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RESEARCH ARTICLE

MANAGEMENT OF ANTIPLATELET THERAPY DURING ACUTE CORONARY SYNDROME (ACS) IN PREGNANT WOMEN: CASE REPORT AND LITERATURE REVIEW

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Abstract

Introduction: The occurrence of ACS during pregnancy is a serious event but remains rare with a trend towards increase. Its incidence is 3-4 times more common in pregnant women/non-pregnant women of childbearing age. Spontaneous coronary dissection and atherosclerosis represent the most common causes of ACS in pregnant women.
Observation: We report the clinical case of a young parturient, who presented at 31weeks of amenorrheaan ACS without ST segment elevation (NSTEMI) on tight and layered lesions of the anterior interventricular artery (IVA). She underwent active stent angioplasty with dual antiplatelet therapy. Delivery in our patient was plannedat 38 weeks after assessment of fetal and maternal well-being. However, the patient underwent emergency surgery at 37 weeks+2 days (obstetrical emergency) with favorable maternal and fetal outcomes.
Discussion and Conclusion: The management of ACS in pregnant women is difficult; it relies on collaboration between anesthesiologists, cardiologists and obstetricians in specialized health centers. Discontinuation of P2Y12 inhibitors around childbirth exposes the parturient to a very significant risk of stent thrombosis. The data concerning the relay by the Glycoprotein IIa/IIIb inhibitors are poor. The aim of our study is to take stock of the management strategy of antiplatelet therapy during the peripartum as well as the antagonization strategy to consider in the event of emergency delivery in a patient on dual antiplatelet therapy.

Introduction:-

The occurrence of acute coronary syndrome (ACS) during pregnancy or the immediate postpartum period is a serious complication, responsible for estimated maternal mortality at 20% with serious risks to the fetus.[1] This is a rare complication with an estimated incidence of 3-7 per 100,000 pregnancies. [2] The causes of ACS in pregnant women are multiple; dominated by spontaneous coronary dissection (SCD) followed by thromboembolic disease.[3] Current standard treatment for ACS includes coronary angioplasty combined with medical therapy including antiplatelet therapy. [2,3] The latter requires interruption for delivery to reduce the risk of hemorrhagic complications. However, it exposes the parturient to a thrombotic risk, which is all the more significant when the time is short between the occurrence of ACS and the interruption of antiplatelet therapy.[4]Through the following

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case, we wish to assess the strategy management of the antiplatelet therapy in pregnant women in cases of ACS as well as on the antiplatelet neutralization strategy to consider during an emergency delivery, taking into account the sometimes unpredictable nature of the delivery and the existence of obstetric indications for emergency cesarean section as is the case for our patient.

Observation:-

Description of the patient:

Y.H, patient aged 37, fourth pregnancy, third parity with two cesarean births due to narrowed pelvis, a history of early miscarriage. Her current pregnancy estimated at 33 WA (weeks of amenorrhea). Admitted to obstetric anesthesia consultation for monitoring and planning of her delivery.

History of the disease:

The patient presented with high-risk non-ST segment elevation ACS (NSTEMI) at 31 weeks, discovered during acute anginal chest pain. She underwent angiography via a radial approach revealing stepped and tight lesions of the anterior interventricular artery (IVA), involving the low proximal, high intermediate and high distal portions with TIMI flowIII. She benefited from angioplasty using double active stents (3^{th} generation) at the level of the IVA with good angiographic control. (Figures 1,2) The patient is under anti-ischemic treatment comprising dual antiplatelet therapy (Clopidogrel 75 mg once a day + Aspirin 75 mg once a day) + beta-blocker (nebivolol 5 mg once a day) without statin or angiotensin converting enzyme inhibitors (ACEI).

History:

Furthermore, the patient presents as cardiovascular risk factors: type 2 diabetes for 10 years poorly controlled on metformin replaced by slow insulin during pregnancy, essential arterial hypertension for 9 years on perindopril replaced by alpha methyl dopa during pregnancy, hereditary coronary heart disease in a mother who died at the age of 41 in a context of acute chest pain.

Clinical data:

The maternal cardiovascular assessment found blood pressure at 120/50 mmHg, a heart rate at 100 bpm with a regular sinus rhythm, cardiopulmonary auscultation without abnormalities and a functional capacity lower than 4MET (metabolic equivalent) when climbing 2 floors.

