LONG QT SYNDROME AND PREGNANCY

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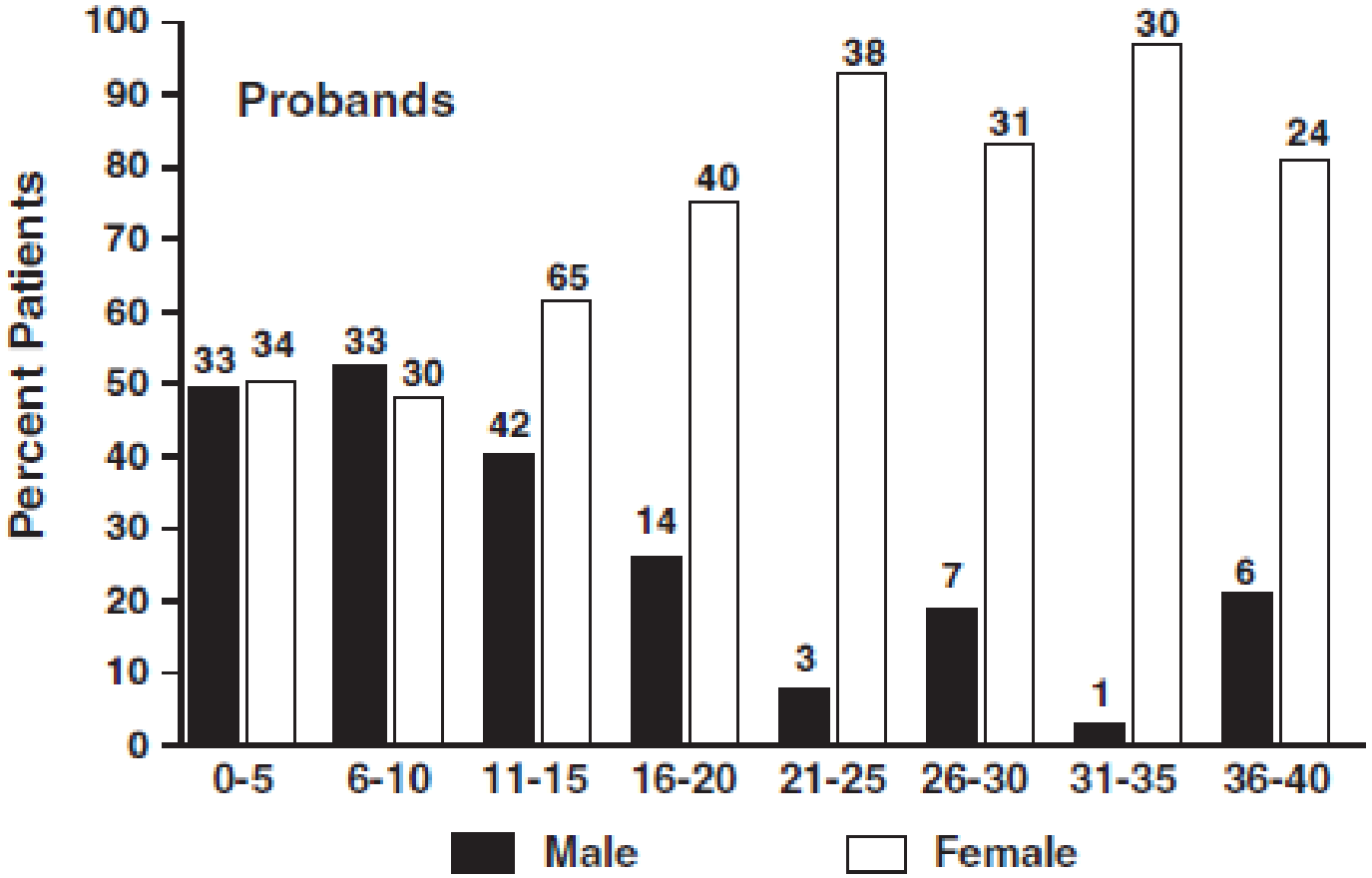
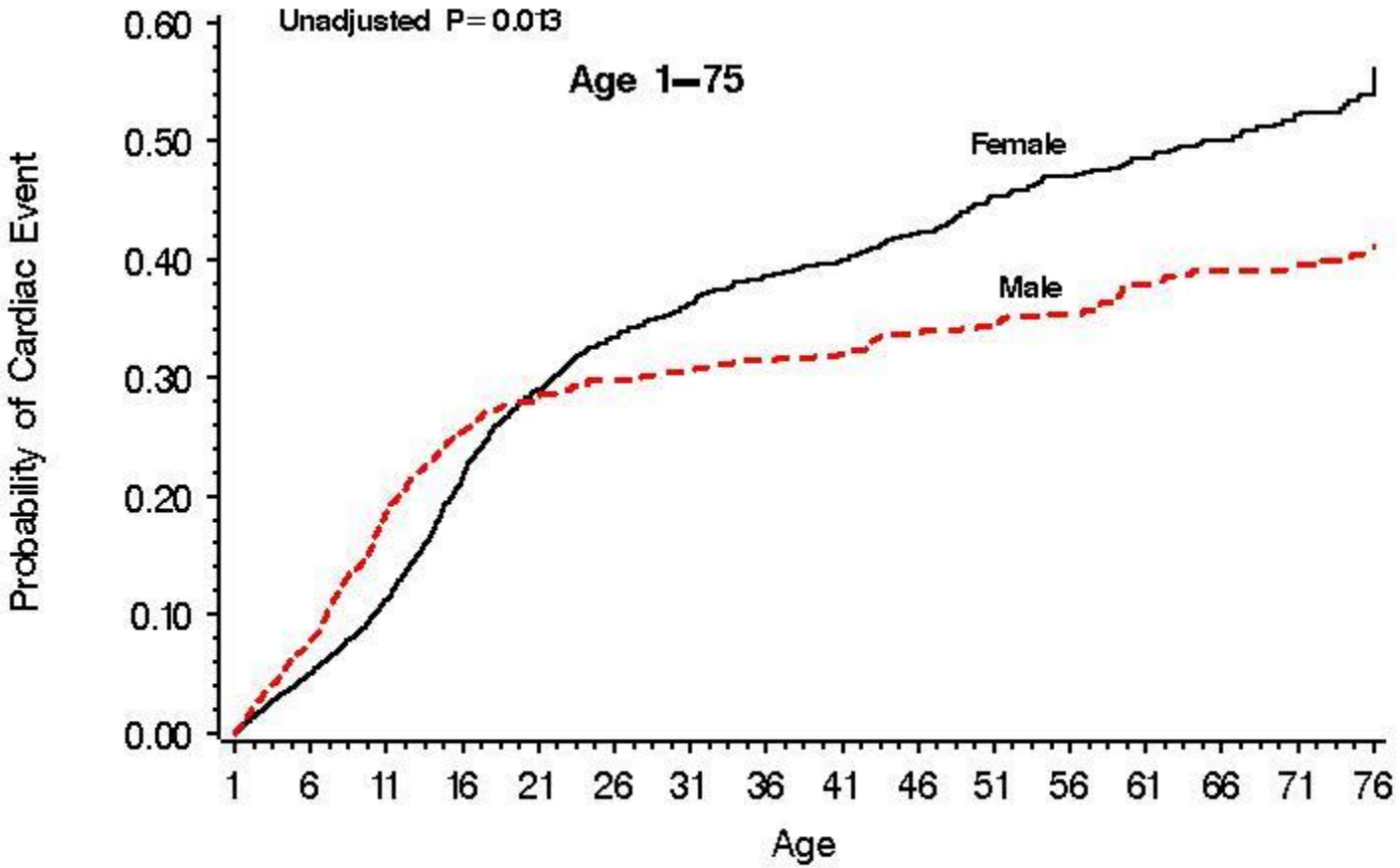
Sex-Specific Risk in Congenital LQTS


