Faculteit Geneeskunde en Levenswetenschappen
School voor Levenswetenschappen

master in de biomedische wetenschappen

Masterthesis

The evaluation of physical activity and medication management in women at risk for gestational hypertensive disorders

Sandy Nouwen

Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen, afstudeerrichting klinische biomedische wetenschappen

PROMOTOR :
Prof. dr. Wilfried GYSELAERS

BEGELEIDER :
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The evaluation of physical activity and medication management in women at risk for gestational hypertensive disorders

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ABSTRACT

BACKGROUND: Gestational hypertensive disorders (GHD) affect about 5 – 8% of pregnancies worldwide. Nowadays, there is still a need to optimize the management of GHD. Therefore, the aim was to investigate the effect of physical activity on the cardiovascular profile of pre-conceptional women at risk for GHD. Additionally, the beliefs and perceptions on medication use in high-risk pregnancies and their experiences with a medication reminder application were assessed.

METHODS: The cardiovascular profile of pre-conceptional women was assessed before and after physical activity for six months using three non-invasive techniques. Furthermore, patients' beliefs and perceptions on medication use, and their preferences regarding the Medisafe app as a medication reminder were assessed in pregnant women using two questionnaires and semi-structured interviews, respectively.

RESULTS: The cardiac output (CO) of pre-conceptional women with a baseline low CO significantly increased by 0.6 L/min after physical activity, while CO decreased by 0.4 L/min in subjects with a baseline high CO. The beliefs and perceptions on medication use among pregnant women at risk for GHD showed positive attitudes towards medicines in general and during pregnancy. However, 88.9% of the women agreed to have a higher threshold for using medicines during pregnancy. The

Medisafe app was perceived as easy and user-friendly.

CONCLUSION: Physical activity improved the CO towards a normal CO in pre-conceptional women at risk for GHD. Additionally, positive attitudes towards medication use in general and during pregnancy were observed in pregnant women at risk for GHD and most women had positive user experiences with the Medisafe app.

INTRODUCTION

Gestational hypertensive disorders – Gestational hypertensive disorders (GHD) affect about 5 – 8% of pregnancies worldwide and are a major cause of maternal and prenatal morbidity and mortality (1-4). In Flanders, ca. 3,000 of 64,000 pregnancies are complicated by this disease each year (2). GHD includes essential/ chronic hypertension (EH), gestational hypertension (GH), and pre-eclampsia (PE) (2, 5). EH is defined as a high blood pressure ($\geq$140/90 mmHg) detected prior to conception or before a gestational age of 20 weeks (1, 2). GH is defined as a high blood pressure ($\geq$140/90 mmHg) diagnosed after 20 weeks of gestation (1, 2). Lastly, PE is a multi-organ gestational disorder involving hypertension, which is defined as a blood pressure $\geq$140/90 mmHg, and may be accompanied by proteinuria (2, 5, 6). Furthermore, the HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome

presents in a subset of women with severe PE (5). PE can be classified into early-onset PE (EPE), diagnosed before 34 weeks of gestation, and late-onset PE (LPE), diagnosed after 34 weeks of gestation (2, 7).

Risk factors – There are some risk factors associated with the development of GHD, such as a high pre-pregnancy BMI, advanced maternal age (≥35 years old), a multiple pregnancy, maternal smoking, in vitro fertilization, a family history of hypertension, previous PE, and maternal comorbidities (e.g., diabetes mellitus, chronic hypertension, chronic kidney disease, and systemic lupus erythematosus) (3, 7).

Complications – GHD, more specifically PE, can lead to serious, even fatal, complications for both the mother and the fetus. Approximately 50% of all women diagnosed with GH will develop PE (2). On the one hand, maternal complications include neurological disorders, renal insufficiency, liver disorders, hematological complications, pulmonary edema, and uteroplacental dysfunction (2, 8). On the other hand, fetal complications include intrauterine growth restriction, low birth weight, preterm birth, and intrauterine or perinatal death (2, 8).

Pathophysiology – An uncomplicated pregnancy is associated with profound adaptations in cardiac and hemodynamic performance to create optimal conditions for the growth and development of the fetus without compromising the mother's health (4, 9). These adaptations involve a uniform vasodilatation and a subsequent increase in the intravascular component by 1500 mL, as well as an increase in the heart rate, resulting in an increased cardiac output (CO) (4, 10). The increase in circulating volume and CO is essential for an adequate blood supply to the uterus and fetus (10). However, in pregnancies complicated by PE, these adaptations are deviating, such as an inadequate plasma volume expansion and lower CO, increased arterial stiffness and reduced arterial compliance, altered cardiac geometry, impaired myocardial relaxation, and diastolic dysfunction (4, 9, 10). This cardiac function impairment is likely related to the increase in high systemic vascular resistance and abnormal left ventricular remodeling (4). Therefore, a critical evaluation of maternal cardiovascular (CV) physiology may be beneficial in screening for GHD and determining the appropriate management strategy (4, 11).

Current management of GHD – The only 'cure' for PE is the delivery of the fetus (4, 7). However, the risk for developing GHD can be managed by preventive measures such as remote monitoring of blood pressure, regular physical activity, and aspirin (Asaflow ©) use started at or before 16 weeks of gestation (2, 7, 12, 13). Since blood pressure measurement is an important component of prenatal care, the Pregnancy Remote Monitoring (PREMOM I) study has shown that telemonitoring of blood pressure is an opportunity to increase the efficiency of follow-up and lower the occurrence of PE (14, 15). It has been shown that women who exercise prior to conception and in early pregnancy have the greatest reduction in risk for GHD (13). The mechanisms for this exercise-induced beneficial effect include an increased plasma volume and CO, and an improved endothelial function (13, 16). During early pregnancy, exercise also enhances placentation, placental growth, and vascularity (13, 16). Additionally, it is known that exercise is associated with emotional well-being and reduced stress and anxiety (16). However, these studies merely describe the association between physical activity and the incidence of GHD or the effect of physical activity on a subset of the CV profile rather than the overall CV profile (13, 16, 17). If the pregnant woman develops hypertension, antihypertensive medication as a therapeutic action is prescribed. The most extensively used in pregnancy are Nifedipine (a calcium blocker), Labetalol (a β-blocker), and Methyldopa (a CNS α-agonist) (18). However, there are controversies regarding the recommendations and guidelines for the use of antihypertensive medication as a treatment for GHD (19). This implies that there is a lack of consensus concerning the blood pressure cutoff value to initiate medication. Besides, insufficient evidence is provided on which antihypertensive medication is most effective (19). The major problem is that the therapy for GHD is mainly focused on hypertension, irrespective of the underlying cause (11).

Medication adherence – Non-adherence to medication is a key barrier to effective treatment, increasing the risk of developing high blood pressure and causing unwanted complications in the mother and fetus (20). In fact, the prevalence of non-adherence to antihypertensive medication in pregnancy is estimated to be between 3% – 65%

(20). However, this is still a wide range, and a precise number representing the non-adherence in high-risk pregnancies is lacking. Additionally, a prevalence of non-adherence to aspirin in pregnancy is shown between 21.4% – 46.3% (21). Pregnant women may have unrealistic perceptions of the teratogenic risks of medicines, resulting in suboptimal treatment (22-24). If their beliefs about medicines negatively affect medication adherence, it may have important health consequences, as described above (24). Therefore, a greater focus on this aspect is of importance. Currently, mobile health (mHealth) interventions, such as smartphone applications, are increasingly relevant to assist in healthcare. It has the potential to improve medication adherence by providing regular reminders, offering education, as well as facilitating communication between patients and health professionals (25, 26). Additionally, medication reminder apps may reduce healthcare costs due to the potentially improved clinical outcomes (26). Of all the medication reminder applications, the Medisafe© app is readily available to the public. It has a high ranking regarding engagement, functionality, desirable characteristics, and overall quality, but this app is not yet used in the pregnant population (27, 28). Hence, the experiences with the Medisafe app in pregnant women are still lacking.

Study aim – On the one hand, we investigated the effect of physical activity on the CV profile in pre-conceptional women at risk for GHD (FARO study). The primary aim of this study was to compare the CV profile of pre-conceptional women with a history of GHD or at risk for the development of GHD before and after the advice to exercise for a period of six months. It was hypothesized that the CV profile of pre-conceptional women at risk for GHD would improve after the advice of physical activity for a period of six months. On the other hand, we evaluated the beliefs and perceptions on medication use and the experiences regarding a mobile app as a reminder to take medication in pregnant women at risk for GHD (CAPROM study). The objectives of this study included comparing the beliefs and perceptions on medication use and therapy adherence of pregnant women at risk for the development of GHD at baseline and postpartum, and evaluating the experiences and preferences regarding the use of a smartphone medication

reminder application (Medisafe) to prospectively register their medication use and as a reminder to take medication.

EXPERIMENTAL PROCEDURES

FARO study – The FARO study is a retrospective study. Women with a history of GHD or at risk for the development of GHD in the following pregnancy had a pre-conceptional (PC) measurement of their CV profile as part of the standard care path. After the first CV measurement, they could receive the advice to exercise, equivalent to one hour of indoor cycling per day, for a period of at least six months. Next, a pre-conceptional post-sport (PCPS) CV measurement was conducted. The CV profile was assessed by the combination of three non-invasive standardized techniques, i.e. an electrocardiogram (ECG) combined with Doppler ultrasound for measuring the hepatic and renal veins and the uterine arteries, a bio-impedance analysis using a multiple-frequency bioelectrical impedance analyzer (Maltron Bioscan 920-II, Maltron International, Essex, UK), and an impedance cardiography in both supine and standing position using the non-invasive continuous cardiac output monitor (NICCOMO, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany) (10, 29). CV measurements were performed between June 2016 and December 2021, of which only those that showed an increased risk of GHD in a subsequent pregnancy were analyzed. This study was approved by the Ethical Committees of Ziekenhuis Oost-Limburg (ZOL) and UHasselt.

