Le infezioni perinatali nei gemelli

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Ambulatorio di malattie infettive perinatali

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Teorema della probabilita’ composta

Consideriamo un evento composto da DUE eventi indipendenti (nel senso che l'accadere del primo non influenza l'accadere del secondo)

La probabilita' (p) dell'evento composto e' uguale al prodotto delle probabilita' degli eventi componenti

p infezione perinatale nei gemelli = **p gravidanza gemellare** × **p infezione perinatale**

1,8 % **variabile**

MALATTIA CRONICA	HIV	HCV	HBV	SIFILIDE
Prevalenza	0,2%	2,5% -3,5 %	1,5%	0,44%
p inf grav gem	**0,36/10.000**	**5,4/10.000**	**2,7/10.000**	**0,8/10.000**
Trasmissione	1%	5%	10%-15%	10,5%
MALATTIA ACUTA	**CMV**	**TOXO**	**ROSOLIA**	**VARICELLA**
Incidenza	1% -2%	0,77%	6 casi di rosolia cong. nel 2009	~1/10.000
p inf grav gem	**2,7/10.000**	**1,4/10.000**		**~2/1.000.000**
Trasmissione	30-40%	7%		

OUTCOME

CONCORDANZA DELL’ESITO (INFETTO/NON INFETTO)

CONCORDANZA NELL’ESPRESSIONE DELLA MALATTIA

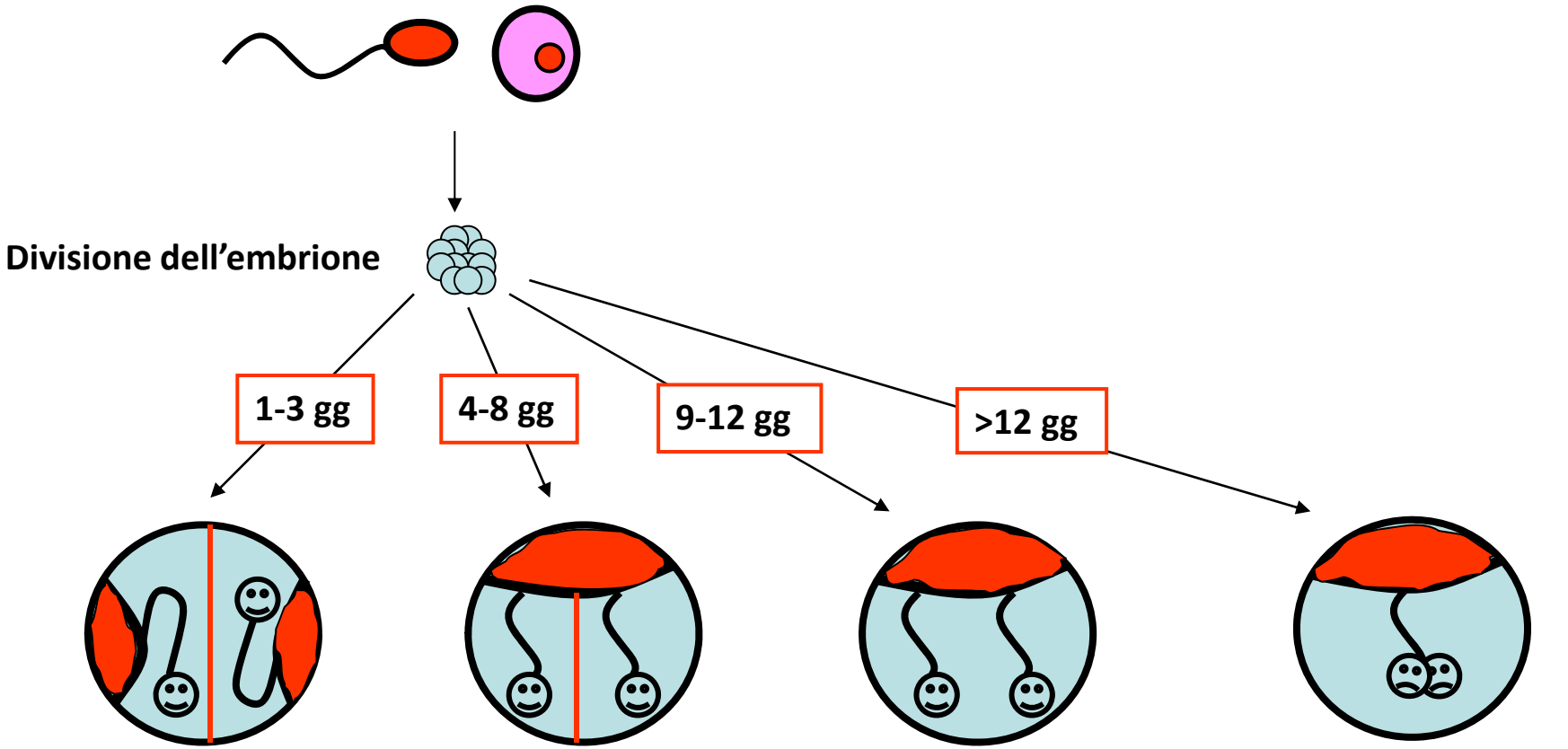
VARIABILI

ORDINE DI NASCITA

ZIGOSITA’

CORIONICITA’

GEMELLI MONOZIGOTICI



High risk of HIV-1 infection for first-born twins. The International Registry of HIV-exposed Twins.