Paraclinical data:

Troponin is at 4.3ng/L. We note the persistence of electrical abnormalities before angioplasty with ST segment undershift associated with negative T waves in the antero-septo-apical territory (Figures 3,4). Echocardiography reveals left ventricular dysfunction in 41%. As for the fetal FHR (fetal heart rate) and obstetric ultrasound assessment, it did not reveal any abnormalities. (Figures 5 and 6)

Support strategy:

Given the good maternal-fetal tolerance, fetal extraction is planned at 38 weeks (i.e. 7 weeks after SCA and angioplasty with double active stents), by cesarean section for a double-scarred uterus. The patient is hospitalized at 37 weeks for preparation and preoperative management of dual antiplatelet therapy. The drug management strategy for our patient included maintaining aspirin, labetalol, alpha methyldopa until the day of the operation, and stopping Clopidogrel for five days.

Unforeseen events and support:

However, after 2 days of stopping clopidogrel (i.e. 3 days before the planned cesarean section), the patient experienced close uterine contractions with significant cervical changes, indicating an emergency cesarean section for work on a double-scarred uterus given the risk of uterine rupture. The preoperative assessment is without abnormalities with a hemoglobin level of 11.2g/dl, and a platelet level of 259 x 10^3 elements/mm^3. The patient is admitted to the operating room shortly after the onset of labor and once platelet transfusion was prepared. She is installed on the operating table, taken two large caliber 16G venous lines, with multimodal monitoring including a 5-wire electro-cardioscope (DII and V5), pulsed oxygen saturation, invasive blood pressure via a left radial arterial line, as well as a urinary probe. After a 5-min pre-oxygenation, a rapid sequence induction with opioids is carried out, with injection of 250gamma of fentanyl, 80mg rocuronium, 28mg of etomidate. Anesthesia is maintained by isoflurane (MAC at 0.6) and reinjection of opioids after extraction. The patient received a transfusion of 10 platelet units (0.7 x 10^{11} for 10kg of weight) after incision to promote good hemostasis given insufficient cessation of

clopidogrel and assessment of intraoperative bleeding by a senior obstetrician. Intraoperative blood loss is estimated at 1L200, with the decision to transfuse packed red blood cells to optimize arterial oxygen transport. The extraction is carried out 3 min after incision of a newborn male with an Apgar score 9/10/10 at 1, 5 and 10 min respectively, with a birth weight of 3320g, transferred to the neonatal intensive care unit for monitoring. During the same operation, the patient underwent tubal ligation based on informed consent obtained preoperatively, then transferred to obstetric intensive care for monitoring and recovery. The patient was extubated 2 hours later after obtaining the respiratory and neurological prerequisites, with warming, relief with sugammadex and analgesia with paracetamol and morphine according to the VAS (visual analogue scale) for pain.

Evolution and post-operative outcomes:
Postoperative analgesia is maintained by parenteral paracetamol and morphine. Aspirin is continued postoperatively without interruption. Clopidogrel is resumed after 48 hours; in the absence of bleeding and in consultation with the obstetrician and cardiologist. For the prevention of thromboembolic disease, enoxaparin 0.4 is started after 24 hours. However, the patient benefited from intermittent pneumatic compression on day 0 with early ambulation the next day. Short-term postoperative outcomes are simple: normal delivery, no postoperative bleeding, no occurrence of chest pain, or electrocardiographic changes. (Figure 7). There is a slight enzymatic movement of troponin (10.9ng/L, 6.11ng/L, 4.5ng/L) at (H6, H24, H48 respectively) compared to 4.3ng/L preoperatively. Ventricular ejection fraction (LVEF) remained stable at 41%. The patient was discharged home on day five on aspirin 75mg 1 tab/day, clopidogrel 75mg 1 tab/day, nebivolol 5mg 1 tab/day, perindopril 5mg 1 tab/day, statin 20mg/day and referred for cardiological and obstetric consultation. As for the newborn, he did not present hypoglycemia, bradycardia or need antagonization of opioids. He was discharged home on D3 and put on exclusive artificial breastfeeding. The evolution after one and six month is favorable for both the fetal and maternal with an increase in LVEF to 51%.

Discussion:-

The occurrence of ACS during pregnancy is linked to all the hemodynamic changes induced by the gravid state in response to the increased metabolic needs of the mother and fetus. [4] The periods most at risk for the occurrence of ACS are the end of pregnancy (maximum increase in cardiac output of 30-50%), as well as childbirth and the postpartum period due to uterine contractions, pushing efforts, blood loss and autotransfusion which takes place after delivery.[4] Furthermore, pregnancy is responsible for a series of hemostatic changes which are responsible for a state of hypercoagulability exposing the parturient to an increased risk of thromboembolic events.[4] Risk factors for ACS are similar between pregnant/non-pregnant women. The main risk factors cited in the literature are advanced age, smoking, high cholesterol, hypertension, diabetes and family history of coronary artery disease. [4,5] In pregnant women, there are particular risk factors which are the existence of thrombophilia, thrombocytosis or the presence of anemia.[5] Other factors have been identified such as obstetric factors. The most important are undoubtedly multiparity, a history of preeclampsia, postpartum hemorrhage, as well as postpartum infections. [5]