Data collection – All study data were captured and saved in Castor EDC. The data include demographical and clinical maternal information: age, BMI, family history of CV diseases, relevant co-morbidities, the indication for the CV measurement, and any previous pregnancy outcomes. Lastly, the collected CV parameters were arterial parameters (i.e. pulse transit time (APTT), pulsatility index (PI), and resistivity index (RI) of the left and right arcuate arteries), venous parameters (i.e. venous pulse transit time (VPTT) of the hepatic and left and right renal veins, hepatic vein impedance index (HVI), and left and right renal interlobar vein impedance indices (RIVI)), cardiac parameters (CO, diastolic blood pressure (DBP), mean arterial pressure (MAP), total peripheral resistance (TPR), left ventricular
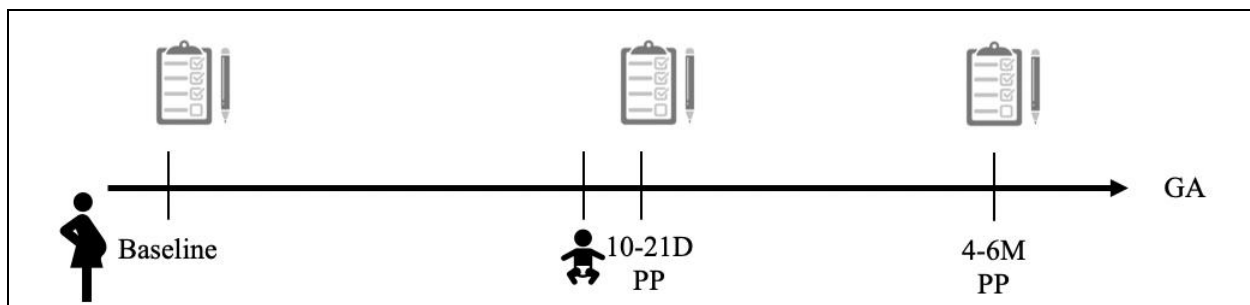
Fig. 1: Timeline of receiving the BMQ and ProMAS questionnaires. GA: gestational age, D: days, M: months, PP: postpartum, BMQ: beliefs about medicines questionnaire, ProMAS: probabilistic medication adherence scale questionnaire.

ejection time (LVET), velocity (VI) and acceleration indices (ACI)), fluid volumes in the body (i.e. total body water (TBW), extracellular (ECW) and intracellular water (ICW)).

Statistical analysis – The statistical analysis was performed with IBM SPSS® Statistics. The study population was analyzed with descriptive statistics (mean/ median, SD/ IQR, n, %). Description, comparison, and association of the CV profiling were analyzed with descriptive statistics (n, %), repeated measures model, Chi-square, and Fisher-exact tests. A p-value <0.05 was considered statistically significant.

CAPROM study – The prospective CAPROM study is being conducted at ZOL, Genk, Belgium since March 2021. This study is performed in accordance with the Declaration of Helsinki. Approval by the Ethical Committees of ZOL and UHasselt was obtained prior to study onset, and informed consent was obtained from all patients.

Study population – Pregnant women were eligible for inclusion if they were ≥18 years old, were able to speak and understand the Dutch language, were not on antihypertensive medication, and had a high-risk pregnancy (>1/100) for the development of GHD according to the Fetal Medicine Foundation (FMF) tool for which remote monitoring follow-up was implemented. The remote monitoring device includes a blood pressure monitor with the corresponding iHealth smartphone application to register blood pressure measurements at home. The exclusion criterium included congenital malformation of the fetus.

Study procedure – CV profiling was performed longitudinally throughout pregnancy every four weeks until delivery, from 12 weeks of gestation onwards. Additionally, CV profiling was

performed before the start or adjustment of antihypertensive medication and again when the blood pressure was normalized. The CV profiling procedure included the same three non-invasive standardized techniques as used in the FARO study (ECG-Doppler ultrasound, a bio-impedance analysis, and an impedance cardiography). In addition, the participants were asked to download the mobile application Medisafe© (MediSafe Inc.) for their daily medication registration throughout pregnancy (**Fig. S 1**). The Medisafe app has a reminder function for medication intake. The study researchers had access to the medication data but did not interfere in case of non-adherence to the medication. Furthermore, the perceptions concerning medication use during pregnancy and in general and the perceptions concerning therapy adherence were assessed by the beliefs about medicines questionnaire (BMQ) and the probabilistic medication adherence scale (ProMAS) questionnaire, respectively (23, 30). The women received these two questionnaires at three time points: at baseline, between ten and 21 days after delivery, and between four and six months after delivery, as shown in **Fig. 1**. In addition, ten women were invited for a semi-structured interview to gain insight into their experiences and preferences regarding the use of a mobile application (such as the Medisafe app). These interviews took place after delivery or at the end of their pregnancy. The duration of an interview was approximately 30 min and was performed online (via Google Meet) or in person at ZOL, depending on the woman's preference. For proper storing and analysis, the semi-structured interviews were recorded and subsequently written out verbatim (= word for word) and coded in Microsoft® Word.

Data collection – All study data were captured and saved in Castor EDC. The data include the results from the semi-structured interviews, the two questionnaires (BMQ and ProMAS), demographical, and clinical maternal information: age, BMI, relevant co-morbidities, medication use, parity, any previous pregnancy outcomes, and the outcome of the current pregnancy. Information regarding education in healthcare and the period of experience with the Medisafe app was additionally collected for the ten interviewed women.

Statistical analysis – The statistical analysis was performed with IBM SPSS® Statistics. The study population was analyzed with descriptive statistics (mean/ median, SD/ IQR, n, %). Description, comparison, and association of the BMQ and ProMAS results were analyzed with descriptive statistics (n, %), repeated measures model, Chi-square, and Fisher-exact tests. A p-value <0.05 was considered statistically significant. The Qualitative Analysis Guide of Leuven (QUAGOL) was used to analyze the semi-structured interviews and identify facilitators and barriers among women regarding the use of the app (Medisafe) to prospectively register their medication use.

RESULTS

FARO study population – Baseline pre-conceptional CV profiling was performed in 176 women between June 2016 and December 2021. Eight women were excluded because the prediction after their first CV measurement was normal, and 14 CV measurements had missing data. Data analysis was performed for a total of 154 women, of which 35 women had a CV measurement both before (PC) and after the advice to exercise for a period of six months (PCPS). The study population was divided into three groups based on baseline CO in accordance with normal reference values (5 – 6.5 L/min) used within the LimPrOn project: 25 women had a low CO (<5 L/min), 84 women had a normal CO (5 – 6.5 L/min), and 45 women had a high CO (>6.5 L/min), as shown in the flowchart (**Fig. 2**) (31). The baseline demographic and clinical characteristics for the three groups are presented in **Table S 1**. The baseline median BMI of the women was
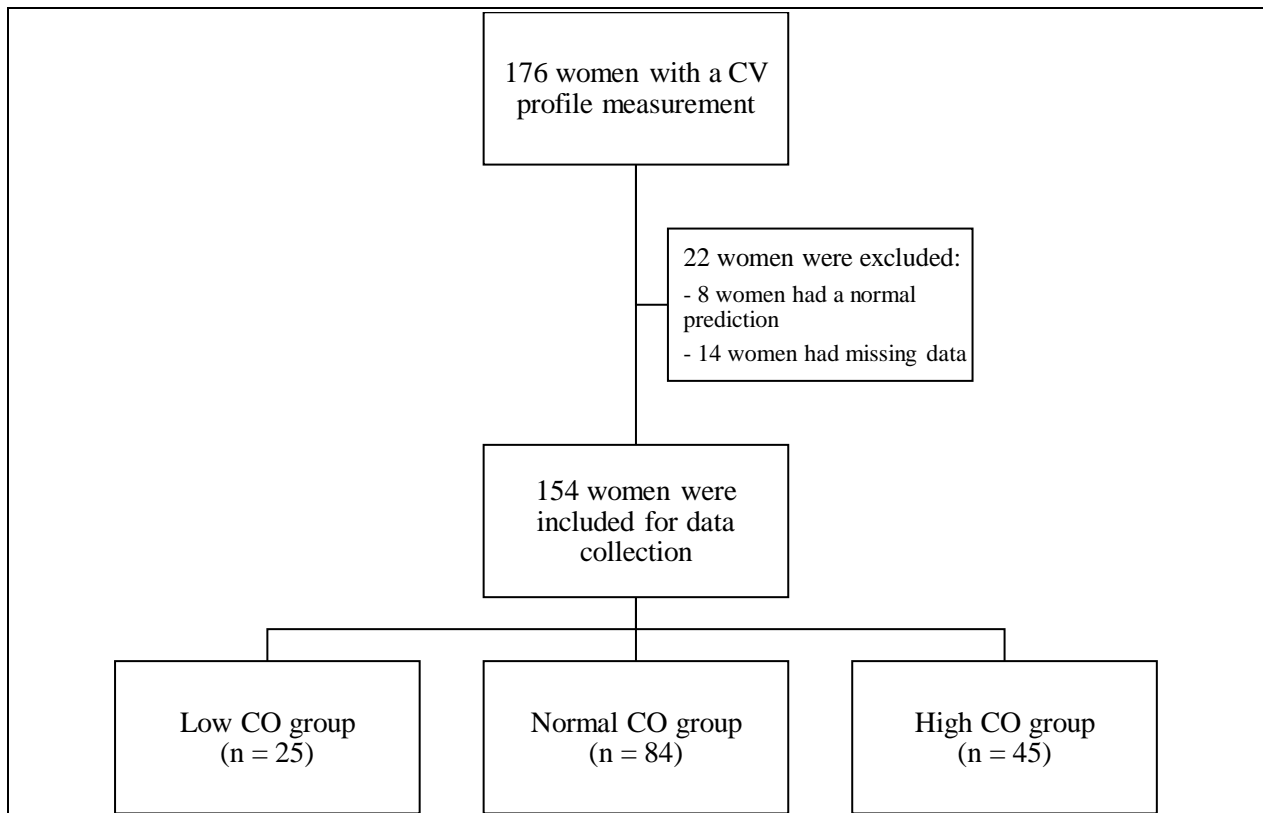

Fig. 2: Study population of the FARO study. CO: cardiac output.

significantly different between the three groups. With regard to the previous pregnancy outcome, there was no significant difference between the three groups. However, it is remarkable that EPE in the previous pregnancy was most common in the low CO group and LPE in the previous pregnancy was most common in the high CO group (**Fig. 3** and **Table S 1**).

