Review Articles/Brief Reviews

Brief review: Anesthetic implications of long QT syndrome in pregnancy

[Article de synthèse court : Implications anesthésiques du syndrome du QT long pendant la grossesse]

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Purpose: To review the effects of the long QT syndrome (LQTS) in the parturient and the current anesthetic management of patients with LQTS.

Source: Relevant articles were obtained from a MEDLINE search spanning the years 1980-2006 and a PubMed search spanning the years 1949-2006. Bibliographies of retrieved articles were searched for additional articles.

Principal findings: The prevalence of LQTS in the developed world is one per 1,100 to 3,000 of the population. Clinically, LQTS is characterized by syncope, cardiac arrest and occasionally, by a history of seizures. The QT interval can also be prolonged by drugs, electrolyte imbalances, toxins and certain medical conditions. Long QT syndrome patients are at risk of torsades de pointes and ventricular fibrillation. Medical management aims to reduce dysrhythmia frequency. The LQTS is subdivided into different groups (LQT1–6) depending on the cardiac ion channel abnormality. Torsades can be precipitated by adrenergic stimuli such as stress or pain (LQT1 and 2), sudden noises (LQT2) or whilst sleeping (LQT3). Patients with LQTS require careful anesthetic management as they are at high risk of torsades perioperatively despite minimal data on the effects of anesthetic agents on the QT interval. While information on effects of LQTS in pregnancy is limited, the incidence of dysrhythmia increases postpartum. Isolated case reports of patients with LQTS women highlight several peripartum dysrhythmias.

Conclusion: An understanding of LQTS and the associated risk factors contributing to dysrhythmias is important for anesthesthesiologists caring for parturients with LQTS.

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Objectif *: Passer en revue les effets du syndrome du QT long (LQTS) chez les parturientes ainsi que la prise en charge actuelle des patientes souffrant du LQTS.*

Source *: Les articles pertinents ont été obtenus d'une recherche sur MEDLINE allant de 1980 à 2006 et d'une recherche sur PubMed couvrant la période allant de 1949 à 2006. Les bibliographies des articles trouvés ont été analysées afin de trouver des articles supplémentaires sur le sujet.*

Constatations principales *: Dans les pays développés, la prévalence du LQTS est de un cas sur 1100 à 3000 personnes. Le LQTS est cliniquement caractérisé par des syncopes, un arrêt cardiaque et, occasionnellement, par des antécédents de convulsions. L'intervalle QT peut également être prolongé par des médicaments, des déséquilibres électrolytiques, des toxines et certains états de santé. Les patients souffrant du LQTS sont à risque de torsades de pointes et de fibrillation ventriculaire. La prise en charge médicale vise à réduire la fréquence des dysrythmies. Le LQTS se divise en plusieurs sous-groupes (LQT1-6) selon l'anormalité du canal ionique cardiaque. Les torsades peuvent être précipitées par des stimuli adrénergiques tels que le stress ou la douleur (LQT1 ou 2), les bruits soudains (LQT2) ou pendant le sommeil (LQT3). Les patients souffrant du LQTS nécessitent une prise en charge anesthésique prudente, étant donné qu'ils présentent un risque élevé de torsades avant, pendant et après la chirurgie et ce, malgré le peu de données disponibles concernant les effets des agents anesthésiques sur l'intervalle QT. Bien que les informations au sujet des effets du LQTS sur la grossesse soient limitées, il a été observé que l'incidence de la dysrythmie augmente en post-partum. Des rapports de cas isolés de patientes souffrant du LQTS soulignent de nombreuses dysrythmies périnatales.*

Conclusion *: Une meilleure compréhension du LQTS et des facteurs de risques associés contribuant aux dysrythmies est importante pour les anesthésiologistes traitant les parturientes souffrant du LQTS.*

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THE long Q-T syndrome (LQTS), a disorder of cardiac ion channels producing prolonged ventricular repolarization, is usually identified by a prolonged QT interval on the electrocardiogram (ECG). The LQTS can be congenital (genetic mutations coding the cardiac ion channels) or acquired, and may be precipitated by certain drugs or electrolyte abnormalities.[1] The prevalence of LQTS is reported to be 1:1,100–3,000 in developed countries.[2] The patient with LQTS is at risk for ventricular tachydysrhythmias, especially torsades de pointes, a ventricular tachydysrhythmia that occurs after a prolonged QT interval in the preceding sinus beat. Torsades de pointes has characteristic ECG features of a twisting of the QRS polarity around an imaginary base line.[1] Usually an episode of torsades is self terminating and produces a syncopal episode from a fall in cerebral perfusion, but it may lead to sudden death when torsades deteriorates to ventricular fibrillation.[2] Congenital LQTS can be diagnosed in utero or much later in adulthood. Clinical diagnosis can be difficult as some patients with LQTS will have normal QT intervals on their ECG and only 60% will be symptomatic when diagnosed.[2] Patients with LQTS have structurally normal hearts.[3]

There is relatively little information in the literature regarding the effects of pregnancy on LQTS and the anesthetic management of these parturients. This review describes the current understanding of LQTS and its effects on anesthesia, pregnancy and delivery. A MEDLINE and PubMed based English language literature search was undertaken for the period 1980 (MEDLINE) and 1949 (PubMed) to 2006 using the following keywords and terms: 'long QT syndrome', 'an(a)esthesia', 'QT interval', 'sudden cardiac death', 'ECG changes', pregnancy', 'obstetric', 'dysrhythmias', 'treatment', 'management', 'outcomes' and 'perioperative care.' Bibliographies of retrieved articles were also reviewed for additional sources.