None of the clinical, biological, electrical or echocardiographic elements can determine the etiology of ACS. The first action for pregnant women with intermediate- or high-risk ACS with ST-segment elevation (STEMI) or non-ST-segment elevation (NSTEMI) is to send them immediately to a qualified intervention center for diagnostic coronary angiography. [4] The latter makes it possible to evaluate the coronary anatomy and determine the etiology of ACS with a therapeutic impact (possibility of percutaneous coronary angioplasty).[6] However, ionizing radiation could have harmful and irreversible effects on the fetus. The average radiation exposure to the unshielded abdomen during diagnostic coronary angiography is 1.5 mGy, increasing to 3 mGy during percutaneous coronary intervention (of which 20% reaches the fetus due to tissue attenuation). [5] However, there is no evidence of an increased fetal risk of congenital malformations, intellectual disability, intrauterine growth restriction (IUGR) or pregnancy loss at the time of exposure of the pregnant woman to radiation doses of 50 mGy, particularly beyond 14 weeks of gestation (after completion of organogenesis). [6] Abdominal protection and the radial approach reduce the risk of radiation to the fetus.[4] Furthermore, thrombolytic therapy should be reserved only for life-threatening ACS, when there is no access to angiography due to the increased risk of bleeding in spontaneous coronary artery dissection (SCD), which represents the leading cause of ACS in pregnant women and an absolute contraindication to thrombolytic therapy.[7]

Stent angioplasty is indicated in cases of ACS of atheromatous origin and in certain cases of DCS. [4] There is currently no consensus regarding the choice of stent type. The main determinant of the choice of stent type during pregnancy is the time between stent placement and delivery. Active stents can be used when delivery occurs within at least 3 to 6 months and bare metal stents are more preferable closer to the delivery date as they provide the option

of discontinuing dual antiplatelet therapy after 4 weeks. [2,6] Aspirin and clopidogrel are the antiplatelet agents (AAP) of choice in cases of stent placement with the need to place the parturient on a DAPT. [7] There are no reports of adverse effects during pregnancy associated with the use of aspirin at doses of 80-150 mg per day. [7] The evidence for P2Y12 inhibitors is less strong. The use of clopidogrel is controversial because there have been no human studies. The general consensus is to use clopidogrel only when strictly indicated and for the shortest possible duration.[4] Both prasugrel and ticagrelor are more potent than clopidogrel, but are associated with a higher bleeding risk and are therefore not preferred. [6,7] The use of short-acting glycoprotein IIa/IIIb inhibitors has not been extensively studied during pregnancy, but they have been suggested as a bridge solution in case it is necessary to interrupt DAPT during delivery in a patient at high risk of stent thrombosis. [8]

Performing a cesarean section or administering neuraxial anesthesia requires interruption of clopidogrel before the procedure for 5 to 7 days. [8] The use of heparin in this situation did not prevent stent thrombosis. It is recommended to stop clopidogrel 5 days in case of general anesthesia and 7 days before neuraxial anesthesia and to switch to intravenous tirofiban or eptifibatide in cases where the risk of stent thrombosis is high. [8] Glycoprotein IIa/IIIb inhibitors should be continued until 4 to 6 hours before delivery and they can be resumed 4 to 6 hours after delivery (depending on the bleeding risk) with resumption of clopidogrel in the 24-48 hours following. [8] However, no major trial has demonstrated the effectiveness of glycoprotein IIB/IIIA inhibitors in preventing stent thrombosis and has been shown to increase the risk of bleeding. [8] Finally, cangrelor is also proposed as a bridging agent. [8] However it is associated with intrauterine growth retardation, fetal loss and incomplete ossification in animal studies and therefore cannot be preferred. [8]

If an emergency cesarean section is indicated in a patient under DAPT, neuro-axial anesthesia is contraindicated because it exposes the patient to a risk of hemorrhagic complications. [4] Platelet transfusion is often recommended to counteract the effects of antiplatelet therapy. [4] The rationale for transfusion in this context is to provide "uninhibited" platelets likely to sufficiently restore primary hemostasis despite the presence of platelets inhibited by the antiplatelet therapy and thus correct the excess hemorrhagic risk linked to these drugs. In situations requiring neutralization of aspirin, it is suggested to transfuse platelets at a dose of 0.5 to 0.7 x 10^{11} per 10kg of weight.[9] On the other hand, the neutralization of clopidogrel or prasugrel requires a higher dose of platelets than for the neutralization of aspirin which could be at least double and much higher for prasugrel than for clopidogrel. [9] The effectiveness of platelet transfusion may be reduced if the last dose of clopidogrel or prasugrel is less than 6 hours, due to the persistence of active metabolites.[9]

