REVIEW ARTICLE

Infective Endocarditis during Pregnancy

Shi-Min Yuan

ABSTRACT

Infective Endocarditis (IE) during pregnancy is a rare but grave condition. The diagnosis and management can be challenging, especially when the pregnant patient warrants a cardiac operation under cardiopulmonary bypass. The present article describes IE during pregnancy based on a series of published case reports in the literature. IE during pregnancy often causes embolic events and mycotic aneurysms. Two-thirds of IE in the pregnant patients requires timely or urgent cardiac surgery to alleviate patients' deterioration. At least a 3-week antibiotic therapy is mandatory before cardiac surgery aiming at improving the patients' conditions. During cardiac surgery, fetal heart rates may temporarily be slowed down but may gradually recover to normal after the operation. The fetal and maternal mortalities were 16.7% and 3.3%, respectively. The fetal deaths were apparently associated with a cardiac surgery during early pregnancy. Cardiopulmonary bypass, hypothermia and rewarming can adversely affect both the mother and the fetus by triggering placental deficits, fetal hypoxia and uterine contraction. Avoidance of cardiac operations before 24th gestation week and preferably deferred until after 28th gestation week have been a plausible argument as per the possible fetal deaths related to immaturity.

Key Words: *Cardiopulmonary bypass. Fetal distress. Infected aneurysm. Intracranial embolism. Uterine contraction.*

INTRODUCTION

Infective Endocarditis (IE) is an infection of the endocardium of the heart, including large intrathoracic vessels, native or prosthetic heart valves, or even cardiac chambers. It more often involves the heart valves on the left side.[1] IE is caused predominantly by *Streptococcus, Staphylococcus aureus* and *Enterococcus*, and less commonly by fungi.[2] It is an evolving disease, with continuing changes in epidemiology, microbiology and major predisposing risk factors in the last decades. This is characterized by new and high risk patient groups, changing microorganisms and new risk factors like intracardiac device implants, intravenous drug use and increasing nosocomial infections.[3,4] Nevertheless, the most common predisposing cardiac risk factor in native valve endocarditis is bicuspid aortic valve, with *Streptococcus viridans* being the most common etiologic organism.[5] Prosthetic valves are a particular risk. Occasionally, mural thrombi, ventricular septal defects, and patent ductus arteriosus become infected. The tissue factors released by the damaged endothelium facilitate the formation of vegetation as a potential source of infection.[6]

Department of Cardiothoracic Surgery, The First Hospital of Putian, Teaching Hospital, Fujian Medical University, Putian, Fujian Province, China.

Correspondence: Dr. Shi-Min Yuan, Department of Cardiothoracic Surgery, The First Hospital of Putian, Teaching Hospital, Fujian Medical University, 389 Longdejing Street, Chengxiang District, Putian 351100, Fujian Province, People's Republic of China.
E-mail: shi_min_yuan@yahoo.com

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Pregnancy at a younger age is often associated with an increased incidence of obstetric complications than at an older age.[7] IE is a rare but grave complication of the pregnant patients with an estimated incidence of only 0.006%.[8] Pregnancy related IE has been subordinated to instant epidemiologic progressions as well as IE in general population does, with past or current intravenous drug abusers being the most outstanding risk factor of all. IE is a predominant risk factor responsible for the maternal and fetal mortality and morbidity with a mortality of 22.1% and 14.7% in mothers and babies, respectively.[9] If left improperly treated, patients' condition may deteriorate rapidly, and result in significant sequelae such as congestive heart failure, pulmonary edema, embolic events, abscess formation, or mycotic aneurysm.[10]

Cardiac operation during pregnancy remains a challenge as for the concern of both maternal and fetal outcomes. The aim of this article is to give a comprehensive analysis on IE during pregnancy based on a series of published case reports in the literature.

METHODOLOGY

Literature of last 15 years (1997-2013) regarding IE that developed during pregnancy was retrieved from the PubMed and Hirewire Press, using the search terms pregnancy and infective endocarditis. Pregnant patients suffering from sterile endocarditis or the onset of IE developed after pregnancy were excluded from this study.

