Editorial


Comentarios a la guía de práctica clínica de la ESC para el tratamiento de las enfermedades cardiovasculares durante el embarazo. Una visión crítica desde la cardiología española

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Along the lines of the new philosophy regarding clinical practice guidelines established by the Executive Committee of the Sociedad Española de Cardiología (SEC; Spanish Society of Cardiology), described and explained in an article recently published in Revista Española de Cardiología (REC), a document has been drafted to provide the framework for the discussion of the most important and novel aspects of the guidelines for the treatment of cardiovascular diseases during pregnancy, issued by the European Society of Cardiology (ESC) and endorsed by other European scientific societies. In the Spanish cardiology setting, the clinical practice recommendations concerning the subject of heart disease and pregnancy were set forth in the document “Guías de práctica clínica de la Sociedad Española de Cardiología en la gestante con cardiopatía” (Practice Guidelines of the Spanish Society of Cardiology for the Management of Cardiac Disease in Pregnancy), published in 2000, and the Sociedad Española de Ginecología y Obstetricia (Spanish Society of Gynecology and Obstetrics) designed a protocol for heart diseases and pregnancy (available at www.prosego.com). More recently, valuable contributions have appeared in our scientific literature, but there has been a need for an update of guidelines encompassing the body of knowledge that has been consolidated over the past decade.

METHODS

The Clinical Practice Guidelines Committee of the SEC has created a task force composed of clinical cardiologists and expert subspecialty cardiologists proposed by the Clinical Cardiology, Pediatric Cardiology and Congenital Heart Disease, Hypertension, and Heart Failure and Arrhythmia Sections, for the overall purpose of reviewing the evidence and recommendations provided by the European guidelines concerning cardiovascular diseases and pregnancy. These are the guidelines accepted by the SEC and their translation is published in REC. Professionals from all of these areas were asked to analyze the guidelines by responding to a basic questionnaire that would serve as a reference and would standardize the information provided. This questionnaire included the following points:

1. Comments on the nature and suitability of the ESC guidelines.
2. Analysis of the methodology of the guidelines (definitions, preparation, searches, tools, limitations).
3. Novel and/or most important contributions to clinical practice.
4. Analysis of the most positive and most controversial aspects of these contributions and a comparison with those of other guidelines regarding this area of interest.
5. Points that should have been included.
6. Implications for actual clinical practice and socioeconomic implications in Spain and other countries with a similar health care setting.
7. Conclusions and a summary of the most important message or messages conveyed by the document.
With this information, a document was drawn up that includes all the inputs and faithfully expresses the conclusions of each participant. This editorial was reviewed by 10 expert external evaluators and, after a definitive revision on the part of the task force, was submitted to REC for evaluation and eventual publication at the same time as the Spanish version of the European guidelines. A declaration of conflicts of interests in relation to this subject area was requested, and is detailed at the end of the article.

**GENERAL COMMENTS AND ANALYSIS OF THE METHODOLOGY**

The incidence of heart disease among pregnant women in Spain is not well known, but if we take previous studies from other countries as a reference, it can be estimated to be 1% to 2%.

This represents a considerable number of patients, but the general cardiologist has little experience in their management. Thus, updated guidelines dealing with heart disease and pregnancy are highly welcome as they aid in deciding which patients have a low risk (similar to that of the population without heart disease), what tests should be performed, and which patients should be referred to specialized centers, whether because of the possibility of developing serious complications during the pregnancy or because they require unconventional management. These guidelines are a revision and an update of the previous document entitled “Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology” published in 2003. Although the structure is similar, the document is longer (51 pages, with 254 references and 21 tables providing recommendations) and, after presenting a number of general considerations, it provides information on 8 broad areas of heart disease: congenital heart disease, aortic disease, heart valve disease, ischemic heart disease, cardiomyopathies, arrhythmias, hypertension, and pulmonary thromboembolism. Each is composed of subsections for the different clinical entities, and for each disease there is a common structure that deals with maternal and fetal risk, pregnancy monitoring, problems at the time of delivery and recommended delivery mode, management during the puerperium, and medical treatment and interventional therapy. In addition, there is a chapter devoted to drug therapy during pregnancy and lactation.

