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Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

INTRAUTERINE FETAL DEATH (IUFD) OF A FETUS IN BICHORIAL-BIAMNIOTIC TWIN PREGNANCY- A CASE REPORT

Dott.ssa Martina Bertin

S.F. 47 aa

• An. familiare: madre con IPA in tp, padre ipertiroideo

• An. fisiologica: nega allergie a iodio, lattice e farmaci, mai fumato, usato E/P per 20 aa senza problemi, diuresi regolare e alvo stiptico

• An. patologica remota: HSC operativa: polipectomia endometriale (2010), nega interventi chirurgici maggiori, nega pato d'organo e/o sistemiche, nega tp in atto

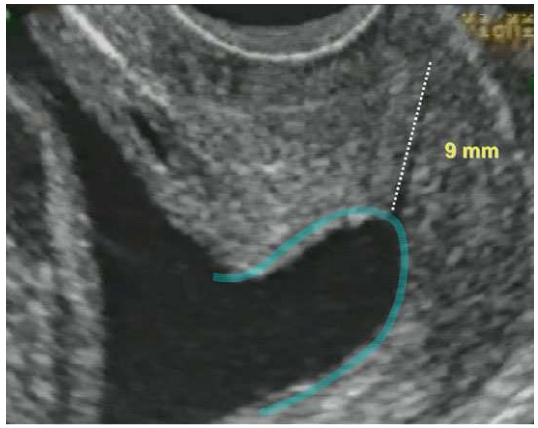
PARA 0000 U.M. 01/03/2012

Gravidanza bicoriale biamniotica ottenuta con tecnica FIVET.

ECO I trimestre (12 s.g.): regolare
Ultrascreeen (12 s.g.): basso rischio per trisomia 13,18 e 21 per entrambi i gemelli

AMNIOCENTESI: cariotipo regolare 46, XX per entrambi i gemelli

ECO II trimestre (20+5 s.g.) morfologia regolare, biometria corrispondente a EA e LA regolare per entrambi i gemelli.

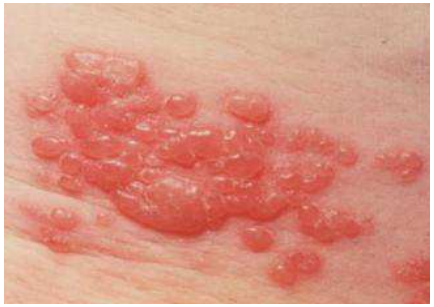


In data 25/08/12 **(25+2 s.g.)** la Paziente si rivolge al PS ostetrico per comparsa di attività contrattile irregolare.

Visita: CU non contratto, collo sacralizzato, raccorciato, chiuso, no perdite atipiche in atto

All'eco office: BCF, MAF, emodinamica fetale e LA regolari per entrambi i gemelli, cervicometria 9 mm con ampio funneling a U che non si modifica sotto sforzo -> ricovero per MINACCIA DI PARTO PRETERMINE IN GRAVIDANZA GEMELLARE

Si segnala la presenza di lesione vescicopapulare perianale sx dolente, non arrossata (simil-herpes genitale).



All'ingresso in Reparto la Paziente si presenta:
apiretica, PAO 134/84, FC 120 bpm.

Esami 25/08/2012: GB negativi, PCR negativa, Hb 118 g/L,
D-dimero 2240 microg/L.

Si imposta RIPOSO RELATIVO e la seguente terapia:

- Induzione della maturità polmonare con Bentelan 12 mg i.m.
- Atosiban
- Fragmin, 5000 UI: 1 fl sc/die
- Progeffik ovuli vaginali: 1 ovulo/la sera

Nei giorni successivi al ricovero il monitoraggio dei parametri clinici ed ematochimici materni persiste regolare e lo stesso dicasi per il benessere fetale e la cervicometria al controllo ecografico. MAF ben percepiti per entrambi i gemelli.

- CMV pregresso
- Toxotest (25/08/2012): soggetto recettivo
- Sierologia (25/08/2012): negativa
- TV (27/08/2012): negativo
- Sierologia HSV 1 (27/08/2012): IgG + IgM –
- Sierologia HSV 2 (27/08/2012): IgG – IgM-
- Sierologia VZV (27/08/2012): IgG + IgM-
- Sierologia Parotite virus (27/08/2012): IgG- Ig M-
- Urocoltura (29/08/2012) positiva per E.Coli per cui si imposta terapia con Amplital 1 gr x 3

Nei giorni successivi al ricovero si aggiunge alla terapia:
- Mag 2 bustine: 1 bustina x 2/die
-una volta terminato il ciclo di Atosiban si continua la tocolisi con Miolene e Isoptin (associati a KCl retard 1 cpr/die) per il persistere di attività contrattile irregolare riferita dalla Paziente.
- Ferro, Folico e Multivitaminico della gravidanza
- Calze elastiche

Cons. dermatologica (30/08/2012):
"Lesioni vescicolose al gluteo sx, presenti da circa 7 gg compatibili con Zoster, si consiglia Rifocin per impacchi fino a risoluzione croste e Ceramol Beta complex"

03/09/2012 (26+4 S.G.): riscontro di assenza di BCF nel gemello sx con segni di recente morte endouterina.

- Sierologia Parvovirus B19 (04/09/2012): IgG+, IgM-
- Sierologia Morbillivirus (04/09/2012): IgG+, IgM-
- OGTT (04/09/2012): negativo
- Pap-test (05/09/2012): negativo

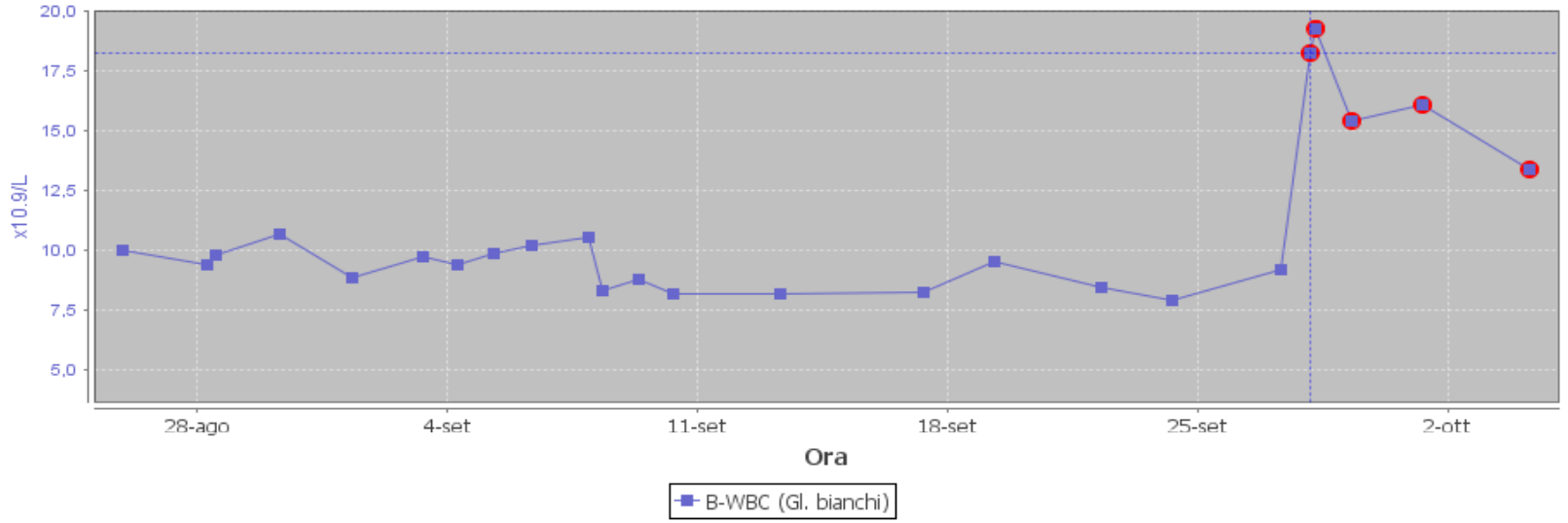
- **Consul infettivologica (04/09/2012):** " Lesioni al gluteo sx compatibili con VZV, ormai in fase di risoluzione"

Consul dermatologica (05/09/2012):
"…lesioni in risoluzione"

- Sierologia VZV (05/09/2012): IgG+ **IgM+**

- **Consul infettivologica (06/09/2012):** " Persiste sintomatologia algica a gluteo e coscia sx ed è presente ulcera da Herpes labiale e ulcera dolente perianale. Tutto depone per Herpes zoster perianale, consiglio di eseguire tamponi perianali e vaginali per HSV DNA e HZV DNA. Suggerisco terapia con Acyclovir 800 mg x 5/die e Becozym 1 cpr x 2/die per 7 giorni"

- Tampone vaginale (06/09/2012): positivo per E.Coli
- Tampone perianale e vaginale per ricerca di HSV e HZV-DNA (07/09/2012): negativo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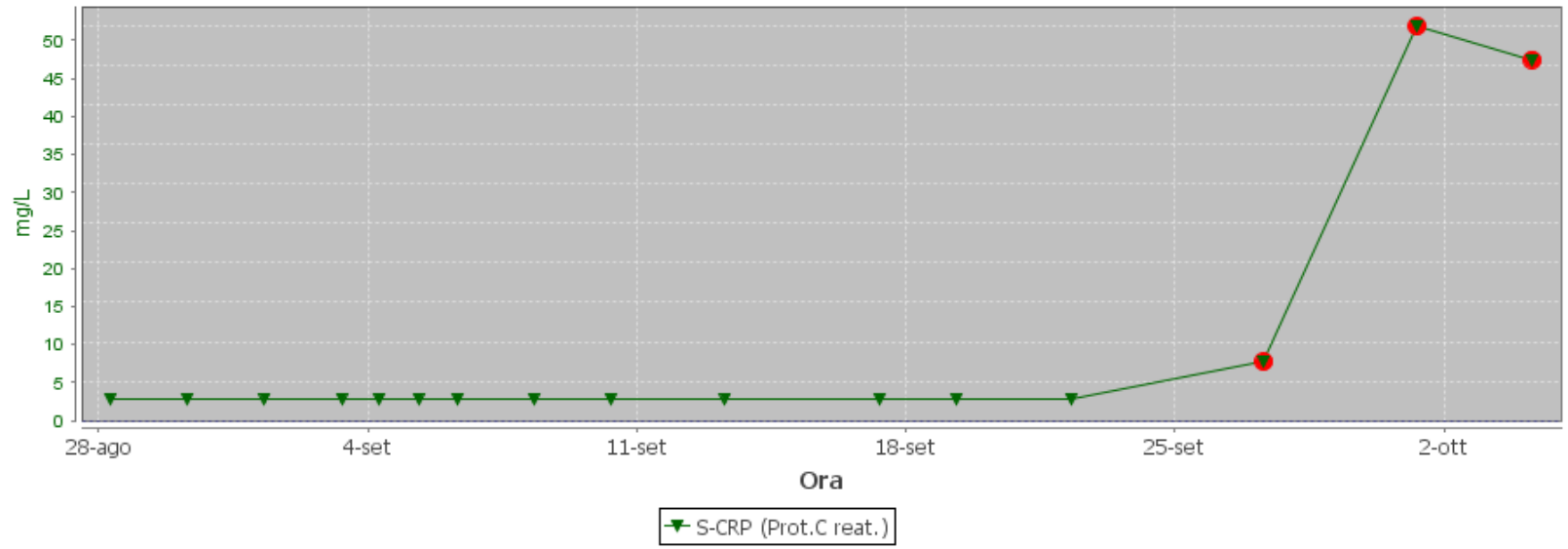
B-WBC (Gl. bianchi)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11-set
18-set
25-set
2-ott
Ora
S-CRP (Prot.C reat.)