Diagnosis of LQTS

The diagnosis of LQTS can be challenging but is usually based on ECG patterns, clinical symptoms and genetic findings. A prolonged QT interval on the ECG is the basis for LQTS diagnosis. However, this is not a sensitive marker of LQTS as 40% of all LQTS patients have borderline or normal QT intervals.[1] This anomaly may exist because the QT interval varies with heart rate – increasing with a slower heart rate. The QT interval is normally measured in lead II on the ECG as the T wave ending is more clearly defined in this lead, with the maximal QT interval correlating with the whole 12 lead ECG.[2] To correct for variations in heart rate, Bazett's equation is used commonly to calculate the QTc, corrected QT (QTc = QT / square root of the RR interval where QT is the time from the start of the Q wave to the end of the T wave measured in seconds, and RR is the cycle time in seconds). The QTc is prolonged when it is greater or equal to 440 msec[2], although it is not a very sensitive or specific marker for establishing the presence or absence of LQTS. Bazett's equation will over-correct the QTc at both fast and slow heart rates.[2] Forty percent of all carriers of chromosomes 7 and 11 mutations will have a QTc between 0.41 and 0.47 sec^{-1} and 6–12% of all carriers will have false negative results.[2] The QTc varies with age gender and is longest if measured shortly after waking from sleep.[2] In most patients with LQTS the QT interval is prolonged but varies in length depending on the lead. QT dispersion is a measure of this response and reflects the difference between the longest and shortest QT interval on the 12-lead ECG.[2]

Other ECG anomalies found in patients with LQTS include T wave alternans (beat to beat variation in T wave amplitude), wide based T waves, biphasic T waves, low amplitude humps on the descending limb of the T wave, indistinct termination of the T waves due to U waves (TU complex) and normally appearing T waves after a prolonged isoelectric ST segment.[4] Resting and exercising heart rates may be lower than normal and dysrhythmias may be seen on 24 hr Holter monitoring.[2] The different subgroups of LQTS display different ECG morphologies. Long QT1 can have a prolonged T wave, LQT2 lower amplitude T waves and LQT3 may have a prolonged T wave following an isoelectric ST segment. However, there may be large interpatient variability and ECG morphology can vary with age.[2]

Because of the difficulty in diagnosing LQTS from the ECG, Schwartz *et al.*[5] devised a score to aid diagnosis. Scoring criteria include ECG findings, symptoms and family history (Table I). The total score gives a probability of having LQTS. A score of more than 4 implies a high probability of LQTS, 2–3 an intermediate risk and less than 1 a low risk. For a low probability score it has been suggested that exercise testing can aid in the diagnosis, as the QT interval during the recovery phase may be prolonged.[1,5]

Diagnosis of LQTS using genetic testing is extremely difficult. Because of the variable penetrance of the different gene mutations, only 60% of families tested can be genotyped successfully. The diagnosis is often made from a combination of genetic and clinical features.[2] First degree relatives of a patient with LQTS should have ECG screening with calculation of the

TABLE I LQTS diagnostic criteria[2,5]

	Points
History of	
1. Fainting with stress	2
2. Fainting without stress*	1
3. Congenital deafness	0.5
Family history†	
1. Family members diagnosed with LQTS	1
2. Unexplained sudden cardiac death in immediate family members < age 30	0.5
ECG findings‡	
1. QTc§	
≥ 480 msec	3
460–480 msec	2
450 msec in males	1
2. Torsades de pointes*	2
3. T wave alternans	1
4. Notched T wave in three leads	1
5. Low heart rate for age¶	0.5

LQTS = long QT syndrome; ECG = electrocardiogram; QTc = corrected QT. *Mutually exclusive; †Same family cannot be counted twice; ‡In the absence of medications or disorders known to affect these electrocardiogram (ECG) features; §QTc calculated by Bazett's formula, where QTc = QT/√RR; ¶Resting heart rate defined as below the second percentile for age.
The ECG findings clinical history and family history are all scored as detailed above and the scoring is the interpreted: a) ≤ 1 point low probability of LQTS; b) 2–3 points intermediate probability of LQTS; c) ≥ 4 points high probability of LQTS.

