increase the RM specialization and to build a specialized unit around it. In this way, more pregnant women will be supervised by a midwife, more personalized care will be given, and hospitalization will occur at the right time, without the need of a reduction of the prenatal ward due to less prenatal hospitalizations.

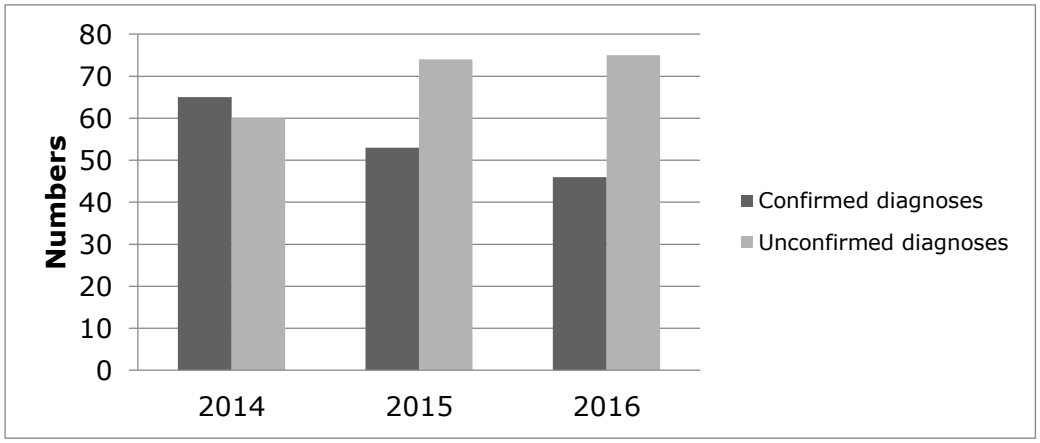

Figure 9.3: prenatal observations

VULNERABLE PREGNANT WOMEN

During the 4 years in which RM was implemented in the prenatal care of women at risk of GHD, a new, unexpected opportunity became apparent: the prenatal follow-up of vulnerable pregnant women. This is a group of women at high risk of poor prenatal care for numerous reasons. One reason is that they often do not keep their appointments. With the RM organization of prenatal care, the RM midwife can actively guide women and manage their prenatal care appointments.

The importance of adequate antenatal healthcare has been demonstrated in recent publications (135-137). In our RM program, a retrospective study of the gestational outcomes of the deliveries at ZOL (Ziekenhuis Oost-Limburg, Genk, Belgium) in 2016 (n = 2084) showed that pregnant women who received ≤ 2 ultrasound scans, as recommended by the Belgian Kenniscentrum voor de Gezondheidszorg (KCE), had an elevated risk of adverse birth outcomes (138). Of the 2084 deliveries performed, 172 (8.25%) had received ≤ 2 ultrasound scans. Thirty-eight (22.09%) of them were for social reasons, 15 (39.47%) for cultural reasons, eight (21.05%) for financial reasons, seven (18.42%) were unplanned/unwanted pregnancies, six (15.79%) were associated with single parent/relationship problems, and one each (2.63%) was associated with family violence and psychological problems. The presence of neonatal complications in the group of pregnant women who had > 3 ultrasound scans are compared with those in pregnant women who had < 3 ultrasound scans are presented in Table 9.5.

Table 9.5: Neonatal complications

	Normal numbers of ultrasound scans (n = 2050)	**≤ 2 ultrasounds scans (n = 38)**
Delivery < 37 weeks of GA	210 (10.24%)	8 (21.05%)
Delivery < 32 weeks of GA	63 (3.07%)	4 (10.53%)
Birth weight < 2500 g	204 (9.95%)	3 (7.89%)
NICU admission	204 (9.95%)	3 (7.89%)
Neonatal death	9 (0.44%)	0 (0.00%)
MIU	4 (0.20%)	0 (0.00%)
TOP	5 (0.24%)	0 (0.00%)
Values are numbers (percentages). GA = gestational age, NICU = neonatal intensive care, MIU = intrauterine death, TOP = termination of pregnancy		

Remarkably, the women who underwent ≤ 2 ultrasound scans experienced more premature deliveries: the number of deliveries before 37 weeks of GA was 21.05% in the group with < 3 ultrasounds and 10.24% in the group with > 3 ultrasounds. The correlation was even more pronounced in deliveries before 32 weeks of GA: 10.53% in the group with < 3 ultrasounds versus 3.07% in the group with > 3 ultrasounds. Although suboptimal antenatal care does not increase neonatal morbidity only in vulnerable pregnancies, it may be very important in optimizing the gestational outcomes of this group of pregnant women.

A possible way to guide these vulnerable women through their prenatal follow-up is in the same way that women at risk of GHD are guided in the RM program. When the responsible gynecologist has reason to believe that a woman is vulnerable (based on her history of previous pregnancies, something said during the consultations, etc.), the midwife who is in charge of the RM can be contacted. She can use the same mechanism that is used for women in the RM group: every time a prenatal consultation is planned for the vulnerable pregnant woman, the midwife will contact both the woman and the responsible gynecologist to make them aware of this consultation. If the pregnant woman does not attend, the midwife can try to contact her to arrange a new appointment and to establish the reason she missed the appointment. When possible, solutions can be developed in collaboration with the responsible gynecologist, a social worker, or other organizations/healthcare workers (such as Campus O3, OCMW, etc.).

In this way, the RM midwife will be the first point of contact not only for a pregnant woman at risk of GHD and for her gynecologist, but also for a pregnant woman in difficult circumstances. By ensuring that all pregnant women have a least three ultrasound scans (combined when necessary with other important prenatal tests, such as screening for *Streptococcus agalactiae*, gestational diabetes mellitus, etc.), it is possible to detect

complications and to prevent their further development. In this way, pregnancy outcomes will be improved and neonates will have the best start possible.

FOLLOWING STEPS

Two major research directions are suggested by this doctoral dissertation, examining: (1) the relationship between compliance rate with RM and personality traits; and (2) a multicenter randomized controlled trial to investigate the added value of a RM program for women at risk for GHD at the Research Foundation–Flanders. These are discussed below.

THE RELATIONSHIP BETWEEN COMPLIANCE RATE IN RM AND PERSONALITY TRAITS

Little is yet known about the relationship between compliance with RM and personality traits. Although most mothers stated that they experienced no problems with taking the required measurements at the specified times (Chapter 6), a preliminary exploratory study in cooperation with the Center for Translational Psychological Research (TRACE) was performed to determine the relationship between compliance with RM and personality traits. We hypnotized that women with high scores for perfectionism, depression and anxiety would be more compliant compared to women with low scores. The results, which are still preliminary, showed that women with compliance rates of 25%–75% had higher scores for depression on the questionnaires than those with other compliance rates. Women with low compliance rates (< 25%) were more perfectionist than the women with compliance rates > 25%. These results indicate the importance of personality traits to the success of an RM design. When RM measurements are not made, the responsible RM midwife or obstetrician cannot respond to the patient appropriately because the values are missing. A risk assignment, based on validated questionnaires, would allow more personalized care to be provided (when necessary, a psychologist or therapist could be asked to support a specific woman) and the risk of missed measurements to be minimized. Further research is necessary to determine the specific relationships between personality traits and the compliance rate with RM. However, our study showed clearly

that a multidisciplinary team is required to guide a pregnant woman at risk of GHD through the RM process.

RESEARCH GRANT AT THE RESEARCH FOUNDATION - FLANDERS

At present, an application for a research grant at the Research Foundation–Flanders (FWO) has been approved which requested funding to set up a multicenter randomized controlled trial (RCT) to investigate the added value of a RM program for women at risk for GHD. Although our results so far have been received very positively by the scientific community and in the AP19 project evaluation, the following aspects must be addressed, in response to the feedback from the AP19 evaluation and recurring remarks from the reviewers of our manuscripts:

- To distinguish the effects of the care of women with GHD by our own team—because Ziekenhuis Oost-Limburg is highly experienced in GHD care—from the effects attributable to RM, in a multicenter randomized trial;
- To thoroughly analyze the aspects that contribute to the value added by RM when used to support women with GHD, because measuring in itself of course has no effect. We assume that the added value is created by the supervision of the midwife, who has experience of both normal and pathological events and can anticipate when necessary. To investigate this, we will meticulously register all (the times of) interventions and include a patient self-measurement control group (see below).

The aim of this FWO study is to compare RM and CC in a prospective, multicenter RCT. We will compare three groups, to which women at risk of GHD will be randomly assigned:

(1) RM group;

(2) patient self-measurement (PSM) group;

(3) CC group.

We will specifically include the PSM group—in which the women will collect the appropriate data, but these data will not be sent to the caregivers in hospitals and interventions will be undertaken as in CC—as a placebo control group for RM. We believe that this group will reflect modern society, in which many health apps are available but no supervision of a responsible caregiver receiving the parameters is provided, and the patient must react as she thinks necessary. Therefore, we hypothesize that patients in the PSM group will contact the responsible caregiver (by phone, unplanned visit, etc.) when they think an abnormal event is occurring. In this scenario, the use of healthcare services could increase without necessarily improving the outcome of the participant. By including this group, we can explore (1) the effect of PSM on the use of healthcare services and outcomes; and (2) the added value of a caregiver as an essential working component of RM.

1. Study design

The study will be conducted as a multicenter, prospective, interventional RCT, in which 6107 pregnant women at risk of GHD will be included. The number of women at risk of GHD in Flanders every year is ~6400. Given a recruitment period of 3 years (see below), we will reach 2018 of these women every year (approximately one third).

Eligible pregnant women at risk of GHD will be recruited after routine GHD screening and randomly assigned to one of the following three groups, in each participating hospital.

1. RM group. Pregnant women in this group will receive a connected blood-pressure monitor and activity tracker. They will follow the RM protocol described in the rationale. Standard prenatal care will be provided, together with the RM protocol. A woman will be excluded from the study if her compliance falls below 50%.
2. PSM group. Pregnant women in this group will also receive a connected blood-pressure monitor and activity tracker. They will be asked to measure their blood

pressure twice a day (in the morning and evening), monitor their activity continuously, and enter their weight on the app once a week. As with the RM group, these data will be automatically transmitted by Wi-Fi and Bluetooth to an online dashboard for collection and storage, but they will not be revised by a healthcare collaborator. No woman will be excluded from the study based on her compliance; accordingly, these women might be less motivated to regularly record their measurements. The women in this group will receive standard prenatal care or the appropriate interventions when they contact their caregivers about their measurements. Data available from the online platform (blood pressure and weight) will be used for analytical purposes at the end of the study.

3. CC group. Pregnant women in the CC group will receive standard prenatal care, as provided by the local institutions. They will receive no devices.