The general methodology is similar to that of previous ESC guidelines: after a description of the current status of each subject area, a series of tables is provided to summarize the guideline recommendations for that subject area (I, IIa, IIb or III) and the weight of the evidence (A, B or C) that supports said recommendation. Given the lack of scientific evidence concerning this condition, it is not surprising that 113 (95%) of the 119 recommendations in the guidelines are based on level C evidence, that is, on historical experience, nonrandomized series, or expert consensus. Five of the recommendations (4%) are based on level B evidence and only 1, the indication for anticoagulation therapy in patients with intracardiac thrombi detected by imaging techniques or evidence of systemic embolism, is based on level A evidence.

This situation should lead to reflection on the need to promote and undertake clinical studies designed to provide evidence-based responses to many questions that are now addressed by means of expert consensus. In the meantime, it is necessary to continue to collect epidemiological data that enable us to define the situation of cardiovascular disease in pregnancy as it now stands. That is the understanding of the ESC, which, from 2006 to 2010, advocated the European Registry on Pregnancy and Heart Disease that has recently been reopened.

**ASSESSMENT OF THE MOST NOVEL ASPECTS**

The most important and/or novel aspects identified by the task force are as follows:

1. Recommendation of risk scores for the assessment of the mother and the fetus.
2. Recommendation to the possibility and importance of offering genetic counseling on certain diseases.
4. In the section on congenital heart disease, the most important new aspect is the inclusion of the different risk factors identified in series that included large numbers of patients.
5. Management of anticoagulation therapy in pregnant women with mechanical valve prostheses.
6. The chapter devoted to coronary artery disease has been limited to acute coronary syndrome, and coronary artery anomalies are no longer an issue.
8. Significantly expanded section devoted to arrhythmias.
10. Diagnosis and therapeutic management of deep vein thrombosis and thromboembolic disease during pregnancy.
11. There is a section on drugs and pregnancy, which did not exist in the preceding guidelines; it includes a table of the drugs most widely used by women with heart disease.

**Recommendation of Risk Scores for the Evaluation of the Mother and the Fetus**

The guidelines expressly recommend the use of the modified World Health Organization (WHO) risk classification, which consists of 4 groups: group I, no increase in the risk of morbidity or mortality during pregnancy associated with a concomitant heart disease; group II, slight increase in the risk of mortality and moderate increase in that of morbidity; group III, significant increase in the risk of mortality and morbidity, the patient requires multidisciplinary counseling and, if she should decide in favor of pregnancy, management in a referral unit; and group IV, includes heart diseases and situations of extreme risk with high risk of mortality, and thus pregnancy is contraindicated; if pregnancy occurs, voluntary termination should be considered. The classification of congenital and acquired heart disease according to each risk score enables the cardiologist who lacks experience with pregnant patients to make a decision that will permit the referral, without delay, of high-risk patients to a multidisciplinary team.

**The Possibility and Importance of Offering Genetic Counseling**

Although genetic studies can be useful in cardiomyopathies and channelopathies, in the presence of dysmorphisms, growth disorders or mental retardation, Marfan syndrome, and other heritable syndromes, and when there is a family history of genetic disease, we should not forget that these conditions are not very frequent among the Spanish population, that they are still very costly, and that their treatment does not always yield definitive results to aid in decision making, which can be complicated. However, the experience of a few Spanish centers should encourage us to promote specific consultations that provide this information. The guidelines do not go into details on the indications for and the interpretations of the results of these genetic studies, and thus we consider that the consensus document of the working group on myocardial and pericardial diseases of the ESC on genetic testing and counseling in cardiomyopathies should be consulted.

**Recognized Risk Factors in Congenital Heart Disease**

In the western world, congenital heart disease is currently the most common cardiovascular disease found during pregnancy (75-82% of cases). The guidelines reflect this reality, as the chapter on this subject is the most extensive of the subsections. Nearly all the congenital heart...
diseases are described in great detail and we fully agree with the recommended management. Severe pulmonary regurgitation is one of the risk factors for cardiovascular complications for patients who have undergone repair of tetralogy of Fallot, although valve replacement prior to pregnancy should be considered only if there is severe dilation of the right ventricle or the patient is symptomatic. The recommendation that anticoagulation therapy be administered to patients with Fontan circulation or that the use of heparin be considered in patients with cyanotic congenital heart disease without pulmonary arterial hypertension are novel contributions in this context. However, we should not forget that anticoagulation therapy should be employed with caution in patients with cyanotic heart disease since these individuals are also at higher risk for hemorrhagic complications.

