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# IVABRADINE DURING PREGNANCY: PHARMACOLOGICAL RATIONALE, MATERNAL CARDIOVASCULAR EFFECTS, AND HUMAN REPRODUCTIVE SAFETY: A NARRATIVE REVIEW

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## Abstract

**Background:** Ivabradine is a selective heart-rate-lowering agent that inhibits the hyperpolarization-activated cyclic nucleotide-gated pacemaker current (*If*) in the sinoatrial node. Because it reduces heart rate without a major direct negative inotropic effect, ivabradine has established therapeutic value in selected patients with chronic heart failure and stable coronary artery disease and has also been used off-label for inappropriate sinus tachycardia (IST), postural orthostatic tachycardia syndrome (POTS), and selected automatic atrial tachyarrhythmias. Pregnancy creates a particular therapeutic dilemma because maternal tachycardia may compromise cardiovascular function, whereas reproductive animal studies have demonstrated embryo-fetal toxicity and teratogenic effects.

**Objective:** To critically review the pharmacological rationale, maternal cardiovascular effects, preclinical reproductive toxicity, human pregnancy exposure data, and current clinical position of ivabradine during pregnancy.

**Methods:** A narrative synthesis of peer-reviewed human reports indexed in PubMed/MEDLINE was performed, supplemented by current regulatory information and cardiovascular pregnancy guidelines. Published reports of maternal ivabradine exposure were evaluated with particular attention to indication, gestational timing, dose, maternal response, fetal and neonatal outcome, and methodological limitations. The literature search was updated through September 2026.

**Results:** The largest human dataset is the German Embryotox observational study, which prospectively followed 38 pregnancies with ivabradine exposure. Thirty-two pregnancies resulted in live births, three in spontaneous abortions, and three in elective terminations. One infant had major congenital anomalies. Most women discontinued ivabradine after pregnancy recognition without cardiovascular deterioration, whereas five continued therapy for substantial periods of pregnancy. Additional case reports describe apparently successful treatment of severe IST-associated cardiomyopathy, incessant focal atrial tachycardia, acute cardiovascular disease, and POTS. A 2026 case documented continuous ivabradine exposure from preconception through delivery with reassuring maternal and fetal surveillance. Nevertheless, the cumulative human sample remains insufficient to exclude moderate or rare reproductive risks.

**Conclusion:** Available human evidence has not demonstrated a consistent pattern of ivabradine-associated congenital malformations, but it remains inadequate to establish reproductive safety. Current European guidance does not recommend

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ivabradine during pregnancy, and European product information lists pregnancy as a contraindication. When exposure occurs inadvertently, it should not be interpreted as evidence of inevitable fetal harm. In exceptional maternal cardiovascular conditions in which established alternatives are ineffective or poorly tolerated, individualized multidisciplinary assessment is essential.

**Keywords:** ivabradine; pregnancy; drug safety; teratogenicity; inappropriate sinus tachycardia; heart failure; postural orthostatic tachycardia syndrome; fetal outcome; pharmacovigilance; cardio-obstetrics.

## Introduction

Cardiovascular adaptation to pregnancy requires substantial changes in maternal hemodynamics. Blood volume, heart rate, stroke volume, and cardiac output increase, whereas systemic vascular resistance generally declines. Cardiac output rises early in pregnancy and may reach approximately 30% or more above non-pregnant levels during later gestation. These normal adaptations are usually well tolerated by healthy women but may precipitate symptoms or decompensation in patients with underlying cardiovascular disease or persistent tachyarrhythmia. [1,2]

Persistent tachycardia during pregnancy is particularly challenging because heart-rate reduction must be balanced against the physiological requirement for an increased cardiac output. Inappropriate sinus tachycardia, focal atrial tachycardia, POTS, cardiomyopathy, and heart failure may all produce clinically important tachycardia. Pregnancy-associated IST is often benign, but symptomatic women may require repeated emergency assessment, hospital admission, or pharmacological therapy. In a cohort of 19 pregnant women with IST, 42% attended an emergency department more than once, 32% required hospitalization, and 26% received pharmacological treatment. [3]