The three study groups were chosen:

1. to determine whether regularly measuring blood pressure and weight added value to the prenatal care program (RM group and PSM group vs CC group); and
2. to determine the exact effect of RM, by comparing the RM group with both the PSM group and CC group, and by registering the interventions that are performed.

Thus, the RM group is the true intervention group and the CC group is the usual control group. A real sham group, in which women were told that they were participating in RM but no caregiver followed up the data, would be unethical. Therefore, we chose to include the PSM group as an extra control (placebo) group that lacked the critical component of RM.

2. Inclusion and exclusion criteria

Inclusion criteria: Women who are at high risk of developing GHD according to the local guidelines of the participating hospitals. Women can be included from the moment the pregnancy is detected or when risk factors occur until discharge after delivery (of both the mother and neonate).

Exclusion criteria: Congenital malformations of the newborn, pregnant women without a smartphone, pregnant women < 18 years old, and pregnant women who do not understand the Dutch, French, or English language.

3. Sample size calculation

The sample size required to detect the following two clinically meaningful differences between RM and CC, based on our previous work, was calculated by Censtat (UHasselt; L. Bruckers, C. Kremer):

1. Gestational age (GA) at birth for GHD pregnancies when birth occurred before 34 weeks into pregnancy. A difference of at least 10 days between the RM group and the CC group was observed in our pilot studies, and was used as a clinically relevant difference in the power calculation. Priority was given to this parameter because an extension of GA by even 1 day has a great effect on the clinical outcome of a neonate (in both the short and long term). Moreover, the highest cost reductions were detected in the group of women who delivered before 34 weeks GA. This reasoning is based on the KCE Trials program, funding noncommercial comparative effectiveness trials, where the main focus was on the cost reduction for the healthcare system.
2. Admission to the Maternal Intensive Care (MIC) for GHD pregnancies when birth occurred after 34 weeks of GA: a proportional difference of 20% between the RM and CC group was considered clinically relevant. This outcome was expected to

occur most often in the PSM group, followed by the CC group, and to occur much less often in the RM group.

To achieve 80% power in this study, at least 168 GHD pregnancies delivered at < 34 weeks GA and at least 360 GHD pregnancies admitted to the MIC at > 34 weeks of GA should be included. In every center, these patients should be divided equally among the three study groups (RM, PSM, and CC).

4. Centers that will be involved

The following MIC centers will participate in this project:

- UZ Leuven (Leuven, Belgium; ~2000 deliveries/yr), increasing to ~9300 deliveries/yr when hospitals from the surrounding area are included; Prof. Dr. Roland Devlieger
- UZ Antwerpen (Antwerpen, Belgium; ~1000 deliveries/yr), increasing to ~1000 deliveries/yr when hospitals from the surrounding area are included; Prof. Dr. Yves Jacquemyn
- St Lucas Brugge-Oostende (Brugge, Belgium; ~2000 deliveries/yr), increasing to ~11,000 deliveries/yr when hospitals from the surrounding area are included; Dr. Hilde Logghe
- Ziekenhuis Oost-Limburg; Genk, Belgium; ~2000 deliveries/yr), increasing to ~7600 deliveries/yr when hospitals from the surrounding area are included; Prof. Dr. Eric De Jonge

In the four selected centers, every eligible woman will be randomly assigned (envelope system) to one of the three study groups (RM, PSM, and CC). Our research team has chosen this type of randomization rather than cluster randomization (in which every hospital treats only one of the three study groups that will be compared in the analysis) to exclude any selection bias arising from local screening and treatments for GHD. In this

way, the study population is representative of each hospital and therefore of the whole of Flanders.

5. Recruitment rate, expected drop out and recruitment strategy

According to the sample size calculations based on the difference in gestational age of neonates born at < 34 weeks of GA, 168 preterm births (< 34 weeks) attributable to GHD must be included across the four MIC centers to achieve 80% power.

As we know from the Studiecentrum van Perinatale Epidimiologie (SPE) data, these 168 births that occurs at < 34 weeks constitute 6.6% of all GHD deliveries, i.e., 2.545 GHD deliveries per year. Furthermore, GHD pregnancies represent 4.6% of the total population of pregnant women, i.e., 55.335 pregnancies per year. As observed in our previous studies, 43.53% of the patients included in the RM group required interventions for their GHD (37 of 85 = one of every 2.29 patients with GHD in the RM group). Therefore, ca. 10.53% (4.6% × 2.29) of these women are at risk of GHD, and this is the population that we will include in our study: 5.826. Taking into account a dropout rate of 4.83% (based on our AP19 project, in which seven of 145 women dropped out), 6107 women must be included.

According to the sample size calculation for women admitted to the MIC at > 34 weeks GA, more than 360 women who deliver at > 34 weeks GA must be included across the four MIC centers. As we know from previous studies, at least 42% of women with GHD will be admitted to the MIC department. Therefore, of the 5931 deliveries that occur at > 34 weeks GA (6107 women included – 176 women [168 + dropout rate of 4.83%] who deliver at < 34 weeks; see above), approximately 2491 mothers will be hospitalized. Therefore, the total number of women required for this group is the number of women required to show the difference between the groups in the gestational age of neonates born at < 34 weeks of GA (i.e., 6107).

In summary, 6107 women will participate in this study. KU Leuven, AZ Brugge, and ZOL each usually responsible for 28.57% of the deliveries that occur at all these centers (2000 each of the 7000 deliveries across the four participating centers), so a total number of 1745 participants/center must be included. This corresponds to an inclusion rate of 16 patients/month per study group over a study period of 36 months. UZA contributes 14.29% of the deliveries (1000/7000), so the number of participants must be halved. Therefore, 873 women must be included in total, i.e., eight inclusions per study group/month

6. Final decisions

The final grant decision is made on the 9th of July 2018 by the FWO in July 2018. Our submission is accepted and the project will start on October 1, 2018.

CONCLUSIONS

Although RM in the prenatal follow-up of women with GHD has proven its value in terms of gestational physiology, clinical outcomes, personal characteristics and perceptions, and the costs to the healthcare system, a prospective, multicenter RCT is required before this program can be adopted for prenatal care in Flanders.

KEY MESSAGES

Below are the final key massages, summarized per part, given. This to provide an overview of our work, which involved four years of research

Part I **Scoping review**	RM can only be recommended for women at risk of premature deliveries. However, most of these studies were published in the mid 1990s, so the technologies used differed from more recent technologies. No reports of the value of RM programs for women at risk of GHD have been published.
Part II **Gestational physiology and RM**	During the gestational period is there a significantly higher thoracic fluid index, with a rapid recovery to the initial prepregnancy values after delivery. The observation of increased thoracic fluid can be explained by well-known physiological cardiovascular changes during the gestation.
Part III **The prenatal follow-up and the gestational outcomes**	We showed reductions in prenatal admissions and prenatal admissions before delivery, and reductions in the prevalence of pre-eclampsia and the total number of inductions when women received RM prenatal follow-up rather than CC. Women in the RM group had a significantly higher risk of gestational hypertension and spontaneous birth than those in the CC group.

Part IV

Perceptions of pregnant women and their caregivers to RM for prenatal care

Although the majority of caregivers had no or very little experience of RM before they participated on the PREMOM project they considered RM an important factor in the follow-up of (high-risk) pregnancies. Most of the mothers were also satisfied with the RM prenatal follow-up.

Part V

The costs for the healthcare system

It became clear that RM is more cost-effective than standard care for pregnant women with GHD. The greatest cost savings occurred in the group who delivered at < 34 weeks of gestation, followed by the group who delivered after 37 weeks of gestation, and were least in the group of women who delivered at 34–37 weeks of gestation.

SUMMARY

SUMMARY

Worldwide, 5 to 8 % of all pregnant women develops GHD. In Flanders and UZ Brussels, the prevalence of gestational hypertensive disorders (GHD) was 4.6% in 2015. This means that yearly ca. 3000 of the 64000 pregnancies in Flanders are complicated with this disorder. This disease is linked to maternal and neonatal morbidity. To closely follow-up pregnant women at risk for GHD, they receive remote monitoring (RM) together with their standard prenatal care. RM can be defined as the use of telecommunication technologies to assist the transmission of medical information and services between healthcare providers and patients. Interventions can be performed when necessary. Current research is focused on investigating if RM has an added value in the care path of pregnancies complicated with GHD. This is called the Pregnancy Remote Monitoring (PREMOM) study.

In this thesis, the study protocol was carried out as follow: the patients at risk received a blood pressure monitor, a weight scale and an activity tracker. They had to measure their blood pressure twice daily, register their weight once a week in the app and wear the activity tracker continuously. Those data were send, via Bluetooth and Wi-Fi, to an online dashboard. The midwife in the hospital controlled those values and contacted the responsible gyneacologist when abnormal events happened. Interventions were performed when necessary. Examples of those interventions are: start up or adjust the antihypertensive treatment, perform an 24h urine collection, an extra CTG or a prenatal hospitalization.

In this thesis, we added some novel insights about the added value of RM in the prenatal care for women at risk for GHD. It became clear that non-invasive impedance monitoring can be a new method for continuous monitoring of the maternal vascular changes during any time window between preconception and postpartum. Also, the addition of RM in the

prenatal care process for women at risk for GHD will lead to a reduction of prenatal hospitalization (until the moment of delivery) inductions and diagnoses of pre-eclampsia, when compared to women who received conventional care (CC). Additionally, is it more likely that the women in the TM group, vs. the CC group, will have more spontaneous starts of their birth process and are more likely to be diagnosed with gestational hypertension instead of pre-eclampsia. Caregivers and recently delivered women consider RM as an important aspect of the prenatal follow-up of women at risk for GHD and would recommend it to their colleagues and other women at risk for GHD. The caregivers only longed for an additional training on the technical aspects of the devices and the counseling of the patients. To conclude, RM can also become an cost saving in the total healthcare system, and this mainly for the National Institution for Insurance of Disease and Disability (RIZIV). This cost reduction is due to a marked reduction in the consumption of health care services for the women who received RM. Further analysis showed that cost savings are mainly located in the group of women who delivered before 34 weeks of gestational age.

That we're standing at the beginning of the technical (r)evolution in the healthcare has become clear. Also in other aspects of obstetrics is research ongoing about the added value of RM (for example in premature contractions or gestational diabetes mellitus). Following on this has the Belgian Government launched Action Point 19 in which is evaluated if RM can receive an reimbursement. The PREMOM project was one of the 24 selected projects. Final decisions will be made in the summer of 2018. However, this evolution not only influences on the policy level, but also midwives will have another task fulfillment when they engage themselves in this project. They will be set back to the care process of high risk pregnancies and will be the first contact person for the pregnant women/gynecologists when problems arise. An additional example of this is the care for vulnerable pregnant women.

