

Editorial

Brugada Syndrome and Pregnancy: Delving Into the Role of Sex Hormones in Ion Channelopathies



Síndrome de Brugada y embarazo: indagando en el papel de las hormonas sexuales en las canalopatías iónicas

Begoña Benito^{a,*} and Antonio Berruezo^b^a Unidad de Arritmias, Servicio de Cardiología, Hospital del Mar, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Parc de Salut Mar, Barcelona, Spain^b Unidad de Arritmias, Servicio de Cardiología, Hospital Clínic, Universidad de Barcelona, Barcelona, Spain

Article history:

Available online 5 February 2014

Since its initial description in 1992 as a clinical syndrome involving a specific electrocardiogram (ECG) pattern and an increased susceptibility for ventricular arrhythmias and sudden cardiac death (SCD), the Brugada syndrome (BrS) has prompted much research activity aimed at defining the clinical, genetic, and molecular aspects of the disease.¹ Major advances in genetics have allowed the identification of mutations linked to the syndrome in more than 10 different genes thus far.² Recognized mutations disturb the expression and/or function of different cardiac ion channels that participate in the cardiac action potential, so the syndrome is now included among the so-called channelopathies. The common functional consequence of these mutations, confirmed by experimental models, is thought to be a heterogeneous imbalance between positive outward and inward currents during early phases of repolarization, which can explain both the ST-segment elevation in the ECG and the susceptibility to ventricular arrhythmias through a phase-2 reentry mechanism.³ However, important questions concerning the mechanisms and/or clinical manifestations of the BrS remain unanswered. For example, only around 20% to 30% of patients have a positive genetic test,² indicating that the disease-causing mutation or mechanism remains unknown for most of them. Also intriguing is the broad phenotypic expression of the syndrome even for a given mutation, which may range from the absence of symptoms or ECG manifestation to the occurrence of SCD at an early age. This latter observation supports the concept that particularities in intrinsic susceptibility and/or the effect of certain modulators (genetic, molecular, or external) might play a role in the final phenotype of patients with BrS.

In line with this last concept, the difference in clinical expression between men and women with BrS is a well-established observation for which there is no full mechanistic understanding yet. All the main series of BrS concur in reporting a higher symptom and event rate among men than among women with the syndrome.^{4,5} The ECG expression is also more pronounced

in men with BrS, who have a higher percentage of spontaneous type-1 ECG pattern and greater ST-segment elevation than women.⁴ Excluding the potential effect of specific mutations, the distinct sex-related phenotype might be explained, at least in part, by constitutional differences in cardiac ion channel expression. In arterially perfused canine preparations, transient outward potassium (I_{to}) current density of right ventricular epicardium, and time constant for inactivation are significantly larger in male than in female samples.⁶ This induces greater transmural and epicardial dispersion of repolarization in males, which facilitates the development of the Brugada-like ECG pattern and ventricular fibrillation.⁶ In the same canine model, sodium current (I_{Na}) amplitude is smaller in female samples, conferring a relative protection against hereditary sodium loss-of-function arrhythmias such as in the BrS.⁷ Similarly, constitutional differences in repolarizing currents, confirmed by numerous animal studies with females showing greater calcium current (I_{CaL}) and reduced potassium currents (I_{Kr} , I_{Ks} , I_{Kl}), provide an explanation for the longer QT intervals and greater susceptibility for long QT-related arrhythmias reported in women as compared to men.⁸

Other factors might be involved in the gender-related differential clinical expression of ion channelopathies. The potential for a cardiac regulation by sex hormones has classically been advocated because the main gonadal steroids (androgen, estrogen, and progesterone) receptors can be found in the cardiac muscle and in isolated cardiac myocytes. Specifically, steroid hormone-responsive elements, particularly sensitive to testosterone, have been identified in genes such as *CACNA1C* (which encodes the L-type calcium channel) and *SCN5A* (which encodes the cardiac sodium channel), among others.⁸ Notably, investigation in this field has been mostly concentrated on the effects of sex hormones on duration of action potential and cardiac repolarization, providing significant insights into the differences in QT interval and susceptibility to QT-related arrhythmias between men and women, with androgens providing a protective effect mostly by an increase in repolarizing currents (I_{Kur} , I_{Kr} , I_{Kl}).^{8,9} Less is known about the effects of hormonal influence in early phases of myocardial repolarization, with potential interest for disorders such as BrS or early repolarization syndromes. A recent population study with healthy subjects shows that J-point and ST-segment elevation are greater in men than in women only after puberty.¹⁰

SEE RELATED ARTICLE:

<http://dx.doi.org/10.1016/j.rec.2013.06.023>, Rev Esp Cardiol. 2014;67:176–80.