QTc and examination of the T wave characteristics. This should be routine for family members of a young victim of sudden unexpected cardiac death.[2]

Congenital LQTS

The congenital form of LQTS results from genetic mutations in the transmembrane sodium or potassium cardiac ion channels[6] which are responsible for the generation of action potentials.[3] Because of the slower repolarization there is a delay in the inactivation of the calcium channels and this may result in late calcium inflow and the development of early after depolarizations, which contribute to the syndrome.[1]

Two clinical syndromes have been described: the Jervell Lange-Nielson (JLN) syndrome and the Romano-Ward (RW) syndrome. The JLN syndrome is an autosomal recessive cardioauditory syndrome, associated with congenital deafness. The RW syndrome, which is more prevalent, has autosomal dominant inheritance with normal hearing and is a pure cardiac phenotype.[3] As the RW syndrome may present with any of six genotypes (LQT1 to LQT6) it is better to describe LQTS based on the gene and channel involved rather than by the clinical syndrome.[1] Only LQT1 and LQT5 are associated with the JLN syndrome.[3]

Long QT1 accounts for 42% of all congenital LQTS; LQT2 45% and LQT3 5%.[2] Long QT1 is caused by mutations to the KCNQ1(KVLQT1) gene and is responsible for the RW and JLN syndromes.[2] The KCNQ1 gene encodes for the alpha subunit of the cardiac potassium channel – I_{Ks} the slow activating potassium delayed rectifier. The abnormal potassium channels produce prolonged ventricular repolarization during the plateau phase of the cardiac action potential. Long QT2 is caused by a mutation in the HERG gene. The HERG gene codes for the subunits of the potassium channel that carry the I_{Kr} – (slow delayed potassium rectifier channels).[1] In the LQT3 the gene SCN5A coding for the cardiac sodium channel - I_{Na} is affected.[2] The LQT4, LQT5 and LQT6 groups are uncommon and comprised of a few families.[7]

Precipitating factors

In most cases of congenital LQTS (LQT1 and 2) the initiation of torsades is adrenergic dependent.[1] Sudden death has been reported in patients with intense exertion, emotional stress, fright, anger[8] or a sudden auditory stimulus.[9] There are gene specific triggers for cardiac events in LQTS.[10] Long QT1 patients are prone to dysrhythmias which occur in the presence of adrenergic stimulation during exercise, particularly swimming. In contrast, exercise is a relatively rare trigger among LQT2 patients and absent amongst LQT3 patients. Long QT2 patients are the most likely to experience a dysrhythmia after auditory stimuli such as the ringing of an alarm clock or telephone.[3] Patients with LQT3 do not trigger with adrenergic stimulation and are at highest risk when at rest or sleeping,[10] presumably due to a bradyarrhythmia-inducing torsades de pointes.[1,3]

Outcomes

The frequency of syncope and sudden cardiac death in congenital LQTS varies among groups. In one study the median age for the first cardiac event was nine years for LQT1, 12 years for LQT2 and 16 years in LQT3.[11] The clinical course can range from malignant ventricular dysrhythmias with recurrent syncope and sudden death to a normal life expectancy in individuals with similar degrees of QT interval prolongation.[4] Among untreated symptomatic LQTS patients mortality is very high; 20% in the first year after an initial syncope and 50% within ten years.[5] However with beta blockade this may decrease to 3–4 %.[2] The JLN syndrome produces symptoms very early in life and may be a more malignant phenotype. Almost 90% of JLN patients become symptomatic and sudden death

exceeds 25% despite medical therapy.[8] Age and gender affect the clinical course of the disease.[12] Males tended to have their first initial symptomatic event at an earlier age than females; 74% by age 15 compared with 51% of females. However by age 40, the rate of events is equal in both sexes.[10]

A prolonged QTc in LQTS is an independent risk factor for sudden cardiac death.[1] A patient with a QTc of greater than 440 msec will have a two to three times greater risk of sudden cardiac death than those patients with a shorter QTc. As the QTc peaks when the patient first awakens, the risk of sudden cardiac death is highest at that time.[12] Other predictors of sudden cardiac death in LQTS include survival from cardiac arrest, recurrent episodes of syncope, failure of medical management, relative bradycardia, congenital deafness, QTc > 600 msec, and having a close relative with LQTS or a family member who suffered a sudden cardiac death at a young age.[12]

Acquired LQTS

Drug use is the commonest cause of acquired LQTS.[13] Cardiac and non-cardiac medications can induce a prolonged LQTS and dysrhythmias[1] (Table II). Cardiac medications which can prolong the QTc include the class IA (e.g., quinidine, procainamide and disopyramide) and III (e.g., amiodarone and sotolol) medications of the Vaughan Williams classification. Non-cardiac triggering drugs may include antibiotics (e.g., erythromycin, trimethoprim), antifungals (e.g., ketoconazole) tricyclic antidepressants, phenothiazines, haloperidol and cisapride.[1] The principal ion channel affected by the QT-prolonging drugs is the same one that causes congenital LQT2. This suggests that patients who develop prolonged QT on exposure to drugs may have a mild form of congenital LQTS and carry a silent gene.[2] When exposed to the drug the QTc will increase in these patients and once the drug is discontinued the QTc will return to normal.[14]

Class IA drugs and class III drugs of the Vaughan Williams classification can precipitate torsades in LQTS susceptible patients even after months of uncomplicated treatment.[2] Concurrent use of antibiotics (e.g., erythromycin and ketoconazole) with terfenadine or cisapride may result in an additive effect because the antibiotic inhibits the liver enzyme CY3A4.[1] Female gender increases susceptibility to an acquired LQTS and torsades de pointes when taking drugs implicated in LQTS.[14]