Despite the positive results which are mentioned, is there a need for an multicentric, randomized controlled to re-evaluate the added value of RM. A proposal for funding is accepted by The Research Foundation – Flanders.

SAMENVATTING

Wereldwijd ontwikkelt 5 tot 8% van alle zwangeren gestationele hypertensieve aandoeningen (GHA). Volgens het Studiecenter van Perinatale Epidemiologie was in 2015 de prevalentie van GHA 4.6% in Vlaanderen en Brussel. Deze complicatie is geassocieerd met maternale en neonatale morbiditeit en mortaliteit. Om zwangeren met een verhoogd risico op GHA prenataal nauwgezet te kunnen opvolgen, krijgen zij telemonitoring (TM) toegevoegd aan hun prenatale follow-up. TM kan gedefinieerd worden als het gebruik van telecommunicatie technologieën om medische informatie vanuit de thuissituatie van de zwangere tot bij de zorgverlener in het ziekenhuis te transporteren. Indien nodig kunnen er interventies uitgevoerd worden. In het huidige onderzoek is er nagegaan of TM een toegevoegde waarde heeft in het zorgproces van zwangeren met een verhoogd risico op GHA. Dit werd de Pregnancy Remote Monitoring (PREMOM) studie genoemd.

De PREMOM studie werd als volgt opgezet: de hoogrisico zwangeren kregen een bloeddrukmeter, weegschaal en activiteitsmeter. Er wordt aan hen gevraagd om twee maal per dag hun bloeddruk te meten, één maal per week hun gewicht in te geven op de app en de activiteitsmeter continu te dragen. Deze data worden via Bluetooth en Wi-Fi naar een online dashboard verzonden. De vroedvrouw in het ziekenhuis controleert deze waardes, en wanneer deze afwijkend zijn wordt er contact opgenomen met de verantwoordelijke gynaecoloog. Indien nodig kunnen er interventies toegepast worden zoals: aanpassen of opstarten van antihypertensiva, 24 uur urine collectie, een extra ambulante monitor of een prenatale opname.

Deze thesis heeft bijgedragen aan een aantal nieuwe inzichten over de toegevoegde waarde van TM in de prenatale zorg van zwangeren met GHA. Zo werd het onder andere duidelijk dat niet invasieve impedantiemonitoring een nieuwe methode kan zijn voor het continu monitoren van de maternale vasculaire veranderingen van preconceptie tot

postpartum. Ook zorgt het toevoegen van TM in het prenataal zorgproces van zwangeren met GHA er voor dat er minder prenatale hospitalisaties (tot het moment van bevalling) en inducties nodig zijn en er minder pre-eclampsies worden vastgesteld bij deze zwangeren, in vergelijking met zwangeren die de standaardzorg ontvangen. Bijkomstig start het geboorteproces bij deze zwangeren vaker spontaan en zullen deze zwangeren een hoger risico hebben voor gestationele hypertensie in plaats voor het ontwikkelen van pre-eclampsie, dan wanneer er geen TM aan hen aangeboden werd. Over het algemeen zijn zowel de recent bevallen moeders als de zorgverleners tevreden over deze technieken en zouden ze het ook aanraden aan hun collega's en andere zwangeren met een verhoogd risico voor GHA. Enkel wensen de zorgverleners eerst een training rondom de technische aspecten van de toestellen en de counseling van de patiënten. Tot slot blijkt dat TM er ook voor zorgt dat er een kostenbesparing bekomen wordt voor de totale gezondheidszorg, en dit voornamelijk voor het Rijksinstituut voor Ziekte en Invaliditeitsverzekering (RIZIV). Deze vermindering van kosten hangt samen met de verminderde consumptie van zorg door de zwangeren die met TM opgevolgd worden. Verdere analyses toonden aan dat de kostenbesparing voornamelijk te vinden is in de groep zwangeren die bevallen voor 34 weken zwangerschap.

Dat we nog maar aan het begin staan van een technologische (r)evolutie in de gezondheidszorg is reeds duidelijk geworden. Ook in andere aspecten van de verloskunde zijn er onderzoeken lopende omtrent de toegevoegde waarde van TM (in bv. preterme contracties of diabetes). Als gevolg hiervan heeft de overheid Actiepunt 19 gelanceerd waarin geëvalueerd wordt of TM in aanmerking komt voor terugbetaling. Het PREMOM project was één van de 24 geselecteerde projecten. De finale beslissing hierover wordt gemaakt in de zomer van 2018. Echter heeft deze evolutie niet enkel invloed op het beleidsniveau, ook de vroedvrouwen hun taakinvulling gaat anders worden wanneer zij zich engageren voor dit project. Zij worden immers teruggeplaatst in het zorgtraject van

zwangerschappen met een verhoogd risico en worden opnieuw het eerste aanspreekpunt van de zwangeren en/of de gynaecologen bij problemen. Een bijkomend voorbeeld hiervan is de zorg rondom kwetsbare zwangeren.

Ondanks deze positieve resultaten, is er nood aan een multicentrische, gerandomiseerde studie die de toegevoegde waarde van TM (opnieuw) onderzoekt. Een beursaanvraag hiervoor is geaccepteerd bij het Fonds Wetenschappelijk Onderzoek.

REFERENCES

1. Becker S, Miron - Shatz, T., Schumacher, N., Krocza, J., Diamantidis, C., & Albrecht, U. mHealth 2.0: Experiences, Possibilities, and Perspectives. JMIR Mhealth Uhealth. 2014;2(2):14.

2. Silva BM, Rodrigues JJ, de la Torre Diez I, Lopez-Coronado M, Saleem K. Mobile-health: A review of current state in 2015. Journal of biomedical informatics. 2015;56:265-72.

3. Cruz J BD, & Marques A. A Home Telemonitoring in COPD: a Systematic Review of Methologies and Patients' Adherence. . INT J MED INFORM. 2014;83(14).

4. Emelda NO WP, & Magann E. Telemedicine in Obstetrics. CLIN OBSTET GYNECOL. 2013;56(3):12.

5. Cowie M, & Lobos, AA. Telemonitoring for patients with hearth failure. CMAJ. 2012;184(5):2.

6. Kitsiou S, Pare G. Effects of home telemonitoring interventions on patients with chronic heart failure: an overview of systematic reviews. 2015;17(3):e63.

7. Giamouzis G MD, Koutrakis K, Karayannis G, Parisis C, Rountas C, Adreanides E, Dafoulas G, Stafylas P, Skoularigis J, Giacomelli S, Olivari Z, & Triposkiadis F. Telemonitoring in Chronic Heart Failure: A Systematic Review. Cardiology Research and Practice. 2012;2012:7.

8. Purcell R, McInnes S, Halcomb EJ. Telemonitoring can assist in managing cardiovascular disease in primary care: a systematic review of systematic reviews. BMC family practice. 2014;15:43.

9. Mushcab H, Kernohan WG, Wallace J, Martin S. Web-Based Remote Monitoring Systems for Self-Managing Type 2 Diabetes: A Systematic Review. Diabetes Technol Ther. 2015;17(7):498-509.

10. Gerris J, Delvigne A, Dhont N, Vandekerckhove F, Madoc B, Buyle M, et al. Self-operated endovaginal telemonitoring versus traditional monitoring of ovarian stimulation in assisted reproduction: an RCT. Human reproduction (Oxford, England). 2014;29(9):1941-8.

11. Gerris J, Geril A, De Sutter P. Patient acceptance of Self-Operated Endovaginal Telemonitoring (SOET): proof of concept. Facts, views & vision in ObGyn. 2009;1(3):161-70.

12. Pereira I, von Horn K, Depenbusch M, Schultze-Mosgau A, Griesinger G. Self-operated endovaginal telemonitoring: a prospective, clinical validation study. Fertility and sterility. 2016;106(2):306-10.e1.

13. Corwin MJ MS, Sunderij SG, Gall S, How H, Patel V, & Gray M. Multicenter randomized clinical trial of home uterine activity monitoring: Pregnancy outcomes for all women randomized. AM J OBSTET GYNECOL. 1996;175(5):5.

14. Wapner JR, Cotton, D.B., Artal, R., Librizzi, R.J., & Ross, M.G. A randomized multicenter trial assessing a home uterine activity monitoring device used in the absence of daily nursing contact. Am J Obstet Gynecol. 1995;172(8):1026.

15. Homko CJ, Santamore, W.P., Whiteman, V., Bower, M., Berger, P., Geifman-Holtzman, O., & Bove, A. A. Use of an Internet-Based Telemedicine System to Manage Underserved Women with Gestational Diabetes Mellitus. Diabetes Technology & Therapeutics. 2007;9(3):10.

16. Homko CJ DL, Rohrbacher K, Mulla W, Mastrogiannis D, Gaughan J, Santamore W, & Bove AA. Impact of a Telemedicine System with Automated Reminders on Outcomes in Women with Gestational Diabetes Mellitus. DIABETES TECHNOL THE. 2012;14(7):6.

17. Pérez-Ferre N GM, Fernandez D, Velasco V, Runkle I, de la Cruz MJ, Rojas-Marcos PR, del Valle L, & Calle-Pascual AL. The Outcomes of Gestational Diabetes Mellitus after a

Telecare Approach Are Not Inferior to Traditional Outpatient Clinic Visists. International journal of endocrinology. 2010;2010:6.

18. Pérez-Ferre N GM, Fernandez D, Velasco V, Runkle I, de la Cruz MJ, Rojas-Marcos PR, del Valle L, & Calle-Pascual AL. A Telemedicine system based on Internet and short message service as a new approach in the follow-up of patients with gestational diabetes. Diabetes Research and Clinical Practice. 2010;87:3.

19. Dalfra MG, Nicolucci A, Lapolla A. The effect of telemedicine on outcome and quality of life in pregnant women with diabetes. Journal of telemedicine and telecare. 2009;15(5):238-42.

20. Rauf Z, O'Brien, E., Stampalija, T., Illioniu, F.P., Lavender, T., & Alfirevic, Z. Home Labour Induction with Retrievable Prostaglandin Pessary and Continuous Telemetric Trans-Abdominal Fetal ECG Monitoring. PloS one. 2011;6(11):5.

21. O'Brien E, Rauf, Z., Alfirevic, Z., Lavender, T. Women's experiences of outpatient induction of labour with remote continuous monitoring. Midwifery. 2013;29:7.

22. Morrison J BN, Jacques D, Coleman S K & Tanziano GJ. Telemedicine: Cost-effective Management of High Risk Pregnancy. MANAG CARE. 2001;10(11):8.

23. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785-99.

