

Supporting Families.
Saving Lives.

Long QT Syndrome in Women



An Information Booklet for Patients and their Families

Being diagnosed with Long QT Syndrome (LQTS) can be a frightening, confusing, and stressful time in your life. There are many things to learn and many aspects of your care that will require difficult decisions. Throughout this process it is normal for you to have many questions. These questions—and their answers—are an important part of making the best decisions for you.

As a woman with LQTS, your risk of experiencing symptoms may change at different stages in your life. This is an important consideration when managing your LQTS. This booklet was written specifically to address issues related to the health of women with LQTS, and to help you start some important discussions with your healthcare team..

We hope that this publication will also help you to realize that you are not alone..

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PART 1

Understanding Long QT Syndrome

What is Long QT Syndrome (LQTS)?

Long QT syndrome, often abbreviated to LQTS, is a disease that affects the electrical activity of the heart. Because the heart is not beating normally, affected individuals are at higher risk for **arrhythmia** (an irregular or inefficient heart beat) or other cardiac events such as fainting (syncope) and **cardiac arrest**. The **cardiac events** associated with LQTS can be life threatening.

The name “Long QT Syndrome” comes from the appearance of the results of a patient’s **electrocardiogram (ECG)**. An ECG is a test that records the electrical activity of the heart and allows doctors to measure and identify the individual electrical changes within each heartbeat. These individual changes are designated specific letters, P through T (Figure 1).

The QT interval simply refers to the time between Q and T for any given heartbeat. The electrical problem in LQTS leads to this specific interval of the heartbeat taking too long (being prolonged). Generally speaking, as the length of the QT interval increases, so too does the risk of a life-threatening arrhythmia.

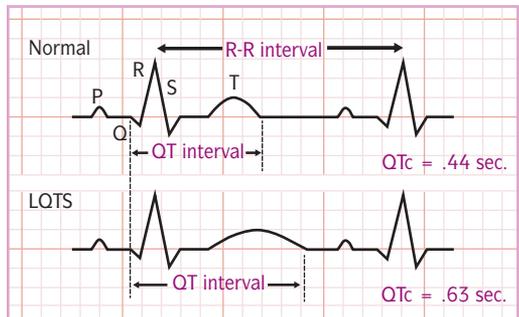


Figure 1: ECG comparing a normal reading and a reading indicating LQTS.

Causes of LQTS

The electrical abnormalities seen in LQTS are caused by changes in specific **genes** that affect heart cells. These changes are called **mutations**. The mutations that cause LQTS are present from the time of conception, but LQTS may not be diagnosed until much later in life.

At least 15 different genes are linked to LQTS. Researchers have designated several LQTS subtypes according to the specific gene affected. The three most common subtypes of LQTS are LQT1, LQT2, and LQT3. Together, these subtypes make up about 75% of all patients with LQTS in which a mutation is identified. LQT1 and LQT2 are approximately equally common, but LQT3 is relatively rare, occurring in only about 8% of identified LQTS mutations. The remaining approximately 25% of cases have even more uncommon mutations.

While genetic testing is often a helpful tool when diagnosing LQTS, it is not required for the diagnosis. LQTS can be diagnosed by an ECG, sometimes supported by the appearance of clinical symptoms such as fainting (syncope), cardiac arrhythmia, or even cardiac arrest. Overall, LQTS is estimated to affect approximately 1:2000 people, making it the most common inherited cardiac rhythm disorder.

Living with LQTS

Being faced with a diagnosis of LQTS can sometimes feel overwhelming and confusing. You have a lot to deal with as you cope mentally and emotionally with the diagnosis. There are so many things to consider, including:

- all the people involved in the decision-making process, including loved ones, family physicians, medical specialists, and other healthcare team members;
- the advantages and disadvantages of each treatment or management option;
- your unique risk factors; and
- the challenges of adopting changes in lifestyle and/or career.