Ivabradine is pharmacologically attractive in this setting because it lowers heart rate through selective inhibition of the sinoatrial *If* current while exerting substantially less direct effect on myocardial contractility than conventional negative chronotropic agents. Outside pregnancy, randomized studies have demonstrated its efficacy in selected heart-failure populations, and controlled studies have also shown clinically relevant heart-rate reduction in IST and POTS. [4–6]

The reproductive safety question, however, remains unresolved. Preclinical studies demonstrated cardiac and vascular abnormalities in rats and fetal toxicity including ectrodactyly in rabbits. Human evidence consists predominantly of a relatively small pharmacovigilance cohort and isolated clinical reports. Consequently, regulatory authorities and current European cardiovascular guidelines continue to advise against routine use during pregnancy.

This review critically evaluates the pharmacology of ivabradine in the context of pregnancy, the biological basis of potential maternal benefit and fetal risk, available human exposure data, and the implications for clinical decision-making and future pharmacovigilance.

This narrative review was based on targeted searches of PubMed/MEDLINE for peer-reviewed reports involving ivabradine, pregnancy, reproductive safety, inappropriate sinus tachycardia, atrial tachycardia, cardiomyopathy, POTS, and fetal or neonatal

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outcomes. Search concepts included combinations of "ivabradine AND pregnancy," "ivabradine AND fetal outcome," "ivabradine AND teratogenicity," "ivabradine AND inappropriate sinus tachycardia AND pregnancy," "ivabradine AND atrial tachycardia AND pregnancy," and "ivabradine AND POTS AND pregnancy."

Human pregnancy exposures were prioritized over secondary reviews. Prospective pharmacovigilance data, case reports, observational studies, regulatory information, pharmacological studies, and current clinical guidelines were included when they contributed directly to assessment of mechanism, maternal efficacy, or reproductive safety. The European Medicines Agency product information and the 2025 European Society of Cardiology guideline on cardiovascular disease and pregnancy were used to define current regulatory and guideline positions. The search was updated through 11 September 2026.

Because randomized controlled trials of ivabradine in pregnant women do not exist and would present substantial ethical and logistical challenges, the available pregnancy literature was interpreted according to source type and susceptibility to bias. Particular emphasis was placed on separating prospectively collected pregnancy outcomes from retrospective reports and individual successful case reports.

Ivabradine is a selective inhibitor of the hyperpolarization-activated cyclic nucleotide-gated channels responsible for the cardiac pacemaker *I*f current. HCN4 is the principal HCN isoform involved in sinoatrial pacemaker activity. Inhibition of this current reduces the slope of spontaneous diastolic depolarization in sinoatrial nodal cells, thereby decreasing the frequency of sinus-node discharge and heart rate. [7]

Unlike beta-adrenergic receptor blockade, the principal therapeutic action of ivabradine is not mediated through suppression of sympathetic signaling. At clinically relevant concentrations, it does not directly produce the same degree of negative inotropy associated with some other heart-rate-lowering agents. This property helps explain interest in its use when tachycardia is clinically important but systemic hypotension or impaired ventricular function limits escalation of beta-blockade.

In the SHIFT trial, which included patients with chronic systolic heart failure in sinus rhythm and an elevated resting heart rate, ivabradine reduced the composite outcome of cardiovascular death or hospitalization for worsening heart failure. Symptomatic bradycardia, however, occurred more frequently with ivabradine than with placebo, demonstrating that selective sinus-node inhibition remains clinically significant and requires dose-dependent monitoring. [4]

Ivabradine also interacts with the retinal *I*h current, accounting for characteristic transient visual symptoms or phosphenes. From a maternal cardiovascular perspective, additional concerns include excessive bradycardia and atrial fibrillation. Regulatory recommendations therefore emphasize heart-rate surveillance and dose reduction or discontinuation in patients with persistent clinically important bradycardia.

The pharmacological characteristics that are advantageous outside pregnancy cannot automatically be extrapolated to pregnant patients. Physiological increases in heart rate participate in maintaining the higher cardiac output required during gestation. Excessive pharmacological slowing of maternal sinus rate could theoretically restrict the maternal cardiovascular response to exertion or hemodynamic stress, particularly in women with limited stroke-volume reserve.

