Assisted reproductive technologies and metabolic syndrome complications: medico-legal reappraisal

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Abstract

In the last 40 years, the number of elderly patients that require Assisted Reproductive Technologies (ART) has risen enormously, especially after heterolougous fertilization techniques have become available. In recent years, the incidence of peripartum cardiomyopathy (PPCM) has substantially grown, as a consequence of the combined effect of increased maternal age, consequent high prevalence of hypertension and metabolic syndrome (MS). That cohort of women may be exposed to a greater number of cardiac, obstetric and anesthesiological complications, therefore the incidence of medico-legal issues, litigation, liabilities and claims over the past years has significantly risen. Cardiovascular and hormonal changes during pregnancy can challenge even the healthiest of individuals, and in that pregnant population the risk is even greater. These patients should be monitored before the ART, during pregnancy, delivery and puerperium, to avoid heart failure, thrombotic problems, embolic complications, stroke and death. Management issues regarding pregnancy and delivery are elaborate, including anesthesia considerations. This new population of women needs an accurate cardiac risk stratification with a thorough cardiovascular history and examination, 12 lead ECG, and transthoracic echocardiogram. Therefore, a comprehensive multidisciplinary assessment and management can provide the best opportunity to improve maternal and neonatal outcomes.

Key words: metabolic syndrome, obstetrics, peripartum cardiomyopathy, assisted reproductive technologies

Introduction

With the implementation of infertility treatment, women with multiple medical problems such as obesity and glyco-metabolic disorders and women near or beyond menopause are now able to conceive. Clinicians should be prepared for the challenges and potential cardiovascular complications related to patients who are epidemiologically different from those seen in the past (1).

In the elderly ART patients with MS an important problem is the PPCM (2). Symptoms and signs of PPCM may be hidden behind normal physiological findings of pregnancy and the diagnosis of PPCM can be often delayed (3-5). Multiple etiologies have been identified as potentially leading to PPCM such as hypertensive disorders, advanced maternal age, multiparty pregnancies, as well as metabolic disorders and obesity. Although PPCM incidence varies greatly worldwide, most likely reflecting differences in population ethnicity, awareness of the disease, and different in classification, there has been an increase in cases in recent years.

MS rates have soared in developed countries, especially the prevalence of obesity, diabetes and cardiovascular disorders appears to be on the rise. When MS and obesity are present in the ART patients, it represents an important morbidity and mortality risk, therefore such patients should be more accurately supervised on a multidisciplinary level. Pregnancy counseling is appropriate to ensure the compliance during future pregnancy, and it should include discussion of maternal and fetal risks associated with various pharmacologic strategies.

Once a patient has expressed the desire to pursue pregnancy, an evaluation should be performed (6). With careful surveillance by a multidisciplinary medical team, most of patients may safely undertake a pregnancy and postpartum period with a relatively low risk of mortality.

In addition, it is fundamental that every medical decision must always be in accordance with the code of medical ethics (7, 8).

In patients of advanced maternal age, a cardiologic echocardiographic evaluation should be performed during the last month of pregnancy and in the first 5 months postpartum in all patient.

Anesthesia-related considerations during labor and delivery deserve close attention, because obstetrical anesthesiologists are involved in the peripartum care of this growing patient population. It is important to plan an anesthesia for this particular segment of patients in order to reduce hemodynamic alterations induced by different anesthetic techniques, and cardiac and obstetric complications that may jeopardize mothers and babies alike.

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Discussion

As a consequence of the combined effects of social changes and medical progress, a large number of women are delaying pregnancy until later in life, when they may be exposed to a greater number of complications. Some complications may occur more frequently in older prospective mothers as a result of previously developed diseases. Hypertension is the most common modifiable risk factor for cardiovascular disease in gravidae, the prevalence and severity of hypertension proportionally rise with age, and blood pressure control becomes increasingly difficult as age progresses in both genders, particularly in women (1).

With the implementation of assisted reproductive technologies (ART) and infertility treatment, women of advanced maternal age can successfully undertake a pregnancy. Women with multiple medical problems such as obesity and glycometabolic disorders and women near or beyond menopause are now able to conceive as well. The exogenous sex hormones, GnRH-a and gonadotropin may affect the secretion of sex hormones through hypothalamic-pituitary-gonadal axis and other mechanism, so the hormone-related complications like diabetes and pre-eclampsia may occur. Once a patient expressed the desire to pursue a pregnancy, a thorough evaluation should be preformed, typically including a detailed history, physical examination electrocardiogram, oxygen saturation assessment, imagining study, Holter monitor and cardiopulmonary exercise test to objectively assess functional capacity. With careful surveillance by a multidisciplinary medical team, most may safely journey through pregnancy and postpartum period with an overall low risk of complications and mortality. There has been an increase in cases of peripartum cardiomyopathy (PPCM) in recent years. As a consequence of the combined effect of increased maternal age and consequent high prevalence of hypertension and Metabolic Syndrome (MS), large numbers of women may be exposed to a greater number of complications. In the elderly ART patients with MS, diabetes and obesity pose an important problem: the symptoms and signs of PPCM may in fact be hidden and go undetected beyond normal physiological findings of pregnancy, and as a result, the diagnosis of PPCM can be often delayed. Another important aspect is that, despite improvement of patient management and therapy, PPCM is often recognized too late and it continues to be associated with high morbidity and mortality rates (2). Despite significant improvements in patient management and treatment, there is still a subgroup of women who die from PPCM or who will not recover their cardiac function. The diagnostic algorithm suggested by the Heart Failure Association (HFA) Working Group on PPCM (3) requires clinical signs of heart failure and an echocardiographic left ventricular ejection fraction (LVEF) of ≤45%. ECG, magnetic resolution imaging (MRI), and laboratory measurement of NT-proBNP are not essential but are recommended for a better prediction of patient out-comes (9).

