

# **Atrial fibrillation during pregnancy: a nine-month period with limited options**

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## **Introduction:**

Atrial fibrillation (AF) is the most common type of arrhythmia in the adult population associated with increased morbidity and mortality [1]. The risk of developing AF rises significantly with aging and in the presence of some comorbidities [2]. Pregnancy is a physiological condition during the reproductive period of females, characterized by hormonal and cardiovascular adaptations of the human body, in order to maintain a safe environment for the growing fetus. AF has a very low prevalence among healthy young women. However, increasing maternal age and concomitant underlying pathologies are risk factors for AF occurrence during pregnancy [3]. The hemodynamic dysregulation and thromboembolic risk caused by AF demand proper and safe therapy for both mother and fetus.

## **Predisposing factors for atrial fibrillation during pregnancy:**

Pregnancy is characterized by a variety of hemodynamic and neurohormonal adaptations of the female body during this 36 to 40-week period of time. These changes provide a safe and appropriate environment for the fetus growth.

Pregnancy is accompanied with a substantial decrease of the peripheral vascular resistance due to a vasodilation of the systemic vasculature [4]. The decrease is almost 40% prior to pregnancy and reaches its lowest values in the fourth and fifth month of pregnancy [5].

Cardiac output is also increasing during pregnancy [6]. Hemodynamic studies in pregnant women have demonstrated increases of the cardiac output up to 45% for singleton pregnancies and up to 55% for twin pregnancies [7,8]. Additionally, nervous system sympathetic activity and heart rate show a parallel increase during a normal pregnancy [9,10]. Apart from the vascular and neurohormonal adaptations of the maternal body, changes of the plasma volume and red cell mass occur during gestation [11, 12].

Erythropoiesis and total blood volume increase significantly close to 45% from baseline values [13], whereas concomitant plasma volume expansion leads to “physiological anemia” from hemodilution.

The mentioned physiological alterations of the vascular, neurohormonal and fluid-status changes in the maternal body are developing in parallel with adaptations of the heart. Left ventricular mass and wall thickness are temporarily increasing above pregnancy values [14], whereas mild four-chamber dilation has been also confirmed from cardiovascular imaging studies in gestating women [15,16]. These temporal physiologic alterations during pregnancy may be confounding factors for maternal cardiac dysrhythmias (Fig. 1).

On the other hand, established risk factors for the development of AF in pregnancy are hypertension, heart failure, hyperthyroidism, rheumatic heart disease and congenital heart disease [17].

#### **Treatment of atrial fibrillation during pregnancy:**

Treatment of AF in pregnancy comprises the same aims as in non-pregnant patients. The choice of pharmacologic therapy however should be very carefully reviewed and individualized. The week of gestation, the potential teratogenic effects and the safety of the medication for the mother and the fetus should be always taken into account. (Fig. 2)

#### *Acute treatment of atrial fibrillation during pregnancy:*

Hemodynamic instability caused by AF needs to be immediately treated. Loss of atrial contraction in combination with fast and irregular ventricular results to decreases of uterine blood supply, compromising the safety of the mother and the fetus. External direct current biphasic electrical cardioversion with 50-100 Joule is generally a safe approach, as long as it is carried out under fetal monitoring [18]. (Fig. 2)

#### *Antiarrhythmic drug therapy during pregnancy:*

Beta-blockers is the most extensively studied and applied category of cardiovascular medicines during pregnancy [19]. There is general recommendation that medical therapy should be avoided during the first trimester of gestation, when organogenesis takes place. Data from large population-based cohort studies failed to report an increased risk between b-blocker exposure during the first trimester of pregnancy and fetal congenital anomalies

when adjusted for maternal age, comorbidities and body mass index [20,21]. However, in unadjusted analysis maternal exposure in b-blockers resulted to higher risk for fetal congenital cardiac anomalies [22]. Metoprolol and Propranolol have an acceptable, but not completely negligible risk profile during the first trimester of gestation [23]. They are considered to be safe medications for the second and third trimester of pregnancy [24], whereas atenolol has been associated with intrauterine growth retardation and should be avoided [25]. (Fig. 3)

Non dihydropyridine calcium channel blockers (CCB) such as Verapamil and Diltiazem can be also used with relative safety during pregnancy [26]. Verapamil is being mainly utilized for the acute termination of SVTs during pregnancy [27]. A prospective multicenter cohort study examining, among other CCBs, the safety of verapamil exposure in the first trimester of pregnancy reported no increased teratogenic risk [28]. Furthermore, a retrospective cohort study found no association between CCB maternal exposure in the third trimester and fetal developmental abnormality, but an increased risk for jaundice, seizures and hematological disorders for the offspring [29]. In the absence of other indications, the use of verapamil for the medical treatment of AF for single rate control during pregnancy should not be the medication of first choice. (Fig. 3)