Data on **66 set** of twins born to women infected with HIV

- HIV-1 infection was more common in first-born than in second-born twins (p = 0·004)

- 50% of first-born twins delivered vaginally and 38% of first-born twins delivered by caesarean were infected, compared with 19% of second-born twins delivered by either route

- HIV-1 infection status tended to be concordant in more monozygotic (14 of 17 sets – 82%) than dizygotic (26 of 43 – 60%) sets

Goedert LL, et al. Lancet 1991

Birth order, delivery route, and concordance in the transmission of human immunodeficiency virus type 1 from mothers to twins

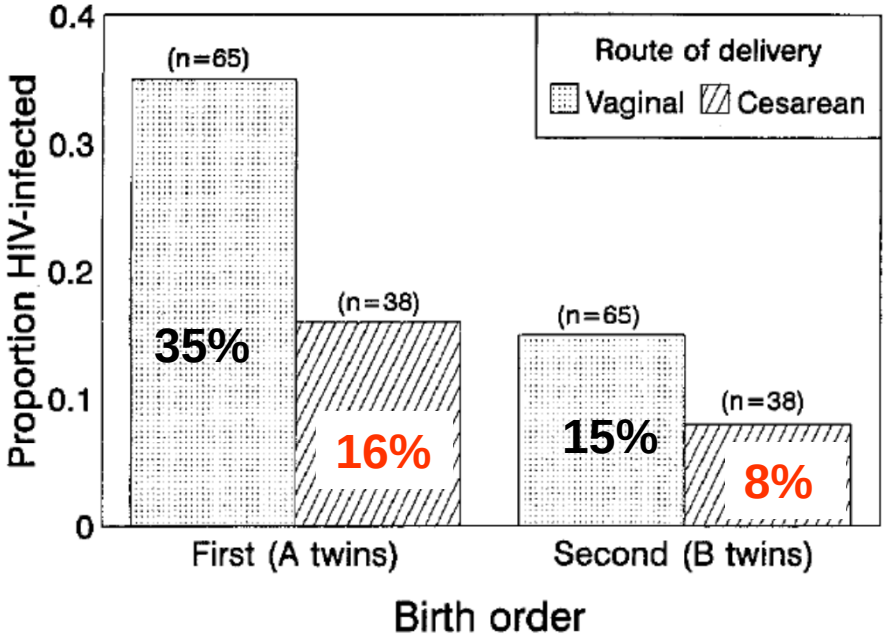


Fig. 1. Proportions of infants infected with HIV-1 from 103 sets of twins born to HIV-1–infected women, by order of birth (first is A twin, second is B twin) and route of delivery (vaginal or cesarean). Rate of infection was increased approximately twofold for A twins compared with B twins and for vaginal compared with cesarean delivery.

Duliege AM,et al. J Pediatr 1995

The Risk of Human Immunodeficiency Virus–1 Infection in Twin Pairs Born to Infected Mothers in Africa

In 260 vaginally delivered infants evaluated for **perinatal infection** (45 infections), risk did not differ by birth order (first born, 15.9%; second born, 18.7%)

Risk of **perinatal infection** was significantly lower in cesarean-delivered infants (odds ratio, 0.19 [95% confidence interval, 0.02–0.78])

Conclusion

These findings indicate that birth-canal exposure is not a major contributor to a newborn's risk of HIV-1 infection

Maternal-fetal microtransfusion related to placental compression and disruption (vigorous uterine contractions associated with delivery)

Biggar RJ, et al. JID 2003

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Although decisions about mode of delivery for women with HIV RNA levels <1,000 copies/mL should be individualized based on discussion between the obstetrician and the mother, **women should be informed that there is no evidence of benefit for scheduled cesarean delivery performed solely for prevention of perinatal transmission in women with HIV RNA <1,000 copies/mL** and that it is not routinely recommended in this group

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 3, 2013 VOL. 369 NO. 14

A Randomized Trial of Planned Cesarean or Vaginal Delivery for Twin Pregnancy

CONCLUSIONS

In twin pregnancy between 32 weeks 0 days and 38 weeks 6 days of gestation, with the first twin in the cephalic presentation, planned cesarean delivery did not significantly decrease or increase the risk of fetal or neonatal death or serious neonatal morbidity, as compared with planned vaginal delivery.

Discordant outcome of perinatal transmission of hepatitis C in twin pregnancies

Four sets of non-identical twins had been investigated for HCV

In all cases only one twin had been infected. In three out of four cases the second twin had become infected

Premature rupture of membranes was associated with transmission in the only case in which the first-born became infected

Conclusion

Transmission of HCV is more likely to affect the second twin, perhaps because placental separation during the delivery exposes the second infant to infection

Boxall E, et al. J Clin Virol 2007

Congenital toxoplasmosis in twins: a report of fourteen consecutive cases and a comparison with published data

MZ

19/20 **95%**

DZ

35/45 **77%**

TABLE 3. Comparison of the clinical profiles of mono- and dizygotic twins with congenital toxoplamosis. Fisher's exact test (monozygote/dizygote); $P = 0.007$

Subjects	Identical Clinical Profiles			Different Clinical Profiles		
	Profile	*n*	%	Profile	*n*	%
Monozygotes: 20 pairs	SI-SI	12	85	AI-SI	2	15
	AI-AI	4		NI-AI	1	
	NI-NI	1				
Dizygotes: 45 pairs	SI-SI	10	44	NI-AI	4	56
	NI-NI	8		NI-SI	6	
	AI-AI	2		AI-SI	15	

NI, not infected; AI, asymptomatic infection; SI, symptomatic infection.