There is currently no cure for LQTS—no way to reverse the genetic problem. However, there are *many* treatment options available to help prevent arrhythmia from occurring so that you can continue to lead a normal, healthy, and productive life. Accept that there is neither a single right answer, nor an approach that will work for all people. Nonetheless, being informed about your condition and management options is critical to making the best personal choices, whatever they may be. Your healthcare team will likely discuss some treatment options and risk factors with you. Be prepared to ask lots of questions. Learn as much as you can to inform your decision-making.

As a woman, being informed of the gender-specific considerations in LQTS may assist you in forming and asking appropriate questions. Raise the issue of your reproductive health and participate actively in your healthcare.

Some Treatment Options and Risk Factors

TREATMENT OPTIONS

- lifestyle modifications
- arrhythmia-preventing medications (**beta-blockers**)
- careful avoidance of QT-prolonging drugs (e.g., many over-the-counter drugs)
- an **implantable cardioverter defibrillator (ICD)**

RISK FACTORS

- your LQTS subtype
- additional genetic differences (beyond LQTS genes)
- the severity of QT prolongation in your case
- personal and family history
- age and gender
- your lifestyle and preferences

LQTS and gender

Gender is a significant risk factor in LQTS: there are differences in risk for cardiac events between males and females. This means that an individual in one group is more likely to experience syncope, arrhythmia, or cardiac arrest than is an individual in the other group. Furthermore, these differences vary across ages and across specific LQTS subtypes. The variation is particularly striking among patients with LQT1 or LQT2. In childhood, male LQT1 and 2 patients are at a higher risk for early life-threatening cardiac events than are female LQT1 and 2 patients. The risk for cardiac events in females then increases during **puberty**. By adulthood, female LQTS patients are at a higher risk for life-threatening events than are males. In fact, being an adult female is considered an important risk factor for life-threatening arrhythmia.

Researchers believe that this variation in risk is associated with the activity of **sex hormones**. Sex hormones are a group of compounds that are made in the body. They include estrogen (estradiol), progesterone, and testosterone. While both men and women have all three sex hormones, they are present in different concentrations: the predominant hormones for women are estrogen and progesterone; for men, the predominant hormone is testosterone.

Sex hormones initiate the physical changes that occur during puberty, such as the development of secondary sexual characteristics: testicular growth, breast development, and hair growth. The body continues to produce sex hormones throughout adulthood, but the amounts vary greatly, particularly in women throughout the menstrual cycle, during pregnancy and post-partum.

Sex hormones and the QT interval

In addition to their function in sexual development, sex hormones also act on other organ systems, including the cardiovascular system (heart and blood vessels). In the context of LQTS, an important consideration is the effect estrogen and progesterone can have on the QT interval. It may come as little surprise that in times of rapid fluctuations in sex hormones—times such as puberty, post-partum, or when taking hormone therapy—are associated with changes in risk for life-threatening events. Subsequently, the connection between sex hormones and the QT interval is an important consideration for minimizing patient risk.

As an area of ongoing study, the specific relationships between these hormones and cardiac cells remains poorly understood. Nonetheless, two main concepts have emerged from the research to-date:

1) Estrogen and progesterone levels can affect the length of QT interval and subsequent risk for cardiac arrhythmias.

Given females experience different stages of hormonal activity throughout their lives (i.e. menstruation, pregnancy, menopause), their risk for cardiac

events related to LQTS can change accordingly. Such changes to their risk for arrhythmias have in fact been well documented in female populations with LQTS. For example, many women with LQTS experience an increased risk of arrhythmias during the post-partum period, related to the rapid changes in hormones during this time. (Further details are covered in Part 2 of this booklet.)

2) The effect of estrogen and progesterone on the QT intervals varies with LQTS genetic subtype.

Research has shown there are significant differences in the effect of sex hormones on arrhythmia risk when comparing the genetic subgroups of LQTS (i.e. LQT1, LQT2 and LQT3). In other words the effect of sex hormones on the QT interval is ‘genotype-specific’. For example, one striking difference is seen among the less common genotype of LQTS3; women of this subgroup do not appear susceptible to effects of sex hormones as in LQT1 and LQT2, but do appear to have a unique increase in risk during pregnancy.