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**Pregnancy Physiology and the Rationale for Heart-Rate Control**

Maternal cardiac output rises early in pregnancy through changes in both stroke volume and heart rate. A meta-analysis of pregnancy hemodynamics found that cardiac output peaked in the early third trimester approximately 1.5 L/min, or 31%, above non-pregnant values. Other physiological studies demonstrate an early decline in systemic vascular resistance, expansion of plasma volume, and progressive cardiac remodeling. [1,2]

Consequently, sinus tachycardia in pregnancy exists on a continuum between normal physiological adaptation and pathological excessive rate elevation. Pharmacological treatment should therefore address not simply a numerical heart rate but the clinical context, including symptoms, ventricular function, blood pressure, rhythm mechanism, structural heart disease, and evidence of tachycardia-mediated myocardial dysfunction.

Ivabradine may theoretically provide a pharmacological advantage when excessive sinus-node automaticity is the predominant mechanism and conventional therapies produce unacceptable hypotension or negative inotropic effects. This concept is supported by non-pregnant studies in IST and POTS. Ptaszynski et al. reported effective heart-rate control with ivabradine in patients with IST who had previously failed beta-blocker or verapamil therapy. In hyperadrenergic POTS, a randomized crossover study also demonstrated significant heart-rate reduction and improvement in selected quality-of-life measures. [5,6]

These efficacy observations establish biological plausibility for selected maternal indications but cannot be used as evidence of fetal safety.

The principal reason for concern about ivabradine during pregnancy originates from reproductive animal studies. In pregnant rats, exposure during organogenesis was associated with increased intrauterine and postnatal mortality and cardiac malformations at exposures comparable with therapeutic human exposure. Interventricular septal defects and complex abnormalities of major arteries occurred at higher exposures, approximately three times the maximum recommended human exposure based on systemic exposure measurements.

In pregnant rabbits, administration during organogenesis increased post-implantation loss. At the highest studied dose, approximately 15 times human exposure, reduced fetal and placental weights were reported together with ectrodactyly. Pre- and postnatal rat studies additionally demonstrated increased postnatal mortality associated with cardiac teratogenic findings at high exposure.

Animal findings do not establish an equivalent teratogenic effect in humans. Species-specific pharmacokinetics, dose-exposure relationships, placental physiology, and developmental sensitivity can substantially modify reproductive toxicity. Nevertheless, structural cardiovascular abnormalities in experimental models are particularly relevant for a drug whose pharmacological target contributes to pacemaker electrophysiology.

The EMA states that ivabradine must not be used during pregnancy, breastfeeding, or in women capable of becoming pregnant who are not using appropriate contraception. The regulatory rationale reflects the limited amount of human pregnancy data combined with reproductive toxicity demonstrated in animals.

Human evidence remains limited. The most informative dataset is the German Embryotox study reported by Hoeltzenbein et al., which evaluated ivabradine-related consultations between 2007 and 2019. Among 38 prospectively ascertained pregnancies

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with completed follow-up, 32 resulted in live births, three in spontaneous abortions, and three in elective pregnancy terminations. One neonate had major congenital abnormalities, including an atrial septal defect and cleft palate. Thirty-three of 38 patients discontinued ivabradine after pregnancy confirmation without reported deterioration of their cardiac condition, whereas five continued treatment during pregnancy. [8]

Importantly, these observations do not provide statistical evidence that the rate of congenital malformations is equivalent to background population risk. The cohort is too small to detect modest increases in overall malformation risk or substantial increases in rare specific malformations. Furthermore, underlying maternal disease, obesity, diabetes, concomitant medications, timing of exposure, and indication-related confounding complicate causal interpretation.

Individual case reports provide additional information on sustained exposure and maternal therapeutic response but are intrinsically vulnerable to publication bias. Favorable or unusual therapeutic outcomes are more likely to be published than uncomplicated exposures without special clinical interest.