Closely corresponding infection status and identical disease patterns between monozygotic twins highlights the crucial role played by the placenta in disease transmissions (vascular anastomoses in a monochorionic placenta)

Peyron F, et al. Ped Infect Dis J 2003

Congenital Cytomegalovirus Infection in Twin Pregnancies: Viral Load in the Amniotic Fluid and Pregnancy Outcome

Lazzarotto T, et al. Pediatrics 2003

TABLE 1. Detailed Results of Maternal and Neonatal Findings in 3 Twin Pregnancies

Case	Mother (13–15 Weeks' Gestation)		Prenatal Findings (21–22 Weeks' Gestation)				Placenta	Postnatal Findings
	Symptoms	DNAemia	Sex/Mz Dz	Tests on amniotic fluid				
				PCR	qPCR GE/mL	Shell Vial		
A	Healthy	–	F/Dz	+	3×10^6	+	Diamniotic dichorionic separate	Death (disseminated CMV infection)
			M/Dz	–	nd	–		Uninfected
B	Healthy	–	F/Mz	nd	nd	nd	Triamniotic dichorionic separate	Infected asymptomatic (delayed sequelae)
			F/Mz	+	1×10^3	+		Infected asymptomatic (delayed sequelae)
			M/Dz	+	1.9×10^5	+		Infected symptomatic
C	Nausea, fever, muscle weakness	1.7×10^3 GE/ 10^5 PMNLs	F/Mz? (left side)	–	nd	–	Dichorionic diamnotic fused	Infected asymptomatic
			F/Mz? (right side)	+	4.9×10^4	+		Infected symptomatic

Mz indicates monozygotic; Dz, dizygotic; F, female; M, male; nd, not determined.

Twin pregnancies showed a marked difference in the quantity of virus

Twin may react differently to primary maternal infection despite being exposed to the same maternal influences

Possibility of viral transfer from one fetus to the other

The primary comparative analysis between the host genetic factors and their relationships with clinical phenotype of HBV infected twins

OBJECTIVE

The primary comparative analysis between the host genetic factors and their relationships with clinical phenotype of 20 pairs of HBV infected and high risk twins

METHODS

Zygosity of twins was diagnosed by STR microsatellite polymorphism analysis

RESULTS:

The significant difference was found in the concordance rate of disease, concordance of clinical phenotype and serological patterns of HBV infection between the MZ and DZ twins ($P < 0.05$), it was also found between MZ and control groups ($P < 0.05$), but not between DZ and control groups ($P > 0.05$).

CONCLUSION:

The high concordance of MZ indicates that host genetic factors may play role in influencing the clinical phenotype

Xu BY, et al. Zhonghua Yi Xue Za Zhi 2004

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Tabella 5 - *Nati vivi, singoli e plurimi, per classe di età gestazionale (residenti). Lazio, 2011.*

Età gestazionale (settimane)*	Singoli		Plurimi		Totale	
	N.	%*	N.	%*	N.	%*
≤25	52	0,1	15	0,8	67	0,1
26-27	66	0,2	27	2,2	93	0,3
28-31	216	0,7	122	8,8	338	1,0
32-36	2.739	6,1	908	57,4	3.647	8,0
37-41	46.268	98,4	795	99,9	47.063	98,4
>41	809	100,0	2	100,0	811	100,0
Totale	50.150		1.869		52.019	

*Percentuale cumulativa

Le nascite nel Lazio
Anno 2011

LAZIOSANITÀ
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REGIONE LAZIO

Tabella 4 - *Nati vivi, singoli e plurimi, per classe di peso alla nascita (residenti). Lazio, 2011.*

Peso alla nascita* (gr.)	Singoli		Plurimi		Totale	
	N.	%*	N.	%*	N.	%*
≤499	13	0,0	2	0,1	15	0,0
500-999	117	0,3	44	2,5	161	0,3
1000-1499	186	0,6	120	8,9	306	0,9
1500-1999	416	1,5	277	23,7	693	2,3
2000-2499	1.808	5,1	693	60,8	2.501	7,1
2500-2999	10.628	26,3	591	92,4	11.219	28,6
3000-3499	21.861	69,8	131	99,4	21.992	70,9
3500-3999	12.391	94,6	10	99,9	12.401	94,7
4000-4499	2.481	99,5	1	100,0	2.482	99,5
≥4500	249	100,0	0	100,0	249	100,0
Totale	50.150		1.869		52.019	

* Percentuale cumulativa

Le nascite nel Lazio

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Early Onset Neonatal Sepsis: The Burden of Group B Streptococcal and *E. coli* Disease Continues