Digoxin may be an alternative option for rate control in pregnant women with AF and concomitant congestive heart failure [30]. Careful titration and serum levels of digoxin in maternal blood is of paramount importance for safety of the mother [31] as there has been reported minimal influence of digoxin in the fetal heart rate in the first half of gestation [32]. Flecainide crosses the blood-placental barrier and can be used with relative safety for the termination of fetal supraventricular tachycardias [33]. It is a less commonly used pharmacological therapy for the maintenance of maternal sinus rhythm during pregnancy, however teratogenic effects have not been reported [34]. Propafenone is an additional Class Ic antiarrhythmic drug, crossing the placental barrier and being also suitable for pharmacological conversion and maintenance of sinus rhythm during pregnancy [34]. Nevertheless, data regarding the effects of propafenone during pregnancy are even more limited. Prior to exposure in both antiarrhythmic substances, underlying structural heart disease of the pregnant woman must be excluded.

Sotalol is a class III antiarrhythmic drug that can be used in the treatment of fetal arrhythmias [35]. Data regarding its safety are conflicting. It is suggested that sotalol can be

safely administered during pregnancy after the first trimester in lower doses [30]. However, increased fetal mortality with sotalol has been reported [34,35] and the inherent proarrhythmic effect of Sotalol requires close monitoring of the patient. Therefore, the administration of Sotalol during pregnancy should be reserved only for highly selected cases, where no further alternative options remain.

Amiodarone and Dronedarone are the remaining Class III antiarrhythmic drugs that can be orally administered for long term maintenance of sinus rhythm. Amiodarone is contraindicated for the treatment of AF during pregnancy, as it has been associated with fetal bradycardia, thyroid dysfunction and fetal abnormalities [36,37]. There is lack of evidence regarding the safety of Dronedarone during pregnancy, thus its use should be avoided.

#### *Anticoagulation during pregnancy:*

The coagulation system during pregnancy undergoes physiologic alterations. These changes are characterized by a new hypercoagulable state due to increase of coagulation factors and decrease of natural anticoagulants [38]. The majority of experience and data regarding the safety and efficacy of anticoagulation therapy arises from vein thromboembolism during pregnancy. Limited experience exists regarding anticoagulation for AF during pregnancy. The recently published 2020 ESC guidelines recommend the same risk assessment for stroke during pregnancy, as in non-pregnant women [30].

Unfractionated heparin (UFH) has the advantages of not crossing the placenta, is not associated with teratogenic effects and it is the first choice for anticoagulation whenever required during gestation [39]. Difficulties of anticoagulation with UFH remain the continuous intravenous infusion of the medication and the daily control of the aPTT time for the titration of the dose. Low-molecular-weight heparin (LMWH) overcomes these difficulties by its subcutaneous route of administration with fixed doses. It generally does not necessitate monitoring of drug levels and observational studies in pregnant women have shown a higher safety profile compared to UFH [40] (Fig. 4). Unfortunately, long-term anticoagulation therapy with heparins carries also risks for the pregnant woman. Allergic skin reaction and bruising at the injection-sites are frequently observed during pregnancy [41]. The risk of bleeding with heparins, as for any type of anticoagulant, increases at the time of delivery and at obstetrical procedures [42].

The incidence of heparin induced thrombocytopenia (HIT) during pregnancy with LMWH is very low [43]. Nevertheless, HIT occurrence should be immediately treated by switching the anticoagulation to danaparoid [44], but with inherent limitations and risks such as lack of dosing guidelines and effectivity in AF, lack of an antagonist in case of bleeding and lack of monitoring assays.

Vitamin K antagonists cross the placenta and should be avoided during pregnancy as their use has been associated with congenital defects [45]. Teratogenic potential of vitamin-K antagonists is more pronounced during the first trimester of gestation, where organogenesis takes place [46]. However, if anticoagulation with vitamin-K antagonists remains the only viable solution, lower daily doses of warfarin carry lower risk for embryopathy and pregnancy loss [47]. (Fig. 4)

Non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to cross the placenta in experimental in vitro studies and extremely limited data exist regarding their safety during pregnancy [48-50]. Therefore, NOACs should not be administered during pregnancy. (Fig. 4)

In the devastating case of a cerebrovascular thromboembolic event related to AF a computed tomography scan of the head should be immediately performed to rule out hemorrhage. Thrombolysis with alteplase (tissue plasminogen activator (tPA) should be initiated within 4,5 hours of symptom onset, adjusted on the pre-pregnancy weight. Alteplase does not cross the placenta and close surveillance is necessary due to low risk of placental abruption [51].

