

Incidence and prevalence of pregnancy-related heart disease

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Worldwide, the numbers of women who have a pre-existing cardiovascular disease or develop cardiac problems during pregnancy are increasing and, due to the lack of evidenced-based data, this provides challenges for the treating physician. Cardiovascular disease in pregnancy is a complex topic as women can present either pre- or post-partum, due to a pre-existing heart disease such as operated on or unoperated on congenital heart disease, valvular heart disease, chronic hypertension, or familial dilated cardiomyopathy. Women often present with symptoms and signs of acute heart failure. On the other hand, there are diseases which are directly related to pregnancy, such as hypertensive disorders of pregnancy and peripartum cardiomyopathy, or where pregnancy increases risk of a disease as, for example, the risk of myocardial infarction. These diseases can have long-term implications to the life of the affected women and their families. There is, in particular, a paucity of data from developing countries of this unique disease pattern and its presentations. This review summarizes the current knowledge of the incidence and prevalence of pregnancy-related cardiovascular disease in women presenting pre- or post-partum.

Keywords Heart disease pregnancy • Peripartum cardiomyopathy • Pre-eclampsia • Hypertension • In pregnancy

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1. Introduction

The physiological changes that occur during pregnancy and in the peripartum period provide a challenge to women with previously undiagnosed or known cardiovascular conditions. Knowledge about the morphological and functional changes in normal pregnancy is important for the timeous recognition of cardiac pathology as cardiovascular disease (CVD) is a leading cause of non-obstetric mortality during pregnancy.

Pregnancy poses a physiological stress test as cardiac output increases by 30–50% close to term.¹ Further haemodynamic stress occurs during labour and many of the effects of pregnancy on CVD persist for several months after delivery.²

The complex morphological and functional adaptations of the maternal heart during pregnancy have recently been studied in detail by Savu *et al.*³ In this study, serial echocardiography was performed to measure conventional parameters such as ventricular dimension and ejection fraction, as well as myocardial deformation (strain). The results revealed increased cardiac performance and progressive left ventricular remodelling throughout pregnancy. Progressive development of eccentric hypertrophy, which recovered post-partum, was also observed.

CVD in pregnancy is a complex topic as women can present either pre- or post-partum, due to a pre-existing heart disease such as operated or unoperated congenital heart disease, valvular heart disease, or an

idiopathic dilated cardiomyopathy. Women often present with symptoms and signs of heart failure.⁴ On the other hand, there are unique diseases such as peripartum cardiomyopathy (PPCM) which most commonly present in the post-partum period to women with no other structural heart disease.⁵ This makes management of women with CVD in pregnancy challenging, needing close interaction by cardiologists, obstetricians, and intensivists. Data from prospective studies and the establishing of prevalence rates are rare and, often, only incidence data from hospital-based registries are available.

There is a general paucity of data on CVD in women from Africa and other developing regions and, in particular, related to pregnancy with its unique disease pattern and presentations.^{6,7}

This review will summarize the data on the incidence and prevalence of pregnancy-related CVD published from different regions of the world.

2. The global burden of CVD in pregnancy and post-partum

Awareness about the different CVDs that can occur in pregnancy or post-partum has received limited attention and the main focus has been on hypertension and pre-eclampsia. The global impact of elevated blood pressure (BP)/hypertension, in general, is profound, being responsible

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for more deaths worldwide than any other cardiovascular risk factor, including tobacco use, obesity, and lipid disorders.^{8,9} As such, hypertension is a key contributor to a global epidemic of CVD that is indirectly manifested via a range of conditions such as stroke, chronic heart failure (CHF), acute coronary syndromes (ACS), and chronic kidney disease.^{10–12} Beyond the higher income countries, 80% of worldwide CVD-related deaths now occur in low- and middle-income countries (LMICs).¹⁰ In LMICs, morbid and fatal CVD-related events typically occur at a younger age and affect more women (commonly in pregnancy), thereby exerting a more profound impact on the family unit and the workforce.⁸ The recently published Global Burden of Disease Study not only reports on the common causes of death, but also on the burden of disease expressed as Years Lived with Disabilities (YLDs). However, the reporting on 1160 sequelae of 289 diseases contributing to YLDS does not report on the prevalence of CVD pre- and post-partum as an entity. It is estimated that globally, hypertensive disorders of pregnancy complicate 2–8% of all pregnancies, thus contributing to a major extent to maternal mortality worldwide.^{13,14} Figure 1 demonstrates global YLDs due to hypertensive disorders of pregnancy in total, due to pre-eclampsia and the long-term sequelae of hypertensive disorders of pregnancy for 1990 and 2010. There is an increase in YLDs of 33%.