Patients were grouped at 2 levels. At the first level, patients were divided into 2 groups according to the treatment strategies: with cardiac surgery and without cardiac surgery; and at the second level, patients were

divided into 3 groups according to the time sequence of delivery and cardiac surgery: cardiac surgery prior to delivery (prior group), consecutive one-stage cardiac surgery and delivery (one-stage group), and cardiac surgery performed after delivery (post group).

Data were expressed in mean ± standard deviation. Kolmogorov-smirnov and Shapiro-wilk tests were taken to test the homogeneity of variance of the data. Unpaired t-test was used to compare quantitative and Fisher's exact test was used to compare the frequency on Statistical Package for Social Sciences (SPSS) version 19 software package. Two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

The search yielded 30 reports that met the requirements of the study design, which were composed of 30 patients.[8,9,11-38] Their ages were 28 ± 5.9 (range, 19 - 39, median, 27) years (n = 30). Their obstetric history was gravid 2.3 ± 2.1 (range, 0 - 9; median, 2) [n = 18] and para 1.1 ± 1.4 (range, 0 - 4; median, 1) [n = 16]. Their gestations were in 23.2 ± 8.2 (range, 12-36; median, 23) weeks. Four patients (13.3%) were in first trimester, 15 (50%) in second, and 11 (36.7%) in third trimester. The gravid and para numbers were both in normal distributions verified by probability-probability plot.

Their onset symptoms of IE could be divided into two types: afebrile (5/30, 16.7%) and febrile (25/30, 83.3%). The five afebrile patients manifested cough and breathlessness (n = 2), breathlessness (n = 1), asthenia (n = 1), and conjunctival petechiae (n = 1), respectively. The associated symptoms to the febrile patients were none (n = 3), cough (n = 2), breathlessness (n = 2), chills (n = 2), fatigue (n = 2), back pain (n = 1), and anorexia (n = 1), respectively. The duration of their onset symptoms was 2.7 ± 3.1 (range, 0.036-12; median, 2) weeks (n = 15). The predisposing factors for the development of IE were documented in 21 patients with current or past intravenous drug use being the most common risk factor (Table I). Their vital signs and laboratory results on admission were listed in Table II. In 13 patients, cardiac murmurs could be audible: 11 (84.6%) were systolic, 1 (7.7%) was diastolic, and 1 (7.7%) was systolic and diastolic.

Echocardiographic examinations on the vegetations were described in 29 patients. One patient did not have a vegetation anywhere in the cardiac chambers, but was still diagnosed as IE. The vegetations of the remaining 28 patients were more located in the left-sided cardiac chamber (75%) than in the right (25%) (p = 0.000) [(Table III)]. One or two pathogens were identified by blood and/or vegetation cultures in 21 patients. *Staphylococcus aureus* (8, 38.1%) was the most common, and *Streptococcus viridans* (4, 19.0%) was the second most common pathogen, followed by

Table I: Predisposing factors for infective endocarditis (n = 21).

Predisposing factor	n (%)
Intravenous drug use	9 (42.9)
Presence of heart disease	8 (38.1)
Mitral valve prolapse	2 (9.5)
Unpaired ventricular septal defect	3 (14.3)
Rheumatic valve disease (mitral)	1 (4.8)
Stenosed bicuspid aortic valve	1 (4.8)
Regurgitant bicuspid aortic valve	1 (4.8)
Foreign material implant	3 (14.3)
Hemodialysis	1 (4.8)
Central venous catheter indwelling	1 (4.8)
s/p mitral and aortic valve replacements	1 (4.8)
Infections	4 (19.0)
Urinary tract infection	3 (14.3)
Dental problems (with an unrepaired large ventricular septal defect)	1 (4.8)

Table II: Vital signs and laboratory results.

