

I progetti dell'Italian Obstetric Surveillance System: la nascita durante la pandemia di SARS-CoV-2, l'aggiornamento dei dati sulla mortalità materna e la programmazione delle attività post-pandemiche

Roma, 18 maggio 2023, Aula Pocchiari, Istituto Superiore di Sanità



La trasmissione materno fetale e la risposta anticorpale all'infezione, i dati dei campioni biologici dello studio ItOSS

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A nome del gruppo di lavoro di Microbiologia

L'inizio di tutto



武汉市卫生健康委员会
Wuhan Municipal Health Commission

北京 (国家城市) 中央 -9°C -1°C 空气质量 良好 12-1°C

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武汉市卫健委关于当前我市肺炎疫情的情况通报

发布机构: 武汉市卫生健康委员会 | 发布时间: 2019-12-31 13:38:05 | 点击数: 400381 | 字号: 大 中 小

近期部分医疗机构发现接诊的多例肺炎病例与华南海鲜城有关联, 市卫健委接到报告后, 立即在全市医疗卫生机构开展与华南海鲜城有关联的病例搜索和回顾性调查, 目前已发现27例病例, 其中7例病情严重, 其余病例病情稳定可控, 有2例病情好转拟于近期出院, 病例临床表现主要为发热, 少数病人呼吸困难, 胸片呈双肺浸润性病灶, 目前, 所有病例均已隔离治疗, 密切接触者追踪调查和医学观察正在进行中, 对华南海鲜城的卫生学调查和环境卫生处置正在进行中。

武汉市组织同济医院、省疾控中心、中科院武汉病毒所、武汉市传染病医院及武汉市疾控中心等单位的临床医学、流行病学、病毒学专家进行会诊, 专家从病情、治疗转归、流行病学调查、实验室初步检测等方面情况分析认为上述病例系病毒性肺炎, 到目前为止调查未发现明显人传人现象, 未发现医务人员感染, 目前对病原的检测及感染原因的调查正在进行中。

病毒性肺炎多见于冬春季, 可散发或暴发流行, 临床主要表现为发热、浑身酸痛、少部分有呼吸困难, 肺部浸润影, 病毒性肺炎与病毒的毒力、感染途径以及宿主的年龄、免疫状态有关, 引起病毒性肺炎的病毒以流行性感冒病毒为常见, 其他为副流感病毒、巨细胞病毒、腺病毒、鼻病毒、冠状病毒等, 确诊则有赖于病原学检查, 包括病毒分离、血清学检查以及病毒抗原及核酸检测, 该病可防可控, 预防上保持室内空气流通, 避免到封闭、空气不流通的公众场合和人多集中地方, 外出可佩戴口罩, 临床以对症治疗为主, 需卧床休息, 如有上述症状, 特别是持续发热不退, 要及时到医疗机构就诊。

2019年12月31日

打印 关闭

- 27 di casi di polmonite ad eziologia sconosciuta
- Probabile causa virale secondo i reperti radiografici
- In corso indagini di laboratorio ed epidemiologiche
- Origine putativa dell'outbreak: mercato Wuhan's South China Seafood City



Il dilemma clinico: che impatto in gravidanza?

- Polmoniti infettive causa importante di morbilità e mortalità in gravidanza → ICU e assistenza ventilatoria in 25%
- Le modificazioni legate allo stato gravidico influiscono su andamento
- SARS-CoV 2002-2003 e MERS-CoV: pochi casi, ricoveri ICU, parti pretermine, aborti spontanei, morti matern
- Molti casi di COVID-19 rispetto ad altri CoV

Schwartz and Graham. *Viruses*, 2020. 12(2): 194. DOI:10.3390/v12020194

Premesse poco rassicuranti...