#### *Ablation of atrial fibrillation during pregnancy:*

Novel three-dimensional-navigation systems, non-traumatic high-density mapping and ablation catheters, utilization of intracardiac echocardiography and increasing operator experience are enabling the performance of radiofrequency (RF) catheter ablation of AF with near-zero, or zero time of fluoroscopy [52]. Very few sporadic cases of RF-catheter ablation for pulmonary vein isolation (PVI) during pregnancy have been reported [53]. Three major safety issues should be taken into account when proceeding to RF-PVI in a pregnant woman:

1. Fluoroscopy may at some point be necessary, exposing the fetus to ionizing radiation.

2. Despite current technological advances the risk of a periinterventional complication during PVI has immediate hemodynamic consequences, jeopardizing simultaneously the life of the mother and the fetus.
3. Data regarding the effect and safety of radiofrequency energy on the fetus are currently unclear [54].

The recently published 2020 ESC guidelines are stating that AF catheter ablation has no role during pregnancy [30].

**Conclusions:**

AF during pregnancy is a very rare arrhythmia in the absence of structural heart disease. Hemodynamic stability is of paramount importance for the safety of the mother and the fetus. Long term medical therapy with antiarrhythmics and anticoagulation should be strongly reviewed and individualized upon pregnant patient and avoided during the first trimester of gestation. There are very limited data opting for an interventional treatment of symptomatic AF during pregnancy.

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Figures:

Fig 1: Changes in maternal body during pregnancy and the effects on the heart

Fig 2: acute treatment of atrial fibrillation during pregnancy

Fig 3: antiarrhythmic treatment during pregnancy

Fig 4: Anticoagulation for atrial fibrillation during pregnancy

Fig 1:

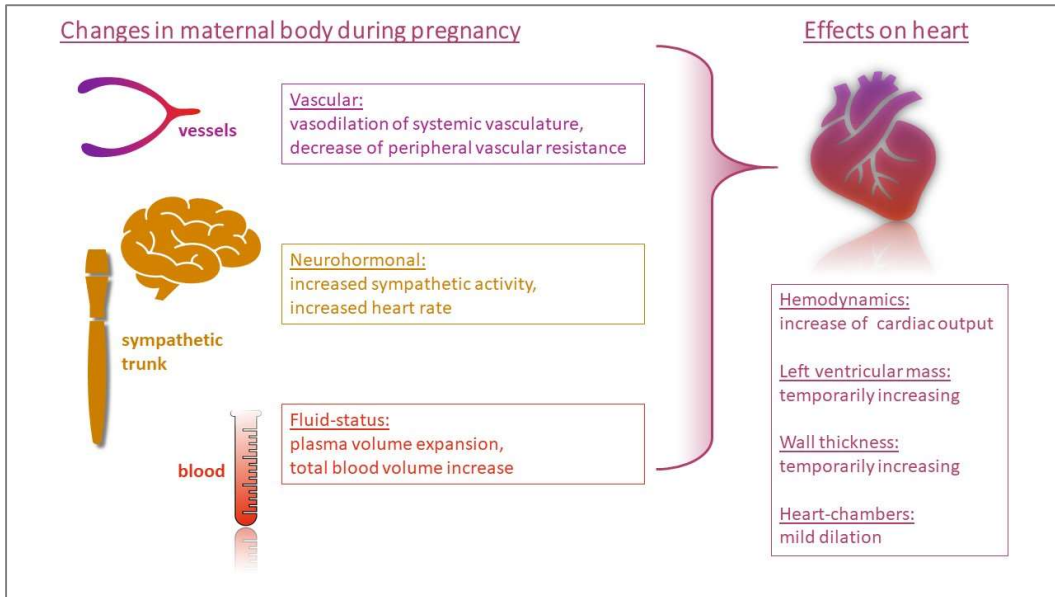


Fig 2

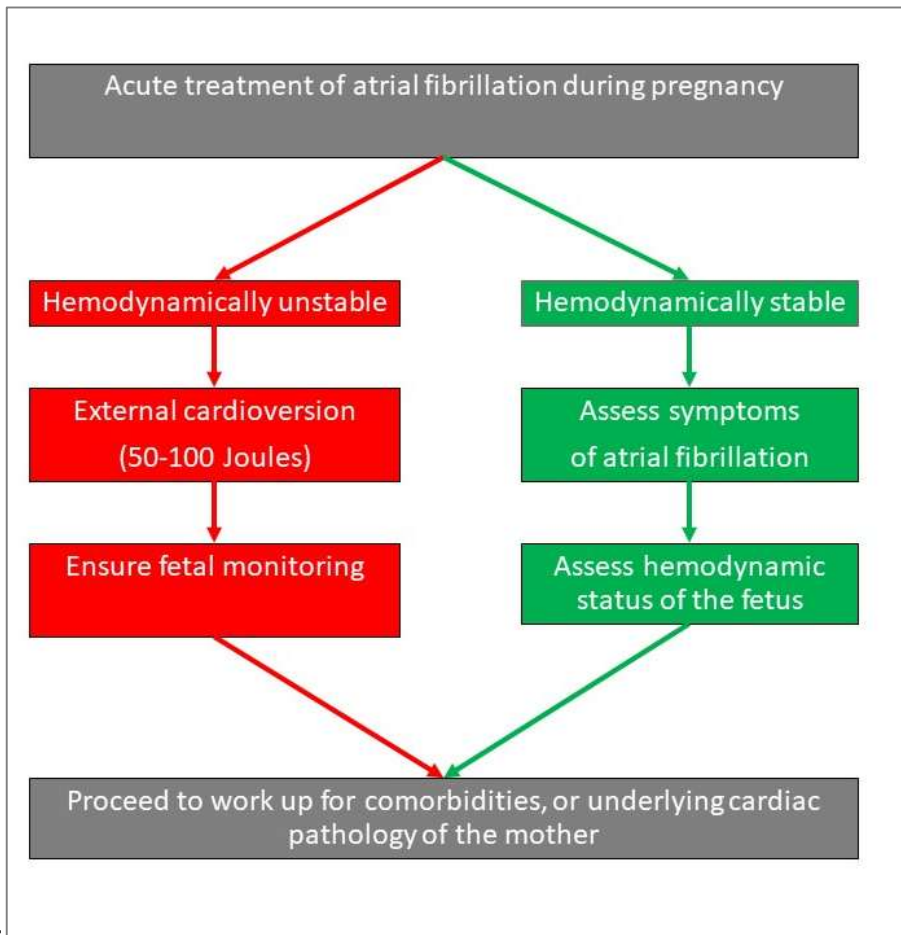


Fig 3:

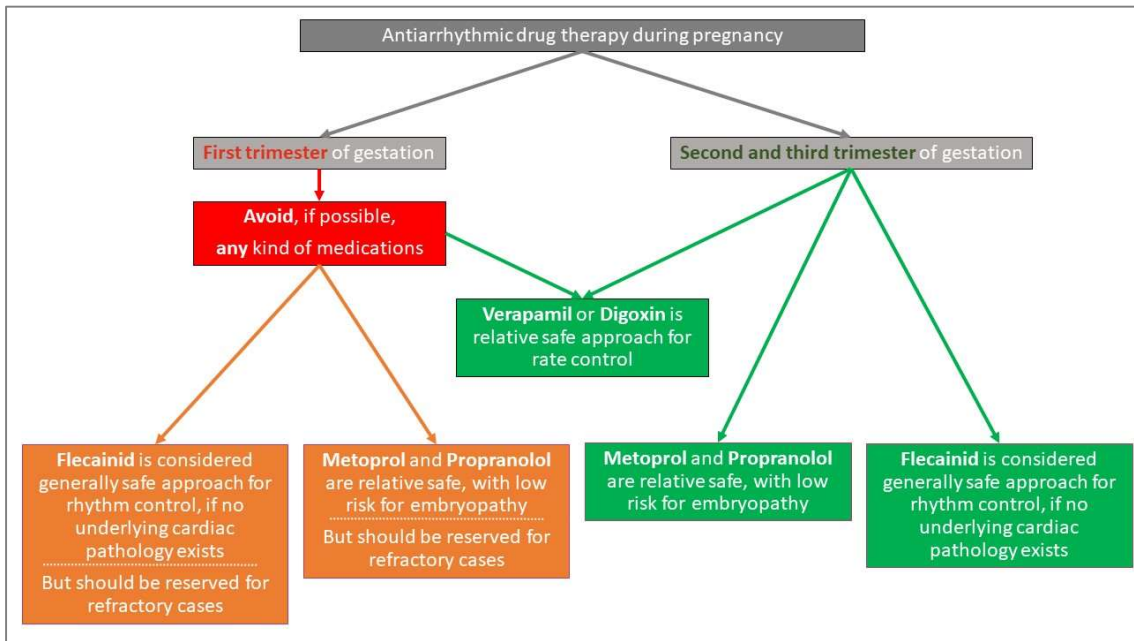


Fig 4:

