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ORIGINAL RESEARCH

Acute Coronary Syndrome and Ischemic Heart Disease in Pregnancy: Data From the EURObservational Research Programme-European Society of Cardiology Registry of Pregnancy and Cardiac Disease

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BACKGROUND: The prevalence of ischemic heart disease (IHD) in women of child-bearing age is rising. Data on pregnancies however are scarce. The objective is to describe the pregnancy outcomes in these women.

METHODS AND RESULTS: The European Society of Cardiology-EURObservational Research Programme ROPAC (Registry of Pregnancy and Cardiac Disease) is a prospective registry in which data on pregnancies in women with heart disease were collected from 138 centers in 53 countries. Pregnant women with preexistent and pregnancy-onset IHD were included. Primary end point were maternal cardiac events. Secondary end points were obstetric and fetal complications. There were 117 women with IHD, of which 104 had preexisting IHD. Median age was 35.5 years and 17.1% of women were smoking. There was no maternal mortality, heart failure occurred in 5 pregnancies (4.8%). Of the 104 women with preexisting IHD, 11 women suffered from acute coronary syndrome during pregnancy. ST-segment–elevation myocardial infarction were more common than non–ST-segment–elevation myocardial infarction, and atherosclerosis was the most common etiology. Women who had undergone revascularization before pregnancy did not have less events than women who had not. There were 13 women with pregnancy-onset IHD, in whom non–ST-segment–elevation myocardial infarction was the most common. Smoking during pregnancy was associated with acute coronary syndrome. Caesarean section was the primary mode of delivery (55.8% in preexisting IHD, 84.6% in pregnancy-onset IHD) and there were high rates of preterm births (20.2% and 38.5%, respectively).

CONCLUSIONS: Women with IHD tolerate pregnancy relatively well, however there is a high rate of ischemic events and these women should therefore be considered moderate- to high-risk. Ongoing cigarette smoking is associated with acute coronary syndrome during pregnancy.

Key Words: acute coronary syndrome ■ infarction ■ ischemic heart disease ■ maternal health ■ pregnancy

Maternal heart disease is an important cause of maternal mortality worldwide and is in fact the number 1 cause of maternal mortality in western countries.[1] From the 2016 Confidential Enquiry into maternal deaths in the United Kingdom, it is known that ischemic heart disease (IHD) and myocardial infarction

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CLINICAL PERSPECTIVE

What Is New?

- To our knowledge, this is the largest prospective study to date on pregnancy in women with ischemic heart disease. We discovered that women with ischemic heart disease are significantly older, more often smoker and diabetic and more hypertensive and overweight than women without ischemic heart disease, and that smoking during pregnancy is predictive of the occurrence of new ischemic events during pregnancy.

What Are the Clinical Implications?

- By identifying these risk factors, pre-pregnancy counseling and management during pregnancy of women at risk, can be done more evidence-based and individually focused.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
CS	caesarean section
EORP	EURObservational Research Programme
ESC	European Society of Cardiology
HELLP	hemolysis, elevated liver enzymes and low platelets
IHD	ischemic heart disease
NSTEMI	non–ST-segment–elevation myocardial infarction
ROPAC	Registry Of Pregnancy And Cardiac disease
SCAD	spontaneous coronary artery dissection
STEMI	ST-segment–elevation myocardial infarction

during pregnancy are the most important contributors to maternal mortality from cardiac disease.[2] In pregnant women, there is a 3- to 4-fold increase in risk of myocardial infarction compared with age-matched non-pregnant women of comparable age.[3] With the trend of delaying motherhood to an older age, the associated rise in traditional risk factors for atherosclerosis such as obesity, and an ongoing prevalence of cigarette smoking, the burden of IHD in women of childbearing age is expected to increase. Coronary events during pregnancy however are not solely attributable to an atherosclerotic substrate. There are several other pathophysiological mechanisms that are generally less common or equally or more prevalent during pregnancy, such as pregnancy-associated spontaneous coronary artery dissection, coronary spasms, and coronary thrombi. Data on maternal and fetal pregnancy outcomes in women with IHD are scarce and current evidence is mostly based on small retrospective studies and expert opinion. The purpose of this study is to describe the cardiovascular, obstetric and fetal outcomes of pregnancy in a prospective cohort of women with ischemic heart disease, and to identify predictors of acute coronary syndrome (ACS) during pregnancy.