Variable	Mean	Range	Median	n
Temperature (°C)	38.6 ± 1.0	36.7 - 40	38.5	16
Pulse (beat/min)	119.2 ± 19.0	90 - 154	120	17
Respiration (breath/min)	25.1± 4.6	20 - 35	24	8
Systolic blood pressure (mmHg)	108.6 ± 14.7	94 - 130	102	15
Diastolic blood pressure (mmHg)	62.56 ± 12.1	43 - 960	60	15
Hemoglobin (g/dl)	9.4 ± 1.8	7.2 - 12.9	9.1	10
White blood cell ($x10^9$/L)	15.30 ± 5.30	5.60 - 22.60	15.85	14
Erythrocyte sedimentation rate (mm/hour)	83 ± 27.8	40 - 120	74	7
C-reaction protein (mg/dl)	20.0 ± 24.8	6.77 - 89.7	13.5	10

Table III: Locations of the vegetations (n = 28).

Location of vegetation	n (%)
Left-sided	21 (75)
Mitral valve	13 (46.4)
Mitral valve leaflet	10 (35.7)
Mitral valve leaflet, subvalvular apparatus	2 (7.1)
Subvalvular apparatus	1 (3.6)
Aortic valve (two were bicuspid)	6 (21.4)
Aortic valve, mitral valve	2 (7.1)
Aortic valve (bicuspid), mitral valve	1 (3.6)
Prosthetic aortic valve, prosthetic mitral valve	1 (3.6)
Right-sided	7 (25)
Tricuspid valve	4 (14.3)
Right ventricular free wall	2 (7.1)
Right atrium, superior vena cava	1 (3.6)

Table IV: Major cardiac operations (n = 20).

Major cardiac operation	n (%)
Mitral valve replacement	8 (40)
Aortic valve replacement	6 (30)
Aortic and mitral valve replacement	2 (10)
Pulmonary valve vegetation removal and leaflet excision without replacement, primary ventricular septal defect closure	1 (5)
Right atrial/superior vena caval thrombectomy	1 (5)
Tricuspid valve repair, ventricular septal defect repair, patent ductus arteriosus closure	1 (5)
Ventricular septal defect (transcatheter-based)	1 (5)

Table V: A comparison of gestations on admission between the prior, one-stage, and post group patients.

Gestation (week)	Prior	One-stage	Post
Mean ± SD	28.4 ± 8.2	32.8 ± 2.2	32.6 ± 3.3
n (%)	9 (45%)	4 (20%)	7 (35%)
p-value:			
p = 0.231 Prior vs. Post			
p = 0.933 One-stage vs. Post			
p = 0.334 One-stage vs. Prior			

Table VI: A comparison of gestations at cardiac surgery between the prior, one-stage, and post group patients.

Gestation (week)	Prior	One-stage	Post
Mean ± SD	19.1 ± 6.0	32.8 ± 2.2	34.1 ± 3.8
n (%)	8 (42.1%)	4 (21.1%)	7 (36.8%)
p value:			
p < 0.0001 Prior vs. Post			
p = 0.536 One-stage vs. Post			
p = 0.001 One-stage vs. Prior			

Streptococcus mitis, Staphylococcus aureus + *Haemophilus (H.) parainfluenzae*, α-hemolytic Streptococci, *Streptococcus agalactiae, Streptococcus mutans* + *Streptococcus sobrinus*, *Streptococcus sanguis, Salmonella typhi, and H. parainfluenzae* (2, 9.5% for each). Initial antibiotic therapy that was carried out before the availability of culture results was prevailed by intravenous penicillin G (12 million units per day) (6, 25%), ceftriaxone (2 g per day) (4, 16.7%), and ampicillin (3, 12.5%), etc.

Three patients had curettage during early pregnancy due to vaginal bleeding. Delivery was at 33.3 ± 3.9 (range, 23 - 40; median, 33.4) gestational weeks (n = 21). There were 2 fetal deaths (9.5%), and 19 (90.5%) were alive. The delivery modes were described in 11 patients, including 8 (72.7%) cesarean sections and 3 (27.3%) spontaneous vaginal deliveries.