Comparison of the CV profile between the three groups at each study visit – The CV parameters were compared between the groups with a low, normal, and high CO at baseline and after physical activity for a period of six months (**Table 1**). The liver VPTT, TBW, ECW, and ICW of the high CO group were significantly higher at baseline compared to the low and normal CO groups (p = 0.006, p<0.001, p<0.001, p<0.001, respectively),

while the baseline liver HVI of the high CO group was significantly lower compared to the normal CO group (p = 0.011). Lastly, the TPR was significantly different between the three groups with a p-value <0.001. With regard to the PCPS measurement, both the PI and RI of the right uterine arteria of the high CO group were significantly higher compared to the low CO group (p-value of 0.030 and 0.016, respectively). The TBW, ECW, and ICW of the high CO group were still significantly higher compared to the other groups. Lastly, the CO of the high CO group was significantly higher than both the low and normal CO groups with a p-value <0.001, and the TPR of the high CO group was significantly lower compared to the low and normal CO groups with a p-value <0.001.
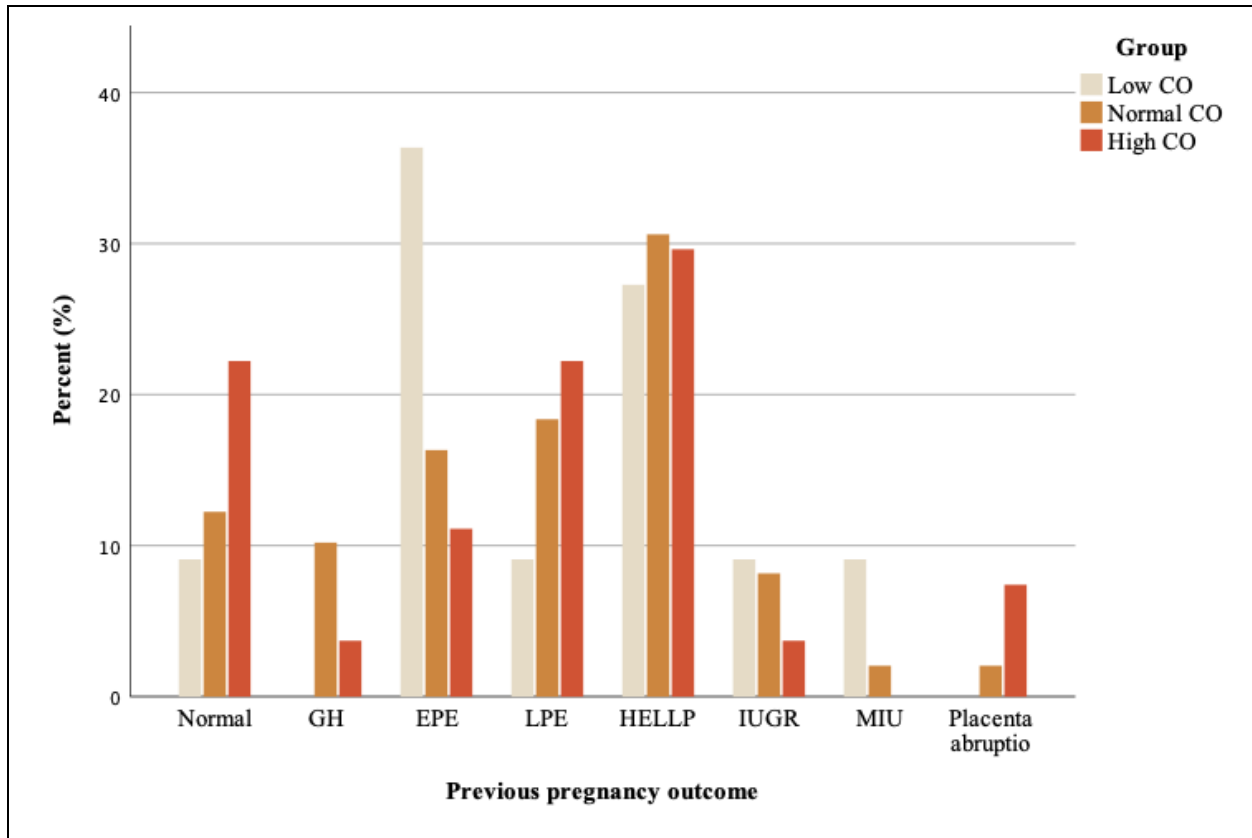
Fig. 3: The previous pregnancy outcome of the FARO population. In the low CO group, 11 women had a previous pregnancy outcome. In the normal CO group, 49 women had a previous pregnancy outcome. In the high CO group, 27 women had a previous pregnancy outcome. There were no significant differences between the three groups. CO: cardiac output, GH: gestational hypertension, EPE: early pre-eclampsia, LPE: late pre-eclampsia, IUGR: intrauterine growth restriction, HELLP: hemolysis – elevated liver enzymes – low platelets, MIU: mors in utero.

Table 1 – Comparison of the CV measurement between the three groups before and after the advice of physical activity.

	PC measurement				PCPS measurement			
	Low CO	Normal CO	High CO	P-value	Low CO	Normal CO	High CO	P-value
	N = 25	N = 84	N = 45		N = 11	N = 15	N = 9	
Liver VPTT (ms)	0.15 (0.12-0.21)	0.16 (0.13-0.21)	0.21 (0.16-0.28)	**0.006** [b,c]	0.11 (0.10-0.20)	0.15 (0.13-0.23)	0.16 (0.11-0.34)	0.346
Liver HVI	1.38 (0.89-1.55)	1.39 (1.22-1.55)	1.18 (0.28-1.44)	**0.011** [c]	1.37 (1.22-1.49)	1.40 (1.16-1.57)	1.28 (0.44-1.57)	0.612
R K VPTT (ms)	0.28 (0.18-0.38)	0.23 (0.17-0.36)	0.28 (0.19-0.40)	0.221	0.25 (0.15-0.33)	0.24 (0.17-0.33)	0.30 (0.15-0.41)	0.728
R RIVI	0.46 (±0.13)	0.50 (±0.13)	0.49 (±0.15)	0.517	0.51 (±0.14)	0.55 (±0.08)	0.50 (±0.12)	0.574
L K VPTT (ms)	0.30 (0.25-0.40)	0.31 (0.25-0.37)	0.34 (0.27-0.39)	0.232	0.31 (0.15-0.33)	0.32 (0.24-0.38)	0.32 (0.21-0.43)	0.346
L RIVI	0.41 (0.35-0.45)	0.43 (0.38-0.50)	0.43 (0.34-0.50)	0.512	0.46 (0.31-0.61)	0.53 (0.44-0.60)	0.53 (0.37-0.59)	0.685
R Ut APTT (ms)	0.24 (0.22-0.25)	0.24 (0.22-0.27)	0.25 (0.22-0.30)	0.680	0.24 (0.20-0.25)	0.24 (0.22-0.29)	0.24 (0.20-0.42)	0.585
R Ut PI	1.28 (±0.26)	1.30 (±0.26)	1.33 (±0.26)	0.761	1.33 (±0.22)	1.40 (±0.24)	1.59 (±0.08)	**0.030** [b]
R Ut RI	0.79 (0.69-0.85)	0.80 (0.73-0.86)	0.80 (0.71-0.88)	0.719	0.79 (0.74-0.88)	0.82 (0.78-0.89)	0.89 (0.87-0.90)	**0.016** [b]
L Ut APTT (ms)	0.22 (0.21-0.24)	0.25 (0.22-0.29)	0.24 (0.22-0.28)	0.123	0.24 (0.21-0.26)	0.23 (0.22-0.28)	0.26 (0.19-0.40)	0.748
L Ut PI	1.32 (1.23-1.56)	1.39 (1.22-1.56)	1.33 (1.21-1.48)	0.353	1.42 (1.20-1.53)	1.36 (1.19-1.60)	1.56 (1.50-1.65)	0.069
L Ut RI	0.83 (0.77-0.88)	0.82 (0.75-0.88)	0.80 (0.75-0.85)	0.363	0.83 (0.75-0.87)	0.81 (0.75-0.89)	0.87 (0.86-0.90)	0.124
TBW (L)	30.9 (28.6-32.6)	32.9 (30.4-37.1)	36.3 (34.2-39.8)	**<0.001** [b,c]	30.7 (28.4-31.2)	32.0 (27.7-38.4)	36.6 (33.1-38.8)	**0.022** [b]
ECW (L)	13.2 (12.2-14.3)	14.1 (12.9-15.6)	16.0 (14.5-17.9)	**<0.001** [b,c]	13.1 (11.9-13.5)	13.9 (11.5-16.9)	15.9 (14.0-16.8)	**0.034** [b]

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ICW (L)	17.6 (16.8-18.1)	18.8 (17.5-20.2)	20.7 (19.9-22.2)	**<0.001** a,b,c	17.5 (16.5-18.1)	17.2 (16.5-19.8)	20.8 (19.1-22.1)	**0.004** b,c
ECW/ICW	0.74 (0.71-0.79)	0.74 (0.72-0.78)	0.76 (0.73-0.80)	0.411	0.72 (0.72-0.77)	0.75 (0.70-0.79)	0.75 (0.73-0.76)	0.927
DBP (mmHg)	91 (84-97)	89 (82-97)	89 (82-100)	0.725	90 (85-92)	91 (84-100)	86 (82-92)	0.524
MAP (mmHg)	102 (94-108)	99 (93-107)	101 (92-112)	0.779	102 (95-102)	101 (93-112)	99 (95-105)	0.780
VI (1/100/s)	58 (49-70)	64 (49-74)	60 (45-77)	0.570	70 (57-79)	67 (55-74)	56 (53-63)	0.086
ACI (1/100/s^2)	134 ($\pm$38)	141 ($\pm$52)	138 ($\pm$46)	0.847	166 ($\pm$38)	146 ($\pm$48)	125 ($\pm$33)	0.109
LVET (ms)	238 (221-252)	241 (222-251)	244 (227-258)	0.394	243 (227-268)	243 (228-267)	228 (219-2364)	0.772
CO (L/min)	4.5 (4.0-4.8)	5.7 (5.3-6.0)	7.3 (6.9-7.8)	**<0.001** a,b,c	5.0 (4.5-5.8)	5.5 (5.0-6.5)	7.1 (6.5-8.0)	**<0.001** b,c
TPR	1820 (1643-2140)	1424 (1298-1541)	1067 (971-1190)	**<0.001** a,b,c	1632 (1413-1813)	1490 (1378-1629)	1053 (1005-1225)	**<0.001** b,c

Data are presented as mean ($\pm$SD) and median (IQR). PC: pre-conceptional, PCPS: pre-conceptional post-sport, Liver VPTT: liver venous pulse transit time, HVI: hepatic vein index, R K VPTT: right kidney venous pulse transit time, R RIVI: right renal interlobar vein impedance index, L K VPTT: left kidney venous pulse transit time, L RIVI: left renal interlobar vein impedance index, R Ut APTT: right uterine arterial pulse transit time, R Ut PI: right uterine pulsatility index, R Ut RI: right uterine resistivity index, L Ut APTT: left uterine arterial pulse transit time, L Ut PI: left uterine pulsatility index, L Ut RI: left uterine resistivity index, TBW: total body water, ECW: extracellular water, ICW: intracellular water, DBP: diastolic blood pressure, MAP: mean arterial pressure, VI: velocity index, ACI: acceleration index, LVET: left ventricular ejection time, CO: cardiac output, TPR: total peripheral resistance. A p-value <0.05 is considered statistically significant. [a] Low CO – normal CO significant difference, [b] low CO – high CO significant difference, [c] normal CO – high CO significant difference.