24. Devlieger R. ME, Martens G., Van Mol C., Cammu H. Perinatale Activiteiten in Vlaanderen 2016. Brussel: SPE; 2017.

25. Uzan J CM, Piconne O, Asmar R, Ayoubi JM. Pre-eclampsia: pathophysiology, diagnosis, and management. VASC HEALTH RISK MANAGEMENT. 2011;7:8.

26. Duley L. The global impact of pre-eclampsia and eclampsia. Seminars in perinatology. 2009;33(3):130-7.

27. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183(1):S1-s22.

28. Tranquili GD, L. Magee, J. Roberts, BM. Sibai, W. Steyn et al. . The Classification, Diagnosis and Management of the Hypertensive Disorders of Pregnancy: A revised Statement from the ISSHP. Pregnancy hypertension. 2014;106(45):7.

29. Murphy DJ, Stirrat GM. Mortality and morbidity associated with early-onset preeclampsia. Hypertens Pregnancy. 2000;19(2):221-31.

30. Redman CW, Sargent IL. The pathogenesis of pre-eclampsia. Gynecologie, obstetrique & fertilite. 2001;29(7-8):518-22.

31. Bartsch E MK, Park AL, Ray JG; High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. Bmj. 2016;19(353):28.

32. Verdecchia P, Angeli F, Poeta F, Reboldi GP, Borgioni C, Pittavini L, et al. Validation of the A&D UA-774 (UA-767Plus) device for self-measurement of blood pressure. Blood pressure monitoring. 2004;9(4):225-9.

33. Collaboration TC. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.02011.

34. Group TCHUMSC. A multicenter randomized controlled trial monitoring: Active versus sham device of home uterine. Am J Obstet Gynecol. 1995;173(4):8.

35. Kuleva M, Salomon, L.J., Benoist, G., Ville, Y., & Dumez, Y. The Value of Daily Fetal Heart Rate Home Monitoring in Addition to Serial Ultrasound Examinations in Pregnancies Complicated by Fetal Gastroschisis. Prenatal Diagnosis. 2012;32:8.

36. Brown HL BK, Brizendine EJ, Hiett K, Ingram D, Turnquest MA, Golichowski AM, & Abernathy MP. A randomized comparison of home uterine activity monitoring in the outpatient management of women treated for preterm labor. AM J OBSTET GYNECOL. 1999;180(4):8.

37. Buysse H, De Moor, G., Van Maele, G., Baert, E., Thienpont, G., Temmerman, M. Cost-effectiveness of telemonitoring for high-risk pregnant women. International Journal of Medical Informatics. 2008;77:7.

38. Baer R, Lyell, D., Norton, M., Currier, R., & Jelliffe-Pawlowski, L. First trimester pregnancy-associated plasma protein-A and birth weight. European Journal of Obstetrics & Gynaecology and Reproductive Biology. 2016;198(2016):6.

39. Gyselaers W SV, & Grieten L. New Technologies to reduce Medicalization of Prenatal Care: a Contradiction with Realistic Perspectives. EXPERT REV MED DEVIC. 2016:10.

40. Cox DA, Ginde S, Kuhlmann RS, Earing MG. Management of the pregnant woman with Marfan syndrome complicated by ascending aorta dilation. Archives of gynecology and obstetrics. 2014;290(4):797-802.

41. Curry RA, Gelson E, Swan L, Dob D, Babu-Narayan SV, Gatzoulis MA, et al. Marfan syndrome and pregnancy: maternal and neonatal outcomes. BJOG : an international journal of obstetrics and gynaecology. 2014;121(5):610-7.

42. Gyselaers W, Tomsin, K., Staelens, A., Mesens, T., Olen, J., & Molenberghs, G. Maternal venous hemodynamics in gestational hypertension and preeclampsia. BMC pregnancy and childbirth. 2014;14(212):8.

43. Morris R, Sunesara I, Rush L, Anderson B, Blake PG, Darby M, et al. Maternal hemodynamics by thoracic impedance cardiography for normal pregnancy and the postpartum period. Obstetrics and gynecology. 2014;123(2 Pt 1):318-24.

44. Wang L. Fundamentals of Intrathoracic Impedance Monitoring in Heart Failure. AJConline. 2007;99(10A):10.

45. Tkachenko O, Shchekochikhin, D., & Schrier, R. Hormones and Hemodynamics in Pregnancy. Int J Endocrinol Metab. 2014;12(2):8.

46. Seth R, Moss, A., McNitt, S., Zareba, W., Andrews, M.L., Qi, M., Robinson, J., Goldenberg, I., Ackerman, M., Benhorin, J., Kaufman, E., Locati, E., Napolitano, C., Priori, S., Schwartz, P., Towbin, J., Vincent, M., & Zhang, L. Long QT Syndrome and Pregnancy. Journal of the American College of Cardiology. 2007;49(10):6.

47. Andreas M, Kuessel, L., Kasti, S.P., Wirth, S., Gruber, K., Rhomberg, F., Gomari-Grisar, F.A., Franz, M., Zeisler, H., & Gottsauner-Wolf, M. Bioimpedance Cardiography in Pregnancy: A Longitudinal Cohort Study on Hemodynamic Pattern and Outcome. BMC pregnancy and childbirth. 2016;16(128):9.

48. Tan EK, & Tan, E. L. Alternations in Physiology and Anatomy during Pregnancy. Best Practice & Research Clinical Obstetrics and Gynaecology. 2013;27:12.

49. Singh R. Hypertensive Disorders in Pregnancy. Clinical Queries: Nephrology. 2013;2:9.

50. Magee LA PA, Helewa M, Rey E, von Dadelszen P, On behalf of the Canadian Hypertensive Disorders of Pregnancy (HDP) Working Group. Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2014;4:41.

51. Gudnadottir TA BB, Hernadez-Diaz S, Luque - Fernandez MA, Valdimarsdottir U, & Zoega H. Body Mass Index, Smoking and Hypertensivve Disorders during Pregnancy: A Populatoin Basec Case-Control Study. PloS one. 2016;11(3):12.

52. van Baaren GJ BK, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, Oudijk MA, Bloemenkamp KWM, Scheepers HCJ, Bremer HA, Rijders RJP, van Loon AJ, Perquin DAM, Sporken JMJ, Papatsonis DNM, van Huizen ME, Vredevoogd CB, Brons JTJ, Kaplan M, van Kaam AH, Groen H, Porath M, van den Berg PP, Mol BWJ, Franssen MTM, Langenveld J for the HYPITAT-II Study Group. An Economic Analysis of Immediate Delivery and Expectant Monitoring in Women with Hypertensive Disorders of Pregnancy,

Between 34 and 37 Weeks of Gestation (HYPITAT-II). BJOG : an international journal of obstetrics and gynaecology. 2016:9.

53. Bolton CE WC, Peirce S, & Elwyn G. Insufficient evidence of benefit: a systematic review of home telemonitoring for COPD. J EVAL CLIN PRACT. 2011;17:1216.

54. Communication from the Commission to the European Parlaiment tC, the European Economic and Social Committee and the Committee of the Regions. eHealth Action Plan 2012 - 2020 - Innovative Healthcare for the 21st Century. Brussels: European Commission; 2012.

55. Bramham K PB, & Chappell LC. Chronic Hypertension and Pregnancy Outcome: Systematic Review and Meta-analysis. Bmj. 2014;348:13.

56. Y B. No Hypertensive Disorder of Pregnancy; No Preeclampsia-eclampsia; No Gestational Hypertension; No Hellp Syndrome. Vascular Disorder of Pregnancy Speaks for All. ETHIOP J HEALTH SCI. 2016;26(2):10.

57. Abalos E DL, & Steyn DW. Antihypertensive Drug Therapy for Mild to Moderate Hypertension during Pregnancy (Review). The Cochrane database of systematic reviews. 2014(2):200.

58. ML C. Preeclampsia: Reflections on How to Counsel about Preventing Recurrence. J OBSTES GYNAECOL CAN. 2015;37(10):7.

59. Klocek M CD. Hypertension during Pregnancy - How to manage Effectiverly? PRZEGI LEK. 2015;72(4):4.

60. Jiang N LQ, Liu L, Yang WW, & Zeng Y. The Effect of Calcium Channel Blokkers on Prevention of Preeclampsia in Pregnant Women with Chronic Hypertension. CLIN EXP OBSTET GYNECOL. 2015;42(1):3.

61. L D. Pre-eclampsia, Eclampsia, and Hypertension. Clinical Evidence. 2011;02(1402):56.

62. Zakiyah N PM, Baker PN, & van Asselt ADI. Pre-eclampsia Diagnosis and Treatment Options: A Review of Published Economic Assessments. PHARMACOECONOMICS. 2015;33:14.

63. E G. New Approaches for Managing Preeclampsia: Clues from Clinical and Basic Research. Clinical therapeutics. 2014;36(12):12.

64. Johanson R NM, & Macfarlane A. Has the Medicalisation of Childbirth gone too far? Bmj. 2002;324:4.

65. Christiaens W VDVS, & Bracke P. Pregnant Women's Fear of Childbirth in Midwife- and Obstetrician-led care in Belgium and the Nederlands: test of the Medicalization Hypothesis. Women Health. 2011;51(3):20.

66. Mobarakabadi SS NK, & Tabatabaie MG. Ambivalence Towards Childbirth in a Medicalized Context: A Qualitative Inquiry Among Iranian Mothers. Iranian Red Crescent medical journal. 2015;17(3):6.

67. SC K. A Gender Perspective on Medicalized Childbirth. HU LI ZA ZHI. 2015;62(1).

68. DC P. "We wanted a Birth Experience, not a Medical Experience": exploring Canadian Women's use of Midwifery. HEALTH CARE WOMEN INT. 2008;29(8):22.

69. JC S. The Medicalization of Birth and Midwifery as Resistance. HEALTH CARE WOMEN INT. 2013;34(6).

70. Wallis AB TE, Saftlas AF, & Sibai BM. Prenatal education is an opportunity for improved outcomes in hypertensive disorders of pregnancy: results form an Internet-based survey. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26(16):3.

71. Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. Acta obstetricia et gynecologica Scandinavica. 2017.

72. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy hypertension. 2014;4(2):97-104.

73. Lanssens D, Vandenberk, T., Smeets, CJ., De Cannière, H., Molenberghs, G., Van Moerbeke, A., van den Hoogen, A., Roibjns, T., Vonck, S., Staelens, A., Storms, V., Thijs, IM., Grieten, L., & Gyselaers, W. Remote Monitoring of Hypertension Diseases in Pregnancy: a Pilot Study. JMIR Mhealth Uhealth. 2017;5(3):10.

74. Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. The Cochrane database of systematic reviews. 2013(5):Cd007752.

