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Facultad de Medicina, Universidad de Chile

Estudio genético en Óbito fetal

Autores:
Dra. Paula Correa
Dra. Catherine Díaz Sanhueza
Dr. Rodrigo Terra

Óbito

- Muerte fetal luego de las 20 semanas de gestación.
- Sin EG clara, muerte de feto sobre 500 gr. (amplia variabilidad en definiciones)
- 14/1000 en el mundo
- FR: Obesidad (dosis dependiente), Drogas: tabaco, Cocaína metanfetaminas, opioides, marihuana. Edad, paridad, historia obstétrica, Embarazo múltiple, TRA, raza y etnia.
- Etiologías: INCODE: causa probable, causa posible o condición presente.
  - Condición obstétrica: 30%
  - Anormalidad placentaria: 24%
  - Anomalía fetal genética o estructural: 14%,
  - Infección 13%
  - Anormalidad cordón umbilical 10%
  - SHE 9% otras condiciones maternas 7.8%

FIGURE 1
Fetal mortality rate: United States, 1990 to 2021

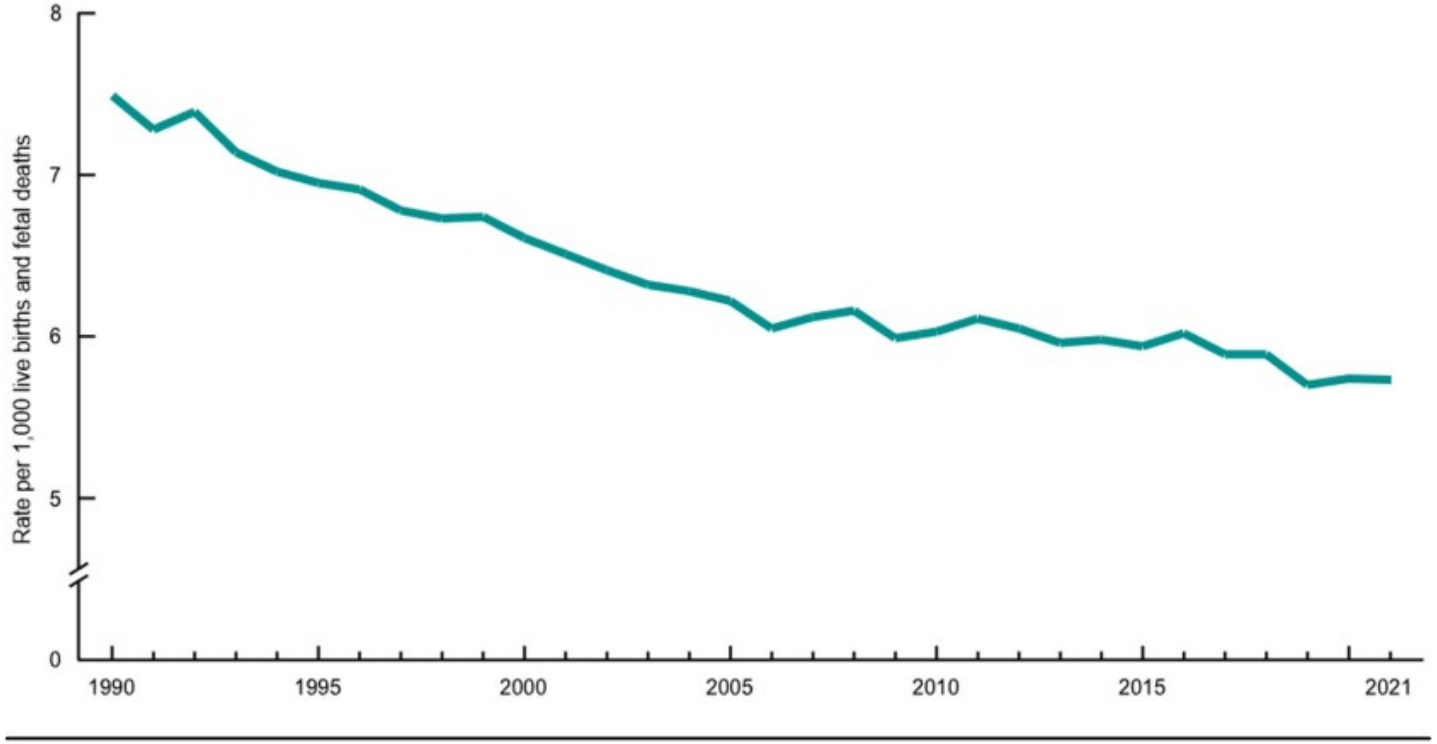

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FIGURE 2
Fetal mortality rates, by age of the mother: United States, 2021

