Long-Term Cardiovascular Morbidity in Children Born Following Fertility Treatment

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Objective To determine the risk of long-term cardiovascular disease (CVD) among children born following in vitro fertilization (IVF) and compared with spontaneous pregnancies.

Study design A population-based cohort study including all singleton deliveries occurring between 1991and 2014 at a tertiary medical center was performed. Hospitalizations up to the age of 18 years involving CVD were evaluated in children delivered following IVF, ovulation induction, and spontaneous pregnancies. CVD included valvular disorders, hypertension, arrhythmias, rheumatic disease, cardiomyopathy, ischemic heart disease, and heart failure. Kaplan-Meier survival curves were used to compare cumulative morbidity incidence, and a Cox regression model controlled for confounders.

Results During the study period, 242 187 singleton deliveries met the inclusion criteria; 1.1% following IVF (n = 2603), and 0.7% following ovulation induction (n = 1721). Hospitalizations up to the age of 18 years involving CVD (n = 1503) were comparable in children delivered following IVF (0.6%), ovulation induction (0.7%), and spontaneous pregnancies (0.6%; $P = .884$). No significant difference in the cumulative incidence of CVD was noted between the groups (log rank $P = .781$). Controlling for maternal age, gestational age, birthweight, maternal diabetes, and hypertensive disorders in pregnancy, fertility treatment was not noted as a risk factor for long-term pediatric CVD (IVF adjusted hazard ratio 1.05, 95% CI 0.63-1.74, $P = .86$; ovulation induction adjusted hazard ratio 0.97, CI 95% 0.55-1.71, $P = .92$).

Conclusions Singletons conceived via fertility treatments do not appear to be at an increased risk of long-term pediatric CVD. *(J Pediatr 2019;204:84-8).*

In the last 50 years, a growing number of couples have undergone assisted reproductive technology (ART) treatment, to conceive.[1] Current evidence indicate a 9% prevalence of infertility worldwide.[2] Since the 1970s, more than 5 million pregnancies have occurred following fertility treatments. The term fertility treatment refers to ovulation induction and in vitro fertilization (IVF). Ovulation induction involves gonadotropins injections followed by coitus or intra-uterine insemination. In cases of failed conservative treatment or in cases of infertility because of severe male factor, female mechanical factor, etc, the couple is referred for IVF. Along with growing experience and success worldwide, demand has increased and indications have expanded.

Over time, concern has been raised regarding long-term consequences of fertility treatments both to mother and child. Potential concerns included the risk for maternal malignancy (ovarian, breast, and uterine), although recent studies are reassuring.[3-5] Potential long-term cardiovascular effects in women undergoing fertility treatments were also investigated. Again, a recent study found no significant difference in rates of maternal cardiovascular morbidity among women undergoing fertility interventions.[6]

Health implications of fertility treatments on offspring are yet to be elucidated. Over the years, data concerning short-term consequences of fertility treatments including perinatal morbidity and mortality as well as congenital malformations have accumulated.[7,8] However, data on long-term health consequences of the offspring is scarce. Previous studies have suggested increased respiratory, endocrine, and metabolic disorders as well as neoplasms in fertility treatments offspring.[9-12] Hints of increased cardiometabolic morbidity in fertility treatments conceived children were published, including increased carotid media thickness and vascular dysfunction.[13-15] The current study was aimed to examine whether fertility treatments influence the long-term incidence of cardiovascular disease among offspring up to the age of 18 years.

Methods

A population-based cohort analysis including all singleton infants born between the years 1991 and 2014 at the Soroka University Medical Center (SUMC) was

ART	Assisted reproductive technology
IVF	In vitro fertilization
SUMC	Soroka University Medical Center

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conducted. SUMC is the sole tertiary hospital in Israel's southern region and the only IVF unit in the region as well as the largest birth center in Israel (~17 000 births in 2016). In Israel, ART treatments are financed by the ministry of health, according to the national health law to all citizens regardless of religion, race, or sex.