Management of Anticoagulation in Pregnant Women With Mechanical Prostheses

In the previous version, in cases in which high-dose oral anticoagulation was required, the subcutaneous or intravenous administration of calcium heparin was recommended during the first trimester and the last 4 weeks of pregnancy, and it was considered that there was little experience with low molecular weight heparin (LMWH) in pregnant patients with mechanical prostheses. In these guidelines, given the growing body of data obtained in recent years, the utilization of oral anticoagulants is recommended as the treatment of choice during the second and third trimester, up to the 36th week based on level I evidence, and the use of unfractionated heparin (UFH) from week 6 to week 12 is proposed when there is an activated partial thromboplastin time greater than twice the control value or LMWH can be administered with monitoring of the anti-Xa concentration, an alternative not offered in the previous version of the guidelines. This version insists (as a class III indication) that, if it is not possible to determine the anti-Xa levels in a given center or laboratory, LMWH should not be considered a therapeutic option given that, in contrast to the use of LMWH in nonpregnant women, the therapeutic levels vary because the pharmacokinetic and pharmacodynamic features change during pregnancy and the patients may require increasing doses of the anticoagulant, up to 50% over the original dose, to obtain the same therapeutic concentration.

In addition, an alternative option if the patient requires low doses of oral anticoagulation (warfarin ≤5 mg/day; phenprocoumon ≤3 mg/day; acenocoumarol ≤2 mg/day) is to administer these medications throughout the entire pregnancy, including the first trimester, avoiding their use during the last 4 weeks.

Management of Advanced Heart Disease

Cardiac resynchronization therapy and defibrillator implantation should be considered 6 months after first presentation of the condition, because many patients improve on their own. Individuals with acute heart disease who are dependent on inotropic agents should be transferred to a center in which counterpulsation with an intraaortic balloon pump, ventricular assistance, and heart transplantation are available. In these cases, priority will be given to ventricular assistance as a bridge toward recovery, given the high rate of improvement of left ventricular ejection fraction. More detailed therapeutic guidelines for pregnant and breastfeeding women are provided, as are alternatives to the contraindicated therapy with antagonists of the renin-angiotensin-aldosterone axis (using a hydralazine-nitrate combination). Recommendations for the appropriate administration of beta blocker and diuretic therapy are provided. There are also obstetric recommendations concerning delivery: preferably vaginal, with close monitoring and epidural analgesia. These circumstances call for urgent delivery and substantiate the importance of the multidisciplinary team. Supervision of the newborn is recommended.

New Aspects of the Section on Arrhythmias

In the first place, these guidelines define the low overall risk associated with the presence of arrhythmias in the mother during pregnancy and rates them as WHO classes I and II. The guidelines reiterate the advisability of avoiding all antiarrhythmic agents during pregnancy and add specific recommendations for the use of drugs listed near the end. The document clearly establishes the magnitude of the risk to the fetus produced by exposure of the mother to ionizing radiation. The fourth month of pregnancy is established as the best time to perform percutaneous therapies, should they be necessary. The authors advise against the use of radiofrequency catheter ablation during pregnancy, and they propose intracardiac echocardiography and 3-dimensional mapping systems to minimize exposure to ionizing radiations during radiofrequency ablation and device implantation. The guidelines specify that, during pregnancy, the indications for the implantation of devices, pacemakers, and defibrillators are similar to those of nonpregnant patients, with the aforementioned recommendations to minimize exposure of the fetus to radiation.