In our patient, in view of the planned cesarean section, aspirin was maintained given the significant thrombotic risk she presents in the face of a moderate hemorrhagic risk. An interruption of clopidogrel for 5 days was considered in order not to increase the excess risk of hemorrhage linked to the cesarean section. Relay with glycoprotein IIa/IIIb inhibitors has been much debated with a balance towards abstinence given the absence of in-depth studies concerning their use during pregnancy and taking into account the existence of certain obstetric emergencies which cannot be postponed for 4 to 6 hours (recommended interruption period before intervention). As is the case for our patient, who presented work on a double-scarred uterus, indicating an emergency cesarean section given the risk of uterine rupture. General anesthesia was performed on our patient due to both insufficient cessation of clopidogrel (48 hours) and also due to left ventricular dysfunction (LVEF 41%).

The transfusion in our patient with a platelet count of 0.7x 10^{11} per 10 kg allowed satisfactory intraoperative hemostasis with the absence of postoperative hemorrhagic or thrombotic complications. This leaves us with the suggestion that if the time taken to last take clopidogrel is 48 hours, its neutralization in the event of bleeding attributable to a medical cause could require a platelet rate comparable to aspirin, i.e. 0.5 to 0.7 x 10^{11} for 10kg of weight. This can be explained by the decrease in active metabolites in the circulation. However, this hypothesis was not verified by functional tests but by clinical observation. Clopidogrel was restarted as recommended at 48 hours. ACE inhibitors and statins were introduced after delivery with good recovery of ventricular function at 1 month and the absence of recurrence of ACS. Furthermore, the patient benefited from definitive contraception by tubal ligation to prevent the occurrence of pregnancy due to ischemic cardiomyopathy.

Conclusion:-

The prevalence of ACS in pregnant women seems worrying in the coming years. The main mechanism is coronary dissection especially in the postpartum period. The management of ACS is hardly different from other populations except for thrombolysis which must be exceptional here. The prescription of AAP complicates the management of

the peripartum, the placement of a bare stent is therefore preferred to an active stent. Discontinuation of P2Y12 inhibitors should be considered before delivery to reduce the risk of bleeding. Lack of evidence regarding relay by glycoprotein IIa/IIIb inhibitors in pregnant women. The prescription for platelet transfusion for the neutralization of antiplatelet therapy in the event of emergency delivery must be adapted to the time of the last dose.

Figures:

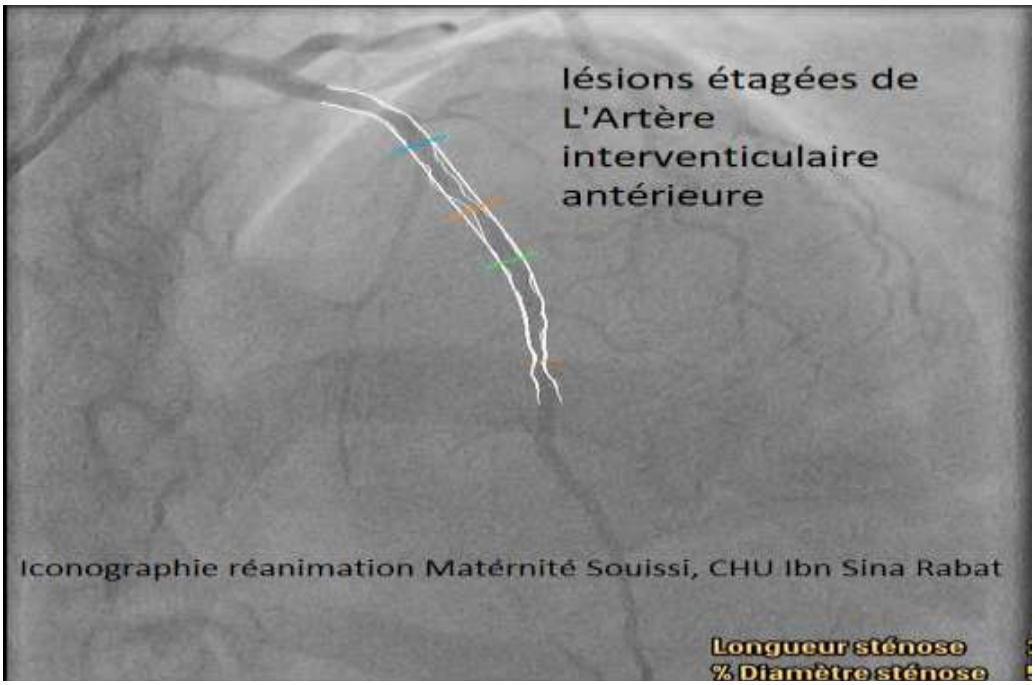

Figure 1:-Angiography of the anterior descending artery: three tight tiered lesions of the low proximal, high intermediate and high distal portion with TIMI flowIII.

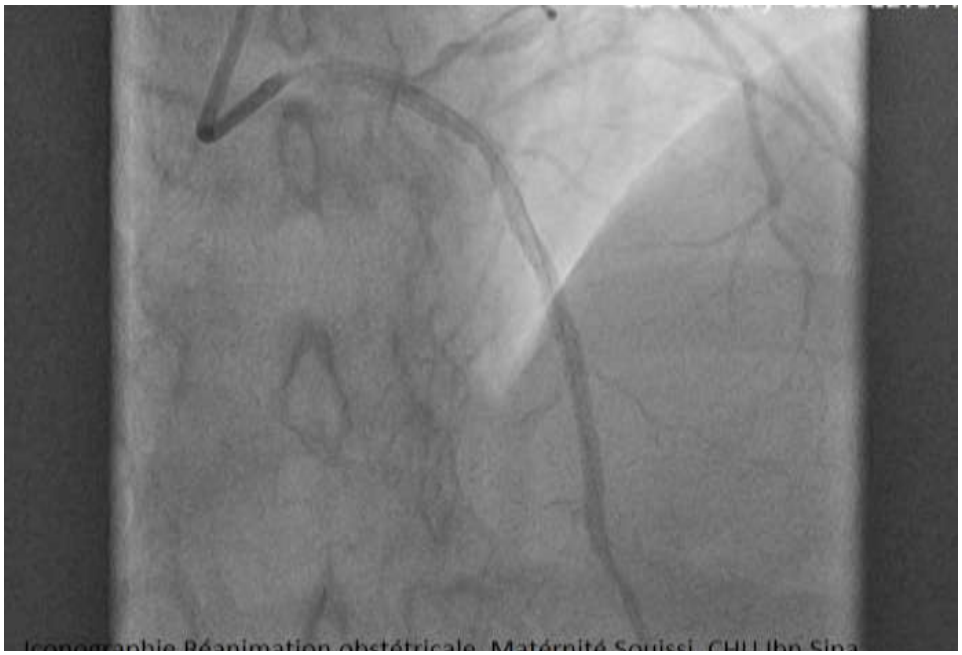

Figure 2:-Angiographic control of the anterior descending artery after angioplasty with double contiguous stents (first straddling the lower proximal and upper intermediate portions and second at the upper distal portion), with TIMI flowII.