75. do Prado AD, Piovesan DM, Staub HL, Horta BL. Association of anticardiolipin antibodies with preeclampsia: a systematic review and meta-analysis. Obstetrics and gynecology. 2010;116(6):1433-43.

76. Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clinical journal of the American Society of Nephrology : CJASN. 2010;5(11):2060-8.

77. Marko KI, Krapf JM. Testing the Feasibility of Remote Patient Monitoring in Prenatal Care Using a Mobile App and Connected Devices: A Prospective Observational Trial. 2016;5(4):e200.

78. Wijsman LW, Richard E. Evaluation of the Use of Home Blood Pressure Measurement Using Mobile Phone-Assisted Technology: The iVitality Proof-of-Principle Study. 2016;4(2):e67.

79. Milani RV, Lavie CJ, Bober RM, Milani AR, Ventura HO. Improving Hypertension Control and Patient Engagement Using Digital Tools. The American journal of medicine. 2017;130(1):14-20.

80. Li WW, Lai WS. [The Use of Telemedicine Interventions to Improve Hypertension Management Among Racial Ethnic Minorities: A Systematic Review]. Hu Li Za Zhi. 2016;63(4):25-34.

81. Omboni S, Caserini M, Coronetti C. Telemedicine and M-Health in Hypertension Management: Technologies, Applications and Clinical Evidence. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension. 2016;23(3):187-96.

82. Goldberg EM, Levy PD. New Approaches to Evaluating and Monitoring Blood Pressure. Current hypertension reports. 2016;18(6):49.

83. Evangelia Kintiraki SP, George Kotronis, Dimitrios G. Goulis, & Vasilios Kotsis. Pregnancy-induced hypertension. Hormones. 2015;14(2):12.

84. Abalos E, Duley, L., Steyn, D.W., & Henderson - Smart, D.J. Antihypertensive Drug Therapy for Mild to Moderate Hypertension during Pregnancy. The Cochrane database of systematic reviews. 2007;2001(2).

85. Forno E, Young, O.M., Kumar, R., Simhan, H., & Celedon, J.C. Maternal Obesity in Pregnancy, Gestational Weight Gain, and Risk of Childhood Asthma. Pediatrics. 2014;134(2):12.

86. Nerenberg K, Daskalopoulou, S. S., & Dasgupta, K. Gestational Diabetes and Hypertensive Disorders of Pregnancy as Vascular Risk Signals: An Overview and Grading of the Evidence. Canadian Journal of Cardiology. 2014;30(7):9.

87. Withworth M, & Dowswell, T. Routine Pre-Pregnancy Health Promotion for Improving Pregnancy Outcomes. The Cochrane database of systematic reviews. 2014(4):38.

88. Saner H, & van der Velde, E. eHealth in Cardiovascular Medicine: A Clinical Update. European Journal of Preventive Cardiology. 2016;23(2S):8.

89. COCIR. COCIR Telemedicine Toolkit for a better Deployment and Use of Telehealth. 2011:37.

90. Lanssens D VT, Smeets C, De Cannière H, Vonck S, Claessens J, Heyrman Y, Vandijck D, Storms V, Thijs I, Grieten L, Gyselaers W. Cost- analysis of prenatal remote monitoring of women with gestational hypertensive diseases. 2018.

91. Lanssens D, Vonck S, Storms V, Thijs IM, Grieten L, Gyselaers W. The impact of a remote monitoring program on the prenatal follow-up of women with gestational hypertensive disorders. Journal of medical Internet research. 2018;223:72-8.

92. Lanssens D, Van Moerbeke, A., van den Hoogen, A., Geusens, N., Grieten, L., & Gyselaers, W. E4. Remote Prenatal Follow-up of Patients at Risk for Gestational Hypertensive Disorders: Maternal and Neonatal Outcomes. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2016;29(sup2)(24):1.

93. Health VHCM. Mhealth als Sleutel tot Kwaliteit en Betaalbaarheid van Zorg. In: Ondernemingen VNv, editor. p. 44.

94. Devlieger R. ME, Martens G., Van Mol C., Cammu H. Perinatale activiteiten in Vlaanderen 2015. Brussel: SPE; 2016.

95. RIZIV. Rijksinstituut voor ziekte- en invaliditeitsverzekering Brussel2017.

96. Malehi A, Pourmotahari, F., & Angali KA. Statistical Models for the Analysis of Skewed Healthcare Cost Data: a simulation study. Health Economics Review. 2015;5(11):16.

97. Korvenranta E, Lehtonen, L., Rautave, L., Häkkinen, U., Andersson, S., Gissler, M., Hallman, M., Leipälä, J., Peltola, M., Tammela, O., & Linna, M. Impact of very preterm birth on health care costs at five years of age. Pediatrics. 2010;125(5).

98. Petrou S, & Khan, K. Economic costs associated with moderate and late preterm birth: primary and secondary evidence. Semin Fetal Neonatal Med. 2012;17(3):9.

99. Petrou S, Eddama, O., & Mangham, L. A structured review of the recent literature on the economic consequences of preterm birth. Arch Dis Child Fetal Neonatal Ed. 2011;96(3):8.

100. Cavallo M, Gugiatti, A., Fattore, G., Gerzeli, S., Barbieri, D., & Zanini, R. Cost of care and social consequences of very low birth weight infants without premature-related morbidities in Italy. Ital J Pediatr. 2015;41(59).

101. Cuevas K, Silver, DR., Brooten, D., Youngblut, JM., & Bobo, CM. The cost of prematurity: hospital charges at birth and frequency of rehospitalizations and acute care visits over the first year of life: a comparison by gestational age and birth weight. Am J Nurs. 2005;105(7):9.

102. Hermida DEARC. Ambulatory Blood Pressure Monitoring for the Early Identification of Hypertension in Pregnancy. Chronobiology International 2012;30(1 - 2):26.

103. Garovic AGKVD. The Management of Hypertension in Pregnancy. Adv Chronic Kidney Dis. 2013;20(3):10.

104. Ganapathy R GA, Castleman JS. Remote monitoring of blood pressure to reduce the risk of preeclampsia related complications with an innovative use of mobile technology. Pregnancy Hypertens. 2016;6(4):12.

105. Rhoads SJ, Serrano CI, Lynch CE, Ounpraseuth ST, Gauss CH, Payakachat N, et al. Exploring Implementation of m-Health Monitoring in Postpartum Women with Hypertension. Telemedicine journal and e-health : the official journal of the American Telemedicine Association. 2017.

106. Rosner BI GM, Anderson WN. Effectiveness of an Automated Digital Remote Guidance and Telemonitoring Platform on Costs, Readmissions, and Complications After Hip and Knee Arthroplasties. J Arthroplasty. 2017;pii: S0883-5403(17):9.

107. Clarke M FJ, Connolly N, Sharma U, Jones R. Evaluation of the National Health Service (NHS) Direct Pilot Telehealth Program: Cost-Effectiveness Analysis. Telemedicine journal and e-health : the official journal of the American Telemedicine Association. 2017.

108. Duffy JM, van 't Hooft J, Gale C, Brown M, Grobman W, Fitzpatrick R, et al. A protocol for developing, disseminating, and implementing a core outcome set for pre-eclampsia. Pregnancy hypertension. 2016;6(4):274-8.

109. Gyselaers W, Spaanderman M. Assessment of venous hemodynamics and volume homeostasis during pregnancy: recommendations of the International Working Group on Maternal Hemodynamics. Ultrasound Obstet Gynecol. 2017.

110. Imershein AW. TC, Wells JG., Pearman A. Covering the Costs of Care in Neonatal Intensive Care Units. Pediatrics. 1992;89(1):8.

111. Pourat N. MA, Jones JM., Gregory KD., Korst L., Kominski GF.,. Costs of Gestational Hypertensive Disorders in California: Hypertension, Preeclampsia, and Eclampsia. . Los Angles: UCLA Center for Health Policy Research; 2013.

112. Staelens AS, Vonck S, Tomsin K, Gyselaers W. Clinical inference of maternal renal venous Doppler ultrasonography. Ultrasound Obstet Gynecol. 2017;49(1):155-6.

113. Staelens AS, Vonck S, Molenberghs G, Malbrain ML, Gyselaers W. Maternal body fluid composition in uncomplicated pregnancies and preeclampsia: a bioelectrical impedance analysis. European journal of obstetrics, gynecology, and reproductive biology. 2016;204:69-73.

114. Gyselaers W, Staelens, A., Mesens, T., Tomsin, K., Oben, J., Vonck, S., Verresen, L., & Molenberghs, G. Maternal venous Doppler characteristics are abnormal in pre-

eclamspia, but not in gestational hypertension. Ultrasound Obstet Gynecol. 2015;45(6):421.

115. Tomsin K VA, Mesens T, Gyselaers W. Non-invasive cardiovascular profiling using combined electrocardiogram-Doppler ultrasonography and impedance cardiography: an experimental approach. . Clin Exp Pharmacol Physiol 2013;40:4.

116. Khalil A, Garcia-Mandujano R, Maiz N, Elkhouli M, Nicolaides KH. Longitudinal changes in uterine artery Doppler and blood pressure and risk of pre-eclampsia. Ultrasound Obstet Gynecol. 2014;43(5):541-7.

117. Staelens A, Tomsin K, Grieten L, Oben J, Mesens T, Spaanderman M, et al. Non-invasive assessment of gestational hemodynamics: benefits and limitations of impedance cardiography versus other techniques. Expert Rev Med Devices. 2013;10(6):765-79.

118. Tomsin K, Mesens T, Molenberghs G, Gyselaers W. Impedance cardiography in uncomplicated pregnancy and pre-eclampsia: a reliability study. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2012;32(7):630-4.

119. Vinayagam D, Patey O, Thilaganathan B, Khalil A. Cardiac output assessment in pregnancy: comparison of two automated monitors with echocardiography. Ultrasound Obstet Gynecol. 2017;49(1):32-8.

120. Hirshberg A, Downes K, Srinivas S. Comparing standard office-based follow-up with text-based remote monitoring in the management of postpartum hypertension: a randomised clinical trial. BMJ quality & safety. 2018.

121. Lanssens D VT, Lodewijckx J, Peeters T, Thijs IM, Grieten L, Gyselaers W. The perceptions of midwives, obstetricians, and recently delivered mothers to remote monitoring for prenatal care. Journal of Maternal- fetal & neonatal medicine. 2018;*under review*.

122. D L. Emerging mHealth: Paths for growth. New York: Pricewaterhouse Coopers, 2012.

123. D W. How Mobile Devices are Transforming Healthcare. Issues in Technology Innovation. 2012;18:14.

124. Perry H, Sheehan E, Thilaganathan B, Khalil A. Home blood-pressure monitoring in a hypertensive pregnant population. 2018;51(4):524-30.