METHODS

Study Design

The ROPAC (Registry on Pregnancy and Cardiac Disease) from EURObservational Research Programme (EORP) of the European Society of Cardiology (ESC), is a worldwide, prospective registry of pregnant women with heart disease. Study design and methods have been described in detail previously.[4] All national societies of the ESC were informed and invited to contact centers in their countries dealing with pregnancy and heart disease. In addition, other centers that were interested in the registry were invited to participate. All participating centers had Medical Ethical Committee approval and all participating patients signed informed consent forms. The data that support the findings of this study are available from the corresponding author upon reasonable request. Pregnant women were included from 2007 up to 2018. For this analysis, all pregnancies in women with preexisting IHD before pregnancy and with ACS during pregnancy were included. Thus, multiple pregnancies in one woman could be included. Because of the anonymized nature of the database it is not possible to check whether multiple pregnancies in one woman were included. Therefore, in ROPAC, each pregnancy is considered an individual patient.

Definitions and End Points

The primary end point was the occurrence of a maternal cardiac event during pregnancy up to 6 months post-partum and included maternal mortality, heart failure, atrial fibrillation or flutter, ventricular tachyarrhythmias, endocarditis, thromboembolic events and, in the women with preexistent IHD, the occurrence of ACS during pregnancy. Prior IHD was defined as either based on prior coronary angiography, ECG changes consistent with ischemia or prior episodes of complaints with elevated troponin levels. ACS was defined according to the ESC Guidelines.[5–7] Secondary end points were obstetric outcome (major post-partum hemorrhage, caesarean section and emergency caesarean section, preeclampsia and eclampsia and

pregnancy-induced hypertension) and fetal outcome (prematurity, fetal mortality, neonatal mortality, intrauterine growth restriction, low birth weight and low Apgar score). Heart failure was defined according to the ESC guidelines[8] and heart failure episodes were only included when they required hospital admission, new treatment or change in existing treatment regimen. Impaired left ventricular function was defined as a left ventricular ejection fraction of <40%. Postpartum hemorrhage was defined as increased blood loss (>500 mL after vaginal delivery or >1000 mL after caesarean delivery) directly after delivery and up until 24 hours postpartum. Pregnancy-induced hypertension, (pre-) eclampsia and hemolysis, elevated liver enzymes and low platelet-syndrome were defined according to the International Society for the Study of Hypertension in Pregnancy 2012 statement.[9] Fetal mortality was defined as the death of a fetus after 24 weeks of gestation up until before birth. Neonatal mortality was defined as the death of a live-born baby within the first 6 months of life. Premature birth was defined as birth before 37 weeks of gestation. Low birth weight was defined as a birth weight of <2500 g. Low Apgar score was defined as an Apgar score at 5 minutes of <7. All primary and secondary outcomes occurring during pregnancy and up to 6 months post-partum were included.

Data

The ROPAC study protocol and the first results of this registry were published in 2013[4] and the results of the complete registry were published in 2019.[10] Baseline characteristics collected before pregnancy included age, New York Heart Association functional classification, ECG rhythm, diagnosis, risk factors (smoking habits, hypertension, diabetes mellitus), medication, previous interventions, parity and obstetric history and echocardiographic measurements. Countries were divided into developed or emerging countries according to the International Monetary Fund Classification. Twin pregnancies were included as one pregnancy.

Statistical Analysis

Numerical data are presented as mean values and SD or median with range depending on normality. Categorical data are presented as frequencies and percentages. Univariable analyses to identify baseline characteristics associated with ACS during pregnancy were performed with Chi-square tests, Fisher exact tests, Student *t*-tests or Mann–Whitney *U* tests as appropriate. Variables with $P<0.05$ in the univariable analysis were used in a multivariable logistic regression analysis to identify independent predictors of ACS during pregnancy. Missing values were handled with multiple imputation, as described in Data S1. A *P* value of <0.05 (2-sided test) was considered significant. All statistical tests and analyses were performed with SPSS version 21.0 and 25.0 (SPSS Inc., Chicago).

RESULTS

Of the 5739 pregnancies in ROPAC, 104 pregnancies in women with preexisting IHD and 13 in women in whom IHD was first diagnosed in pregnancy (a total of 117 pregnancies in women with IHD) were included in this study. Median age was 35.5 years and in 25.6% of pregnancies women were nulliparous. Median body mass index was 27.1 and 17.1% of women were smoking during pregnancy. The baseline characteristics for the total IHD group and specified for the preexisting and pregnancy-onset groups are shown in Table 1. Of the 104 pregnancies in women with preexisting IHD, 73 (70.2%) women had undergone a coronary intervention before pregnancy: in 60 this was a percutaneous coronary intervention, in 9 a coronary artery bypass grafting and in 4 both percutaneous coronary intervention and coronary artery bypass grafting. The severity of the preexisting IHD is shown in Figure S1. The majority of patients suffered from single-vessel disease (43%). Table 1 also shows the baseline characteristics of the IHD group compared with the non-IHD patients within ROPAC. Women with IHD were significantly older, had higher body mass index, higher incidences of hypertension, diabetes mellitus, and were more often smoking. A total of 24 women suffered from ACS during or after pregnancy, 1 in the first trimester, 1 in the second trimester, 21 in the third trimester, and 1 8 weeks post-partum.