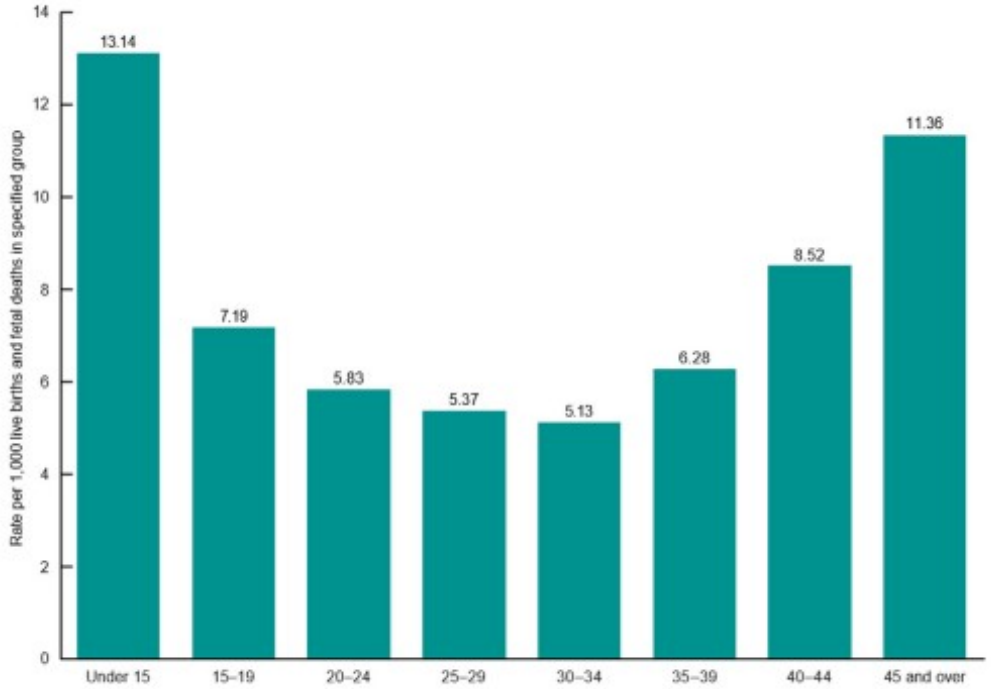

TABLE
Recommended evaluation for stillbirth

Test/procedure	Details
Fetal autopsy/postmortem examination	• All cases • Perinatal pathologist • Alternatives include magnetic resonance imaging, photographs, X-ray imaging, ultrasonography, and selective minimally invasive sampling of tissues.
Placental evaluation	• All cases • Perinatal pathologist • Should include evaluation for evidence of viral and bacterial infections including targeted pathogen testing if indicated.
Fetal genetic testing	• All cases • Chromosomal microarray is first-line test if available. Can use fetal or placental tissue. Need to exclude maternal cell contamination. • If karyotype is the only option, cells with the highest chance of yielding a result are amniocytes obtained by an amniocentesis prior to delivery. Other options include fetal blood and fetal chorionic plate near the cord insertion. • Whole genome or exome sequencing may be useful if microarray or karyotype is normal. However, at present it is costly, requires expertise, and is not widely available.
Medical history via interview and medical record abstraction	• Maternal medical history • Maternal obstetric history • Family genetic history • Current pregnancy • Clinical course
Tests performed in selected cases based on suspicion/other results • Fetal-maternal hemorrhage screen • APS testing with lupus anticoagulant, anticardiolipin antibodies, and β2 glycoprotein antibodies • Syphilis testing • Glucose screening • Toxicology screening • Indirect Coombs testing • Infection testing	• Kleihauer-Betke test or flow cytometry • Placental insufficiency, severe preeclampsia, FGR • If suggested based on placental histology or autopsy • Large for gestational age baby • Drug use is suspected or cases of placental abruption • Consider if not previously performed, hydrops, or anemia • Serology, culture, or nucleic testing in cases suspected based on history, placental evaluation, and autopsy.

Modified with permission from Management of Stillbirth: Obstetric Care Consensus No, 10. Obstet Gynecol 2020;135:e110-e32.[9]

AGS, antiphospholipid syndrome; *FGR*, fetal growth restriction.

Evaluación

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- La evaluación genética se debería ofrecer siempre frente a un óbito
- CMA se considera la primera línea frente a la posibilidad económica.

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Corner of Academy