For this reason, patients with a known positive genetic test may find it helpful to discuss their identified LQTS GENETIC subtype (if known) with their healthcare professionals, if they have not done so already.

How do sex hormones modulate risk?

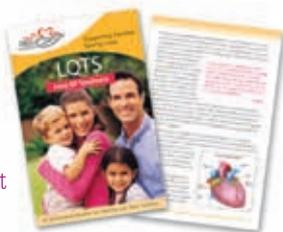
The short answer is the exact mechanism remains unclear. To date, results across a number of studies have been inconsistent: Table 1.

SEX HORMONE	EFFECT ON QT INTERVAL
Progesterone	Some research has proposed progesterone may have a protective effect by shortening the QT interval. Other studies, however, have failed to replicate these findings, and suggest that progesterone may not play a significant role in the QT interval.
Estrogen	There is evidence in support of a QT-prolonging effect associated with increased levels of estrogen, suggesting an increase in the risk for arrhythmias. However, this theory has been recently challenged by results demonstrating QT-shortening related to estrogen activity on cardiac cells*.

Table 1. Sex Hormone Effect on QT Interval

*Anneken, L., Baumann, S., Vigneault, P., Biliczki, P., Friedrich, C., Xiao, L., Girmatson, Z., Takac, I., Brandes, R.P., Kissler, S., et al. (2015). Estradiol regulates human QT-interval: acceleration of cardiac repolarization by enhanced KCNH2 membrane trafficking. *Eur. Heart J.*

The Canadian SADS Foundation has produced a comprehensive publication about Long QT Syndrome. If you would like to receive a complimentary copy of *LQTS: An Information Booklet for Patients and Their Families*, please contact us by email at info@sads.ca or by phone at 905-826-6303 or toll free at 1-877-525-5995.



PART 2

LOTS and Women's Life Stages

The menstrual cycle

The female menstrual cycle is a monthly sequence of events that, in the absence of pregnancy, results in menstruation. Each cycle lasts an average of 28 days, beginning at puberty and continuing throughout a woman's reproductive years until **menopause** (with certain exceptions such as pregnancy and severe illness). Day 1 of the menstrual cycle is the day on which menstrual bleeding begins. The events throughout the cycle are controlled by predictable monthly fluctuations in estrogen and progesterone (Figure 2).

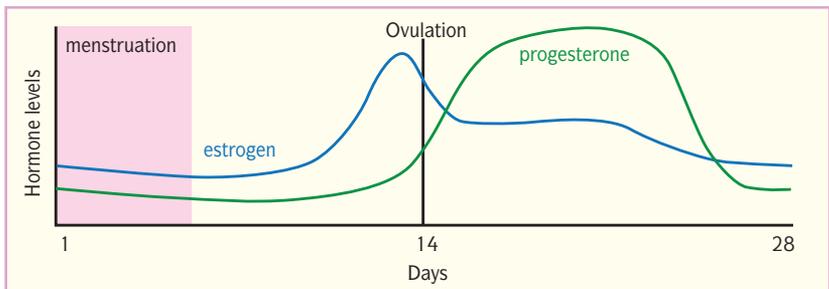


Figure 2: Fluctuation of female sex hormones over the menstrual cycle

Researchers have suggested these cyclical changes in hormones are associated with cyclical changes in the QT interval. One theory proposes the cyclical shortening of the QT interval is related to periods of increased progesterone, and subsequent decrease in risk for cardiac events. The evidence supporting this theory, however, has been inconsistent. This relationship continues to be an area of active research. Our understanding of the process is evolving.

Oral contraception

Oral contraceptives (OC) contain synthetic estrogen and progesterone in doses that typically result in blood concentrations higher than those that occur naturally in the body. While many women use OC to prevent unwanted pregnancy, it is also commonly prescribed for other benefits, including as a treatment for acne, irregular menstrual cycles, and other gynecologic disorders.

In light of the relationships between sex hormones and the QT interval (and the subsequent risk for cardiac events), researchers are starting to investigate the safety of OC use in women with LQTS. The first study to specifically examine the effect of OC in female patients with LQTS was published in 2014. The researchers found no association between the use of OC and any change in risk for cardiac events. From this, the researchers concluded that OC medications appear to have no effects—either beneficial or harmful—in women with LQTS.