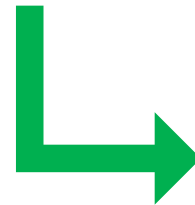


RISCHI EVIDENZIATI IN COVID-19

JAMA Pediatrics | [Original Investigation](#)

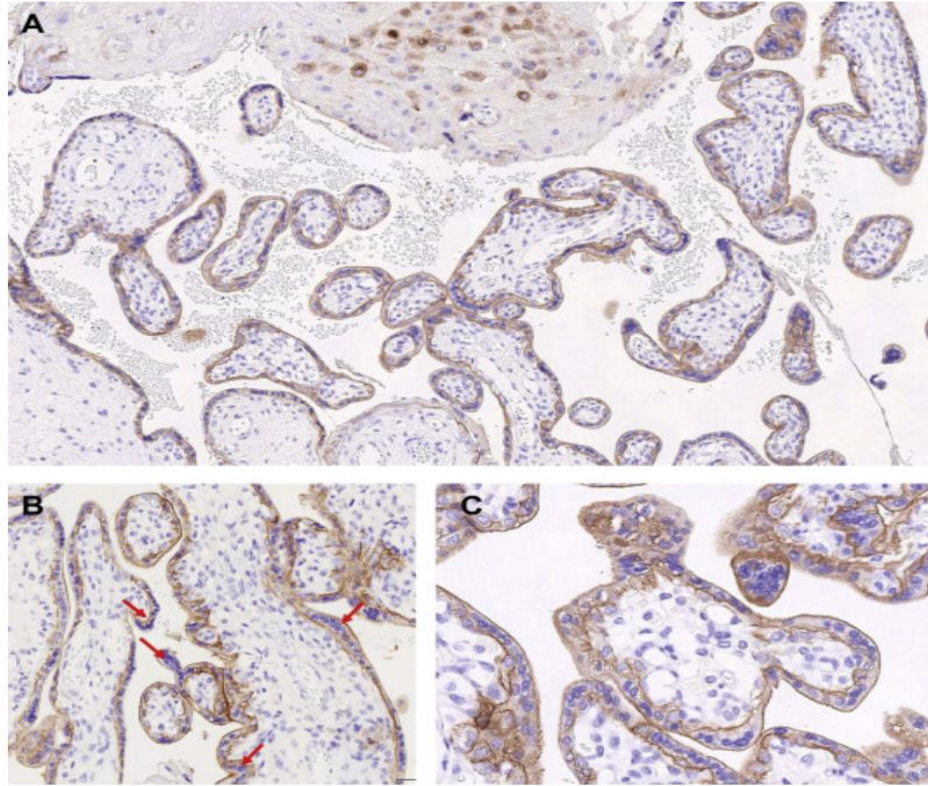
Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection The INTERCOVID Multinational Cohort Study

CONCLUSIONS AND RELEVANCE In this multinational cohort study, COVID-19 in pregnancy was associated with consistent and substantial increases in severe maternal morbidity and mortality and neonatal complications when pregnant women with and without COVID-19 diagnosis were compared. The findings should alert pregnant individuals and clinicians to implement strictly all the recommended COVID-19 preventive measures.



- Preeclampsia/eclampsia
- Infezioni severe
- Ammissione in ICU
- Mortalità materna
- Parto pretermine
- Morbidity neonatale severa
- Severa morbidity e mortalità perinatali





Clinical Microbiology and Infection, 2021, 27:489-490

- Espressione di ACE2 a livello placentale-fetale
- Presenza di RNA virale in circolo in pazienti gravi
- Danno vascolare da infiammazione che può riguardare la placenta

RESEARCH

Open Access



Viral RNA load in plasma is associated with critical illness and a dysregulated host response in COVID-19

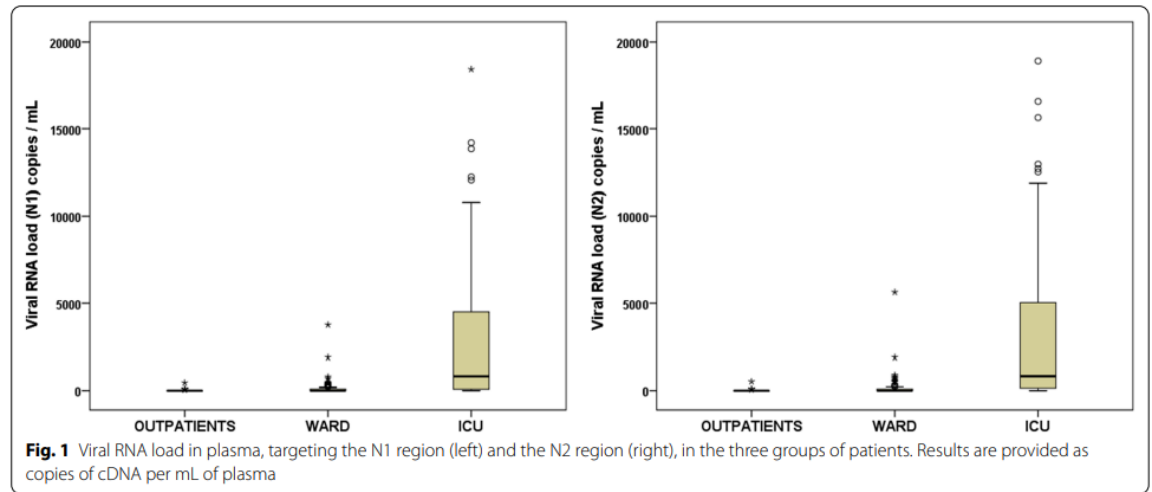


Fig. 1 Viral RNA load in plasma, targeting the N1 region (left) and the N2 region (right), in the three groups of patients. Results are provided as copies of cDNA per mL of plasma





Scopo dello studio

Investigare:

- Presenza di virus in matrici biologiche rilevanti → tamponi vaginali, rettali, placentari, rinofaringei materni, rinofaringei neonatali, latte
- Trasmissione verticale
- Infezione neonatale
- Risposta anticorpale materna
- Cross-protezione materno-fetale





Disegno dello studio

- Gravide SARS-CoV-2 positive
- 25/02/2020 - 30/06/2021
- Campania, Emilia Romagna, Lombardia, Toscana, Trento PA → network di centri di riferimento
- Campioni raccolti e saggiati:

T1 - GRAVIDANZA

Tampone vaginale → RT-PCR
Siero materno → Ab

T2 - PARTO

Tampone vaginale → RT-PCR
Tampone rettale → RT-PCR
Tampone placentare → RT-PCR
Siero materno → Ab
Tampone nasofaringeo neonatale → RT-PCR
Siero cordonale → Ab

T3 - PUERPERIO

Latte → Ab + RT-PCR



Popolazione e dati molecolari

Table 1
Women's characteristics (N = 1086).

Maternal characteristics	N = 1086	
	n	%
Age (13 missing)		
<30 years	338	31.5
30-34 years	381	35.5
≥35 years	354	33.0
Citizenship (6 missing)		
Italian	892	82.6
Not Italian	188	17.4
COVID-19 disease severity^a (10 missing)		
Mild	1031	95.8
Moderate	29	2.7
Severe	16	1.5
Gestational trimester at SARS-CoV-2 diagnosis (13 missing)		
I (<14 weeks)	103	9.6
II (14-27 weeks)	187	17.4
III (≥28 weeks)	783	73.0
Previous comorbidities (35 missing)		
No	914	87.0
Yes	137	13.0
Body mass index ≥30 Kg/m² (18 missing)		
No	941	88.1
Yes	127	11.9
Maternal outcomes		
Severe morbidity	14	1.3
Death	1	0.1
Mode of delivery^b (3 missing)		
Vaginal	694	73.0
Elective CS	121	12.7
Urgent/emergency CS due to maternal/fetal indication	125	13.1
Urgent/emergency CS due to COVID-19	11	1.2
Gestational age at birth^b (6 missing)		
≤31 weeks	10	1.1
32-36 weeks	47	5.0
≥37 weeks	891	94.0
	N = 968	
Perinatal outcomes	n	%
Stillbirths	2	0.2
Livebirths	966	99.8
Neonatal deaths	2	0.2
SARS-CoV-2-positive swab at birth	8	0.8

A large series of molecular and serological specimens to evaluate mother-to-child SARS-CoV-2 transmission: a prospective study from the Italian Obstetric Surveillance System

[International Journal of Infectious Diseases 126 \(2023\) 1–9](#)

Table 2
Adequacy of samples and results of molecular assays for viral genome detection.

Results	Vaginal specimen during pregnancy (N = 459)		Vaginal specimen at birth (N = 545)		Rectal specimen at birth (N = 497)		Placental specimen at birth (N = 538)	
	n	%	n	%	n	%	n	%
Adequate samples ^a	449	97.8	527	96.7	467	94.0	527	98.0
Weakly positive	1	0.2	5	1.0	21	4.5	3	0.6
Positive	2	0.4	4	0.8	18	3.9	2	0.4
Negative	443	98.9	516	98.1	425	91.0	516	98.5
Indeterminate	2	0.4	1	0.2	3	0.6	3	0.6
Missing	1		1		0		3	

^a Sufficient amount of biological material according to the assay requirements and absence of hemolysis for vaginal, rectal, and placental swabs.

Alto tasso di negatività in tutti i materiali biologici
Unica eccezione: il tampone rettale

Alcune considerazioni molecolari

Table 1 Maternal and pregnancy outcomes in the study population

	III Trimester <i>n</i> 46
Age, median (range)	32 (22–42)
Mode of delivery	
-VB, <i>n</i> (%)	32 (70)
-CS, <i>n</i> (%)	14 (30)
Severity	
-Asymptomatic, <i>n</i> (%)	18 (39)
-Mild, <i>n</i> (%)	11 (24)
-Moderate, <i>n</i> (%)	12 (26)
-Severe/critical, <i>n</i> (%)	5 (11)
Therapy	
-Antiviral, <i>n</i> (%)	12 (26)
-Antibiotics, <i>n</i> (%)	12 (26)
-Hydroxychloroquine, <i>n</i> (%)	11 (24)
-Oxygen supply, <i>n</i> (%)	6 (13)
-IMV, <i>n</i> (%)	1 (2)
Viremia	
-Total, <i>n</i>	41
-Positive, <i>n</i> (%)	2 (5)
Vaginal swab	
-Total, <i>n</i>	45
-Positive, <i>n</i> (%)	0 (0)
Rectal swab	
-Total, <i>n</i>	34
-Positive, <i>n</i> (%)	9 (27)

VB vaginal birth, CS cesarean section, IMV invasive mechanical ventilation

Reproductive Sciences (2021)
28:2939–2941

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2022, VOL. 35, NO. 25, 5456–5463
<https://doi.org/10.1080/14767058.2021.1882984>

REVIEW ARTICLE

SARS-CoV-2 detection in human milk: a systematic review

Jogender Kumar^{a*}, Jitendra Meena^{a*}, Arushi Yadav^b and Praveen Kumar^a

Prolonged Shedding of SARS-CoV-2 in Feces of COVID-19 Positive Patients: Trends in Genomic Variation in First and Second Wave

The results showed that fecal samples of 173 of 280 patients were positive for SARS-CoV-2 RNA, with a positive rate of 61.78%. Among them, the positive rate of SARS-CoV-2 RNA in fecal samples of critical/severe, moderate, and asymptomatic cases was 63.7% (51/80), 55.5% (60/108), and 67.39% (62/92), respectively.

replicating virus and observed Ct value in three of them. Virus isolation from fecal samples was not successful, irrespective of viral RNA concentration.

Front. Med. 9:835168. doi: 10.3389/fmed.2022.835168

Rara positività, nessuna evidenza di virus replicante

116 donne → 10 latte
positivi → 2.16%



I dati sierologici

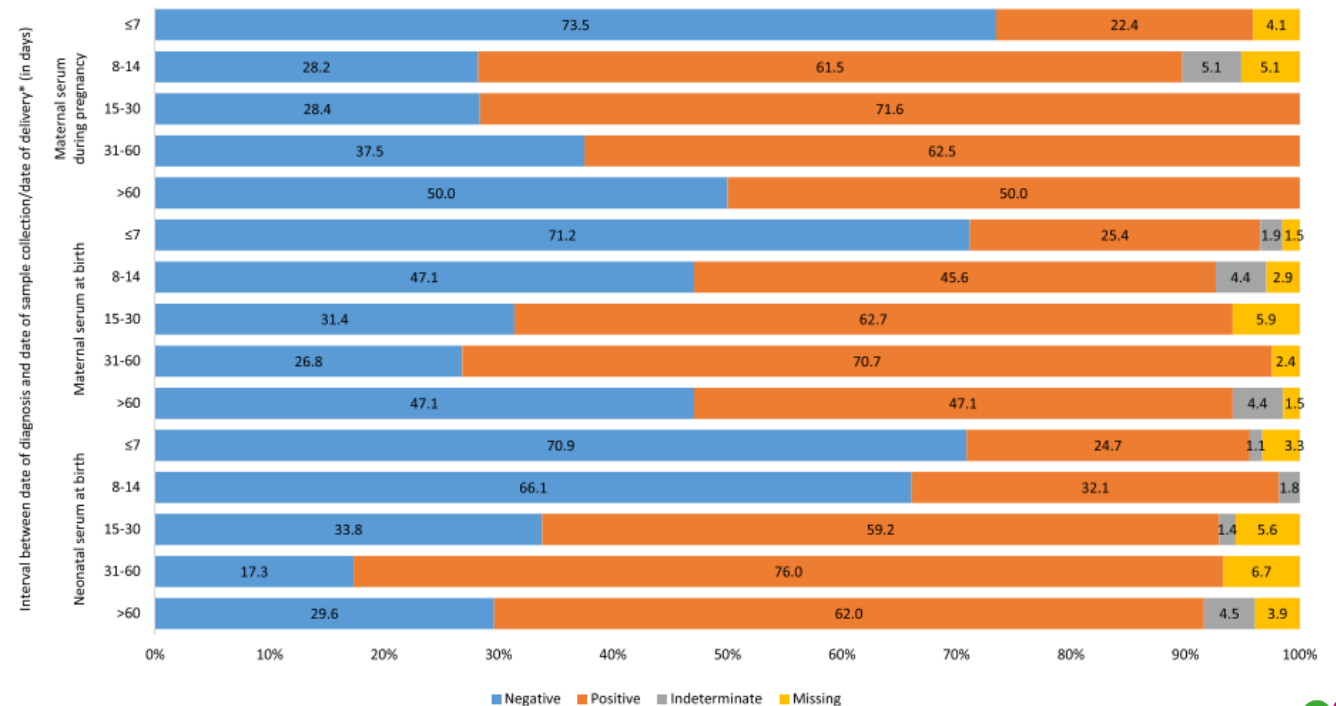
- Bassa positività IgM
- IgM: maggiore % in latte
- Tasso IgG più alto,
- Influenza di distanza temporale tra infezione e prelievo per IgG

Table 3

Adequacy of samples and results of serological assays for IgG detection and IgM detection.

Molecular assay	Maternal serum during pregnancy (N = 422)		Maternal serum at birth (N = 555)		Neonatal serum at birth (N = 628)		Maternal milk at birth (N = 183)	
	n	%	n	%	n	%	n	%
Adequate samples ^a	408	96.7	493	88.8	564	89.8	141	77.0
IgG detection								
Negative	211	53.0	279	58.0	256	47.3	125	92.6
Positive	180	45.2	191	39.7	273	50.5	4	3.0
Indeterminate	7	1.8	11	2.3	12	2.2	6	4.4
Missing	10		12		23		6	
IgM detection								
Negative	252	97.7	247	93.9	337	98.5	118	88.1
Positive	5	1.9	16	6.1	5	1.5	10	7.5
Indeterminate	1	0.4	0	0.0	0	0.0	6	4.5
Missing	1		0		0		7	
No detection of IgM	149		230		222		0	

^a Sufficient amount of maternal and neonatal serum according to the assay requirements and absence of hemolysis and clots; >0.5 ml of milk and absence of lipid clots.





I dati sierologici

Table 4
OR of positive IgG detection - logistic regression models.