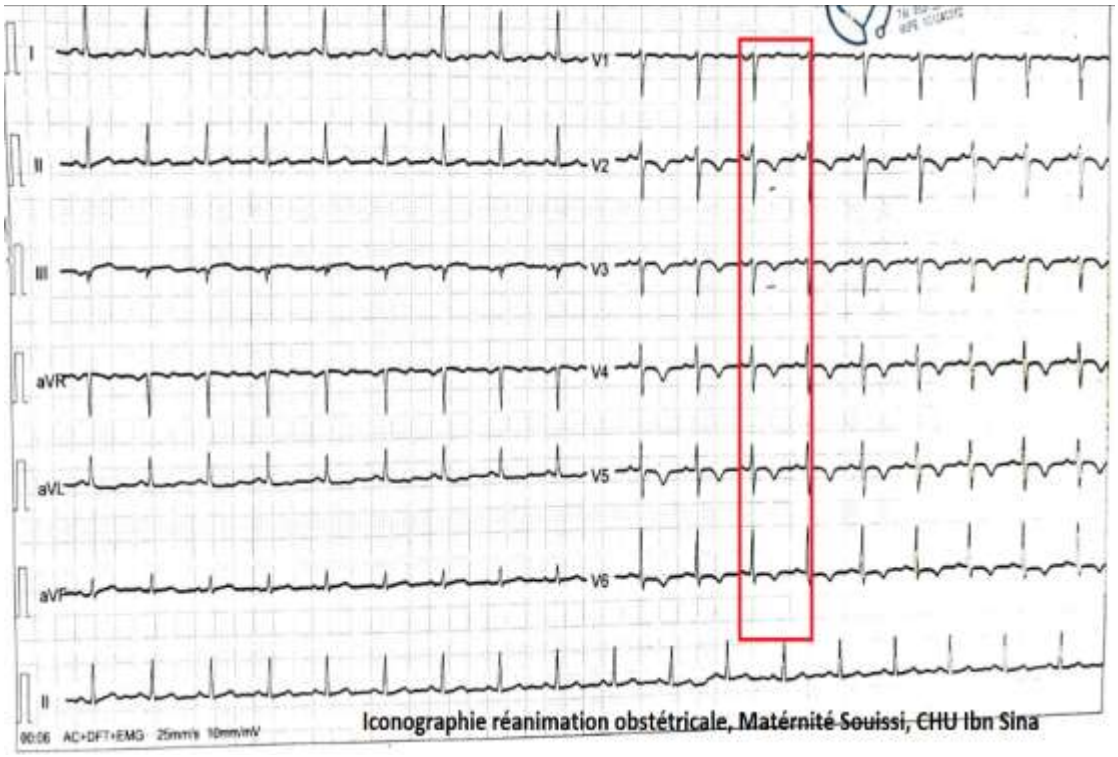

Figure 3:- Electrocardiogram before angioplasty of the anterior descending artery, showing negative T waves at the antero-septo-apical territory (V1-V5) with slight ST segment shift.

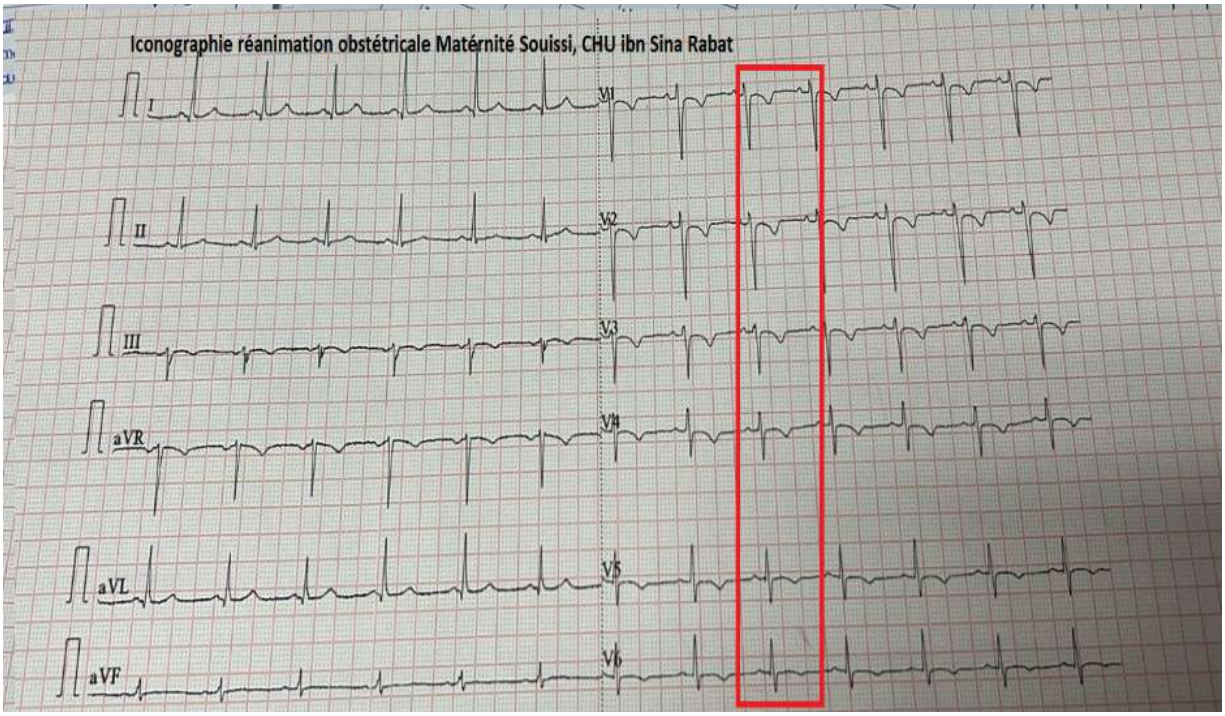

Figure 4:- Electrocardiogram 2 weeks after angioplasty of the anterior descending artery showing negative T waves in the antero-septo-apical territory (V1-V6) with slight ST segment shift.

