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IUGR e rischio cardio vascolare nell'età adulta: dalle origini alle scienze «omiche»

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DEFINIZIONE

Table 1. Comparison of Clinical Practice Guidelines on FGR (UK, USA, Canada and Ireland)

	RCOG Green-top Guideline (No. 31)	ACOG/ SMFM Practice Bulletin (No. 134)	SOGC Clinical Practice Guideline (No. 295)	HSE/ RCPI Clinical Practice Guideline (No. 29)
Country	United Kingdom	United States	Canada	Ireland
Issued	February 2013	May 2013	August 2013	March 2014
Name	The Investigation and Management of the Small-for-Gestational-Age Fetus	Fetal Growth Restriction	Intrauterine Growth Restriction: Screening, Diagnosis, and Management	Fetal Growth Restriction – Recognition, Diagnosis & Management
Pages	34	12	8	26
References	197	142	55	48
Quality evaluation & Grading of recommendation	Yes, system not specified	US Preventive Services Task Force	Canadian Task Force on Preventive Health Care	No (given little RCT evidence for management of FGR pregnancies)
Definition	SGA: EFW/ AC <10 th centile Severe SGA: EFW/ AC <3 rd centile FGR: pathological restriction	FGR: EFW <10 th centile SGA: BW <10 th centile	SGA: EFW <10 th centile IUGR: EFW <10 th centile (pathological)	FGR: EFW <10 th centile SGA: physiological IUGR: pathological (ie abnormal UA, poor interval growth velocity, EFW <3 rd centile)
Viability	>24 weeks and EFW >500 grams	not mentioned	>24 weeks and EFW >500 grams	>24 weeks and EFW >500 grams
Detection	Palpation limited accuracy Serial customised SFH after 24 weeks	FH 65-85% sensitivity, 96% specificity Ultrasonography may be better screening modality (maternal obesity, multiple pregnancy, fibroids)	SFH poor sensitivity and specificity SFH limited value, however only physical examination available	FH limited value, however only physical examination available Clinical assessment of fetal size at each visit Ultrasound better screening modality (obesity, fibroids)
Screening	Assess risk factors First/ second trimester screening Women with RF: serial biometry and UA Women with 3+ RF: Uta Doppler 20-24 PAPP-A<0.415 MoM Fetal echogenic bowel	Assess risk factors Review medical/ obstetric history FH at each visit between 24-38 weeks Discrepancy >3cm concerning	Accurate dating, assess risk factors First/ second trimester screening Women with RF: Uta Doppler 19-23 weeks Discrepancy >3cm concerning	Accurate dating, assess risk factors Review medical/ obstetric history Women with RF: serial biometry and UA every 2-4 weeks Clinical assessment of fetal size at each visit, if concerns, refer for biometry

IUGR versus SGA

IUGR e SGA non sono sinonimi!!

...anche se spesso in letteratura e pratica clinica sono spesso usati in maniera intercambiabile

SGA (piccolo costituzionale)

condizione post-natale per i nati con peso < al 10° centile.

- Feto piccolo sulla base di cause costituzionali o fisiologiche
- Normale crescita durante la gravidanza (con velocità di crescita della CA secondo curva di crescita) e biometria adeguata rispetto alle caratteristiche genitoriali (altezza, peso, etnia) - necessità di curve di crescita customizzate!
- Normale fisiologia (LA e Doppler normali)
- Outcome favorevole

IUGR

processo fisiopatologico che avviene in utero inibendo la normale crescita fetale.

- outcome variabile a seconda dello staging

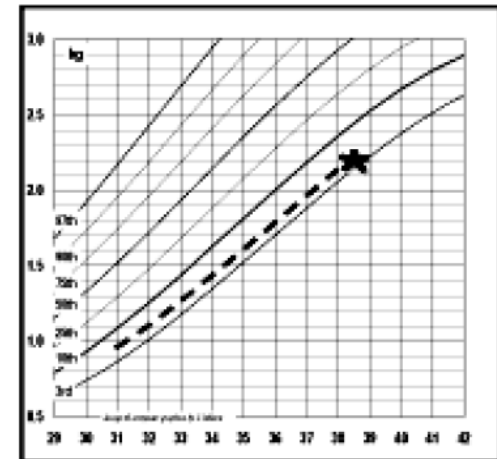


Figura 1: Curva di crescita di un feto SGA

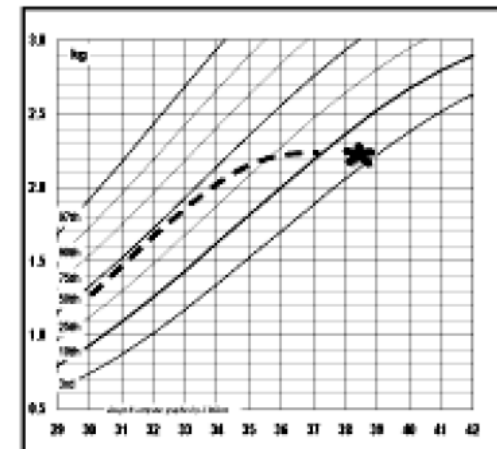
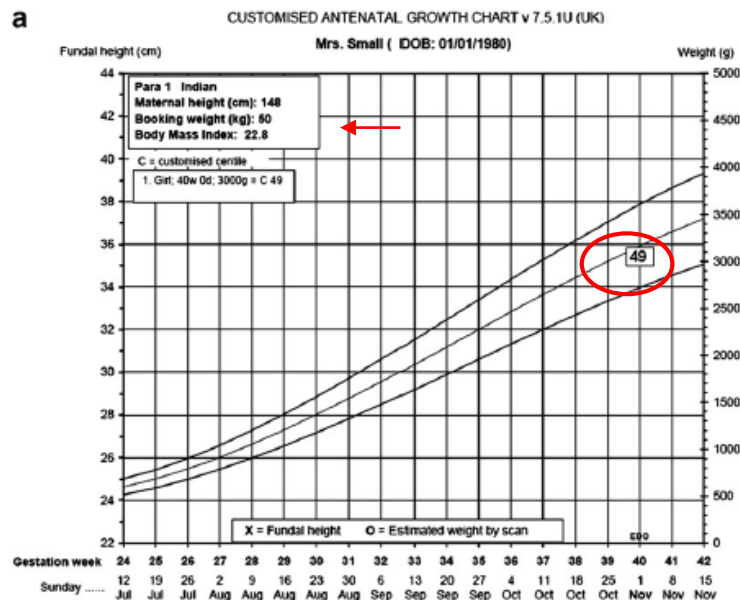


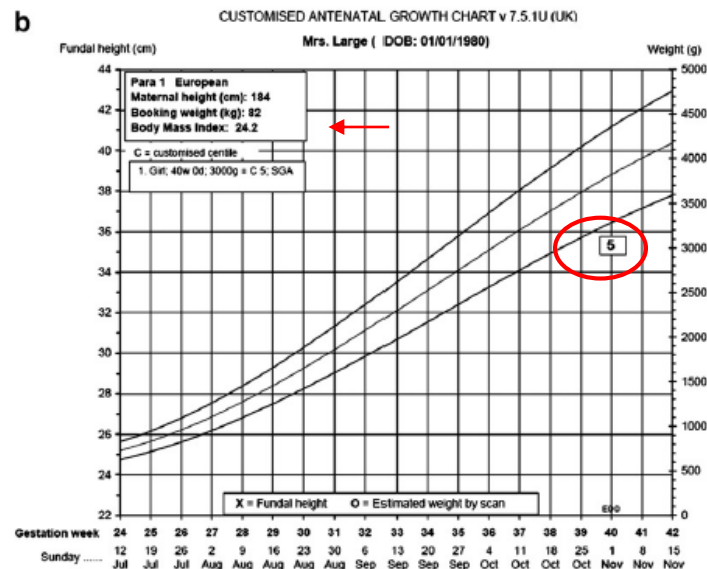
Figura 2: Curva di crescita di un feto IUGR

Curve di crescita customizzate

‘Mrs Small’ and ‘Mrs Large’



**h 148 cm, peso 50 kg
EWF 3000 g a 40 sg**



**h 184 cm, peso 82 kg
EWF 3000 g a 40 sg**

Le curve customizzate permettono:

- differenziare i piccoli costituzionali non a rischio dai piccoli patologici a rischio
- identificare un numero maggiore di feti a significativo rischio che ad oggi con i centili di popolazione non verrebbero etichettati come IUGR

IUGR

(Intra Uterine Growth Retardation)

L'accrescimento e lo sviluppo fetale è dato dal

- POTENZIALE GENETICO : derivato da entrambi i genitori ed è mediato da fattori di crescita
- SUPPORTO NUTRIZIONALE: legato alla corretta funzione della placenta e al corretto apporto di sostanze nutrienti e ossigeno al feto.



Meccanismo di adattamento a condizioni sfavorevoli in utero



Alterazione permanente del metabolismo, della crescita e dello sviluppo del feto

Mortalità 10-20 volte superiore dei neonati AGA (adeguati all'età gestazionale)

Aumento della morbidità e mortalità sia **antepartum** (morti intrauterine, oligoidramnios) che **post partum** (inalazione di meconio, distress neonatale, morte intrapartum)

FATTORI DI RISCHIO

Materne	Fetali	Placentari
Età materna avanzata	Gravidanza gemellare	Arteria ombelicale singola
Precedentefeto con IUGR o MEF		
Patologie croniche: <ul style="list-style-type: none"> – diabete pregest – disordini ipertensivi, – patologie renali – ipertiroidismo, – emoglobinopatie, – disordini autoimmuni, – patologie cardiache – Ab anti fosfolipidi) 	Infezioni (Rubeo, CMV, hsv, Toxo, Malaria, Sifilide, Chagas)	Anomala inserzione del cordone (velamentosa)
Obesità Nutrizione inadeguata, malassorbimenti, basso incremento ponderale	Anomalie cromosomiche e genetiche (T 13,18, Difetti cardiaci congeniti, gastroschisi)	Placenta bilobata o circumvallata
Farmaci(Fenitoina, ac Valproico, Trimetadione, Warfarin, Ciclofosfamide)		Placenta piccola
Abuso di sostanze (tabacco, alcool, cocaina, metanfetamine, narcotici)		Mosaicismo confinate alla placenta