**Table 1. Published human evidence on ivabradine exposure during pregnancy**

| Source | Design / indication | Gestational exposure | Dose | Maternal outcome | Fetal/neonatal outcome | Principal limitation |
|---|---|---|---|---|---|---|
| **Babić et al., 201**] [9] | Case report; acute STEMI with ventricular fibrillation and subsequent heart-rate management | MI occurred at 10 weeks; ivabradine included in therapy during early pregnancy | ot clearly reported | Successful resuscitation and PCI; LVEF 40–45% before discharge; pregnancy maintained | Normal fetal growth; healthy male infant delivered vaginally | Multiple cardiovascular drugs and PCI exposure; ivabradine-specific effect impossible to isolate |
| **Lappegård & Nordmo, 2011** [10] | Case report/letter; IST | Early first trimester before pregnancy recognition | 5 mg twice daily | Improvement in tachycardia; nightmares led to discontinuation | Pregnancy subsequently electively terminated; fetal safety could not be assessed | Report focused on adverse dreams, not reproductive outcome |
| **Sağ et al., 2016** [11] | Case report; severe IST with tachycardia-induced cardiomyopathy | Treatment introduced during second trimester after presentation at 17 weeks | 5 mg twice daily | HR decreased to ~90 bpm; LVEF improved from 30% to 50%; mitral regurgitation improved | Serial fetal HR remained approximately 148–156 bpm; healthy male infant | Single patient; extensive preceding/concomitant therapy |
| **Hoeltzenbein et al., 2021** [8] | Prospective German Embryotox cohort; predominantly supraventricular tachycardia | 37/38 exposed in first trimester; five continued for prolonged periods | Median daily dose reported as 7.5 mg; heterogeneous dosing | Most discontinued after pregnancy recognition without cardiac deterioration | 32 live-birth pregnancies, 3 spontaneous abortions, 3 elective terminations; one infant with major anomalies | Small observational cohort; heterogeneous exposure and maternal disease; insufficient power for rare outcomes |

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| Source | Design / indication | Gestational exposure | Dose | Maternal outcome | Fetal/neonatal outcome | Principal limitation |
|---|---|---|---|---|---|---|
| **Hoeltzenbein et al., 2021, retrospective reports** [8] | Three retrospectively reported exposed pregnancies | Variable, including first-trimester and prolonged exposure | Incompletely reported | Limited information | Included one perinatal death with tracheal atresia, one growth-restricted preterm infant, and one healthy term infant | Strong reporting bias, confounding and incomplete dose information |
| **Tonko et al., 2021** [12] | Case report; incessant focal atrial tachycardia with deteriorating LV function | Late second/early third trimester | 5 mg twice daily, increased to 7.5 mg twice daily | Rapid ventricular-rate control; LVEF improved from 46% to 55% | Serial fetal assessments normal; healthy 3900-g male infant delivered at term | Late gestational exposure; single case; concomitant beta-blockade and maternal comorbidity |
| **Kahlon et al., 2026** [13] | Case report; long-COVID-associated POTS | Preconception through entire pregnancy | Dose not stated in indexed report | Therapy continued under multidisciplinary supervision with reassuring maternal outcome | Normal growth, Dopplers and NSTs; no fetal bradycardia, arrhythmia or structural abnormality; healthy female infant at 38+5 weeks | Single favorable case; concomitant pharmacological therapy; long-term offspring outcome unavailable |

Data summarized from primary reports.

## Ivabradine for Inappropriate Sinus Tachycardia and Tachycardia-Induced Cardiomyopathy

The case reported by Sağ et al. is among the most clinically informative examples of therapeutic ivabradine use during pregnancy. A 32-year-old woman presented during the second trimester with symptomatic IST and severe left ventricular dysfunction. Despite substantial conventional therapy, including beta-blockade, verapamil and digoxin, the maternal heart rate remained approximately 120 beats/min. Following introduction of ivabradine, heart rate fell to approximately 90 beats/min. Left ventricular ejection fraction subsequently improved from approximately 30% to 50%, consistent with reversal of tachycardia-mediated myocardial dysfunction. [11]

Fetal monitoring in that case is notable because the reported fetal heart rate was 156 beats/min before ivabradine, 150 beats/min after the first day of therapy, and 148 beats/min after one week. No clinically significant fetal bradycardia was reported. The pregnancy ultimately resulted in a healthy male infant.