The research protocol was confirmed by the SUMC institutional review board. The method of conception was determined as the independent variable: spontaneous vs fertility treatments. The study included a group of patients undergoing conservative fertility treatment including controlled ovarian hyperstimulation followed by timed triggered ovulation with or without intra-uterine insemination (the ovulation induction group), a group of IVF patients, and spontaneous pregnancies, serving as controls.

Information on method of conception was obtained by maternal report and verified through medical records. The perinatal dataset includes information collected immediately after delivery by an obstetrician and verified by a team of skilled designated medical secretaries prior to entering it into the database. Personal identifying numbers were used to match and cross-link the entire perinatal dataset to the pediatric hospitalization dataset. This dataset includes *International Classification of Diseases, Ninth Revision* codes for all medical diagnoses, and demographic information for all hospitalized children. All the diagnoses and includes *International Classification of Diseases, Ninth Revision* codes were grouped and are displayed in the **Appendix**.

The primary outcome variable was the first pediatric hospitalization of the offspring associated with any cardiovascular diagnosis. A cardiovascular event was defined as the first hospitalization with any diagnosis from the predefined list detailed in the **Appendix** (available at www.jpeds.com). Follow-up time was completed if any of the following occurred: a cardiovascular event, death of a child during hospitalization (noncardiovascular related), age 18 years, or the end of the study period. To reduce potential confounders, we excluded from the research offspring with congenital malformations and multiple gestations.

Background and perinatal characteristics included maternal age, ethnicity, parity, pregnancy complications (pregestational or gestational diabetes mellitus and hypertensive disorders of pregnancy), gestational age at delivery, mode of delivery, offspring sex, birthweight, Apgar score, etc. A period variable was created (offspring year of birth, which was defined as after or before 2002, the middle study year) to address changes in fertility treatment protocol and technology over the study period. Initial analysis compared background, pregnancy, and perinatal characteristics of the 3 study groups, with the use of χ^2, ANOVA, and Kruskal-Wallis tests, based on variable characteristics and distribution. All analyses were 2-sided, and a P value of <.05 was considered statistically significant.

Kaplan-Meier survival curves were constructed and the Cox-Mantel log-rank test used for comparing between the 3-cumulative cardiovascular hospitalization incidence curves. A Cox regression model was constructed to assess the independent risk for cardiovascular disorders in offspring, based on mode of conception, while adjusting for confounders. Baseline variables that were statistically different between the groups and potentially associated with cardiovascular morbidity were suspected as confounders and included in the regression analysis, as were variables with clinical importance.

Results

During the study period, a total of 242 187 newborns were included and divided into 3 groups according to method of conception. The IVF group included 2603 of the newborns (1.1%); 1721 were in the ovulation induction group (0.7%), and 237 863 were considered unexposed (ie, spontaneous pregnancy, 98.3%).

Table I presents the demographic, obstetrical, and perinatal characteristics in the 3 study groups. Patients in the IVF group were older than ovulation induction mothers (32.51 vs 29.54 years), and both were older than the unexposed group (28.1 years, $P < .001$). The ART groups also demonstrate lower parity rates. Both fertility treatment groups exemplify significantly lower rates of macrosomia, and higher rates of oligohydramnios and labor induction. Gestational age at birth was lower in the fertility treatments groups and higher rates of preterm births (14.9%, 9.8% vs 6.4%, $P < .001$), diabetes mellitus (including both pregestational or gestational) (14.2%, 13.0% vs 4.8%, $P < .001$), hypertensive disorders (10.2%, 11.9% vs 4.9%, $P < .001$), fetal growth restriction (3.2%, 3.8% vs 1.8%, $P < .001$), low birthweight (11.1%, 11.4% vs 6.3%, $P < .001$), malpresentation of the fetus, and cesarean delivery (39.0%, 25.9% vs 13.1%, $P < .001$) were noted in IVF, ovulation induction, and spontaneous pregnancies, respectively.