EARLY versus LATE IUGR

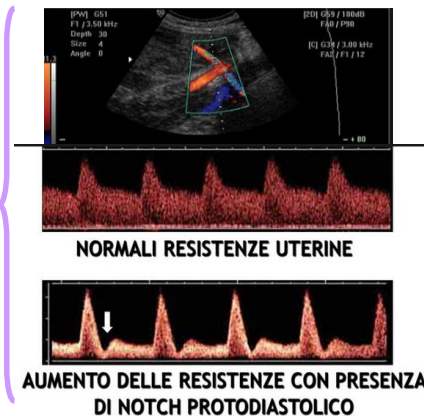
EARLY IUGR (precoce severo)	LATE IUGR (tardivo)
< 32 s.g.	> 32 s.g.
Bassa incidenza	Più comune
Frequentemente correlato con preeclampsia	Raramente correlato con preeclampsia
Difficoltoso management	Difficile differenziazione con SGA
Spesso riscontro di ombelicale con resistenza aumentata	Spesso arteria ombelicale con flussimetria normale
Modificazioni emodinamiche progressive	A volte flussimetria arterie uterine alterata

Early-onset FGR (1-2%)	Late-onset FGR (3-5%)
Problem: management	Problem: diagnosis
Placental disease: severe (UA Doppler abnormal, high association with preeclampsia)	Placental disease: mild (UA Doppler normal, low association with preeclampsia)
Hypoxia ++: systemic cardiovascular adaptation	Hypoxia +/-: central cardiovascular adaptation
Immature fetus = higher tolerance to hypoxia = natural history	Mature fetus = lower tolerance to hypoxia = no (or very short) natural history
High mortality and morbidity; lower prevalence	Lower mortality (but common cause of late stillbirth); poor long-term outcome; affects large fraction of pregnancies

Screening IUGR

➤ Ecografico:

Arterie uterine



➤ Ematochimico :

Papp-A (Proteina Plasmatica associata alla gravidanza)
< 0,5 mom

Valutazione del benessere nel feto IUGR

Markers Cronici	Markers Acuti
Arteria ombelicale	} Dotto Venoso } cardiocografia
Arteria cerebrale media	
Liquido amniotico/PBF	



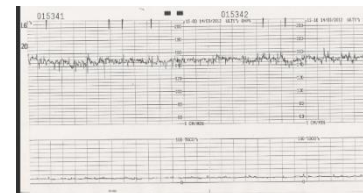
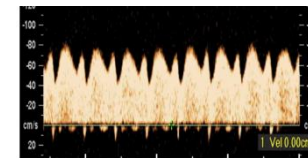
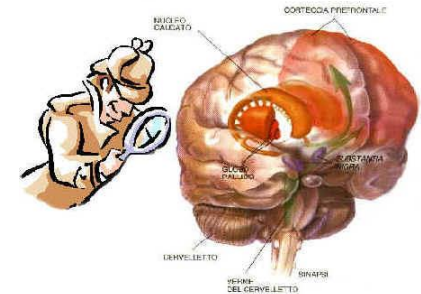
Truffle Study (Trial of umbilical and fetal flow in Europe)

Ultrasound Obstet Gynecol 2013; 42: 400–408
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.13190



Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE)

	CTG STV (n=166)	DV p95 (n=167)	DV no A (n=170)	Total (n=503)
Fetal death no intervention*	2 (1%)	1 (1%)	2 (1%)	5 (1%)
Unexpected death†	0	3 (2%)	4 (2%)	7 (1%)
Livebirth	164 (99%)	163 (98%)	164 (96%)	491 (97%)
Neonatal death	10 (6%)	6 (4%)	11 (7%)	27 (6%)
Death due to congenital abnormality	0	0	2 (1%)	2 (1%)
Overall mortality	12 (7%)	10 (6%)	17 (10%)	39 (8%)
Neonatal data missing	1 (1%)	0	0	1 (<1%)
Survival at discharge	153 (92%)	157 (94%)	153 (90%)	463 (92%)
Neonatal morbidity				
Received mechanical ventilation	72 (44%)	63 (39%)	69 (42%)	204 (42%)
Received supplemental oxygen	98 (60%)	96 (59%)	103 (63%)	297 (61%)
BPD >28 days	32 (20%)	28 (17%)	31 (19%)	91 (19%)
BPD >36 weeks‡	16 (10%)	17 (10%)	16 (10%)	49 (10%)
Sepsis (proven)‡	33 (20%)	31 (19%)	23 (14%)	87 (18%)
NEC, pneumatosis‡	3 (2%)	3 (2%)	1 (1%)	7 (1%)
Perforation‡	2 (1%)	2 (1%)	5 (3%)	9 (2%)
GMH grade III or IV‡	0 (0%)	4 (2%)	8 (5%)	12 (2%)
PVL grade II or III‡	1 (1%)	2 (1%)	2 (1%)	5 (1%)
Death following severe morbidity†	10 (6%)	6 (4%)	9 (5%)	25 (5%)
Adjusted age of survivors at discharge, days§	-9 (-17 to 6)	-7 (-15 to 2)	-10 (-17 to 2)	-9 (-16 to 3)
Survival following severe neonatal morbidity (% of survivors)	38 (25%)	42 (27%)	38 (25%)	118 (25%)
Survival without severe neonatal morbidity (% of all study entrants)	115 (69%)	115 (69%)	115 (68%)	345 (69%)



Staging dello IUGR

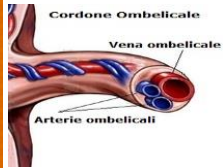
Stage	Pathophysiological correlate	Criteria (any of)	Monitoring*	GA/mode of delivery
I	Severe smallness or mild placental insufficiency	EFW <3rd centile CPR <p5 UA PI >p95 MCA PI <p5 UtA PI >p95	Weekly	37 weeks LI
II	Severe placental insufficiency	UA AEDV Reverse AoI	Biweekly	34 weeks CS
III	Low-suspicion fetal acidosis	UA REDV DV-PI >p95	1-2 days	30 weeks CS
IV	High-suspicion fetal acidosis	DV reverse a flow cCTG <3 ms FHR decelerations	12 h	26 weeks** CS

F. Figueras et al., Fetal Diagn Ther 2014

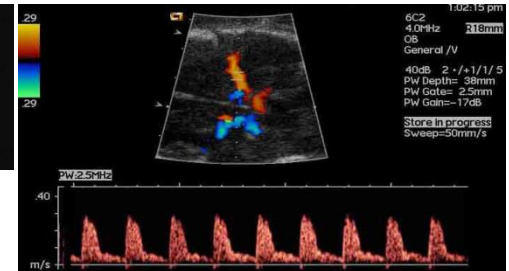
Stage	UA		MCA		DV		UV		TV E/A	TR
	aPI	ARF	aPI	aPSV	aPI	RF	P	RF		
I	+		+							
II		+		+	+		+			
III						+		+	+	+

G. Mari et al., J Ultrasound Med 2007

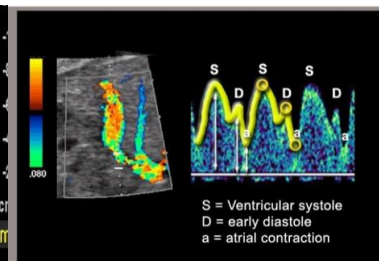
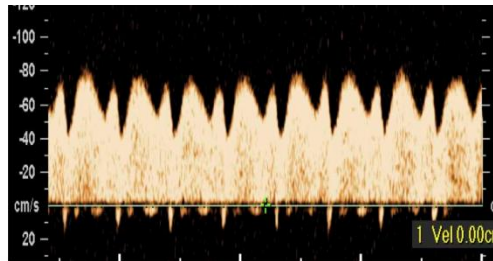
Monitoraggio benessere nel feto IUGR



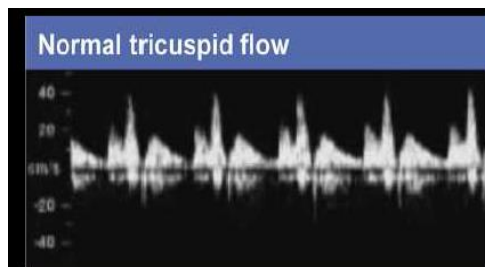
Arteria ombelicale(AO)



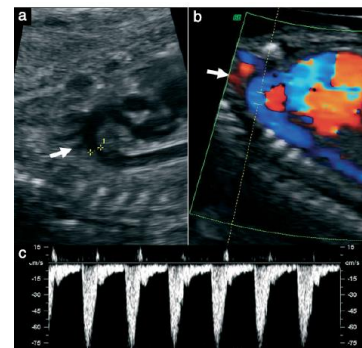
Arteria Cerebrale Media (MCA)



Dotto venoso (DV)



Tricuspide



Istmo aorta

L'Istmo dell'Aorta

Table 3 Predictive value of the aortic isthmus (AoI) and other Doppler parameters evaluated for an adverse perinatal outcome and overall mortality

	Sensitivity (% (n))	Specificity (% (n))	PPV (% (n))	NPV (% (n))	LR+
Adverse perinatal outcome					
Absent/reversed flow in UA	73.7 (14/19)	65.6 (21/32)	56 (14/25)	80.8 (21/26)	2.1
Vasodilatation of MCA	84.2 (16/19)	78.1 (9/32)	41 (16/39)	75 (9/12)	1.2
Absent/reversed DV a-wave	36.8 (7/19)	96.9 (31/32)	87.5 (7/8)	72.1 (31/43)	11.5
Retrograde diastolic AoI	47.4 (9/19)	96.9 (31/32)	90 (9/10)	75.6 (31/41)	15.2
UV pulsation	36.8 (7/19)	84.3 (27/32)	70 (7/10)	69.2 (27/39)	2.3
GA < 28 completed weeks	68.4 (13/19)	93.7 (30/32)	86.7 (13/15)	83.3 (30/36)	10.8
Overall mortality					
Absent/reversed flow in UA	88.9 (8/9)	59.5 (25/42)	32 (8/25)	96.1 (25/26)	2.2
Vasodilatation of MCA	88.9 (8/9)	76.2 (11/42)	26.5 (8/30)	91.7 (11/12)	1.2
Absent/reversed DV a-wave	77.8 (7/9)	97.6 (41/42)	87.5 (7/8)	95.3 (41/43)	32.3
Retrograde diastolic AoI	77.8 (7/9)	92.9 (39/42)	70 (7/10)	95.1 (39/41)	10.8
UV pulsation	66.7 (6/9)	90.5 (38/42)	60 (6/10)	92.7 (38/41)	6.9
GA < 28 completed weeks	100 (9/9)	85.7 (36/42)	60 (9/15)	100 (36/36)	7.0

DV, ductus venosus; GA, gestational age; LR+, positive likelihood ratio; MCA, middle cerebral artery; NPV, negative predictive value; PPV, positive predictive value; UA, umbilical artery; UV, umbilical vein.

