Influence of socioeconomic factors on pregnancy outcome in women with structural heart disease

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Abstract

Objective: Cardiac disease is the leading cause of indirect maternal mortality. The aim of this study was to analyse to what extent socioeconomic factors influence the outcome of pregnancy in women with heart disease.

Methods: The Registry Of Pregnancy And Cardiac disease (ROPAC) is a global prospective registry. For this analysis, countries that enrolled ≥10 patients were included. A combined cardiac endpoint included maternal cardiac death, arrhythmia requiring treatment, heart failure, thromboembolic event, aortic dissection, endocarditis, acute coronary syndrome, hospitalisation for cardiac reason or intervention. Associations between patient characteristics, country characteristics (income inequality expressed as Gini-coefficient, health expenditure, schooling, gross domestic product, birth rate, and hospital beds) and cardiac endpoints were checked in a three-level model (patient-centre-country).

Results: A total of 30 countries enrolled 2924 patients from 89 centres. At least one endpoint occurred in 645 women (22.1%). Maternal age, New York Heart Association, and modified World Health Organization risk classification, were associated with the combined endpoint and explained 37% of variance in outcome. Gini-coefficient and country-specific birth rate explained an additional 4%. There were large differences between the individual countries, but the need for multilevel modelling to account for these differences disappeared after adjustment for patient characteristics, Gini and country specific-birth rate.

Conclusion: While there are definite interregional differences in pregnancy outcome in women with cardiac disease, these differences seem to be mainly driven by individual patient characteristics. Adjustment for country characteristics refined the results to a limited extent, but maternal condition seems to be the main determinant of outcome.

Keywords: pregnancy, cardiac disease, global differences, socioeconomic status

- What is already known about this subject?

  Previous studies have shown that human development index is a strong predictor of maternal and fetal mortality rate in the global population. Inequality of socioeconomic circumstances, lower educational level and lower human development index have been reported to be associated with maternal adverse outcome.

- What does this study add?

  To what extent these correlations can be extrapolated to women with pre-existent cardiac disease, has not been determined until now. The Registry Of Pregnancy And Cardiac disease (ROPAC) is the largest recorded cohort of pregnant women with cardiac disease. The current study shows that differences in outcome between centres and countries are largely explained by differences in individual patient characteristics, such as NYHA classification, prior signs of heart failure and modified WHO classification.

- How might this impact on clinical practice?

  Socioeconomic factors were partly explainable for differences in pregnancy outcome in women with cardiac disease, but the main denominator was the individual's condition. Raising awareness and improving access to medical resources as advocated by the World Health Organization, will help to improve the outcome for pregnant women, hopefully also for women with heart disease.

Introduction

Cardiac disease is an important cause of maternal mortality and morbidity. Recent data from the Global Burden of Disease study has demonstrated that geographical disparities widened between 1990 and 2015 and that in 2015, 24 countries still had a maternal mortality ratio greater than 400 per 100 000. Those recent data have shown that overall maternal mortality pattern is influenced by Socio-Demographic index (SDI) with women in the highest SDI quintile dying frequently due to indirect maternal disorders as cardiovascular and thrombotic disease[1, 2]. The Registry Of Pregnancy And Cardiac disease (ROPAC) is a global cohort including pregnant patients from both advanced and emerging countries. Several analyses from ROPAC data have been published with marked differences between advanced and emerging countries[3, 4, 5]. These differences could be partly explained by variations in underlying cardiac condition, with acquired valvular disease being more prevalent in emerging countries[6] and congenital heart disease in advanced countries. In addition, the demographic differences may also influence outcome. For instance, in some cultures women gain status by having (many) children and thus they may be reluctant to take a doctor's advice to avoid pregnancy. Also, there is widespread difference in the availability of health care and access to female contraception. Although tertiary care is provided in the urban areas, many women in less developed countries are from rural areas and, consequently, might present with pregnancy complaints much later than their peers from rural areas in countries with more advanced economies[7].