TABLE 2

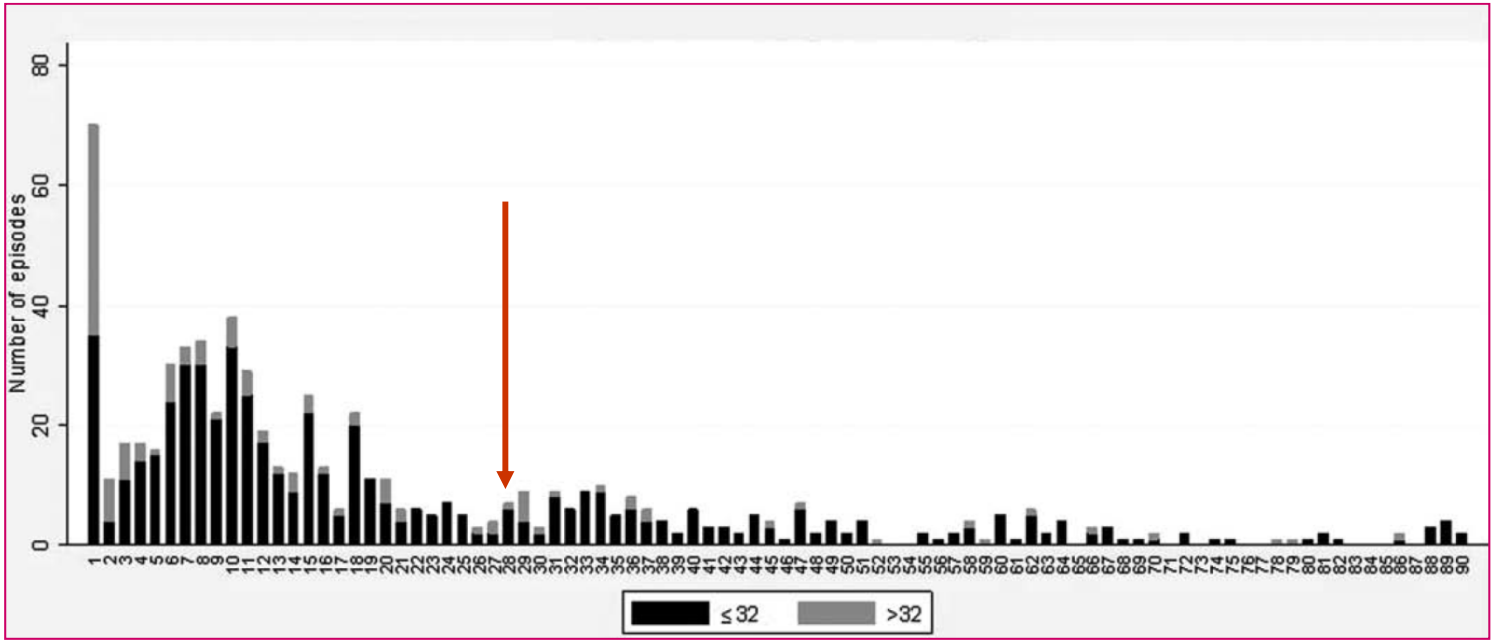
Rates of EO Infections per 1000 LBs According to Birth Weight

	BW, g			
	401–1500[a]	**1501–2500**	**>2500**	**All**
All	10.96	1.38	0.57	0.98
GBS	2.08	0.38	0.35	0.41
E coli	5.09	0.54	0.07	0.28

[a]Rates previously reported by the NRN for VLBW (401–1500 g) infants were: 1991–1993: all pathogens 19.3 per 1000 LBs, GBS 5.9 per 1000 LBs,*E coli* 3.2 per 1000 LBs; 1998–2000: all pathogens 15.4 per 1000 LBs, GBS 1. per 1000 LBs,*E coli* 6.8 per 1000 LBs; 2002–2003: all pathogens 17.0 per 1000 LBs, GBS 1.8 per 1000 LBs, *coli* 7.0 per 1000 LBs.[9,13] Previously reported rates for all pathogens included all treated CoNS; rates for 2006–2009 excluded infants with CoNS except those with >1 blood culture positive for CoNS or treated polymicrobial infections involving CoNS. The changes in rates of GBS and *E coli* between 2002–2003 and 2006–2009 among VLBW infants were not significant.

Stoll BJ, et al. Pediatrics 2011

Neonatal infections in England: the NeonIN surveillance network



The majority of infections occurred in premature (<37 weeks) and low birthweight (<2500 g) infants (82% and 81%, respectively)

Vergnano, et al. Arch Dis Child Fetal Neon Ed 2011

Late-Onset Sepsis in Very Low Birth Weight Infants from Singleton and Multiple-Gestation Births

Table I. Rates of LOS by birth weight and gestational age in VLBW singletons and multiples in the NRN, 2002-2008

	Singletons		Multiples	
	Total, n (%)	LOS, n (% of cases)	Total, n (%)	LOS, n (% of cases)
Birth weight, g				
<400	6 (<0.1)	3 (50.0)	0 (-)	0 (-)
400-500	223 (1.5)	146 (65.5)	55 (1.0)	36 (65.4)
501-750	2680 (17.7)	1372 (51.2)	754 (14.2)	407 (54.0)
751-1000	4030 (26.6)	1309 (32.5)	1228 (23.2)	384 (31.3)
1001-1250	3983 (26.2)	648 (16.3)	1480 (28.0)	226 (15.3)
1251-1500	4256 (28.0)	319 (7.5)	1777 (33.6)	143 (8.0)
Total	15 178	3797 (25.0)	5294	1196 (22.6)
Gestational age, weeks				
<25	1570 (10.3)	971 (61.8)	438 (8.3)	284 (64.8)
25-28	7239 (47.7)	2227 (30.8)	2250 (42.5)	680 (30.2)
29-32	5537 (36.5)	569 (10.3)	2259 (42.7)	214 (9.5)
>32	830 (5.5)	30 (3.6)	345 (6.5)	18 (5.2)
Total	15 176*	3797 (25.0)	5292*	1196 (22.6)

The incidence of LOS is similar for singleton and multiple-birth infants

Boghossian NS, et al. J Pediatr 2013

Risk Factors for Early-onset Group B Streptococcal Sepsis: Estimation of Odds Ratios by Critical Literature Review

TABLE 9. Risk Factors Associated With Very High Early-onset GBS Attack Rates

Clinical Risk Factor	Approximate Prevalence (%)	Approximate Attack Rate (%)	References
Twin with early-onset GBS disease	≪.1	40	142, 144, 146
PPROM* in a GBS-colonized mother	<.5	33–50	114, 115
Chorioamnionitis	1–4	6–20	88, 118, 125–128
GBS bacteriuria during current pregnancy	2.5	8	134–136
Sibling with early-onset GBS disease	<1	Unknown	137–139

* PPROM, preterm (<37 weeks) premature (before onset of labor) rupture of membranes.