Preexisting IHD: Maternal Outcome, Pathophysiology, Predictors, and Treatment

There were no cases of maternal mortality, while heart failure complicated 5 pregnancies (4.8%), see Table 2. Of the 5 women who suffered from heart failure, only 2 had impaired left ventricular function before pregnancy, while the other 3 concomitantly suffered from ACS during pregnancy. In 11 of the 104 women (10.6%) an ACS occurred during the current pregnancy, 8 had an ST-segment–elevation myocardial infarction (STEMI) and 3 a non–ST-segment–elevation myocardial infarction (NSTEMI). Of the 11 women with ACS during pregnancy, there were 5 cases of primary atherosclerosis (of which 3 also had a thrombus), 3 cases with a primary thrombus without atherosclerotic disease and 3 patients with a spontaneous coronary artery dissection (SCAD). In Table S1, the treatment regimens for the ACS in women with preexisting IHD are shown for the different pathological mechanisms. Nine percutaneous

Table 1. Baseline Characteristics of the Total IHD Group Compared With the Rest of the ROPAC Cohort Without IHD, and the Preexisting IHD Group Compared With the Pregnancy-Onset IHD Group

Baseline Characteristics	Total Cohort (n=117)	ROPAC Without IHD (n=5622)	*P* Value	Preexisting IHD (n=104)	Pregnancy-Onset IHD (n=13)	*P* Value
Demographics						
Age, y (median, range)	35.5 (18–49)	29.3 (18–52)	<0.001	35.5 (18–49)	38.1 (23–49)	0.73
Nulliparity	30 (25.6%)	2543 (45.2%)	<0.001	28 (26.9%)	2 (15.4%)	0.37
BMI in kg/m^2 (median, range)	21.7 (18.3–41.7)	23.9 (14.3–47.8)	<0.001	26.8 (18.3–40.7)	28.1 (23.9–41.7)	0.97
Emerging country	43 (36.8%)	2238 (39.8%)	0.33	36 (34.6%)	7 (53.8%)	0.68
Pre-pregnancy characteristics						
Non-smoker	68 (58.1%)	4186 (74.5%)	<0.001	60 (57.7%)	8 (61.5%)	0.29
Former smoker	16 (13.7%)	426 (7.6%)	0.01	13 (12.5%)	3 (23.1%)	0.29
Current smoker	20 (17.1%)	208 (3.7%)	0.01	20 (19.2%)	2 (15.4%)	0.22
Hypertension	32 (27.4%)	348 (6.2%)	<0.001	28 (26.9%)	4 (30.8%)	0.76
Atrial fibrillation	0 (0%)	106 (1.9%)	0.134	0 (0%)	0 (0%)	n.a.
Signs of heart failure	18 (15.4%)	578 (10.3%)	0.18	15 (14.4%)	3 (23.1%)	0.01
Diabetes mellitus	18 (15.4%)	72 (1.3%)	<0.001	16 (15.4%)	2 (15.4%)	0.54
History of NSTEMI	19 (16.2%)	0 (0%)	n.a.	19 (18.3%)	0 (0%)	n.a.
History of STEMI	26 (22.2%)	0 (0%)	n.a.	26 (25.0%)	0 (0%)	n.a.
History of CABG	13 (11.1%)	0 (0%)	n.a.	13 (12.5%)	0 (0%)	n.a.
History of PCI	64 (54.7%)	0 (0%)	n.a.	64 (61.5%)	0 (0%)	n.a.
History of angina pectoris without NSTEMI/STEMI	25 (21.4%)	0 (0%)	n.a.	25 (24.0%)	0 (0%)	n.a.
LVEF <40%	15 (12.8%)	289 (5.1%)	<0.001	13 (12.5%)	2 (15.4%)	0.69
Cardiac medication use	57 (48.7%)	1990 (35.4%)	<0.001	72 (69.2%)	7 (53.8%)	0.26
Beta blocker	21 (17.9%)	425 (7.6%)	<0.001	20 (19.2%)	1 (7.7%)	0.31
ACE-inhibitor	11 (9.4%)	66 (1.2%)	<0.001	11 (10.6%)	0 (0%)	0.001
Diuretics	2 (1.7%)	46 (0.8%)	0.42	2 (1.9%)	0 (0%)	0.35
Anti-platelet therapy*	39 (33.3%)	195 (3.5%)	<0.001	38 (36.5%)	1 (7.7%)	0.04
VKA	3 (2.6%)	393 (7.0%)	0.06	3 (2.9%)	0 (0%)	0.54
NYHA class†						0.15
NYHA class I	83 (70.9%)	4124 (73.4%)	0.56	76 (73.1%)	7 (53.8%)	
NYHA class II	23 (19.7%)	1168 (20.8%)	0.77	21 (20.2%)	2 (15.4%)	
NYHA class III	7 (6.0%)	169 (3.0%)	0.07	4 (3.8%)	3 (23.1%)	