Interpretation of ROPAC results needs to be done with caution in the light of these differences. Insights in country level socioeconomic data and the associated pregnancy outcomes will help interpreting existing and future analyses. Such an analysis could define the influence of socioeconomic background on pregnancy outcome exerted by the countries of residence, the alternative approach, of an in depth analysis of individual socioeconomic data, is not possible.

The aim of this study was to elucidate the interregional differences in the countries contributing to ROPAC, by analysing to what extent socioeconomic factors on country level, such as gross domestic product, income distribution/inequality (Gini-coefficient), HDI, health expenditure, birth rate, number of hospital beds and schooling, influence the outcome of pregnancy in women with heart disease. We hypothesized that country

level socioeconomic indices do influence pregnancy outcome and that cardiac status (such as severity of disease and NYHA) affects the outcome of mother and baby to a greater extent.

Methods

The Registry Of Pregnancy And Cardiac disease (ROPAC) is an ongoing prospective worldwide registry that includes all consecutive pregnant women with structural heart disease. Study design and methods have been described in detail previously[3]. Patient enrollment started from January 2008 and for this interim analysis we included patients with a term date up to October 2013, and 6 months follow-up in April 2014. Patient informed consent was obtained when required by the local independent review board. Patients with either congenital, valvular or ischemic heart disease, a cardiomyopathy, pulmonary hypertension, aortic pathology were included. Women with non-structural disease such as arrhythmia were excluded. More specific details on disease have been published previously [3, 8].

Data

The patient characteristics collected at baseline (before pregnancy) included age, ECG rhythm, New York Heart Association (NYHA) functional classification, diagnosis, risk factors for cardiovascular disease (smoking, diabetes, hypertension), previous interventions, medication, parity, obstetric history and if available echocardiographic parameters. Every patient was stratified according to the modified World Health Organization (WHO) classification, as stated in the latest guidelines[9, 10] by two authors (IH;JRH). Modified WHO-class I implies no increased risk of events during pregnancy, compared to the general pregnant population. Modified WHO-class II has a small increased risk, class II-III a moderate increased risk, and class III has a 'significantly' increased risk. Class IV bears an unacceptable high risk of complications and consensus suggests that pregnancy should be avoided.

For the current study, pre-pregnancy patient characteristics that were included in statistical modelling were age, nulliparity, modified WHO class, NYHA class and signs of heart failure.

Socioeconomic data on patient level were not available. As a result, pre-defined socioeconomic factors were assigned to represent country characteristics, and included: human development index (HDI), Gini-coefficient, health expenditure, schooling, gross domestic product per capita based on purchasing power parity (GDP),

birth rate per 1,000, and hospital beds per 1,000. Definitions and sources of these characteristics are listed in **Supplementary Material Appendix 1**. HDI is a combination of three factors; life expectancy from birth, mean years of schooling and the country standard of living. As these factors correlate with the other predefined country characteristics, the HDI was not included in further modelling. The HDI categories (low, medium, high, very high) were only used to categorize and understand the frequency of events within the different categories.

Endpoints

The following endpoints that occurred up to one week after delivery were studied: combined cardiac endpoint (including maternal cardiac death, arrhythmia requiring treatment, heart failure, thromboembolic event, aortic dissection, endocarditis, acute coronary syndrome, hospitalisation for cardiac reason, or a cardiac intervention), heart failure, fetal or neonatal mortality (excluding miscarriage in the first trimester), and small-for-gestational-age (SGA, birth weight <10th percentile). All-cause mortality data was also collected, but not used for statistical modelling due to low numbers. Heart failure was defined according to ACC/AHA guidelines[11], as a clinical syndrome that is characterised by specific symptoms (dyspnea and fatigue) and signs (of fluid retention, such as oedema, rales) on the physical examination as judged by the treating cardiologist. The heart failure episode was only registered when signs or symptoms of HF were present which required new treatment, change of treatment or hospital admission.

