ORIGINAL RESEARCH ARTICLE

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 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 classification and modified WHO 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.

INTRODUCTION

Cardiac disease is an important cause of maternal mortality and morbidity. Recent data from the Global Burden of Disease study have 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.[3–5] 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 healthcare 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 in 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 inter-regional differences in the countries contributing to ROPAC, by analysing to what extent socioeconomic factors on country level, such as gross domestic product (GDP), income distribution/inequality (Gini coefficient), Human Development Index (HDI), health expenditure, birth rate, number of hospital beds and schooling, influence the outcome of pregnancy in women with heart disease. We hypothesised that country-level socioeconomic indices do influence pregnancy outcome and that cardiac status (such as severity of disease and New York Heart Association (NYHA) classification) affects the outcome of mother and baby to a greater extent.

METHODS

The 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 enrolment started from January 2008, and for this interim analysis, we included patients with a term date up to October 2013,[1] 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 ischaemic heart disease, a cardiomyopathy, pulmonary hypertension and 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, 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 WHO classification, as stated in the latest guidelines[9 10] by two authors (IMvH, JWRH). Modified WHO class I implies no increased risk of events during pregnancy, compared with 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 this study, prepregnancy 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, predefined socioeconomic factors were assigned to represent country characteristics and included HDI, Gini coefficient, health expenditure, schooling, gross domestic product per capita based on purchasing power parity (GDP), birth rate per 1000 and hospital beds per 1000. Definitions and sources of these characteristics are listed in online supplementary 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 categorise and understand the frequency of events within the different categories.

Endpoints

The following endpoints that occurred up to 1 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 were also collected, but not used for statistical modelling due to low numbers. Heart failure was defined according to American College of Cardiology/American Heart Association guidelines[11] as a clinical syndrome that is characterised by specific symptoms (dyspnoea and fatigue) and signs (of fluid retention, such as oedema, rales) on the physical examination as judged by the treating cardiologist. The heart failure (HF) 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 χ^2 tests and are presented as percentages; in case of three categories, Pearson χ^2 tests were performed. Continuous variables are presented as mean and SD, or as median and first and third quartiles (Q1–Q3), as appropriate. Differences were tested using Student's t-tests; in case of three categories, one-way ANOVA tests were performed.

Generalised linear mixed models (GLMMs) 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% CIs (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 V.21.0 (IBM, Armonk, New York, USA). Multilevel modelling was performed in R V.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 1000 and hospital beds per 1000, are presented for all countries (see online supplementary 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 with women from countries with a very high HDI. Indeed, signs of HF 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 with 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.

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
				UK
				USA
		<10 patients per country	<10 patients per country	<10 patients per country
			Brazil	Ireland
			Bulgaria	
			Georgia	
			Macedonia	
			Romania	
			Serbia and Montenegro	
			Turkey	

*Human Development Index for women according to United Nations Development Report 2013.[3] —>remove citation. No value was available for Bosnia and Herzegovina (<10 inclusions).
ROPAC, Registry of Pregnancy and Cardiac 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.

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%) and small for gestational age in 270 (10.6%). Maternal mortality up to 1 week post partum 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 prepregnancy 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 analyses of the remaining endpoints are shown in the online supplementary data. The results for HF as a separate endpoint were largely comparable to the results of the combined cardiac endpoint (see online supplementary 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 (see online supplementary 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 (see online supplementary 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%–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 ORs for a combined cardiac endpoint for each country compared with the average OR. Several countries do not include the 0 in their 95% CI in the unadjusted model. However, when adjusted for patient and country characteristics, the 95% CIs 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.

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 multicentre and multinational nature of the registry. This 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 SGA, 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 HDI 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

Table 2 Baseline characteristics

	Total*		Low HDI	Medium HDI		High HDI		Very High HDI		
N (% of total inclusions)	**2966**		**0**	**634**	**21.7%**	**118**	**4.0%**	**2172**	**74.3%**	**p Value**
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
Antiarrhythmic	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%	
Ischaemic 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-converting enzyme; AF, atrial fibrillation; HDI, Human Development Index; HF, heart failure; NYHA, New York Heart Association.

