

# Sudden intrauterine unexplained death: time for change

Claudio Giorlandino<sup>1</sup>,  
Alvaro Mesoraca<sup>2</sup>,  
Pietro Cignini<sup>1</sup>

<sup>1</sup> Artemisia Fetal Maternal Medical Centre, Department of Prenatal Diagnosis, Rome, Italy

<sup>2</sup> Artemisia Fetal Maternal Medical Centre, Department of Molecular Biology, Rome, Italy

## Corresponding author:

Claudio Giorlandino  
Artemisia Fetal Maternal Medical Centre,  
Department of Prenatal Diagnosis  
Viale Liegi, 45  
00198 Rome, Italy  
E-mail: claudio.giorlandino@artemisia.it

Stillbirths contribute substantially to perinatal mortality in developed countries with a prevalence ranging between 4 and 6 per 1000 births (1-3). Despite careful evaluation during pregnancy of fetal well-being, about 25-50%, 1 remains without a clear cause, coding for a new entity called Sudden Intrauterine Unexplained Death Syndrome (SIUDS). Moreover, an important cause of early sudden death is represented by sudden infant death syndrome (SIDS) (4-6), which is still considered the most important basis of mortality during the first year of life. Finally, a relatively enormous number of sudden deaths in infants, children, and teenagers is due to long-QT syndrome (LQTS) (7-10). Inherited forms of the long-QT syndrome (LQTS) have been associated with 200 different mutations in 7 genes encoding cardiac ion channels, their regulatory subunits, and a membrane anchoring protein (11,12). The LQTS is characterized by an abnormality in cardiac repolarization that leads to prolongation of the QT interval, T wave changes, and *torsade de pointes* (TdP).

The vast majority of these mutations are dominant point sporadic mutations (Romano-Ward syndrome). Recently, case reports and an epidemiological study have implicated LQTS in SIUDS (13-15) but genetic testing for QTS is not widely available and is infrequently performed in cases of perinatal death. Hence, the extent of the contribution of LQTS to SIUDS remains unknown. Direct and indirect evidence that some deaths from SIUDS are caused by long QT syndrome (LQTS) was published recently (13,15).

LQTS is caused by mutations in ion channel genes including the cardiac sodium channel gene SCN5A, and potassium channel subunit genes KCNQ1, KCNH2, KCNE1, and KCNE2. Schwartz et al. (13) reported a prospective study of 34.000 Italian newborns where the presence of a prolonged QT interval increased the risk of SIDS by a

factor of 41. Moreover, this group identified a *de novo* mutation in KVLQT1, the gene most frequently associated with long QT syndrome, in a child who died of SIDS (15). In the last decades many studies try to better identify the causes of these conditions. More recently a new trend of research evaluates a possibly correlation between these apparently unrelated conditions. In other words it could be possible that the latter might be a contributor to the former? This hypothesis if proven to be correct could offer a way to prevent those fetal and infant deaths on the basis of a similar genetic mechanism.

In order to verify this hypothesis from 2009 to 2012 every pregnant woman coming to our centre for ultrasound examination showing a SIUDS was enrolled in a prospective observational study including an extensive genetic analysis (Tab. 1). Of fourteen cases observed, 5 cases were lost to follow-up due to impossibilities to have tissue for genetic test. Then 9 women were enrolled and analyzed by Denaturing High Pressure Liquid Chromatography and sequencing analysis (Tab. 2). Seven subjects were found to be positive for gene mutations tested. In all these case parents were analyzed showing a direct transmission in 1/7 (14,2%) case and a *de novo* mutation in 6/7 (85,8%) cases.

Our findings demonstrate that most cases of unexplained stillbirths have remained unexplained due to unsatisfactory post mortem examination or documentation.

Infect in our cases a large number (85.8%) were "*de novo*" mutations.

Probably the risk factor correlated with SIUDS (i.e. smoking, obese woman etc.) among women carrying these mutation could be considered not just the cause but a phenotypic aspects of the population affected with these gene alterations.

**Table 1. Genes Tested for LQTS**

GENES
KCNQ1
KCNH2
SCN5A
ANK2
KCNE1
KCNE2
KCNEJ2
CACNA1C
CAV3
SCN4B
AKAP9
SNTA1

**Table 2. Results of subjects tested**

Case	Mutation found	Parent	De novo
#1	none	-	-
#2	SCN5A (V1951L)	NEGATIVE	YES
#3	SCN5A (P2006A)	NEGATIVE	YES
#4	none	-	-
#5	SCN5A (R1623Q)	NEGATIVE	YES
#6	KCNH2 (IVS9-28A – G)	MOTHER	NO
#7	SCN5A (T1304M)	NEGATIVE	YES
#8	KCNQ1 (Y148X)	NEGATIVE	YES
#9	SCN5A (S216L)	NEGATIVE	YES

We strongly believe that occurrence of SIUDS is higher than reported in the literature, but epidemiological surveillance is inadequate: SIUDS represents a major contributor to the perinatal and fetal mortality in general and to deaths close to term of pregnancy in particular. Despite this fact, common approaches that could facilitate cross-country comparisons and enable studies of development over time are lacking. Because of these reasons we suggest to perform genetic analysis in all cases of stillbirths with apparently unexplained causes and in general in women with recognized risk factors for SIUDS.

In conclusion we strongly suggest prenatal screening in those women with recognized risk factors because of both the high prevalence of SIUDS (even when compared with SIDS) and the possibility to perform an in-utero pharmacologic therapy.

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