Statistical analysis

Categorical variable differences were tested using chi-square tests and are presented as percentages; in case of 3 categories Pearson chi square tests were performed. Continuous variables are presented as mean and standard deviation (SD), or as median and first and third quartile (Q1-Q3), as appropriate. Differences were tested using Student's t-tests; in case of 3 categories one-way ANOVA tests were performed.
Generalized linear mixed models (GLMM) were used as a result of the multilevel structure in the data. The ROPAC database consists of three levels: patients (level 1) were nested in centres (level 2), and centres were nested in countries (level 3). To account for differences in outcome between countries and between centres, random effects for country and centre were added to the model. Patient and country characteristics were

entered as fixed effects and those with a significant trend ($p<0.10$) in univariable analysis were assessed in multivariable analysis. Countries that included less than 10 patients were excluded from this study.

To determine the influence of fixed and random effects in our cohort, we further analysed the model for the combined cardiac endpoint. A conditional R^2 (for GLMM) was derived from the model before and after including the fixed effects (patient characteristics, followed by country characteristics) [12]. This is an estimate of the percentage explained variance by the complete model (fixed and random effects). The random effect estimates of the individual countries for the combined cardiac endpoint were plotted with 95% confidence intervals (caterpillar plot), unadjusted and adjusted for the fixed effects.

The rate of missing patient and country characteristics was relatively low, and therefore a complete case analysis approach was taken (96%). All analyses, except for multilevel modelling, were performed in SPSS version 21.0 (IBM Corp., Armonk, NY). Multilevel modelling was performed in R version 3.1, package lme4 [13]**.**

Results

From January 2008 until April 2014, 2966 patients were included, from 99 centres in 39 countries. Nine countries enrolled less than 10 patients, and were excluded. The remaining 30 countries enrolled 2924 patients from 89 centres. An overview of the countries is presented and arranged according to the HDI categories in **Table 1**. Socioeconomic indexes, including HDI, Gini coefficient, health expenditure, schooling, GDP, birth rate per 1,000 and hospital beds per 1,000 are presented for all countries in **Supplemental material Table S1.**

Baseline characteristics are presented for patients per HDI category (**Table 2**). Maternal age at conception was higher in women from countries with a very high HDI, while these women were also more often nulliparous. Fewer women from countries with a medium or high HDI had a prior cardiac intervention and were in NYHA class I, compared to women from countries with a very high HDI. Indeed, signs of heart failure prior to pregnancy were more common; cardiac medication, mainly diuretics, were more commonly used before pregnancy by women from countries with a medium or high HDI compared to those from countries with a very high HDI. Valvular heart disease was much more common in women from countries with a medium HDI, while women from countries with a high or very high HDI more often had congenital heart disease.

Women with modified WHO class III or IV more often came from countries with a medium or high HDI, while women with a lower risk WHO class more often came from countries with a very high HDI.

Table 1 Human development index categories

	Low	**Medium**	**High**	**Very high**
Human development index*	<0.555	0.555-0.699	0.700-0.799	≥0.800
		(n=634)	(n=118)	(n=2130)
Countries in ROPAC		Egypt	Azerbaijan	Argentina
		South-Africa	Russian Federation	Australia
				Austria
				Belgium
				Canada
				Czech Republic
				France
				Greece
				Germany
				Hungary
				Italy
				Japan
				Lithuania
				Israel
				Malta
				Netherlands
				Norway
				Poland
				Portugal
				Slovenia
				Spain
				Sweden
				Switzerland
				United Arab Emirates
				United Kingdom
				United States
	<10 patients per country	*<10 patients per country*	*<10 patients per country*	
			Brazil	Ireland
			Bulgaria	
			Georgia	
			Macedonia	
			Romania	
			Serbia&Montenegro	
			Turkey	

*Human development index for female according to United Nations Development Report 2013. No value was available for Bosnia&Herzegovina (<10 inclusions)

Table 2 Baseline characteristics

	Total*		Low HDI	Medium HDI		High HDI		Very High HDI		p
N (% of total inclusions)	2966		0	634	21.7%	118	4.0%	2172	74.3%	
Mean age (sd)	29.3	±5.6		27.7	±5.9	26.4	±5.3	29.9	±5.4	<0.001
Nulliparous	1334	45.2%		160	25.2%	57	48.3%	1099	50.7%	<0.001
Pre-existent hypertension	188	6.5%		26	4.1%	18	16.2%	139	6.5%	<0.001
Current smoker	110	4.3%		11	1.8%	4	3.6%	95	5.3%	0.001
Pre-existent diabetes	46	1.6%		10	1.6%	1	0.8%	34	1.6%	1.000
Prior cardiac intervention	1585	53.6%		223	35.2%	44	37.3%	1304	60.1%	<0.001
NYHA functional class										<0.001
NYHA I	2154	74.1%		399	62.9%	48	42.1%	1686	79.3%	
NYHA II	659	22.7%		191	30.1%	62	54.4%	395	18.6%	
NYHA III	86	3.0%		42	6.6%	4	3.5%	39	1.8%	
NYHA IV	7	0.2%		2	0.3%	0	0.0%	5	0.2%	
Signs of HF before pregnancy	283	9.7%		138	21.8%	66	58.4%	74	3.5%	<0.001
AF before pregnancy	68	2.3%		47	7.4%	1	0.9%	20	0.9%	<0.001
Prior medication	824	27.9%		292	46.1%	17	14.4%	510	23.5%	<0.001
Beta-blocker	365	12.3%		75	11.8%	7	5.9%	280	12.9%	0.073
Anti-arrhythmic	90	3.0%		58	9.1%	3	2.6%	28	1.3%	<0.001
ACE-inhibitor	116	3.9%		38	6.0%	9	7.6%	67	3.1%	0.001
Diuretic	170	5.8%		93	14.7%	7	5.9%	68	3.1%	<0.001
Cardiac diagnosis										<0.001
Congenital heart disease	1654	55.9%		88	13.9%	91	77.1%	1458	67.1%	
Valvular heart disease	942	31.8%		489	77.1%	15	12.7%	424	19.5%	
Ischemic heart disease	47	1.6%		7	1.1%	0	0.0%	40	1.8%	
Cardiomyopathy	201	6.8%		45	7.1%	4	3.4%	151	7.0%	
Aortic pathology	101	3.4%		3	0.5%	6	5.1%	90	4.1%	
Pulmonary hypertension	13	0.4%		2	0.3%	2	1.7%	9	0.4%	
WHO classification										<0.001
WHO class I	583	19.7%		73	11.5%	27	22.9%	474	21.8%	
WHO class II	520	17.6%		18	2.8%	17	14.4%	481	22.1%	
WHO class II-III	932	31.5%		150	23.7%	34	28.8%	735	33.8%	
WHO class III	486	16.4%		187	29.5%	8	6.8%	286	13.2%	
WHO class IV	437	14.8%		206	32.5%	32	27.1%	196	9.0%	

*Percentages are of total valid cases, excluding missing cases.*Total cohort includes countries with less than 10 patients. ACE = Angiotensin Receptor Enzym; AF = Atrial fibrillation; HDI = Human development index; HF = Heart failure; NYHA = New York Heart Association; WHO = World Health Organization.*

Frequency of endpoints

Clinical event rates are presented for each HDI group (**Figure 1**) and for all countries separately (**Table 3**). A combined cardiac endpoint occurred in 645 women (22.1%); heart failure in 365 (12.5%); fetal/neonatal loss in 60 (2.1%); small-for-gestational age in 270 (10.6%). Maternal mortality up to one week postpartum occurred in 11 cases (0.9% medium HDI, 0.8% high HDI, and 0.2% very high HDI, p=0.016) and was not included in the univariable or multivariable analysis.