Variable	IgG detection: positive vs negative								
	Model 1 ^a maternal serum during pregnancy (N = 262)			Model 2 ^a maternal serum at birth (N = 446)			Model 3 ^a neonatal serum at birth (N = 514)		
	OR	95% CI		OR	95% CI		OR	95% CI	
Period									
Wild-type (February 25, 2020-January 31, 2021)	1			1			1		
→ Alpha variant (February 01, 2021-June 30, 2021)	2.13	1.10	4.13	0.98	0.55	1.75	1.46	0.87	2.46
Maternal age									
<30 years	1			1			1		
30-34 years	0.78	0.41	1.50	0.98	0.59	1.63	0.66	0.40	1.08
≥35 years	0.88	0.45	1.71	1.08	0.64	1.80	0.67	0.41	1.11
Citizenship									
Italian	1			1			1		
Not Italian	1.11	0.51	2.43	1.47	0.87	2.48	1.19	0.72	1.98
Gestational trimester at SARS-CoV-2 diagnosis									
I (<14 weeks)	1			1			1		
II (14-27 weeks)	0.83	0.39	1.78	1.23	0.33	4.56	2.61	1.08	6.32
III (≥28 weeks)	0.80	0.37	1.73	0.59	0.12	2.78	2.46	0.90	6.72
COVID-19 pneumonia									
No	1			1			1		
Yes	1.30	0.16	10.74	1.06	0.38	2.94	0.97	0.35	2.68
Body mass index ≥30 Kg/m²									
No	1			1			1		
Yes	2.47	0.94	6.50	1.65	0.83	3.28	1.50	0.75	3.02
Comorbidities									
No	1			1			1		
Yes	0.67	0.32	1.44	0.98	0.53	1.82	1.66	0.90	3.06
Gestational age at delivery									
<37 weeks				1			1		
≥37 weeks				1.15	0.47	2.81	1.74	0.68	4.47
→ Interval between date of diagnosis and date of sample collection/date of delivery^b									
≤14 days	1			1			1		
15-30 days	4.81	2.40	9.63	4.36	2.23	8.56	4.19	2.28	7.72
31-60 days	2.84	1.25	6.46	7.14	3.21	15.88	11.98	6.00	23.89
>60 days	1.24	0.48	3.23	1.36	0.46	4.02	6.63	3.19	13.77



Antibody levels to SARS-CoV-2 spike protein in mothers and children from delivery to six months later

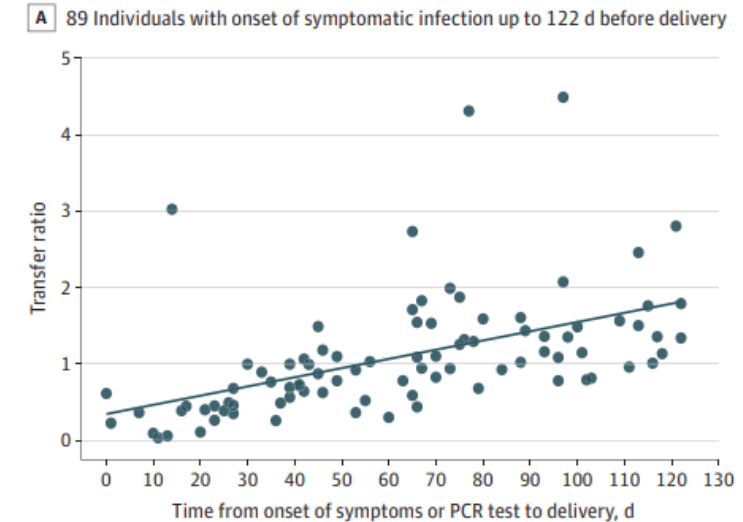
samples, and 63.2% of milk samples. A significant relationship between the positive antibodies to SARS-CoV-2 S protein and the time of infection was only found in maternal sera. Mothers diagnosed more than two weeks before delivery had higher percentages of positive sera for IgG (94.3% vs. 68.6%; $P = 0.003$), IgM (65.7% vs. 36.8%; $P = 0.009$), and IgA (65.7% vs. 45.7%; $P = 0.056$) than mothers diagnosed later (at two weeks before delivery or at the childbirth). The presence/absence of antibodies to SARS-CoV-2 S protein correlated between mother sera, cord sera, and milk. Thus,