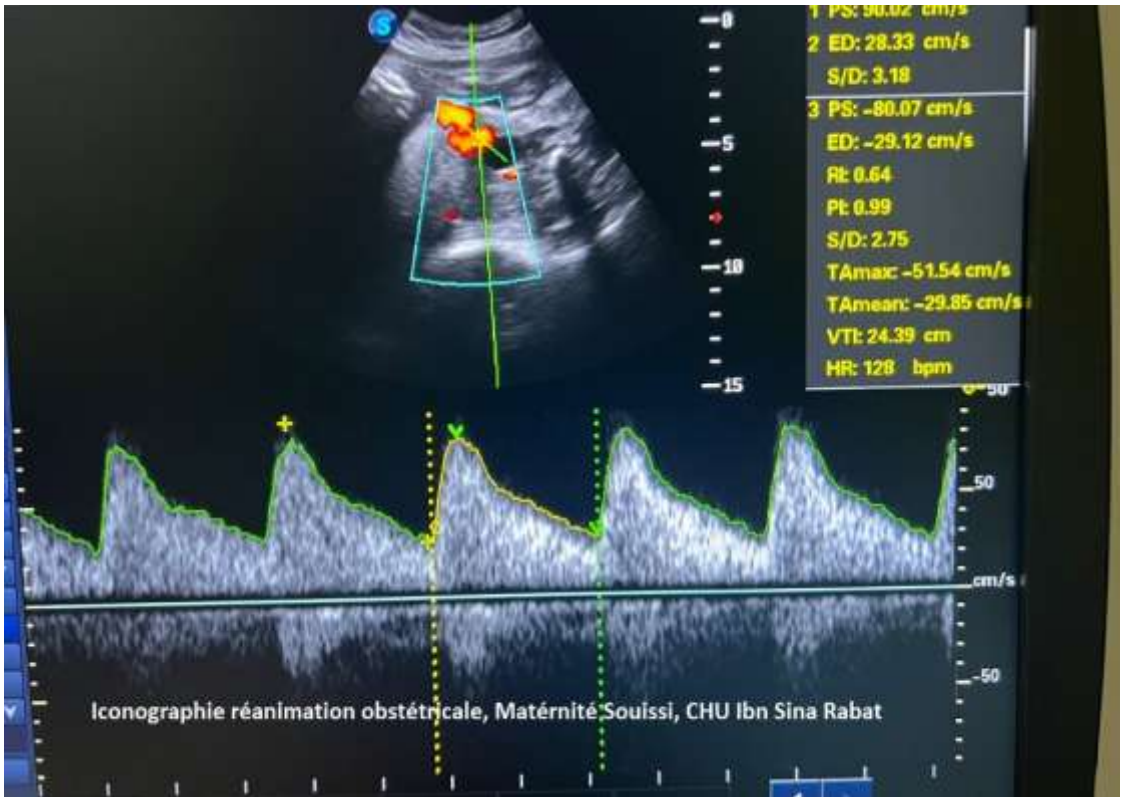

Figure 5:- Fetal Doppler ultrasound at 33 weeks of amenorrhea, revealing no abnormality.

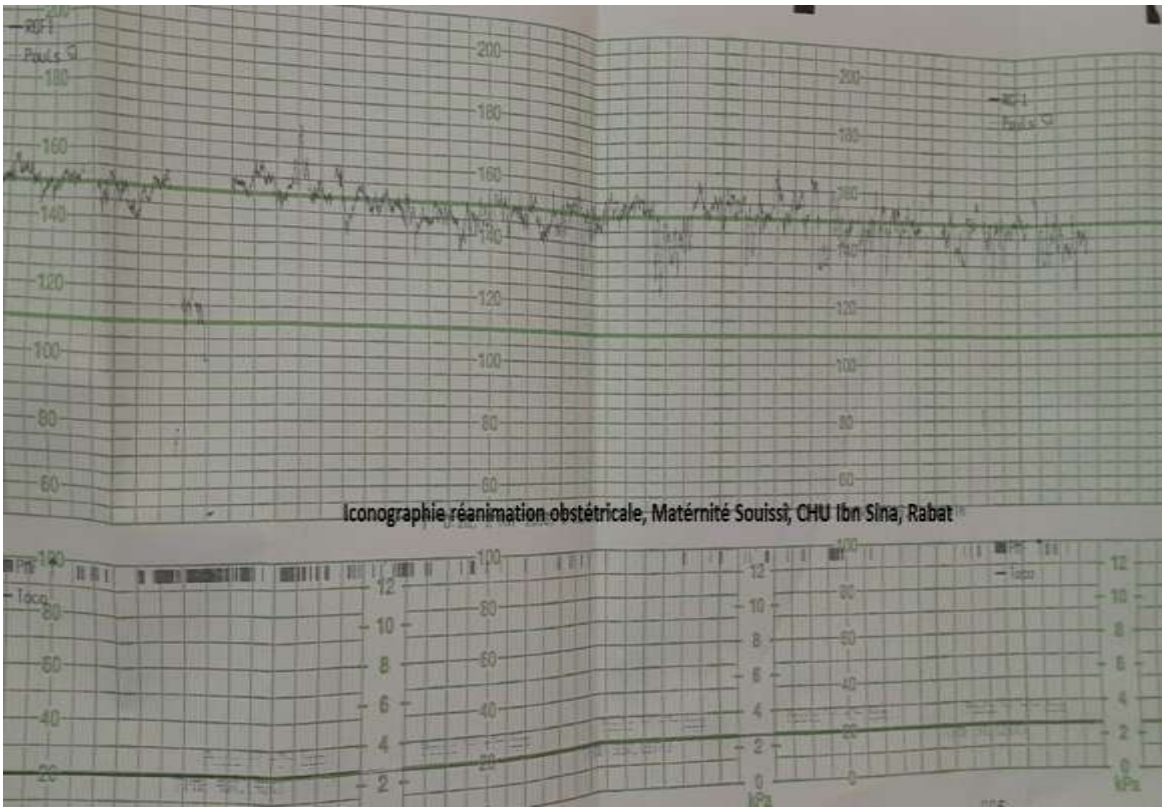

Figure 6:- Fetal heart rate tracings at 33 weeks gestation, revealing no abnormality.