Given that different types of OC contain different amounts of estrogen and progesterone, it is possible that they affect the QT interval in different ways. Furthermore, the different subtypes of LQTS may not all be equally affected by hormone concentrations. For these reasons, if you are considering using oral contraception, you should discuss the issue with your cardiologist so that the appropriate type of OC for your situation will be chosen. While you are using OC, your QT interval should be monitored periodically.

LQTS and having a baby

Getting pregnant and having a baby is a life-changing experience for many women: an experience that they do not want to miss. You are likely to have questions about whether it is safe for you to bear children if you have LQTS. Many such women have normal pregnancies and give birth to healthy babies, so there is a good chance that you can too.

Pregnancy

Pregnancy is an exciting time. It brings significant physical changes as well as a whole range of emotional changes to a woman's life. Among these changes are the increased demands on the mother's heart, which has to adapt to support the developing baby. Despite this, pregnancy does not appear to be harmful for many women with LQTS. In fact, studies have consistently shown a **decrease** in risk for cardiac events for women with the most common LQTS mutations (LQT1 and 2).

The exception to this protective effect, however, appears to be for women with LQT3. Women with this less common genetic subtype appear to have an increased rate of cardiac events throughout pregnancy. The reason for this is still under research.

Labour and Delivery

Currently, there is no evidence to suggest that labour and delivery present higher risks for women with LQTS, although research in this area is lacking. Nonetheless, it is important to inform your delivery team (including your obstetrician, family practitioner, or midwife) that you have LQTS. They should also know what medication(s) you are taking. It is extremely important that you continue to take your beta-blocker therapy if it has been prescribed, as this medication will continue to minimize the risk of arrhythmia occurring.



Post-Partum

The post-partum period generally refers to the first 12 months following delivery. Unlike the protective effect of pregnancy, post-partum is considered a particularly high-risk time for women with LQT1 and LQT2. In fact, the risk of experiencing a life-threatening event post-partum for some women may be four times higher than in the year before pregnancy. While women from both subgroups have an increased number of cardiac events during this time, the risk for women with LQT2 is substantially higher. Again, women with LQT3 do not follow the same pattern and show similar risk of cardiac events in the post-partum period as in the period before pregnancy.

Summary: Risk of Cardiac Events During Pregnancy Compared to Pre-Pregnancy

WOMEN WITH LQTS	PREGNANCY	POST-PARTUM
LQT1	↓	↑↑
LQT2	↓	↑↑↑↑
LQT3	↑↑	↓

The post-partum period is perhaps the most studied area of the health of women with LQTS. Researchers have learned a great deal about the events that frequently precipitate arrhythmia at this time, and have developed strategies that can effectively prevent them.

The change in risk during the post-partum period appears to have several contributing factors, including

- rapid decline in progesterone—important to facilitate breastfeeding (lactation) but, since progesterone has been implicated in fluctuations of QT duration, a rapid change may increase a women's susceptibility to arrhythmias;

- rapid reduction of stress on heart, with the reduction occurring much faster than the gradual increase that occurred throughout pregnancy, possibly increasing the heart's susceptibility to arrhythmia;
- severe anxiety, illness, post-partum depression, and particularly sleep deprivation;
- loud and unexpected noise or sudden arousal from sleep, such as the cry of your new baby; and
- poor eating habits, extreme weight loss, or excessive exercise.

Your healthcare team will want to help you reduce your risk of cardiac events at this critical time. The most important and well-documented treatment is the use of beta-blocker therapy. For this reason, if your doctor has prescribed a beta-blocker for you, it is very important that you take the medication as recommended.

If you breastfeed your baby, you may be concerned about passing on medications to your infant through your breast milk. Don't worry. Beta-blockers are transmitted in breast milk, but the risk posed to the nursing infant is considered to be negligible and far outweighed by the benefits to the mother. Nevertheless, it is important that you discuss any concerns related to these issues with your healthcare providers.