Associations of patient and country characteristics with clinical endpoints

Univariable analysis of pre-pregnancy patient characteristics for the combined cardiac endpoint is shown in **Table 4**. The only variable that was not significantly associated with the combined cardiac endpoint was nulliparity. Modified WHO II was not significantly different from modified WHO I. Of the country characteristics, Gini coefficient (p=0.017) and birth rate (although p=0.050) were independently associated with the combined cardiac endpoint, in addition to age, NYHA class, modified WHO class and signs of heart failure before pregnancy.

The univariable and multivariable analysis of the remaining endpoints are shown in the **online supplemental data**. The results for heart failure as a separate endpoint were largely comparable to the results of the combined cardiac endpoint (**online supplemental Table S2**). While schooling, GDP, birth rate and number of hospital beds were associated with fetal/neonatal mortality in the univariable analysis, only GDP was independently associated with this endpoint (**online supplemental Table S3**). None of the country characteristics were associated with SGA, on top of NYHA II and III, and modified WHO class III and IV (**online supplemental Table S4**).

Influence of variability between countries and centres

The total explained variability of the model, the conditional R^2, for the combined cardiac endpoint including patient characteristics only, was 37%. By adding the country characteristics, the R^2 increased by 4% to 41%. Without any of these fixed effects in the model the conditional R^2 including random effects only, was 33%. **Figure 2** depicts the estimated unadjusted and adjusted odds ratios for a combined cardiac endpoint for each country compared to the average odds ratio. Several countries do not include the 0 in their 95% confidence

interval in the unadjusted model. But when adjusted for patient and country characteristics, the 95% confidence intervals of almost all countries do include 0. This means that for the vast majority of the countries, the need to account for random effects (patient within centre, within country) disappears when adjusting for patient and country characteristics.

Table 3 Events per country

		Maternal mortality (all cause)		Heart failure		Combined cardiac endpoint		Fetal/neonatal mortality (no miscarriage)		Small for gestational age	
	total n	n	%	n	%	n	%	n	%	n	%
ARGENTINA	10	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	10,0%
AUSTRALIA	19	0	0,0%	2	10,5%	4	21,1%	0	0,0%	2	10,5%
AUSTRIA	83	0	0,0%	1	1,2%	4	4,8%	1	1,2%	1	1,2%
AZERBAIJAN	10	0	0,0%	2	20,0%	2	20,0%	0	0,0%	0	0,0%
BELGIUM	125	0	0,0%	2	1,6%	5	4,0%	0	0,0%	3	2,4%
CANADA	57	1	1,8%	3	5,3%	6	10,5%	2	3,5%	2	3,5%
CZECH REPUBLIC	14	0	0,0%	0	0,0%	0	0,0%	0	0,0%	1	7,1%
EGYPT	573	6	1,0%	120	20,9%	198	34,6%	31	5,4%	30	5,2%
FRANCE	58	0	0,0%	13	22,4%	26	44,8%	0	0,0%	10	17,2%
GERMANY	229	0	0,0%	3	1,3%	10	4,4%	1	0,4%	23	10,0%
GREECE	27	0	0,0%	3	11,1%	11	40,7%	0	0,0%	6	22,2%
HUNGARY	44	0	0,0%	0	0,0%	1	2,3%	1	2,3%	4	9,1%
ISRAEL	61	0	0,0%	19	31,1%	25	41,0%	1	1,6%	7	11,5%
ITALY	238	1	0,4%	12	5,0%	33	13,9%	3	1,3%	28	11,8%
JAPAN	33	0	0,0%	2	6,1%	2	6,1%	0	0,0%	6	18,2%
LITHUANIA	60	0	0,0%	5	8,3%	5	8,3%	1	1,7%	8	13,3%
MALTA	19	0	0,0%	0	0,0%	1	5,3%	0	0,0%	2	10,5%
NETHERLANDS	299	0	0,0%	9	3,0%	38	12,7%	2	0,7%	23	7,7%
NORWAY	28	0	0,0%	4	14,3%	6	21,4%	0	0,0%	1	3,6%
POLAND	113	0	0,0%	11	9,7%	27	23,9%	3	2,7%	13	11,5%
PORTUGAL	13	0	0,0%	0	0,0%	0	0,0%	1	7,7%	0	0,0%
RUSSIAN FEDERATION	108	1	0,9%	57	52,8%	90	83,3%	0	0,0%	13	12,0%
SLOVENIA	128	0	0,0%	2	1,6%	10	7,8%	3	2,3%	12	9,4%
SOUTH AFRICA	61	0	0,0%	30	49,2%	34	55,7%	5	8,2%	8	13,1%
SPAIN	221	1	0,5%	20	9,0%	32	14,5%	3	1,4%	29	13,1%

SWEDEN	33	0	0,0%	5	15,2%	7	21,2%	1	3,0%	6	18,2%
SWITZERLAND	45	0	0,0%	2	4,4%	5	11,1%	0	0,0%	5	11,1%
UNITED ARAB EMIRATES	31	0	0,0%	13	41,9%	16	51,6%	0	0,0%	5	16,1%
UNITED KINGDOM	120	1	0,8%	16	13,3%	31	25,8%	0	0,0%	15	12,5%
UNITED STATES	64	0	0,0%	9	14,1%	16	25,0%	1	1,6%	6	9,4%
TOTAL	2924	11	0,4%	365	12,5%	645	22,1%	60	2,1%	270	9,2%

Table 4 Univariable and multivariable analysis of patient and country characteristics with the combined cardiac endpoint

	Univariable		Multivariable	
Variable	**OR**	**95% CI**	**OR**	**95% CI**
Age	1.026	1.008 – 1.045	1.020	1.000 – 1.039
Nulliparity	0.955	0.777 – 1.174		
NYHA I	NA		NA	
NYHA II	2.735	2.179 – 3.434	1.944	1.487 – 2.541
NYHA III	9.18	5.435 – 15.506	3.062	1.657 – 5.658
NYHA IV	26.01	2.634 – 256.826	7.456	0.792 – 70.209
WHO I	NA		NA	
WHO II	1.088	0.689 – 1.719	0.997	0.618 – 1.607
WHO II-III	2.261	1.575 – 3.246	1.992	1.371 – 2.895
WHO III	4.351	2.947 – 6.426	3.862	2.586 – 5.767
WHO IV	8.383	5.67 – 12.394	4.954	3.238 – 7.578
Signs of heart failure	4.165	3.037 – 5.711	1.708	1.167 – 2.502
Gini*	1.706	1.266 – 2.297	1.393	1.06 – 1.831
Health expenditure*	0.739	0.463 – 1.178		
Schooling*	0.965	0.468 – 1.991		
GDP*	0.737	0.453 – 1.200		
Birth Rate*	2.896	1.742 – 4.815	1.622	1.001 – 2.629
Hospital beds*	0.708	0.446 – 1.123		

Data are clustered within hospitals within countries. The categorical variable NYHA classification and WHO are tested against the reference category I. WHO II is not significantly different from WHO I. The only variable that is not significant is nulliparity.

GDP = Gross domestic product, NYHA = New York Heart Association, WHO = World Health Organization
*Numerical data were standardized before analysis

Discussion

The ROPAC registry is the largest recorded cohort of pregnant women with cardiac disease. Women from many different countries were included. Results may be influenced by the multicenter and multinational nature of the registry. The current study shows that indeed there are differences in outcome between centres and countries, but these differences are largely explained by differences in individual patient characteristics, such as NYHA classification, prior signs of heart failure and modified WHO classification. Only a few country characteristics had some impact: maternal cardiac event was associated with Gini coefficient and to a lesser extent with birth rate of the patients' residential country. Also fetal outcome, such as small for gestational age was mainly associated with the maternal condition and to a minor extent with country characteristics.