Chronic hypertension is now prevalent in 3% of women falling pregnant in the USA¹⁵ and will also influence the prevalence of ACS in pregnancy. Two population-based studies report the incidence of ACS in pregnancy to be between 2.7 and 6.2 per 100 000 deliveries.^{16,17} This figure is likely to increase due to an increase in hypertension, higher prevalence of obesity, and an older age when falling pregnant.^{16–18}

3. Prevalence of hypertensive disorders in pregnancy and long-term consequences

Hypertensive disorders occurring during pregnancy or post-partum include pre-eclampsia, gestational hypertension, and pre-existing chronic hypertension (Figure 2). Pre-eclampsia is a multisystem disorder of pregnancy, generally defined as new hypertension (diastolic blood pressure of ≥ 90 mmHg) and proteinuria (≥ 300 mg in 24 h), at or after 20 weeks gestation.¹⁹ The cause of pre-eclampsia remains largely debated, but the leading hypothesis strongly relies on abnormal placental function due to remodelling of spiral arteries in early pregnancy.¹⁹ The highest perinatal risk is found in women presenting with pre-eclampsia at < 32 weeks, with an increase in mortality by 20-fold, compared with women presenting with this condition at ≥ 37 weeks.²⁰ Hypertensive disorders of pregnancy complicate 2–8% of pregnancies in the Western world. In Latin America and the Caribbean they contribute to $> 25\%$ of maternal death, whereas in Africa and Asia they contribute to $> 10\%$ of maternal death. The confidential inquiry into maternal deaths in South Africa (Figure 3) reported that of the 4867 deaths reported over 2 years, 14% were due to hypertensive disorders, with another 8.8% due to medical and surgical conditions (www.hst.org/za/saving-mothers-2008–2010).

The incidence of pre-eclampsia has risen in the USA,¹⁵ possibly due to an increased prevalence of pre-disposing factors such as chronic hypertension, obesity, and diabetes. Certain ethnic groups, e.g. African-American and lower socio-economic status, are associated with increased risk.²¹ Pre-eclampsia is a cause of severe maternal morbidity, e.g. stroke and HELLP (haemolysis, elevated liver enzymes, and low platelet count) and patients can present with a range of symptoms and signs

(Table 1). Since delivery is the only cure, up to 15% of pre-term births are associated with pre-eclampsia. This often leads to an adverse perinatal outcome, such as pre-maturity, intra-uterine growth restriction, and foetal death.¹⁹ Women with early onset pre-eclampsia are at an increased risk for future cardiovascular events. Because the risk of developing chronic hypertension could be $> 20\%$, BP should be checked regularly and the first focus should be on lifestyle modification.²²

Interestingly, men and women born to mothers with pre-eclampsia, and women who were born small for gestational age, have an increased risk of fathering or having a future pregnancy that is complicated by pre-eclampsia.²³ These children have a heightened risk of features of metabolic syndrome, including high BP at an early age.²⁴ Data by Kajantie et al.²⁵ in a cohort of 6410 babies born in Helsinki and followed for 60–70 years showed an increased risk of stroke in people born after pregnancies complicated by pre-eclampsia or gestational hypertension.

Chronic hypertension in pregnancy is defined as a BP of at least 140 mmHg systolic or 90 mmHg diastolic before gestation or for women who first present during pregnancy before 20 weeks gestation. Pre-existing hypertension complicates 1–5% of pregnancies.²² The risk of adverse outcome increases with the severity of hypertension and end-organ damage.¹⁵ Importantly, some antihypertensive agents, such as mineralocorticoid antagonists and angiotensin-converting enzymes, carry risk in pregnancy and should be discontinued before conception.