During the newborn period, a pediatric cardiologist should see your baby to determine if the baby has LQTS. Some pediatric cardiologists will prescribe a beta-blocker for the baby – even before the diagnosis is certain – as a means of preventative protection. This prescribed dose may be higher than what would be transmitted through breast milk.



In addition, you can use several strategies to reduce the risk of triggering arrhythmia in the post-partum period. These strategies include

- eating a healthy diet (particularly including potassium-rich foods);
- getting sufficient sleep, or as much as possible, and seeking practical support when possible;
- removing alarm clocks and telephones from sleep areas; and
- seeking medical help if you experience depression or anxiety.

Will my baby have LQTS?

If you have LQTS but the biological father does not, the chance of each of your children having LQTS is generally 50%. This is because LQTS follows a pattern of inheritance known as **autosomal dominant**, which means that the LQTS gene is *not* on the X or Y (sex-determining) chromosomes. This pattern of inheritance requires only *one* copy of the LQTS gene for a person to have the condition.

Humans have two copies of every gene: one copy from each parent. If you have LQTS you likely have one mutated LQTS gene and one normal, “healthy” version of the gene. On average, half of your eggs will contain the LQTS gene and half will contain a corresponding normal gene. The baby’s father will have only normal versions of the gene, and so can only pass on normal versions to his children. There is a 50% chance that any one of your eggs, before it is fertilized, contains the LQTS gene. Even when fertilization pairs a normal gene with the LQTS gene, random selection creates a 50/50 chance of the mutated copy being passed on in the egg to your baby (Figure 3).

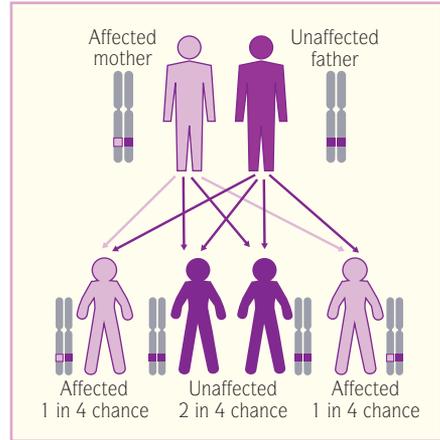


Figure 3: If the mother has LQTS and the father does not, the pattern of inheritance results in, on average, 50% of their children having LQTS.

Menopause

Menopause refers to the time in your life when your menstrual cycle ends permanently. It is a natural stage of aging and occurs when all of the eggs in your ovaries have been released. The transition into menopause, known as perimenopause, lasts about four years and is famously associated with symptoms such as hot flashes, sleep disturbances, and mood swings. These symptoms are largely related to declining levels of estrogen as you transition out of the monthly menstrual cycles. After menopause, you enter into post-menopause for the remainder of your life.

Research indicates that the onset of menopause is associated with changes in risk in women with LQTS. These changes are different for the different LQTS subtypes.

- For women with LQT1, the onset of menopause brings a *reduction* in risk for cardiac events.

- For women with LQT2, menopause brings a significant *increase* in risk for cardiac events. This increased risk continues into post-menopause and warrants close follow-up with your doctor and long-term therapy.
- Women with LQT3 have not been included in these studies because there seems to be no association between cardiac events and gender.



Hormone therapy (HT)

Some women in perimenopause experience symptoms that are severe enough to affect their quality of life. In this situation, doctors sometimes recommend **hormone therapy (HT)** to ease these symptoms or for other health benefits. HT contains synthetic estrogen and sometimes progesterone. The synthetic hormones are similar to those in oral contraception, but in higher quantities.

The safety of HT in women with LQTS has been an area of concern following reports QT prolongation with estrogen-alone HT. Interestingly, QT prolongation was not observed in women treated with combined (estrogen-progesterone) HT. This has led to the theory that estrogen and progesterone may have a counterbalancing effect on the QT interval. Further study is needed to validate this theory.