Consul infettivologica (13/09/2012): "Guarite le lesioni perianali. Sospesa ieri la terapia antivirale. Persiste prurito perianale, per cui consiglio esame parassitologico delle feci".

- Es. parassitologico delle feci (13/09/2012): negativo

- Es urine (13/09/2012): <u>leucocituria</u> 70 el/uL per cui si imposta terapia con Neofuradantin 50 mg cpr: 1 cpr x 3/die

Eco ostetrica (13/09/2012): "Per il gemello di dx: BCF e MAF visualizzati. LA regolare. Emodinamica fetale regolare. Buon tono fetale. Cervicometria di 7,2 mm, ampio funneling a U che non si modifica dopo le manvre da sforzo."

26/09/2012: la Paziente lamenta perdite rosate, alla visita: CU non contratto, collo sacralizzato, raccorciato del 70%, chiuso, non perdite atipiche in atto. Si invia la Paziente in Sala Parto.

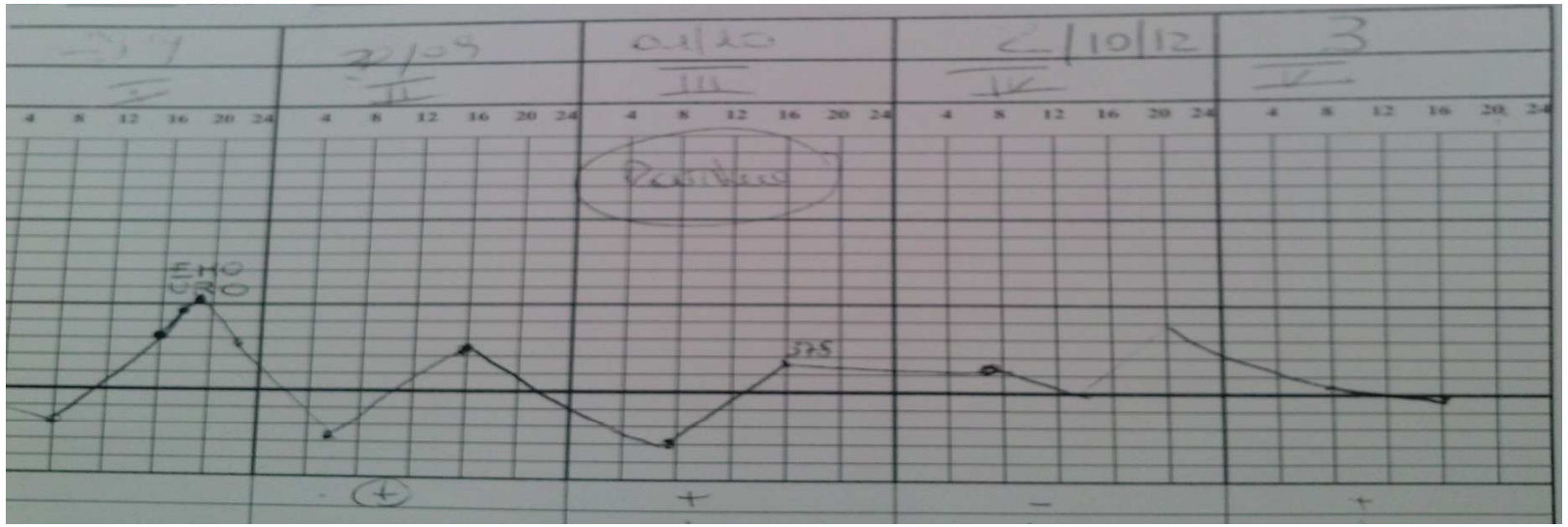
NST: reattivo, attività contrattile irregolare.

Reimpostata terapia con Miolene ev a 60 cc/h e Buscopan 1 fl al bisogno. In osservazione…

27/09/2012 (30 s.g.): la Paziente lamenta attività contrattile, alla visita: CU non contratto, collo appianato, dilatazione 3-4 cm, sacco integro.

NST: reattivo, attività contrattile regolare.
Il Responsabile di Guardia dispone per TC Urgente previa somministrazione di Bentelan 12 mg i.m.

28/09/2012 H 01.03 "…..Rexi del primo sacco*:* LA fortemente tinto, rexi del secondo: **LA lievemente tinto** in normale quantità. Estrazione difficoltosa…(vacuum extractor e incisione a T sulla breccia uterina). Neonato vivo e vitale, sesso femminile, PP cefalica,1575 gr, **Apgar 6-7-8 (pH 7,27; BE (B) -4,1 mmol/L) trasferita in Patologia Neonatale**. Estrazione di secondo gemello morto, sesso femminile, PP cefalica, 1015 gr inviato per esame autoptico"



Decorso puerperale caratterizzato da **rialzo febbrile** in assenza di altri segni e/o sintomi per cui si imposta terapia antibiotica con Cromezin 1 gr x 3 e.v. per le prime 48 h, poi convertito in tp per os con Keforal 1 cpr x 3.
Lochi regolari.

- In quinta giornata remissione dell'andamento febbrile
- Dimissione in settima giornata

ESAME ISTOLOGICO DELLE PLACENTE

-**Placenta A** (9x 22 cm): funicolo normospiralizzato, biancastro,lungo 23 cm a inserzione marginale (0 cm dal margine più vicino). Le membrane appaiono lisce, trasparenti di colorito grigiastro. Il versante materno appare diffusamente lacerato, quello fetale è regolare. Si segnala corangiosi, aumento dei nodi sinciziali e aspetti di ritardata maturazione dei villi.

-**Placenta B** (22x 11 cm): **funicolo iperspiralizzato**, grigio-brunastro,lungo 34 cm a **inserzione velamentosa-marginale** (0 cm dal margine più vicino). Le membrane appaiono lisce, trasparenti di colorito grigiastro. Il versante materno presenta cotiledoni regolari, quello fetale è regolare. Si segnala **corionamniosite acuta** (risposta infiammatoria materna: stadio 3 grado 3 secondo Readline RW, 2005), aumento dei nodi sinciziali, alcuni villi avascolari e/o fibrotici e/o con aspetti dismaturi.

INTRAUTERINE FETAL DEATH (IUFD)

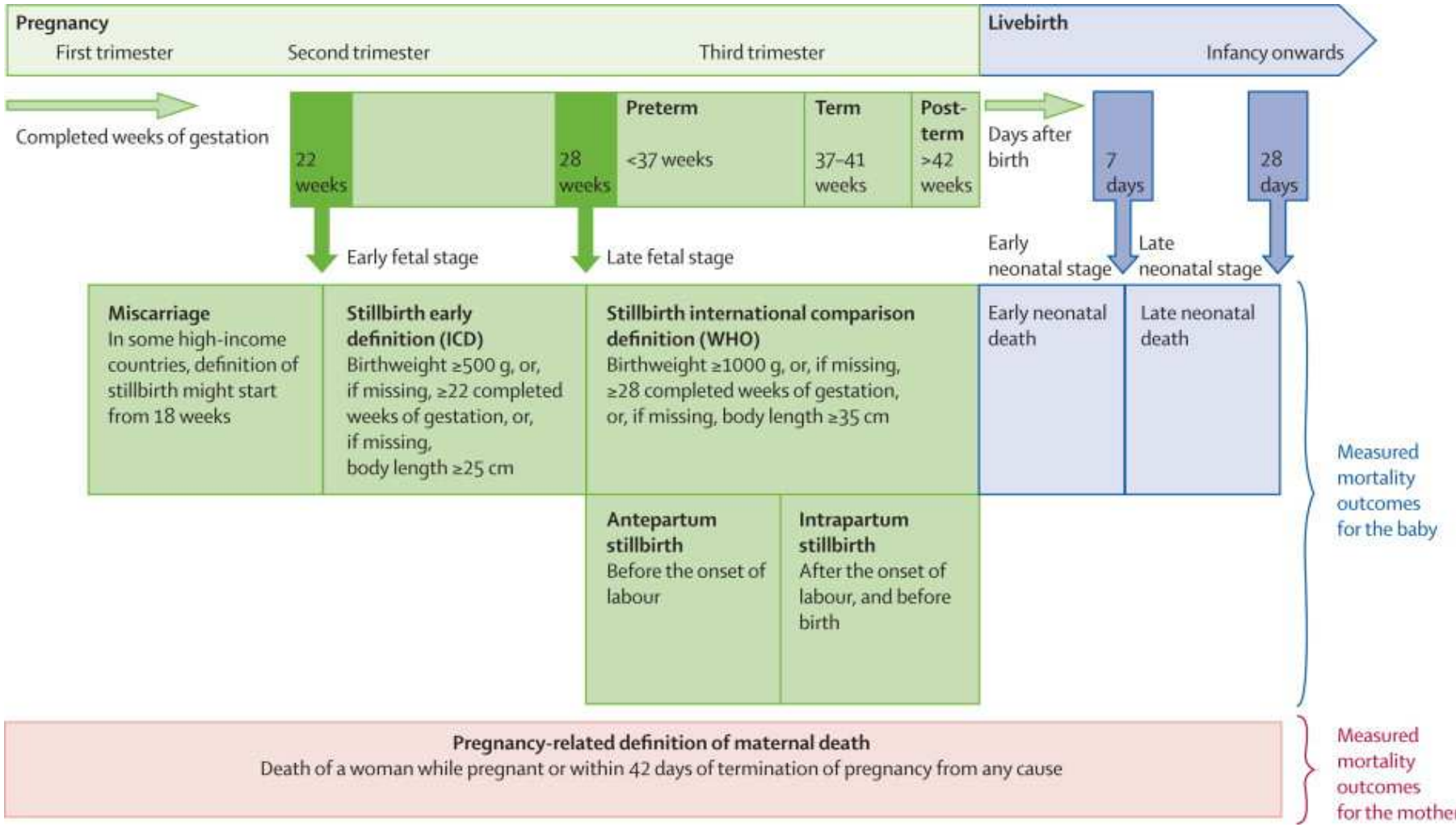
Definition

The WHO defines stillbirth as a "fetal death late in pregnancy" and allows each country to define the gestational age at which a fetal death is considered a stillbirth for reporting purposes .