P values were calculated between the women with IHD to the rest of the ROPAC cohort and between the preexisting and the pregnancy-onset IHD group with Chi-square tests and Mann–Whitney *U* tests where appropriate. ACE indicates angiotensin-converting enzyme; BMI, body mass index; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; IHD, ischemic heart disease; n.a., indicates not applicable; NSTEMI, non–ST-segment–elevation myocardial infarction; NYHA, New York Health Association; PCI, percutaneous coronary intervention; ROPAC, Registry of Pregnancy and Cardiac Disease; STEMI, ST-segment–elevation myocardial infarction; and VKA, Vitamin K antagonist.

*Antiplatelet therapy includes aspirin, ticagrelor, prasugrel, and clopidogrel.

†Unknown NYHA class in 3.4%.

coronary interventions were performed (7 for STEMI and 2 for NSTEMI), 1 patient underwent a coronary artery bypass grafting for STEMI and 1 NSTEMI was treated conservatively. Table 2 shows the most important cardiovascular events in women with preexisting IHD comparing women who underwent prior coronary interventions and women who did not. There were no significant differences between the 2 groups. Figure 1 shows the results of the univariable logistic regression analysis in women with preexisting IHD. In these women, smoking during pregnancy is significantly associated with new ACS during pregnancy.

Pregnancy-Onset ACS: Maternal Outcome, Pathophysiology and Treatment

Of the 13 women with a pregnancy-onset coronary event that did not have preexisting IHD, there were no cases of maternal mortality, but 1 woman suffered from heart failure during pregnancy, as shown in Table 3. Of

Table 2. Maternal Cardiovascular Outcome

Maternal Cardiovascular Outcome	Total Cohort (n=117)	Preexisting IHD (n=104)	Pregnancy-Onset IHD (n=13)	*P* Value	Prior Intervention (n=73)	No Prior Intervention (n=31)	*P* Value
Maternal mortality	0 (0%)	0 (0%)	0 (0%)	n.a.	0 (0%)	0 (0%)	n.a.
Hospital admission for cardiac reasons	26 (22.2%)	16 (15.4%)	10 (76.9%)	<0.001	11 (15.1%)	15 (34.1%)	0.02
Acute coronary syndrome	24 (20.5%)	11 (10.6 %)	13 (100%)	<0.001	9 (17.0%)	2 (6.5%)	0.17
Heart failure during pregnancy	6 (5.1%)	5 (4.8%)	1 (7.7%)	0.66	4 (5.5%)	2 (4.5%)	0.82
Heart failure post-partum	1 (0.9%)	1 (1.0%)	0 (0%)	0.54	3 (4.1%)	0 (0%)	0.17
Atrial fibrillation or flutter	0 (0%)	0 (0%)	0 (0%)	n.a.	0 (0%)	0 (0%)	n.a.
Ventricular tachyarrhythmias	2 (1.7%)	1 (1.0%)	1 (7.7%)	0.08	1 (1.9%)	0 (0%)	0.44
Thrombo-embolic events	1 (0.9%)	1 (1.0%)	0 (0%)	0.72	1 (1.9%)	0 (0%)	0.44

P values were calculated using Chi-square tests between pregnancy-onset ischemic heart disease and preexisting ischemic heart disease and between women who have undergone prior coronary interventions and women who have not. IHD indicates ischemic heart disease.

the 13 women with ACS, 3 suffered from STEMI and 6 from NSTEMI, all during pregnancy. There were 3 women with unstable angina pectoris and in 1 woman the type of ACS was unknown. There were 2 cases of SCAD (1 STEMI and 1 NSTEMI), in 4 women there was underlying atherosclerotic disease (of which 2 with a thrombus and 1 of which was a STEMI), one woman suffered from coronary spasm (NSTEMI) and 1 from an isolated coronary thrombus (NSTEMI). In 5 women no coronary angiography was performed and thus no clear cause was defined. In Figure 2 the distribution of the different types of ACS is shown and in Table S1, the treatment regimens for the ACS in women with pregnancy-onset IHD are shown for the different pathological mechanisms. Six percutaneous coronary interventions were performed, of which 1 was for an SCAD (STEMI).