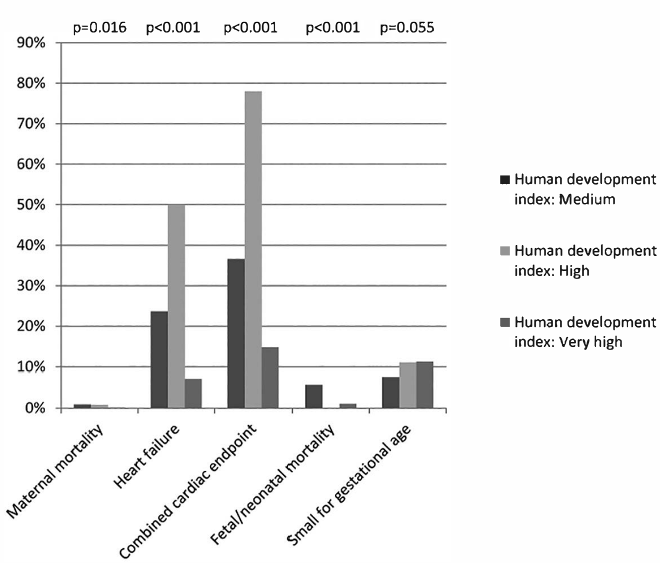

Figure 1 Event rate for Human Development Index categories.

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, and 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 HF. These socioeconomic parameters need to be considered when interpreting data from registries; however, we feel that the

Table 3 Events per country

	N	Maternal mortality (all cause)		Heart failure		Combined cardiac endpoint		Fetal/neonatal mortality (no miscarriage)		Small for gestational age	
		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
The 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
UK	120	1	0.8	16	13.3	31	25.8	0	0.0	15	12.5
USA	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

number of factors actually showing a relationship to pregnancy outcome in these high-risk patients is actually relatively small compared with 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 counselled 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 and perinatal and maternal care certainly deserves attention. It is part of the United Nations Millennium Goals, and this study emphasises 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 inter-regional 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

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

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

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.
*Numerical data were standardised before analysis.
GDP, gross domestic product, NYHA, New York Heart Association.

analysis, but it largely disappeared after correction for maternal condition. Thus, the higher event rate in emerging compared with advanced countries is mainly based on a worse prepregnancy condition of patients. Also, the need for multilevel modelling in this analysis was lost after adding the patient and country characteristics.

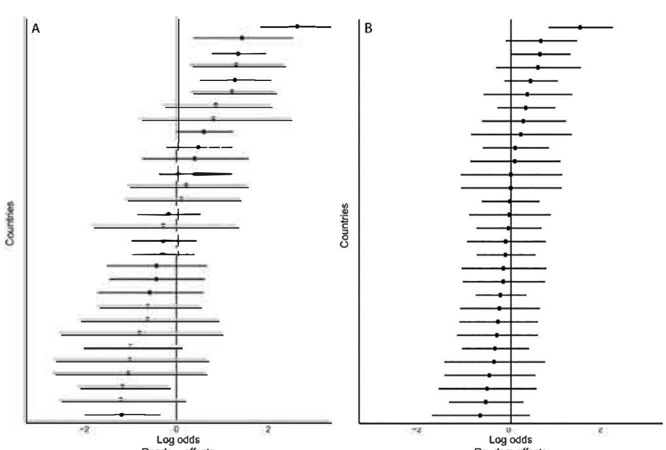

Figure 2 Between-country differences in outcome, unadjusted for fixed effects (A) and adjusted for fixed effects (B). Estimated unadjusted and adjusted ORs for a combined cardiac endpoint for each country compared with the average OR. Several countries do not include the 0 in their 95% CI in the unadjusted model. However, when adjusted for patient and country characteristics, the 95% CIs 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.

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. However, 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 particularly in remote areas, is an important goal as formulated by 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 WHO is reduction of maternal mortality by means of increasing the number of women receiving at least four 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 socioeconomic factors. One study pointed out that the country-level socioeconomic factors explained two-thirds of the variation in preventive drug use compared with only a third explained by individual factors (such as smoking, gender and 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) healthcare 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 it 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 socioeconomic data (income, education, social status and employment, among others) were available at patient level, it may have 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 a 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. However, 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 post partum. 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 a 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 WHO will help to improve the outcome for pregnant women, hopefully also for women with heart disease.

Key messages

What is already known on this subject?

Previous studies have shown that Human Development Index (HDI) is a strong predictor of maternal and fetal mortality rate in the global population. Inequality of socioeconomic circumstances, lower educational level and lower HDI have been reported to be associated with maternal adverse outcome.

What might 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 is the largest recorded cohort of pregnant women with cardiac disease. This study shows that differences in outcome between centres and countries are largely explained by differences in individual patient characteristics, such as New York Heart Association 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 WHO will help to improve the outcome for pregnant women, hopefully also for women with heart disease.

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