Update on Pregnancy and Hypertension

The guidelines insist on the seriousness of hypertension during pregnancy. It is the most common nonobstetric problem and the major cause of maternal, fetal, and neonatal morbidity and mortality, both in developing and developed countries. The diagnosis is simplified, based on the finding of levels greater than or equal to 140/90 mmHg, and its correct classification is stressed. Drug therapy is not considered necessary in cases of mild hypertension without target organ damage and the threshold for treatment is set at 150/95 mmHg, as indicated by the current European Society of Hypertension (ESH)/ESC guidelines.9 Even in patients with previously treated hypertension, treatment can be discontinued, at least during the first trimester when there is a physiological decrease in arterial blood pressure levels. With respect to general measures, neither salt restriction nor weight loss is advised. When medication is required, the guidelines continue to recommend, as first-line therapy, alpha-methyldopa (the only drug studied specifically, but over 30 years ago), followed by beta blockers such as labetolol and metoprolol or calcium antagonists like nifedipine. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (angiotensin receptor blockers [ARB]) is specifically contraindicated because of the possible teratogenic effects. For women at risk for preeclampsia, the administration of calcium and low doses of acetylsalicylic acid may be indicated. The guidelines recognize that the different forms of hypertension in pregnancy constitute a risk factor for future cardiovascular disease. Thus, although the arterial blood pressure of these women is normalized, they should watch their cardiovascular risk closely and maintain healthy lifestyles.

Recommendations for the Prevention and Treatment of Thromboembolism During Pregnancy and the Puerperium

This aspect has been developed very extensively. The information on the signs and symptoms of thromboembolic events for patients at risk for these complications is considered to be a class I recommendation. Moreover, antenatal and postpartum heparin prophylaxis should be administered and physical measures applied. These aspects are easily forgotten in our patient population, partly due to the limited connection between the specialties of obstetrics and cardiology, with the exception of those centers in which there are specific units for the multidisciplinary monitoring of those pregnancies in which the mother or the fetus is at risk.
Drug Therapy During Pregnancy and Lactation

The long-term use of beta blockers throughout the entire pregnancy is established as a class IC indication in patients with highly symptomatic long QT syndrome, idiopathic ventricular tachycardia (VT), or recurrent paroxysmal supraventricular tachycardia. Beta blockers, as well as digitalis, are recommended for the control of the ventricular response in atrial tachycardia, atrial fibrillation (AF), and atrial flutter. Nondihydropyridine calcium channel blockers can also be utilized for this purpose. The administration of atenolol is expressly contraindicated (class III) during the entire pregnancy, as is that of doredonarol. The guidelines recommend the use of metoprolol, as it is a cardioselective beta blocker, or of propranolol because of the extensive experience with this drug. The use of sotalol, flecanide, propafenone, and even amiodarone is accepted when the previously mentioned drugs fail in cases of highly symptomatic recurrent arrhythmias, with poor hemodynamic tolerance and no response to beta blockers. In the current guidelines, the use of intravenous sotalol is accepted during the acute phase, and this drug can be administered orally in place of amiodarone as chronic treatment because of the secondary effects of the latter, especially in the fetal thyroid gland. Information on the use of medication during pregnancy and breastfeeding is provided in the form of an extensive table that details the drugs employed in cardiology, with their corresponding pregnancy risk and their category according to the United States Food and Drug Administration (5 categories ranging from greater to lesser safety: A, B, C, D, and X). Moreover, it includes information from 2 databases, available at www.embryotox.de in Germany and www.safeftetus.com in the United Kingdom, summarizing the available evidence on a list of more than 50 drugs. It is noteworthy that the drugs most widely employed in cardiology (statins, ACE inhibitors/ARB, renin inhibitors, and atenolol) are absolutely contraindicated during pregnancy.

CRITICAL ASSESSMENT OF THE MOST CONTROVERSIAL ASPECTS

The writing style of the guidelines is not exactly concise and the considerable extension, similar to that of a chapter from a cardiology textbook, may limit their use in routine clinical practice. Some of the recommendations are unclear since there is an excessive use of double negatives and the lettering in the tables is not easy to read.

There is a need for a simple management algorithm for the nonspecialized clinical cardiologist. As it should be, the chapter on general considerations begins with a well-designed course of action that is barely stressed in the text; a table summarizing it, like the one that we propose (Table), would have been of interest. It would also have been helpful to include specific recommendations—such as “when to suspect heart disease” or “when to refer to cardiology”—to avoid consultations due to symptoms like palpitations or dyspnea, which usually are not disease-related.

One aspect that we consider has been stressed too little in these clinical practice guidelines is the insistence that at least 50% of the complications associated with heart disease and pregnancy develop during the immediate postpartum period, and that medical attention should be extended to the first days after childbirth in these patients.

We wish to highlight the excessively broad indications for some of the recommended complementary studies, particularly Holter monitoring, which according to the guidelines is indicated in patients with previously documented arrhythmias or in those who complain of palpitations, in the absence of a more detailed definition of the differential diagnosis of palpitations during pregnancy. This indication is not justified as it is unnecessary and it is not supported by scientific evidence. The same can be said for the recommendation that echocardiographic studies be carried out monthly in patients with certain cardiac valve diseases.