PPCM is a diagnosis by exclusion, the definitive diagnosis of PPCM depends on echocardiographic identification of new-onset heart failure during a limited period around parturition. The management of transthoracic echocardiogram. Despite several unanswered questions, an echocardiographic evaluation should be performed during the last month of pregnancy and in the first 5 months postpartum in all patient with at least two risk factors, including advanced maternal age (>35 years), history of hypertensive disorders or metabolic disorders, obesity (BMI >30), especially if associated with polycystic ovarian syndrome and with a history of fertility issues, and multiple pregnancies due to previous ART. A relatively high proportion of such women could be exposed to the risk of developing cardiovascular complications. Close attention should be paid to fetal safety and to the excretion of drug during breastfeeding following delivery. Various guidelines provided disparate recommendations about starting anti-hypertensive therapy (10). We think that pregnant women with systolic blood pressure ≥2140/90 mmHg (or with a history of hypertensive disorders) and presenting other risk factors including advanced maternal age (>35 years), metabolic disorders, obesity (BMI >30) and multiple pregnancies should start the pharmacological treatment. We consider methyldopa the first choice and we have used it up to the maximum dosage of 2000mg/day without any maternal and fetal consequences. Polypharmacy may be required for optimal management (11) and labetalol, in our experience, can be safely used in association with methyldopa until 800mg/day. Safe alternatives during pregnancy include hydralazine and nitrates (12). Medications should be continued until evidence indicates a recovered or improved left ventricular function. Similarly, as gestational diabetes mellitus (GDM) is characterized by increased cardiovascular maternal risk and risk of macrosomia and birth complications (13), we suggest test for GDM with fasting plasma glucose and the 2-h plasma glucose value during a 75-g oral glucose tolerance test (OGTT), at 24–28 weeks of gestation in pregnant women not previously known to have diabetes with at least two of risk factors including advanced maternal age (>35 years), overweight (BMI between 25 and 30) and hypertensive disorders (14). Anesthetic objectives are manifold, and some of them have to do with avoiding decreases and increases in systemic vascular resistance (SVR), maintaining adequate blood volume and venous return, preventing myocardial depressants, avoiding excessive fluid administration, maintaining stable heart rate, considering afterload reduction. Close hemodynamic monitoring and maintenance of sinus rhythm is crucial (15). Over the past 40 years, the number of women seeking motherhood later in life, who then require Assisted Reproductive Technologies (ART), has significantly gone up, especially after heterolougus fertilization techniques became available. That has in turn led to a sharp increase in the incidence of obstetric and anesthesiological complications (16, 17), as well as ensuing medico-legal issues, litigation, lawsuits and claims (18). In the last year, the ART rules have been amended in Italy and Europe (19-22) and in the world, and technological advancements have been moving very fast and new opportunities continue to defy the attempt to regulate once and for all this field (23-25). In fact, uterus transplantation with successful child birth was recently achieved, and that is bound to increase the legal,
ethical and medico-legal implications (26-29). In such complex scenarios with elderly patients, the management of labor, delivery and puerperium is fundamental to stave off risks of thromboembolic, cardiac and other complications (30-31), in order to ensure favorable prospects with high quality of life for both mothers and babies. In case of vaginal delivery, the Valsalva maneuver and fundal pressure should be avoided (32-36) for high risk patients who have already experienced postpartum hemorrhage, uterine rupture (especially in presence of scarred uterus) (37-42) and third or four degree lacerations (43-45) and infections (46-48). The post-operative puerperal pain requires the administration of non-steroidal anti inflammatory drugs, but paracetamol should be used with caution, due to the risk of hepatotoxicity in patients with correlated pre-existing conditions (49-51). The number of women who seek motherhood later in life has significantly increased in developed countries and among that segment, it is not rare to find obesity, diabetes and cardiovascular disorders (52-54). When MS and obesity are found in ART patients, they pose an important morbidity and mortality risk (55), therefore these patients should be more accurately supervised through a multidisciplinary approach. The management of these pregnant women is of growing importance. More knowledge will be derived from national multicenter and worldwide registries in the future.

Declaration of interest

The authors report no declaration of interest.

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