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Coronary Artery Disease and Pregnancy

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Coronary Artery Disease and Pregnancy

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Abstract- The current classification and protocols that are followed in the Heart Disease and Pregnancy National Center (SNCE abbreviation for Servicio Nacional de Cardiopatía y Embarazo, in Spanish); regarding coronary artery disease associated to pregnancy are presented. Concise guiding principles concerning the diagnosis, evaluation, and management of coronary artery disease during pregnancy, labor, and postpartum period are offered.

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I. INTRODUCTION.

Although coronary artery disease (CAD) is not frequent in pregnancy, its incidence is rising (approximately 6.2 cases per 100 000 pregnancies in USA), as a consequence of planning reproduction at ages higher than 35, the presence of coronary risk factor such as hypertension, preeclampsia, diabetes, smoking, and the use of assisted reproduction techniques.¹⁻³ The SNCE set the CAD related to pregnancy in three different clinical context: 1) known CAD in a patient planning getting pregnant, 2) known, stable or unstable CAD, in the already pregnant woman or parturient, and 3) CAD debuting during pregnancy, labor or puerperium – usually as acute coronary syndrome-.

II. DIAGNOSIS AND ASSESSMENT OF CAD ASSOCIATED TO PREGNANCY

Diagnosis of CAD is principally based on the history, confirmed by some laboratory investigations. The clinical presentation is similar to non-pregnant patients, with some features that should be kept in mind.^{4,5} As pregnancy advances a reduction in functional capacity is normal. Most patients in the third trimester are in New York Heart Associations (NYHA) functional class II.^{1,5} Pregnancy itself predisposes to myocardial ischemia, due to increased cardiac output, heart rate, and heart dimensions; in the other hand, myocardial oxygen supply could be compromised by a reduction in hematocrit, diastolic blood pressure, and subsequence coronary driving pressure. Pregnancy, as well as puerperium, increases the likelihood of thrombosis, as a consequence of higher serum levels of

fibrinogen, coagulations factors, and enhanced platelet aggregation. The fibrinolytic activity is also reduced. Pregnancy increases the risk of myocardial infarction in four or five thresholds, compared with non-pregnant women.^{1,2,6}

Some patients might confuse symptoms corresponding to CAD with discomfort caused by pregnancy. An episode of thoracic pain, with typical location and radiation, require excluding CAD. When chest pain is atypical or occurs in particular settings – e.g. immediately after a cesarean delivery-, a high grade of suspicion is necessary for making diagnosis.

The *Electrocardiogram* (EKG) in pregnant women shows several variations considered to be normal ones, such as, left QRS axis deviation, atrial and ventricular ectopic beats, sinus tachycardia, T wave inversion, ST segment depression without a rise in serum markers of cardiac damage. New Q waves in DIII, and less frequent in aVF have been described.^{1,2,6,7} That is why, the combination of clinical data, serum markers of cardiac damage, and cardiac image (echocardiography) is recommended for a correct diagnosis. For identifying acute coronary syndrome the use of cardiac Troponins is mandatory, because serum levels of Creatine Kinase and its MB fraction are elevated because of the gravid uterus and placenta.^{1,2,5} The *Holter Monitoring* could be useful in some cases, without any risk. In selected patients, with a high suspicion of CAD, the *Exercise Testing* might be helpful, using stationary bicycle ergometer or treadmill submaximal protocols –first modality is preferred-, with a 70 - 80% of predicted maximum heart rate as goal. The use of echocardiography improves the sensitivity and specificity of the test, and it is secure.^{1,2}

The assessment of *Myocardial Perfusion with Radionuclide Imaging* is proscribed. *Dobutamine Stress Echocardiography* should also be avoided. *Coronary Computed Tomography Angiography*, where high doses of radiation are delivered to mother and fetus, is not recommended unless absolutely necessary.² When coronary anatomy evaluation is needed, the use of *Invasive Coronary Angiography* is preferred. The maternal radiation exposure should be kept in mind; though the procedure represents a 7 mGy maternal exposure dose, only 20 - 30% corresponds to fetal exposure (1,5 mGy), which is far enough of the estimated “secure” radiation exposure dose in pregnancy of 50 mGy (5 rad).^{2,5,6,8,9} Radiation exposure to the fetus can be minimized by lead shielding of the

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mother's abdomen and pelvis, and –if possible- abstain to irradiates pelvis and abdomen during catheter advance to thoracic aorta. Radial arterial access is preferred. Contrast ventriculography is not recommended since ventricular function can be appropriately assessed with other methods.^{2,8,9} The procedure should be performed in centers with extensive experience, and if it is undertaken after 26 weeks of pregnancy, obstetric and neonatology standby should be available in case of premature labor.