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<tr>
<th>Table</th>
<th>General Guidelines for the Management of Pregnant Heart Disease Patients</th>
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<tr>
<td>1.</td>
<td>Counseling and monitoring of heart disease patients of reproductive age should commence prior to pregnancy, ideally from the time of menarche</td>
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<td>2.</td>
<td>Monitoring of the pregnancy should be carried out by multidisciplinary teams</td>
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<td>3.</td>
<td>Patients at high risk should be referred to specialized centers</td>
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<tr>
<td>4.</td>
<td>Diagnostic tests and therapeutic approaches should be carried out by experts in the management of pregnant women</td>
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The authors base the estimate of the overall risk in pregnant heart disease patients on the WHO classification (WHO class I to IV) and, although they briefly describe the CARPREG and ZAHARA studies, they do not comment on the utility of the findings of these efforts in risk prediction in the individual patient. Many of the reports dealing with maternal and fetal risk, especially in cases of congenital diseases, were based on the tables summarizing the predictors identified in these studies. Moreover, in the table showing the predictors of the ZAHARA study, the relationship between the score obtained and the risk classification is not provided. In contrast to the WHO classification, in which only the maternal disease is considered, these tables include clinical and hemodynamic data, a circumstance that improves individual risk stratification. For example, a patient with corrected tetralogy of Fallot has a risk level of II according to the WHO, regardless of the grade of pulmonary regurgitation or right ventricular function.

Among the debatable aspects are the indications for preconception surgical repair of heart disease-related lesions that are usually well tolerated.

The consideration of pulmonary valve replacement in asymptomatic patients with severe right ventricular dilation should probably be classified as a IIb, rather than a IIa, indication. This lower class is based on the results of a study, referred to in the guidelines, dealing with the tolerance of pregnancy in patients with right ventricular outflow tract lesions (47 women with 76 pregnancies), that only detected as markers of risk for maternal adverse events (heart failure) the association of severe pulmonary regurgitation with twin pregnancy or the presence of branch pulmonary artery stenosis.

With regard to the controversial aspects relative to specific heart diseases, it is worth mentioning the management of aortic dilation in cases of bicuspid aortic valve (BAV), which does not specify the approach in patients with significant dilation of ascending aorta who did not meet the surgical criteria. The lack of information on this subgroup of patients almost certainly has resulted in the guidelines being less specific. The association between aortic dissection and BAV probably occurs less frequently than we think and the indication for interventional management in this setting should be redefined.

The use of antiplatelet therapy in ischemic heart disease is a generic approach, as there is little scientific evidence. The recently published recommendations of the Canadian Cardiovascular Society establish that 75 mg to 162 mg of acetylsalicylic acid can be taken daily during the first trimester of pregnancy (class IIA A) and during the second and third trimesters (class I A). Given that the experience with clopidogrel and other antiplatelet agents is limited to a few published cases, the recommendation is classified as IIB C.

The recommendation for the use of bromocriptine in peripartum cardiomyopathy appears to be somewhat premature, as it is based on a single pilot study; evidence that has been firmly established by more than one study has yet to be provided.

Although peripartum cardiomyopathy receives the attention it deserves—the fact that systolic dysfunction will persist in 50% of the cases and that the risk of recurrence in later pregnancies ranges between 30% and 40% is stressed — very little attention is paid to hypertrophic cardiomyopathy (HCM); any clinician will probably confront, more than once, the problems of management of a pregnant
woman with this disease, which affects 1 of 500 adults and is frequently found in women of reproductive age. Cardiomyopathies that have become highly relevant because of their prognostic and therapeutic implications, such as arrhythmogenic cardiomyopathy and noncompaction cardiomyopathy, are not even mentioned in the document, nor is restrictive cardiomyopathy referenced.