Some medical conditions, such as electrolyte imbalance, may cause LQTS. Other conditions that may prolong the QT interval and precipitate torsades include sick sinus syndrome, high grade atrioventricular block, hypothermia, hypothyroidism, subarachnoid hemorrhage, brain stem injury, radical right sided neck dissection, cocaine use, organophosphorous poisoning, anorexia nervosa, protein sparing diets, autonomic neuropathy and human immunodeficiency virus disease.[1,6]

TABLE II Drugs that prolong the QT interval and or induce torsades de pointes[13,15,54]

*Risk of torsades**	*Possible risk of torsades/case reports**	*Drugs to be avoided in congenital LQTS**	*Unclear Association (at therapeutic doses)†*
Cardiac			
Amiodarone	Alfuzosin	Dobutamine	Melexitine
Disopyramide	Flecanide	Dopamine	
Procainamide	Moexipril	Ephedrine	
Quinidine	Nicardipine	Epinephrine	
Sotalol		Isoproterenol	
		Norepinephrine	
		Phenylephrine	
Antibiotics			
Clarithromycin	Azithromycin		Ampicillin
Erythromycin	Levofloxacin		Ciprofloxacin
	Moxifloxacin		Fluconazole
	Voriconazole		Ketoconazole
			Trimethoprim
Psychotrophics			
Chlorpromazine	Clozapine	Amitryptyline	Citalopram
Haloperidol	Lithium		Clomipramine
Thirodizine	Quietapine		Desipramine
	Risperidone		Doxepin
	Venlafaxine		Fluoxetine
	Ziprasidone		Imipramine
			Nortriptyline
			Paroxetine
			Sertraline
Miscellaneous			
Chlorpromazine	Amantadine	Cocaine	
Cisapride	Fosphenytoin	Levalbuterol	
Domperidone	Granisetron	Metoproterenol	
Droperidol	Indapamide	Phentermine	
Methadone	Octreotide	Pseudoephedrine	
Organophoshpates	Ondansetron	Ritodrine	
	Salmeterol	Salbutamol	
	Tacrolimus	Terbutaline	
	Terfenadine		
	Tamoxifen		

LQTS = long QT syndrome. *These medications should be avoided in patients with congenital LQTS. †Limited case reports available. This drug list is continuously updated at www.torsades.org.

Management

Many episodes of torsades are short and self-limited, but if prolonged with hemodynamic compromise, cardioversion is recommended. Intravenous magnesium is the agent of choice for the immediate treat-

ment and prevention of torsades de pointes for both the congenital and acquired forms of LQTS.[1,2,14] Magnesium does not shorten the QT interval[15] so its precise mechanism of action is unknown. One possible explanation is that magnesium reduces early after depolarization amplitudes to sub-threshold values *in vitro* studies.[14] If magnesium fails to prevent recurrences of torsades, then transvenous pacing at rates of 100–140 beats·min^{-1} can be employed. These pacing rates prevent pauses and shortening of the QT interval that could lead to torsades.[1,2,12,14] Magnesium and pacing are especially useful in congenital LQTS. Use of lidocaine[14] and phenytoin[1] is uncertain and as amiodarone prolongs the QT interval, its use is contraindicated.[2] Although lidocaine may suppress early after depolarizations by blocking sodium inflow, only 50% of torsades respond to lidocaine.[1] Isoprotenerol can be used to increase the heart rate and prevent recurrence of torsades in the acquired form of LQTS.[1,14] Maintenance of high normal concentrations of serum potassium is important, especially for LQT2 where high serum potassium levels shorten the QTc interval and reduce QTc dispersion.

Long term treatment, such as beta blockers for LQT1 and LQT2, insertion of a permanent pacemaker or cardioverter defibrillator and rarely, left thoracic sympathectomy, aims to reduce the QTc interval and prevent recurrence of torsades.[2] Understanding gene function has allowed development of specific therapy for different subgroups of the disease. For example, beta blockade is useful and reduces the rate of cardiac events in LQT1, is less successful in LQT2[2,10,14] and is contraindicated in LQT3.[7] Sodium channel blockers such as flecanide and mexiletine are beneficial in LQT3 patients.[1,3]

Permanent pacemakers are implanted into LQTS patients who are symptomatic despite adequate beta blockade and into those where bradycardia is an important feature (e.g., LQT3 group).[14] Pacing at high rates is normally required to reduce the QT interval. If the combination of beta blockers and pacemaker fails to prevent dysrhythmias, then an implantable cardioverter-defibrillator (ICD) pacemaker is inserted. This does not prevent torsades but will prevent sudden death if the torsades degenerates to ventricular fibrillation.[2] Implantable defibrillators are indicated in those patients with recurrent symptoms and those who have survived cardiac arrest. Defibrillators are not without risk to patients with LQTS with risk of malfunction, inappropriate shocks, lead misplacements and infection increasing each time the device is replaced.[16] Left thoracic sympathectomy has been used as a second line therapy in patients who have developed torsades. It is an effective anti-adrenergic therapy but has been largely superseded today by pacemaker or defibrillator implantation.[1,12]

Obstetric implications of LQTS

The cardiovascular changes of pregnancy can cause clinical decompensation in patients with structural heart disease, but little is known about the effects of pregnancy on patients with cardiac rhythm abnormalities.[16,17] Case reports suggest that pregnancy increases the risk of tachyarrhythmias, mainly supraventricular, in normal healthy patients,[16,17] and it is plausible that pregnant women with preexisting dysrhythmias might experience a similar increase.