As a result, some countries define stillbirth as early *as* ***16 weeks*** of gestation, whereas others use a threshold as late *as* ***28 weeks***. Fetal deaths under the threshold are considered products of miscarriage (abortuses). The majority of individual states in the United States use **20 weeks** of gestation as the threshold for distinguishing a stillbirth from a miscarriage; the International Stillbirth Alliance also suggests this cut-off.

World Health Organization. Definitions and indicators in Family Planning Maternal & Child Health and Reproductive Health. Geneva: WHO Press, 2001.

INTRAUTERINE FETAL DEATH (IUFD) Definition



Lawn JE et al.Stillbirths: Where? When? Why? How to make the data count? Lancet 2011; 377: 1448–63

INTRAUTERINE FETAL DEATH (IUFD) Incidence

In 2006 the U.S. fetal mortality rate was 6.05 fetal deaths at 20 weeks of gestation or more per 1,000 live births, 3% lower than in 2005.

CDC/NCHS National Vital Statistics Reports,Vol.60,No.8,August 28,2012

World-wide, there are between 3 and 4 million stillbirths delivered each year, 98% of these deaths occur in the developing world. 26'000 stillbirth in the United States, where the chances that a pregnancy will end as a stillbirth is about 1/200 for white women and 1/87 for black women. The stillbirth rate among multiple gestations is 4-fold higher than singletons.

Fretts R. Stillbirth Epidemiology, Risk Factors and Opportunities for Stillbirth Prevention.Clin Obstet Gynecol. 2010 Sep;53(3):588-96.

The incidence of late fetal demise was 3.5 per 1000 pregnancies.

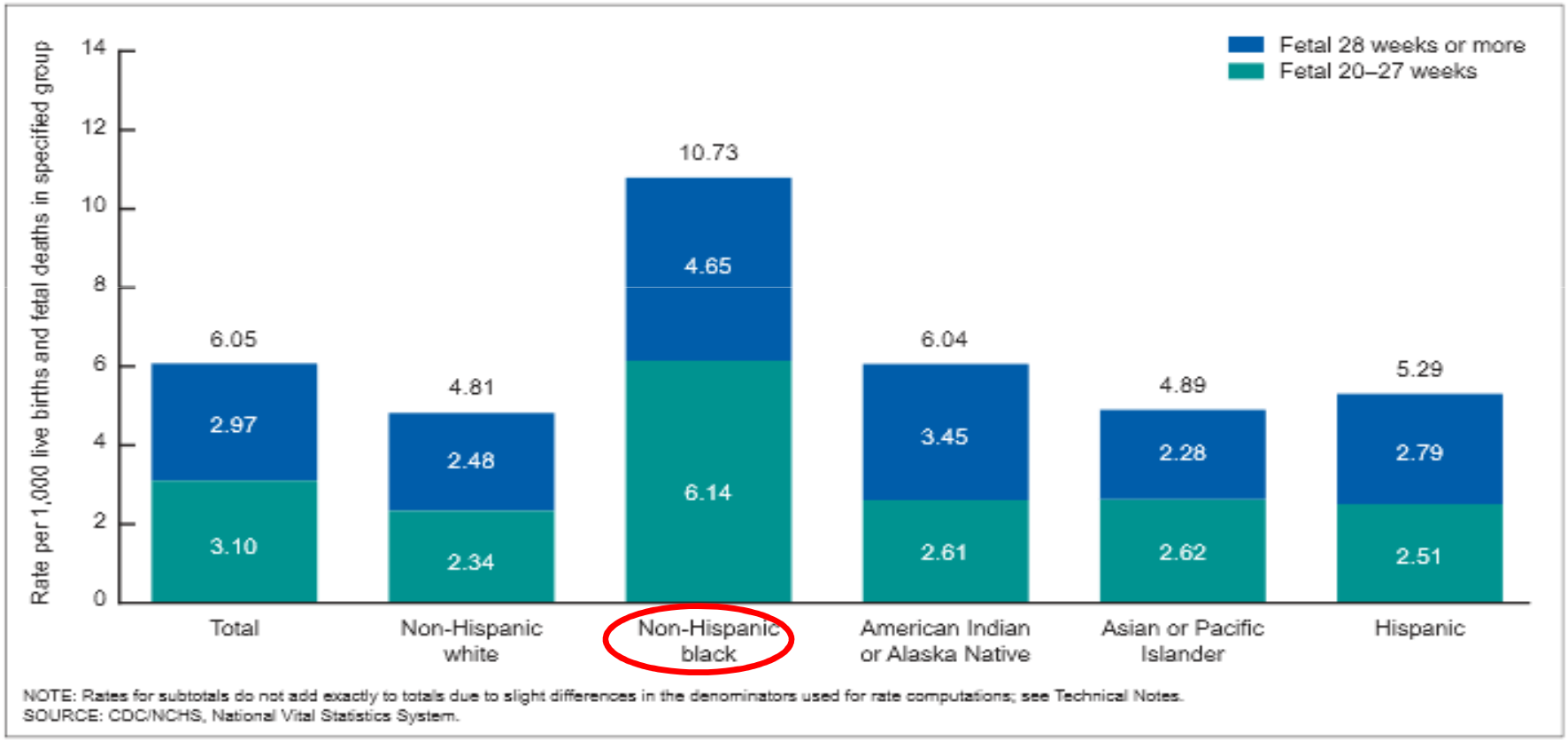
Robalo R et al. Late Stillbirth: a ten year Cohort Study. Acta Med Port. 2013 Jan-Feb;26(1):39-42.

INTRAUTERINE FETAL DEATH (IUFD) Risk factors

- non-Hispanic black race/ethnicity,
- multiple gestation
- maternal age (<20 y and >35y),
- prior stillbirth,
- prior pregnancy loss at less than 20 weeks'gestation,
- nulliparity and plurality,
- diabetes,
- maternal obesity,
- being unmarried and not cohabitating,
- smoking and illicit drug use

The Stillbirth Collaborative Research Network Writing Group. Association Between Stillbirth and Risk Factors Known at Pregnancy Confirmation JAMA, December 14, 2011—Vol 306, No. 22

INTRAUTERINE FETAL DEATH (IUFD) Risk factors

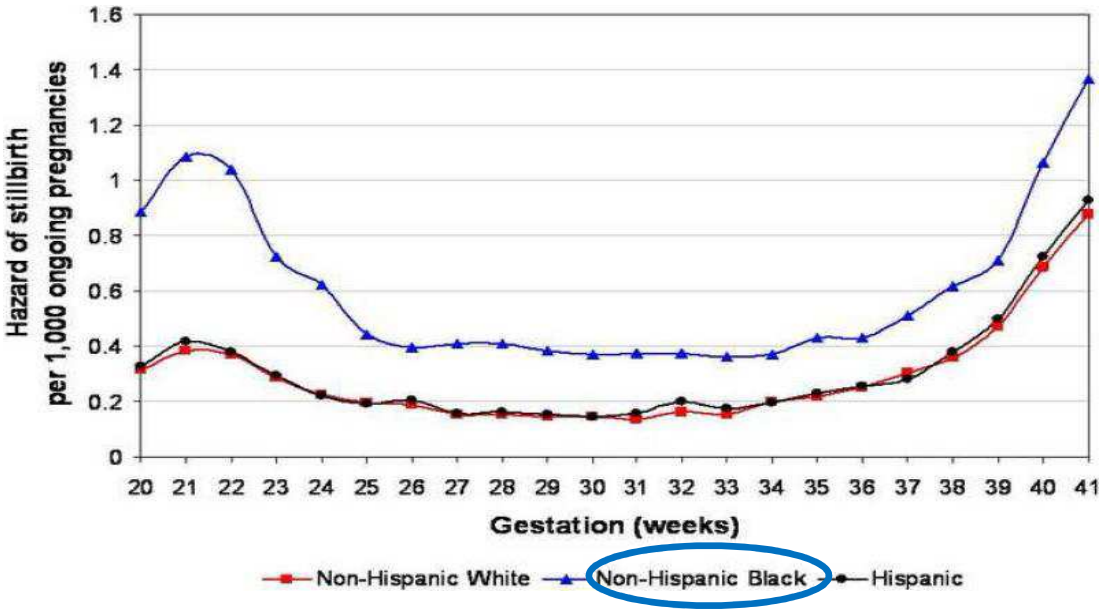


NOTE: Rates for subtotals do not add exactly to totals due to slight differences in the denominators used for rate computations; see Technical Notes.
SOURCE: CDC/NCHS, National Vital Statistics System.

Figure 5. Fetal mortality rates, by race and Hispanic origin of mother: United States, 2006

Fetal and Perinatal Mortality, United States, 2006 , CDC/NCHS National Vital Statistics Reports Vol.60,No.8,August 28,2012

INTRAUTERINE FETAL DEATH (IUFD) Risk factors



Black women have a 2.2-fold increased risk of stillbirth compared with white women. The black/white disparity in stillbirth hazard at **20-23 weeks** is 2.75, decreasing to 1.57 at **39-40 weeks**.