The observation is mechanistically important but should not be generalized. A single dramatic therapeutic response cannot quantify fetal risk, and spontaneous improvement of cardiomyopathy, effects of concomitant treatment, and changes in hemodynamics may all contribute to recovery. Nevertheless, it demonstrates a clinical scenario in which uncontrolled maternal tachycardia itself may represent a substantial maternal-fetal risk.

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**Focal Atrial Tachycardia During Pregnancy**

Tonko et al. described a 38-year-old pregnant woman with a history of peripartum cardiomyopathy who developed incessant atrial tachycardia and deterioration in ventricular function. The rhythm was resistant to beta-blockade. Ivabradine produced a rapid rate-control response, and escalation from 5 mg twice daily to 7.5 mg twice daily was associated with improvement of left ventricular ejection fraction from approximately 46% to 55%. [12]

Fetal ultrasound examinations later in pregnancy were reassuring, and a healthy male infant weighing 3900 g was delivered at term. Because exposure began relatively late, this report is more informative regarding late gestational tolerability than first-trimester structural teratogenic risk. It nevertheless supports the concept that *I*f inhibition may be therapeutically useful in selected automatic tachyarrhythmias when conventional treatment is inadequate.

**POTS and Continuous Pregnancy Exposure**

The 2026 case report by Kahlon et al. adds an important type of exposure not well represented in earlier literature. A 35-year-old gravida 2 para 1 woman with long-COVID-associated POTS continued ivabradine and her other pharmacological treatments from before conception through delivery. Serial fetal growth assessments, Doppler examinations, and non-stress tests remained reassuring, with no reported fetal bradycardia, arrhythmia, or structural anomaly. A healthy female infant was delivered at 38 weeks and 5 days. [13]

The case is clinically valuable because exposure covered all major developmental stages, including organogenesis. However, one normal pregnancy following prolonged exposure cannot materially narrow confidence intervals around rare congenital outcomes. It should therefore be interpreted as evidence that a favorable pregnancy is possible during ivabradine exposure, rather than evidence that ivabradine is reproductively safe.

This distinction is critical in teratology. Case reports can disprove the assumption that exposure inevitably causes fetal injury, but they cannot establish absence of a moderate increase in risk.

**Assessment of Fetal and Neonatal Risk**

The human dataset currently does not show a reproducible pattern analogous to the cardiac and limb abnormalities observed in experimental animals. In the prospective Embryotox cohort, only one neonate was reported with major congenital abnormalities, and clinically important confounders were present. Nevertheless, the sample size is insufficient for exclusion of organ-specific teratogenic risks.

Assessment of spontaneous abortion is similarly difficult. Three spontaneous abortions among 38 prospectively followed pregnancies cannot be interpreted in isolation because miscarriage is common in clinically recognized pregnancy, and meaningful risk estimation requires an appropriately matched unexposed comparison group and adjustment for maternal characteristics.

Late-pregnancy safety requires separate consideration. Theoretical effects include fetal or neonatal heart-rate reduction, altered placental perfusion secondary to maternal hemodynamic changes, fetal growth effects, and neonatal adaptation. Published cases have not demonstrated a consistent fetal bradycardic response, but the number of exposed fetuses with detailed serial heart-rate measurements is extremely small.

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Long-term follow-up represents an even larger evidence gap. Current literature provides virtually no robust information regarding later cardiovascular electrophysiology, growth, neurodevelopment, exercise tolerance, or metabolic health in children exposed to ivabradine in utero.

Maternal benefit is most plausible when excessive sinus or automatic atrial rate contributes directly to symptoms, ventricular dysfunction, or inability to maintain adequate cardiovascular function. Unlike beta-blockers, ivabradine can reduce sinus rate with relatively limited direct reduction in contractility and often less blood-pressure lowering. This pharmacodynamic distinction may be relevant in pregnant women who are hypotensive or who cannot tolerate sufficient beta-blocker dosing.

Potential maternal adverse effects remain relevant. Excessive sinus slowing may lead to symptomatic bradycardia, dizziness, fatigue or syncope. Ivabradine is also associated with an increased incidence of atrial fibrillation in non-pregnant cardiovascular populations. In pregnancy, these effects must be interpreted against changing preload, systemic vascular resistance, autonomic tone, and cardiac output requirements.