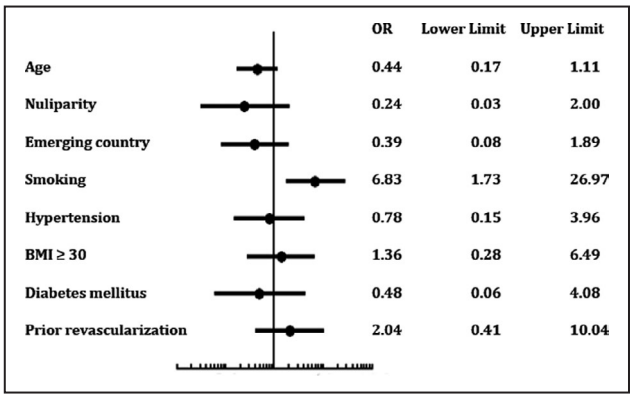

Figure 1. Results of the univariable logistic regression analysis, identifying predictors of acute coronary syndrome in pregnancy in women with preexisting ischemic heart disease (n=104).
Age was divided into ordinal categories defined as <25, 25 to 34, 35 to 44 and ≥45 years, with age <25 years as the reference category. Smoking was defined as current smoking with reference category former and never smoking. Lower Limit=95% CI lower limit, upper Limit=95% CI upper limit. BMI indicates body mass index; and OR, odds ratio.

Obstetric and Fetal Outcome

The obstetric and fetal outcomes are summarized in Table 3. Gestational hypertension and (pre-)eclampsia occurred in respectively 5.8% and 4.8% of women. There were high rates of deliveries by caesarean section (55.8% in preexisting IHD and 84.6% in pregnancy-onset IHD) and high rates of preterm births (20.2% in preexisting IHD and 38.5% in pregnancy-onset IHD). Three neonates died within 6 months after birth, all of whom were born prematurely and of whom 1 had trisomy 18.

Medication During Pregnancy

Table S2 shows the cardiac medication use before and during pregnancy. There were 26 women who

Table 3. Obstetric and Fetal Outcomes

Obstetric and Fetal Outcome	Preexisting IHD (n=104)	Pregnancy-Onset IHD (n=13)	*P* Value
Fetal mortality	1 (1.0%)	0 (0%)	1.00
Neonatal mortality	2 (1.9%)	1 (7.7%)	0.30
Congenital heart disease	2 (1.9%)	0 (0%)	1.00
Other congenital disease	5 (4.8%)	0 (0%)	1.00
Pregnancy-induced hypertension	6 (5.8%)	0 (0%)	1.00
HELLP or (pre-)eclampsia	5 (4.8%)	0 (0%)	1.00
Caesarean section	58 (55.8%)	11 (84.6%)	0.053
Emergency caesarean	5 (4.8%)	1 (7.7%)	0.42
For cardiac reasons	2 (1.9%)	1 (7.7%)	0.30
Post-partum hemorrhage	5 (4.8%)	2 (15.4%)	0.17
Preterm delivery	21 (20.2%)	5 (38.5%)	0.15
Low Apgar score	9 (8.7%)	1 (7.7%)	1.00
Low birth weight	11 (10.6%)	3 (23.1%)	0.06
IUGR	8 (7.7%)	2 (15.4%)	0.31

P values were calculated using Fisher exact tests. HELLP indicates hemolysis, elevated liver enzymes and low platelets; IHD, ischemic heart disease; and IUGR, intra-uterine growth restriction.

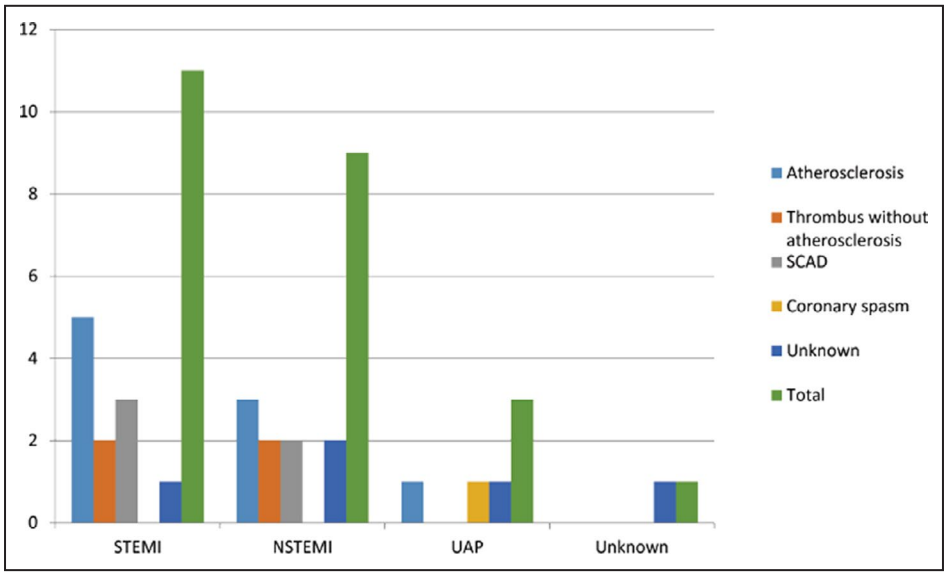

Figure 2. Distribution and pathophysiology of the different types of acute coronary syndrome during pregnancy.
NSTEMI indicates non–ST-segment–elevation myocardial infarction; SCAD, spontaneous coronary artery dissection; STEMI, ST-segment–elevation myocardial infarction; and UAP, unstable angina pectoris.