Willinger M et al. Racial disparities in stillbirth risk across gestation in the United States. Am J Obstet Gynecol. 2009 Nov;201(5):469.e1-8.

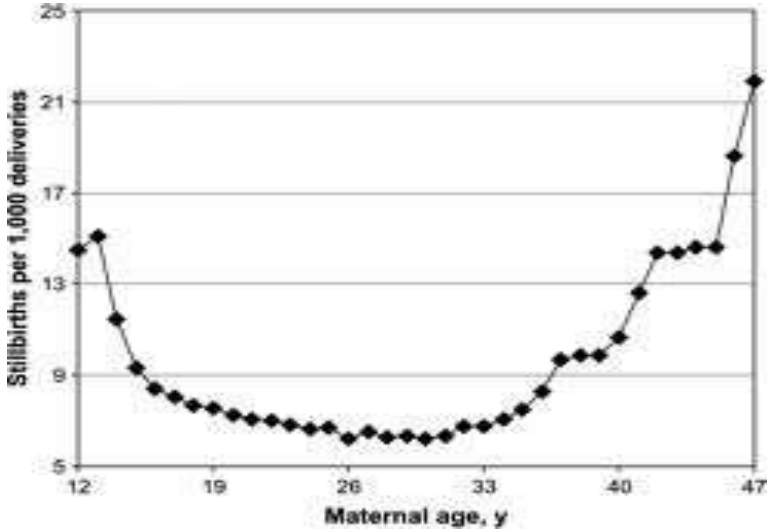
Risk of stillbirth was elevated in **black fetuses** compared with white fetuses among singletons (adjusted odds ratio [OR] 2.9, 95% confidence interval [CI] 2.8-3.0) and **twins** (OR 1.3. 95% CI 1.2-1.4) but comparable among **triplets** (OR 1.2, 95% CI 0.7-2.1).

Salihu HM et al. Racial disparity in stillbirth among singleton, twin, and triplet gestations in the United States. Obstet Gynecol. 2004 Oct;104(4):734-40.

INTRAUTERINE FETAL DEATH (IUFD) Risk factors

Fetal mortality rates vary considerably by **maternal age**. Rates were lowest for women aged 25–34 and higher for teenagers and those **aged 35 and over,** showing a typical U-shaped distribution curve. The higher risk for **teenagers** may relate to less favorable socioeconomic and behavioral conditions among pregnant teenagers.

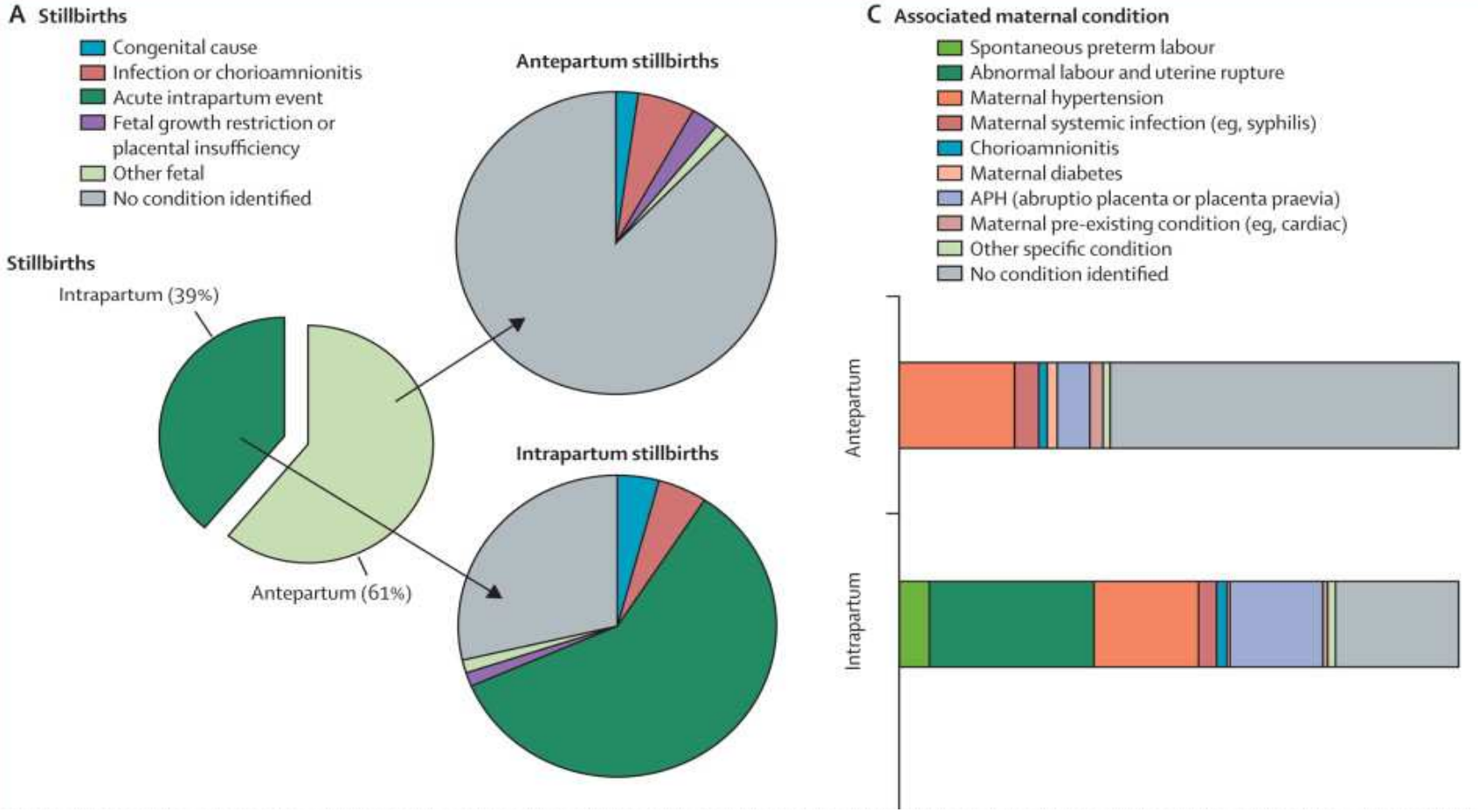
Fetal and Perinatal Mortality, United States, 2006 , CDC/NCHS National Vital Statistics Reports Vol.60,No.8,August 28,2012



This review supports the widely held view of an association between advanced maternal age and stillbirth. Of eight reviewed studies considering this association, seven found advanced maternal age (**35–40 years**) to be an independent risk factor for stillbirth and perinatal/neonatal death. Although the association is established, the exact relationship is **not** yet well understood.

Carolan M. et al. Advanced maternal age and adverse perinatal outcome: A review of the evidence. Midwifery Volume 27, Issue 6, December 2011, Pages 793–801

INTRAUTERINE FETAL DEATH (IUFD) Etiology



Lawn JE et al.Stillbirths: Where? When? Why? How to make the data count? Lancet 2011; 377: 1448–63

INTRAUTERINE FETAL DEATH (IUFD) Etiology

BOX 1. CONDITIONS ASSOCIATED WITH STILLBIRTH

Infection

- Severe maternal illness
- Placental infection leading to hypoxemia
- Fetal infection leading to congenital deformity
- Fetal infection leading damage of a vital organ
- Precipitating preterm labor with the fetus dying in labor

Maternal medical conditions

- Hypertensive disorders
- Diabetes mellitus
- Thyroid disease
- Renal disease
- Liver disease
- Connective tissue disease (systemic lupus erythematosus)
- Cholestasis

Antiphospholipid syndrome

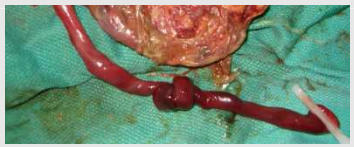
Heritable thrombophilias

Red cell alloimmunization

Platelet alloimmunization

Congenital anomaly and malformations

Chromosomal abnormalities including confined placental mosaicism



Fetomaternal hemorrhage

Fetal growth restriction

Placental abnormalities including vasa previa and placental abruption

Umbilical cord pathology including velamentous insertion, prolapse, occlusion and entanglement

Multifetal gestation including twin–twin transfusion syndrome and twin reverse arterial perfusion

Amniotic band sequence

Central nervous system lesions

Stillbirth Classification—Developing an International Consensus for Research Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM et al. ACOG vol. 114, no. 4, october 2009

INTRAUTERINE FETAL DEATH (IUFD) Infective etiology

INFECTIONS are associated with 10% to 20% of stillbirths in developed countries and with a much greater percentage in developing countries

Ascending infection **from the vagina** in the space between the maternal decidua and the fetal membranes.

- Ureaplasma urealyticum
- Mycoplasma hominis
- Strepto agalactiae

Infections may arise systemically, spread **hematogenously**, and reach the fetus through the placenta.

- influenza
- pneumonia,
- pyelonephritis
- appendicitis
- other bacterial (E.Coli, Listeria monocytogenes), viral diseases (rubella,VZV) and malaria

INTRAUTERINE FETAL DEATH (IUFD) Maternal etiology

Preeclampsia (20/1,000) and **HELLP** (50/1,000)

Untreated hyperthyroidism ex. Graves' disease (100/1,000) and **untreated hypothyroidism** (40/1,000)

Insulin-dependent diabetes mellitus with signs of either intrauterine or intrapartum asphyxia, LGA or SGA fetus, or severe malformation.

The risk of stillbirth increases with severity of renal impairment. Positive linear relationship between maternal **creatinine levels** and stillbirth rates.

Antiphospholipid syndrome with a clear histopathologic or clinical evidence of placental insufficiency

Raised bile acid levels (>50 micromol/L) plus a history of pruritus historically (60–70/1,000)

Two large prospective cohort studies found no association between the **factor V Leiden mutation** and pregnancy loss.