Comparison of the PC and PCPS measurement – A comparison of the CV measurements before and after physical activity was performed within each group. In the group with a low CO, there was a significant increase in CO after physical activity with a p-value of 0.015, as

the low CO group and three (33.3%) women of the high CO group could be assigned to the normal CO group based on the reference values (**Table S 5**). However, five (33.3%) women of the normal CO group could be assigned to the low or high CO group after physical activity (**Table S 5**).
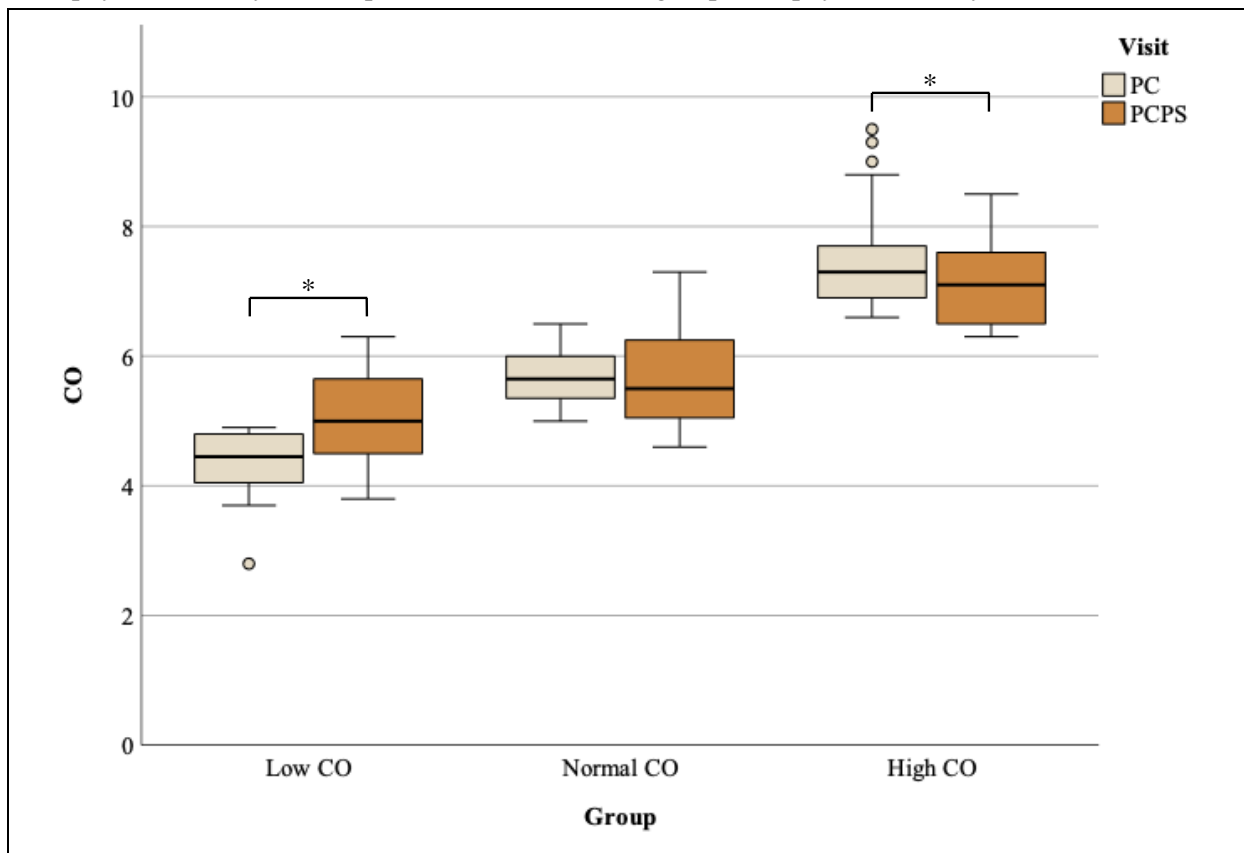

Fig. 4: CO evaluated before and after physical activity in pre-conceptional women. The CO of the women was compared before and after the advice to exercise for a period of six months within each group. Data are presented as boxplots with median and interquartile range. CO: cardiac output, PC: pre-conceptional, PCPS: pre-conceptional post-sport. *p<0.05. °Outlier.

shown in **Fig. 4** and **Table S 2**. Furthermore, the TPR was significantly decreased after physical activity (p = 0.004), while the ACI was significantly increased (p = 0.016) (**Table S 2**). In the group with a normal CO, there was only a significant increase in the left RIVI after physical activity (p = 0.031) (**Table S 3**). There was no significant difference for the CO (**Fig. 4**). Lastly, in the group with a high CO, the CO was significantly decreased after physical activity with a p-value of 0.041, as shown in **Fig. 4**. Additionally, the left uterine PI was significantly higher after physical activity with a p-value of 0.021 (**Table S 4**). After physical activity for a period of six months, six (54.5%) women of

CAPROM study population – Seventy pregnant women at risk for GHD, for whom remote monitoring follow-up was implemented, were screened for participation in the CAPROM study. Eleven women refused participation, four women were not followed up at ZOL, three women had started antihypertensive medication prior to inclusion, three women were going to be induced for delivery, and one woman did not understand the Dutch language. A total of 48 women were included in the study, of which two women were lost to follow-up, one woman withdrew from the study, and three women had a stillbirth before 24 weeks gestation. Of these, a total of 37 women

completed the baseline questionnaires, and 14 women completed both the baseline and postpartum questionnaires, as seen in the flowchart (**Fig. S 2**).

Fifteen women are still ongoing in the study. The baseline demographic and clinical characteristics of the study population are presented in **Table 2**.

Table 2 – Demographics and clinical characteristics of the CAPROM population.		
	Study population	Interviewed women
	N = 37	N = 10
Age (years)	30.57 (±3.88)	31.40 (±3.57)
BMI (kg/m^2)	29.59 (±5.69)	24.39 (±2.40)
Parity		
Nulliparous	30 (81.1%)	10 (100.0%)
Multiparous	7 (18.9%)	0 (0.0%)
Outcome previous pregnancy		
Uncomplicated	*2 (18.2%)*	/
EH	*0 (0.0%)*	/
GH	*3 (27.3%)*	/
EPE	*3 (27.3%)*	/
LPE	*3 (27.3%)*	/
SGA	*0 (0.0%)*	/
IUGR	*0 (0.0%)*	/
HELLP	*0 (0.0%)*	/
Other	*2 (18.2%)*	/
Comorbidity		
Hypertension	3 (8.1%)	0 (0.0%)
Diabetes	2 (5.4%)	0 (0.0%)
Thyroid problems	1 (2.7%)	0 (0.0%)
Thrombophilia	0 (0.0%)	0 (0.0%)
Kidney problems	2 (5.4%)	2 (20.0%)
Other	8 (21.6%)	3 (30.0%)
Medication use during pregnancy		
Asaflow	37 (100.0%)	10 (100.0%)
Antihypertensive medication		
Bisoprolol	1 (2.7%)	1 (10.0%)
Amlodipine	3 (8.1%)	0 (0.0%)
Catapressan	2 (5.4%)	0 (0.0%)
Trandate	4 (10.8%)	0 (0.0%)
Diabetes medication	5 (13.5%)	0 (0.0%)
Thyroid medication	4 (10.8%)	3 (30.0%)
Asthma medication	4 (10.8%)	0 (0.0%)
Lupus medication	3 (8.1%)	0 (0.0%)
Antidepressiva	1 (2.7%)	0 (0.0%)
Antibiotics	2 (5.4%)	0 (0.0%)
Vitamins	23 (62.2%)	7 (70.0%)
Other	16 (43.2%)	3 (30.0%)
Pregnancy outcome		

Normal	11 (29.7%)	2 (50.0%)
EH	0 (0.0%)	0 (0.0%)
GH	5 (13.5%)	1 (25.0%)
EPE	0 (0.0%)	0 (0.0%)
LPE	1 (2.7%)	1 (25.0%)
SGA	0 (0.0%)	0 (0.0%)
IUGR	1 (2.7%)	0 (0.0%)
HELLP	0 (0.0%)	0 (0.0%)
Other	2 (5.4%)	0 (0.0%)
Education in healthcare*	/	4 (40.0%)
Period of experience with Medisafe app (weeks)*	/	21.60 (±7.83)

Data are presented as mean (±SD), median (IQR), and n (%). BMI: Body mass index, EH: essential hypertension, GH: gestational hypertension, EPE: early pre-eclampsia, LPE: late pre-eclampsia, SGA: small for gestational age, IUGR: intrauterine growth restriction, HELLP: hemolysis – elevated liver enzymes – low platelets. * Information only concerning the ten interviewed women.

The beliefs and perceptions on medication use and medication adherence at baseline – In general, the women had positive attitudes towards medicines at baseline (**Table 3**). With regard to the pregnancy-specific statements at baseline, it was remarkable that 88.9% of the women agreed to have a higher threshold for using medicines during pregnancy (P3). However, 73.5% agreed that it is better for the fetus to use medicines and get better than to have an untreated illness during pregnancy (P5), and 54.3% agreed that the lives of many unborn children are saved thanks to treatment with medicines during pregnancy (P4). Merely 2.9% agreed that doctors prescribe too many medicines during pregnancy (P6). Furthermore, 16.7% of the women had a high adherence, and 36.1% had a medium-high adherence at baseline (**Fig. 5**). In the Medisafe app, a median medication non-adherence to Asaflow of 8.96% (2.08% – 17.86%) was detected.

Comparison of the beliefs and perceptions at baseline and postpartum – With regard to the pregnancy-specific statement 'doctors prescribe too many medicines during pregnancy' (P6), the answers were significantly different between baseline and postpartum (p = 0.046), as seen in **Table 3** and **Table S 6**. Postpartum, nobody agreed to this statement anymore. The beliefs regarding the other statements of medication use at postpartum were similar to the beliefs at baseline (**Table 3**). Furthermore, there was no significant difference in medication adherence score between baseline and postpartum as assessed by the ProMAS questionnaire (**Fig. 5**).