Probands
Percent Patients
100
90
80
70
60
50
40
30
20
10
0
33
34
33
30
42
65
14
40
3
38
7
31
1
30
6
24
0-5
6-10
11-15
16-20
21-25
26-30
31-35
36-40
Male
Female

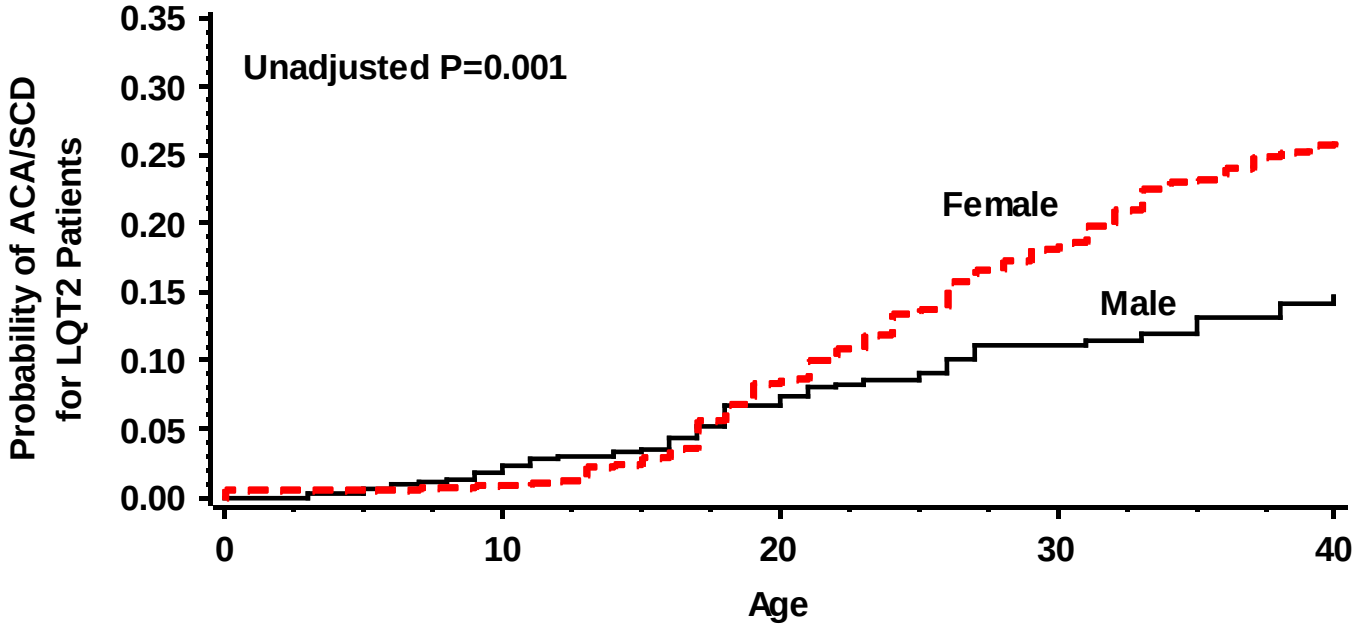
Clinical Course: Cardiac Events by Sex



PATIENTS AT RISK

Female	2319	1506 (0.22)	919 (0.36)	587 (0.42)	305 (0.48)	87 (0.56)
Male	1450	786 (0.26)	530 (0.31)	383 (0.34)	222 (0.38)	73 (0.41)