There is limited information on the incidence of dysrhythmias during pregnancy in patients with LQTS.[18] In one retrospective study, the course of pregnancy in 111 probands with LQTS and 311 first degree relatives of probands was reviewed.[18] The authors found that women with LQTS were at significant risk for cardiac events during pregnancy and the postpartum period with 10% having their initial cardiac event postpartum. Possible reasons for the increase in dysrhythmias during pregnancy include elevated levels of estrogen and progesterone that may amplify adrenergic responses and influence the number and function of the mutant ion channel proteins in LQTS.[18] The physiological increase in heart rate may be protective during pregnancy in LQTS women who have an increased QT interval at slower heart rates,[18] but postpartum the QT interval may lengthen as the heart rate slows, increasing the risk of a cardiac event.[16]

Women with LQTS are best managed by a multidisciplinary team composed of obstetricians, cardiologists and anesthesiologists. Consultation with the team members should occur early in pregnancy with follow-up visits to ensure continuity of care. To decrease the risk of cardiac events throughout pregnancy[18] pregnant women with LQTS should take their cardiac medications throughout the perinatal period, including labour and delivery.[2,15] Women with a cardiac pacemaker or ICD should have a review of the type and nature of the device[19] and this should be recorded on the antenatal chart. The effect of a magnet on the ICD should also be noted, whether the magnet will deactivate the defibrillator function, and whether the ICD program will be altered once the magnet is removed.[19,20] An ECG can be used to assess the frequency of paced beats.[2]

Beta blockers are the mainstay of drug therapy in patients with LQTS with the exception of LQT3. There is no evidence that beta blockers are terato-

genic[18] but possible fetal effects include intra-uterine growth restriction, bradycardia, hyperbilirubinemia, hypoglycemia and premature uterine contractions.[16] Most beta blockers are secreted in breast milk but adverse effects are low in neonates with normal renal and hepatic function. The risk of dysrhythmia in a pregnant woman with LQTS outweighs any risk to the fetus or newborn of beta blocker therapy.[16]

The fetus and neonate are at risk for inheriting LQTS. As there are reports of neonatal LQTS, the neonate of patients with LQTS should have ECG screening at birth.[2,21] Long QT syndrome has been implicated as a cause of sudden unexplained infant death and there are case reports of fetal loss secondary to LQTS.[21] Genetic counselling and testing should be offered to all LQTS women.

Peripartum

There are only two reports of cardiac events in pregnant women with LQTS. One developed ventricular tachycardia during pregnancy[22] and the other had a cardiac arrest five months postpartum[23] (Table III). Labour and delivery are high risk periods for the LQTS parturient due to sympathetic stimulation and need for medications which may increase the QTc. Dysrhythmia risk can be predicted on the basis of poorly controlled symptoms in the presence of beta blockade.[6]

It is important to reduce the adrenergic response by nursing LQTS parturients, especially LQT1 and LQT2 women,[1,2] in a calm, quiet and reassuring environment.[2,6,15] High sympathetic activity postpartum, which may be augmented by physiological stress, altered sleep patterns and newborn crying,[18] may precipitate ventricular dysrhythmias.[24] Continuous ECG monitoring during labour is important and attention should be paid to electrolyte balance.[9,15,25] Prophylactic magnesium may be beneficial[2,25] as it prevents the inward flow of potassium and sodium avoiding early after depolarizations which predispose to torsades.[2,15] Beta blockers should be continued throughout pregnancy and the peripartum period.[9,20,22,23,26–30] Any drugs that prolong the QT interval (Table II) should be withdrawn or reduced.[2]

Obstetric medications known to prolong the QT interval include terbutaline and ritrodine which are used to arrest preterm labour.[15] Oxytocin is a commonly used uterotonic agent but can produce profound hypotension in hypovolemic patients. In two women having dilation and curettage for a spontaneous abortion, with a prolonged QT interval, ventricular tachycardia followed the administration of oxytocin.[31] During a study of the effects of oxytocin during termination of pregnancy a 10 U bolus of oxytocin prolonged the QTc in normal women at one minute with a return to normal at three minutes.[32] The variation in the QTc was independent of the effects of general anesthesia. The underlying mechanism for QTc prolongation is unclear but may be a direct effect of oxytocin on cardiac repolarization or alterations to the autonomic nervous system. The authors suggest that oxytocin is potentially dysrhythmogenic, especially in patients with LQTS.[32] However, oxytocin has been used for induction of labour[33] and to aid uterine contraction post delivery[34] in LQTS women without effect. There is no information on the effects of 15 methyl prostaglandin $F_{2\alpha}$ or ergometrine on the QT interval. Other potential dysrhythmia triggers include antibiotics and antiemetics.[15] These drugs should be avoided wherever possible, or used with due caution in the presence of ECG monitoring.