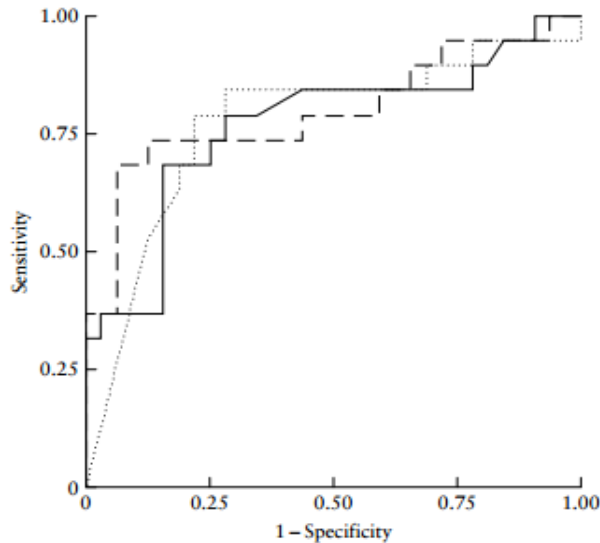
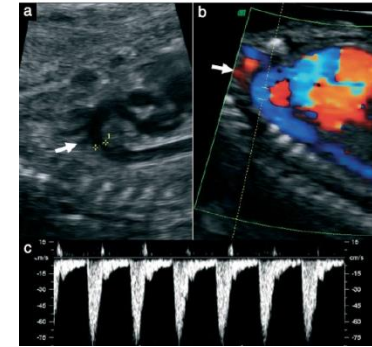
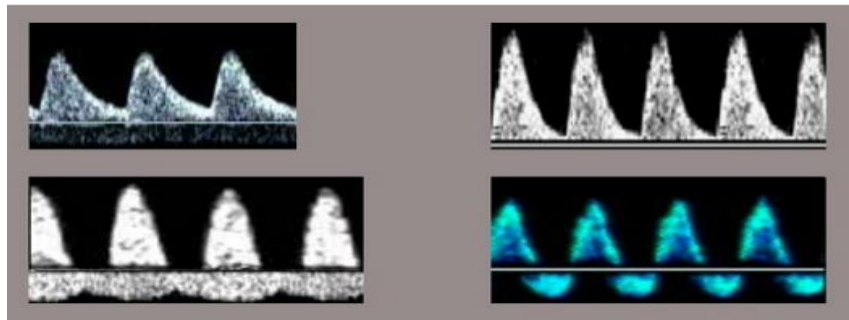


Figure 6 Receiver–operating characteristics curves of the ductus venosus pulsatility index centile (—), the aortic isthmus pulsatility index centile (.....) and the combined variable (— —) for the prediction of adverse perinatal outcome.

- I feti IUGR mostrano una marcata riduzione della velocità in AoI
- Un flusso retrogrado dell'AoI è fortemente associato ad outcome perinatale avverso
- Parametro aggiuntivo nella valutazione dello scompenso emodinamico nei feti IUGR

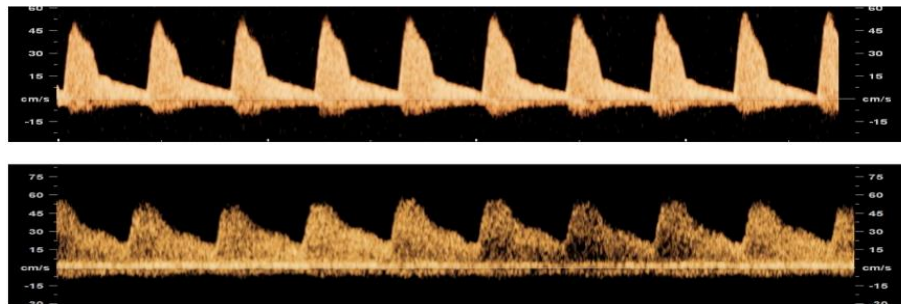
Deterioramento emodinamica fetale nello IUGR



AEDF

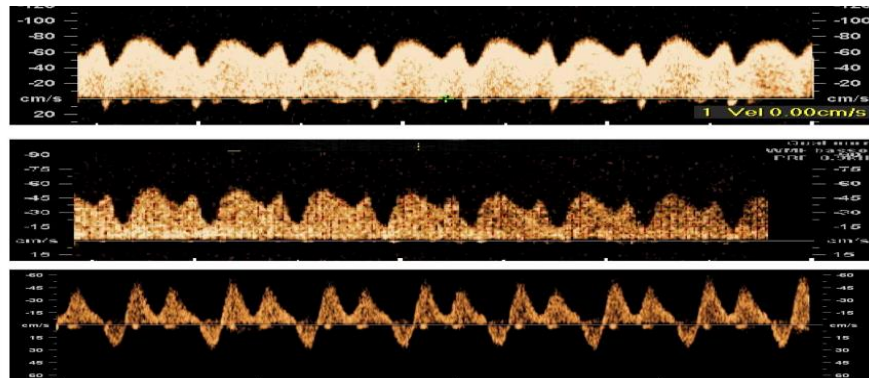
REDF

Anomalie dell'AO



Anomalie della MCA

Brain Sparing Effect

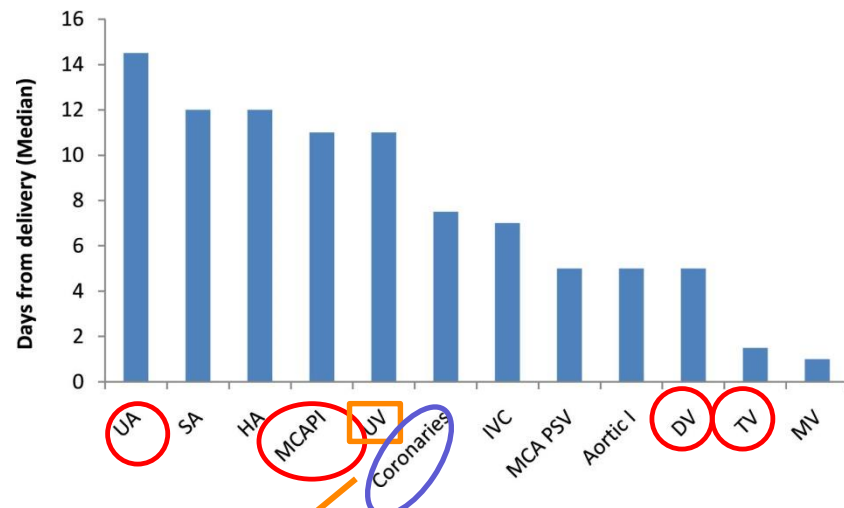
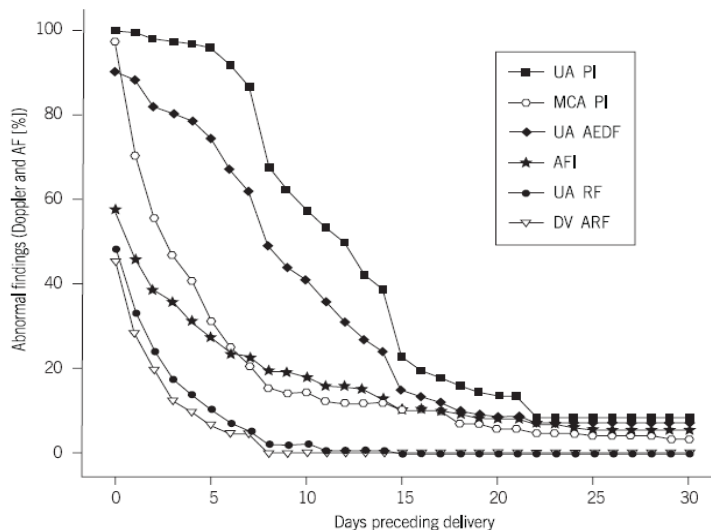


Anomalie del DV

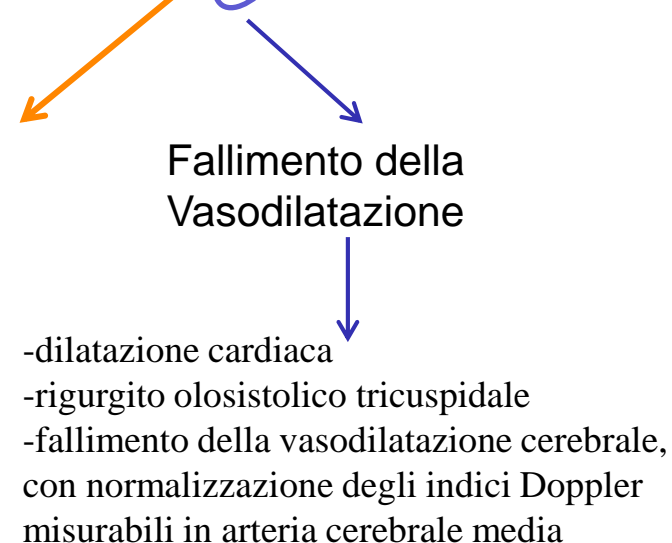
AEDF (Absent end diastolic flow)

REDF (Reverse end diastolic flow)

Deterioramento emodinamica fetale nello IUGR

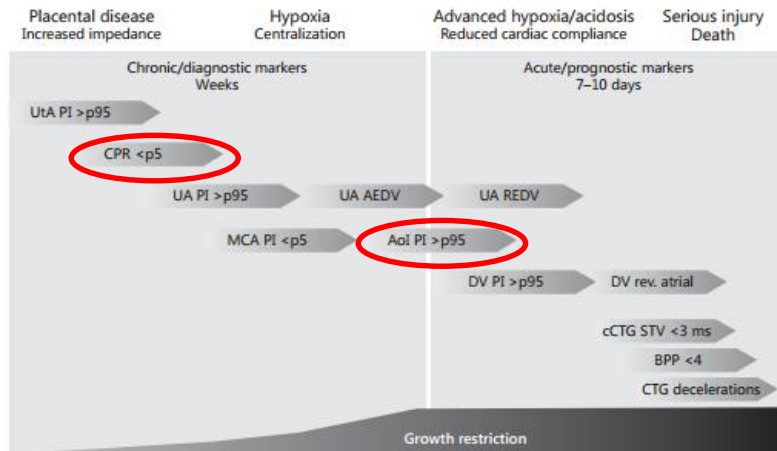


In casi estremi, la pressione atriale viene trasmessa in maniera retrograda alla vena ombelicale (visibile come pulsatilità nella vena ombelicale stessa).