Maternal outcome and socioeconomic influences

Previous studies have shown that human development index is a strong predictor of maternal and fetal mortality rate in the global population[14]. Inequality of socioeconomic determinants within a country further increases the rate of maternal death[15]. A lower educational level and lower HDI have been reported to be associated with maternal adverse outcome[16]. Less educated women, for instance, have an increased risk of presenting to an emergency department in a severe condition[17]. This may be related to several issues: women from emerging countries tend to have a later presentation to a medical centre, which is probably associated with limited knowledge and awareness of risks and lack of money, but also to factors like a less well developed infrastructure, longer travel-time and perhaps less availability of skilled medical staff. To what extent these correlations can be extrapolated to women with pre-existent cardiac disease, and whether they need to be taken into account while analysing multinational registry data, has not been determined until now.

Although the number of maternal deaths was too low to allow for statistical analysis, the risk of a cardiac event (combined endpoint) was indeed associated with income inequality (expressed as the Gini-coefficient) in a country. Also, a higher country birth rate correlated with a higher frequency of heart failure. These socioeconomic parameters need to be considered when interpreting data from registries, however, we feel that the number of factors actually showing a relationship to pregnancy outcome in these high risk patients, is actually relatively small compared to their impact in the general pregnant population. In fact, the most important determinant of pregnancy outcome was the underlying medical condition.

This cohort consists of a rather large subgroup of women with a cardiac condition considered modified WHO group 3 and 4. Category 4 involves women who should rather be advised to avoid pregnancy. However, in the end, the woman will decide herself whether she will proceed to try and get pregnant, and of course clinical care will not be denied to this group of women. Whether this group involves women who were not appropriately counseled about their risks following the latest guidelines, may also be subject to further discussion. The fact that a greater part of women from less well developed countries were in a higher modified WHO category (3 or 4), has undoubtedly influenced the outcome of our study. While the underlying disease is

a given fact, availability of good preconception, perinatal and maternal care certainly deserves attention. It is part of the United Nations Millennium Goals, and this study emphasizes the need for improvement of care.

Fetal outcome

With regard to fetal and obstetric outcome, previous reports showed that a higher income inequality (Gini coefficient) and educational level, rather than household income, seem to be associated with intrauterine growth but not with shorter gestational age at delivery[18, 19]. The exact underlying mechanism is difficult to determine. A recent large prospective cohort study of pregnant women showed that women from low socioeconomic subgroups have higher placental resistance indices, which may be explained by smoking. This association may contribute to a higher incidence of pregnancy complications and even stillbirth[20, 21].

In our cohort of women with cardiac disease, country characteristics did not significantly influence the SGA rate, while maternal condition expressed as NYHA class and modified WHO classification did influence the frequency of SGA. In women with reduced cardiac function, an abnormal uteroplacental flow is present, which is an important predictor of adverse obstetric and fetal outcome[22] and this may explain the association in this study.

Research and clinical implications

The results imply that interregional differences need to be acknowledged, also in research, but that the maternal condition seems to outweigh the influence of socioeconomic factors on reported cardiac and fetal outcome. A clear association between socioeconomic factors and events was present in univariable analysis, but it largely disappeared after correction for maternal condition. Thus, the higher event rate in emerging compared to advanced countries is mainly based on a worse pre-pregnancy condition of patients. Also, the need for multilevel modelling in this analysis was lost after adding the patient and country characteristics.

Data on cultural background were lacking, but would be very interesting to study. Differences in pregnancy outcome between emerging and advanced countries, may be related to for instance religion. Women may have a strong feeling that their fate is predetermined and therefore less sensible to a doctor's advice. But this

hypothesis is rather philosophical and needs further investigation to determine whether this indeed influences pregnancy outcome.

Reducing adverse pregnancy outcome in any region, but in particular in remote areas, is an important goal as formulated by the WHO. While this goal resulted in major declines in maternal death rates globally, this trend has definitely not been observed in maternal death due to cardiac disease[23]. Creating awareness in young women with cardiac disease about the potential high risks of pregnancy should be part of standard care and preferably initiated at a young age. The fifth millennium goal of the World Health Organization is reduction of maternal mortality, by means of increasing the number of women receiving at least 4 antenatal care visits and the number of births attended by skilled staff[24]. An increase in the number of women receiving this level of care and a decline in maternal death rate has been observed in the past 10-15 years, but about 50% of women still do not receive the recommended minimum of four antenatal visits. Also, a well-developed infrastructure for cardiovascular health screening is warranted to ensure early diagnosis and management[25]. Improvements in these medical resources may also reduce the burden of adverse events in pregnant women with cardiac disease.