The body weight of the newborns were 1999 ± 766.8 (range, 820 - 3505; median, 1859) grams (n = 12), and their Apgar scores at 1 and 5 minutes were 6.5 ± 2.8 (range, 1-10; median, 6.5) [n = 8] and 8 ± 1.9 (range, 4 - 10; median, 8) [n = 8].

Six (20%) neonates were admitted into the Neonate Intensive Care Unit immediately after the birth with a duration of Neonate Intensive Care Unit stay of 25.6 ± 25.9 (range, 1-59; median, 21) days (n = 5) for premature or respiratory distress.

For the management of IE, 20 patients (66.7%) underwent a cardiac operation, and 10 (33.3%) patients received conservative treatment. Twenty patients received cardiac surgery, including 9 (45%) cardiac operations before, 4 (20%) cardiac operations consecutively as one-stage with, and 7 (35%) cardiac operations after delivery (or curettage, Table IV). The gestation durations at delivery were not compared between groups due to the inhomogeneity of the data by Kolmogorov-Smirnov and Shapiro-Wilk tests. No intergroup differences were noted in gestation durations on admission, and the prior group patients had the shortest gestation than the one-stage and post group patients at the time of cardiac surgery (Tables V and VI). These results may indicate that one-stage and post group patients with their babies were likely to be in a much safer condition than the prior groups. The patients receiving a cardiac surgery had 4 fetal deaths with a fetal death rate of 20% (4/20); whereas it was 10% (1/10) in the conservatively managed patients (p = 0.640). Patients of the prior, one-stage, and post groups had 2 (22.2%), 0 (0%), and 2 (28.6%) fetal deaths, respectively, with no significant difference between the three subgroups (p = 0.509).

The indications for cardiac surgery in the 14 patient who had cardiac surgery before or simultaneous with delivery varied including clinical deterioration (n = 4),[14,23,25,29] evidence of enlarging vegetation (n = 3),[30,34,37] uncontrollable infection (n = 2),[11,15] valvular dysfunction (n = 2),[8,19] large vegetation with associated lung infection (n = 1),[26] free-floating superior vena cava vegetation extending into the right atrium (n = 1),[13] and not given (n = 1).[7] The duration of antibiotic use in these 14 patients was 18.4 ± 17.7 (range, 0-58; median, 16) days (n = 8).

Besides, 8 patients developed neurological complications including cerebral infarct (n = 5),[7,14,21,24,30] cerebral artery aneurysm (n = 2),[10,11] and intracerebral hematoma (n = 1).[22] Three of them received neurological operations, and 5, conservative treatment without undergoing a neurosurgery. All 8 patients recovered and led a self-caring life thereafter.

Eight (26.7%) patients had embolic events with cerebral emboli being the most (3, 37.5%), followed by splenic, pulmonary, peripheral, and combined emboli (1, 12.5% for each). Splenic embolic infarction occurred in 2 patients.[8,9] One of them died during cardiac surgery because she could not be weaned from cardiopulmonary bypass,[9] constituting the only maternal death of this patient setting with a mortality of 3.3%. Two small pulmonary emboli were noted in one of the patients.[14] Besides, one patient had complete heart block after aortic valve replacement which required permanent pacemaker implantation.[36]

DISCUSSION

Patients with IE may present with low-grade fever, heart murmurs, petechiae, anemia, embolic events, and endocardial vegetations. The presence of vegetations may result in valvular incompetence or obstruction, abscess formation, or mycotic aneurysm.[1] With sufficient antibiotic therapy, patients with progressed or unchanged vegetations may show a significant predilection of valve replacement, embolic events,