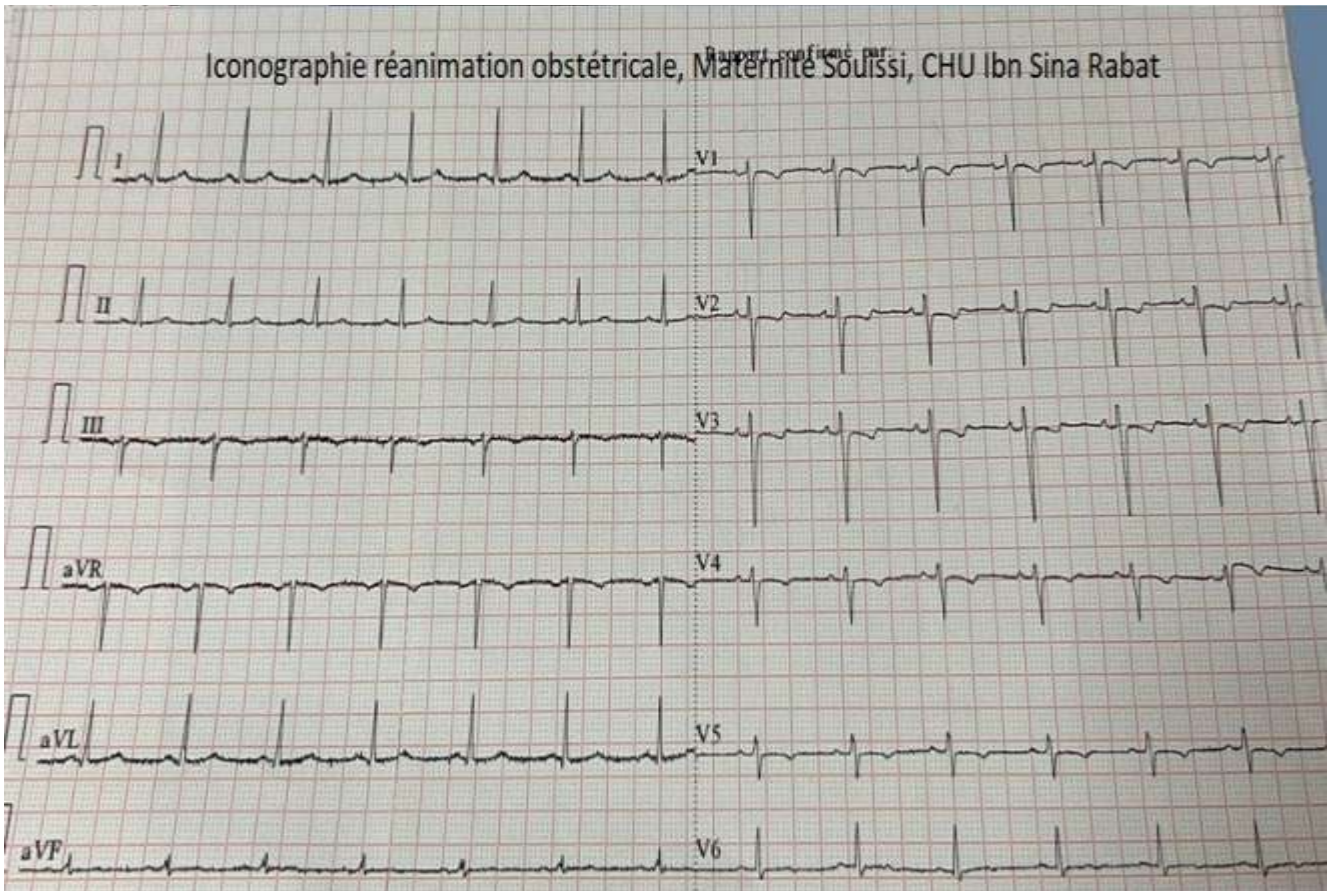

Figure 7:- Electrocardiogram H6 postoperative stationary appearance, showing negative T waves (V1-V6) with slight shift, without Q waves of necrosis.

Conflicts of interest
The authors declare no conflict of interest.

Contribution of the authors
All authors participated in the patient's care.

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