Deterioramento emodinamica fetale nello IUGR

Early IUGR



Late IUGR

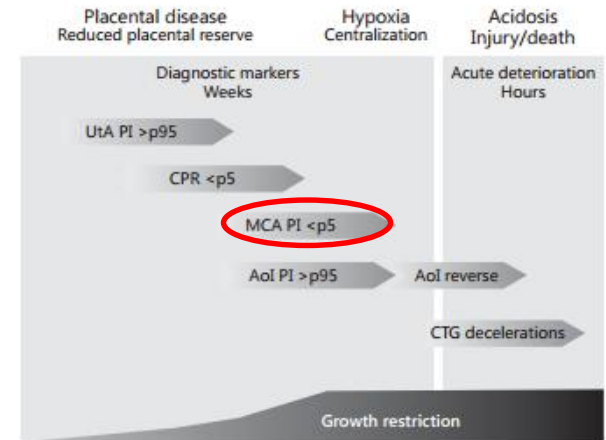


TABLE 3

CPR in comparison with UA Doppler in the prediction of adverse perinatal outcomes

Predictor	Adverse perinatal outcome		
	Sensitivity	Specificity	OR (95% CI)
UA (PI >95th centile)	85% (35/41)	54% (454/840)	6.9 2.9–16.5
UA (PI >95th centile, AEDF, REDF)	90% (37/41)	54% (452/831)	10.8 3.8–30.5
CPR (PI) <1.0	66% (27/41)	85% (721/840)	11.7 6.0–22.9

Perinatal outcome was defined as a composite outcome of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary, sepsis, and death.

AEDF, absent end diastolic flow; CI, confidence interval; CPR, cerebroplacental ratio; OR, odds ratio; PI, pulsatility index; REDF, reversed end diastolic flow; UA, umbilical artery.

Flood. Brain sparing in IUGR. Am J Obstet Gynecol 2014.

CPR(Cerebroplacental Ratio) :

PI MCA/PI AO

Se basso = BSE



Predizione degli avventi avversi neonatali

Sequela delle alterazioni flussimetriche nello IUGR

1° : riduzione del flusso nella vena ombelicale → Riduzione delle dimensioni epatiche → ↓ CA

2° Riduzione del flusso di fine diastole in **AO** con aumento del PI

3° Aumento del flusso di fine diastole in **MCA** e Riduzione del PI
(Brain Sparing Effect)



In
Late
IUGR

→ 4° flusso di fine diastole assente o invertito in **AO** (AEDF-REDF)

5° Normalizzazione degli indici di MCA
(Perdita dello Brain Sparing Effect)

Deterioramento funzionalità cardiaca a causa dell'ipossia cronica e della carenza di nutrienti

Ipercapnia

→ 6° flusso di fine diastole assente o invertito
in **DV** e flusso pulsatile in vena ombelicale

Ipossia
(AEDF)/Acidosi
fetale(REDF)

Algoritmo della gestione degli IUGR

Finding	Interpretation	Action
Abnormal UA+/-or CPR; normal MCA & veins BPS≥8/10, AFV normal	Asphyxia extremely rare Increased risk for intrapartum distress	Deliver for obstetric, or maternal factors only, fortnightly Doppler Weekly BPS
Low MCA, normal veins BPS≥8/10, AFV normal	Blood flow redistribution Hypoxemia possible, asphyxia rare Increased risk for intrapartum distress	Deliver for obstetric, or maternal factors only, weekly Doppler BPS 2 times/week
UA A/REDV, normal veins BPS≥6/10, oligohydramnios	Significant blood flow redistribution Hypoxemia common, acidemia or asphyxia possible Onset of fetal compromise	>34 weeks: deliver <32 weeks: antenatal steroids repeat all testing daily
Increased DV pulsatility BPS≥6/10, oligohydramnios	Fetal compromise Hypoxemia common, acidemia or asphyxia likely	>32 weeks: deliver <32 weeks: admit, steroids, individualize testing daily vs. tid
Compromise by above criteria Absent or reversed DV a-wave, pulsatile UV BPS<6/10, oligohydramnios	Fetal decompensation Cardiovascular instability, metabolic compromise, stillbirth imminent, high perinatal mortality irrespective of intervention	Deliver at tertiary care center with the highest level of NICU care

I feti con IUGR hanno un aumentato rischio di mortalità e morbilità

- emorragia intraventricolare displasia broncopolmonare
- enterocolite necrotizzante
- Infezioni
- emorragia polmonare
- Ipotermia
- ipoglicemia.

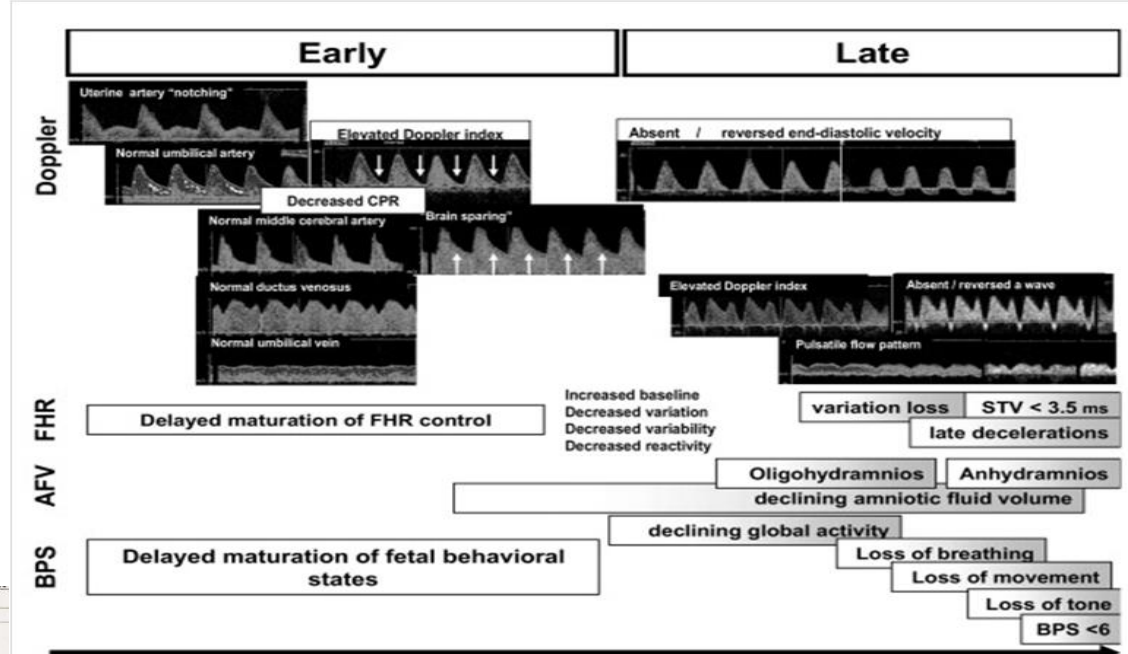
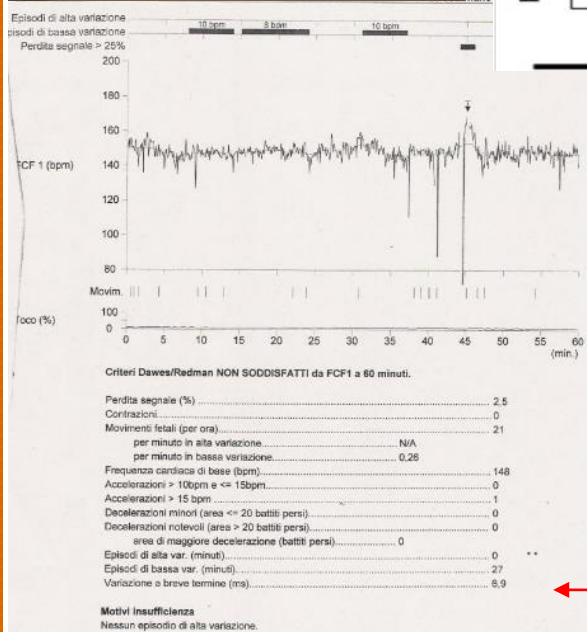
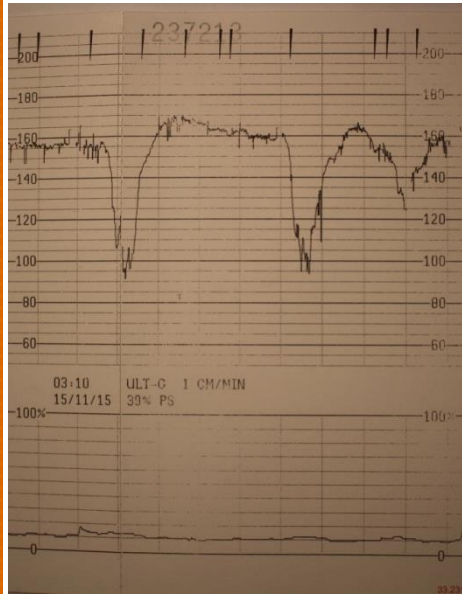
Più del 50% delle MEF di feti non malformati, sono associate a IUGR

(< 10° centile in base alle curve customizzate)

Le MEF < 32 sg sono strettamente associate allo IUGR

I feti IUGR hanno un rischio 5-10 volte superiore di MEF

Monitoraggio cardiocotografico nello IUGR



STV (Short Term Variability)

Feti < 26 sg : STV < 3.5 msec
indice di acidosi metabolica

Management

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Country	United Kingdom	United States	Canada	Ireland
Issued	February 2013	May 2013	August 2013	March 2014
Customisation	Yes, may improve prediction of perinatal outcome	Not been shown to improve outcomes	Not mentioned	Consider, may improve prediction of perinatal outcome
Management	Examination of fetal anatomy Offer MFM referral Serial biometry every 3 weeks	Examination of fetal anatomy Serial biometry every 3-4 weeks	Examination of fetal anatomy Serial biometry every 2 weeks Detailed ultrasound of placenta, if abnormal → MFM consultation	Examination of fetal anatomy, if abnormal → MFM consultation Serial biometry, AFI and UA every 2 weeks
Amniocentesis	Consider if additional soft markers or structural abnormalities	Consider if additional soft markers or structural abnormalities	Consider if additional soft markers or structural abnormalities	Consider if additional soft markers or structural abnormalities
TORCH	Consider +/- malaria and syphilis	Not mentioned	Consider	Consider
UtA Doppler	Yes (20-24 weeks), moderate predictive value	Not mentioned	Yes (19-23 weeks)	Not recommended
UA Doppler	Yes	Yes	Yes	Yes
MCA	Limited accuracy, should not be used to time delivery	Not mentioned	Yes (if UA abnormal)	Optional (if UA abnormal), should not be used to time delivery
DV	Yes (if UA abnormal), use to time delivery	Not been shown to improve outcomes	Yes (if UA abnormal)	No
UV	Yes	Not mentioned	Consider	Not mentioned
CTG	Yes STV (not in isolation)	Yes	Yes (not in isolation)	Yes, ideally STV
Amniotic fluid	Assess single DVP (not in isolation)	Yes	Yes	Yes
BPP	Not in preterm SGA fetuses	Yes	Yes (consider weekly)	No, limitations preterm FGR
Delivery		Depends on underlying aetiology, patient-choice at preterm gestations, individualised, multidisciplinary		Individualised, multidisciplinary
Timing	Consider after 37 weeks AREDF UA: 30-32 weeks, earlier based on abnormal DV or UV Abnormal MCA: 37 weeks Abnormal UA > 32 weeks: 37 weeks	Isolated FGR: 38+0 – 39+6 weeks FGR+ additional RF (oligo, abnormal PI, maternal comorbidities): 34+0 – 37+6 weeks	Consider after 37 weeks Abnormal CTG (based on fetal viability) Isolated: 38-40 weeks	SGA: consider ≥ 37-40 weeks UA PI >95 th centile: 37 weeks AEDF: no later than 34 weeks REDF: no later than 30 weeks Abnormal CTG (based on fetal viability)
Mode	CS if AREDF If positive EDF: offer IOL with continuous monitoring once contracting	FGR alone not an indication for CS	Not mentioned	CS likely if AREDF or preterm Abnormal UA: consider IOL with continuous monitoring once contracting