abscess formation, and mortality comparing to those with dwindling sized vegetations.[39] Vegetation length and serum matrix metalloproteinase-9 level were found to be significantly higher in patients with new embolic events compared to controls. The incidence of new embolic event was 64% when vegetation was > 10 mm and serum matrix metalloproteinase-9 level was > 167 ng/ml.[40] Valve perforation, valve destruction, and valvular, perivalvular, or myocardial abscess are common, especially in bicuspid aortic valve endocarditis.[41] In the presence of perivalvular abscess, the infection may involve the bundle of His or the atrioventricular node leading to bundle branch or atrioventricular blocks.[41] In IE patients, mycotic aneurysms can form in any major artery, most commonly in the intracranial cerebral arteries. Rapid exaggeration or even rupture of the mycotic cerebrovascular aneurysm often cause lethal subarachnoid or intra-parenchymal hemorrhages, which may eventually warrant emergent craniotomy and aneurysm clipping.[42,43] In pregnant patients, IE is rare, and the secondary splenic infarction is even rarer. Prompt diagnosis and proper management of IE are crucial to minimize the embolic events and avoid serious sequelae.[44,45] Pulmonary embolism is the usual complication of the right-sided endocarditis and emboli may continue to develop in spite of successful infection control.[46] In this patient setting, the splenic infarct developed in 2 patients representing a high incidence of 13.3%. The only case of pulmonary emboli was associated with IE of the right atrium and superior vena cava.

The predominant echocardiographic signs of IE are vegetation, abscess, and new dehiscence of a prosthetic valve.[47] Duke's criteria for possible endocarditis is based on one major criterion (*Staphylococcus aureus* bacteremia) and one minor criterion (intravenous drug use).[48] One of the patients from this setting was diagnosed of IE despite lack of intracardiac vegetation. Such a finding demonstrated that a negative trans-esophageal echocardiogram should not debar from a diagnosis of IE.[13]

Recommendations of antimicrobial therapy for IE with particular microorganisms have been advocated.[49] Some 50% of the IE patients necessitate a cardiac operation with the most common indications of congestive heart failure (60%), refractory sepsis (40%), embolic complications (18%), and vegetation size (48%), or with a combination of the above factors.[50] Timing for surgical treatment of IE is usually delayed until the infection is eradicated.[8] Despite a slightly higher risk of embolism, short-term antibiotic therapy prior to surgery is still preferred.[29] This study revealed an average 18-day antibiotic therapy prior to cardiac surgery. However, patients with progressively deteriorating conditions, such as acute heart failure caused by severe valvular lesions and enlarging vegetations, usually require an emergency cardiac operation.[51] Nevertheless, cardiac operations before 24 gestation weeks should be deferred until after 28 gestation week due to the possible risks of fetal death related to the immaturity.[52] For one-stage consecutive cesarean section and cardiac surgery, the uterus and abdominal wall may be left open until full heparinization and establishment of cardiopulmonary bypass,[20] in order to avoid the adverse effect of cardiopulmonary bypass, hypothermia, and rewarming.[52] The risk is particularly high when cardiac surgery is carried out during an early gestation period. This is at least partly supported by findings of the present study. The morbidity and mortality rates are higher for the fetus than for the mother.

Intravenous tocolytic (ritodrine and Prepar®) and antiepileptic (phenytoin and Epdantoin®) drugs were recommended and administered during cardiac operation to prevent a preterm labor.[30] Moreover, intraoperative continuous cardiotocography is important for fetal heart rhythm monitoring. Transient or sporadic fetal bradycardias and absence of fetal heart-rate variability may be seen during the operation, and spontaneous recovery of fetal heart rate may occur.[26] Uterine activity is an alternative sign of fetal viability, and scanty uterine activity during cardiac operation should attract special attentions.[35] Postoperative fetal bradycardia indicates inadequate placental perfusion that may result in fetal distress and thus urge a termination of pregnancy.[35]

CONCLUSION

IE in pregnancy is a rare but grave condition. It is often associated with embolic events and mycotic aneurysms. In spite of a higher risk of embolism, short-term antibiotic treatment prior to surgery is still preferred. Two-thirds of the IE in pregnant patients require timely or urgent cardiac surgery in order to alleviate patients' deterioration. Cardiac operations before 24 gestation week should be deferred until after 28 gestation week due to the potential risks of fetal death in relation to immaturity.

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