Ioannis Tsakiridis, Sonia Giouleka, Apostolos Mamopoulos, Apostolos Athanasiadis and Themistoklis Dagklis*

Investigation and management of stillbirth: a descriptive review of major guidelines

- ACOG, RCOG, PSANZ, SOGC
- Todos recomiendan estudio histopatológico, análisis genético y microbiología de tejido fetal y placentario.
- Se recomienda cariotipo en todos los casos de óbito sin causa clara: Anomalía cromosómica en 6-13%
  - Muestras de piel o cartílago fetal y tejido placentario en su superficie fetal. Medio de cultivo con ATB. Si rechazo, tomar AMCT previo al parto. Líquido amniótico tiene el mayor rendimiento.
- ACOG, SOGC y PSANZ recomiendan CMA por sobre cariograma dado su mayor rendimiento para detección de anomalías genéticas y mayor tasa de diagnóstico para consejeria en futuras gestaciones.
- ACOG y SOGC: Cariotipo es de gran importancia frente a anomalías congénitas, dismorfias fetales, hidrops, genitales ambiguos y RCIU.

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REVIEW

PRENATAL DIAGNOSIS WILEY

The genetic approach to stillbirth: A »systematic review«

Maja Dolanc Merc[1] | Borut Peterlin[2,3] | Luca Lovrecic[2,3]

TABLE 1 Details of the studies included in this review.

Reference	Title	Methods	Included cases/genes assessed	Results and details
Reddy et al. (2012)	Karyotype versus microarray testing for genetic abnormalities after stillbirth.	Standard karyotyping and CMA	- 532 stillbirths, - 67 with congenital anomalies, not clear how many with placental or maternal pathology	- CMA yielded results more often than karyotype (87.4% vs. 70.5%; $p < 0.001$) - CMA has higher detection rate of significant genetic abnormalities (8.3% vs. 5.8%; $p = 0.007$) - CMA provided a relative increase of 41.9% in the diagnosis of genetic abnormalities in all stillbirths - Stillbirths with anomalies were significantly more likely to have abnormal results as compared to nonanomalous, no statistical data on placental/maternal causes
Sahlin et al. (2014)	Molecular and cytogenetic analysis in stillbirth: Results from 481 consecutive cases.	Standard karyotyping, QF-PCR and CMA	- 481 stillbirths, subselected 90 cases were tested with CMA - Consecutive stillbirths were included, no data available on the presence of congenital anomalies, maternal or placental pathology	- 7.5% pathogenic findings by karyotype/QF-PCR analysis - CMA testing revealed 2 additional pathogenic finding - CMA has a higher success rate and aberration detection frequency (10%–20%) than karyotype or QF-PCR (7.5%)