Management

Table 1. Comparison of Clinical Practice Guidelines on FGR (UK, USA, Canada and Ireland)

	RCOG Green-top Guideline (No. 31)	ACOG/ SMFM Practice Bulletin (No. 134)	SOGC Clinical Practice Guideline (No. 295)	HSE/ RCPI Clinical Practice Guideline (No. 29)
Country	United Kingdom	United States	Canada	Ireland
Issued	February 2013	May 2013	August 2013	March 2014
Steroids	Between 24+0 and 35+6 weeks	Prior to 34 weeks	Prior to 34 weeks	Between 24+0 and 34+0 weeks, up until 38+0 if elective CS
MgSO ₄	(Prior to 30 weeks)	Prior to 32 weeks	Not mentioned	Prior to 32 weeks
Placental histology	Not mentioned	Not mentioned	Yes	Yes
Prevention	Smoking cessation, Aspirin (prior to 16 weeks), no evidence for dietary modifications, progesterone, calcium	Insufficient evidence for Aspirin, bedrest, nutritional/ dietary supplementation	Smoking cessation, Aspirin (12-36 weeks)	Smoking cessation, Aspirin (prior to 16 weeks)
Recurrence	At least 2-fold	20%	Not mentioned	25%
Postnatal Management	Not mentioned	Not mentioned	Not mentioned	Postnatal counselling if IUGR and preterm delivery <34 weeks Review of placental histology and investigation of underlying causes (ie thrombophilia testing)

Management

Algorithm–Management of Fetal Growth Restriction

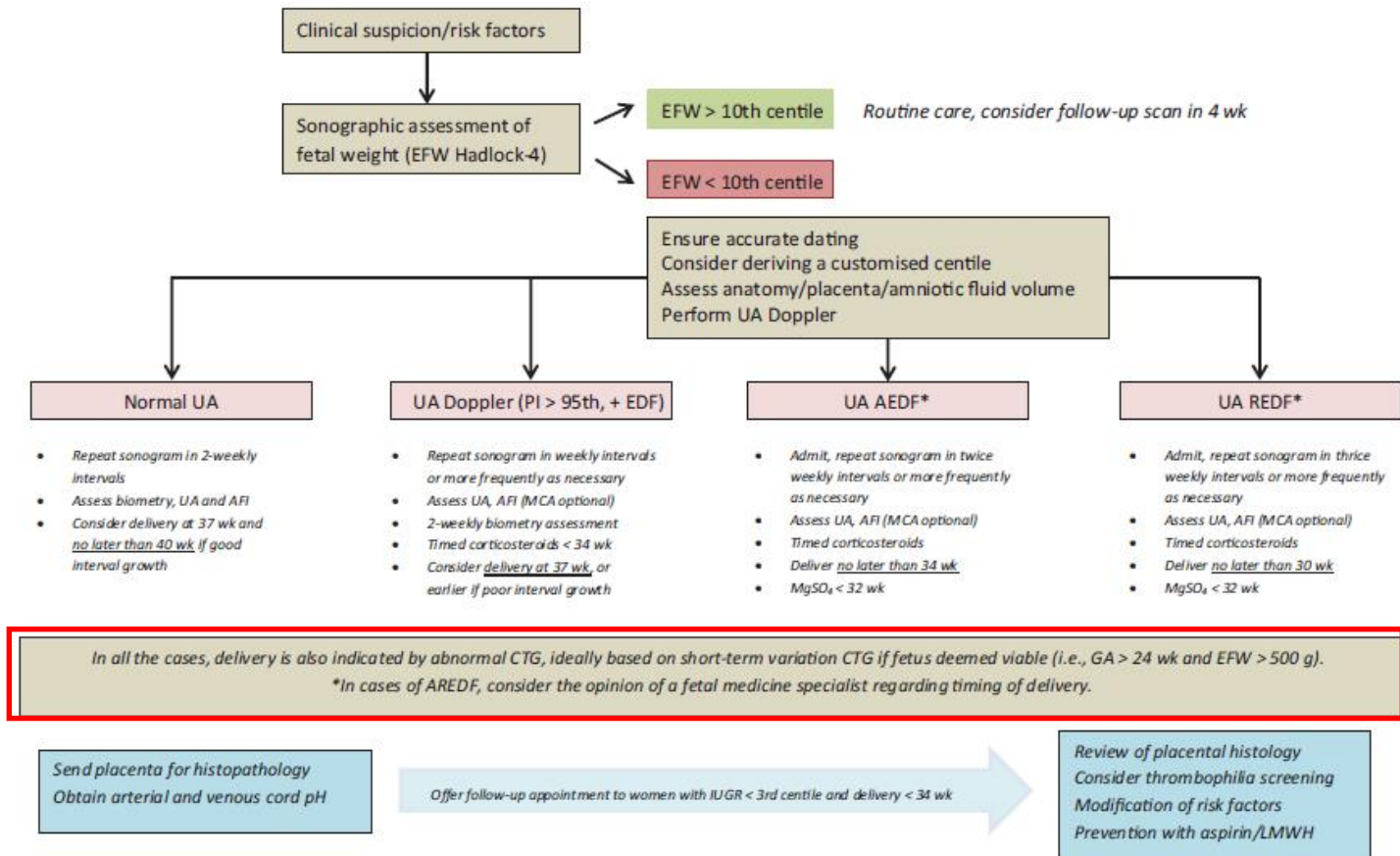
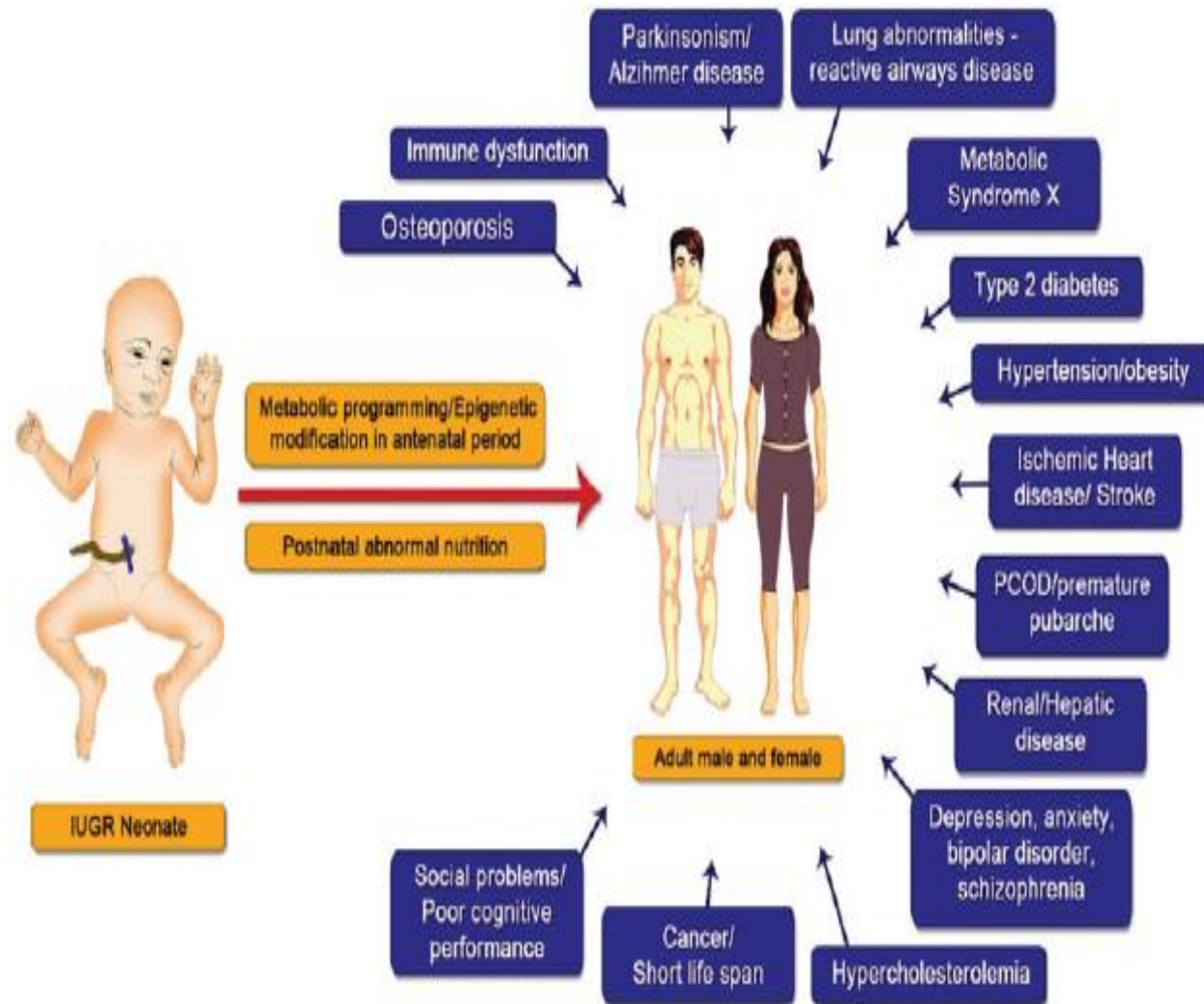


Fig. 1 Algorithm–management of fetal growth restriction. AEDF, absent end-diastolic flow; AREDF, absent or reversed end-diastolic flow; AFI, amniotic fluid index; CTG, cardiotocograph; GA, gestational age; EDF, end-diastolic flow; EFW, estimated fetal weight; LMWH, low-molecular-weight heparin; MCA, middle cerebral artery; PI, pulsatility index; REDF, reversed end-diastolic flow; UA, umbilical artery.