* Corresponding author: Unidad de Arritmias, Servicio de Cardiología, Hospital del Mar, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Pg Marítim 25-29, 08003 Barcelona, Spain.

E-mail address: bbenito@hospitaldelmar.cat (B. Benito).

The inter-sex differences are no longer evident when comparing women and men under androgen-deprivation therapy for treatment of prostate cancer.¹⁰ These findings strongly support a role of testosterone in modulating early phases of ventricular repolarization. Consistent with this hypothesis, Matsuo et al described regression of the characteristic type-1 ECG pattern in 2 patients with BrS after surgical castration for prostate cancer.¹¹ A more recent case has been reported in which diurnal ECG changes of a patient with BrS were associated with the circadian variation of circulating testosterone, with greatest ST-segment elevation and highest levels of testosterone at nighttime (especially around 2:00 AM).¹² The effects of androgens on early phases of repolarization could be explained by their potential to increase net outward currents (mainly potassium), accentuate transmural and epicardial dispersion of repolarization, and potentially cause loss of the epicardial dome of the action potential, leading to ST-segment elevation and theoretically facilitating arrhythmia susceptibility. Of note, probably favored by the evident male predominance in all BrS populations, most investigations thus far have addressed the effects of testosterone, whereas the role of estrogens on early phases of repolarization has been scarcely described. Estrogens have been reported to downregulate Kv4.3 channel expression, an important component of I_{to} current, in other tissues such as the uterus myometrium,¹³ indicating their potential to reduce transmural and epicardial dispersion of repolarization and ST-segment elevation in the heart. However, the final clinical consequences of female sex-hormone modulation in patients with BrS remain largely unknown.

In their article published in *Revista Española de Cardiología*, Rodríguez-Mañero et al, from the group of Pedro Brugada, provide new data in this regard by describing the clinical manifestations of BrS during pregnancy, a particular setting under relevant hormonal influence.¹⁴ Pregnancy induces well-described autonomic and hemodynamic changes, and a gradual and profound increase of estrogens and progesterone blood levels, with a marked drop of both hormones at the peripartum period. Previous information on the matter is anecdotal. Two independent cases of women with BrS have been reported in which pregnancy was complicated by electrical storm.^{15,16} The first occurred in a patient who electively discontinued chronic amiodarone therapy and required extracorporeal membrane oxygenation for stabilization, reinitiation of antiarrhythmic therapy, and emergent delivery of the neonate.¹⁵ The second was the case of a 22-year-old woman, 12 weeks pregnant and previously healthy, who presented with recurrent polymorphic ventricular tachycardia as the first manifestation of the BrS, and responded to intravenous isoproterenol and subsequent quinidine.¹⁶ Based upon our limited understanding thus far, as previously discussed, it would seem that pregnancy and female hormone rise should not carry a particularly high risk in women with BrS. Therefore, the case reports' authors speculated on the elevated testosterone levels secondary to estrogen-induced increase in sex hormone-binding globulin during pregnancy to explain their findings.^{15,16}

In contrast to the previous available information, Rodríguez-Mañero et al describe the clinical course of 104 women with BrS and a total of 219 pregnancies.¹⁴ The study, including one of the largest series of women with the syndrome, is certainly more likely to describe a more realistic picture of pregnancy outcomes in the BrS population. However, before drawing any conclusions, it is worth mentioning certain important limitations of the work. First, patients were retrieved from the global BrS database and included in the study on the basis of history of previous deliveries. This introduces a significant patient selection bias. Since the BrS was diagnosed in almost all patients after the pregnancy years (mean age at diagnosis 43.3 years, mean age at first pregnancy 24.9 years), those patients who could have had serious events during pregnancy (such as SCD)

before the diagnosis of BrS was made were presumably missed and not included in the present analysis. Additionally, data on pregnancy course were collected by interview retrospectively, with the potential for missing or forgotten information when recalling events, in some instances many years after the pregnancy.