Reference	Title	Methods	Included cases/genes assessed	Results and details
Sahlin et al. (2019)	Identification of putative pathogenic single nucleotide variants (SNVs) in genes associated with heart disease in 290 cases of stillbirth.	NGS for panel testing	- 290 stillbirth cases tested for 70 selected channelopathy and cardiomyopathy genes - Limited data available on congenital anomalies, maternal or placental pathology	- One ($n = 31$) or two ($n = 4$) putative pathogenic variants in 12%,1% of cases - 20 cases with putative pathogenic variant in channelopathy gene (7.93%) - 12 cases with putative pathogenic variant in cardiomyopathy gene (5.17%)) - 3 cases with 1 putative pathogenic variant in channelopathy gene and one in cardiomyopathy gene - Parental samples unavailable.
Stanley et al. (2020)	Causal genetic variants in stillbirth	Exome sequencing	- 246 stillbirth cases tested for genes previously associated with stillbirth; the cases included also those with probable placental disease, umbilical cord abnormalities, obstetrical conditions (preterm labor, placental abruption, cervical insufficiency, preterm premature rupture of membranes), fetal structural anomalies	- 9 cases (3.7%) with pathogenic variants in 7 OMIM morbid genes, previously described in stillbirths - 6 additional cases (2.4%) with molecular diagnosis in 6 OMIM disease genes, that are strong candidates for phenotype expansion (according to the authors). - Among these 15–6 (40%) had a multisystem developmental disorder and 5 (33.3%) had an isolated cardiac disorder.

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- Objetivo: Identificar **causas monogénicas relacionadas a etiologías cardiológicas de muerte fetal inexplicada.**
- Se buscó un **panel de 98 genes** asociados a óbito, Muerte súbita, cardiomiopatía, patología arritmogénica.
- El 89.5% de los casos porta una variante functional rara que podría contribuir a la Muerte, sin embargo en ningún caso se identificó una causa clara.

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ORIGINAL ARTICLE

PRENATAL DIAGNOSIS WILEY

Further exploration of cardiac channelopathy and cardiomyopathy genes in stillbirth

Maja Dolanc Merc[1] | Urška Kotnik[2,3] | Borut Peterlin[2,3] | Luca Lovrecic[2,3]