Original Investigation | Infectious Diseases

Comparison of Maternal and Neonatal Antibody Levels After COVID-19 Vaccination vs SARS-CoV-2 Infection

Dustin D. Flannery, DO, MSCE; Sigrid Gouma, PhD; Miren B. Dhudasia, MBBS, MPH; Sagori Mukhopadhyay, MD, MMSc; Madeline R. Pfeifer, BS; Emily C. Woodford, BA; Sara M. Briker, BS; Jourdan E. Triebwasser, MD, MA; Jeffrey S. Gerber, MD, PhD; Jeffrey S. Morris, PhD; Madison E. Weirick, BS; Christopher M. McAllister, BS; Scott E. Hensley, PhD; Karen M. Puopolo, MD, PhD

Figure 2. Association Between Placental Transfer Ratio and Time From SARS-CoV-2 Infection or First Vaccine Dose to Delivery



- Trasferimento efficace in infezione e vaccinazione, anche se seconda sembra migliore
- Dipendenza da intervallo temporale rispetto a nascita





Cosa ci dice l'anatomia patologica?

Placental Characteristics of a Large Italian Cohort of SARS-CoV-2-Positive Pregnant Women

Microorganisms 2022, 10, 1435. <https://doi.org/10.3390/microorganisms10071435>

Table S2. Placentas by severity of chorioamnionitis and severity of placental disc inflammation (N=975).

Chorioamnionitis	Placental disc inflammation *							
	Absent		Mild		Moderate/severe		Total	
	n	%	n	%	n	%	n	%
Absent	287	78.6	162	51.4	132	44.7	581	59.6
Mild	38	10.4	89	28.3	96	32.5	223	22.9
Moderate/severe	40	11.0	64	20.3	67	22.7	171	17.5
Total	365	100.0	315	100.0	295	100.0	975	100.0

* Absent inflammation: no intervillous fibrin, no acute, chronic or mixed villitis and intervillitis;
 Mild inflammation: mild intervillous fibrin and/or mild acute, chronic or mixed villitis and/or intervillitis;
 Moderate or severe inflammation: moderate or severe intervillous fibrin and/or moderate or severe acute, chronic or mixed villitis and/or intervillitis; the inflammation was classified as severe when all three conditions were present.

CA was present in 40.4% ($n = 394$) of the analysed membranes, 22.9% being mild and 17.5% moderate/severe (Table S2). F was identified in 18.2% ($n = 177$) of the cords, divided into 14.1% mild and 4.1% severe, respectively (Table S3).

Table S3. Placentas by severity of funisitis and severity of placental disc inflammation (N=975).

Funisitis	Placental disc inflammation *							
	Absent		Mild		Moderate/severe		Total	
	n	%	n	%	n	%	n	%
Absent	327	89.6	238	75.6	233	79.0	798	81.8
Mild	29	7.9	57	18.1	51	17.3	137	14.1
Moderate/severe	9	2.5	20	6.3	11	3.7	40	4.1
Total	365	100.0	315	100.0	295	100.0	975	100.0

* Absent inflammation: no intervillous fibrin, no acute, chronic or mixed villitis and intervillitis;
 Mild inflammation: mild intervillous fibrin and/or mild acute, chronic or mixed villitis and/or intervillitis;
 Moderate or severe inflammation: moderate or severe intervillous fibrin and/or moderate or severe acute, chronic or mixed villitis and/or intervillitis; the inflammation was classified as severe when all three conditions were present.

- Corioamnionite e funisite presenti → 42.3% combinando → aumento d'inflammatione da infezione di SARS-CoV-2
- Scarse conseguenze su esiti di gravidanza





Conclusioni

- Rara presenza di genoma virale in materiali non respiratori, in assenza di prove per virus competenti
- Trasmissione in gravidanza e durante il parto altamente improbabile → neonati positivi per contatto post-parto con madre o altri soggetti positivi
- Patologia severa nella madre → possibile danno placentare da infiammazione → rischio maggiore per conseguenze negative
- Passaggio significativo di anticorpi al feto → cross-protezione
- Creazione di rete di esperti e protocollo condiviso → pronti a nuove sfide