One debatable aspect in the management of HCM during pregnancy is the use of beta blockers, and the type of beta blocker to be administered is not specified. The authors indicate that they should be considered for patients with “more than mild” dynamic outflow tract obstruction and/or a maximum wall thickness greater than 15 mm, but this criterion means that practically all the women with HCM would have to receive beta blockers during pregnancy, since a thickness greater than 15 mm is usually the criterion required for the diagnosis of this disease.13 Asymptomatic women with HCM without relevant obstruction or tachyarrhythmias do not need beta blocker therapy during pregnancy. Another questionable recommendation made is that cardioversion should be considered for persistent AF because this arrhythmia is poorly tolerated. However, it must be pointed out that cardioversion may not offer a significant benefit in cases of marked atrial dilation or recurrent or prolonged episodes, and in any case the patients with HCM will have to continue to receive anticoagulation therapy.

There are no comments on the possibility of the presence of familial disease in the fetus: whereas the guidelines recommend the performance of fetal echocardiography in women with congenital heart disease, this recommendation does not apply to women with inherited heart disease. The manifestations of hereditary cardiomyopathies (hypertrophic, dilated, or noncompaction cardiomyopathy) may be severe during the neonatal period and can be diagnosed in the fetus, although this is exceptional in HCM.

We find fault with the limited expansion on the recommendations concerning familial arrhythmogenic syndromes: the authors mention that genetic studies may be interesting in cases of long QT syndrome, recommend the use of beta blockers in these patients, and refer to the increased risk of arrhythmias during the postpartum, but they do not point out that this increase in the risk is especially marked in patients with long QT syndrome type 2 linked to mutations in the KCNH2 gene,14 nor do they mention the possibility of arrhythmic complications in fetuses whose mothers have a prolonged QT interval.15 They make only passing reference to Brugada syndrome and catecholaminergic VT, despite the potential relevance of these conditions during pregnancy and delivery.16

The guidelines have adopted the restrictions of the new recommendations concerning prophylaxis in infective endocarditis. They affirm that it is not necessary to administer antibiotics during the peripartum, even to high-risk heart disease patients, such as individuals with prostheses or uncorrected cyanotic heart disease, and restrict antibiotic prophylaxis only to dental procedures and high-risk heart disease patients.

We find it surprising that the guidelines advocate monitoring activated coagulation factor X in patients treated with LMWH, since the use of this determination is very limited in our setting. As this test is not usually performed, some members of this expert panel maintain, contrary to what the guidelines expressly state, that UFH or LMWH could be used every 12 hours, but always under strict medical supervision based on close monitoring.

These guidelines establish differences in the management of anticoagulation therapy in AF depending on whether it is valvarular or lone AF. They recommend the application of the CHA2DS2VASc score; when it is greater than or equal to 2, oral anticoagulation should be administered from the second trimester until 1 month before delivery, and LMWH during the first trimester and the last month. In the case of valvarular AF, immediate anticoagulation therapy is required with intravenous UFH, followed by LMWH during the first and last trimesters and oral anticoagulation agents or LMWH during the second trimester.

CONCLUSIONS AND A SUMMARY OF THE MOST IMPORTANT MESSAGES

The clinical practice guidelines for the treatment of cardiovascular diseases during pregnancy, carried out by experts of the ESC, constitute the most recent update on the subject. In this document,
we find general information and basic aspects of the management of pregnant women with heart disease, their classification into 4 categories that enables the clinical cardiologist to establish the most appropriate actions to be undertaken in a given patient, and finally a systematic review of the management and treatment of congenital or acquired heart diseases during pregnancy.

These guidelines are required reference matter in the management of pregnant women with heart disease. Their length and ambiguity, which can jeopardize their utility, reflect the limitations of our current knowledge of this aspect of cardiology and the need to allocate resources for research on the multiple questions that remain to be solved. Advancing this knowledge inevitably requires collaboration between cardiologists, obstetricians, and pediatricians; the creation of multidisciplinary reference units within the healthcare system; and the development of procedural protocols and well defined circuits that enable us to optimize the treatment of women with heart disease and their children.

Finally, we must insist on the importance of committing ourselves to the communication and implementation of these guidelines in routine clinical practice, as there is evidence that clinical activity to the communication and implementation of these guidelines in routine clinical practice, as there is evidence that clinical activity

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CONFLICTS OF INTERESTS

L. Monserrat: board member, staff member, stockholder (Health in Code). J.M. Oliver: consultancy (Actelion) and presentations (Actelion). J. Serrano: attendance at a scientific meeting (Menarini). All authors: manuscript preparation (Fundación Casa del Corazón).

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