Cumulative Probability of a First ACA or SCD in LQT2 Patients by Sex

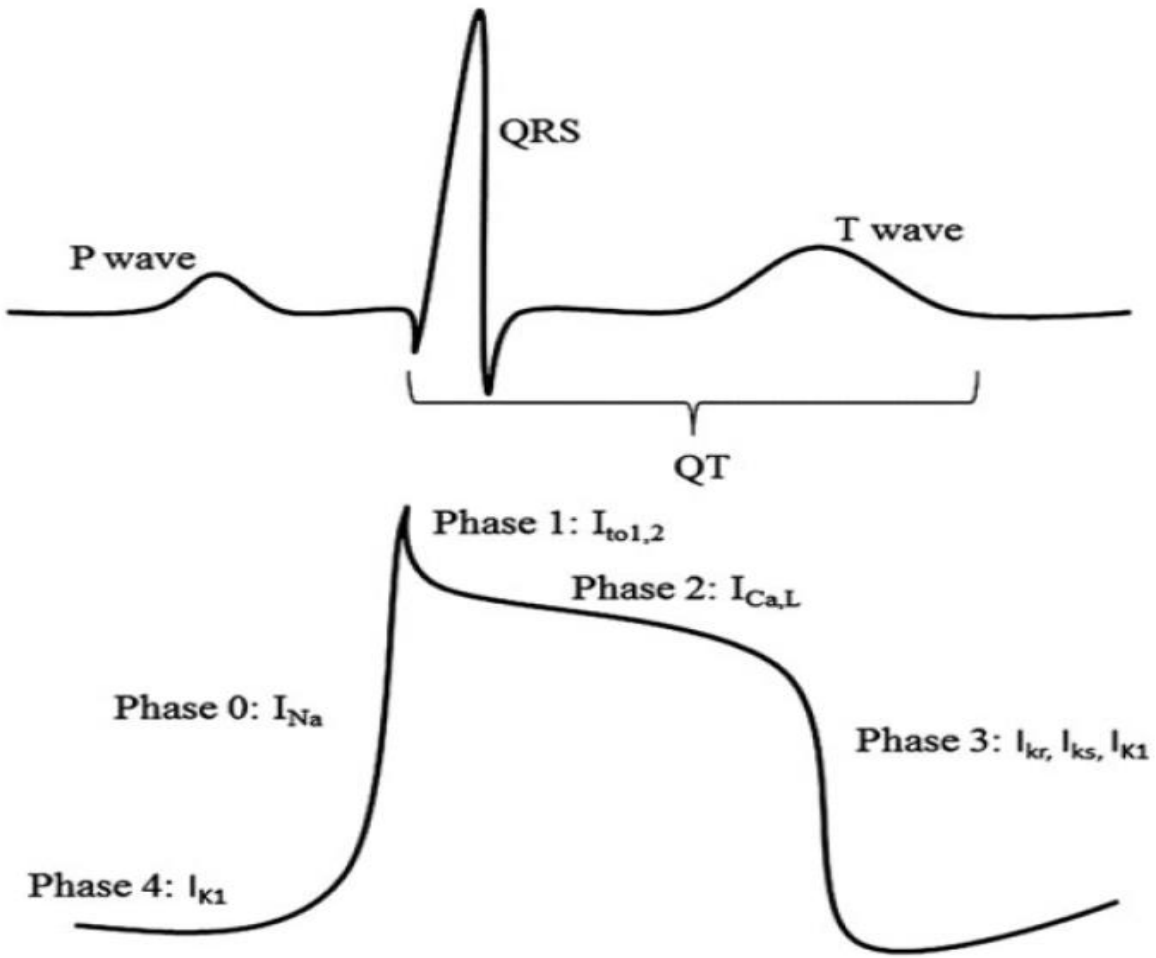


Patients at Risk					
Male	490	411 (0.02)	300 (0.07)	235 (0.11)	171 (0.14)
Female	676	613 (0.01)	488 (0.08)	366 (0.18)	245 (0.26)

Migdalovich and Goldenberg, Heart Rhythm, 2011

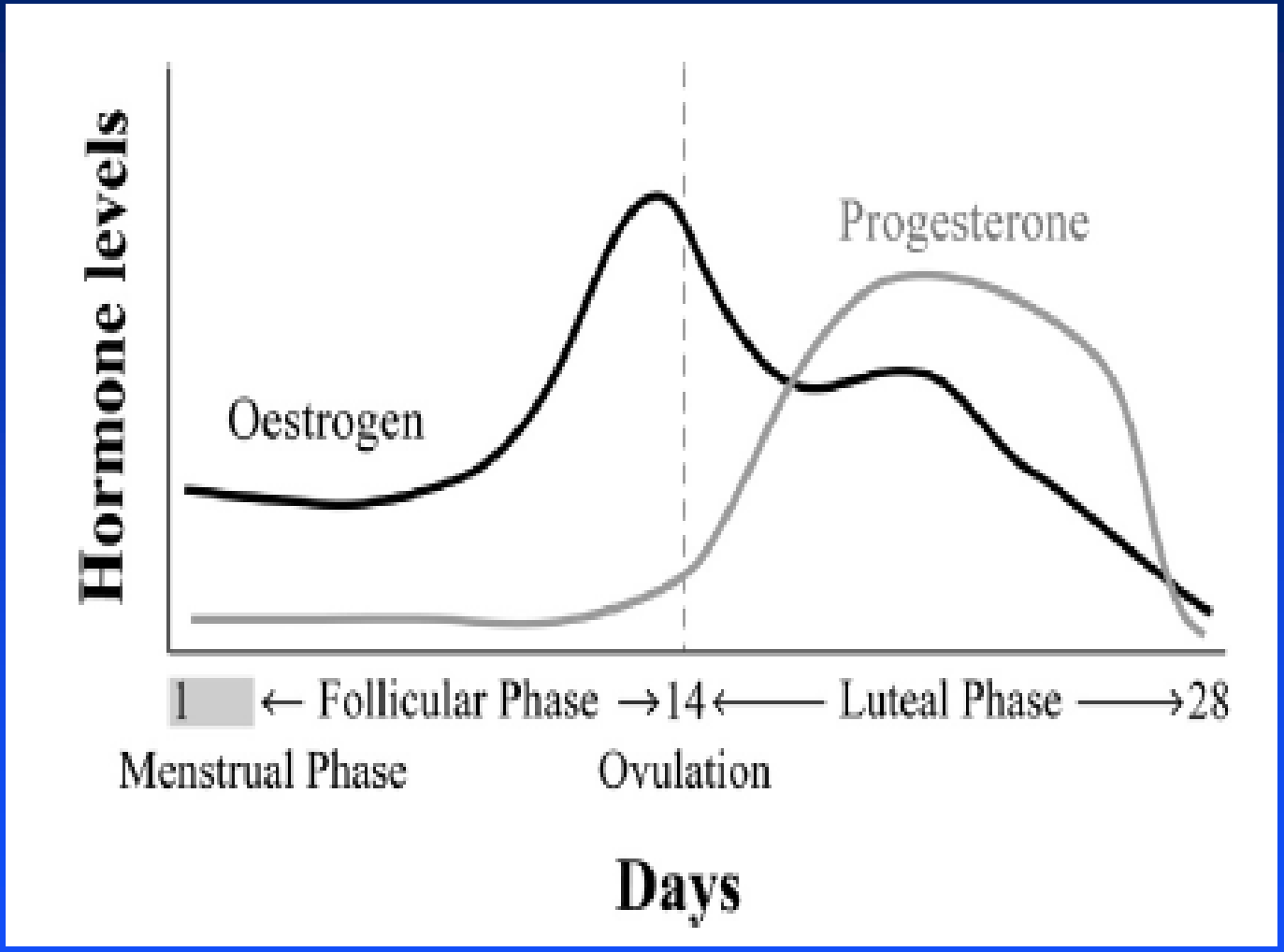
Effect of Sex Hormones on Congenital Long-QT Syndrome