Origine fetale delle patologie dell'età adulta



Teoria della programmazione fetale di Barker

DEVELOPMENTAL ORIGINS HYPOTHESIS



Gli esseri umani nel periodo iniziale della loro vita sono plastici e capaci di adattarsi all'ambiente

Una noxa patogena che intervenga in un periodo finestra dello sviluppo fetale risulta in grado di programmare quel feto allo sviluppo di eventi cardiovascolari e metabolici in epoca adulta, quali ictus e diabete di tipo II

DEVELOPMENTAL PLASTICITY



fenomeno per cui un singolo genotipo può dar origine a differenti fenotipi in risposta a stimoli ambientali diversi



RISCHIO CARDIOVASCOLARE

DEVELOPMENTAL ORIGINS HYPOTHESIS

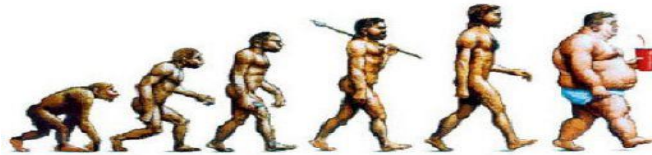
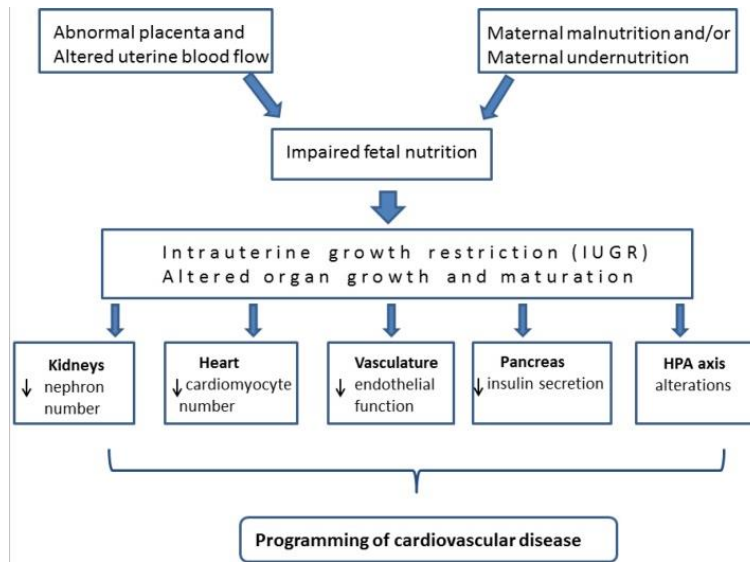
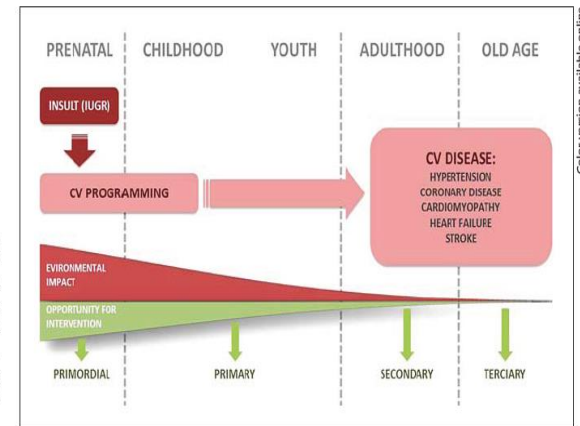


Fig. 1. Cardiovascular programming in IUGR. Cardiovascular programming is triggered by an insult in utero, which can lead to functional changes in key organs persisting in postnatal life and leading to a greater risk of various diseases in adulthood. Therefore, it is critical to intervene as early as possible in order to prevent CVD in adult life.



Color version available online

NELL'HERTFORDSHIRE...



Si è visto che su una coorte di 10.636 uomini nati in questa regione tra gli anni 1911-1930 quelli con minore peso alla nascita avevano più rischio di morte per coronaropatia .

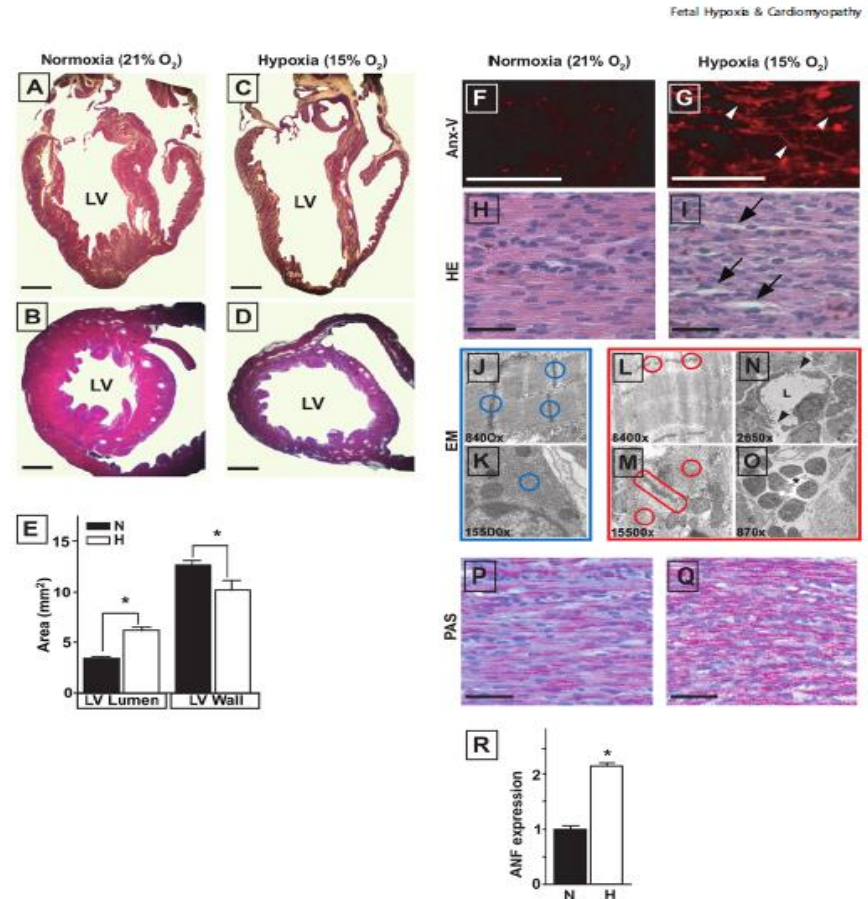
Table 1. Premature death from coronary heart disease (aged <65 years) according to birthweight in 10,636 men born in Hertfordshire between 1911 and 1930 [3, 4]

Birth weight, kg (pounds)	Hazard ratios (95% confidence interval)
≤2.5 (5.5)	1.37 (1.00–1.87)
-2.95 (6.5)	1.30 (1.01–1.67)
-3.4 (7.5)	1.17 (0.92–1.47)
-3.85 (8.5)	1.11 (0.88–1.41)
-4.3 (9.5)	0.90 (0.69–1.18)
≥ 4.55 (10)	1.00
p for trend	<0.001

La stessa associazione si è poi vista con lo sviluppo di DM2 e di alterata tolleranza al glucosio

RIMODELLAMENTO CARDIACO

Aumento delle resistenze placentari e l'esposizione cronica ad una condizione ipossica porta a modificazioni cardiache paragonabili a quanto accade in una cardiomiopatia dilatativa



OPEN ACCESS Freely available online

PLoS one

Hypoxia Induces Dilated Cardiomyopathy in the Chick Embryo: Mechanism, Intervention, and Long-Term Consequences

Andrei Tintu^{1,2,3}, Ellen Rouwet^{3,5}, Stefan Verlohren^{1,4,5}, Joep Brinkmann^{1,5}, Shakil Ahmad⁶, Fatima Crispi⁶, Marc van Bilsen⁷, Peter Carmeliet⁸, Anne Cathrine Staff⁹, Marc Tjwa¹⁰, Irene Cetin¹¹, Eduard Gratacos⁶, Edgar Hernandez-Andrade⁶, Leo Hofstra¹², Michael Jacobs², Wouter H. Lamers¹³, Ingo Morano¹⁴, Erdal Safak¹⁵, Asif Ahmed⁵, Ferdinand le Noble¹

RIMODELLAMENTO VASCOLARE

DEVELOPMENTAL ORIGINS HYPOTHESIS

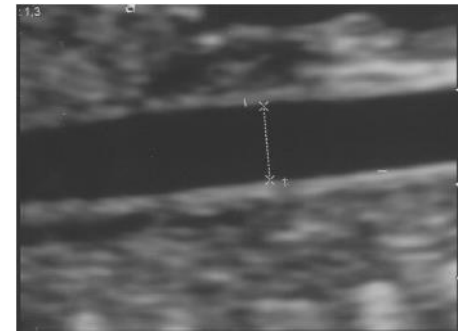
- Feti con ritardo di crescita ed alterazioni velocimetriche fetali sembrano presentare segni ecografici ed anatomici patologici a livello della parete aortica addominale riferibili ad una iniziale disfunzione endoteliale



Aumento dello stress alle pareti vasali e conseguente rimodellamento della struttura vasale



**AUMENTO DELLO SPESSORE INTIMALE
SVILUPPO DI PLACCHE ATEROMATOSE**



Cosmi et al Consequences in Infants that were intrauterine Growth restricted, Journal of Pregnancy 2011

Coehn et al. Intrauterine growth restriction: impact on cardiovascular development and function throughout infancy, Pediatric Research 2016

IPERTENSIONE

DEVELOPMENTAL ORIGINS HYPOTHESIS

Minori cellule in organi chiave: anche a livello renale

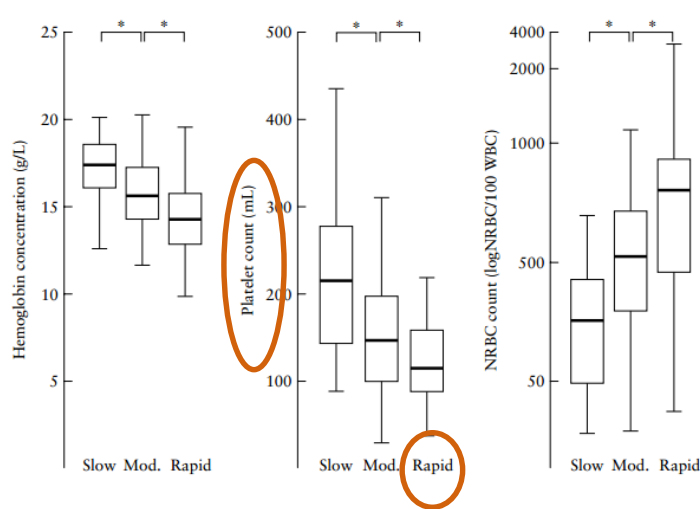


↓ numero di glomeruli renali e quindi ↑ flusso sanguigno ai rimanenti glomeruli → Ipertrofia glomerulare

Attivazione del sistema RAA per compensazione (mantenere il flusso) e scarsa riserva renale agli insulti

esposizione massiva dei trasportatori apicali del Sodio in molteplici zone del nefrone e, di conseguenza, possibile sviluppo di ipertensione NaCl-sensibile