were using statins before pregnancy (22.2%), of which 9 continued during pregnancy and 1 woman newly started statins during pregnancy. The risk of structural congenital anomalies in the newborns of women using statins (*P*=0.99), antiplatelet therapy (*P*=0.50) and beta blockers (*P*=0.99) during pregnancy was not different compared with those not on these medications. Between women who were using beta-blockers during pregnancy and women who were not, the incidences of intra-uterine growth restriction (*P*=0.79) and low birth weight (*P*=0.98) were not significantly different.

DISCUSSION

To our knowledge, this is the largest prospective study to date on pregnancy outcomes in women with preexisting and pregnancy-onset IHD. In women with preexisting IHD, no maternal mortality occurred and the incidence of ACS during subsequent pregnancy was 10.6%. Women with IHD were older and had more often co-morbidities. Smoking during pregnancy was associated with the occurrence of ACS during pregnancy in women with known IHD. Also, no maternal mortality occurred in the women with pregnancy-onset IHD. Rates of deliveries by caesarean section were extremely high, especially in the group with pregnancy-onset IHD (84.6%).

Maternal Cardiovascular Outcome

There were no maternal deaths in our study. The 5% heart failure rate suggest that the majority of women with preexisting IHD coped well with the increased cardiovascular demands induced by pregnancy. In 104 women with preexisting IHD, an ACS occurred during pregnancy in 11 (10.6%). This is in accordance with a recent systematic review by Lameijer et al on pregnancy outcomes in 124 pregnancies in 116 women with preexistent IHD, in which authors found a coronary ischemic event rate of 9%.[11] According to the guideline definition of ACS, we have included unstable angina pectoris in our study as a coronary ischemic event, which could explain why our incidence of ACS is slightly higher than that found in the systematic review, although this might not be a significant difference In accordance with the current literature, the vast majority of women suffered from ACS in the third trimester.[12,13] Possibly the increase in cardiac output during pregnancy gradually increases the myocardial oxygen demand, peaking in the third trimester.[14] Also, the integrity and constitution of the coronary artery wall may be affected by hormonal alterations in the last stages of pregnancy, leading to changes in collagen and thus an increased risk of coronary dissection.[12]

Maternal smoking status seems to be important for predicting the ACS risk during pregnancy in women with preexisting IHD. While former smoking was not a predictor of ACS in our study, smoking during pregnancy was most strongly associated with the occurrence of ACS in women with preexisting IHD. Elkayam et al[15] also found this cardiovascular risk factor to be common in women with acute

myocardial infarctions during pregnancy. Ladner et al[12] found that chronic hypertension, diabetes mellitus, advanced maternal age, and (pre-)eclampsia were additional independent risk factors for ACS during pregnancy.

Of the 24 cases of ACS in our study, 55% were STEMI and 45% NSTEMI. Elkayam et al[15] also found that during pregnancy, STEMI is more common than NSTEMI. Furthermore, coronary atherosclerosis was the most common pathophysiological basis of ACS during pregnancy in our study (39%), a finding that is consistent with the literature.[11,16] It is notable however, that the women who had undergone pre-pregnancy coronary revascularization did not have significantly different outcome than those who had not. Lameijer et al[11] also found that revascularization therapy pre-pregnancy did not influence the primary end point of ischemic cardiovascular events. These findings are in relative contradiction to the current ESC guideline,[3] in which it is stated that women with prior IHD and residual ischemia should be discouraged from having subsequent pregnancies. Unfortunately, in our study the pathology of the ischemic events that women suffered before pregnancy is not known (ie, SCAD, coronary spasm, atherosclerotic disease). It can of course be that the women who were not revascularized before pregnancy, were those without an underlying atherosclerotic substrate and thus had no residual ischemia to begin with, or that they had less severe disease. Further studies are needed to assess the need for revascularization before pregnancy, especially when the underlying coronary artery disease is non-atherosclerotic. Of course, when there is detectable ischemia, this should evidently be treated before embarking upon a pregnancy.