125. Xydopoulos G, Perry H. Home blood-pressure monitoring in a hypertensive pregnant population: cost minimisation study. 2018.

126. Mackillop L, Hirst JE. Comparing the Efficacy of a Mobile Phone-Based Blood Glucose Management System With Standard Clinic Care in Women With Gestational Diabetes: Randomized Controlled Trial. 2018;6(3):e71.

127. Altini M, Rossetti, E., Rooijakkers, M., Penders, J., Lanssens, D., Grieten, L., & Gyselaers, W. Combining electrohysterography and heart rate data to detect labour. Biomedical & Health Informatics; Orlando, FL, USA2017.

128. Altini M, Mullan P, Rooijakkers M, Gradl S, Penders J, Geusens N, et al. Detection of fetal kicks using body-worn accelerometers during pregnancy: Trade-offs between sensors number and positioning. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference. 2016;2016:5319-22.

129. Hurkmans E, Matthys C. Face-to-Face Versus Mobile Versus Blended Weight Loss Program: Randomized Clinical Trial. 2018;6(1):e14.

130. Bogaerts A, Ameye L, Bijlholt M, Amuli K, Heynickx D, Devlieger R. INTER-ACT: prevention of pregnancy complications through an e-health driven interpregnancy lifestyle intervention - study protocol of a multicentre randomised controlled trial. 2017;17(1):154.

131. Lanssens D, Vonck, S., Thijs, I.M., Grieten, L., Gyselaers, W. . Nieuwe opportuniteiten en uitdagingen voor de vroedvrouw in een beleid met telemonitoring van

zwangere vrouwen met gestationele hypertensie aandoeningen. Tijdschrift voor Vroedvrouwen. 2018;24(1):4.

132. Dekkers N, Goemaes, R., Neirinckx, J., Seuntjens, L. & Smets, K. Zwangerschapsbegeleiding 2015. Available from: https://www.domusmedica.be/varia/docman-alles/publiek/praktijkdocumenten/richtlijnen/731-zwangerschapsbegeleiding-1/file.html.

133. Vroedvrouwen FRvd. Het beroeps- en competentieprofiel van de Belgische vroedvrouw. In: Federale Overheidsdienst Volksgezondheid VvdVeL, editor. Brussel2016. p. 24.

134. Zeitlin J ML, Prunet C, Macfarlane A, Hindori-Mohangoo AD, Gissler M, Szamotulska K, van der Pal K, Bolumar F, Andersen AM, Ólafsdóttir HS, Zhang WH, Blondel B, Alexander S; Euro-Peristat Scientific Committee. Socioeconomic inequalities in stillbirth rates in Europe: measuring the gap using routine data from the Euro-Peristat Project. BMC pregnancy and childbirth. 2016;19(16):19.

135. Linard M, Blondel B, Estellat C, Deneux-Tharaux C, Luton D, Oury JF, et al. Association between inadequate antenatal care utilisation and severe perinatal and maternal morbidity: an analysis in the PreCARE cohort. BJOG : an international journal of obstetrics and gynaecology. 2018;125(5):587-95.

136. Linard M, Deneux-Tharaux C, Azria E. Authors' reply re: Association between inadequate antenatal care utilisation and severe perinatal and maternal morbidity: an analysis in the PreCARE cohort. BJOG : an international journal of obstetrics and gynaecology. 2018;125(5):626.

137. Pandey S, Tyagi R, Tyagi I. Re: Association between inadequate antenatal care utilisation and severe perinatal and maternal morbidity: an analysis in the PreCARE cohort: Antenatal care utilisation and severe perinatal/maternal morbidity in PreCARE cohort. BJOG : an international journal of obstetrics and gynaecology. 2018;125(5):625.

138. Gyselaers W JP, Ahmadzai N, Ansari MT, Carville S, Dworzynski K, Gaudet L, Glen J, Jones K, Miller P, Tetzlaff JM, Alexander S, Allegaert K, Beeckman K, Ceysens G, Christiane Y, De Ronne N, De Thysebaert B, Dekker N, Denys A, Eeckeleers P, Hernandez A, Mathieu E, Seuntjens L, Verleye L, Stordeur S. Welke onderzoeken zijn aanbevolen bij een zwangerschap? 2015.

CURRICULUM VITAE

LANSSENS DORIEN PAULA JEANNE

Date of birth:	15 January 1991 (Hasselt Belgium)
Nationality:	Belgian
Address:	Laar 65E
	2440 Geel
E-mail	dorienlanssens@hotmail.com

EDUCATION

2012 – 2014	Master in Nursing and Midwifery, Obstetrics Specialization	KULeuven Leuven, Belgium
2009 – 2012	Professional bachelor in Midwifery	Vroedkunde Limburg Hasselt, Belgium
2003 – 2012	Secondary education - Human sciences	Kindsheid Jesu Hasselt, Belgium

CERTIFICATES AND TRAINING

2017	Good Clinical Practice training	Formalis Genk, Belgium
2017	Economical evaluations of medical interventions	ME-TA Sint-Martens-Latem, Belgium
2015	Applied pharmacology for midwives	PXL Hasselt, Belgium
2015	Good clinical Practice for Investigator Site Teams & Ethics Committees	Ziekenhuis Oost Limburg Genk, Belgium
2014	Cochrane Systematic Reviews: Training workshop (3 days)	KULeuven Leuven, Belgium
2012	STAN certification	Ziekenhuis Oost Limburg Genk, Belgium
2012	VLOV price: Midwife of the year	Vroedkunde Limburg Hasselt, Belgium

PROFESSIONAL EXPERIENCE

2014 – 2018	PhD research	Hasselt University Diepenbeek, Belgium
2017 - …	Member of 'Platform Wetenschap en Praktijk'	Platform Wetenschap en Praktijk Brussels, Belgium
2016 - …	Member of the Working Group 'Digital Healthcare' of 'Vlaamse Beroepsorganisatie van Vroedvrouwen'	Vlaamse Beroepsorganisatie van Vroedvrouwen Antwerp, Belgium
2014 - …	Member of the Working Group 'Research' of 'Vlaamse Beroepsorganisatie van Vroedvrouwen'	Vlaamse Beroepsorganisatie van Vroedvrouwen Antwerp, Belgium
2014 - …	Co - organizer of Limburg STAN evenings	Vroedkunde Limburg & Hasselt University Diepenbeek, Belgium
2013 - 2014	Nurse in the first line care Independent in a secondary occupation	Vera Colemont Hasselt, Belgium
2013	Maternity of Wit Gele Kruis Limburg Student Job	Wit Gele Kruis Genk, Belgium
2012	Maternity of Sint Trudo Student Job	Sint Trudo Sint Truiden, Belgium
2012 – 2013	Nurse/midwife Student job	Sint Trudo Sint Truiden, Belgium
2011	Internship abroad	Dakar & 'Mbour

	Delivery room, maternity ward & first line care	Senegal
2011	Maternity Student job	Ziekenhuis Oost Limburg Genk, Belgium
2009 – 2012	Internships Several hospitals during the three-year degree 'Bachelor of Midwifery'	Vroedkunde Limburg Hasselt, Belgium

SCIENTIFIC ACHIEVEMENTS

PAPERS PUBLISHED IN INTERNATIONAL PEER-REVIEWED JOURNALS

1. **Lanssens D**, Vandenberk T, Smeets CJ, De Cannière H, Vonck S, Claessens J, Heyrman Y, Vandijck D, Storms V, Thijs IM, Grieten L, Gyselaers W.

Prenatal Remote Monitoring of Women with Gestational Hypertensive Diseases: Cost Analysis.

J Med Internet Res. 2018; 20(3): e102.

2. Vandenberk T, Stans J, Mortelmans C, Van Haelst R, Van Schelvergem G, Pelckmans C, Smeets CJ, **Lanssens D**, De Cannière H, Storms V, Thijs IM, Vaes B, Vandervoort PM.

Metadata Correction: Clinical Validation of Heart Rate Apps: Mixed-Methods Evaluation Study.

JMIR Mhealth Uhealth. 2018; 6(3): e19.

3. **Lanssens D**, Vonck S, Storms V, Thijs IM, Grieten L, Gyselaers W.

The impact of a remote monitoring program on the prenatal follow-up of women with gestational hypertensive disorders.

Eur J Obstet Gynecol Reprod Biol. 2018; 223: 72 – 78.

4. Smeets CJ, Vranken J, Van der Auwera J, Verbrugge FH, Mullens W, Dupont M, Grieten L, De Cannière H, **Lanssens D**, Vandenberk T, Storms V, Thijs IM, Vandervoort PM.

Bioimpedance Alerts from Cardiovascular Implantable Electronic Devices: Observational Study of Diagnostic Relevance and Clinical Outcomes.

J Med Internet Res. 2017; 19(11): e393.

5. **Lanssens D,** Vandenberk T, Thijs IM, Grieten L, Gyselaers W.

Effectiveness of Telemonitoring in Obstetrics: Scoping review.

J Med Internet Res. 2017; 19(9): e327.

6. Vandenberk T, Stans J, Mortelmans C, van Haelst R, Van Schelvergem G, Pelckmans C, Smeets CJ, **Lanssens D**, De Cannière H, Storms V, Thijs IM, Vaes B, Vandervoort PM.

Clinical Validation of Heart Rate Apps: Mixed-Methods Evaluation Study.

JMIR Mhealth Uhealth. 2017; 5(8): e129.

7. **Lanssens D**, Vandenberk T, Smeets CJ, De Cannière H, Molenberghs G, Van Moerbeke A, van den Hoogen A, Robijns T, Vonck S, Staelens A, Storms V, Thijs IM, Grieten L, Gyselaers W.

Remote Monitroing of Hypertension Diseases in Pregnancy: A Pilot Study.

JMIR Mhealth Uhealth. 2017; 5(3): e25.

8. Smeets CJ*, **Lanssens D*,** Gyselaers W, Bertrand PB, Grieten L, Vandervoort P.

Detection of subclinical transient fluid accumulation during pregnancy in a patient with an implantable cardioverter defibrillator and OptiVol® fluid monitoring algorithm.

Int J Cardiol. 2016; 214: 163-5.

** Shared first authorship*

9. Smeets CJP, Verbrugge FH, Vranken J, Van der Auwera J, Mullens W, Dupont M, Grieten L, De Cannière H, **Lanssens D,** Vandenberk T, Storms V, Thijs IM, Vandervoort P.

Protocol – driven remote monitroing of cardiac resynchronization therapy as part of a heart failure disease management strategy.

Acta Cardiol. 2017: 1 – 10.

10. Bogaerts A, **Lanssens D**, Devlieger R.

Weightloss in Obese Pregnant Women and Pregnancy Outcomes: A Systematic Review.