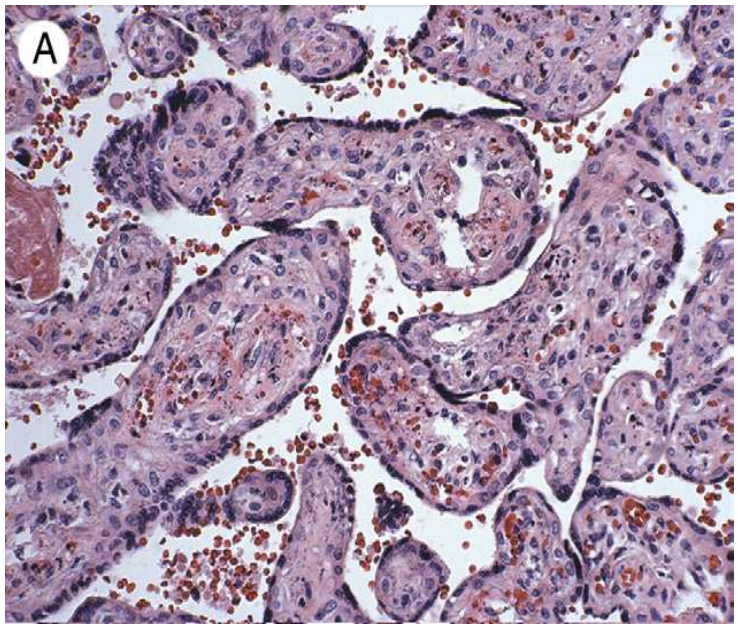
Stillbirth Classification—Developing an International Consensus for Research Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM et al. ACOG vol. 114, no. 4, october 2009

INTRAUTERINE FETAL DEATH (IUFD) Placenta etiology

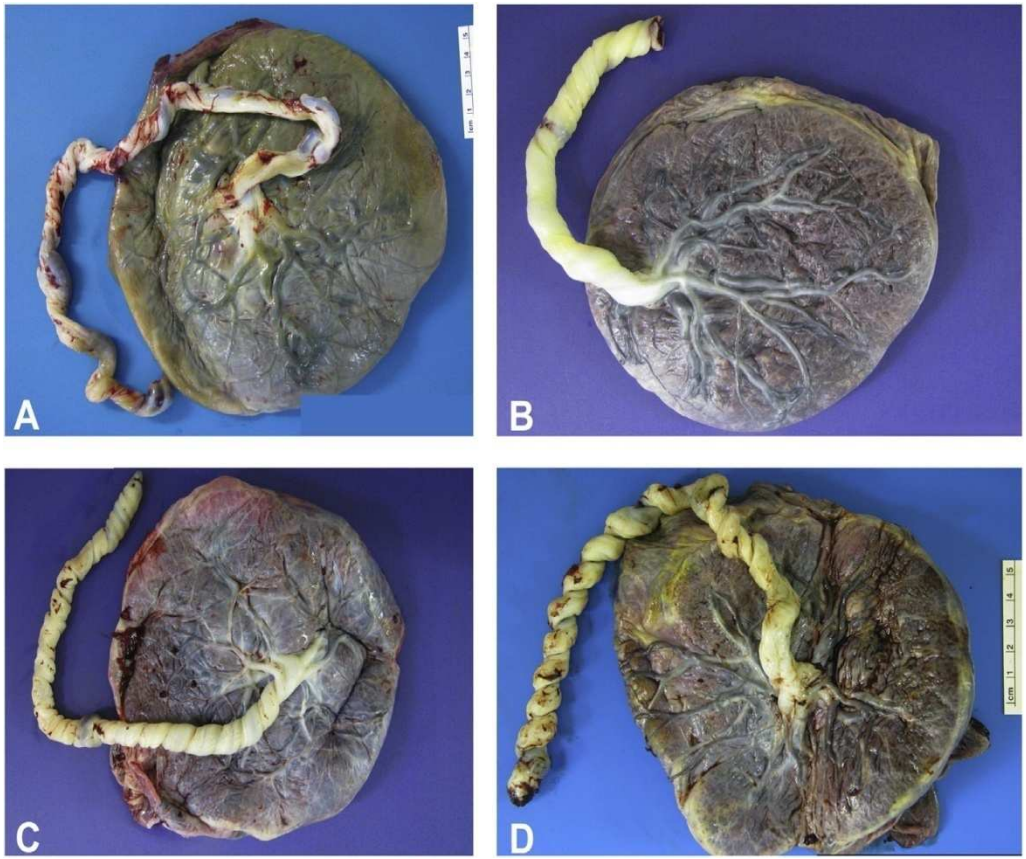
Half of the women (n = 190) had placental and 19.4% (n = 73) unknown cause of stillbirth. Placental-associated conditions were registered in 18% (n = 68) of cases with a non-placental or an unknown cause. Two-thirds of all stillbirths (**68%**) were caused by or associated with placental pathology. *Helgadòttir LB et al. Classification of stillbirths and risk factors by cause of death – a case-control study. Acta Obstet Gynecol Scand 2013; 92:325–333*.

Of 25 stillbirth cases with an unknown cause of death, a significantly larger subset (13 cases or 52%) met the **minimal** (fetal vascular ectasia and thrombosis involving the muscular branches of the fetal vascular tree) and **additional** criteria (avascular villi and/or villous stromal karyorrhexis, for **cord accident** (P = .0038). Thus, we find non acute cord compression implicated in over half of "unexplained" fetal deaths.

Parast MM et al. Placental histologic criteria for umbilical blood flow restriction in unexplained stillbirth. Human Pathology (2008) 39, 948–953.



INTRAUTERINE FETAL DEATH (IUFD) Cord etiology



Placental images representing the four gross umbilical cord coiling patterns. A. Undulating, B. Rope, C. Segmented, D. Linked .

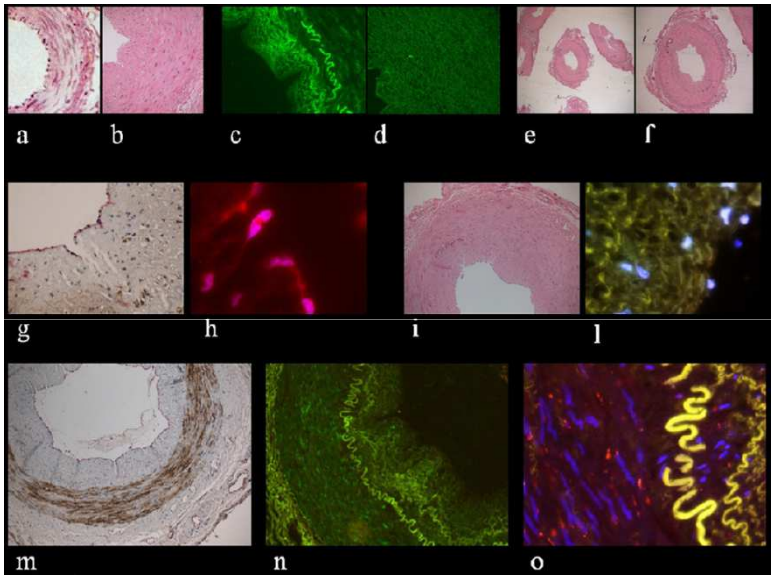
Stillbirth was identified in 18 cases and occurred across all cord coiling groups, but was by far most frequently associated with the **linked pattern** of coiling, occurring in nearly half (5/12, 42%) of cases showing that coiling pattern. In addition, 56% of the stillbirths had either the **segmented** or linked pattern of umbilical cord coiling. The segmented and linked patterns, are associated with histologic evidence of chronic fetal vascular obstruction/ FTV in the placenta and stillbirth.

Ernst LM et al. Gross patterns of umbilical cord coiling: Correlations with placental histology and stillbirth. Placenta 34 (2013) 583e588

INTRAUTERINE FETAL DEATH (IUFD) Unexplained etiology

Microscopy observations of the abdominal aorta wall of **one IUGR stillbirth** in which ultrasound had detected aIMT confirmed the intima thickening and detected condensation of the elastic fibers forming an evident internal elastic membrane and presence of inflammatory elements, such as macrophages, activated endothelial cells, and fibroblastoid cells.

Lo Vasco VR et al. Fetal aorta wall inflammation in ultrasound-detected aortic intima/media thickness and growth retardation. Journal of Reproductive Immunology 91 (2011) 103– 107

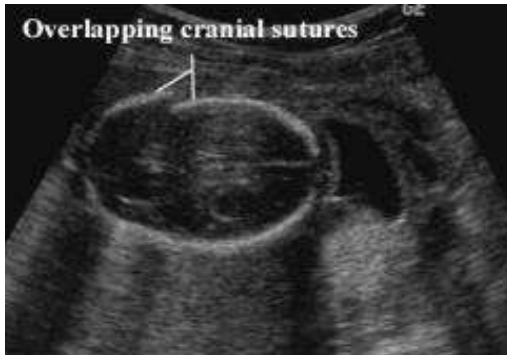


Of 91 cases of intrauterine fetal death, missense mutations associated with **Long QT syndrome (LQTS)** susceptibility were discovered in 3 cases (3.3%) and overall, genetic variants leading to dysfunctional LQTS associated ion channels in vitro were discovered in 8 cases (8.8%). These preliminary findings may provide insights into mechanisms of some cases of stillbirth.

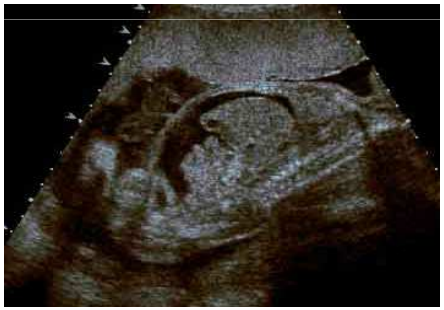
Crotti L. et al. Long QT Syndrome–Associated Mutations in Intrauterine Fetal Death. JAMA, April 10, 2013—Vol 309, No. 14

INTRAUTERINE FETAL DEATH (IUFD) Ultrasound sign

In addition to the absence of fetal cardiac activity and movements, other secondary features after several days (>2 days) from death:



1) Collapse of the fetal skull with overlapping bones (**Spalding**'s sign)



2) Hydrops

3) Maceration resulting in unrecognisable fetal mass with separation of the skin from the head and thorax, creating a bubble-like image

4) Intrafetal gas (within the heart, blood vessels and joints- **Robert**'s sign)

Ultrasound in Obstetrics and Gynecology: Obstetrics. Vol 1 Eberhard Merz - 2005 – Medical Theme

INTRAUTERINE FETAL DEATH (IUFD) Twin pregnancy

Single twin demise occurs in up to 6% of twin pregnancies and may occur at any trimester with potentially profound consequences. One of the key influential factors of twin morbidity and mortality is **zygosity**. One large retrospective study demonstrated that monozygotic twins had an almost 20 times relative risk (RR) for both twins being stillborn, a 1.63 RR for one twin being a stillborn and 2.26 RR for the live cotwin dying as a neonate when compared to dizygotic pregnancies.