Mortality rates in women with preexisting IHD vary in the literature, with reported incidences between 0% and 23%.[3] From the 2016 Confidential Enquiry into maternal deaths in the United Kingdom, we know that IHD and ACS during pregnancy are the most important contributors to maternal mortality from heart disease.[2] We found no maternal deaths in our study, neither in the women with preexisting IHD nor in women with pregnancy-onset IHD.

Obstetric and Fetal Outcome

In our study, there were high rates of Caesarean section (CS) (55.8% in preexisting IHD and 84.6% in pregnancy-onset IHD) and high rates of premature births (20.2% and 38.5%, respectively) compared with healthy pregnancy. Lameijer et al[13] also reported an overall caesarean section rate of 57%, with a rate of 62% for women with pregnancy-onset IHD. These rates are more than twice as high as the CS rate in Europe.[17] Burchill et al[18] showed a lower CS rate (38%) in women with preexiting IHD.

The most likely explanation for the high rates of premature birth in our study is that it is iatrogenic and secondary to CS. Especially in the case of a cardiovascular event, a CS seems like the most stable and controlled situation for (immediate) delivery. From an earlier ROPAC analysis on mode of delivery however, we know that a planned CS in general does not improve maternal or fetal outcome in women with stable heart disease. In women with preexisting IHD without recent coronary events and with good cardiac function, vaginal delivery thus has important and prevailing benefits for both mother and child. The hemodynamic stress of labor and delivery can be attenuated by epidural anesthesia and assisted instrumental delivery. Planned CS should be reserved for obstetric indications only with some extremely high-risk cardiac exceptions in which the prolonged stress of labor forms a risk for the maternal and neonatal well-being, ie, after a recent ischemic event or in women with reduced left ventricular function.[3,19] After maternal stabilization after ACS, it is advisable when possible to delay the delivery for a few weeks, to reduce the need for a high cardiac output state immediately after the event.[3,16] In our study we found no relationship between maternal medication use during pregnancy and congenital abnormalities in the children, albeit our sample size is not big enough to support this claim. Optimal medical therapy remains unclear however, and further research in this field is warranted.

Future Perspectives and Clinical Implications

In comparison with the non-IHD part of the ROPAC cohort, women with IHD were significantly older, more overweight, more often smoking, hypertensive, diabetic, and were significantly more often multiparous. This highlights the importance of pre-pregnancy counseling and professional help with smoking cessation therapy in these women. It is known that the risk of cardiac death during pregnancy or in the post-partum period is strongly related to age, being 4 times higher in women aged >40 years.[2] Also, multiparity could be a contributing factor to adverse pregnancy outcome. Any woman of advanced age and with additional traditional cardiovascular risk factors, who wishes to become pregnant, should thus be counseled about the associated risks. Needless to say, smoking during pregnancy should be strongly discouraged at all times, to improve both maternal and neonatal outcome, and smoking cessation therapy should be an integral part of the pre-conceptional counseling of such women.

In our study, pre-pregnancy revascularization therapy did not significantly influence the occurrence of

ACS. This can be because of selection bias of more severely affected patients undergoing revascularization and possibly be explained by the inclusion of women with prior SCAD or coronary spasm for which they did not need to undergo revascularization therapy, therefore our data do not permit to refute the current recommendation that in women with preexistent IHD and residual ischemia, subsequent pregnancies should be discouraged.[3]

In the most recent modified World Health Organization classification for maternal cardiovascular risk during pregnancy, IHD as a diagnosis is not included.[3] With ACS rate of 10.6% and concomitant heart failure rate of 4.8%, it seems defendable to, based on our results, consider women with preexistent IHD as modified World Health Organization II-III. This means that, apart from the need for pre-conceptional investigation, including assessment of ventricular function and signs of residual ischemia followed by counseling, pregnancies in these women should be managed in referral hospitals with bi-monthly follow-up and women should be alerted to the symptoms of ACS and heart failure.[3]

Limitations

ROPAC is a registry and is therefore limited by several factors. Despite the prospective nature of ROPAC, there might still be some form of selection bias present, as we cannot guarantee that all consecutive patients from all centres were included. Furthermore, ROPAC includes pregnancies and not patients, therefore it could be possible that subsequent pregnancies in one woman could have been included as 2 patients. This could form a bias in the sense that it can be hypothesized that women who become pregnant more than once usually have less severe disease. Furthermore, the sample sizes in our study are very small, therefore the results of our study cannot be extrapolated to the general female IHD population and further studies are needed in the future to assess pregnancy-associated risks and outcomes. In ROPAC, we have collected information on all consecutive pregnancies in women with heart disease. We cannot guarantee that each included pregnancy in ROPAC represents a different patient, as some women will have had multiple pregnancies over time included. Unfortunately, because of the anonymized nature of the database, we cannot track which included pregnancies belong to the same patient, therefore we have decided to consider each included pregnancy a separate patient. This could of course lead to bias in favor of women with more favourable pregnancy outcome as women who are more seriously afflicted might not embark upon a subsequent pregnancy. Another limitation is that we have not collected data on former ischemic events and have therefore no information on the pathophysiological basis of the coronary artery disease in the women with preexistent IHD. We have done logistic regression analyses on the maternal cardiac outcome, but not on the obstetric or fetal outcome. Finally, data on smoking before pregnancy were dichotomized, and thus we have no information on pack-years.