III. MANAGEMENT OF CAD DURING PREGNANCY, LABOR, AND PUERPERIUM

The available information about the management of heart disease during pregnancy is based on case reports, case series, or retrospective analysis of large series, and sometimes, expert opinions. Prospective randomized trials, and the experimentation with new drugs or procedures during pregnancy or lactation is forbidden for ethical reasons, so pharmaceutical companies usually caution about the use of their products in pregnant women. That is why; recommendations are nearly all wide-ranging, and based on accumulated experience. Many of these strategies are current practice in SNCE.

1. *Known CAD in a patient planning getting pregnant:* women of reproductive ages with known CAD should be included in the Preconception Risk Program of Primary Health Care Setting (PHCS). Pregnancy is feasible when the patient is free of symptoms. Referral from PHCS to a cardiovascular specialist is mandatory, and the information flow bidirectional. Exercise testing before pregnancy might identify whether the patient will tolerate the hemodynamic changes of pregnancy, labor, and puerperium.^{1,2} Those women with NYHA functional class II or more before pregnancy could not be capable to tolerate it, with worsening of symptoms as pregnancy progress.^{1,2,6,8} When the patient decides to get pregnant angiotensin-converting enzyme (ACE) inhibitor therapy, angiotensin receptor blocker (ARB), direct renin inhibitor Aliskiren, and statins should be withdraw. Aldosterone antagonists such as eplerenone and spironolactone should also be avoided.² Beta blockers are safe, and cardioselective agents are better. Atenolol (FDA D category) should be avoided unless necessary; metoprolol and propranolol (noncardioselective) are preferred.^{1,2} Oral nitrates are considered to be safe. Calcium channel blockers (CCB) are relatively safe too. The most employed in pregnancy has been nifedipine in the treatment of hypertension. If CAD is diagnosed the sustained-release preparations are the best choice. Verapamil and diltiazem are most used for their negative chronotropic effect (both FDA C category),

but diltiazem is seldom used in SNCE for some report of fetal malformation.^{1,2,4,6} Low dose of aspirin is safe. There is less information regarding clopidogrel, but recent reports indicate that the administration during pregnancy is secure.^{1,2,10,11} If the patient is receiving dual antiplatelet therapy for intracoronary stent, it is reasonable to delay pregnancy until one year after stenting, then clopidogrel could be withdraw and continue with aspirin alone. If previous myocardial infarction has occurred, getting pregnant should be wait until the patients is free of symptoms –NYHA class I-, there is not an ischemic systolic dysfunction of the left ventricle –left ventricle ejection fraction less than 0.50-, inducible ischemia, nor electrical or hemodynamic instability.^{1,2,5,6,8}

2. *Known, stable or unstable CAD, in the already pregnant woman o parturient:* patient care in this category should be multidisciplinary, including obstetricians, cardiologists, and anesthetists in first place, and also psychologists, genetics professionals, and others. In the first contact with the SNCE the patient undergoes to risk assessment for mother and fetus, and also counseling. The presence of symptoms, functional class, left ventricle dysfunction, arrhythmias, inducible ischemia, and other feature, are considered. The majority of recommendations commented before concerning cardiovascular drugs remains. Anemia in the pregnant ischemic woman should be promptly treated. If there are no symptoms, or they are mild, pregnancy should advance until spontaneously ends. If frequent symptoms or further complications are suspected as pregnancy progresses, patient should be given corticosteroids for fetal lung maturity. In these cases pregnancy conclusion might be counseled. Obstetric team will pay special attention to fetal well-being, observing any influence of cardiovascular drugs on fetal growth, heart rate, amniotic fluids, and uterine perfusion. Vaginal and spontaneous delivery is better in stable CAD patients.^{1,2,6,8} Pain, anxiety, and adrenergic stimulation during labor could be risky, so; it is recommended to maintain anti-ischemic therapy, epidural analgesia, and obstetrical procedures to shorten the total duration of labor, particularly the second stage, if needed. Obstetric team should keep a low threshold for cesarean surgery if labor prolongs or patient deteriorates.² Unstable patients (NYHA class III-IV) should undergo to urgent cesarean delivery.^{6,8} Cesarean surgery when using anti-platelet therapy increases the risk of bleeding. In some cases, our team has decided to interrupt the use of anti-platelet (aspirin and clopidogrel), and began administration of peripartum heparins protocols. Excessive bleeding

should be avoided, and treated promptly. The use of prolonged tocolysis with adrenergic agents could be dangerous. Postpartum ergot derivatives are proscribed. Use of selective 5-hydroxytryptamine agonists for migraine headache has been associated to coronary vasoconstriction. Neonatologist should be told about mother's antepartum beta blocker consumption, because several complications in newborn are likely (e.g. apnea, bradycardia, hypoglycemia, prolonged jaundice).^{1,2} The multidisciplinary team should operate resting on an appropriated infrastructure, and if any complications occurs, provide immediate high quality care, including treatment for acute coronary syndrome, with cardiac catheterization laboratory access, ICU, operating room for cesarean, newborn intensive care units; and facilitated communications and motion of all parts.