The Valsalva maneuver prolongs the QTc in healthy non-pregnant individuals[35] suggesting that the second stage of labour should be shortened and active pushing limited in patients with LQTS. In some non-pregnant LQTS patients the increase in intrathoracic pressure from the Valsalva maneuver produced runs of ventricular dysrhythmias. This effect was greater in patients who were symptomatic, and less if they had received a beta blocker.[35]

Analgesia and anesthesia for labour and delivery

There is no contraindication to the use of opioids or non-pharmacological methods of labour analgesia in women with LQTS. However, as these methods are relatively ineffective and as pain and stress may trigger dysrhythmias in LQTS patients, they are not the methods of choice in LQTS parturients. Regional analgesia/anesthesia is advantageous for LQTS parturients as reduction of the stress response and provision of effective analgesia moderates catecholamine release, reducing the risk of torsades.[20] An epidural block also decreases the need for pushing and facilitates operative delivery. The disadvantage of regional anesthesia in LQTS is the potential for a high block, causing hypotension and bradycardia-induced parasympathetic override.[20]

Most LQTS parturients described in case reports received neuraxial anesthesia [epidural,[22,23,26–29,33,36–39] spinal[20,38] or combined spinal epidural[9,25] (CSE)] for labour analgesia or surgical delivery. All local anesthetics have been used successfully for regional anesthesia in parturients with LQTS.[9,23,27,36] Some authors recommend omitting epinephrine from the epidural solution as it may prolong the QTc and induce dysrhythmia.[23,27,33] Opioids, including fentanyl and

TABLE III Case reports of LQTS parturients

Reference	*Pregnancy history*	*Symptoms*	*Treatment*	*Delivery mode*	*Delivery anesthesia*	*Maternal outcome*
9	G3P0	NI	Declined ICD: Atenolol-questionable compliance.	Vaginal	CSE: levobupivacaine, diamorphine. Test dose with epinephrine. Prior surgery-no dysrhythmias	Electrolytes monitored, magnesium infusion; quiet room
20	G2P1, 35/40, GD, APS	CA after startled ICD inserted	Oxyprenolol	Em CD	Spinal: hyperbaric bupivacaine, fentanyl and morphine ICD deactivated preop & reactivated postop Bipolar diathermy.	Moderate ↓BP: Rx phenylephrine otherwise stable
22	NI	Sudden onset LOC attacks: Prolonged QT	VT requiring DC cardioversion & esmolol antepartum	CD	Epidural: lidocaine	No dysrhytmias
23	38/40	LOC attacks Rx propranolol. VF age 12 with aspiration pneunonitis.	Atenolol	CD	Epidural: chloroprocaine and morphine, *iv* diazepam post delivery	5 months postpartum CA, recovered – some neurological deficit
25	G1 P0, 38/40	2 episodes VF, ICD	ICD	El CD	CSE: hyperbaric bupivacaine and diamorphine.	Magnesium preoperatively no dysrhythmias
30	Uneventful pregnancy	Stokes Adams attack: Rx digoxin, β blocker	Propranolol	El CD	GA: diazepam, thiopental, succinylcholine, halothane and nitrous oxide	No dysrhythmias postoperatively 2 years later had GA for CS with one episode of bradycardia
33	G1 PO induction at term.	CA, ICD implanted	ICD, atorvastatin	Vaginal	Epidural: bupivacaine and sufentanil: no epinephrine	No dysrhythmias or firing of ICD
34	G2P1, 32/40 Previous vaginal delivery: epidural	Recurrent ventricular dysrhythmias	Left stellate block, high sympathectomy, pacemaker for sinus node bradycardia	El CD Poor Doppler flow	GA: thiopental, remifentanil, rocuronium for intubation nitrous oxide and isoflurane	No dysrhythmias
38	38/40	LOC following exercise	β blocker to age 13 then stopped	El CD	Spinal: isobaric bupivacaine and fentanyl epidural for postoperative analgesia	Moderate ↓ blood pressure; Rx ephedrine QTC ↑ in OR to 560 msec Rx: landiolol infusion QTC ↓ 480 msec

G = gravida; P = parity; NI = no information; CA = cardiac arrest; LOC = loss of consciousness; Rx = treated; CD = Cesarean delivery; CSE = combined spinal epidural; VF = ventricular fibrillation; VT = ventricular tachycardia; ICD = implantable cardioverter defibrillator device; Em = emergency; El = elective; GA = general anesthesia; APS = antiphospholipid syndrome; GD = gestational diabetes; QTC = corrected QT.

morphine are useful and safe adjuvants to neuraxial blockade[15] (Table III).