Benitz WE, et al. Pediatrics 1999

Red Book: 2009 Report of the Committee on Infectious Diseases

Twin gestation is a known risk factor for invasive GBS infection, with a 25-fold greater likelihood of a twin of an affected infant to acquire infection compared with the same age population

"… the twin of an index case with early- or late-onset disease should be observed carefully and evaluated and treated empirically for suspected systemic infection… **if any signs of illness occur**"

LATE-ONSET SEPSIS IN A PRETERM TWIN MAY HARBINGER LIFE-THREATENING SEPSIS FOR THE ASYMPTOMATIC CO-TWIN

CASE REPORT

An extremely preterm twin developed late-onset Escherichia coli sepsis in the second postnatal week

The asymptomatic twin was not treated and initially observed, and within 2 days developed life-threatening septicemia and meningitis

CONCLUSION

Occurrence of late-onset sepsis in a twin should prompt concurrent investigation and consideration of presumptive treatment of the apparently asymptomatic co-twin

Pai JR, et al. Ped Infect Dis J 2010

SEVERE INFECTIONS IN TWINS

E. Coli sepsis (blood and CSF) in a 9-day-old boy, born after a normal term twin pregnancy

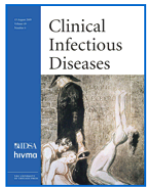
Co-twin: blood, urine and CSF cultures were sterile, and the neonate was discharged after 48 hours of observation

5 days later, he presented with fever and decreased feeding → urine culture was positive for E. coli

CONCLUSION

Laboratory evaluation might not be enough and early treatment of the asymptomatic twin may be necessary

Levy Erez D, et al. Ped Infect Dis J 2013



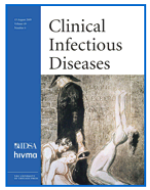
C. glabrata Sepsis Associated With Chorioamnionitis in an In Vitro Fertilization Pregnancy: Case Report and Review

Table 1. Published Cases of *Candida glabrata* Chorioamnionitis

First Author [Ref] (Year)	In Vitro Fertilization	Foreign Body	Gestation at Diagnosis, wks	Prebirth Antifungal Treatment	Outcome and Delivery Gestation, wks
Quirke [19] (1980)	No	IUCD	23	Nil	Stillborn singleton (23)
Sander [20] (1983)	No	Cervical stitch	22	Nil	Stillborn twins (22)
Bruner [21] (1986)	No	IUCD	23	Nil	Rapid singleton death (23^{+2})[a]
Catanzarite [22] (1997)	No	No	27	IV amphotericin for 11 d, and PV terconazole	Singleton survival (CS at 28^{+4})
Sfameni [4] (1997)	Yes	No	20	Nil	1 twin stillborn and 1 twin rapid death (21^{+5})
	Yes	No	15	Nil	Stillborn triplets (15^{+3}–16^{+5})
Salem [23] (2000)[b]	Yes	No	20	Nil	Stillborn twins (21^{+5})
Arai [24] (2002)	No	No	26	IV fluconazole for 2 wk	Twin survival (CS at 29)
Ibara [17] (2004)	Yes	No	34	Nil	Twin survival (CS at 34)
	Yes	No	21^{+4}	Nil	Stillborn twins (22)
Freydiere [25] (2005)	Yes	No	21	Nil	Singleton survival (CS at 25)
Matsuzawa [2] (2005)	Yes	No	26	Nil	1 twin survival and 1 twin rapid death (CS at 26)
	No	No	25	Nil	Singleton death on day 5 (25)
Carbonnel [18] (2007)[c]	Yes	No	19^{+5}	IV amphotericin B for 9 d then termination of pregnancy for PPROM	Stillborn twins (21^{+2})
Asemota [16] (2011)	Yes	No	16	Nil	Stillborn twins (16)
Jackel (current case)	Yes	No	21	IV liposomal amphotericin for 17 d with concomitant 5-flucytosine for 10 d; 1 d caspofungin	Stillborn twins (24)

Abbreviations: CS, cesarean section; IUCD, intrauterine contraceptive device; IV, intravenous; PPROM, preterm premature rupture of membranes; PV, per vaginal.

Yackel D, Lai K. CID 2013



C. glabrata Sepsis Associated With Chorioamnionitis in an In Vitro Fertilization Pregnancy: Case Report and Review

- Candida glabrata lower urogenital tract carriage rates during pregnancy range from 2% to 8%

- Reduced virulence compared to Candida albicans

- Because C. glabrata has difficulty penetrating intact membranes, it benefits from direct inoculation into the uterus

- The process of IVF allows potential C. glabrata uterine contamination at several points (infected semen and embryo transfer)

Yackel D, Lai K. CID 2013

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Gravidanza insorta dopo FIVET

Nato da madre con Insufficienza Cervicale sottoposta a cerchiaggio a 20 sett
Tampone vaginale: ***Candida Glabrata***

↓

Emocoltura: ***Candida Glabrata***
Urinocoltura: ***Candida Glabrata***

↓

Trattato efficacemente con **Micafungina**


Grazie!