Nonetheless, the reported estrogen-related QT-prolongation does raise the possibility of serious harm to women with LQTS. It also suggests that if HT is needed, combined HT may be a safer option than estrogen-alone HT, at least until stronger consensus on hormone effects is reached. These findings, together with the changes in risk associated with the menopause, make this an extremely important time to involve your cardiologist in this transition. This is particularly true for women with LQT2 or for any women with LQTS contemplating the use of HRT.

Comparing Risk of Cardiac Events in LQTS across Reproductive Stages

	Childhood	Adolescence and Reproductive Years	Menopause and Post-menopausal period
LQT1	↓	↑↑	↓
LQT2	↓	↑	↑↑
LQT3	Unaffected by age or gender		

Overall higher lethality of events, equal to males.

Summary

If you are a woman with LQTS, your risk of experiencing serious symptoms will change throughout your life. It is important that you

- find out as much as you can about your particular subgroup of LQTS and your unique risk factors,
- inform any medical professional who is treating you that you have LQTS, and
- involve your cardiologist in any decisions regarding your treatment, medication, lifestyle, and life changes.

For reference sources, please visit www.sads.ca, select the “Publications” tab at the top of the Homepage, then choose *Long QT Syndrome in Women: An Information Booklet for Patients and their Families*.

We hope that the information presented in this booklet has been useful in opening the door to much-needed conversations with your healthcare professionals. If you have any questions and/or concerns about your personal health, please do not hesitate to contact your healthcare providers.

Glossary

arrhythmia – a potentially lethal irregular heart rhythm

beta-blocker – a medication that treats abnormal heart rhythms by blocking the heart's response to adrenaline

cardiac arrest – a potentially fatal sudden stoppage of the heart due to a malfunction of the heart's electrical system

cardiac event – a symptom involving the heart such as syncope, arrhythmia, or cardiac arrest

electrocardiogram (ECG) – a graph showing the electrical activity of the heart over time

gene – a part of the inherited genetic material that is responsible for producing a specific protein in the body

hormone therapy (HT) – a prescribed course of estrogen and sometimes progesterone, usually to reduce the symptoms of perimenopause

implantable cardioverter defibrillator (ICD) – a device, implanted in the chest, that detects any arrhythmia in the heart and administers an electric shock to stop the fibrillation and permit normal heart function to resume

long QT syndrome (LQTS) – a collection of symptoms resulting from a genetic abnormality affecting the electrical system in the heart; diagnosed by a characteristic ECG reading or genetic testing

menopause – the life stage at which ovulation and menstruation stop permanently

mutation – a change in a gene, often resulting in a malfunction in the body

oral contraceptives (OC) – a prescribed course of estrogen and progesterone, usually to prevent unwanted pregnancy

puberty – the life stage at which the young body matures sexually

sex hormones – chemicals produced in the body that (in women) coordinate the menstrual cycle; estrogen, progesterone, and testosterone



Supporting Families.
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Preventing Sudden Cardiac Death In Children and Young Adults

The Canadian SADS Foundation, a registered Canadian charity, is the only patient advocacy group in Canada dedicated to supporting families affected by inherited cardiac rhythm disorders and committed to raising awareness about the warning signs for these sometimes devastating disorders.

The Canadian SADS Foundation is committed to promoting awareness to health care professionals, educators, sports groups, and the general public and to providing information and support to families affected by inherited cardiac rhythm disorders.

It is estimated that as many as 50% of young people who experience a sudden cardiac death (SCD) had symptoms prior to their event. These symptoms may have been either misdiagnosed or dismissed as insignificant. Recognition of the warning signs and early medical intervention are the keys to preventing a SCD in children and young adults:

- **Fainting (syncope) or seizure** during physical activity.
- **Fainting (syncope) or seizure** resulting from emotional excitement, emotional distress, or startle.
- **Family history of unexpected sudden death** during physical activity or during seizure, or any other unexplained sudden death of an otherwise healthy young person.

A young person who has experienced any one of these warning signs should be referred to a cardiologist or an electrophysiologist for a complete cardiac assessment. This assessment should include an analysis of the heart rhythm and, where indicated, cardiac imaging and exercise testing.

For more information, please contact
The Canadian SADS Foundation at
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Supporting Families. Saving Lives.

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