Experiences and preferences regarding the Medisafe app – Ten women participating in the CAPROM study were interviewed about their experiences and preferences regarding the Medisafe app to prospectively register their medication use and as a reminder to take their medication as prescribed. The demographic and clinical characteristics of these ten women are presented in **Table 2**. During the analysis, five major themes were identified.

Experience with the Medisafe app – All women were positive about the use of the Medisafe app. It was an easy, straightforward, and user-friendly app. *'In terms of usability, very easy. For me, everything was clear.' – CAPROM_032.* For example, CAPROM_014 mentioned the available library of medication as a good function. *'I found it user-friendly. [...] A lot of medication was already there in the library. You could see for yourself which medication to add.' – CAPROM_014.* Furthermore, CAPROM_002 indicated that the possibility to adjust the shape and color of the pills was a nice function, especially for the elderly. *'I've always found that to be user-friendly. Also clearly indicating which shape it is and so on. For older people, if they can see which shape they have to take, that might be a little bit easier than just having them read it.' – CAPROM_002.* The app was also convenient for CAPROM_011 because she experienced the app as

Table 3 – Beliefs about Medicines Questionnaire

	Baseline N = 37			Postpartum N = 14			P-value
	Agree	Disagree	Uncertain	Agree	Disagree	Uncertain	
General statements							
G1. Doctors use too many medicines.	8 (22.2%)	17 (47.2%)	11 (30.6%)	3 (21.4%)	6 (42.9%)	5 (35.7%)	0.739
G2. People who take medicines should stop their treatment for a while every now and again.	8 (22.2%)	15 (41.7%)	13 (36.1%)	4 (28.6%)	7 (50.0%)	3 (21.4%)	0.157
G3. Most medicines are addictive.	7 (18.9%)	24 (64.9%)	6 (16.2%)	0 (0.0%)	11 (78.6%)	3 (21.4%)	0.458
G4. Natural remedies are safer than medicines	11 (29.7%)	19 (51.4%)	7 (18.9%)	4 (28.6%)	9 (64.3%)	1 (7.1%)	1.000
G5. Medicines do more harm than good.	4 (10.8%)	28 (75.7%)	5 (13.5%)	2 (14.3%)	11 (78.6%)	1 (7.1%)	0.655
G6. All medicines are poisons.	1 (2.7%)	33 (89.2%)	3 (8.1%)	1 (7.1%)	11 (78.6%)	2 (14.3%)	0.083
G7. Doctors place too much trust on medicines.	6 (17.1%)	20 (57.1%)	9 (25.7%)	3 (21.4%)	9 (64.3%)	2 (14.3%)	0.705
G8. If doctors had more time with patients, they would prescribe fewer medicines.	9 (25.7%)	17 (48.6%)	9 (25.7%)	3 (21.4%)	7 (50.0%)	4 (28.6%)	0.739
Pregnancy – specific statements							
P1. All medicines can be harmful for the fetus.	5 (13.5%)	25 (67.6%)	7 (18.9%)	0 (0.0%)	11 (78.6%)	3 (21.4%)	0.257
P2. Even if I am ill and if not pregnant would have taken a medicine, I believe it's better for the fetus that I refrain from using medicines during pregnancy.	13 (35.1%)	18 (48.6%)	6 (16.2%)	5 (35.7%)	7 (50.0%)	2 (14.3%)	0.279
P3. I have a higher threshold for using medicines when I am pregnant than when I am not pregnant.	32 (88.9%)	3 (8.3%)	1 (2.8%)	11 (84.6%)	2 (15.4%)	0 (0.0%)	0.157
P4. Thanks to treatment with medicines during pregnancy, lives of many unborn children are saved each year.	19 (54.3%)	0 (0.0%)	16 (45.7%)	8 (61.5%)	1 (7.7%)	4 (30.8%)	0.655

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P5. It is better for the fetus that I use medicines and get well than to have an untreated illness during pregnancy.	25 (73.5%)	0 (0.0%)	9 (26.5%)	9 (69.2%)	2 (15.4%)	2 (15.4%)	0.527
P6. Doctors prescribe too many medicines during pregnancy.	1 (2.9%)	22 (62.9%)	12 (34.3%)	0 (0.0%)	10 (76.9%)	3 (23.1%)	**0.046**
P7. Natural remedies can generally be used by pregnant women.	8 (22.9%)	8 (22.9%)	19 (54.3%)	3 (23.1%)	4 (30.8%)	6 (46.2%)	1.000
P8. Pregnant women should preferably use natural remedies during pregnancy.	10 (28.6%)	12 (34.3%)	13 (37.1%)	4 (30.8%)	7 (53.8%)	2 (15.4%)	0.783
P9. Pregnant women should not use natural remedies without the consent of a doctor.	24 (68.6%)	2 (5.7%)	9 (25.7%)	11 (84.6%)	1 (7.7%)	1 (7.7%)	1.000

Data are presented as n (%). G: General, P: Pregnancy – specific.
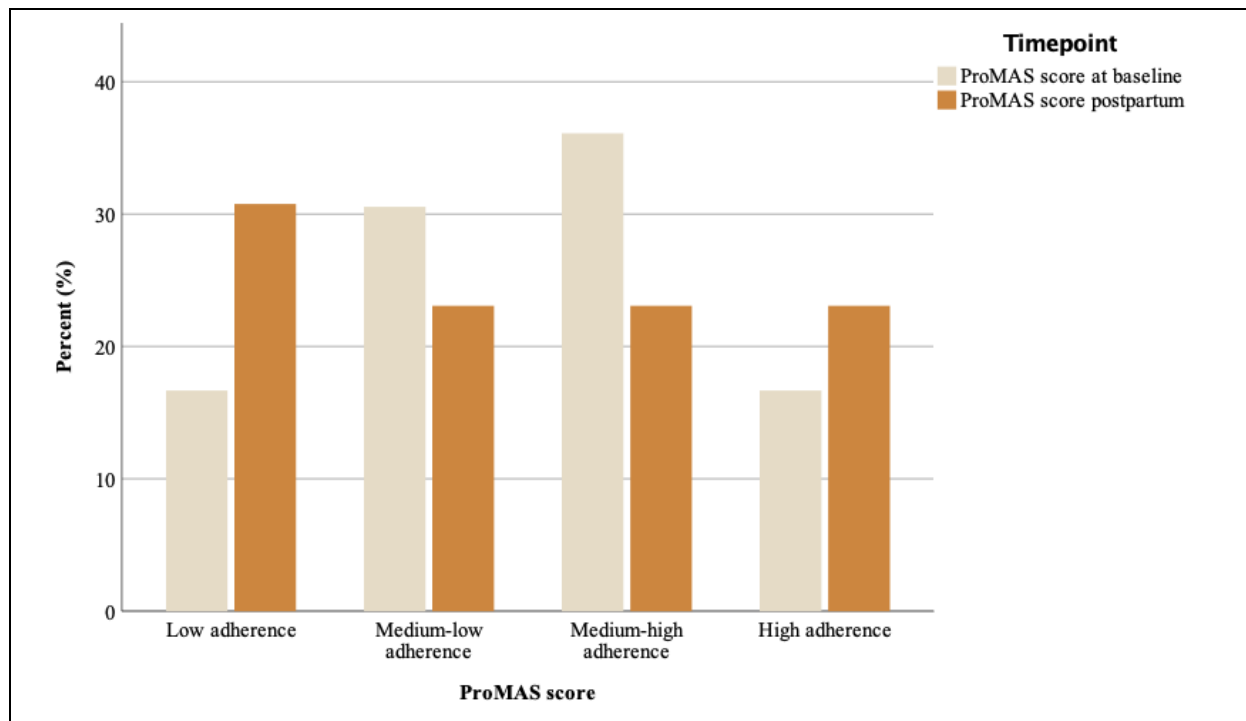
Fig. 5: Probabilistic Medication Adherence Scale questionnaire. The ProMAS score was calculated for 36 women at baseline and 13 women postpartum. Data are presented as bar charts. There was no significant difference between the medication adherence score at baseline and postpartum. ProMAS: Probabilistic Medication Adherence Scale questionnaire.

a medication box. *'Very easy. Very clear yes. It's basically a medicine box on your smartphone. It's very convenient.' – CAPROM_011.*

Experience with the notifications – The experiences with the notifications that reminded the women to take their medication were divided. Some women indicated that the notifications were disturbing. *'Irritating. But it is a help. [...] If you only have to take one pill, it's not so bad. But I took six for the thyroid only, and my pregnancy vitamins were also added, and I also had to take something for the heart ... Asaflow. That was a lot, and that was too much.' – CAPROM_011.* However, others did not experience the notifications as disturbing. *'Not disturbing at all. I haven't used the snoozing feature. Because usually I had already taken it, or I was going to take it right away as soon as I got the notification, and then I could accept it.' – CAPROM_010.* Some women stated that the notifications were helpful to remind them. *'Yes, good and also necessary. Because otherwise, I don't think I would have used that very consistently. So, I felt it was absolutely necessary that it was on my screen every day, yes.' – CAPROM_032.*

Influence of the app on their medication use – Some women indicated that they were forgetful, and therefore the app was helpful and a good reminder for them. *'Yes, because I think if the app didn't report those reminders, I would have regularly forgotten to take it. [...] Yes, I often needed the notification.' – CAPROM_032.* Moreover, CAPROM_036 stated that she had less stress thanks to the app. *'It makes me remember well to take my pills. That's good because otherwise, I might forget them once in a while. You have less stress because you have a little hold that reminds you every day.' – CAPROM_036.* Although some women mentioned that they were punctual with regard to medication intake, they believe that it may be a good reminder for other people. *'Yes, because I think I was taking my medication anyway if I didn't have that app. I've never actually forgotten my medication. But I think it might be a good reminder for some people.' – CAPROM_037.* CAPROM_010, for example, stated that she would also be punctual without the app. However, the app helped her to take her medication at the exact time. *'I think it can be a*

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tremendously good reminder for people to think about their medication. I'm pretty punctual about that though on my own. But perhaps less at the punctual hour. If it was at 6:00 AM during a working week and at 7:30 AM at the weekend, I didn't use to make such a big deal of it. Then it was just at breakfast. With the Medisafe app, I was much more punctual, and sometimes I even set the alarm clock to take the pill.' – CAPROM_010. Furthermore, CAPROM_034 indicated that she had more control about her medication intake thanks to the app. *'I'm just saying it helped remind me to take the pill every day, yes. I think you have better control to check whether you took your pill or not. Because sometimes when I don't have the app, I don't know if I took it or not.'* – CAPROM_034.