Cardiovascular related hospitalization of the offspring are presented in **Table II**. Rates (per 10 000 person years) of hypertension, arrhythmias, pericarditis, myocarditis, endocarditis, other cardiac morbidities, or total cardiovascular hospitalizations were comparable between the groups.

The **Figure** presents the Kaplan-Meier log of survival for total cardiovascular morbidity of the study groups. There were no significant differences between the study groups (log-rank, $P = 781$).

Table III demonstrates the multivariable model assessing the independent association between mode of conception and cardiovascular related hospitalization. Although maternal age and birthweight were associated with long-term cardiovascular morbidity of the offspring, no significant association between cardiovascular hospitalizations of the offspring and IVF or ovulation induction was noted.

Discussion

Several mechanisms may underline the possible association between fertility treatment and long-term cardiovascular morbidity of the offspring. During the early reproductive stages of gametogenesis, fertilization, and early embryo development, the epigenome undergoes a sequence of changes. These stages are susceptible to epigenetic dysregulation.[16] Imprinting

Table I. Demographic characteristics and perinatal outcome of the study groups*.

Characteristics presented by mean (SD)	Offspring born as a result of IVF n = 2603	Offspring born as a result of ovulation induction n = 1721	Offspring born as a result of spontaneous pregnancy n = 237 863	*P* value
Maternal demographic and background characteristics				
Maternal age (y)	32.51 (5.385)	29.54 (5.223)	28.10 (5.809)	<.001
Ethnicity				
Jewish	2118 (81.4)	1381 (80.2)	111 292 (46.8)	<.001
Bedouin	485 (18.6)	340 (19.8)	126 571 (53.2)	
Parity				
1	1355 (52.1)	987 (57.4)	54 790 (23.0)	<.001
2-4	1211 (46.5)	697 (40.5)	121 962 (51.3)	
5 +	36 (1.4)	37 (2.1)	61 076 (25.7)	
Obesity	48 (1.8)	46 (2.7)	2367 (1.0)	<.001
Pregnancy and labor characteristics and complications				
Diabetes mellitus (gestational and pregestational)	369 (14.2)	223 (13.0)	11 515 (4.8)	<.001
Hypertensive disorders	265 (10.2)	204 (11.9)	11 638 (4.9)	<.001
Fetal growth restriction	84 (3.2)	66 (3.8)	4253 (1.8)	<.001
Pathologic presentation	238 (9.1)	133 (7.7)	11 085 (4.7)	<.001
Oligohydramnios	74 (2.8)	63 (3.7)	5285 (2.2)	<.001
Placental abruption	25 (1.0)	9 (0.5)	1094 (0.5)	<.001
Macrosomia (birthweight >4000 g)	84 (3.2)	62 (3.6)	11 213 (4.7)	<.001
Induction of labor	1019 (39.1)	769 (44.7)	61 324 (25.8)	<.001
Sex				
Male	1288 (49.5)	854 (49.6)	120 973 (50.9)	.226
Female	1315 (50.5)	867 (50.4)	116 890 (49.1)	
Gestational age at delivery, wk, mean (SD)	38.25 (1.895)	38.74 (1.957)	39.16 (1.741)	<.001
Preterm birth (<37 wk)	173 (14.9)	281 (9.8)	15251 (6.4)	<.001
Birthweight, g, mean (SD)	3079.89 (522.427)	3096.27 (533.348)	3216.26 (492.814)	<.001
Low birthweight (<2500 g)	290 (11.1)	196 (11.4)	14 960 (6.3)	<.001
Very low birthweight group (<1500 g)	25 (1.0)	16(0.9)	759 (0.3)	<.001
SGA	116 (4.5)	118 (6.9)	10 764 (4.5)	.003
Cesarean delivery	1016 (39.0)	445 (25.9)	31 267 (13.1)	<.001
Apgar score <7 at 1 min	154 (5.9)	106 (6.2)	11 452 (4.8)	.002
Apgar score <7 at 5 min	21 (0.8)	12 (0.7)	4274 (1.8)	<.001

SGA, small for gestational age.
*All numbers represent n (%) unless otherwise stated.

is a process in which genes are epigenetically adjusted according to the parental origin. Fetal anomalies caused by altered imprinting, although infrequent in the general population, are more frequent in the children of infertile parents.[17] Epigenetic modifications in general and imprinting in particular may result in fetal abnormal development including cardiac long-term consequences.