Prenatal diagnosis and outcome of congenital cytomegalovirus infection in twin pregnancies

20 infected women (14 DC/DA 6 MC/DA)

Table 2. Results of prenatal diagnostic tests and pregnancy outcome in CMV-infected twins

Case no.*	Type of infection	GA at infection	Placentas	Zygosity	GA at amniocentesis	Amniotic fluid results	Ultrasound finding	Congenital CMV infection	Postnatal findings
1.A	Primary	18	DC/DA, fused	Unknown	27	+	–	+	Asymptomatic
1.B						–	–	+	Asymptomatic
2.A	Primary	16	DC/DA, separate	Unknown	24	–	–	+	Asymptomatic
2.B						+	–	+	Asymptomatic
3.A	Primary	10	DC/DA, separate	Dizygotic	22	–	–	–	Asymptomatic
3.B						+	–	TOP	
4.A	Primary	20	DC/DA, separate	Dizygotic	31	+	–	TOP	
4.B						+	–	TOP	
5.A	Primary	10–12	DC/DA, fused	Dizygotic	22	+	+	IUFD	
5.B						+	+	IUFD	
6.A	Recurrent	7–8	DC/DA, fused	Dizygotic	–		–	+	Asymptomatic
6.B							+	+	CMV disease, death**

GA, gestational age; IUFD, intrauterine fetal death; TOP, termination of pregnancy.
*A refers to twin A and B refers to twin B.
**Intra ventricular haemorrhage, hepatitis, pancytopenia.

Possibility of intrauterine transmission of the virus from one fetus to the other

Yinon Y, et al. BJOG 2006

Birth order, delivery route, and concordance in the transmission of human immunodeficiency virus type 1 from mothers to twins

Adjusted odds ratios for HIV infection were:

- 11.8 (confidence interval: 3.1 to 45.3) for concordance of infection with the co-twin
- 2.8 (confidence interval: 1.6 to 5.0) for A versus B twins
- 2.7 (confidence interval: 1.1 to 6.6) for vaginally delivered versus cesarean-delivered twins
- Among A twins, 52% of the transmission risk was related to vaginal delivery
- Comparing vaginally delivered A twins (infants most exposed to vaginal mucus and blood) to cesarean-delivered B twins (infants least exposed), 76% of the transmission risk was related to vaginal exposure

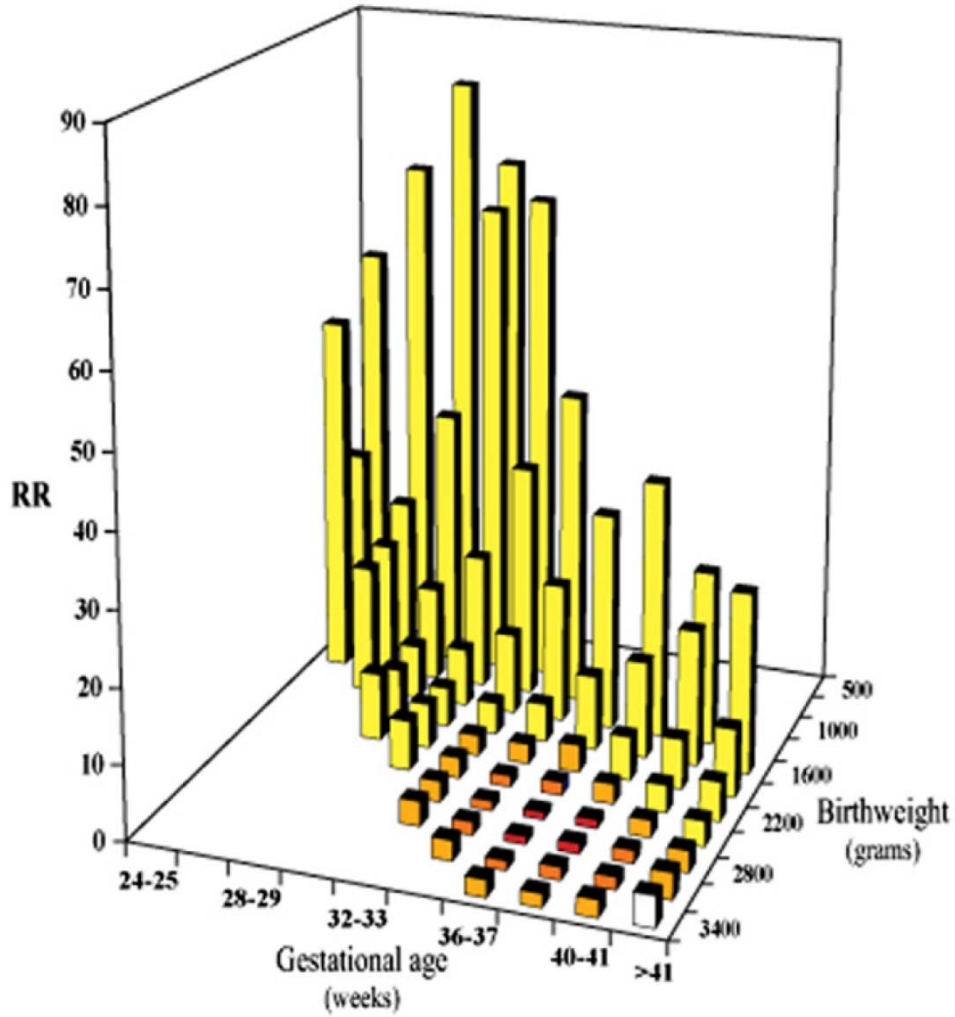
The Impact of Environmental and Genetic Factors on Neonatal Late-Onset Sepsis