Hillman SC et al. Single twin demise: consequence for survivors. Seminars in Fetal & Neonat Med 15 (2010) 319-326

The most effective fetal surveillance system for multiple gestations is currently not known(..) If **growth discordance** (>20% to 30%, calculated as a percentage of the larger twin's weight) or growth restriction (<10%) is discovered, US is recommended every 2 weeks. The incidence of infant death is 25%, congenital anomalies 38%, and small for gestational age 32% in premature infants with body weight discordance >30%.

ACR Appropriateness Criteria Multiple Gestations. Ultrasound Quarterly & Vol. 28, N. 2, June 2012

INTRAUTERINE FETAL DEATH (IUFD) Co-twin outcome

A recent systematic review of 19 studies found that following the death of one twin the risk of death in the co-twin was 12% (95% CI 7-18) for monochorionic pregnancies and 4% (2-7) in dichorionic pregnancies. The odds ratio for **monochorionic co-twin intrauterine death** was six times that of dichorionic twins (6.04; 95% CI: 1.84-19.87).

Ong SS, Zamora J, Khan KS, Kilby MD. Prognosis for the co-twin following single-twin death:a systematic review. BJOG 2006;113:992-8

A recent systematic review found that the risk of **preterm delivery** in case of single intrauterine fetal demise (sIUFD) in twin pregnancy before 34 weeks' gestation is **not** affected by **chorionicity** and is 68% (95% CI: 56-78) following sIUFD in monochorionic pregnancies and 57% (34-77) in dichorionic pregnancies. **Opposite sex twins** with a sIUFD at 20-24 weeks are associated with a **survival** of 12% (8-16%). This rises to 98% (92-100%) after 37 weeks. Same sex twins with a sIUFD at 20-24 weeks have an 8% (6-9%) survival rate, which after 37 weeks rises to 85% (79-89%).

Johnson CD, Zhang J. Survival of other fetuses after a fetal death in twin or triplet pregnancies.Obs Gynecol 2002;99;703.

INTRAUTERINE FETAL DEATH (IUFD) Co-twin outcome

The rate of **neurological abnormality** in monochorionic co-twin demise was 18% (95% CI:11-26) compared with 1% (0-7) in dichorionic survivors. This gave an odds ratio of 4.07 (1.32-12.5) for monochorionic survivors compared with dichorionic survivors.

Ong SS, Zamora J, Khan KS, Kilby MD. Prognosis for the co-twin following single-twin death: a systematic review. BJOG 2006;113:992e8

The rate of **cerebral palsy** in **same sex twins** that survived to infancy was 106 per 1000. This is compared with different sex twins that had a cerebral palsy rate of 29 per 1000 infant survivors, leading the authors to conclude that cerebral palsy rates were higher in monozygous twins.

Pharoah POD, Adi Y. Consequences of in-utero death in a twin pregnancy. Lancet 2000;355(9215)

Neurological follow-up for 18 twins survived after co-twin death (10 from MC and 8 from DC pregnancies). All 10 MC twins were **neurologically normal** at 12 months.

Fichera A,et al. Perinatal outcome and neurological follow up of the cotwins in twin pregnancies complicated by single intrauterine death. Eur J Obstet Gynecol Reprod Biol 2009;147:37e40.

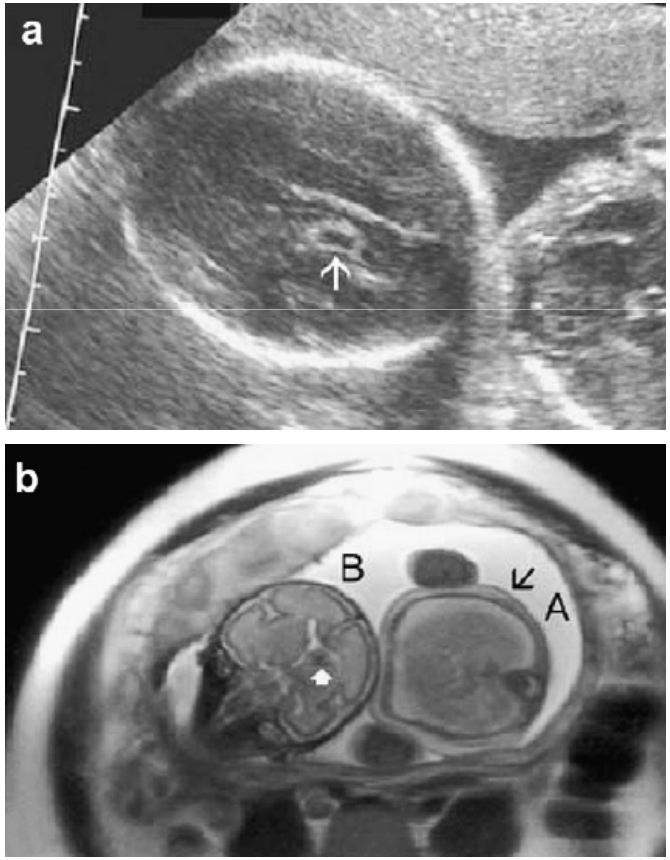
INTRAUTERINE FETAL DEATH (IUFD) Co-twin outcome

Three patterns of brain pathology have been described in surviving twins of sIUFD:

1. Hypoxic ischaemic lesions of white matter. These usually occur in the area supplied by the middle cerebral

2. Haemorrhagic lesions either isolated or in combination with ischaemic lesions (fig.a)

3. Anomalies secondary to a vascular disturbance. These include neural tube defects, limb reduction anomalies and optic nerve hypoplasia.



Murphy KW. Intrauterine death in a twin: implications for the survivor. In: Ward RH, Whittle M, editors. Multiple pregnancy. London: RCOG Press; 1995

INTRAUTERINE FETAL DEATH (IUFD) Co-twin surveillance

A conservative approach is advocated with regular fetal and maternal surveillance.
Ultrasound examination of the surviving twin should be performed for abnormalities and then regular scans for growth and liquor volume on a two-weekly basis are recommended. If time permits, the best timing for **MRI** is at 32 weeks or later, when white matter is developed and minor (yet clinically important) lesions in the white matter can be visualized.

Murphy KW. Intrauterine death in a twin: implications for the survivor. In: Ward RH, Whittle M, editors. Multiple pregnancy. London: RCOG Press; 1995. p.218-30

Of the range of monitoring interventions evaluated:

- fetal movement counting
- Doppler monitoring

} promising for further evaluation in high-risk pregnancies in developing countries

- low amniotic fluid measurements were strongly predictive of stillbirth (interventions to restore adequate amniotic fluid volume or to deliver the baby based on identification of oligohydramnios have not been systematically tested)

Haws RA et al.Reducing stillbirths: screening and monitoring during pregnancy and labour. BMC Pregnancy and Childbirth 2009, 9(Suppl 1):S5

INTRAUTERINE FETAL DEATH (IUFD) Delivery

The main risk with dichorionic pregnancies is **preterm delivery.** However, in the absence of spontaneous preterm delivery or other obstetric complications, elective preterm delivery of the survivor is not indicated sIUFD in DC twins is not an indication for abdominal delivery.

Blickstein I and Pearlman S. Single fetal death in twin gestations. J. Perinat. Med. 41 (2013) 65–69

Nous avons accouché 53,6 % (n = 15) des gestantes avec grossesse gémellaire(GG) et mort foetale in utero par **voie basse** et 46,4 % (n = 13) par **césarienne**. L'accouchement a été prématuré dans 85,2 % des cas. (…)En cas de GG BC, il n'y a aucun risque spécifique pour le survivant. Ainsi, en l'absence de pathologie menacante pour la mère et/ou le Co-J, la poursuite de la grossesse est acceptée par la plupart des auteurs **jusqu'à 34 à 36 SA**.

Chelli T et al. Grossesse gémellaire avec mort foetale in utero d'un jumeau : étiologies, prise en charge et pronostic. Journal de Gynecologie Obstetrique et Biologie de la Reproduction (2009) 38, 580—587

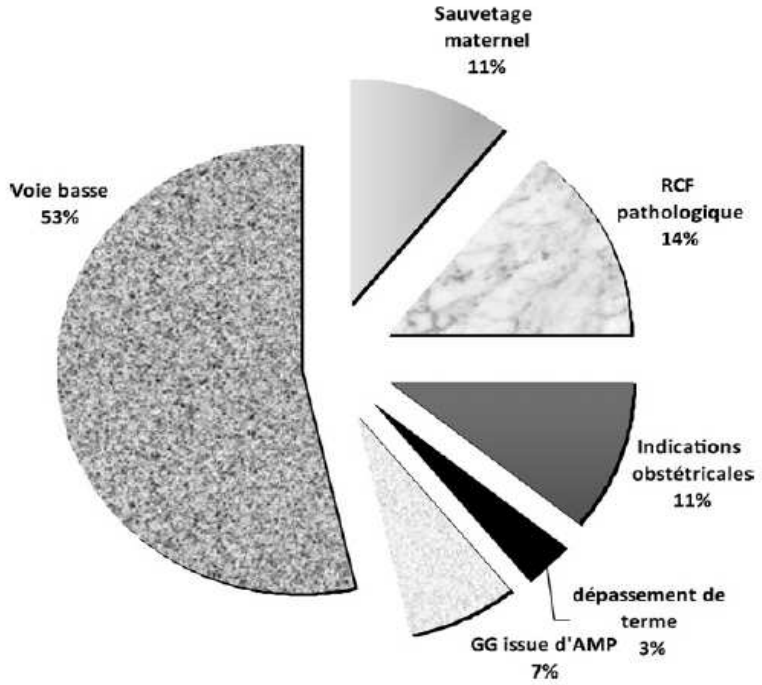


Figure 2 Voies d'accouchement et indications.