With these important limitations in mind, the study still shows a relatively benign course of pregnancy among women with BrS. Among the 104 women experiencing 219 pregnancies, 6 presented syncope (a total of 11 syncopal episodes), 2 had unspecific palpitations, and none had serious events such as ventricular fibrillation or SCD.¹⁴ There were no major events in the peripartum period. Of note, the incidence of syncope (5.7%) or palpitations (2%) described in the present BrS series does not differ from the actual rate described for normal pregnancies. However, the presence of syncope, a potential manifestation of ventricular arrhythmias, should always warrant further attention in patients with BrS. Close inspection of the results published by Rodríguez-Mañero et al indicates that a history of syncope during pregnancy did not provide any significant additional diagnostic or prognostic value in their series. All 6 patients with syncope during pregnancy also had syncopal episodes outside the setting of pregnancy, so the presence of symptoms during pregnancy by itself did not improve the diagnostic yield of the syndrome. However, it must be noted that in 3 patients the first syncopal episode occurred during pregnancy. The characteristics of such syncopal episodes are not available, so it is difficult to ascertain whether these could have propelled a specific cardiac investigation leading to an earlier diagnosis of the syndrome.

The presence of syncope during pregnancy did not seem to be related to worse outcome. All 6 patients with syncope during pregnancy had recurrent episodes after the delivery, and 4 of them received an implantable cardioverter defibrillator after complete risk stratification. None had major events during follow-up.¹⁴ Although the results do not show a prognostic implication, caution should be taken when drawing conclusions from a population with a small number of events. In fact, the low event rate reported for women with BrS has classically defied the identification of risk markers in this population.⁴ Consistently with previous data, Rodríguez-Mañero et al report that only 2 of the 104 patients in their series received an appropriate implantable cardioverter defibrillator shock during a mean follow-up of 298 days, with no other major events.¹⁴ However, because BrS is a genetic condition and thus presumably present since birth, not only follow-up events but all major events during a patient's lifetime should be taken into consideration when assessing prognosis, including those that occurred prior to diagnosis. This notion is particularly pertinent in this series, since the diagnosis of BrS was mostly made many years after pregnancy. Four patients presented with SCD as the first symptom of the disease. One of them is also one of the patients who subsequently had an appropriate implantable cardioverter defibrillator shock during follow-up. This yields a total of 5 patients with major events in their lifetimes: SCD prior to diagnosis ($n = 3$), implantable cardioverter defibrillator shock in follow-up ($n = 1$), or both ($n = 1$). Importantly, all 5 patients had an uneventful pregnancy course.

Rodríguez-Mañero et al also provide some data on the pre-natal and post-natal course of infants from mothers with BrS, and who are thus potential carriers of the syndrome. This information is of potential relevance because ion channelopathies may underlie a non-negligible percentage of stillbirths and sudden infant deaths.¹⁷ Given the retrospective nature of the study, however, the authors give only a succinct description of events, including a total of 15 miscarriages among the 234 pregnancies and 1 sudden infant death at age 3 months among the 219 live-birth deliveries.¹⁴ The number of miscarriages is not particularly different from those expected in the general population, whereas the single episode of sudden infant death does not allow any definitive conclusion.

Without further data and with no genetic information available to confirm how many of these events occurred in affected babies, these results should be understood as merely observational. However, they do suggest that pre-natal death, at least, seems to be within the expected range for ordinary pregnancies.

In conclusion, the data by Rodríguez-Mañero et al suggest that pregnancy and the peripartum period can probably be negotiated safely in patients with BrS. These results seem to be in line with our current although limited understanding of the modulating role of sex hormones in ion channelopathies, where a female-hormone rise would not be expected to particularly increase the arrhythmic risk in an early repolarization disorder such as BrS. Of course, pregnancy induces important changes other than hormonal, including sympathetic activation and independent sinus tachycardia, which could potentially exert a protective role in patients with BrS, whose phenotype is known to be under autonomic and chronotropic regulation.¹⁸ Importantly, although consistent with these hypotheses, the results by Rodríguez-Mañero et al must be put into perspective along with the limitations of their work. In fact, some of the findings, especially because of the incomplete data due to the retrospective nature of the study, open up the possibility to other interpretations. Rodríguez-Mañero et al report a relatively low rate of symptomatic patients (5.7%), and within the expected range reported for normal pregnancies. However, given that women with BrS are usually asymptomatic throughout their lifetime, and taking into account that pregnancy lasts only 9 months, the event rate could be higher if not all syncopal events were characteristically neuromediated. Because of this and the other important study limitations discussed earlier, especially those concerning the patient selection bias, a prospective validation of the results by Rodríguez-Mañero et al is warranted before drawing any definite conclusions. Such validation should ideally recruit a cohort of BrS women, including probands and all those identified during family screening, and prospectively collect detailed information on symptoms (including exhaustive data on the characteristics and number of syncopal episodes) and potential ECG fluctuations during the pregnancy and the postpartum periods. In the meantime, the study by Rodríguez-Mañero et al provides initial data suggesting an overall benign pregnancy course and peripartum period in women with BrS. This is an important message to transmit to our patients of childbearing age.