Accumulating data support Barker's "fetal programming" theory.[18] According to this theory, chronic diseases may result from an abnormal intra-uterine environment. Another potential association between the uterine environment and later chronic cardiovascular disease is an intra-uterine activation of genes adjusting for the atypical uterine milieu. Hence, the abnormal uterine environment may result not only in cardiovascular disease later on in life but also in an increased risk for obesity, hypertension, and diabetes.

Scherrer et al evaluated vascular function in 65 children born following fertility treatments and compared it with 57 spontaneously conceived children.[14]

Systemic circulation was assessed by endothelium-dependent and independent dilation of the brachial artery reflecting elastic artery stiffness. Structural alterations were evaluated by measuring carotid intima-media thickness. The authors reported children conceived by fertility treatments exhibited vascular dysfunction in the systemic and pulmonary circulation. The altered vascular function was not related to parental or hormonal factors but to the fertility treatments procedure itself.[14] In a prospective cohort study comparing 100 fetuses conceived

Table II. Method of conception and long-term cardiovascular hospitalizations in the offspring

Offspring long-term morbidity	Offspring born as a result of IVF n = 2603	Offspring born as a result of ovulation induction n = 1721	Offspring born as a result of spontaneous pregnancy n = 237 863	*P* value
Hypertension %(n/N)	1 (0%)	3 (0.2%)	141(0.1%)	.137
Arrhythmia	4 (0.2%)	6 (0.3%)	480 (0.2%)	.344
Peri-myo-endocarditis	3 (0.1%)	1 (0.1%)	96 (0.0%)	.164
Other cardiac morbidity	6 (0.2%)	3 (0.2%)	707 (0.3%)	.534
Total hospitalizations because of cardiovascular morbidity	15 (0.6%)	12 (0.7%)	1476 (0.6%)	.884

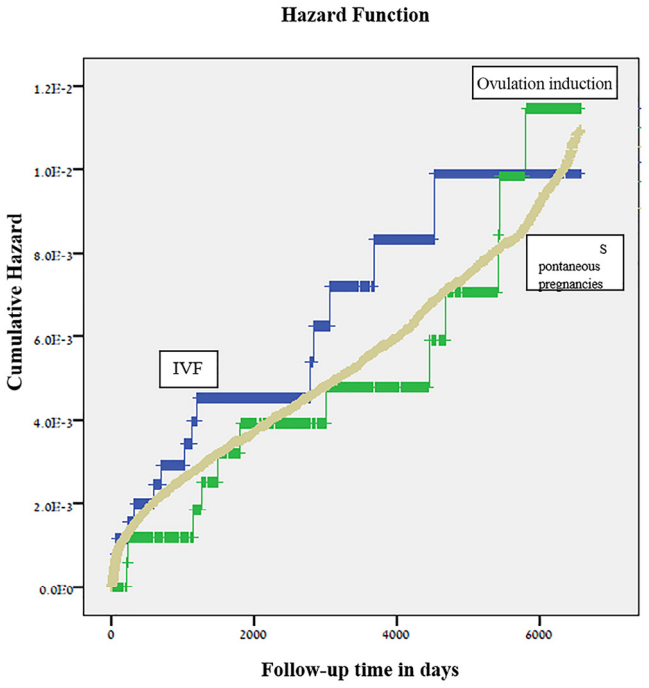

Figure. Kaplan-Meier survival analysis of cardiovascular hospitalization incidence by study groups*. *Log rank (Mantel-Cox) $P < .001$.

by ART and 100 control pregnancies, Valenzuela-Alcaraz et al reported that children conceived by ART displayed cardiac and vascular remodeling that is present in fetal life and persists in the postnatal life.[19]