CONCLUSIONS

Compared with pregnant women without IHD, pregnant women with IHD are more often smoking, hypertensive, overweight, and diabetic. Overall, women with IHD tolerate pregnancy relatively well. However, while there were no maternal deaths and heart failure rates were low, there was a high rate of ACS during pregnancy in our study. Ongoing cigarette smoking is associated with ischemic events during pregnancy and should strongly be discouraged. Pregnancy in women with ischemic heart disease should be considered moderate-to-high risk (moderate World Health Organization II-III) and all women with known IHD should undergo thorough pre-pregnancy investigations and counseling accordingly and strict follow-up in a referral center.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Appendix S1
Data S1
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SUPPLEMENTAL MATERIAL

Appendix

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Data S1.

Supplemental Methods

Statistical analysis:

Missing values for the following variables were imputed via multiple imputation (SPSS version 25.0):
Age, smoking status, BMI, parity, prior hypertension, prior diabetes, prior revascularization.
We used a MCMC multiple imputation model as we considered the missing values to be arbitrarily missing. Five imputations per variable were done, and the imputed values were saved in the imputed dataset. Within SPSS, binary logistic regression analysis is a supported procedure within imputed datasets and univariate pooling was standardly used. Binary logistic regression analyses were done on each of the 5 imputed and the observed dataset, after which the results of each analysis were pooled.

Table S1. ACS treatment per pathological mechanism.

	Coronary atherosclerosis	**Coronary thrombus + atherosclerosis**	**Isolated coronary thrombus**	**SCAD**	**Coronary spasm**	**No CAG**	**Total**
ACS in pre-existing IHD							
Conservative treatment	0	0	0	1	0	0	**1**
Thrombolysis	0	0	0	0	0	0	**0**
PCI	2	3	3	1	0	0	**9**
CABG	0	0	0	1	0	0	**1**
Other	0	0	0	0	0	0	**0**
Total	**2**	**3**	**3**	**3**	**0**	**0**	**11**
ACS in pregnancy-onset IHD							
Conservative treatment	0	0	0	1	0	4	**5**
Thrombolysis	0	0	0	0	0	1	**1**
PCI	2	2	1	1	0	0	**6**
CABG	0	0	0	0	0	0	**0**
Other	0	0	0	0	1	0	**1**
Total	**2**	**2**	**1**	**2**	**1**	**5**	**13**

Table S2. Cardiac medication use and anticoagulation during pregnancy.

	Total cohort (n=117)	**Pre-existing IHD (n=104)**	**Pregnancy-onset IHD (n=13)**	**P-value**
Cardiac medication use prior to pregnancy	57 (48.7%)	72 (69.2%)	7 (53.8%)	0.26
Beta blocker	21 (17.9%)	20 (19.2%)	1 (7.7%)	0.31
ACE-inhibitor	11 (9.4%)	11 (10.6%)	0 (0%)	0.001
Diuretics	2 (1.7%)	2 (1.9%)	0 (0%)	0.35
Statins	26 (22.2%)	25 (24.0%)	1 (7.7%)	0.18
Anti-platelet therapy	39 (33.3%)	38 (36.5%)	1 (7.7%)	0.04
Vitamin K antagonists	3 (2.6%)	3 (2.9%)	0 (0%)	0.54
Cardiac medication use during pregnancy	41 (35.0%)	36 (34.6%)	5 (38.5%)	0.78
Beta blocker	31 (26.5%)	28 (26.9%)	3 (23.1%)	0.77
ACE-inhibitor	1 (0.9%)	1 (1.0%)	0 (0%)	0.72
Diuretics	1 (0.9%)	1 (1.0%)	0 (0%)	0.72
Statins	10 (8.5%)	9 (8.7%)	1 (7.7%)	0.91
Anti-platelet therapy	48 (41.0%)	44 (42.3%)	4 (30.8%)	0.43
Vitamin K antagonists	1 (0.9%)	1 (1.0%)	0 (0%)	0.72

*Cardiac medication: all cardiac medication minus antiplatelet and anticoagulation therapy.

Figure S1. Vessel-involvement of pre-existing IHD.