SEX HORMONES AND QT INTERVAL

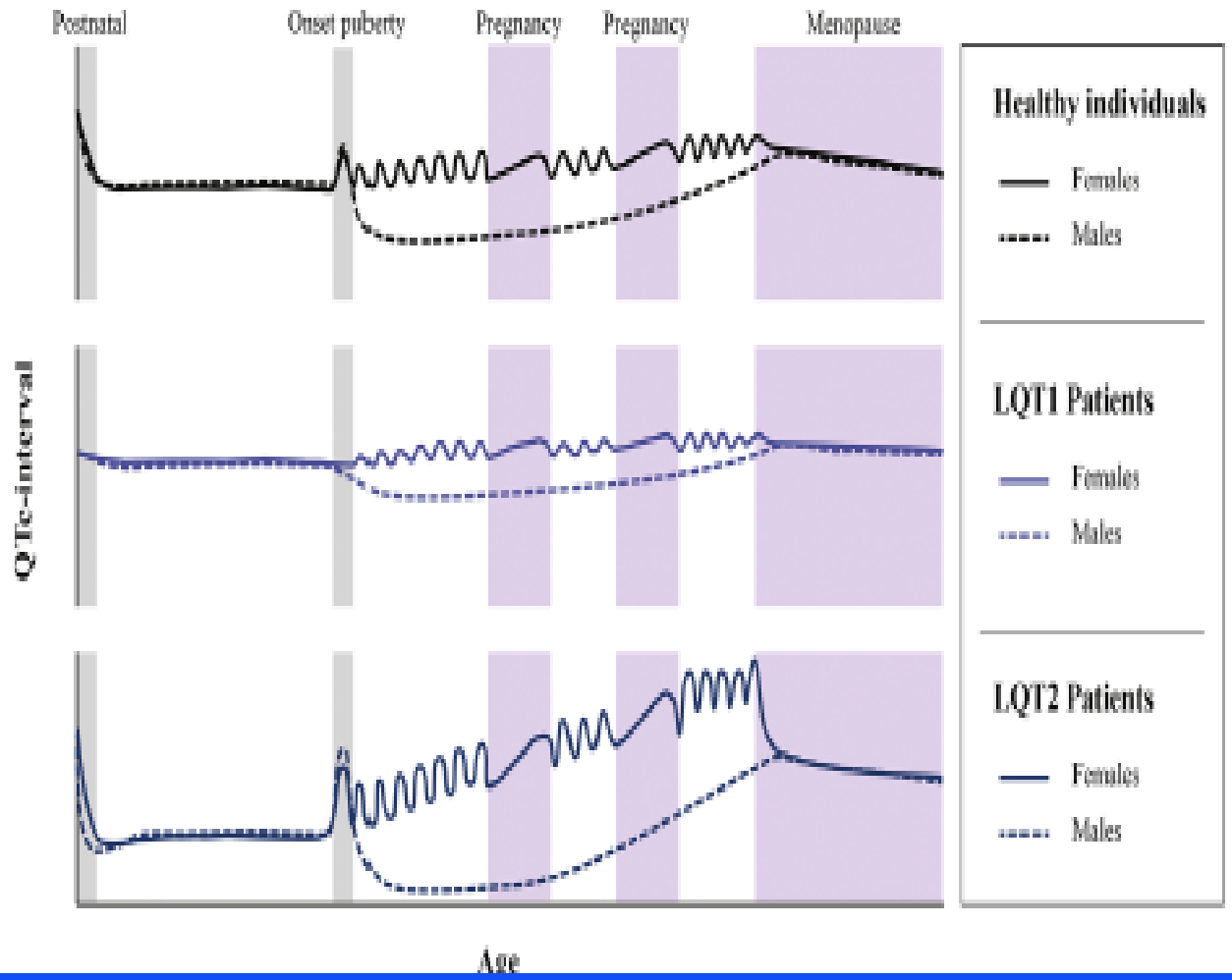


	L-type calcium channel current ($I_{Ca,L}$) Phase 2	*Rapidly activating delayed rectifier current (I_{Kr}) Phase 3*	*Slowly activating delayed rectifier current (I_{Ks}) Phase 3*	*Inward rectifier current (I_{K1}) Phase 3*	*Overall Effect on QT interval*
Estrogen	↓	↓	↓	↓	↑
Progesterone	↓	N/A	↑	N/A	↓
Testosterone	↓	↑	↑	↑	↓

SEX HORMONES DURING THE MENSTRUAL CYCLE



HYPOTHETICAL EFFECT OF SEX HORMONES ON QTc



ORAL CONTRACEPTIVES AND QTc

	Estrogen effect on QT	*Progestin effect on QT*	*Overall effect on QT*
First generation OC	↑↑	↓↓↓	↓
Second generation OC	↑	↓	↔/↓
Third generation OC	↑	↓	↔
Fourth generation OC	↑	↑	↑↑

LONG QT SYNDROME AND PREGNANCY

Long QT Syndrome and Pregnancy

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Rochester, New York; Rochester, Minnesota; Jerusalem, Israel; Cleveland, Ohio; Milan and Pavia, Italy; Houston, Texas; and Salt Lake City, Utah

Objectives This study was designed to investigate the clinical course of women with long QT syndrome (LQTS) throughout their potential childbearing years.

Background Only limited data exist regarding the risks associated with pregnancy in women with LQTS.

Methods The risk of experiencing an adverse cardiac event, including syncope, aborted cardiac arrest, and sudden death, during and after pregnancy was analyzed for women who had their first birth from 1980 to 2003 (n = 391). Time-dependent Kaplan-Meier and Cox proportional hazard methods were used to evaluate the risk of cardiac events during different peripartum periods.

Results Compared with a time period before a woman's first conception, the pregnancy time was associated with a reduced risk of cardiac events (hazard ratio [HR] 0.28, 95% confidence interval [CI] 0.10 to 0.76, p = 0.01), whereas the 9-month postpartum time had an increased risk (HR 2.7, 95% CI 1.8 to 4.3, p < 0.001). After the 9-month postpartum period, the risk was similar to the period before the first conception (HR 0.91, 95% CI 0.55 to 1.5, p = 0.70). Genotype analysis (n = 153) showed that women with the LQT2 genotype were more likely to experience a cardiac event than women with the LQT1 or LQT3 genotype. The cardiac event risk during the high-risk postpartum period was reduced among women using beta-blocker therapy (HR 0.34, 95% CI 0.14 to 0.84, p = 0.02).

Conclusions Women with LQTS have a reduced risk for cardiac events during pregnancy, but an increased risk during the 9-month postpartum period, especially among women with the LQT2 genotype. Beta-blockers were associated with a reduction in cardiac events during the high-risk postpartum time period. (J Am Coll Cardiol 2007;49: 1092–8)

SEX HORMONES AND PREGNANCY

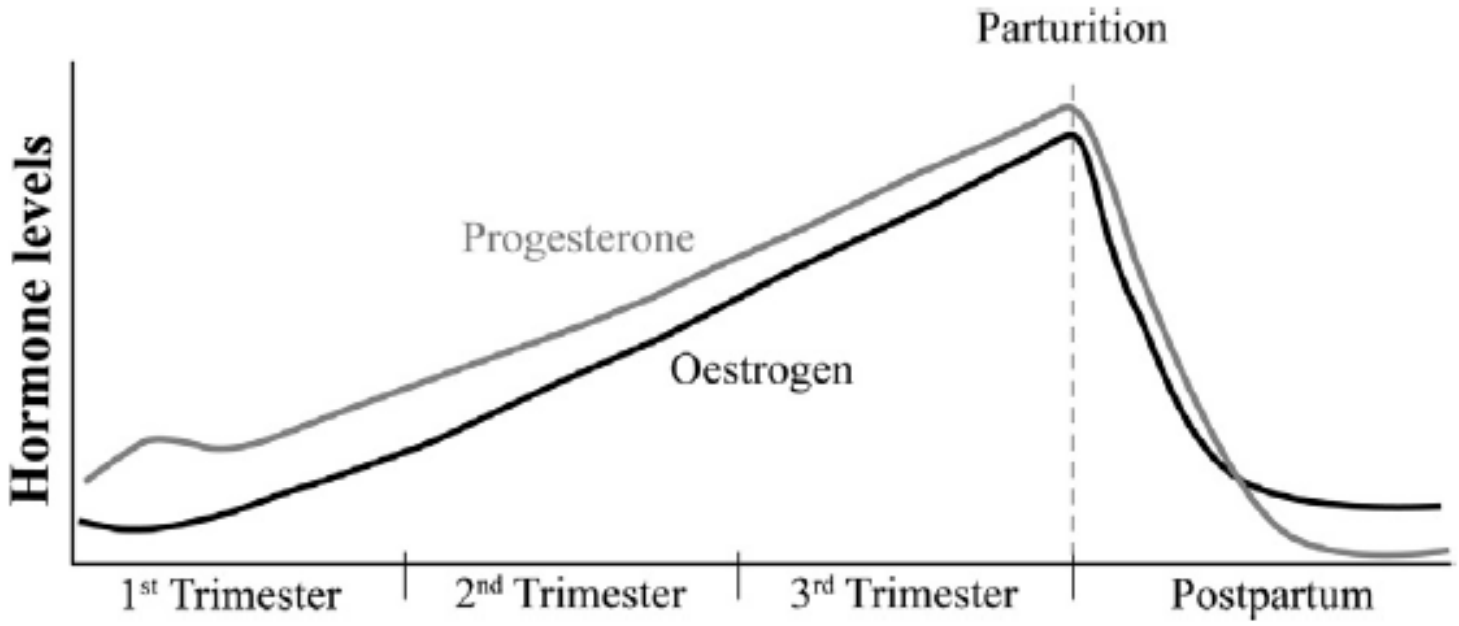
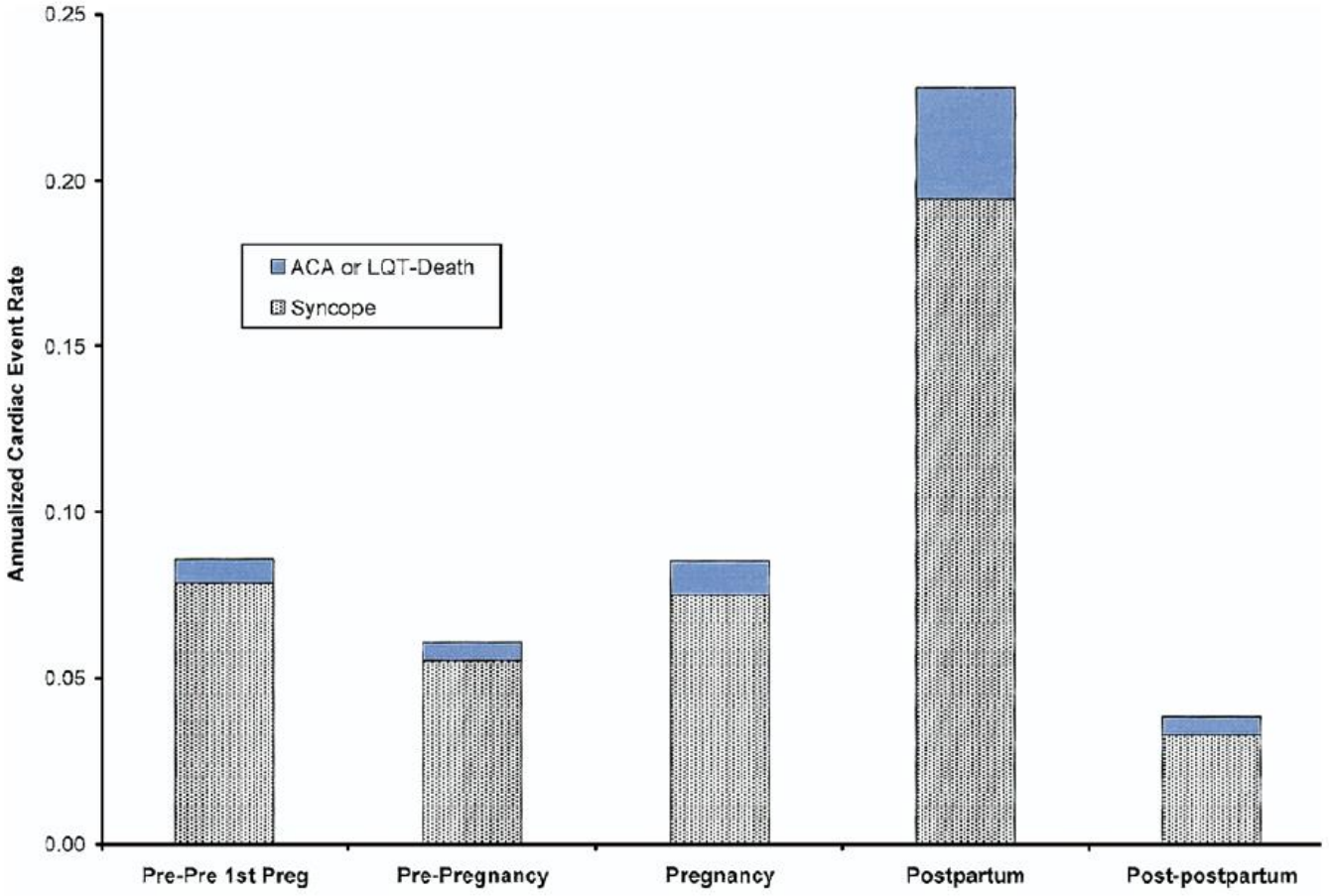


Fig. 3 – Estrogen and progesterone levels during pregnancy and after parturition.