Anesthesia for Cesarean delivery

General principles

As noted earlier, all LQTS parturients should be thoroughly assessed by an anesthesiologist during their pregnancy as Cesarean delivery may be required on an emergent basis. In the untreated, anesthetized, LQTS patient, ventricular dysrhythmias may be refractory to treatment.[2,10] If a diagnosis of LQTS is suspected at an antenatal visit cardiac consultation should be obtained, the diagnosis confirmed, and therapy initiated. For emergency surgery in patients with suspected LQTS, precipitating factors for torsades should be avoided, and an urgent cardiology consultation obtained.

Perioperative beta blockade is most likely to benefit patients in the LQT1 and LQT5 subgroups and is less able to reduce dysrhythmia risk in LQT2 and LQT6.[2] Perioperative care of patients in the LQT3 subgroup involves avoiding pharmacological, surgical and physiological factors which cause bradycardia. Dysrhythmias in the perioperative period can be treated by defibrillation, intravenous magnesium, lidocaine and rapid acting beta blockers in the LQT1 and LQT2 subgroups, and cardiac pacing in the LQT3 group.[7]

Prevention of pain, anxiety, hypoxia, hypercarbia,[2] hypothermia,[2,40] shivering and hypo/hyperglycemia are important management principles. One case report describes an episode of torsades in a patient with LQTS following massive blood transfusion, possibly precipitated by hypothermia or hypomagnesemia.[41] Hypothermia prolongs the QT interval[40] possibly due to the prolonged recovery of the inactivated sodium channels.[15]

High positive airway pressures may increase the QTc so that caution must be exercised to avoid this problem.[35] Because of the potential for dysrhythmias, there should be a low threshold for invasive monitoring: intra-arterial monitoring to follow blood gases, and central venous access to assess fluid status, administer drugs and electrolytes, and for transvenous pacing if required.[2]

Monopolar diathermy may interfere with pacemaker and ICD function so bipolar diathermy should be used, whenever possible. If this is not possible the pacemaker or ICD may need to be reprogrammed to an asynchronous pacing mode prior to surgery.[19] External defibrillation is possible in patients with ICDs, and those patients at very high risk for torsades should have external defibrillator pads applied before deactivating the ICD function. Postoperatively, the ICD should be reactivated.[15] The external defibrillator should be kept in close proximity to the LQTS patient during the perioperative period.

As many drugs prolong the QT interval, these potential triggers should be avoided perioperatively, if possible (Table II). Many of the cardiac drugs act on all or part of the sympathetic nervous system and so are likely to prolong the QTc. Epinephrine increases the QTc in healthy and LQTS patients, and recent studies suggest that QTc prolongation is greatest in the LQT1 subgroup compared to the LQT2 or LQT3 groups.[42] Change in QT dispersion indicates the potential for dysrhythmia, and epinephrine not only produces a prolonged QTc, but also a change in QT dispersion,[43] suggesting that epinephrine has the potential to induce dysrhythmias. Phenylephrine, as an alpha adrenergic agonist that produces a vagally mediated bradycardia in response to vasoconstriction-induced increases in afterload, increases the QTc in healthy volunteers and patients with LQTS, but fortunately the QT dispersion remains unchanged.[43] Phenylephrine has been used successfully in a LQTS patient who developed hypotension following a CSE for Cesarean delivery.[20] There are no published data on the effects of ephedrine on the QTc in patients with LQTS, however this drug should be avoided in LQTS patients because of its sympathomimetic effects. Other drugs that are relatively contraindicated in LQTS include dobutamine and dopamine.[15] There should be a low threshold for monitoring LQTS parturients in a high dependency unit for 24 to 48 hr postpartum (Table IV).

TABLE IV Obstetric management of a woman with LQTS

Preconception
• Genetic testing
• Genetic counselling
• Cardiology referral and review of medications and pacemaker/ICD interrogation
Pregnancy
• Routine obstetric care
• Continuation of cardiac medications
• Anesthesia consultation to discuss anesthesia and analgesia necessary during labour and delivery
Labour and delivery
• Nurse in calm, quiet environment
• Monitor electrocardiogram
• Check electrolytes and replace where appropriate
• Resuscitation equipment and defibrillator in vicinity
• Avoid sympathetic stimulation – provide good labour analgesia, consider early epidural
• Continue beta blockers, intravenously if mother unable to tolerate medications orally
• Care with drugs which may prolong QT e.g., antibiotics, antihistamines, oxytocin, terbutaline
• Consider assisted delivery in prolonged second stage (pushing may increase QTc)
Postpartum
• Continue electrocardiogram
• Nurse in calm environment
• Provide support to mother and aim to avoid excessive fatigue
• Continue cardiac medications
• Cardiology review – interrogate pacemaker
• Screen baby for LQTS

LQTS = long QT syndrome; ICD = implantable cardioverter defibrillator device; QTc = corrected QT.