A crucial clinical principle is that fetal drug avoidance cannot be evaluated independently of maternal disease severity. Persistent maternal tachyarrhythmia with ventricular deterioration, heart failure, syncope or hemodynamic instability may itself compromise uteroplacental perfusion and pregnancy outcome. Thus, in rare cases the comparison is not between ivabradine exposure and a completely risk-free pregnancy, but between uncertain pharmacological risk and significant untreated maternal cardiovascular disease.

For most maternal tachyarrhythmias, ivabradine should not be considered a first-line substitute for treatments with a larger pregnancy safety experience. Therapeutic selection depends on the precise rhythm diagnosis. Beta-blockers, selected calcium-channel blockers, adenosine, digoxin, antiarrhythmic drugs, and catheter-based interventions may have specific roles depending on the arrhythmia and maternal clinical state.

Beta-blockers have far greater pregnancy experience than ivabradine but are not free of fetal concerns. Maternal hypotension, fetal growth effects and neonatal beta-blockade must be considered for certain agents and exposure patterns. The existence of risks with conventional treatments does not in itself justify use of ivabradine; rather, it reinforces the need for individualized selection based on maternal disease, gestational age and available alternatives.

For IST specifically, non-pregnant controlled data suggest that ivabradine may provide more effective symptom relief in some patients who respond poorly to metoprolol. However, efficacy evidence from non-pregnant adults cannot replace pregnancy-specific reproductive safety evidence. [5]

The 2025 ESC Guidelines for the management of cardiovascular disease and pregnancy represent the most current major European framework. Ivabradine is included among cardiovascular drugs that are not recommended during pregnancy because of adverse fetal concerns; this recommendation is categorized as Class III, Level C in the guideline context. [14]

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European regulatory information similarly states that ivabradine must not be used during pregnancy and emphasizes the requirement for appropriate contraception in women of childbearing potential receiving treatment.

The evidence level is important. The recommendation is not based on randomized evidence demonstrating fetal harm in humans. Rather, it reflects a precautionary assessment integrating reproductive animal toxicity, limited human exposure experience, and availability of better-characterized alternatives for many cardiovascular indications.

This distinction should be communicated clearly in both scientific interpretation and patient counselling.

Accidental first-trimester exposure is clinically different from a decision to initiate ivabradine deliberately during pregnancy. Recognition of exposure should prompt documentation of dose, exposure dates, gestational age, indication, concomitant medication, maternal cardiac status and the feasibility of alternative therapy.

Available human evidence does not support the conclusion that inadvertent ivabradine exposure inevitably produces congenital malformations. The German Embryotox experience is particularly relevant because most prospectively observed women discontinued ivabradine after pregnancy recognition and subsequently continued pregnancy without deterioration in maternal cardiac status.

A reasonable clinical approach is multidisciplinary reassessment involving cardiology and obstetric expertise, preferably through a Pregnancy Heart Team when significant cardiovascular disease is present. Detailed fetal anatomical assessment and appropriate surveillance of fetal growth may be considered according to exposure timing and the maternal clinical context. The need for fetal echocardiography should be individualized, particularly after first-trimester exposure, because preclinical reproductive toxicity included cardiovascular abnormalities.

Importantly, the currently available evidence does not justify treating isolated ivabradine exposure as an automatic indication for pregnancy termination.

**Critical Interpretation of the Evidence**

The human evidence is simultaneously reassuring and inadequate.

It is reassuring because prospectively collected pregnancy outcomes have not revealed a strong recurring malformation pattern, several women have delivered apparently healthy infants after clinically substantial exposure, and prolonged exposure has now been documented with normal fetal monitoring and a healthy neonatal outcome.

It is inadequate because the number of systematically followed pregnancies remains very small. A dataset of several dozen pregnancies cannot exclude a twofold or even greater increase in a rare specific abnormality. Exposure is heterogeneous with respect to dose, treatment duration, gestational period, cardiovascular indication and concomitant medication. Patients receiving ivabradine also frequently have underlying cardiovascular or autonomic disease that may independently influence pregnancy outcome.