Reproductive Sciences. 2014: 21(3) Suppl S: 148A – 149A.

PAPERS AT INTERNATIONAL CONFERENCES, PUBLISHED IN FULL IN PROCEEDINGS

11. Vonck S, Oben J, Staelens A, **Lanssens D,** Tomsin K, Gyselaers W.

G5. 12-week cardiovascular profiles differ between patients with essential hypertension, gestational hypertension, late preeclampsia and intra-uterine growth retardation.

The Journal of Maternal-Fetal & Neonatal Medicine. 2016; 29, sup. 2: 36-36.

12. **Lanssens D,** Van Moerbeke A, Van Den Hoogen A, Geusens N, Grieten L, Gyselaers W. *E4. Remote prenatal follow-up of patients at risk for gestational hypertensive disorders: maternal and neonatal outcomes.*

The Journal of Maternal-Fetal & Neonatal Medicine. 2016: 29, sup. 2: 24 – 24.

13. Vonck S, Oben J, Staelens AS, **Lanssens D,** Tomsin K, Gyselaers W.

B4. Normal and abnormal blood pressures in early pregnancy: are we using the right cut off values?

The Journal of Maternal-Fetal & Neonatal Medicine. 2016: 29, sup. 2: 9 – 9.

14. Altini M, Rossetti E, Rooijeakkers M, Penders J, **Lanssens D**, Grieten L, Gyselaers W. *Combining electrohysterography and heart rate data to detect labour.*

Biomedical & Health Informatics (BHI). 2017.

15. Altini M, Rossetti E, Rooijeakkers M, Penders J, **Lanssens D**, Grieten L, Gyselaers W. *Variable-length accelerometer features and electromyography to improve accuracy of fetal*

kicks detection during pregnancy using a single wearable device.

Biomedical & Health Informatics (BHI). 2017.

PAPERS IN REVIEW IN INTERNATIONAL PEER-REVIEWED JOURNALS

16. **Lanssens D**, Vonck S, Vandenberk T, Schraepen C, Storms V, Thijs IM, Grieten L, Gyselaers W.

A prenatal remote monitoring program in pregnancies complicated with gestational hypertensive disorders: what are the contributors to the cost savings?

17. **Lanssens D*,** Vandenberk T*, Lodewijckx J, Peeters T, Thijs IM, Grieten L, Gyselaers W.

The perception of midwives, gynecologists and recently delivered women to remote monitoring for prenatal care.

**Shared first authorship.*

18. Vonck S, Staelens AS, **Lanssens D,** Tomsin K, Oben J, Bruckers L, Gyselaers W.

Uterine flow promoting peripheral resistance in normotensive pregnancies with healthy neonates small for gestational age.

19. Vonck S, Staelens AS, **Lanssens D,** Tomsin K, Oben J, Bruckers L, Gyselaers W.

Obesity in pregnancy causes a volume overload in third trimester.

20. Gyselaers W, Vonck S, Staelens AS, **Lanssens D**, Tomsin K, Oben J, Bruckers L.

First trimester maternal cardiovascular dysfunctions characterize gestational hypertensive diseases.

21. Vonck S, Staelens AS, **Lanssens D**, Tomsin K, Oben J, Bruckers L, Gyselaers W.

Relevance of maternal hemodynamics assessment in phenotype-specific screening for gestational hypertensive diseases.

22. **Lanssens D***, Smeets JP C, Vandervoort P, Grieten L, Gyselaers W.

Intrathoracic fluid changes form preconception to postpartum as measured by bio-impedance monitoring.

OTHER PUBLICATIONS

23. **Lanssens D,** Vandenberk T, Lodewijckx J, Peeters T, Thijs iM, Grieten L, Gyselaers W.

De perceptie van pas bevallen moeders, vroedvrouwen en gynaecologen over een prenatale opvolging aangevuld met telemonitoring.

Tijdschrift voor Vroedvrouwen. 2017; 23(1): 19-28.

24. Vrielinck C, **Lanssens D,** Goossens J, Tency I.

Complementaire en alternatieve therapieën (CAT). Advies vanuit de werkgroep Wetenschappelijk Onderzoek van de VBOV vzw.

Tijdschrift voor Vroedvrouwen. 2017; 23(3): 144 – 155.

25. **Lanssens D,** Vonck S, Thijs IM, Grieten L, Gyselaers W.

Nieuwe opportuniteiten en uitdagingen voor de vroedvrouw in een beleid met telemonitoring van zwangere vrouwen met gestationele hypertensie aandoeningen.

Tijdschrift voor Vroedvrouwen. 2018; 24(1): 28 -31.

26. Bollen I, Broekx L, Vonck S, Staelens A, **Lanssens D,** Gyselaers W.

Maternale Cardiovasculare Veranderingen in de Vroege Zwangerschap.

Tijdschrift voor Geneeskunde. 2015; 71(22): 1473 – 1482.

ABSTRACTS AT (INTER)NATIONAL CONFERENCES

1. **Lanssens D,** Van Moerbeke A, van den Hoogen A, Geusens N, Grieten L, Gyselaers W.

'Remote prenatal follow-up of patients at risk for gestational hypertensive disorders'

XXV European Congress Perinatal Medicine.

Location: Maastricht, The Netherlands. Date: 16 June, 2016.

2. **Lanssens D,** Vandenberk T, Lodewijckx J, Peeters T, Grieten L, Gyselaers W.
'Telemonitoring bij zwangeren met GHD'
VBOV Trefdag.
Location: Ghent, Belgium. Date: 20 October, 2016.

3. **Lanssens D,** Vandenberk T, Lodewijckx T, Peeters T, Grieten L, Gyselaers W.
'The perception of an implemented remote monitoring follow-up program by patients, midwives and obstetricians'
Third European Congress on eCardiology and eHealth.
Location: Berlin, Germany. Date: 26 – 28 October 2016.

ORAL PRESENTATIONS

1. **Lanssens D**, Gyselaers W.

'PREMOM: remote monitoring in high risk pregnancies'

Maternal Hemodynamics Workshop.

Location: Maastricht, The Netherlands. Date: 11 December, 2015.

2. **Lanssens D,** Van Moerbeke A, van den Hoogen A, Geusens N, Grieten L, Gyselaers W.

'Remote prenatal follow-up of patients at risk for gestational hypertensive disorders: maternal and neonatal outcomes'

2nd International Congress on Maternal Hemodynamics

Location: Rome, Italy. Date: 13 May, 2016.

3. Gyselaers W, **Lanssens D**, Thijs IM, Grieten L

'PREMOM: prenatal remote monitoring of mothers at risk'

Actiepunt 19: Mobile Health

Location: Brussels, Belgium. Date: 10 November, 2016.

4. **Lanssens D,** Van Moerbeke A, Grieten L, Storms V, Thijs IM, Gyselaers W.

'Effectiveness of a remote monitoring program for pregnant women at risk for gestational hypertensive disorders'

CARE4: International Scientific Nursing and Midwifery Congress

Location: Antwerp, Belgium. Date: 07 February 2017.

5. **Lanssens D,** Van Moerbeke A, Grieten L, Storms E, Thijs IM, Gyselaers W.

'Effectiveness of a remote monitoring program for pregnant women at risk for gestational hypertensive disorders'

Med-E-Tel.

Location: Luxembourg, Luxembourg. Date: 06 April, 2017.

6. **Lanssens D,** Gyselaers W.

Remote prenatal care: The PREMOM project in Limburg, Belgium'

fTales: Mobile Health Congress

Location: Genk, Belgium. Date: 27 April, 2017.

7. **Lanssens D**, Gyselaers W.

'Remote monitoring in high risk pregnancies'

Internationele week van de vroedkunde.

Location: Ghent, Belgium. Date: 11 October, 2017.

8. Gyselaers W, **Lanssens D**, Thijs IM, Grieten L

'AP19: Mobile Health Pilootprojecten – P16/72 Premom'

Actiepunt 19: Mobile Health

Location: Brussels, Belgium. Date: 13 October, 2017.

9. **Lanssens D,** Gyselaers W

'Health and health care benefits of remote monitoring for GHD: the Belgian Project PREMOM'

Maternal Hemodynamics Workshop.

Location: London, UK. Date: 24 November, 2017.

10. **Lanssens D,** Gyselaers W.

'PreMoM: The Belgian project on remote monitoring for women at risk for GHD'

3nd International Congress on Maternal Hemodynamics

Location: Cambridge, UK. Date: 13 April, 2018.

11. **Lanssens D**, Gyselaers W.

'Intrathoracic fluid changes from preconception to postpartum as measured by bioimpedance monitoring'

45th Annual Meeting of the Fetal and Neonatal Physiological Society 2018

Location: Kerkrade, The Netherlands. Date: 25 June, 2018.

AWARDS

2016	Nominated for the Agoria eHealth Award – Agoria eHealth Awards 2016, Brussels, Belgium
2016	Mustella Award – Foundation Mustella, Leuven, Belgium
2016	VBOV Prijs Bachelorproef 2016, 2nd place – VBOV, Antwerp, Belgium
2017	Best oral presentation – CARE4 Congress, Antwerp, Belgium
2018	VBOV Prijs Bachelorproef 2018 – VBOV, Antwerp, Belgium

DANKWOORD

We should be taught not to wait for inspiration to start a thing.

Action always generates inspiration. Inspiration seldom generates action.

~ Frank Tibolt ~

Zoals bovenstaande quote zo mooi beschrijft, is dit een doctoraat geweest van veel (durven) doen en kijken welke gevolgen hieruit voortkwamen, om hier vervolgens weer uit te leren. We begonnen met een volledig wit blad papier en hadden de mogelijkheid om ons eigen telemonitoringsprogramma uit te werken. Dit doctoraat is dan ook tot stand gekomen na vier jaar intensief werk, waarbij ik veel steun en hulp kreeg van familie, vrienden en collega's. En ik heb niet enkel veel geleerd op professioneel vlak, ook op persoonlijk vlak was dit een enorme ontdekkingsreis voor mij. Een reis waarin ik mezelf regelmatig ben tegen gekomen, af en toe de deksel op mijn neus kreeg, maar (naar mijn aanvoelen) ook veel in gegroeid ben. Graag zou ik de gelegenheid willen grijpen om iedereen die aan mijn zijde stond oprecht te bedanken op de volgende pagina's. Ik weet dat er enorm veel mensen hebben bijgedragen aan dit doctoraat, en het risico om iemand te vergeten bij naam te noemen is groot. Gelieve mij dit te vergeven, en het te wijten aan de zwangerschapsdementie ☺.