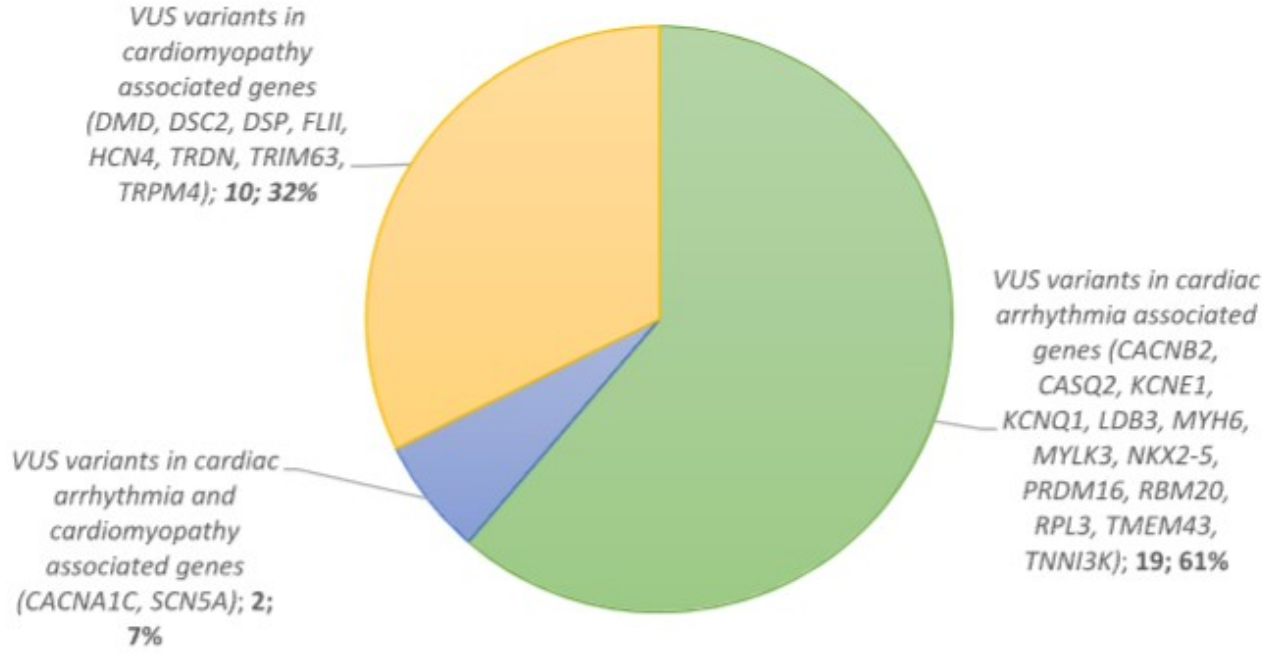

FIGURE 1 Distribution of variants of uncertain significance related to disease group. VUS variants in autosomal dominant genes were grouped according to the disease they were associated with. Most variants (19 variants, 61%) were found in genes associated with cardiac arrhythmia, and 10 variants (32%) were found in genes associated with cardiomyopathy. Two variants were found in genes associated with both of those disease groups (CACNA1C and SCN5A). [Colour figure can be viewed at wileyonlinelibrary.com]

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SYSTEMATIC REVIEW

A systematic review to assess the utility of genomic autopsy using exome or genome sequencing in cases of congenital anomalies and perinatal death

Camille Schubert[1,*], Joanne Milverton[1], Stephen Goodall[2], Tracy Merlin[1]

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ABSTRACT

Purpose: Exome or genome sequencing (ES or GS) can identify genetic causes of otherwise unexplained congenital anomaly and perinatal death (PND) but is not routine practice. The evidence base for "genomic autopsy" after termination of pregnancy for fetal anomaly (TOPFA) and PND has been synthesized to determine the value of this investigation.

Methods: We conducted a systematic review and meta-analysis of studies meeting prespecified inclusion criteria and containing ≥10 cases of TOPFA or PND (with or without major congenital abnormality), in which ES or GS was conducted. We determined test performance, including diagnostic yield, accuracy, and reliability. We also reported outcomes associated with clinical utility and harms, where described.

Results: From 2245 potentially eligible studies, 32 publications were eligible and had data extracted, representing 2120 cases that could be meta-analyzed. No diagnostic accuracy or comparative studies were identified, although some analysis of concordance between different ES/GS methodologies could be performed. Studies reporting parent-related outcomes or long-term follow-up did not do so in a systematic or quantifiable manner.

Conclusion: Evidence suggests that approximately one-fourth to one-third of fetal losses associated with TOPFA or unexplained PND are associated with a genetic cause identifiable on ES or GS—albeit this estimate varies depending on phenotypic and background risk factors. Despite the large body of evidence on ES and GS, little research has attempted to validate the accuracy of testing, nor measure the clinical or societal outcomes in families that follow the diagnostic investigation in this context.

ULTRASOUND in Obstetrics & Gynecology

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Original Paper

Molecular autopsy for fetal structural anomaly: diagnostic and clinical utility of multidisciplinary team approach

E. Wall ✉, E. Petley, F. Mone, S. Doyle, L. Hartles-Spencer, S. K. Allen, J. Castleman, T. Marton, D. Williams

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Abstract

Objective: In the West Midlands regional genetics service, cases of perinatal death with a possible genetic diagnosis are evaluated by the perinatal pathology genetic multidisciplinary team (MDT). The MDT assesses autopsy findings and suggests appropriate genomic assessment. The objective of this retrospective service evaluation was to determine the clinical utility of the MDT in assessing perinatal deaths associated with structural anomaly. This is the first evaluation since the introduction of whole-genome and whole-exome sequencing in routine clinical care.