Regional anesthesia

Combined spinal epidural anesthesia for Cesarean delivery has potential advantages over both epidural

TABLE V Effects on the QT interval of anesthetic agents[6,15]

	Prolong the QT interval	*Do not prolong the QT interval*
Induction agents	Ketamine[6] Thiopental[49,55]	Etomidate[48] Methohexital[6] Propofol[56–58]
Inhalational anesthetics[43,59–63]	Desflurane Enflurane Halothane Isoflurane Sevoflurane	Nitrous oxide[15]
Neuromuscular blocking drugs	Pancuronium[64] Succinylcholine[58]	Atracurium[47] Vecuronium[47] Cisatracurium[2]
Opioids	Methadone[65] Sufentanil[6]	Alfentanil[52] Fentanyl[15,63,66,67] Morphine[15,63,66,67]
Benzodiazepines		Midazolam[47, 48]
Neuromuscular blocker reversal agents	Edrophonium[68] Neostigmine[68] Atropine[69,70] Glycopyrrolate[69,70]	
Antiemetics	Droperidol[15] Ondansetron[15*]	Dexamethasone† Cyclizine†
Sympathomimetics	Epinephrine[52,71] Norepinephrine[15] Dobutamine[15] Dopamine[15] Isoproterenol (congenital form only)[2]	Phenylephrine[71]

*Previous case reports with no effect on the QT interval but in vitro studies suggest drug interaction with cardiac ion channels; †No data on the effect of drug on QT prolongation.

and single shot spinal anesthesia. The smaller dose of local anesthetic intrathecally, combined with the ability to control the height of block with fractionated epidural doses, may reduce the risk of hypotension. There are statistically significant changes in the QTc level at one, five and 15 min after induction of spinal anesthesia in normal healthy males and in some, the QTc was ≥ 440 msec.[44] This prolongation was thought to be secondary to hypotension as the heart rate did not change.[44] In a study comparing preeclamptic patients (not LQTS parturients) with healthy controls, the QTc was prolonged prior to induction of spinal anesthesia in the preeclamptic group (452 ± 17.5 msec) but not in the control group (376 ± 21.4 msec).[45] When the spinal was administered the QTc normalized in the preeclamptic group and remained stable in the control group.[45] The authors suggested that the prolonged QTc at baseline was possibly secondary to hypocalcemia and hypertension, or to autonomic imbalance and sympathetic over activity. There are no studies investigating the effects of preeclampsia in LQTS, but one should be aware of the potential increase in the QTc. It has been suggested that regional anesthesia may be more effective than general anesthesia in reducing sympathetic activity in non-LQTS parturients with severe preeclampsia.[46] This reduction in sympathetic activity might be beneficial in the LQTS parturient by decreasing the risk of dysrhythmias.

General anesthesia

General anesthesia for the LQTS parturient can be challenging due to the risk of prolonging the QT interval and precipitating torsades. Many studies examining the effect of anesthetic agents on QT interval employed combinations of drugs or healthy volunteers, making it difficult to extrapolate the results to the LQTS patient.[2] Several recommendations originate from case reports of patients with LQTS.[7]

The anesthesiologist should aim to avoid the sudden release of catecholamines which can precipitate torsades de pointes. Anxiolysis may be beneficial[2,6] and in healthy patients the QT interval is not prolonged nor are dysrhythmias induced by midazolam alone[47] or in combination with fentanyl.[48] Catecholamine release can be reduced during laryngoscopy, tracheal intubation and extubation[49] by administering additional beta blockers and/or opioids, or by topical anesthesia to the vocal cords or intravenous lidocaine. Esmolol is thought to be problematic in the parturient as its administration has been associated with fetal bradycardia and acidosis[50] but in the LQTS parturient, the risk to the fetus may be justified. Labetalol may be more suitable in the peripartum period.

No inhalational agent is completely safe in LQTS as all can prolong the QTc. In several case reports involving pregnant[30,34] and non-pregnant patients, volatile anesthetic agents have been used uneventfully,[15] while in other reports ventricular dysrhythmias[51] and torsades[52] occurred in beta blocked LQTS patients. Some authors suggest that total intravenous anesthesia with propofol, rather than the use of inhalational agents, may reduce the incidence of ventricular dysrhythmias.[53] Neuromuscular blocking drugs, reversal agents and opioids have varying effects on the QT interval (Table V).

Two case reports of general anesthesia for Cesarean delivery in the LQTS parturient have been reported. In one report, thiopental, rocuronium and remifentanil were used for induction and intubation, and isoflurane was used for maintenance of general anesthesia.[34] In the second report diazepam, thiopental, succinylcholine and halothane were used.[30] There were no dysrhythmias in either case.

Conclusions

The physiological changes of pregnancy produce an increase in cardiac output and heart rate, increasing the risk of dysrhythmias in normal healthy women. Case reports and case series of pregnant women with LQTS suggest that they are more susceptible to ventricular dysrhythmias during pregnancy, labour and delivery. The highest risk period occurs postpartum. The LQTS is a disease of young people with significant morbidity and mortality, making the management of pregnant LQTS patients challenging. These at-risk parturients benefit from a multidisciplinary approach to their management and care throughout pregnancy and delivery. Anesthetic management aims to prevent prolongation of the QTc, while the anesthesiologist must be prepared to treat immediately any episode of torsades. The QTc can be prolonged by drugs (including anesthetic agents), pain, and sudden noises. The effects of various anesthetic agents on the QTc have not been fully elucidated, and recommendations are often based on isolated case reports or studies in patients who do not have LQTS.

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