First of all, I would like to thank **the members jury**. Not only for their time and extreme patience to read this thesis, but also for their intellectual contributions to my development as a scientist. Ook dank aan mijn beide co-promotoren: **Prof. dr. Lars Grieten** en **dr. ir. Inge Thijs**. Lars, jij had mij in het begin van mijn doctoraat opgevangen en op weg gezet. Jouw enthousiasme werkte aanstekelijk, en je moedigde ons steeds aan om het beste van onszelf te laten zien. Inge, zoals Lars dit doctoraat zo goed heeft helpen

opstarten, zo goed heb jij dit helpen beëindigen. Bedankt voor je steun en hulp bij zowat alles. Het behalen van het FWO-TBM hebben we voor een groot deel aan u te danken. Enorm bedankt hiervoor.

De **Universiteit Hasselt** en het **Limburg Clinical Research Program** verdienen een bijzondere vermelding voor hun financiële steun van dit doctoraatsonderzoek, en het beschikbaar maken van de faciliteiten om dit onderzoek uit te voeren. Hiervoor mijn oprechte dank. Ook wil ik graag **Prof. De Schepper** als rector aan de Universiteit Hasselt bedanken, evenals **Prof. Stinissen**, decaan van de faculteit Geneeskunde en Levenswetenschappen en voorzitter van het Limburg Clinical Research Program, voor de mogelijkheid om mijn doctoraatsonderzoek aan de UHasselt te realiseren. Ook graag een speciaal woord van dank aan **Marleen Missotten**, **Helene Piccard** en **Véronique Pousset** om alle administratie die bij mijn doctoraat kwam kijken in goede banen te leiden.

Prof. Dr. Gyselaers, u wil ik voor zoveel bedanken dat de plaats die hiervoor voorzien is te klein lijkt. Zonder uw onuitputbaar enthousiasme, uw continue aanmoedigingen om 'out of the box' te denken, uw aansporingen om ideeën uit te proberen en oplossingen te zoeken wanneer de probeersels niet lukten, was dit doctoraat niet geweest wat het nu was. Bedankt voor alles: voor het geloof in het project, het geloof in mij, voor de deur die continu opstond voor (soms ook persoonlijke) zorgen, het op sleeptouw nemen op internationale congressen, en zoveel meer. U bent niet enkel als 'baas' iemand om naar op te kijken, maar ook als persoon. Ik kijk uit naar de volgende vier jaar, waarin we PREMOM gaan uitrollen over Vlaanderen.

Vervolgens wil ik graag alle andere **gynaecologen van het Ziekenhuis Oost-Limburg**, en in het bijzonder Dr. Van Holsbeke, Dr. Mesens en Dr. Thaens, bedanken voor hun medewerking aan het project en hun constructieve feedback die wij vaak kregen

doorheen het proces. Bedankt om de opvolging van de hoogrisico zwangeren ook een beetje in mijn handen te leggen, en mij te vertrouwen met het toezicht op deze patiënten. Bijkomend de **participerende ziekenhuizen van het LimPrOn project** (JESSA Ziekenhuis te Hasselt, Sint Franciskus Ziekenhuis te Heusden Zolder, Heilig Hart Ziekenhuis te Mol, Ziekenhuis Maas en Kempen te Bree, Mariaziekenhuis Noord-Limburg te Overpelt, Sint Trudo te Sint Truiden en AZ Vesalius te Tongeren): een welgemeende dankjewel voor het doorverwijzen en het toevertrouwen van de zwangeren aan onze onderzoeksgroep.

Ook een dikke merci aan **de vroedvrouwen van de MIC afdeling** van het Ziekenhuis Oost-Limburg. Ik kon steeds op jullie rekenen (ook vaak voor een leuke babbel), en hoewel het ook voor jullie vaak niet makkelijk was omdat jullie lang niet wisten welke richting we uitgingen met ons project, stonden jullie wel steeds klaar om te hierover te leren en feedback te geven. Alsook **Anja Moors**: bedankt voor de samenwerking, de vergaderingen en de hulp. En natuurlijk ook **Els Papy**, voor de Barbouffe momentjes en de gezellige babbels.

Er zijn enkele **studenten** die een woord van dank verdienen: Tiziana Robijns, Sarah De Jonge, Shana Wouters, Anne Van Moerbeke, Anne van den Hoogen, Yenthel Heyrman, Cédric Schraepen, Liesanne Gerits, Jana Nilis, Sofie Rector, Paulien Pijpops, Loubna Lamkharrat en Jade Claessens. Jullie werk heeft altijd een belangrijk deel uitgemaakt van dit groter geheel.

Vervolgens mijn **(ex-) (doctoraats)collega's**: Hélène, Christophe, Melanie, Thijs, Philippe, Julie, Joren, Lieselotte, Pauline, Petra, Ward, Rob, Cornelia, Annelies, Anneleen, Amber, Frederik, Pieter, Sharona, Dana, Elien, Özgur, Sébastien, Kristof (x2), Ingrid, Elisa, Kathleen, Hanne: dank jullie wel! Jullie zijn allemaal fantastische collega's, die de werksfeer zo aangenaam maakten. Bedankt voor alle fijne babbels, de fijne eerste

teambuilding (waarom hebben we hier zo lang mee gewacht??), het komen naar mijn dansles (tot spierverrekkingen toe), de hulp bij statistiek en zoveel meer. Een speciale dank gaat naar Thijs, Hélène, Melanie en Christophe: voor het plezier op de bureau, het elkaar helpen wanner we vast zaten met onze statistiek/methodologie/…, het bespreken van de weekendplannen, het kunnen vertrouwen van grote en kleine bekommernissen, etc. Jullie zijn fantastisch. Valerie en Inge, bedankt voor het trekken van de Mobile Health Unit. Zonder het geloof hierin stonden we niet waar we nu staan. Thijs, een kleine extra vermelding. Jij bracht vaak de kritische blik die nodig was om de kwaliteit van de studie te verbeteren, je kon eindeloos discussiëren over welke veranderingen er nodig waren aan DHARMA om de kwaliteit voldoende hoog te houden, je durfde iets anders te zeggen dan iedereen. En dit bracht diepgang (en vooruitgang). Ook wanneer iets niet werk gerelateerd was kon ik hiervoor bij je terecht. Bedankt. Ik hoop dat we elkaar in de toekomst nog eens tegen komen.

Mijn lieve collega's van de **gynaecologie researchgroep**. Anneleen, Kathleen en Jolien: bedankt om het pad voor mij te effenen. Zonder jullie werk was het LimPrOn project nooit van start kunnen gaan. Sharona, ongeveer een jaar geleden begon je aan je nieuw avontuur in Leuven, en ik mis u nog steeds bij ons in de groep. Jij was meer een vriendin dan een collega. Je wervelend enthousiasme zorgde ervoor dat je in mum van tijd meer dan 1000 zwangeren in je studie had, je deelde tips en tricks over het reilen en zeilen van een doctoraat onder de supervisie van Dr. G, en je creativiteit met afbeeldingen/presentaties/illustraties is bewonderingswaardig. De congressen in Londen en Rome waren leerrijk, er waren goede dessertjes en ik leerde je beter kennen. Bedankt voor de vele babbels en de mails. Veel plezier met jullie babytje, geniet van je gezinnetje, en tot binnenkort! Pauline, Kristof en Inge, bedankt mededoctoraatsstudentjes voor alles! We verschillen elk van karakter, maar passen goed samen als groep. Tijdens ons uitje naar Cambridge leerden we elkaar beter kennen en sindsdien lijken we ook goed op

elkaar ingespeeld. Ik kan alleen maar zeggen: doe zo verder. Pauline: bedankt je luisterend oor, je grapjes, je continue drive en motivatie en je onophoudelijke steun. Kristof: bedankt voor je humor, je hulp en je out of the box thinking. Inge: bedankt voor je relativeringsvermogen en de rust die je brengt in de groep. En tot slot Lieve: bedankt voor de hulp de laatste maanden. Dit is van onmiskenbare waarde geweest.

Mijn lieve vrienden, die er altijd onvoorwaardelijk voor mij zijn met hun raad en daad, hun glazen wijn, bolletjes ijs en onvergetelijke avondjes/nachten uit. Speciale dank aan **Lotte Neyens**, mijn lieve bestie. Voor de duffe berichtjes, onze uitstapjes naar zee, de cursussen wijn leren drinken/EHBO/kalligrafie, de citytrip naar Londen, het klaar staan met raad en daad, en zoveel meer. En stiekem ook een beetje dank aan Bart, voor het uitlenen van Lotte en onze vrouwendrama continu te moeten aanhoren. Jullie zijn fantastische mensen, met een fantastische mini-bestie. Vervolgens ook mijn **vroedvrouwensquad**: Lieselot, Inge, Nienke, Evelien, Loes, Néna en Heleen. Bedankt voor alle feestjes en uitstapjes. De babyboom is bij ons beginnen, laat de trouwfeesten nu maar komen (Lieselot, ik ben mij al aan het voorbereiden). Jullie zijn de beste.

Mijn grootste dank gaat uit naar **mijn ouders, en mijn twee zussen Lize en Helène**. Zonder het warme nest van waar ik kom, stond ik niet waar ik nu sta. Ik kon en mocht ook altijd terugkeren naar huis. Bedankt voor alle kansen die jullie mij gegeven hebben, en nog steeds geven. Sorry voor de momenten dat ik misschien niet de meest aangenaamste persoon was om mee om te gaan, of dat ik misschien wat emotioneler reageerde dan gepast. Bedankt om steeds in mij te geloven, en mij aan te sporen om het beste van mezelf te geven en niet op te geven. En ook bedankt voor de kleinere dingen: mij ophalen van het station als ik het vroeg, op de hond te letten wanneer we langere dagen maakten, luisteren naar grote en kleine bekommernissen, de bloemenboeketjes, en zoveel meer.

En tot slot, mijn grootste liefde: **Gert**. Degene tegen wie ik altijd kan zagen en klagen, die er altijd voor mij is. Bedankt dat ik elke avond bij u thuis mag komen. Bedankt dat ik u mag vervelen met mijn (voor u niet zo interessante) verhalen. Bedankt om mijn grote en kleine stressmomenten met een grapje te doen verdwijnen. Bedankt om te kunnen lachen met mijn mopjes. Bedankt voor de kritische blik die je vaak bracht. Bedankt voor je eeuwige eerlijkheid. Bedankt om al een dikke drie jaar met mij samen te zijn. En bedankt om de papa van ons kindje te worden. Ik kijk uit naar onze volgende jaren, in ons nieuw huisje met onze Springveer en alle nieuwe avonturen en reizen. Ik zie je ongelooflijk graag.

Kortom, bedankt iedereen voor alles wat jullie (al dan niet bewust) gedaan hebben om dit doctoraat mee tot stand te laten komen!

Lieve groetjes,