Other global observational studies, for instance those dealing with factors influencing secondary cardiovascular prevention, did find related socio-economic factors. One study pointed out that the country level socio-economic factors explained two-thirds of the variation in preventive drug use compared to only a third explained by individual factors (such as smoking, gender, education)[26]. Although these results are not in line with our findings, this knowledge needs to be appreciated for our population as well: it does show the between-country differences in (level of) health care availability.

Limitations

While ROPAC provides a unique view on global pregnancy outcome, including women from 39 countries, the current distribution of countries was within a range of medium to very high HDI. However, the range of country specific characteristics was sufficient to illustrate the differences between more developed countries and those with poorer resources. Including patients from countries categorised with a low HDI may strengthen

this study, but is hard to achieve with limited availability of organised/specialised medical care in these countries.

In previous studies, ethnicity was shown to influence maternal outcome[27]. In particular, non-Hispanic black women seem to have an increased risk of pregnancy-related mortality. ROPAC did not include demographic socioeconomic data at a patient level, which is why we performed the analysis at a country level. If the socio-economic data (income, education, social status, employment, among others) were available at patient level, it may had been possible to find stronger relationships. Since we performed the statistical analyses at three levels (patient, within centre, within country), we believe that meaningful conclusions can be drawn from our data. In future registries it would be desirable to collect more socioeconomic data on patient level.

The majority of the participating centres were university or tertiary centres (86%). Unfortunately, only 75% responded to the question whether they were a university, community or private clinic, which is why we did not include this information in the statistical analysis. But it is likely that our data are derived from women cared for in larger centres with a specialised department for pregnancy.

ROPAC included 6 months follow-up postpartum. However, due to large differences in follow-up availability between countries, it was decided not to include these results to this analysis. Follow-up at 1 week was available in all patients. For future research, inclusion of long-term follow-up would be favourable. Finally, the number of pregnancies complicated by fetal and neonatal mortality was relatively low, which hampered statistical modelling and conclusions should be interpreted carefully.

This study aimed to comment on associations, rather than causal relations. It should be interpreted as a hypothesis generating study, and may be a starting point for future research studying for instance socioeconomic factors on patient level.

Conclusion

Socioeconomic factors were partly explainable for differences in pregnancy outcome in women with cardiac disease, but the main denominator was the individual's condition, at least in countries with a medium to very high HDI. Raising awareness and improving access to medical resources as advocated by the World Health Organization, will help to improve the outcome for pregnant women, hopefully also for women with heart disease.

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Conflict of interest

Dr. Maggioni reports grants from Novartis, Cardiorentis, and Bayer outside the submitted work.

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Figures

Figure 1 Event rate for HDI categories

Figure 2 Between country differences in outcome, unadjusted for fixed effects (A) and adjusted for fixed effects (B)

Legend: Estimated unadjusted and adjusted odds ratios for a combined cardiac endpoint for each country compared to the average odds ratio. Several countries do not include the 0 in their 95% confidence interval in the unadjusted model. But when adjusted for patient and country characteristics, the 95% confidence intervals of almost all countries do include 0. This means that for the vast majority of the countries, the need to account for random effects (patient within centre, within country) disappears when adjusting for patient and country characteristics.

Online supplementary material:

Table S1 Socioeconomic indices per country

Reference numbers from World Bank/ UNDP / UNESCO / HDI UNDESA

Table S2 Univariable and multivariable analysis of patient and country characteristics with heart failure

Table S3 Univariable and multivariable analysis of patient and country characteristics with fetal/neonatal mortality

Table S4 Univariable and multivariable analysis of patient and country characteristics with small-for-gestational-age

Appendix 1 Definitions