Rimodellamento dell'assetto emocromocitometrico nei feti IUGR



Deterioramento cardiovascolare

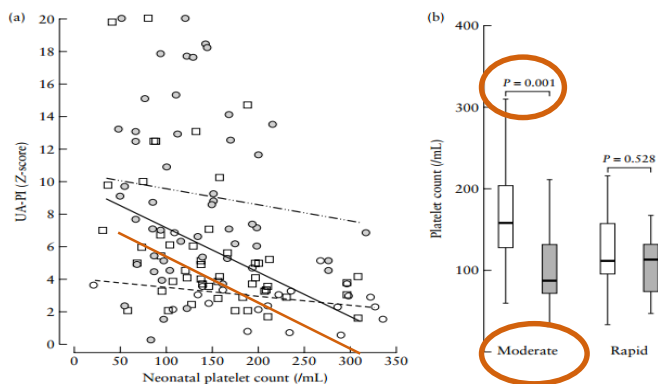
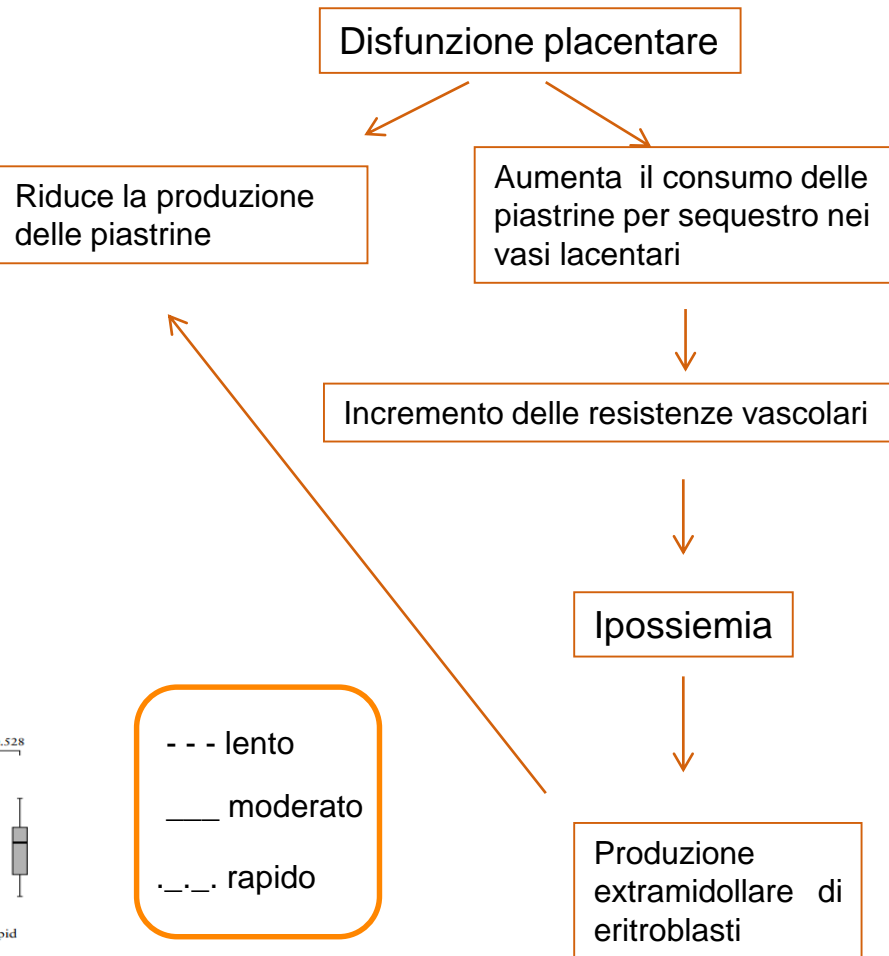


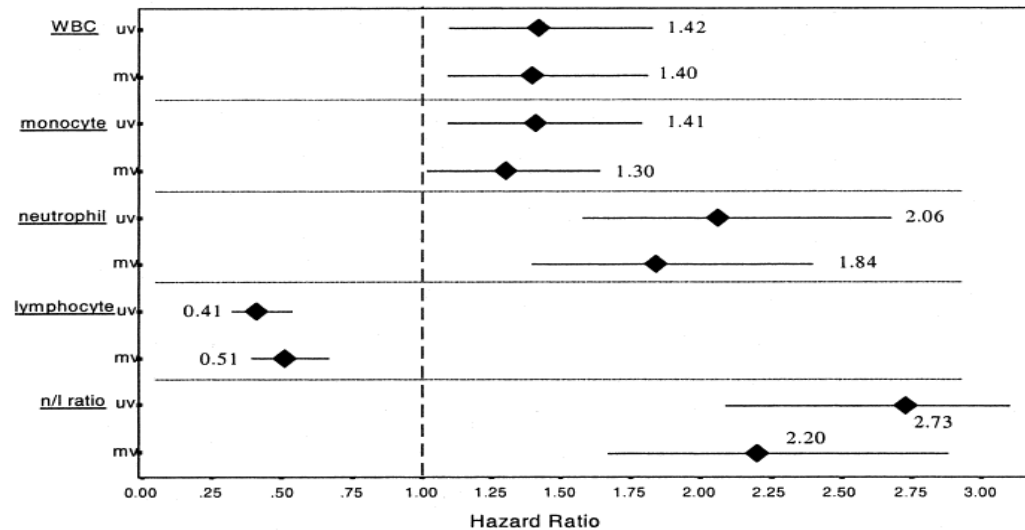
Figure 2 Relationship between platelet count and umbilical artery (UA) Doppler in 130 cases of fetal growth restriction. (a) Correlation between platelet count and UA pulsatility index (PI) Z-score in patients with slow (○, - - - -), moderate (□, ———) or rapid (◊, - · - · -) cardiovascular deterioration. A significant relationship (Spearman ρ_s -0.439, $P = 0.001$) between rising UA blood-flow resistance and falling platelet count was only demonstrated for fetuses with moderate deterioration. (b) Median, interquartile range and range for platelet counts stratified by present UA end-diastolic velocity (EDV) (□) and absent UA-EDV (◊) according to moderate or rapid deterioration. Platelet counts were significantly lower with absent UA-EDV in neonates with moderate deterioration (Mann-Whitney U -test).



Utilizzo dell'emocromo nelle patologie cardiovascolari dell'adulto

Neutrofili
Linfociti

Piastrine
Linfociti



Emocromo

Neonato pretermine

- Anemia del prematuro
- Bassa conta neutrofili (G-CSF)
- Ridotta conta piastrinica

Neonato pretermine IUGR

- Anemia
- Bassa conta piastrinica
- Eritroblastosi
- RDW



Hematologic profile and Doppler abnormalities in neonates with intrauterine growth restriction



S. Visentin, L. Falcone, E. Salviato, V. Di Giovanni, E. Cosmi

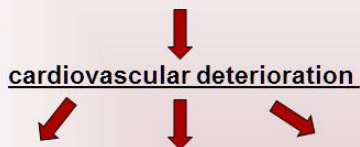
Department of Women's and Children's Health
University of Padua

BACKGROUND:

Fetuses with intrauterine growth restriction (IUGR):



- increasing blood flow resistance in the umbilical arteries
- villous vascular abnormalities



intra-placental platelet activation microthrombosis lower platelet counts at birth.

AIM:

To analyze the relationship between :

- Hematologic parameters at birth
- Doppler abnormalities
- Vascular markers of fetal endothelial dysfunction

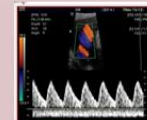
MATERIALS AND METHODS:

prospective study conducted between April 2013 and June 2015

PATIENT SELECTION

100 singleton pregnant women in the third trimester :

- ❖ routine scan
- ❖ suspected growth retardation



IUGR n° 50		AGA n° 50
GROUP 1	GROUP 2	
> Estimated fetal weight (EFW) below the 10th percentile > Umbilical artery Doppler abnormalities, above 2 standard deviations	> EFW below the 3th percentile > Normal fetal Doppler velocimetry for gestational age	

All newborns were recovered in NICU for preterm delivery. For both groups, a complete blood count was performed at birth.

Criteria di esclusione :

- Anomalie cromosomiche o malformazioni fetali
- Sospetta corioamniosite
- Gravidanze gemellari

La nostra esperienza..



Hematologic profile and Doppler abnormalities in neonates with intrauterine growth restriction

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..outcome neonatale

	IUGR (n=50)	AGA (n=50)	p-Value
Settimana gestazionale all'ecografia	30,84 (±3,39)	30,98 (±3,33)	0,84
aIMT parete posteriore (mm)	1,06 (±0,52)	0,56 (±0,07)	<0,0001
Diametro aortico	3,50 (±0,76)	3,00 (0,29%)	0,53
PI art ombelicale (7 AEDF)	1,57 (±0,53)	1,05 (±0,09)	<0,0001
PI art cerebrale media	1,63 (±0,28)	1,98 (±0,34)	0,007
PI dotto venoso	0,59 (±0,21)	0,48(±0,10)	0,05
PI medio art uterine	1,98 (±0,34)	0,79 (±0,24)	<0,0001

	IUGR	AGA	p-Value
Età	34,16 ±5,61	33,12±5,52	0,25
Nulliparità	66,70%	56,90%	0,08
Etnia	Caucasica	94,12%	78,43%
	Orientale	0,00%	5,88%
	Afro-Caribbean	3,92%	1,96%
	Nord Africa	1,96%	13,73%

	IUGR con anomalie Doppler (n=)	IUGR senza anomalie Doppler (n=)	AGA (n=50)	p-Value
Settimana gestazionale al parto	32 (± 2,45)	32 (± 4,20)	32 (± 2,36)	0,65
Peso alla nascita (g)	1277 (± 456)	1421 (± 981)	1960 (± 558)	<0,0001
Lunghezza alla nascita (cm)	38,89 (± 5,31)	40,31 (±5,17)	42,27 (±3,86)	0,01
Percentile del peso al parto	4 (± 2,23)	3 (± 1,17)	55 (± 14,42)	0,001
Apgar 5'	8,50 (± 1,04)	7,81 (± 0,98)	8.20 (±1,21)	0,20



La nostra esperienza..