Case-report publication bias is another major problem. Successful treatment of severe maternal tachycardia is clinically interesting and therefore publishable. Uncomplicated incidental exposure may never reach the scientific literature, while adverse pregnancy outcomes may be preferentially reported to pharmacovigilance systems. These mechanisms can operate in opposite directions and make crude counting of published cases misleading.

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Confounding by indication is especially important. For example, fetal growth restriction or preterm birth in a woman with significant maternal cardiovascular disease cannot automatically be attributed to medication. Conversely, a healthy infant after maternal cardiovascular stabilization does not prove that the drug was harmless, because an adverse drug effect may simply not have occurred in that individual pregnancy.

Thus, the appropriate scientific conclusion is neither that ivabradine is a proven human teratogen nor that available reports establish safety.

Ivabradine illustrates a broader problem in pharmacotherapy during pregnancy: therapeutic selectivity in adults does not necessarily translate into developmental selectivity in the fetus. The drug's targeted inhibition of HCN-mediated pacemaker current is pharmacologically attractive because it can reduce maternal heart rate without the same direct negative inotropic profile as some alternatives. At the same time, ion channels and electrophysiological pathways may have developmental roles that differ across fetal tissues and stages of gestation.

The gestational timing of exposure therefore matters. First-trimester exposure raises the greatest concern regarding structural organogenesis. In contrast, later exposure may be more relevant to fetal growth, electrophysiology, placental function, neonatal heart rate and physiological adaptation after birth. The available literature is too small to provide gestational-age-specific quantitative risk estimates.

Dose also requires greater attention. Pregnancy case reports frequently emphasize clinical outcomes while providing incomplete pharmacokinetic information. Future pharmacovigilance studies should systematically capture daily dose, treatment interruptions, maternal heart rate, maternal drug interactions, renal and hepatic function, and gestational timing.

The most important next step is development of larger prospective pregnancy registries that distinguish planned treatment from inadvertent exposure. Standardized data collection should document the maternal indication, dose, treatment period, relevant cardiovascular severity markers, concomitant medications, fetal anatomy, fetal growth, gestational age at birth, neonatal heart rate, neonatal adaptation and longer-term childhood outcomes.

International collaboration is essential because deliberate use during pregnancy is likely to remain uncommon. A multicenter registry would allow substantially greater statistical power than isolated case series and would permit comparison with disease-matched women treated with alternative agents.

Pharmacokinetic investigation is also needed. Pregnancy-related changes in plasma volume, protein binding, hepatic metabolism and renal function may alter systemic ivabradine exposure. Direct information on transplacental transfer in humans is limited, and the relationship between maternal concentration and fetal electrophysiological exposure remains poorly characterized.

Future studies should also evaluate whether specific clinical phenotypes, such as severe drug-refractory IST with tachycardia-induced cardiomyopathy, represent situations in which maternal benefit may outweigh uncertain fetal risk.

**Conclusion**

Ivabradine is a pharmacologically distinctive heart-rate-lowering drug whose selective inhibition of the sinoatrial *If* current can provide substantial clinical benefit in

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selected cardiovascular disorders. Pregnancy, however, presents a difficult benefit-risk environment because preclinical reproductive studies demonstrated embryo-fetal toxicity and teratogenicity, while human pregnancy data remain sparse.

The German Embryotox cohort and published clinical cases do not reveal a consistent strong human teratogenic signal. Successful pregnancy outcomes have been documented following first-trimester, later gestational, and even continuous preconception-to-delivery exposure. These findings are clinically reassuring but are not sufficient to establish safety.

Accordingly, routine ivabradine therapy during pregnancy cannot currently be recommended. Established alternatives with greater pregnancy experience should generally be preferred when clinically appropriate, consistent with current European guidance. Nevertheless, rare maternal conditions characterized by severe, treatment-refractory tachycardia or tachycardia-mediated ventricular dysfunction may require individualized risk-benefit assessment.

Inadvertent exposure should be approached through evidence-based counselling rather than assumptions of inevitable fetal injury. When ivabradine use is considered unavoidable because of serious maternal cardiovascular disease, management should involve multidisciplinary cardio-obstetric expertise, careful maternal monitoring and appropriate fetal surveillance. Larger prospective pharmacovigilance studies are required before the reproductive safety profile of ivabradine can be defined with clinically meaningful precision.

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