Adjustments in the medication schedule – The women who adjusted their medication schedule indicated that it was easy and straightforward to do. *'I did add or remove medication myself a few times when I didn't have to take Asaflow anymore. [...] I immediately removed it from the list, so that went very well. Very easy, very clear yes.'* – CAPROM_011. Some women were unaware that it was possible or allowed to adjust it. However, CAPROM_032 mentioned that she would have added pregnancy vitamins to get reminders if she was aware of this function. *'No, but also because I was not aware it was possible. Because I had to take vitamins for a certain period, if I had known, I probably would have added them. [...] Yes, in the sense of being reminded not to forget to take the medication.'* – CAPROM_032. A few women mentioned that they did not add their other medication because they took it simultaneously with Asaflow. Thus, one notification was sufficient for them to take all medications at the same time. *'Yes, I haven't adjusted anything. I just take everything at the same time, I take the Navalit and the Asaflow together. [...] I use that one notification for everything.'* – CAPROM_036.

Use of the Medisafe app after the study – Most women stated that they would use the app after the study or in a following pregnancy if they need to take medication because it is helpful and a good reminder. *'But if I still have to take medication, I think that could be useful, or I can imagine that it could be useful for people who have to take medication. Yes, it's a good reminder, yes.'* – CAPROM_035. Moreover, CAPROM_032 indicated that it would be helpful to use the app for

the baby as well. *'Yes, maybe not only for my own medication but also for the baby. There will be things coming my way that need to happen with regularity, and it would be handy that these things can be entered.'* – CAPROM_032. A few women did not want to use the app in the future because it had no added value for them. *'No, then I wouldn't do it because it has no added value for me in itself. If it's for the follow-up of the doctors, I can perfectly agree, but purely for that reminder, I wouldn't do it.'* – CAPROM_014.

DISCUSSION

FARO study – In the study population, there was a significant difference in BMI at baseline between the groups. However, it is demonstrated in literature that a higher BMI is correlated with a higher CO, which was also shown in our study (32, 33). EPE in the previous pregnancy outcome was more prevalent in the low CO group, while LPE in the previous pregnancy was more prevalent in the high CO group, which is also demonstrated in literature. In the Italian population with a high-risk pregnancy, the CO at 24 weeks gestation in pregnancies complicated by EPE was significantly lower than the normotensive pregnancies, and the CO in pregnancies complicated by LPE was significantly higher than both normotensive pregnancies and EPE pregnancies (34). One year postpartum, the CO of women who had LPE in their pregnancy was still significantly higher compared to the women who had a normotensive pregnancy and who had EPE in their pregnancy (34). Thus, these results are in line with the observation from our study, however, there was no significant difference in the previous pregnancy outcome between the groups, which may be due to the small sample size.

In the PC measurement, a significant difference in TPR between the groups was demonstrated. A higher CO corresponds with a lower TPR, which was expected since the MAP was not significantly different between the groups. The TPR and the CO are the key determining factors for the MAP according to Ohm's equation: MAP = CO * TPR (10). The key result, comparing the CO before and after physical activity, showed a significant increase within the group with a low CO, a significant decrease within the group with a high CO, and no difference within the group with a normal CO. This implies that physical activity

improved the CO towards a normal CO. Long-term physical activity is associated with morphologic adaptations such as left ventricle (LV) dilatation, resulting in increased LV end-diastolic volume, and cardiac hypertrophy (i.e. increased wall thickness) (35, 36). These adaptations result in an increased stroke volume and CO (35, 36). On the other hand, physical activity reduces intrahepatic fat in adults with overweight or obesity, which is associated with a high CO (33, 37). Reduced intrahepatic fat may have a beneficial effect on the blood-storage capacity of the veins in the splanchnic bed and liver, subsequently improving the storage of passive reserve blood and reducing the amount of actively moving blood in the circulation (9). This may explain a decrease in CO in the high CO group after a period of physical activity. Another prospective study with pre-conceptional women planning a pregnancy showed an association between pre-conceptional CO and subsequent pregnancy outcome. A significantly lower pre-conceptional CO was shown in women affected by pre-eclampsia or IUGR compared to uncomplicated pregnancies (38). In the English pregnant population, it was shown that women with preterm GH had a significantly lower CO compared with normotensive pregnancies (39). In another study with pregnant English women, it was shown that pregnancies complicated with only PE had a significantly higher CO, and pregnancies complicated with PE and IUGR had a significantly lower CO compared to uncomplicated pregnancies (40). Therefore, it is of importance to improve the CO before conception can be pursued. In the PCPS measurement, the CO of the high CO group was still significantly higher than the CO in the low and normal CO groups, while there was no longer a significant difference in CO between the low CO group and the normal CO group. Thus, after the advice of physical activity, the group with a low CO was sufficiently improved to reach a normal CO. A randomized controlled trial (RCT) that examined supervised physical activity in pregnant Spanish women had shown that maternal exercise may be a preventive tool for hypertension. The incidence of hypertension and PE were significantly lower in the exercise group (41). Furthermore, a case-control study with Swedish women had demonstrated that physical activity during the year before pregnancy was associated with a 33% reduction in risk for PE (42). Moreover, women who were physically active before and during pregnancy experienced a 41% reduced risk of PE compared to women who were inactive before and during pregnancy (42).

Despite this promising result, our study had some limitations, such as missing demographic data. Furthermore, there was no supervision or objective measurement to check whether or not the women followed the advice to exercise. Hence, some women may have exercised more than recommended, while others may not have exercised or may have exercised less than recommended. Therefore, exercising must be followed up correctly in a subsequent study in order to draw conclusions.

As a future perspective, the following prospective study is recommended to overcome the limitations previously described. In this future RCT, pre-conceptional women at risk for the development of GHD will be divided into two groups. For ethical reasons, both groups will be advised to exercise for a period of 12 weeks. However, only one group will be supervised during the exercise under the assumption that this group engages in more physical activity compared to the other group. With this study design, we can compare the improvement of the CV profile after physical activity and the pregnancy outcomes of their following pregnancy between the two groups.

CAPROM study – The results demonstrated that pregnant women showed positive attitudes towards medicines in general. Although pregnant women had a higher threshold to use medicines during pregnancy, most of them recognized the potential benefits of medication use during pregnancy. The latter result was also shown in Norwegian pregnant women, although they had a less positive attitude towards medicines in general (24). Merely half of the Norwegian women disagreed that medicines do more harm than good and that all medicines are poisons (24). In contrast, Ethiopian pregnant women had a very positive attitude towards medicines in general (43). However, these women's beliefs on medication use during pregnancy were ambiguous. In this Ethiopian population, 69.4% disagreed to have a higher threshold to use medicines during pregnancy, and 84.7% agreed that it is better for the fetus to use medicines and get better than to have an untreated illness during pregnancy (43). On the other hand, 62.5% of the Ethiopian women agreed that all medicines are harmful to the fetus, which is in conflict with the previous statements (43). In our

study, the beliefs on medication use showed a more positive attitude concerning the statement 'doctors prescribe too many medicines during pregnancy' at postpartum compared to baseline. Because the study is still ongoing, the sample size at this moment is relatively small regarding the beliefs and perceptions on medication use and medication adherence. Additionally, follow-up has not yet been completed for most participating women, especially with regard to the six-month postpartum follow-up, which was therefore not included in the analysis.

The results concerning the Medisafe app revealed that it was easy and user-friendly, and that it helped to remind the women, who are forgetful, to take their medication. Most women would use the app again in the future if they had to take medication. Thus, the app was considered feasible among pregnant women who had to take medication. This is of importance because medication non-adherence to Asaflow and antihypertensive medication during pregnancy is estimated to be between 21.4% – 46.3% and between 3% – 65%, respectively (20, 21). Furthermore, 59.1% of Australian pregnant women were non-adherent to prescribed medication, mainly because of forgetfulness (44). The median medication non-adherence to Asaflow in our study was 8.96%, which is lower compared to the non-adherence demonstrated in literature. This could indicate that the Medisafe app might improve medication adherence in pregnant women at risk for GHD. The ten interviewed women were all nulliparous, therefore it is recommended to interview multiparous women as well to rule out that parity may influence the experiences with the Medisafe app. The results in pregnant women in this study were similar to the perceptions of the Asian population with type 2 diabetes regarding the Medisafe app (45). In this population, 90.9% agreed that the app was easy to use, and 86.4% would continue to use the Medisafe app after the study (45). The experiences with the Medisafe app of American patients with chronic conditions were also comparable to the experiences of the pregnant women (46). The reminders of the app were helpful, and some patients stated that they would use the app in the future. One of the patients stated that customizing the shape and color of the pills was nice, which was also appointed by CAPROM_002 (46). As a future perspective, an RCT is recommended to investigate if the Medisafe app improves medication adherence among pregnant women. The intervention group will use the Medisafe, while the control group will not use the Medisafe app. With this study design, the medication adherence between the two groups can be compared.

CONCLUSION

In conclusion, physical activity improved the CO towards a CO within normal reference ranges in pre-conceptional women at risk for GHD. This promising result is of importance because the pregnancy outcomes for both the mother and fetus may be more favorable if the CV profile has been improved prior to conception by physical activity. Further research is required to investigate physical activity as potential preventive therapy for GHD. Furthermore, positive attitudes towards medicines in general and during pregnancy were observed among pregnant women at risk for GHD. Their attitudes towards medicines and their medication adherence postpartum were similar to baseline. Lastly, the Medisafe app was perceived as easy and user-friendly. The majority of pregnant women had positive experiences with this app, however, further research is required to examine if the Medisafe app improves medication adherence within this population.

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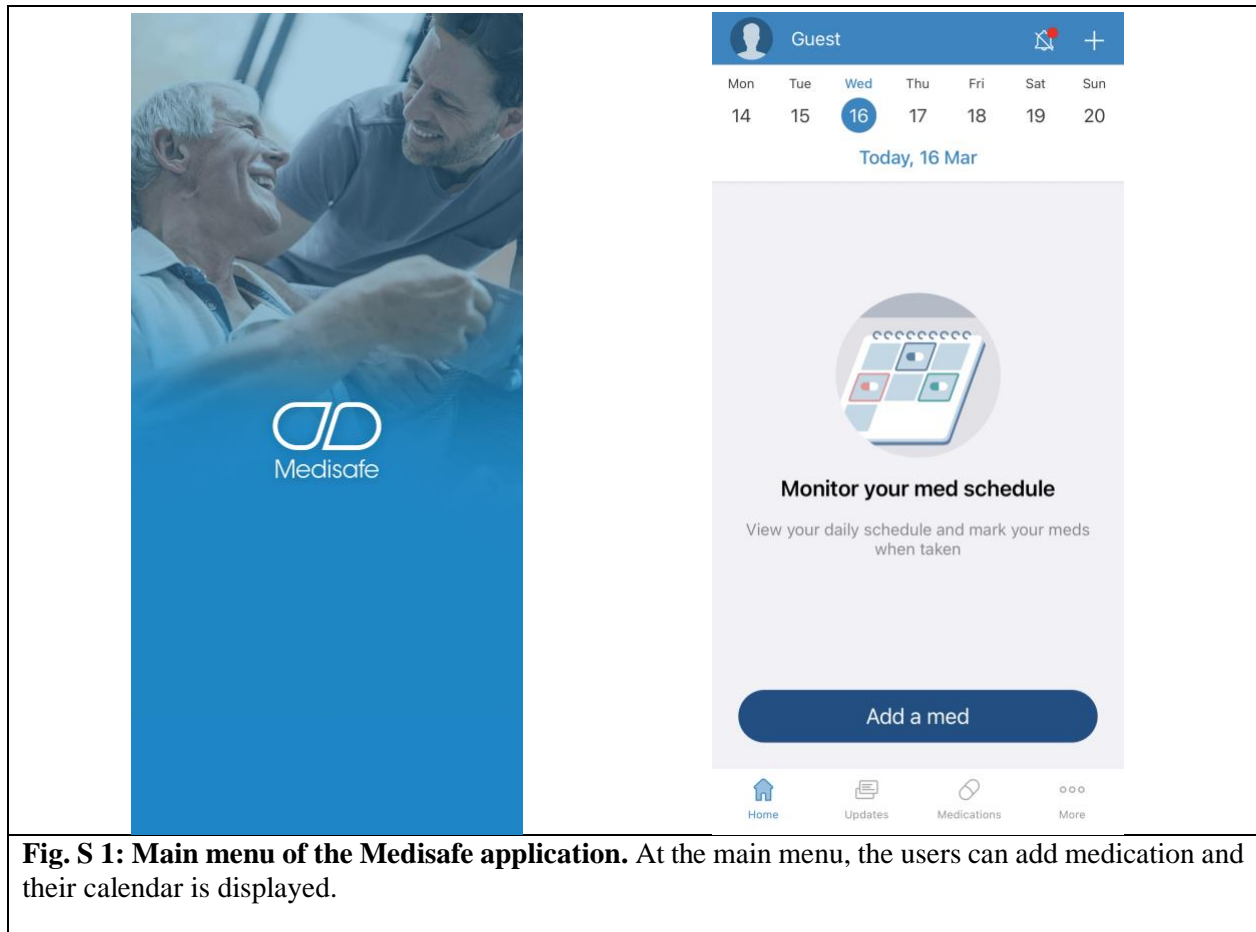
SUPPORTING INFORMATION

Fig. S 1: Main menu of the Medisafe application. At the main menu, the users can add medication and their calendar is displayed.

Table S 1 – Demographics and clinical characteristics of the FARO population.

	Low CO	Normal CO	High CO	P-value
	N = 25	N = 84	N = 45	
Age (years)	32.0 (29.0-35.5)	31.0 (29.0-35.8)	31.0 (28.5-33.0)	0.471
BMI (kg/m^2)	20.1 (19.2-22.6)	23.1 (21.4-26.7)	27.5 (24.8-32.5)	**<0.001** [a,b,c]
Indication CV measurement				
EH	6 (24.0%)	13 (15.5%)	9 (20.0%)	0.578
Previous pregnancy complications	15 (60.0%)	65 (77.4%)	28 (62.2%)	0.106
GH	*1 (6.7%)*	*8 (12.3%)*	*2 (7.1%)*	*0.901*
EPE	*4 (26.7%)*	*21 (32.3%)*	*7 (25.0%)*	*0.792*
LPE	*4 (26.7%)*	*16 (24.6%)*	*7 (25.0%)*	*1.000*
IUGR	*3 (20.0%)*	*11 (16.9%)*	*4 (14.3%)*	*0.871*
HELLP	*6 (40.0%)*	*15 (23.1%)*	*8 (28.6%)*	*0.370*
Other	*1 (6.7%)*	*13 (20.0%)*	*6 (21.4%)*	*0.465*
Familial GH	0 (0.0%)	4 (4.8%)	1 (2.2%)	0.702
Familial EH	1 (4.0%)	1 (1.2%)	3 (6.7%)	0.186
Low birth weight	2 (8.0%)	10 (11.9%)	1 (2.2%)	0.177
Other	9 (36.0%)	27 (32.1%)	17 (37.8%)	0.823
Comorbidity				
Hypertension	9 (52.9%)	15 (31.3%)	8 (29.6%)	0.232
Diabetes	0 (0.0%)	4 (8.3%)	2 (7.4%)	0.730
Thyroid problems	0 (0.0%)	9 (18.8%)	2 (7.4%)	0.088
Kidney problems	0 (0.0%)	3 (6.3%)	0 (0.0%)	0.429
Other	6 (35.3%)	18 (37.5%)	6 (22.2%)	0.436
Family history of CV	9 (90.0%)	16 (51.6%)	12 (52.2%)	0.085
Previous pregnancy outcome				
Normal	1 (9.1%)	6 (12.2%)	6 (22.2%)	0.563
GH	0 (0.0%)	5 (10.2%)	1 (3.7%)	0.481
EPE	4 (36.4%)	8 (16.3%)	3 (11.1%)	0.184
LPE	1 (9.1%)	9 (18.0%)	6 (22.2%)	0.732
HELLP	3 (27.3%)	15 (30.6%)	8 (29.6%)	1.000
IUGR	1 (9.1%)	4 (8.2%)	1 (3.7%)	0.712
MIU	1 (9.1%)	1 (2.0%)	0 (0.0%)	0.332
Placenta abruptio	0 (0.0%)	1 (2.0%)	2 (7.4%)	0.527

Data are presented as mean (±SD), median (IQR), and n (%). BMI: body mass index, CV: cardiovascular, EH: essential hypertension, GH: gestational hypertension, EPE: early pre-eclampsia, LPE: late pre-eclampsia, IUGR: intrauterine growth restriction, HELLP: hemolysis – elevated liver enzymes – low platelets, MIU: mors in utero. A p-value <0.05 is considered statistically significant. [a] Low CO – normal CO significant difference, [b] low CO – high CO significant difference, [c] normal CO – high CO significant difference.

Table S 2 – Comparison before and after physical activity within the group with a low CO.

	PC	PCPS	P-value
	N = 11	N = 11	
Liver VPTT (ms)	0.15 (0.12-0.21)	0.11 (0.10-0.20)	0.169
Liver HVI	1.38 (0.89-1.55)	1.37 (1.22-1.49)	0.286
R K VPTT (ms)	0.28 (0.18-0.38)	0.25 (0.15-0.33)	0.722
R RIVI	0.46 (±0.13)	0.51 (±0.14)	0.317
L K VPTT (ms)	0.30 (0.25-0.40)	0.31 (0.15-0.33)	0.594
L RIVI	0.41 (0.35-0.45)	0.46 (0.31-0.61)	0.929
R Ut APTT (ms)	0.24 (0.22-0.25)	0.24 (0.20-0.25)	0.612
R Ut PI	1.28 (±0.26)	1.33 (±0.22)	0.886
R Ut RI	0.79 (0.69-0.85)	0.79 (0.74-0.88)	0.374
L Ut APTT (ms)	0.22 (0.21-0.24)	0.24 (0.21-0.26)	0.173
L Ut PI	1.32 (1.23-1.56)	1.42 (1.20-1.53)	0.534
L Ut RI	0.83 (0.77-0.88)	0.83 (0.75-0.87)	0.799
TBW (L)	30.9 (28.6-32.6)	30.7 (28.4-31.2)	0.722
ECW (L)	13.2 (12.2-14.3)	13.1 (11.9-13.5)	0.657
ICW (L)	17.6 (16.8-18.1)	17.5 (16.5-18.1)	0.646
ECW/ICW	0.74 (0.71-0.79)	0.72 (0.72-0.77)	0.859
DBP (mmHg)	91 (86-96)	90 (85-92)	0.266
MAP (mmHg)	105 (95-108)	102 (95-102)	0.386
VI (1/100/s)	57 (48-74)	70 (57-79)	0.110
ACI (1/100/s^2)	136 (±42)	166 (±38)	**0.016**
LVET (ms)	238 (223-252)	243 (227-268)	0.657
CO (L/min)	4.4 (4.1-4.5)	5.0 (4.5-5.8)	**0.015**
TPR	1867 (1767-2009)	1632 (1413-1813)	**0.004**

Data are presented as mean (±SD) and median (IQR). Liver VPTT: liver venous pulse transit time, HVI: hepatic vein index, R K VPTT: right kidney venous pulse transit time, R RIVI: right renal interlobar vein impedance index, L K VPTT: left kidney venous pulse transit time, L RIVI: left renal interlobar vein impedance index, R Ut APTT: right uterine arterial pulse transit time, R Ut PI: right uterine pulsatility index, R Ut RI: right uterine resistivity index, L Ut APTT: left uterine arterial pulse transit time, L Ut PI: left uterine pulsatility index, L Ut RI: left uterine resistivity index, TBW: total body water, ECW: extracellular water, ICW: intracellular water, DBP: diastolic blood pressure, MAP: mean arterial pressure, VI: velocity index, ACI: acceleration index, LVET: left ventricular ejection time, CO: cardiac output, TPR: total peripheral resistance. A p-value <0.05 is considered statistically significant.

Table S 3 – Comparison before and after physical activity within the group with a normal CO.