CONFLICTS OF INTEREST

None declared.

REFERENCES

- Benito B, Brugada J, Brugada R, Brugada P. Síndrome de Brugada. *Rev Esp Cardiol*. 2009;62:1297–315.
- Crotti L, Marcou CA, Tester DJ, Castelletti S, Giudicessi JR, Torchio M, et al. Spectrum and prevalence of mutations involving BrS1– through BrS12–susceptibility genes in a cohort of unrelated patients referred for Brugada syndrome genetic testing: implications for genetic testing. *J Am Coll Cardiol*. 2012;60:1410–8.
- Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation*. 1999;100:1660–6.
- Benito B, Sarkozy A, Mont L, Henkens S, Berrueto A, Tamborero D, et al. Gender differences in clinical manifestations of Brugada syndrome. *J Am Coll Cardiol*. 2008;52:1567–73.
- Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. *Circulation*. 2010;121:635–43.
- Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Pérez GJ, et al. Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. *Circulation*. 2002;106:2004–11.
- Barajas-Martinez H, Haufe V, Chamberland C, Roy MJ, Fecteau MH, Cordeiro JM, et al. Larger dispersion of INa in female dog ventricle as a mechanism for gender-specific incidence of cardiac arrhythmias. *Cardiovasc Res*. 2009;81:82–9.
- James AF, Choisy SpCM, Hancox JC. Recent advances in understanding sex differences in cardiac repolarization. *Prog Biophys Mol Biol*. 2007;94:265–319.
- Pham TV, Sosunov EA, Gainullin RZ, Danilo Jr P, Rosen MR. Impact of sex and gonadal steroids on prolongation of ventricular repolarization and arrhythmias induced by I(K)-blocking drugs. *Circulation*. 2001;103:2207–12.
- Ezaki K, Nakagawa M, Taniguchi Y, Nagano Y, Teshima Y, Yufu K, et al. Gender differences in the ST segment: effect of androgen-deprivation therapy and possible role of testosterone. *Circ J*. 2010;74:2448–54.
- Matsuo K, Akahoshi M, Seto S, Yan K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. *Pacing Clin Electrophysiol*. 2003;26:1551–3.
- Yamaki M, Sato N, Okada M, Fujita S, Go K, Sakamoto N, et al. A case of Brugada syndrome in which diurnal ECG changes were associated with circadian rhythms of sex hormones. *Int Heart J*. 2009;50:669–76.
- Song M, Helguera G, Eghbali M, Zhu N, Zarei MM, Olcese R, et al. Remodeling of Kv4.3 potassium channel gene expression under the control of sex hormones. *J Biol Chem*. 2001;276:31883–90.
- Rodríguez-Mañero M, Casado-Arroyo R, Sarkozy A, Leysen E, Sieira JA, Namdar M, et al. The Clinical Significance of Pregnancy in Brugada Syndrome. *Rev Esp Cardiol*. 2014;67:176–80.
- Page PS, Lilly RE, Nicolosi AC. Use of ECMO to temporize circulatory instability during severe Brugada electrical storm. *Ann Thorac Surg*. 2009;88:982–3.
- Sharif-Kazemi MB, Emkanjoo Z, Tavooosi A, Kafi M, Kheirkhah J, Alizadeh A, et al. Electrical storm in Brugada syndrome during pregnancy. *Pacing Clin Electrophysiol*. 2011;34:e18–21.
- Van Norstrand DW, Ackerman MJ. Sudden infant death syndrome: Do ion channels play a role? *Heart Rhythm*. 2009;6:272–8.
- Mizumaki K, Fujiki A, Tsuneda T, Sakabe M, Nishida K, Sugao M, et al. Vagal activity modulates spontaneous augmentation of ST elevation in the daily life of patients with Brugada syndrome. *J Cardiovasc Electrophysiol*. 2004;15:667–73.