In a recent clinical practice article in the *New England Journal of Medicine*, Seely and Ecker¹⁵ summarizes the risk associated with women who are hypertensive when falling pregnant. Women with chronic hypertension have an increased frequency of pre-eclampsia (17–25 vs. 3–5% in the general population), as well as foetal growth restriction (50% increase in risk) and pre-term birth (five times increase in risk). In addition to the women with chronic hypertension who develop pre-eclampsia, another 7–20% of women have worsening of hypertension in pregnancy. In a population-based prospective cohort study among 6902 pregnant women, the Generation R Study examined the association of maternal body mass index and gestational weight gain with the risks of pregnancy-induced hypertension and pre-eclampsia. The risk of pregnancy-induced hypertension and pre-eclampsia was increased for obese mothers (BMI: 30–34.9 kg m²), with an odds ratio of 4.67 (95% confidence interval: 3.07–7.09) and odds ratio 2.49 (95% confidence interval: 1.29–4.78).²⁶ Post-partum hypertension is common. BP usually rises over the first 5 days after delivery. Women who are hypertensive during pregnancy may be normotensive after birth, but then become hypertensive again in the first postnatal week.²² This can lead to hypertensive heart failure which is commonly observed, in particular, in African populations.

4. Incidence of peripartum cardiomyopathy and other cardiomyopathies diagnosed in pregnancy

PPCM is a pregnancy-associated myocardial disease with significant morbidity and mortality.²⁷ A recent position statement from the European Society of Cardiology Working Group on PPCM defined the disease as an 'idiopathic cardiomyopathy presenting with heart failure secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found'.⁵

Global Burden of Disease Study 2010

	All ages YLDs (thousands)			YLDs (per 100 000)		
	1990	2010	%Δ	1990	2010	%Δ
Maternal disorders	1394 (935–2271)	1790 (1138–2936)	28.4%	26 (18–43)	26 (17–43)	-1.2%
Maternal haemorrhage	143 (84–234)	98 (61–151)	-31.7%	3 (2–4)	1 (1–2)	-47.5%
Maternal haemorrhage	29 (18–46)	19 (12–29)	-34.2%	1 (0–1)	<0.5 (0–0.5)	-49.4%
Anaemia due to maternal haemorrhage	114 (65–193)	79 (47–124)	-31.1%	2 (1–4)	1 (1–2)	-47.0%
Maternal sepsis	80 (46–128)	42 (25–65)	-48.4%	2 (1–2)	1 (0–1)	-60.3%
Hypertensive disorders of pregnancy	69 (41–111)	93 (53–151)	33.2%	1 (1–2)	1 (1–2)	2.5%
Pre-eclampsia	60 (33–100)	83 (44–141)	38.9%	1 (1–2)	1 (1–2)	6.9%
Eclampsia	4 (1–7)	3 (1–7)	-14.6%	<0.5 (0–0.5)	<0.5 (0–0.5)	-34.3%
Long-term sequelae for hypertensive disorders of pregnancy	6 (1–15)	7 (2–15)	6.3%	<0.5 (0–0.5)	<0.5 (0–0.5)	-18.2%
Obstructed labour	809 (458–1493)	1182 (641–2194)	46.0%	15 (9–28)	17 (9–32)	12.4%
Obstructed labour	77 (40–140)	34 (19–57)	-56.1%	1 (1–3)	<0.5 (0–1)	-66.3%
Fistula	732 (390–1425)	1148 (601–2138)	56.8%	14 (7–27)	17 (9–31)	20.6%
Abortion	27 (15–52)	32 (19–59)	19.8%	1 (0–1)	<0.5 (0–1)	-7.8%
Other maternal disorders	264 (180–420)	343 (225–526)	30.1%	5 (3–8)	5 (3–8)	0.1%

Figure 1 Years lived with disability for maternal and hypertensive disorders of pregnancy (reproduced with permission from the study of Vos *et al.*⁸).

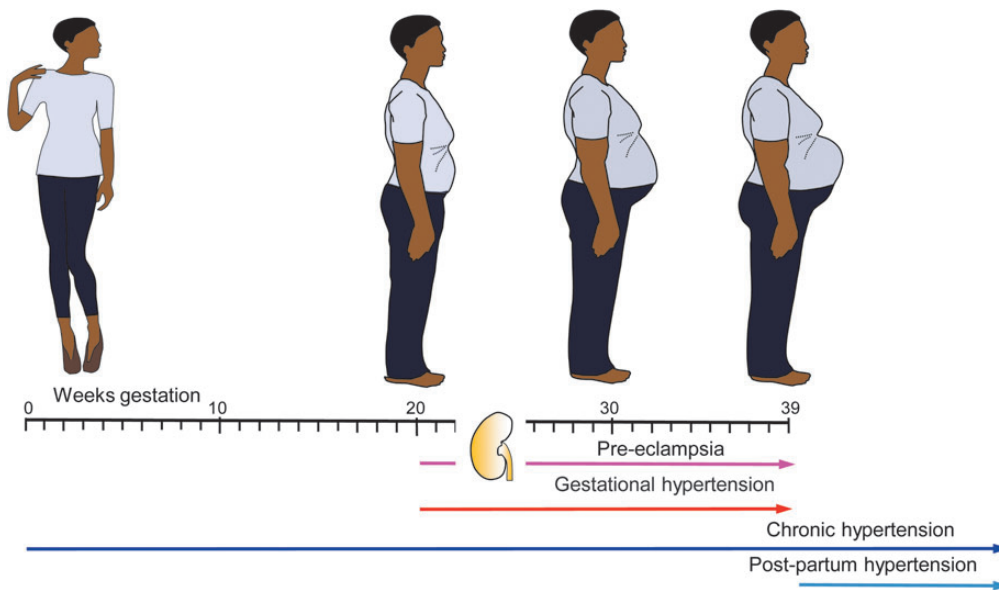


Figure 2 Hypertensive disorders of pregnancy.

It may be difficult to distinguish from other forms of cardiomyopathy, such as familial or pre-existing idiopathic dilated cardiomyopathy, which usually presents pre-partum in the second or third trimester.⁵ Symptoms are similar to that of other forms of heart failure (Table 1).

The Nationwide Inpatient Sample of Health Care costs and Utilization Project, a cross-sectional study using 14 323 731 hospitalizations for pregnancy, performed in the USA from 2004 to 2006, reported on pregnancy hospitalizations with cardiomyopathy per 100 deliveries and in the

post-partum period.²⁸ The rate of pregnancy hospitalizations with cardiomyopathy was 0.46 per 1000 deliveries (0.18 for apparent PPCM and 0.28 for other cardiomyopathies). Myocardial disorders were rare during delivery hospitalizations (0.01%), but were not uncommon among post-partum hospitalizations (4.2%).

Accurate data on the incidence of PPCM are unavailable as few population-based registries exist. Recent studies suggest a wide variation in the estimated incidences: one case per 299 live births in Haiti;^{29,30} one

Primary obstetric cause	2002–2004		2005–2007		2008–2010	
	n	%	n	%	n	%
Direct	1767	53.6	1819	45.9	2252	46.3
Hypertension	628	19.1	622	15.7	679	14.0
Indirect	1430	43.4	1966	49.7	2389	49.3
Non-pregnancy-related infections	1246	37.8	1729	48.7	1969	40.5
Medical and surgical conditions	184	5.6	237	6.0	430	8.8
Total	3296	100	3959	100	4867	100

Figure 3 A comparison of underlying obstetrics causes of death between 2002–2004, 2005–2007, and 2008–2010 (www.hst.org.za/publications/saving-mothers-2008-2010).

Table 1 Symptoms and signs of severe pre-eclampsia and peripartum cardiomyopathy

Pre-eclampsia	PPCM
Right upper quadrant pain due to liver oedema and haemorrhage	Shortness of breath due to left ventricular dysfunction
Headache, visual disturbances, and convulsions due to cerebral oedema	Stroke and embolic phenomenon due to left ventricular thrombus dislocating
Hyper-reflexia	Leg oedema and ascites due to biventricular involvement
HELLP syndrome: haemolysis, elevated liver enzymes, low platelet count	Palpitations due to arrhythmia

Table 2 Incidence of PPCM

Author	Year	Country	Incidence	Cohort	Consecutive	Definition of PPCM	Echocardiographic assessment
Fett <i>et al.</i> ²⁹	2002	Haiti	1 in 400 live births	Afro-Caribbean	Consecutive	(1) CHF 1 month before to 5 months after delivery(2) No pre-existing heart disease(3) (3) No other cause identified for the CHF	EF < 45%
Fett <i>et al.</i> ³⁰	2005	Haiti	1 in 300 live births	Afro-Caribbean	Consecutive	(1) CHF 1 month before to 5 months after delivery(2) No pre-existing heart disease(3) (3) No other cause identified for the CHF	EF < 45%
Desai <i>et al.</i> ³¹	1995	South Africa	1 in 1000	Black Africans	Non-consecutive	(1) CHF 1 month before to 5 months after delivery(2) No pre-existing heart disease(3) (3) No other cause identified for the CHF	EF < 45%
Mielniczuk <i>et al.</i> ³⁷	2006	USA	1 in 2289	50% non-white	Consecutive	(1) CHF 1 month before to 5 months after delivery(2) No pre-existing heart disease(3) (3) No other cause identified for the CHF	Not defined
Chapa <i>et al.</i> ³²	2005	USA	1 in 1149	African American 80%	Consecutive	(1) CHF 1 month before to 5 months after delivery(2) No pre-existing heart disease(3) (3) No other cause identified for the CHF	Not defined

^aOnly studies using echocardiography have been included.

case per 1000 live births in South Africa,³¹ and one case per 1149–4000 live births in USA^{32,33} (Table 2). The reason for this variation remains unclear and could possibly be linked to ethnic and socio-economic factors, but this needs further investigation. A study conducted in the USA by Brar *et al.*³³ found a large difference in incidence among different

ethnic groups, with 1 : 1421 in African Americans, 1 : 2675 in Asians, 1 : 4075 in Caucasians, and 1 : 9861 in Hispanics. Another study from the USA³⁴ found a 15-fold higher incidence of PPCM in African-American women, compared with non-African Americans. Interestingly, left ventricular recovery and survival rates of PPCM in African Americans are

similar to those reported from Haiti and South Africa, but different from that of Caucasians diagnosed in the USA.³⁵ Socio-economic factors may limit access to timely and advanced medical care. However, in the USA and South African studies, patients had a similar rate of optimal drug therapy including ACE-inhibitors and beta-blockers, compared with the other ethnic groups.^{35,36}

Mielniczuk *et al.*³⁷ reported an increase in incidence over time from 1 in 4350 in 1990 to 1993 to 1 in 2229 in 2000–02. The reported increase in incidence over time in the USA has been attributed to increase in maternal age, substantial increase in multifoetal pregnancies due to contemporary reproductive techniques and possible increase in recognition of the disease.³⁸ Recognition of the disease at an earlier stage is likely due to the increase in awareness promoted by the European Cardiac Society and the activities of a dedicated working group on PPCM (www.escardio.org) and the international registry on PPCM as part of the

EURObservational Research Programme (<http://www.eorp.org>). In the USA, awareness has been promoted via web-based recruitment facilities.³⁹ The number of original and review publications on PPCM reported on Pubmed has increased substantially over the past 20 years (Figure 4). A further increase in awareness and reporting can be expected with the EURObservational Research Programme now having >77 centres in 38 countries registered (Figure 5).

5. Incidence of acute myocardial infarction in pregnancy

Although myocardial infarction is a rare event in women of reproductive age, pregnancy increases the risk due to a number of factors—some unique to pregnancy. Coronary artery dissection is a rare cause of

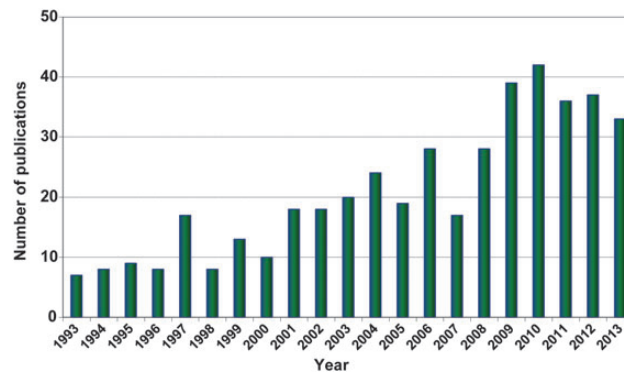


Figure 4 Number of original publications and reviews on PPCM over two decades (1993–2013).

EURObservational Research Programme

Peripartum Cardiomyopathy Registry Recruitment status as of 21st August 2013

77 participating centres across 38 countries

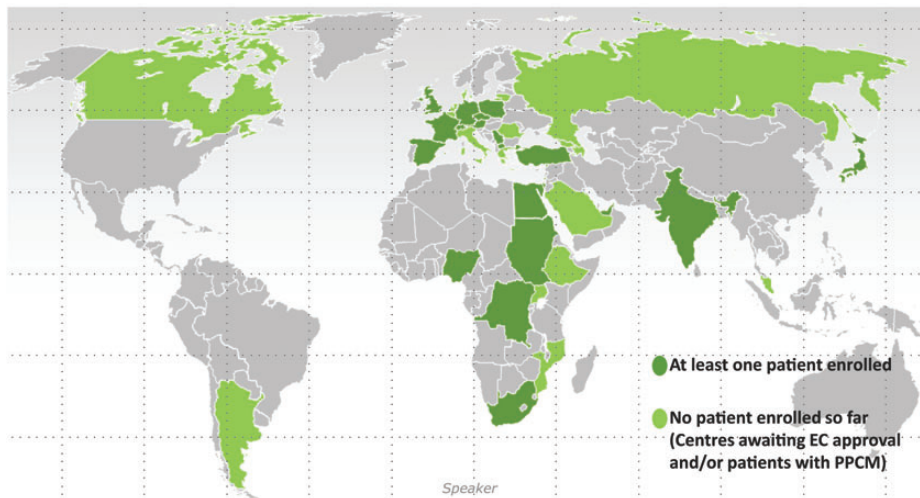


Figure 5 EURObservational Research Programme on PPCM (<http://www.eorp.org>).

myocardial infarction. However, in one series,⁴⁰ 20% of patients involved had recently delivered. It is postulated that post-partum degeneration of the intima and media of the coronary arteries lead to those events.⁴¹ Hypertension is also strongly associated with myocardial infarction in pregnancy, as it possibly further damages blood vessels that have already undergone changes due to haemodynamic stress of pregnancy or endothelial activation. Oral oestrogens and progesterone have been implicated as a CVD risk factor, as the risk for coronary artery disease and non-fatal myocardial infarction is increased by 24% by hormone replacement therapy.⁴²

James *et al.*¹⁶ reported on the incidence, mortality, and risk factors for pregnancy-related acute myocardial infarction in the USA, using a Nationwide In-patient Sample for the years 2000–02, for all pregnancy-related discharges. A total of 859 discharges included the diagnosis of acute myocardial infarction, with a rate of 6.2 (95% CI: 3.0–9.4) per 100 000 deliveries. Among these there were 44 deaths, with a case fatality rate of 5.1%. Advanced age, hypertension, and smoking emerged as the most important risk factors. The odds of acute myocardial infarction were 30-fold higher for women aged 40 years and older than for women aged <20. Hypertension increased the risk 20-fold and smoking 8-fold. Combined with the risk of stroke, which is 1.4 per 100 000 deliveries, the risk of death due to arterial thrombo-embolism in pregnancy exceeds the risk from venous thrombo-embolism by 50%.¹⁶

6. Summary and conclusion

Accurate data about the prevalence and incidence of pregnancy-related heart disease is limited from most parts of the world. Hypertensive disorders of pregnancy, in particular pre-eclampsia commonly complicate pregnancy and can have long-term consequences. PPCM and acute myocardial infarction presenting in pregnancy are associated with a high mortality and are often not diagnosed timeously. Physicians are also often not aware that the risk of maternal death due to thrombo-embolic causes, including stroke and myocardial infarction, exceeds the risk of death due to venous thrombo-embolism. Data are usually collected for the pregnancy period and, therefore, cardiovascular events such as heart failure occurring post-partum is inadequately recorded and, possibly, under reported in most datasets. The spectrum of disease differs profoundly between regions, with data from developing countries being scarce. Interestingly, studies have found a >15-fold higher incidence of PPCM in certain ethnic groups, with a possible different behaviour of disease progression and outcome. The reason for this variation remains unclear and requires further investigation. This makes management of women with CVD in pregnancy challenging, needing close interaction by cardiologists, obstetricians, and intensivists.

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