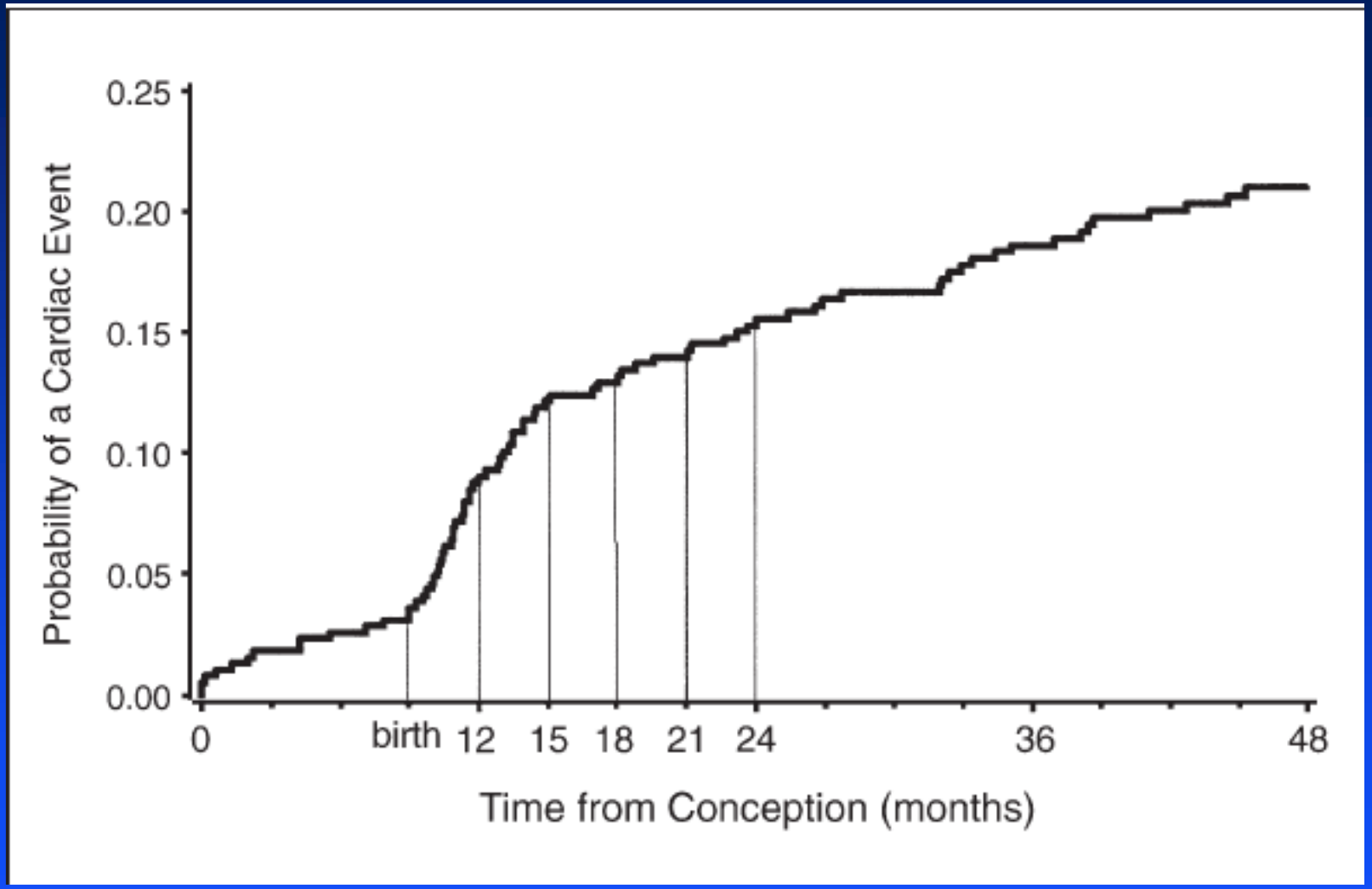
Risk of cardiac events before and after pregnancy



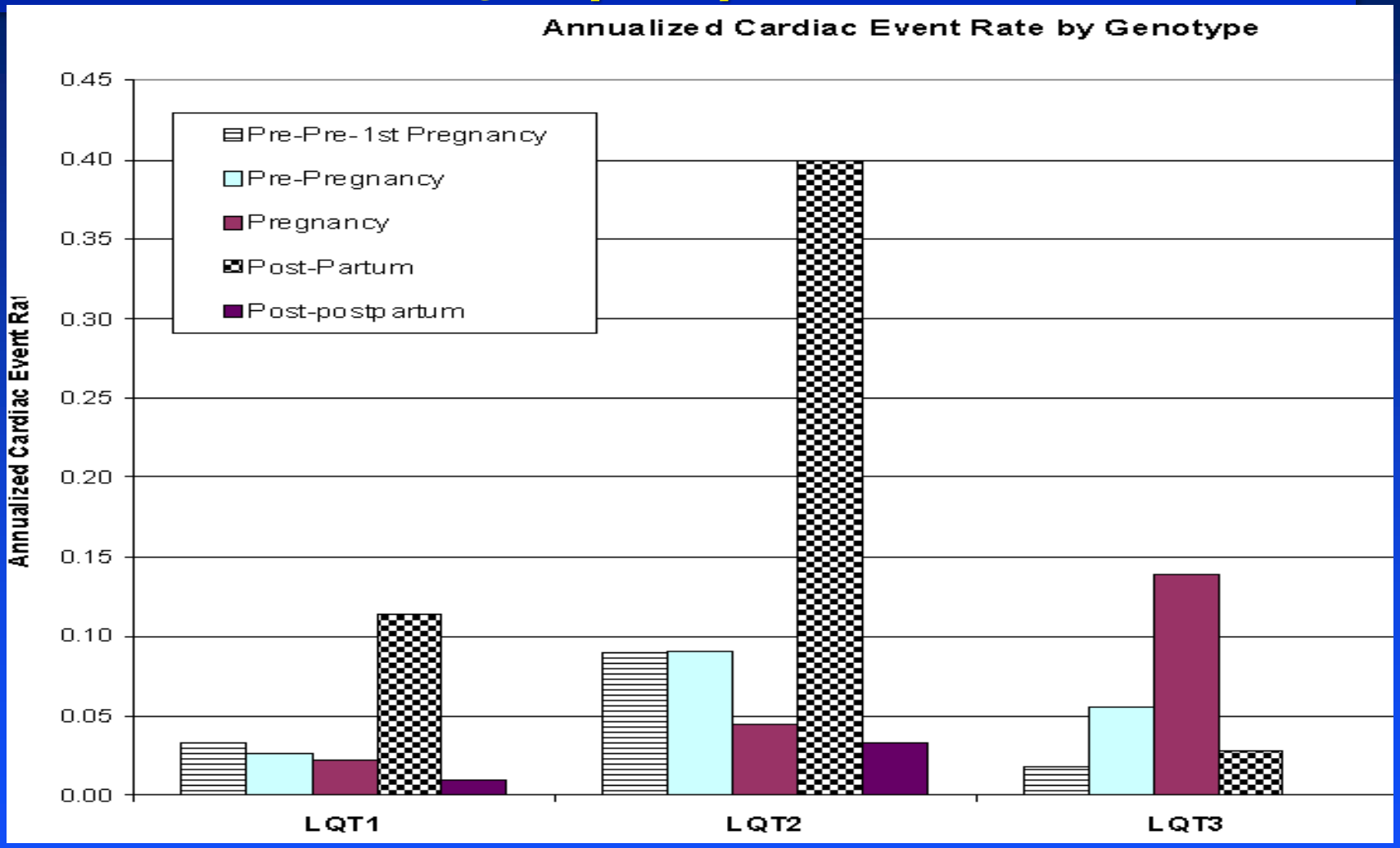
Risk of cardiac events before and after pregnancy