Table V. AE model analysis for late-onset sepsis

Variables/effects	Estimate	*P*
BW	-0.001	<.001
RDS	1.122	<.001
TPN	0.025	<.001
Genetic	0.490	.002
Residual environmental	0.510	.001

- 49.8% of the variance in liability to sepsis was the result of genetic factors alone, and 50.2% of the variance in liability to sepsis was the result of residual (non-shared) environmental factors

Bizzarro MJ, et al. J Pediatr 2011


RR
90
80
70
60
50
40
30
20
10
0
24-25
28-29
32-33
36-37
40-41
>41
Gestational age
(weeks)
500
1000
1600
2200
2800
3400
Birthweight
(grams)

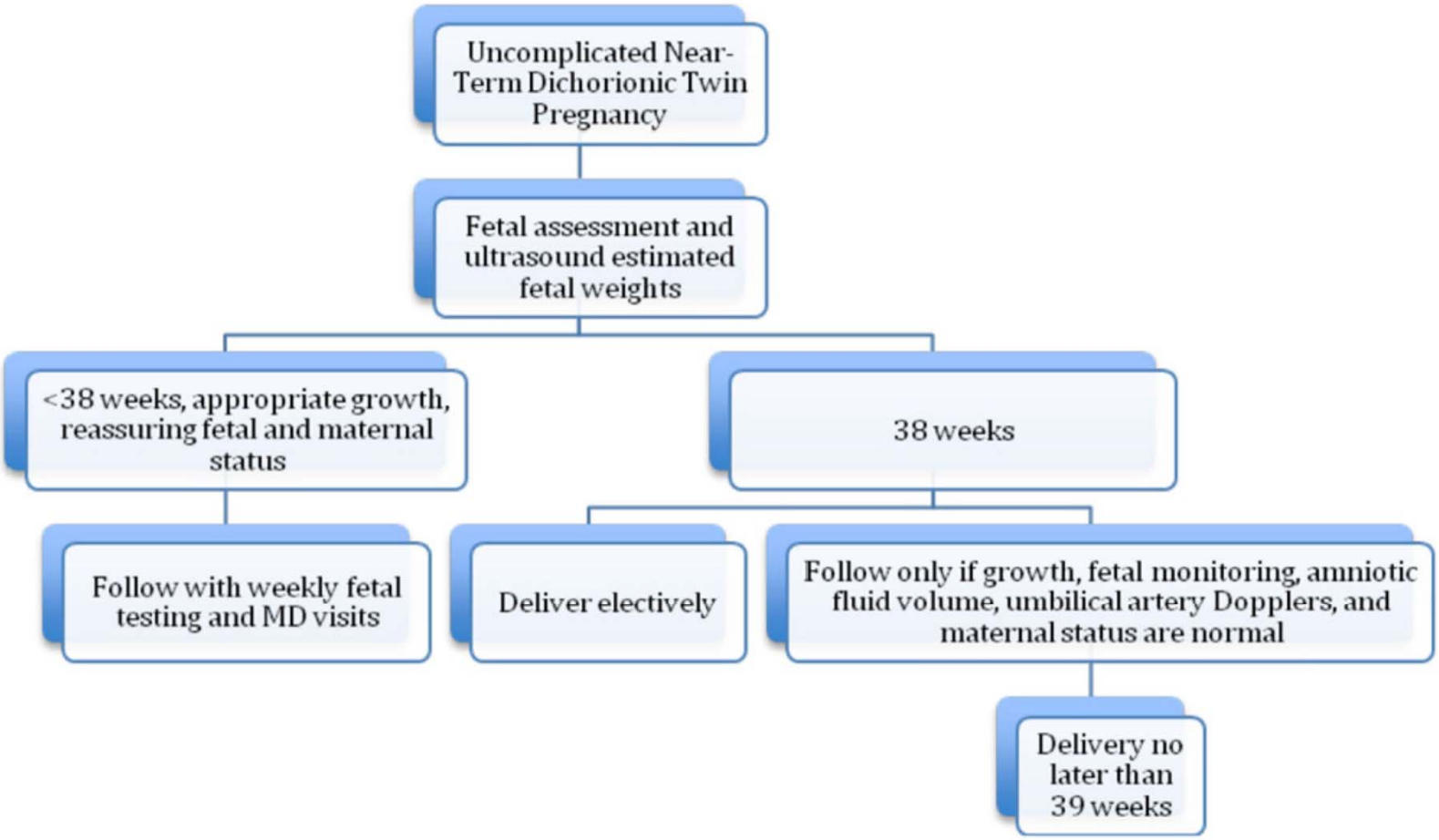


Figure 2 Algorithm for determining the timing of delivery in uncomplicated, near-term dichorionic twins.