INTRAUTERINE FETAL DEATH (IUFD) Maternal outcome

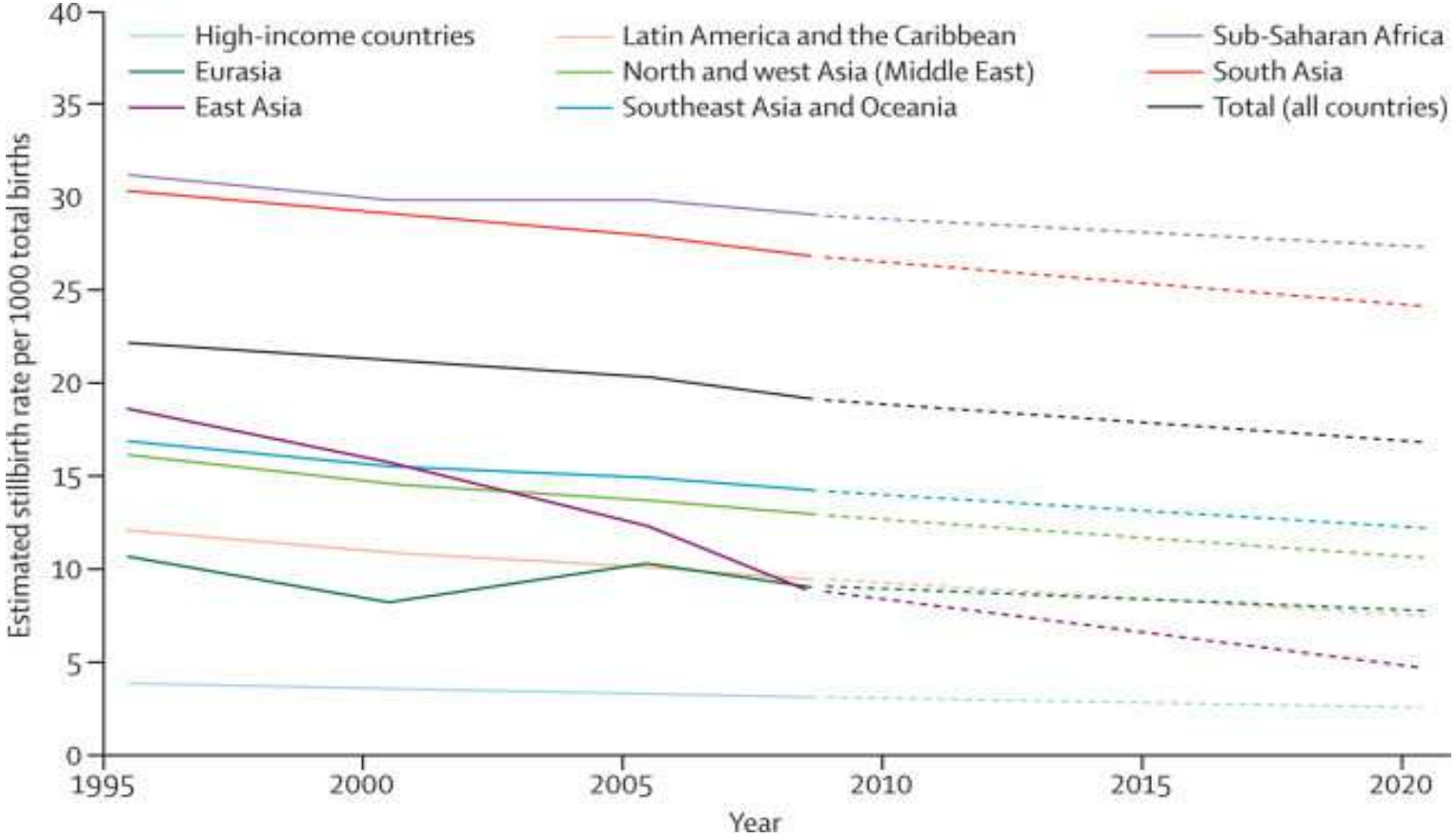
Unlike the case of IUFD in singletons, maternal disseminated intravascular coagulation (**DIC**, the so-called dead fetus syndrome) is, for an unclear reason, extremely rare or never exists in multiples.

Romero R et al. Prolongation of a preterm pregnancy complicated by death of a single twin in utero and disseminated intravascular coagulation. Effects of treatment with heparin. NEJM 1984; 310:772 – 4.

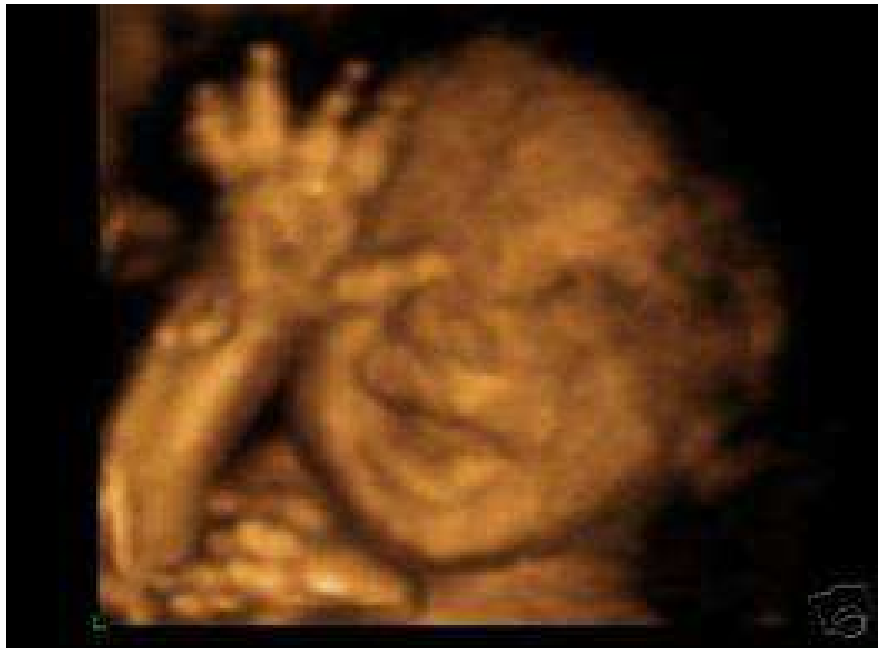
Inherited thrombophilia combined and **F2 rs179963 alone** were significantly associated with stillbirth from placental causes. The association of F2 rs179963 and stillbirth is consistent with the results of a meta-analysis of case-control studies. The main pathogenesis of thrombophilia related stillbirth is assumed to be through abnormalities in placental vasculature. The literature is not consistent regarding the association between **factor V Leiden** and IUFD. Whether coagulation abnormalities are the causes of abnormal placentation or just exert an effect on an already compromised placenta is not known.

Robertson L et al. Thrombophilia in pregnancy: a systematic review. Br J Haematol. 2006;132:171–96.
Redline RW. Thrombophilia and placental pathology. Clin Obstet Gynecol. 2006;49:885–94.

INTRAUTERINE FETAL DEATH (IUFD) Prevision



Lawn JE et al.Stillbirths: Where? When? Why? How to make the data count? Lancet 2011; 377: 1448–63

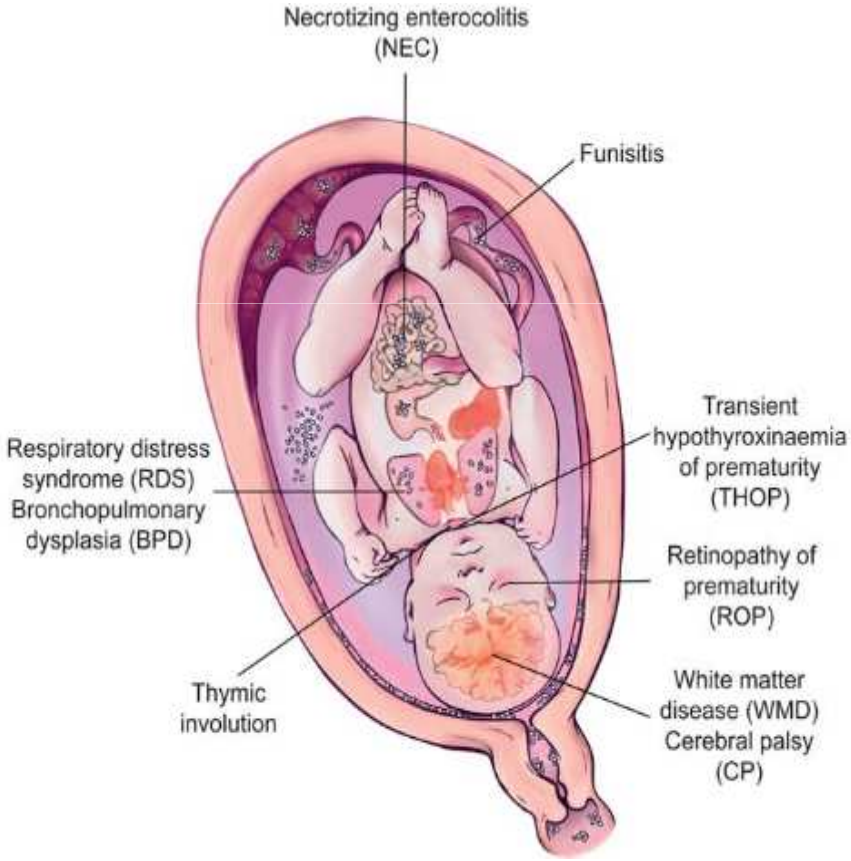


GRAZIE
PER L'ATTENZIONE

CHORIONAMNIONITIS News

The response to chorioamnionitis has been described to as the fetal inflammatory response syndrome (**FIRS**). Although earlier studies have focused mainly on the respiratory and neurological outcomes, additional fetal sequelae of chorioamnionitis have more recently been described in several other organ systems. Moreover, evidence is increasing that the effects of chorioamnionitis on health and disease may extend well beyond the neonatal period.

Gantert M et al. REVIEW Chorioamnionitis: a multiorgan disease of the fetus? Journal of Perinatology (2010) 30, S21–S30



CHORIONAMNIONITIS News

The amniotic fluid analysis showed significant differences between women with **preterm** and term delivery in the levels of **IL-1alpha, IL-1beta, IL-4, IL-6, IL-8, MCP-1, IFN-gamma** and anti-HSV2 IgG. No significant differences were observed in the levels of TNF-alpha, MMP-2, MMP-9 and specific IgG for seven vertically transmitted pathogens

La Sala GB et al. Protein m
diagnosis of early intraute
Pharmacol. 2012 Oct-Dic;

Experimental human studies have shown that **periodontal pathogens** may disseminate toward placental and fetal tissues accompanied by an increase in inflammatory mediators in the placenta…First, periodontal bacteria can directly cause **infections** both of the uteroplacenta and the fetus; second, systemic inflammatory changes induced by periodontal diseases can activate responses at the maternal-fetal interface.