Methods: This was a retrospective service evaluation including all cases of perinatal death with an associated structural anomaly and suspected genetic etiology that underwent perinatal MDT assessment between January and December 2021. All cases received a full or partial postmortem examination and at least a chromosomal microarray analysis. Demographic characteristics, phenotype, genotype, MDT recommendations, diagnoses, outcomes and impact of postmortem analysis and genetic testing data were collected from patient case notes.

Results: Overall, 123 cases were discussed at the MDT meetings in 2021. Genetic evaluation was recommended in 84 cases and accepted in 64 cases. A range of genetic tests were requested according to indication and availability. Thirty diagnoses were made in 29 cases from 26 unrelated families. The diagnostic yield was 24% (29/123) in all cases or 45% (29/64) in cases with a suspected genetic diagnosis who underwent genetic testing. Postmortem examination provided clinically actionable phenotypic data in 79% of cases. A genetic diagnosis enabled accurate recurrence risk counseling and provision of appropriate follow-up, including prenatal testing and preimplantation diagnosis for patients with inherited conditions.

Conclusions: Genomic testing was a clinically useful addition to (but not a substitute for) postmortem examination in cases of perinatal death associated with structural anomaly. The MDT approach helped assess cases and plan appropriate follow-up. Expedited whole-genome sequencing or panel-agnostic analysis were most appropriate for heterogeneous presentations. This broad approach can also expand knowledge of prenatal phenotypes and detect novel disease genes, and should be a priority in future research.

Table 2 Genetic test modality and turnaround time (TAT) between test being requested and result being available in 123 cases of perinatal death with associated structural anomaly and suspected genetic etiology that were discussed at multidisciplinary team meeting

Test modality	*Total diagnostic yield*	*Dx*	*VUS*	*IF*	*Failed or cancelled test*	*TAT (days)*
Chromosomal microarray	3/123 (2)	3	1	2	4	Rapid, 9 (7–27); routine, 62.5 (14–132)
Panel	5/15 (33)	5	0	0	0	82.5 (27–175)
Whole-exome sequencing	8/24 (33)					
Rapid prenatal (R21)	5/6 (83)	3	2*	0	0	15 (7–29)
Rapid postnatal (R14)	2/8 (25)	2	1†	0	0	14 (7–32)
Other (e.g. R412)	1/10 (10)	1	1†	0	0	83 (14–208)
Whole-genome sequencing	8/26 (31)	7	1*	0	3	201 (84–624)
Single-gene sequencing	4/11 (36)	4	1†	0	0	29 (5–128)

Data are given as *n*/*N* (%), *n* or median (range). Total diagnostic yield indicates yield after evaluation of variants of uncertain significance (VUS) and phenotype fit. Two diagnoses were made with targeted testing of a familial variant and are excluded from this table. R21, R14, R412 are test codes for standard NHS diagnostic tests as per the NHS test directory[27] (see Appendix S1). *Upgraded VUS. †Downgraded VUS. Dx, diagnosis (likely pathogenic or pathogenic variant); IF, incidental finding.

Conclusiones

- El estudio genético contribuye de forma importante al estudio de la muerte fetal intrauterina.
- El consenso de sociedades internacionales recomiendan CMA de entrada mientras sea económicamente plausible.
  - Presenta mayor rendimiento diagnóstico que cariograma y/o QF-PCR.
- Un 25-30% de las muertes fetales e interrupciones de embarazo por anomalías fetales podría encontrar una causa identificable con estudio genético (ES y CMA).
- El rendimiento diagnóstico del estudio genético mejora de un 25% a un 45% con una adecuada asesoría genética.

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