Time Period	Any Cardiac Event (n = 214 of 391)		Life-Threatening Event (n = 55 of 391)	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Pregnancy	0.28 (0.10–0.76)	0.01	1.5 (0.49–4.5)	0.49
Postpartum	2.7 (1.8–4.3)	<0.001	4.1 (1.7–9.5)	0.001
Post-postpartum	0.91 (0.55–1.5)	0.70	1.9 (0.84–4.1)	0.13

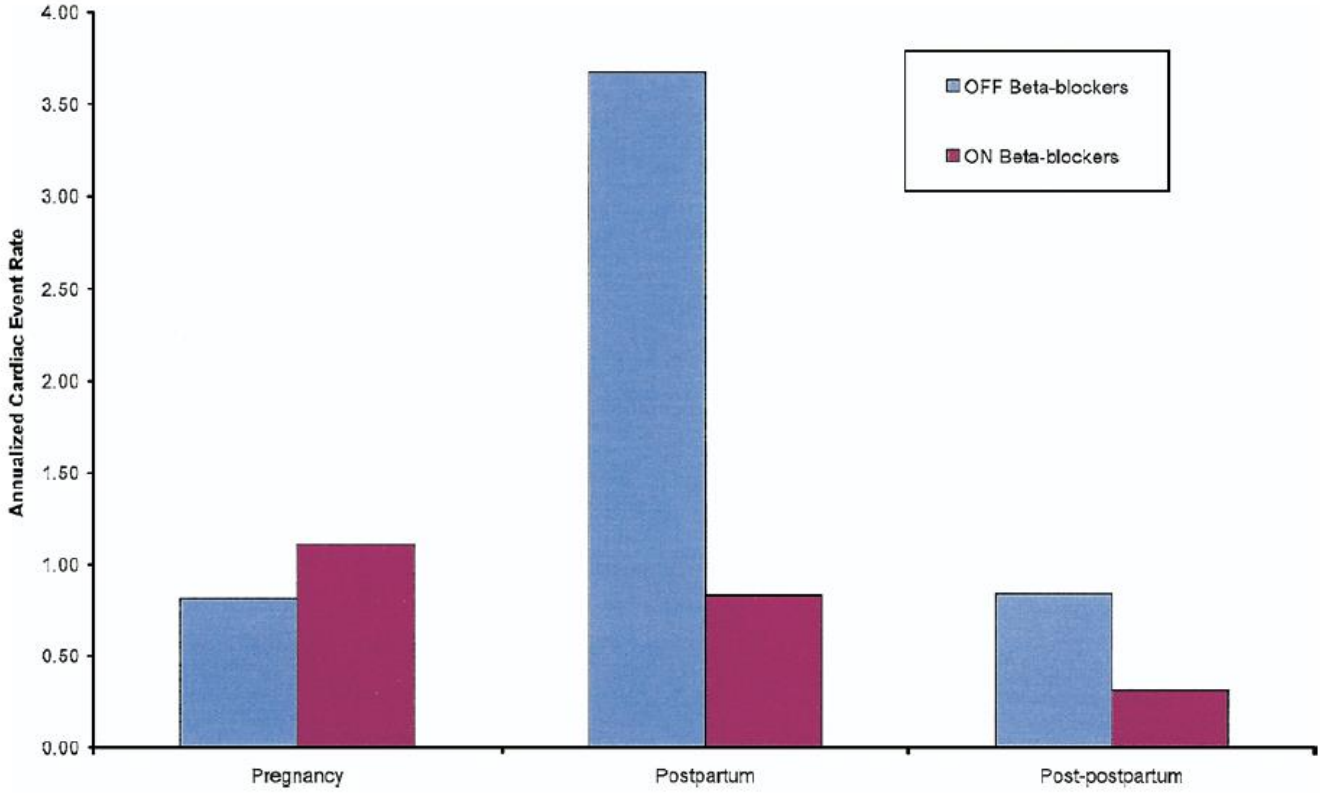
Risk of cardiac events from conception



Increased risk for Women with Ikr mutations: LQT2 postpartum



PROTECTIVE EFFECT OF BETA-BLOCKERS



PROTECTIVE EFFECT OF BETA-BLOCKERS

Time Period	Any Cardiac Event	
	Hazard Ratio (95% CI)	p Value
Time-dependent beta-blocker use		
Pregnancy	0.16 (0.02–1.3)	0.08
Postpartum	0.34 (0.14–0.84)	0.02
Post-postpartum	0.52 (0.14–1.9)	0.32

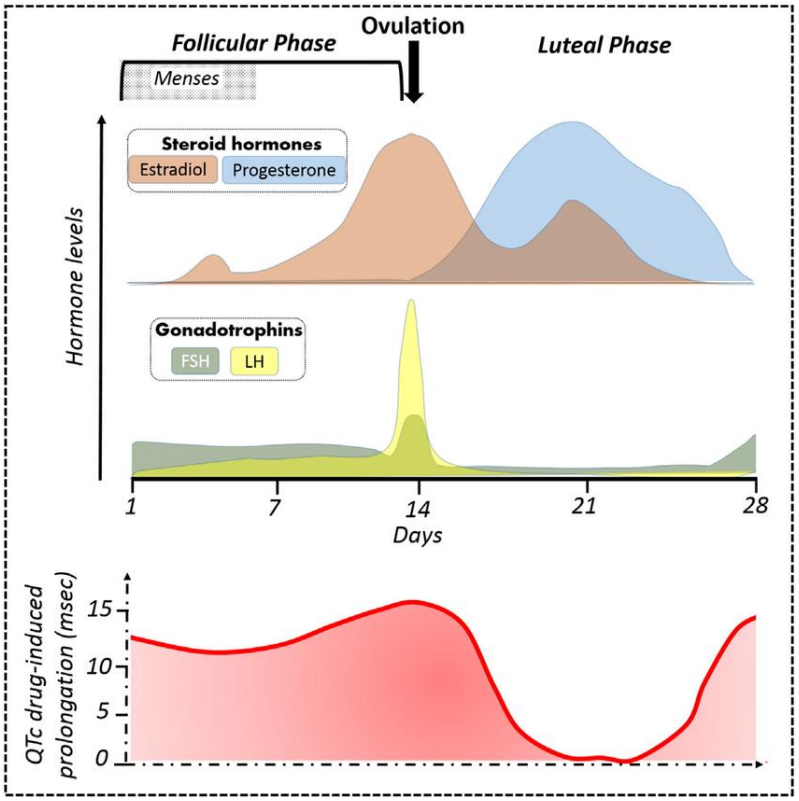
FUTURE DIRECTIONS

Sex Hormones and Arrhythmias

1. What is the association between female sex hormones and arrhythmic risk?

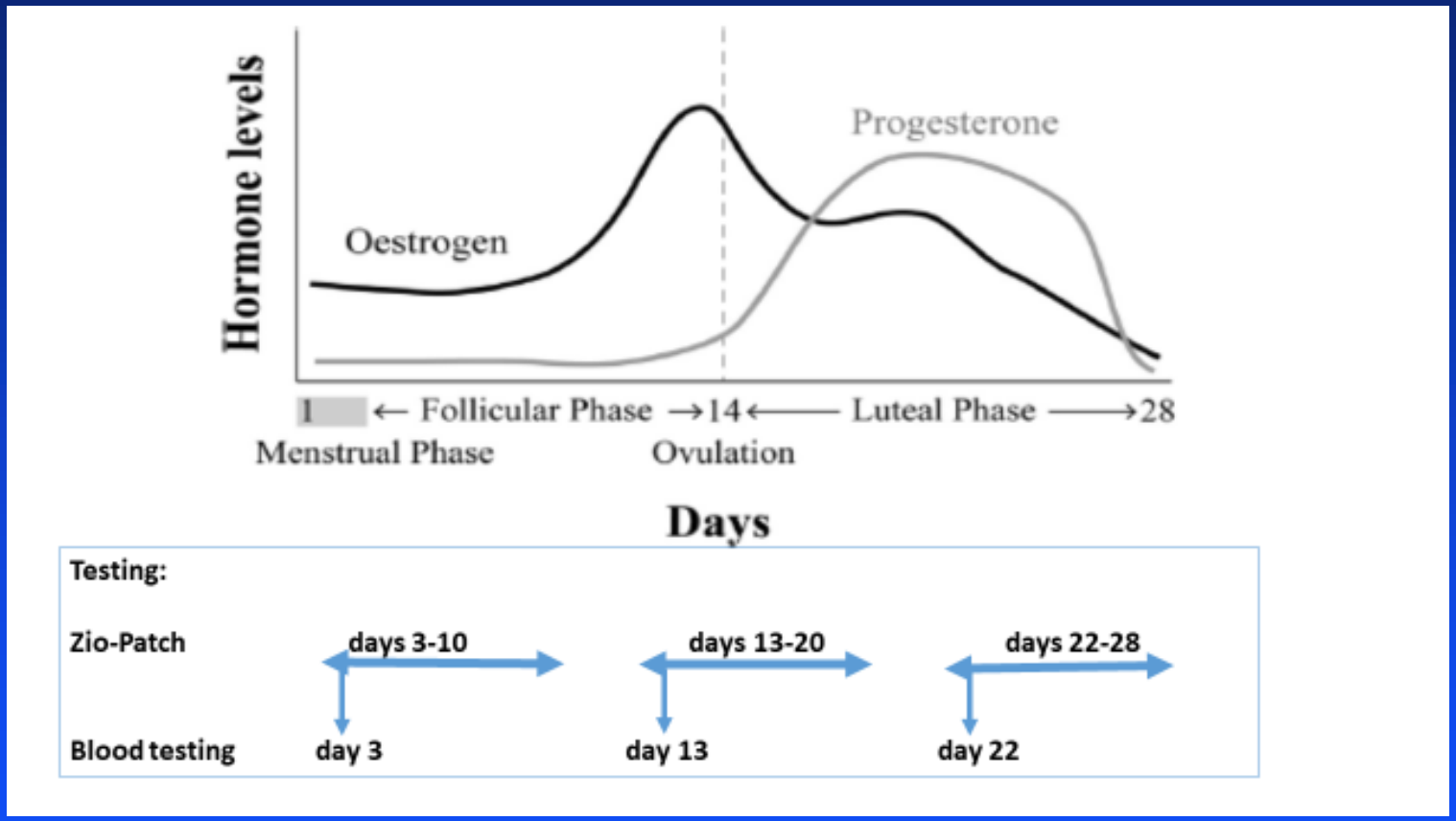
1. Can sex-specific risk factors improve risk stratification for SCA in patients with LQTS?

2. Are there sex-differences in response to medical and defibrillator therapy in LQTS?



Understanding the relation between **sex hormones, genetics, and SCA risk** may lead to novel, hormonal-based, therapeutic interventions in inherited and acquired arrhythmic disorders

Clinical Study: Congenital and Drug-Induced LQTS



CONCLUSIONS

- Sex hormones affect the clinical course of LQTS patients from birth through adulthood
- The effects are most pronounced in women with LQT1 and especially LQT2
- The risk of cardiac events decreases during pregnancy and increases postpartum
- Beta-blockers are protective during and after pregnancy

THANK YOU