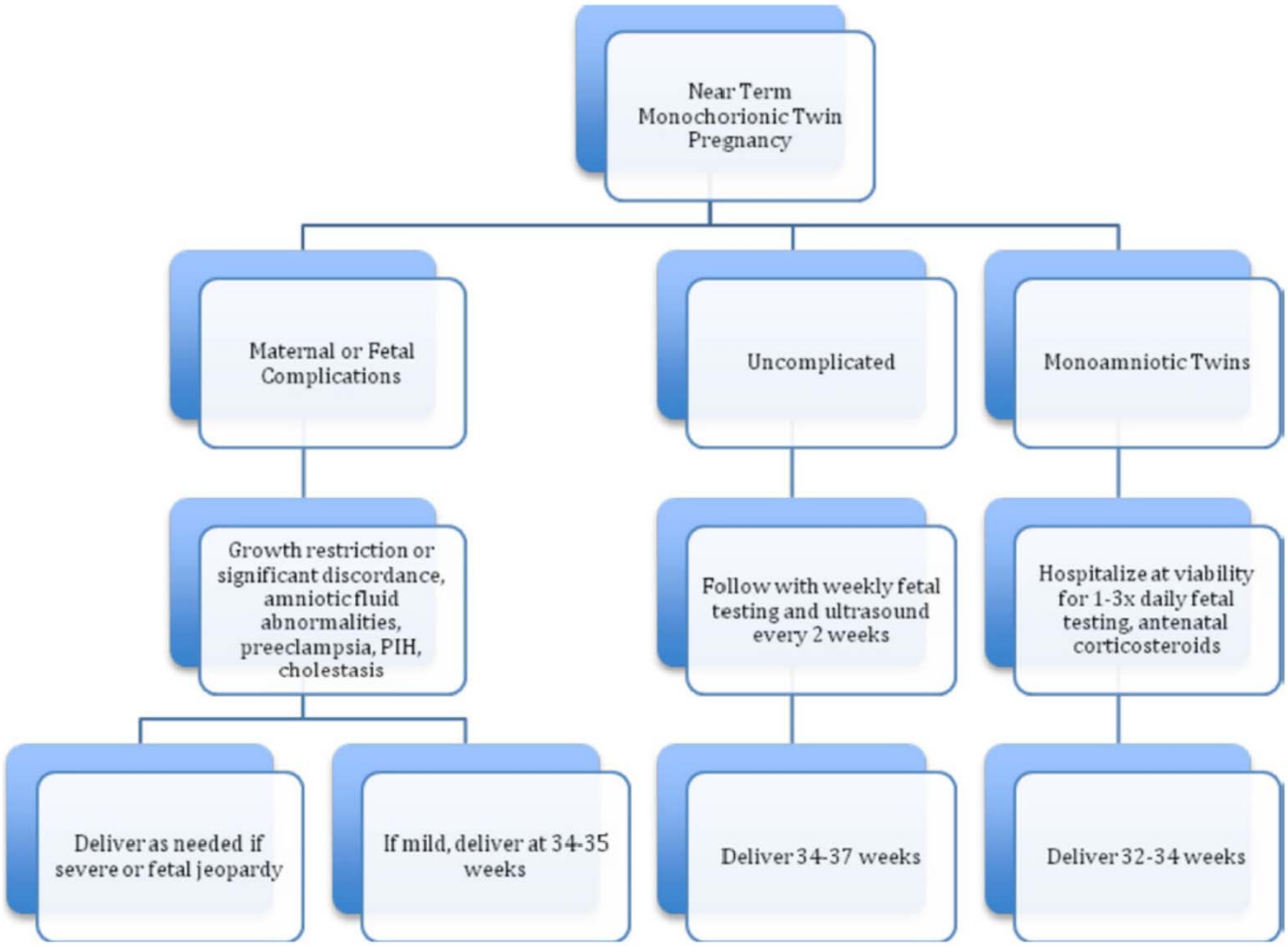


Figure 3 Algorithm for determining the timing of delivery in uncomplicated, near-term monochorionic twins.

Early and Late Onset Sepsis in Late Preterm Infants

Observational cohort study of infants 121 days of age with estimated gestational age at birth between 34 and 36 weeks admitted to 248 neonatal intensive care units in the United States between 1996 and 2007

119,130 infants less than or equal to 3 days of life

- The incidence of early onset sepsis was 4.42 episodes per 1000 admissions

Cohen-Wolkowiez M, et al. Ped Infect Dis J 2009

PATOLOJİ DERNEKLERİ FEDERASYONU

Intrauterine Fetal Loss Associated with Candida Glabrata Chorioamnionitis: Report of Two Cases

A 28-year-old woman, primagravida, with a dichorionic diamniotic twin pregnancy

She had undergone successful IVF and the transfer of two embryos

She developed preterm premature rupture of membranes and eventually delivered both fetuses at 18

Different outcomes of vertical transmission of hepatitis C virus in a twin pregnancy

Monochorionic diamniotic twins

Uncomplicated vaginal delivery 3min apart and they were both bottle fed

The second baby developed clinical hepatitis that persisted to 30 months follow up

Conclusion

The intrauterine environment should have been identical for these twins, and therefore, the maternal HCV factors, including viral load are not the sole determining factors for mother-to-infant transmission of HCV

Inui A, et al. J Gastro Hepat 2002

Dizygotic twins discordant for HIV and hepatitis C virus

Non-identical female twins were born at 37 weeks' gestation by spontaneous vaginal delivery

Twin 1 developed symptomatic HIV infection at 9 months of age

Twin 2 positive for HCV antibody and HCV RNA-PCR

Conclusion

Discordance in HIV infection has been noted even in monozygotic twins

Placenta, viral tropism, and host or genetic factors might contribute to the infant's susceptibility to infection

Barlow K & Mok J. Arch Dis Child 1993