Scherrer et al relate the increased risk of cardiovascular in ART children to the increased pathologic events during fetal life in these pregnancies.[15] For instance, an increased risk of preeclampsia and preterm delivery in ART pregnancies is well established.[20] These complications were also observed in higher rates with ART in the present study. Likewise, preterm delivery increases left ventricular mass, an independent predictor of cardiovascular morbidity and mortality in adulthood.[21] By increasing the short-term adverse perinatal outcome such as preterm delivery and preeclampsia, ART may induce increased prevalence of risk factors for cardiovascular disease later in life.[15]

The current study carries some limitations because of its retrospective nature. Correspondingly, the unknown infertility etiology and the precise fertility treatment protocol patients underwent are another limitation.

The results of the current study suggest that fertility treatments do not appear to be associated with an increased risk for long-term pediatric cardiovascular disorders in the offspring. This study may provide some reassurance and prevent unnecessary tests. Further prospective research is required to more accurately assess the long-term pediatric implications of fertility treatments. ■

Table III. Multivariate analysis of delivery mode and long-term cardiovascular morbidity in offspring

Variables	Adjusted hazard ratio	95%CI	*P* value
Spontaneously conceived	1		
IVF	1.05	0.63-1.74	.86
Ovulation induction	0.97	0.55-1.71	.91
Maternal age (y)	0.99	0.98-1.00	.046
Birthweight (g)	1.000	1.000-1.000	<.001
Maternal diabetes	1.34	1.09-1.66	.006
Preterm delivery	1.16	0.95-1.43	.14
Hypertensive disorders during pregnancy	0.98	0.79-1.23	.89
Period: before vs after 2002	0.49	0.43-0.55	<.001

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50 Years Ago in *The Journal Of Pediatrics*

A New Disorder of Purine Metabolism with Behavioral Manifestations

Nyhan WL, James JA, Teberg AJ, Sweetman L, Nelson LG. J Pediatr 1969;74:20-7.

In 1964, Lesch et al reported an X-linked condition characterized by hyperuricemia and disorder of the central nervous system.[1] The description of the Lesch-Nyhan syndrome with lack of hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) initiated an enormous interest the next decades for hyperuricemia related to developmental disease. Fifty years ago, Nyhan et al reported in *The Journal* another disorder of purine metabolism also characterized by hyperuricemia and behavioral manifestations, however, normal HGPRT. The 4-month-old boy had mild developmental retardation, absence of tears, and dysplastic teeth, marked overproduction of uric acid, glandular hypospadias, and hematuria. The red color of the urine could perhaps be explained not only by hematuria but also by uric acid crystals, which occasionally is misdiagnosed as hematuria?

Excessive production of uric acid is found in inborn errors of metabolism as glucose 6 phosphatase (glycogen storage disease type 1A) as well as phosphoribosyl-pyrophosphate (PRPP) synthetase deficiencies. Page and Coleman described a subclass of patients with classic infantile autism with a 4 fold increased de novo purine synthesis without any enzyme defects and estimated that hyperuricosuric autistic individuals may comprise 20% of the autistic population.[2]

In 1972, Sperling et al reported male subjects with excessive PRPP synthetase activity and purine overproduction.[3] Subsequently, a case similar to that of Lesch et al as a possible X-linked condition was published. A 3-year-old boy had hyperuricemia, mild mental handicap, and later sensorineuronal deafness including normal HGPRT and a superactive PRPP synthetase.[4]

Today it is recognized that phosphoribosylpyrophosphate synthetase superactivity is a rare inborn error of purine metabolism that is caused by mutations in the X-chromosomal gene PRPS1 (Xq22.3). Only few families have been reported to date.[5]

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Diagnosis Code	Diagnosis Description	Subgroup
3940	MITRAL STENOSIS	2
3949	OTHER AND UNSPECIFIED MITRAL VALVE DISEASES	2
3961	MITRAL VALVE STENOSIS AND AORTIC VALVE INSUFFICIENCY	2
3963	MITRAL VALVE INSUFFICIENCY AND AORTIC VALVE INSUFFICIENCY	2
3968	MULTIPLE INVOLVEMENT OF MITRAL AND AORTIC VALVES	2
3970	DISEASES OF TRICUSPID VALVE	2
4240	MITRAL VALVE DISORDERS	2
4241	AORTIC VALVE DISORDERS	2
4242	TRICUSPID VALVE DISORDERS, SPECIFIED AS NONRHEUMATIC	2
4243	PULMONARY VALVE DISORDERS	2
4019	UNSPECIFIED ESSENTIAL HYPERTENSION	3
4372	HYPERTENSIVE ENCEPHALOPATHY	3
40390	UNSP. HYPERTENSIVE KIDNEY DIS. WITH CHRONIC KIDNEY DISEASE STAGE I THROUGH STAGE IV, OR UNSPECIFIED	3
40391	UNSP. HYPERTENSIVE KIDNEY DIS. WITH CHRONIC KIDNEY DISEASE	3
40391	UNSP. HYPERTENSIVE KIDNEY DIS. WITH CHRONIC KIDNEY DISEASE STAGE V OR END STAGE RENAL DISEASE	3
40391	UNSP. HYPERTENSIVE RENAL DIS.+ RENAL FAILURE	3
40591	UNSPECIFIED RENOVASCULAR HYPERTENSION	3
4260	ATRIOVENTRICULAR BLOCK, COMPLETE	4
4263	OTHER LEFT BUNDLE BRANCH BLOCK	4
4264	RIGHT BUNDLE BRANCH BLOCK	4
4267	ANOMALOUS ATRIOVENTRICULAR EXCITATION	4
4270	PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA	4
4271	PAROXYSMAL VENTRICULAR TACHYCARDIA	4
4272	PAROXYSMAL TACHYCARDIA, UNSPECIFIED	4
4273	ATRIAL FIBRILLATION AND FLUTTER	4
4275	CARDIAC ARREST	4
4279	CARDIAC DYSRHYTHMIA, UNSPECIFIED	4
7850	TACHYCARDIA, UNSPECIFIED	4
7851	PALPITATIONS	4
42611	FIRST DEGREE ATRIOVENTRICULAR BLOCK	4
42612	MOBITZ (TYPE) II ATRIOVENTRICULAR BLOCK	4
42613	OTHER SECOND DEGREE ATRIOVENTRICULAR BLOCK	4
42682	LONG QT SYNDROME	4
42689	OTHER SPECIFIED CONDUCTION DISORDERS	4
42731	ATRIAL FIBRILLATION	4
42732	ATRIAL FLUTTER	4
42741	VENTRICULAR FIBRILLATION	4
42760	PREMATURE BEATS, UNSPECIFIED	4
42761	SUPRAVENTRICULAR PREMATURE BEATS	4
42769	OTHER PREMATURE BEATS	4
42789	OTHER SPECIFIED CARDIAC DYSRHYTHMIAS	4
427811	SINUS BRADYCARDIA	4
4267 1	WOLFF-PARKINSON-WHITE SYNDROME	4
390	RHEUMATIC FEVER WITHOUT MENTION OF HEART INVOLVEMENT	5
3911	ACUTE RHEUMATIC ENDOCARDITIS	5
3918	OTHER ACUTE RHEUMATIC HEART DISEASE	5
3919	ACUTE RHEUMATIC HEART DISEASE, UNSPECIFIED	5
3920	RHEUMATIC CHOREA WITH HEART INVOLVEMENT	5
3929	RHEUMATIC CHOREA WITHOUT MENTION OF HEART INVOLVEMENT	5
3941	RHEUMATIC MITRAL INSUFFICIENCY	5
3951	RHEUMATIC AORTIC INSUFFICIENCY	5
39890	RHEUMATIC HEART DISEASE, UNSPECIFIED	5
414	OTHER FORMS OF CHRONIC ISCHEMIC HEART DISEASE	7
4100	ACUTE MYOCARDIAL INFARCTION OF ANTEROLATERAL WALL	7
4109	ACUTE MYOCARDIAL INFARCTION OF UNSPECIFIED SITE	7
4111	INTERMEDIATE CORONARY SYNDROME	7
4149	CHRONIC ISCHEMIC HEART DISEASE, UNSPECIFIED	7
4292	CARDIOVASCULAR DISEASE, UNSPECIFIED	7
4295	RUPTURE OF CHORDAE TENDINEAE	7
41000	AC. M.I. ANTEROLATERAL, EPISODE OF CARE UNSP.	7
41011	AC. M.I. OTHER ANTERIOR, INITIAL EPISODE OF CARE	7
41071	AC. M.I. SUBENDOCARDIAL, INITIAL EPISODE OF CARE	7
41091	AC. M.I. UNSP. SITE, INITIAL EPISODE OF CARE	7
41410	ANEURYSM OF HEART (WALL)	7
42979	OTHER, MURAL THROMBUS (ATR.)(VENT.)ACQUIRED,FOLLOWING M.I.	7
4160	PRIMARY PULMONARY HYPERTENSION	8
4168	OTHER CHRONIC PULMONARY HEART DISEASES	8
4169	CHRONIC PULMONARY HEART DISEASE, UNSPECIFIED	8

(*continued*)

Diagnosis Code	Diagnosis Description	Subgroup
4171	ANEURYSM OF PULMONARY ARTERY	8
41512	SEPTIC PULMONARY EMBOLISM	8
41519	OTHER PULMONARY EMBOLISM & INFARCTION	8
4210	ACUTE AND SUBACUTE BACTERIAL ENDOCARDITIS	9
4211	ACUTE + SUBACUTE INFEC.ENDOCARDITIS IN DIS.CLASS.ELSEWHERE	9
4230	HEMOPERICARDIUM	9
4232	CONSTRICTIVE PERICARDITIS	9
4233	CARDIAC TAMPONADE	9
4238	OTHER SPECIFIED DISEASES OF PERICARDIUM	9
4239	UNSPECIFIED DISEASE OF PERICARDIUM	9
4251	HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY	9
4252	OBSCURE CARDIOMYOPATHY OF AFRICA	9
4253	ENDOCARDIAL FIBROELASTOSIS	9
4254	OTHER PRIMARY CARDIOMYOPATHIES	9
4257	NUTRITIONAL AND METABOLIC CARDIOMYOPATHY	9
4259	SECONDARY CARDIOMYOPATHY, UNSPECIFIED	9
4289	HEART FAILURE, UNSPECIFIED	9
4290	MYOCARDITIS, UNSPECIFIED	9
42090	ACUTE PERICARDITIS, UNSPECIFIED	9
42099	OTHER ACUTE PERICARDITIS	9
42290	ACUTE MYOCARDITIS, UNSPECIFIED	9
42291	IDIOPATHIC MYOCARDITIS	9
42292	SEPTIC MYOCARDITIS	9
42490	ENDOCARDITIS, VALVE UNSPECIFIED, UNSPECIFIED CAUSE	9
4280	CONGESTIVE HEART FAILURE	10
4280	CONGESTIVE HEART FAILURE, UNSPECIFIED	10
4281	LEFT HEART FAILURE	10
42841	ACUTE COMBINED SYSTOLIC AND DIASTOLIC HEART FAILURE	10
4299	HEART DISEASE, UNSPECIFIED	11
9971	CARDIAC COMPLICATIONS, NOT ELSEWHERE CLASSIFIED	11
42989	OTHER ILL-DEFINED HEART DISEASES	11
7852	FUNCTIONAL AND UNDIAGNOSED CARDIAC MURMURS	99
7852	UNDIAGNOSED CARDIAC MURMURS,(HEART MURMUR NOS)	99
7859	OTHER SYMPTOMS INVOLVING CARDIOVASCULAR SYSTEM	99
7852 1	SYSTOLIC MURMUR	99