3. *CAD debuting during pregnancy, labor or puerperium (acute coronary syndrome)*: the largest part of available data regarding acute coronary syndrome (ACS) during pregnancy correspond to ACS with ST segment elevation (ACS-STE), with a related maternal mortality that ranges from 5.7 to 37%.¹ Usually mortality rate is about 10%, as well as fetal mortality. Most of fetal deaths are consequence of maternal loss.⁴ In almost half of ACS during pregnancy, the typical etiology of thrombotic occlusion due to atherosclerotic plaque rupture is not present.^{4,10,11} Thus, reperfusion strategies using thrombolytic agents would be ineffective in a lot of cases. Based on maternal age, presence of coronary risk factors, moment of occurrence (antepartum, peripartum, or postpartum) the possible etiology might be suspected, but only coronary angiography would provide certainty. In patients with coronary risk factors, few weeks of gestation, and 35 years old, or more, is very likely the presence of thrombus with unstable plaque, but also has been described thrombus without atherosclerotic plaque, coronary vasospasm, and even normal coronary arteries.^{4,10,11} In peripartum and postpartum, coronary artery dissection is most frequently seen, affecting in 80% of cases de left anterior descending coronary artery. In this period vasospasm, embolus, and thrombosis has also been reported.⁴

In case of ACS during pregnancy, labor, or puerperium, the standard procedures for management of ACS should be followed,^{1,2,4,6,8,11} admitting the mother in ICU, and her life been priority at that moment. Obstetricians should be consulted about the exact weeks of gestation and fetal viability. Diagnostic criteria for ACS-STE remain the same for non-pregnant women. Ideally all patients should undergo to urgent coronary angiography for diagnosis of specific etiology.

Whenever not possible, the reperfusion strategy is selected for the physician analyzing risks and benefits of thrombolytics. Pregnancy is a *relative* contraindication for thrombolytics use. It is the authors' opinion that, in case of hemodynamic and electrical stability, inferior myocardial infarction, and a setting where coronary dissection or spasm is likely –young women, no coronary risk factors, peripartum or postpartum–, does not initiate a fibrinolytic therapy. When anterior myocardial infarction is diagnosed with hemodynamic compromise, lethal arrhythmias, women 35 years of age, or more, presence of coronary risk factors, antepartum period, and other situations indicating the probability of plaque rupture and thrombosis; then, use of fibrinolytic therapy should be considered. Thrombolytic agents practically do not cross placental barrier,^{2,4} but are associated with placental micro hemorrhage and hematomas; this is the mechanism implicated if fetal damage. After cesarean delivery, and one week after vaginal delivery, fibrinolytic therapy is absolutely contraindicated.^{2,12,13}

Cardiovascular medications commented before are also useful in ACS. Same precautions remain. The use of unfractionated heparin and low-molecular-weight heparins is secure.^{2,4} In this circumstance, clopidogrel is indicated as usual, in combination with aspirin. For pain relief morphine remains the drug of choice, and it is safe during pregnancy. Its administration near delivery is associated with respiratory depression in neonates.^{2,4,6,8,10,12} Glycoprotein IIb/IIIa receptor antagonists have not been evaluated in pregnancy, in high-risk acute coronary syndromes undergoing scheduled percutaneous coronary intervention (PCI), the physician might consider use them after detailed discussion with the patient regarding the risks and benefits.^{1,2,4} It is important to favor the use of radial access, and bare-metal stents. Drug-eluting stents (DES) have not been investigated. The use of DES requires dual anti-platelet therapy for six months to a year, depending of kind used, so the risk of bleeding increases in case of progression of pregnancy, and further vaginal or cesarean delivery.^{2,4,6,8} In unstable angina/non-ST-segment elevation myocardial infarction, a conservative strategy is better, reserving the invasive approach for high-risk patients. All previous comments concerning medications remain the same.

It is very important a multidisciplinary approach to pregnant patient with cardiovascular disease. Centers with greater experience and expertise are better. After an ACS recovery, the evaluation of etiology and consequences of the event is significant. Referral to genetic specialist, rheumatologist, hematologist, and other, depending on each case, is useful for identifying vasculitis, antiphospholipid syndrome, thrombophilia, and other possible non atherosclerotic causes of ACS. Differential diagnosis of ACS in pregnancy include preeclampsia, pulmonary embolism, amniotic

embolism, aortic dissection, and hypovolemic shock.^{2,4,5,11}

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