Cetin I et al. Pathogenic mechanisms linking periodontal diseases with adverse pregnancy outcomes. Reprod Sci. 2012 Jun;19(6):633-41.

VZV is a DNA virus of the herpes family and is highly contagious. The human is the only source and the virus enters the host through the conjunctivae and mucus membranes of the nasopharynx. First trimester spontaneous abortion is not associated with chickenpox.

366 cases of **herpes zoster** in pregnancy were followed up (320 in Germany and 46 in UK) of which:119 occured between 0-12 weeks, 117 between 13-24 weeks and 130 between 25-36 weeks of gestation.
7 pregnancies (2%) ended in spontaneous or therapeutic abortion. No defects consistent with congenital varicella syndrome and no cases of zoster were reported in the remaining 359 infants.Two infants had other abnormalities reported: one with achondroplasia (IgM and PCR negative at birth) and the other with a cleft lip and palate.

Enders G et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases Lancet. 1994 Jun 18;343(8912):1548-51

CHORIONAMNIONITIS Hystologi findings

The prevalence of chorionamnionitis in uncomplicated (term) pregnancies varies from 4 to 5% and increases as much as up to **58%** in prenatal deaths.

Hystologic findings of chorionamnionitis :
- Acute inflammatory infiltrate composed of maternal neutrophils from the intervillous circulation and small venules in the membranous decidua.
- In many cases there is also a fetal response composed of neutrophils emanating from large vessels of the umbilical cord and chorionic plate.

Maternal inflammatory response begins in the decidua of the external membranes as patchy deciduitis and progresses to margination of neutrophils along the deciduochorionic junction, and additionally infiltration of the subchorionic maternal space.

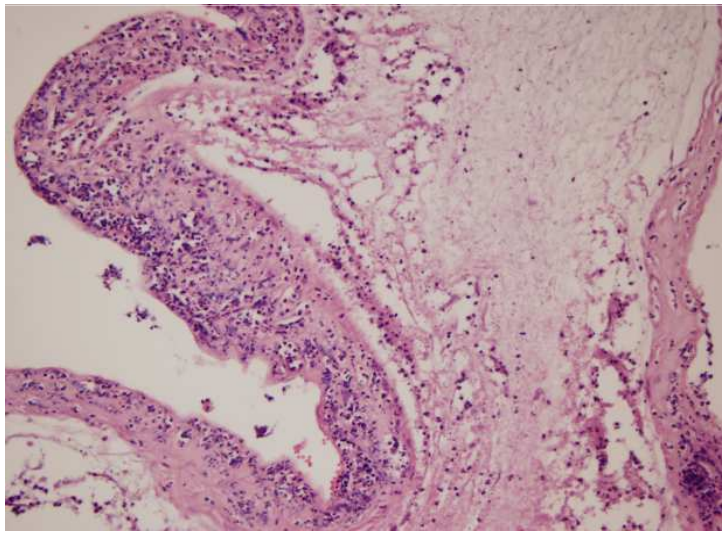
Erdener Ozer (2013). Placenta in Preterm Birth, Preterm Birth, Dr. Offer Erez (Ed.), ISBN: 978-953-51-0952-5, InTech, DOI: 10.5772/54887.

CHORIONAMNIONITIS Hystologic findings

- **STAGE 1** (early chorioamnionitis or acute subchorionitis): Neutrophils are restricted to subchorionic fibrin and the membranous decidual-chorionic interface.

-**STAGE 2** (acute chorioamnionitis): Neutrophils are located at in chorion and amnion.

- **STAGE 3** (necrotizing chorioamnionitis): There are signs of amnion necrosis including karyorhexis of neutrophils, desquamation of amnionic epithelial cells, and bandlike eosinophilia of the amnionic basement membrane.



Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Redline RW et al. Society for Pediatric Pathology, Perinatal Section, Amniotic Fluid Infection Nosology Committee. Pediatr Dev Pathol. 2003 Sep-Oct;6(5):435-48.

CHORIONAMNIONITIS Diagnosis

Clinical and amniotic fluid laboratory diagnosis of chorioamnionitis

Test	Result suggesting chorioamnionitis	Comments
Clinical parameters		Generally non-specific [4]
Fever	Temperature >100.4 twice or >101 once	95–100 sensitive [4]
Maternal tachycardia	> 100/min	50–80% sensitive
Fetal tachycardia	>160/min	40–70% sensitive
Fundal tenderness	tenderness on palpation	4–25% sensitive
Vaginal discharge	Foul-smelling discharge	5–22% sensitive
Amniotic fluid parameters		
Culture	Microbial growth	Diagnostic gold-standard

Diagnosis is based on the presence of maternal fever (>38 degrees °C) at least 2 of these conditions: maternal leukocytosis (> 15,000 cells/mmc), maternal tachycardia, fetal tachycardia, stained or foul smelling amniotic fluid, uterine tenderness.

Tita ATN, Andrews WW. Diagnosis and Management of Clinical Chorioamnionitis. Clin Perinatol. 2010 June ; 37(2): 339–354.

CHORIONAMNIONITIS
Risk factors

Risk factor	Relative risk
Prolonged membrane rupture (including PPROM)	
≥ 12 hours	5.8
> 18 hours	6.9
Prolonged labor	
Second stage > 2 hours	3.7
Active labor > 12 hours	4.0
Multiple digital exams with membrane rupture	
≥ 3 exams	2 to 5
Nulliparity	1.8
Group B streptococcus colonization	1.7 to 7.2
Bacterial vaginosis	1.7
Alcohol and tobacco use	7.9
Meconium-stained amniotic fluid	1.4–2.3
Internal monitoring	2.0

Seaward PG et al. International Multicentre Term Prelabor Rupture of Membranes Study: evaluation of predictors of clinical chorioamnionitis and postpartum fever in patients with prelabor rupture of membranes at term. Am J Obstet Gynecol 1997;177(5):1024–9.

CHORIONAMNIONITIS Ethiology

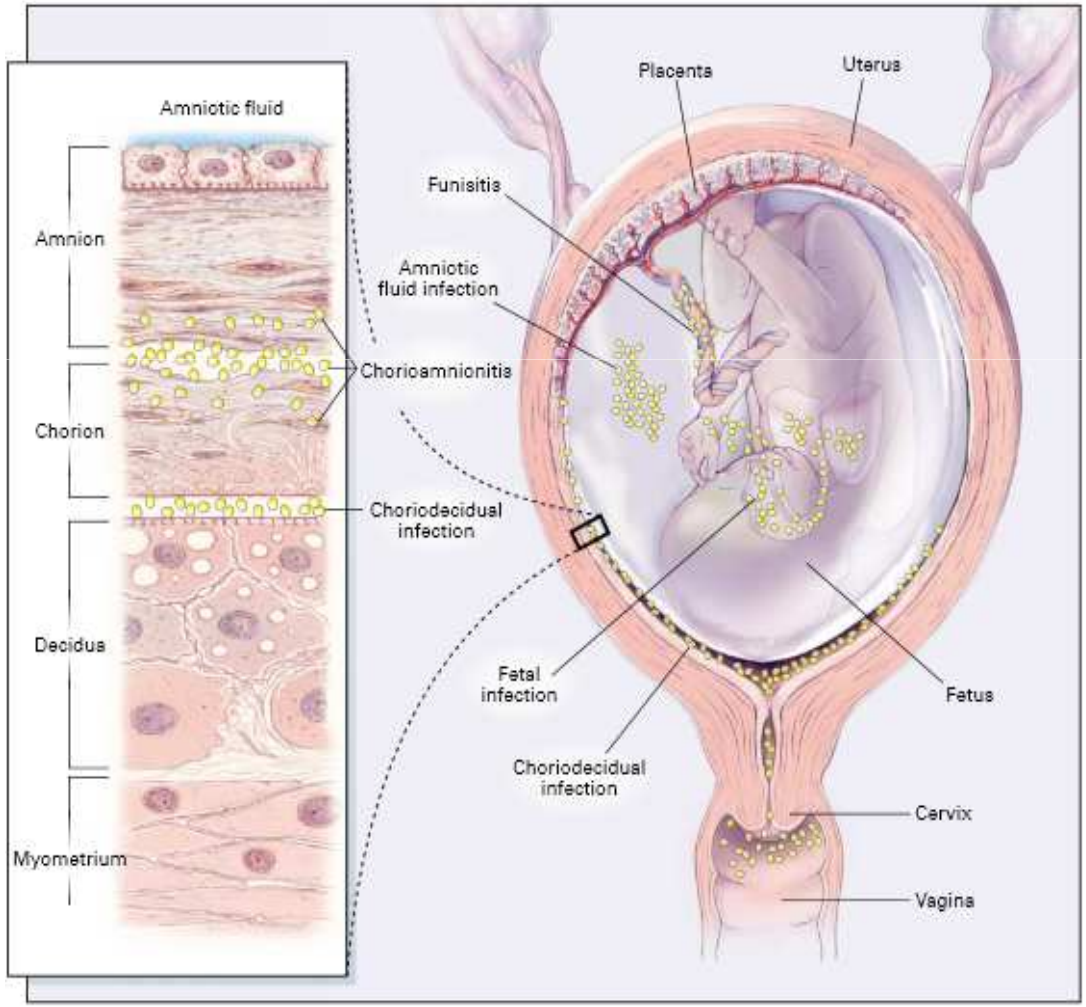


Figure 1. Potential Sites of Bacterial Infection within the Uterus.

In women in spontaneous preterm labor with intact membranes, the most commonly identified bacteria are **Ureaplasma urealyticum**, **Mycoplasma hominis**, **Gardnerella vaginalis**, **peptostreptococci**, and **bacteroides** species — all vaginal organisms of relatively low virulence. Rarely, non–genital tract organisms, such as **mouth organisms of the genus capno-cytophaga**, are found in the uterus in association with preterm labour, may reach the uterus through the placenta from the circulation or perhaps by oral–genital contact.

Goldenberg RL et al. Intrauterine infection and preterm delivery. NEJM 2000