	PC	PCPS	P-value
	N = 15	N = 15	
Liver VPTT (ms)	0.16 (0.13-0.21)	0.15 (0.13-0.23)	0.164
Liver HVI	1.39 (1.22-1.55)	1.40 (1.16-1.57)	0.334
R K VPTT (ms)	0.23 (0.17-0.36)	0.24 (0.17-0.33)	0.820
R RIVI	0.50 (±0.13)	0.55 (±0.08)	0.154
L K VPTT (ms)	0.31 (0.25-0.37)	0.32 (0.24-0.38)	0.334
L RIVI	0.43 (0.38-0.50)	0.53 (0.44-0.60)	**0.031**
R Ut APTT (ms)	0.24 (0.22-0.27)	0.24 (0.22-0.29)	1.000
R Ut PI	1.30 (±0.26)	1.40 (±0.24)	0.128
R Ut RI	0.80 (0.73-0.86)	0.82 (0.78-0.89)	0.103
L Ut APTT (ms)	0.25 (0.22-0.29)	0.23 (0.22-0.28)	0.401
L Ut PI	1.39 (1.22-1.56)	1.36 (1.19-1.60)	0.164
L Ut RI	0.82 (0.75-0.88)	0.81 (0.75-0.89)	0.140
TBW (L)	32.9 (30.4-37.1)	32.0 (27.7-38.4)	0.691
ECW (L)	14.1 (12.9-15.6)	13.9 (11.5-16.9)	0.820
ICW (L)	18.8 (17.5-20.2)	17.2 (16.5-19.8)	0.443
ECW/ICW	0.74 (0.72-0.78)	0.75 (0.70-0.79)	0.469
DBP (mmHg)	91 (82-99)	91 (84-100)	0.775
MAP (mmHg)	101 (93-110)	101 (93-112)	0.614
VI (1/100/s)	70 (48-80)	67 (55-74)	0.909
ACI (1/100/s^2)	145 (±55)	146 (±48)	0.908
LVET (ms)	242 (224-261)	243 (228-267)	0.712
CO (L/min)	5.3 (5.2-5.6)	5.5 (5.0-6.5)	0.513
TPR	1538 (1353-1613)	1490 (1378-1629)	0.609

Data are presented as mean (±SD) and median (IQR). Liver VPTT: liver venous pulse transit time, HVI: hepatic vein index, R K VPTT: right kidney venous pulse transit time, R RIVI: right renal interlobar vein impedance index, L K VPTT: left kidney venous pulse transit time, L RIVI: left renal interlobar vein impedance index, R Ut APTT: right uterine arterial pulse transit time, R Ut PI: right uterine pulsatility index, R Ut RI: right uterine resistivity index, L Ut APTT: left uterine arterial pulse transit time, L Ut PI: left uterine pulsatility index, L Ut RI: left uterine resistivity index, TBW: total body water, ECW: extracellular water, ICW: intracellular water, DBP: diastolic blood pressure, MAP: mean arterial pressure, VI: velocity index, ACI: acceleration index, LVET: left ventricular ejection time, CO: cardiac output, TPR: total peripheral resistance. A p-value <0.05 is considered statistically significant.

Table S 4 – Comparison before and after physical activity within the group with a high CO.

	PC	PCPS	P-value
	N = 9	N = 9	
Liver VPTT (ms)	0.21 (0.16-0.28)	0.16 (0.11-0.34)	0.139
Liver HVI	1.18 (0.28-1.44)	1.28 (0.44-1.57)	0.214
R K VPTT (ms)	0.28 (0.19-0.40)	0.30 (0.15-0.41)	0.678
R RIVI	0.49 (±0.15)	0.50 (±0.12)	0.802
L K VPTT (ms)	0.34 (0.27-0.39)	0.32 (0.21-0.43)	0.110
L RIVI	0.43 (0.34-0.50)	0.53 (0.37-0.59)	0.173
R Ut APTT (ms)	0.25 (0.22-0.30)	0.24 (0.20-0.42)	1.000
R Ut PI	1.33 (±0.26)	1.59 (±0.08)	0.286
R Ut RI	0.80 (0.71-0.88)	0.89 (0.87-0.90)	0.213
L Ut APTT (ms)	0.24 (0.22-0.28)	0.26 (0.19-0.40)	0.715
L Ut PI	1.33 (1.21-1.48)	1.56 (1.50-1.65)	**0.021**
L Ut RI	0.80 (0.75-0.85)	0.87 (0.86-0.90)	0.213
TBW (L)	36.3 (34.2-39.8)	36.6 (33.1-38.8)	0.515
ECW (L)	16.0 (14.5-17.9)	15.9 (14.0-16.8)	0.594
ICW (L)	20.7 (19.9-22.2)	20.8 (19.1-22.1)	0.859
ECW/ICW	0.76 (0.73-0.80)	0.75 (0.73-0.76)	0.594
DBP (mmHg)	86 (84-95)	86 (82-92)	0.286
MAP (mmHg)	99 (92-106)	99 (95-105)	0.953
VI (1/100/s)	52 (47-73)	56 (53-63)	0.779
ACI (1/100/s^2)	124 (±39)	125 (±33)	0.976
LVET (ms)	247 (201-269)	228 (219-2364)	0.343
CO (L/min)	7.5 (7.3-8.0)	7.1 (6.5-8.0)	**0.041**
TPR	1056 (937-1093)	1053 (1005-1225)	0.086

Data are presented as mean (±SD) and median (IQR). Liver VPTT: liver venous pulse transit time, HVI: hepatic vein index, R K VPTT: right kidney venous pulse transit time, R RIVI: right renal interlobar vein impedance index, L K VPTT: left kidney venous pulse transit time, L RIVI: left renal interlobar vein impedance index, R Ut APTT: right uterine arterial pulse transit time, R Ut PI: right uterine pulsatility index, R Ut RI: right uterine resistivity index, L Ut APTT: left uterine arterial pulse transit time, L Ut PI: left uterine pulsatility index, L Ut RI: left uterine resistivity index, TBW: total body water, ECW: extracellular water, ICW: intracellular water, DBP: diastolic blood pressure, MAP: mean arterial pressure, VI: velocity index, ACI: acceleration index, LVET: left ventricular ejection time, CO: cardiac output, TPR: total peripheral resistance. A p-value <0.05 is considered statistically significant.

Table S 5 – A cross-tabulation of the group division based on CO at baseline and after physical activity.

		PCPS			
		Low CO	Normal CO	High CO	Total
PC	Low CO	5	6	0	11
	Normal CO	3	10	2	15
	High CO	0	3	6	9
	Total	8	19	8	35

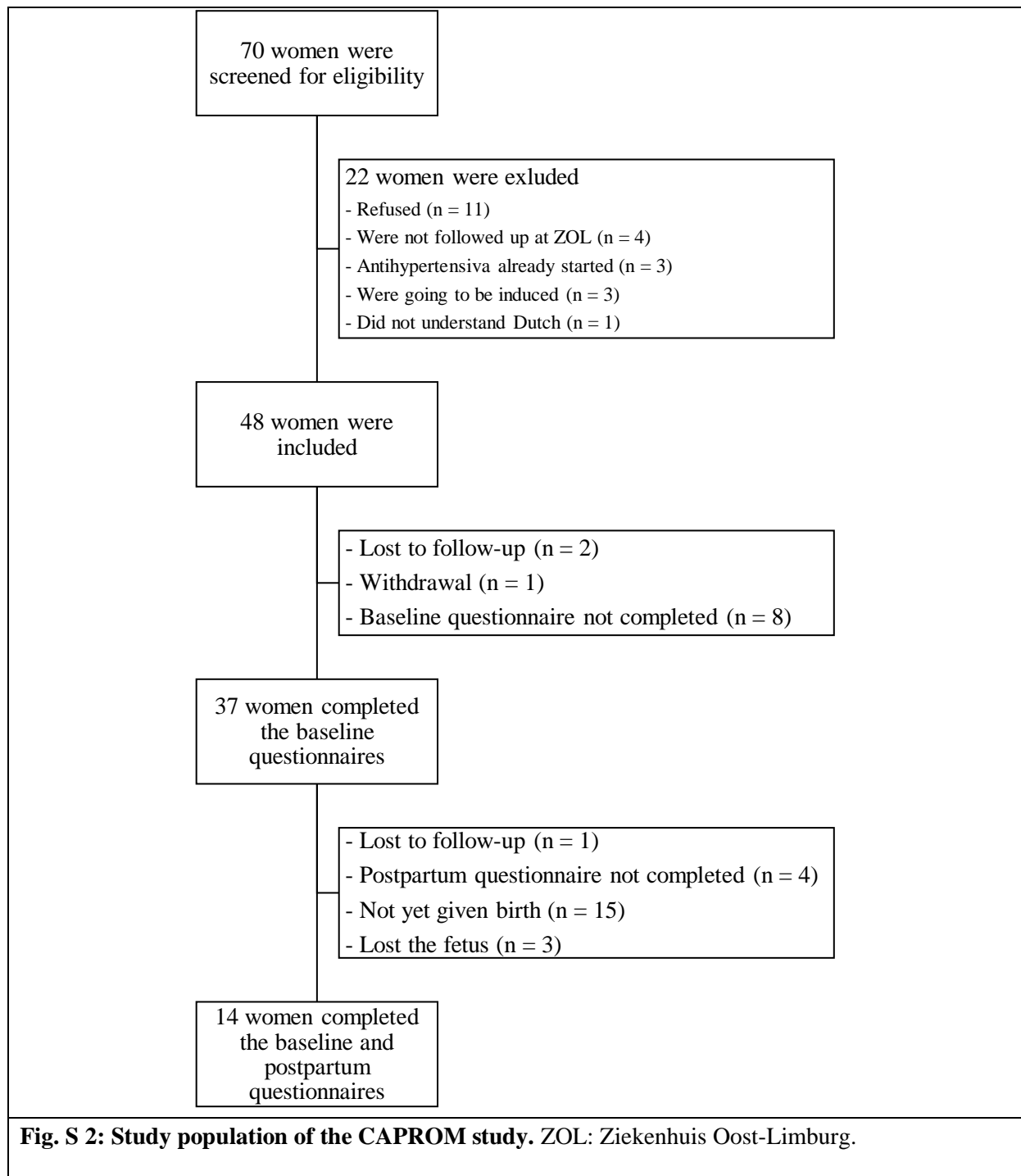CO: cardiac output, PC: pre-conceptional, PCPS: pre-conceptional post-sport.

Fig. S 2: Study population of the CAPROM study. ZOL: Ziekenhuis Oost-Limburg.

Table S 6 – A cross-tabulation of the statement 'Doctors prescribe too many medicines during pregnancy'.

		BMQ Postpartum (P6)		
		Disagree	Uncertain	Total
BMQ Baseline (P6)	Agree	0	1	1
	Disagree	7	0	7
	Uncertain	3	2	5
	Total	10	3	13

BMQ: Beliefs about medicines questionnaire, P6: Doctors prescribe too many medicines during pregnancy.