Hematologic profile and Doppler abnormalities in neonates with intrauterine growth restriction



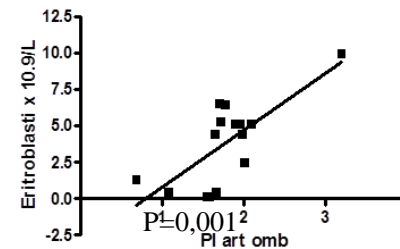
S. Visentin, L. Falcone, E. Salviato, V. Di Giovanni, E. Cosmi

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..profilo emocromocitometrico al 1° giorno di vita

	IUGR con anomalie Doppler	IUGR senza anomalie Doppler	AGA	p-Value
Leucociti (x10.9/L)	5,91 (±3,12)	7,49 (±3,63)	12,23 (±5,96)	<0,0001
Eritrociti (x10.12/L)	4,42 (±0,52)	4,08 (±0,95)	4,13 (±0,57)	0,19
Hb (g/L)	166,40 (±18,92)	154,63 (±34,72)	147,02 (±20,43)	0,004
Ematocrito (%)	0,49 (±0,05)	0,45 (±0,10)	0,43 (±0,06)	<0,0001
MCV (fL)	112,00 (±9,30)	111,67 (±9,27)	103,68 (±5,31)	0,0007
MCH (pg)	37,82 (±3,45)	37,10 (±3,12)	35,56 (±1,59)	0,0008
Piastrine (10.9/L)	145,45 (±59,00)	213,63 (±79,40)	250,12 (±60,86)	<0,0001
Neutrofili (10.9/L)	2,79 (±2,03)	3,26 (±2,14)	7,44 (±4,73)	0,0001
Eritroblasti (10.9/L)	5,69 (±9,06)	1,75 (±1,51)	0,79 (±1,40)	0,002



Feti IUGR

Neonati prematuri con diagnosi di **restrizione di crescita** intrauterina presentano profili emocromocitometrici differenti rispetto a neonati prematuri di peso corretto, in particolar modo quando presente un'**anomalia della Doppler** velocimetria fetale

La nostra esperienza..



Hematologic profile and Doppler abnormalities in neonates with intrauterine growth restriction

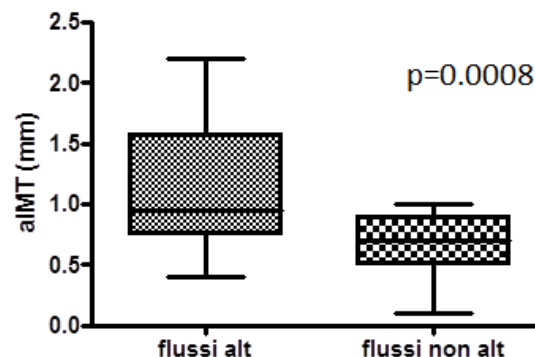
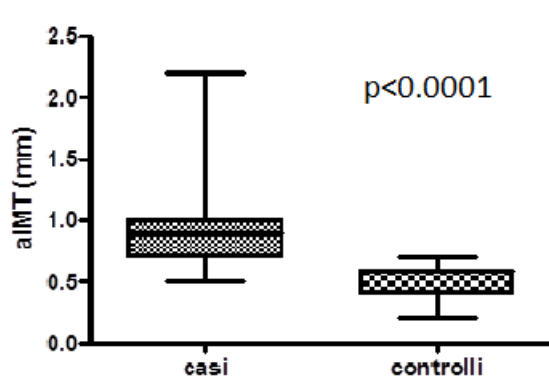
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..spessore intimo-media aortico (aIMT)



	IUGR senza anomalie Doppler	AGA	P-Value
aIMT (mm)	0,7 ($\pm 0,19$)	0,56 ($\pm 0,07$)	P=0,0001

L'aumento dello spessore aIMT nel gruppo IUGR, associato ad una riduzione della conta piastrinica, che a sua volta correla con la flussimetria fetale, potrebbe contribuire all'ulteriore definizione del rischio neonatale

La nostra esperienza..



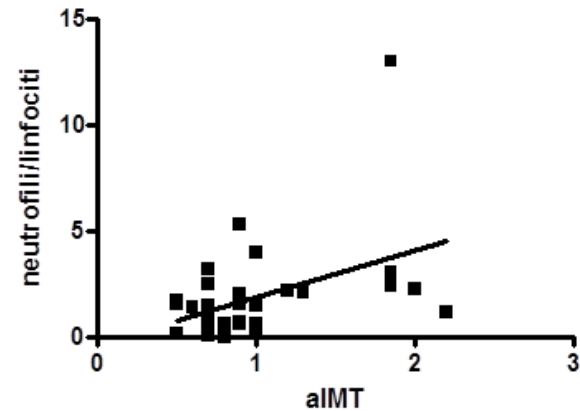
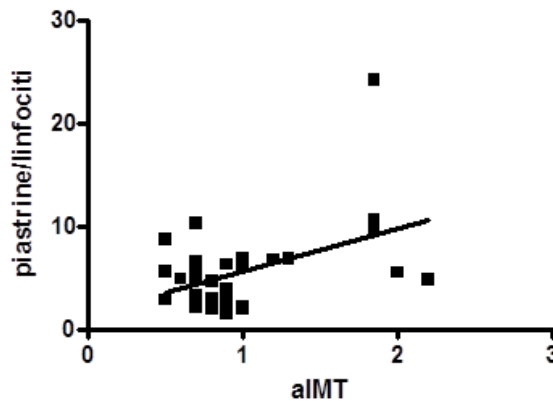
Hematologic profile and Doppler abnormalities in neonates with intrauterine growth restriction



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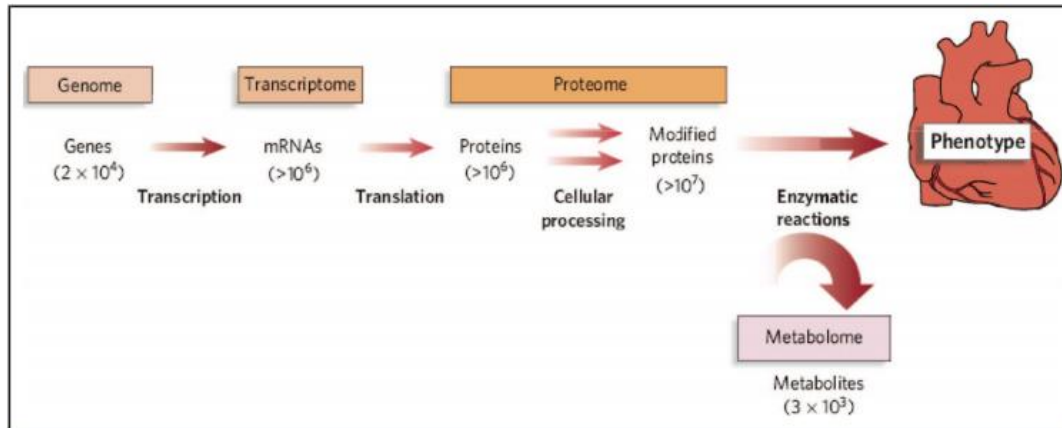
..correlazioni fra alterazioni emocromocitometriche e aIMT negli IUGR



Il rapporto piastrine/linfociti, che nella popolazione adulta rappresenta una modalità di stratificazione di rischio del paziente vasculopatico, risulta statisticamente significativo nel gruppo IUGR

aIMT markers per investigare i cambiamenti pre aterosclerotici nei feti

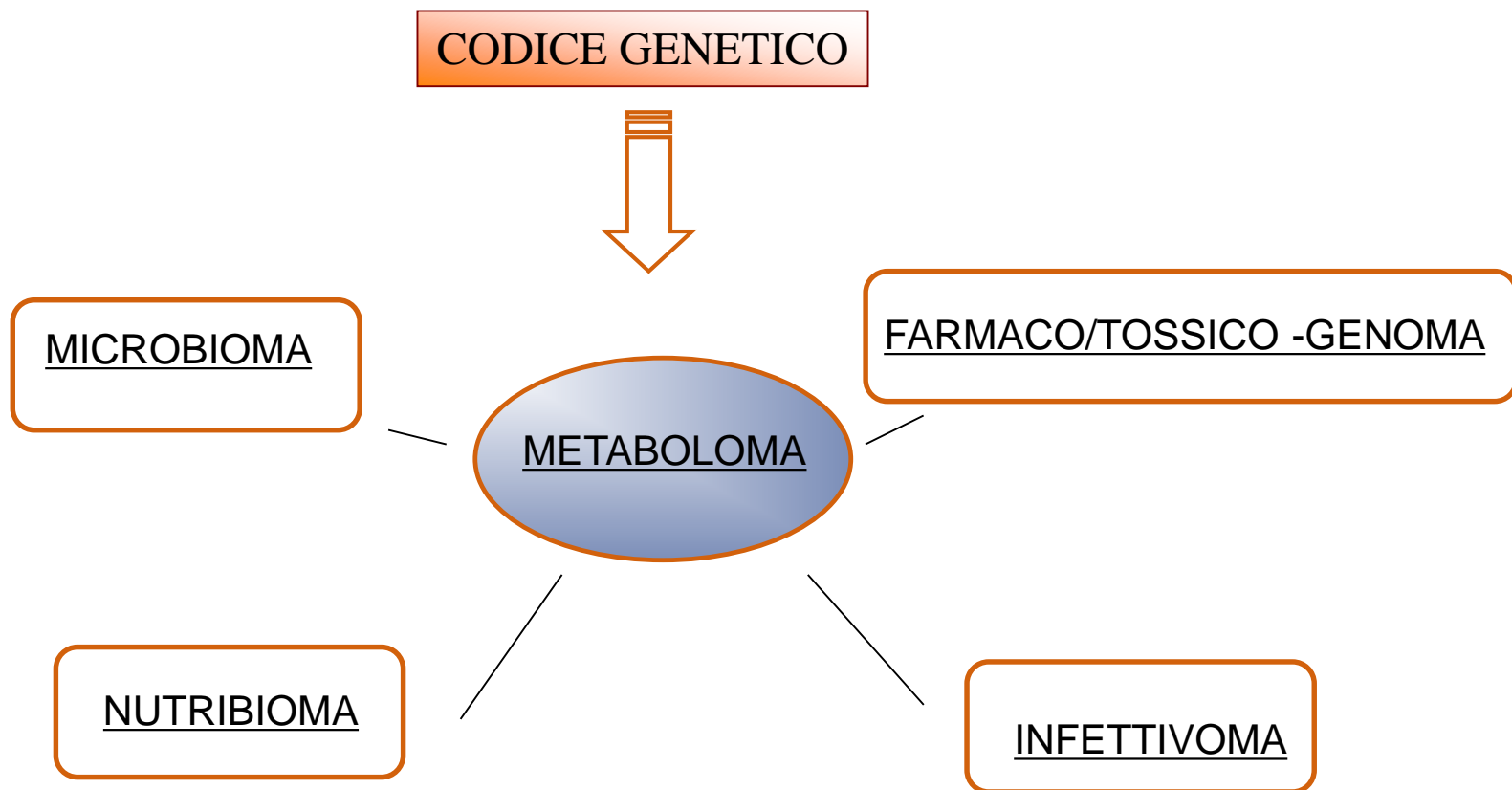
Le scienze omiche



METABOLOMICA

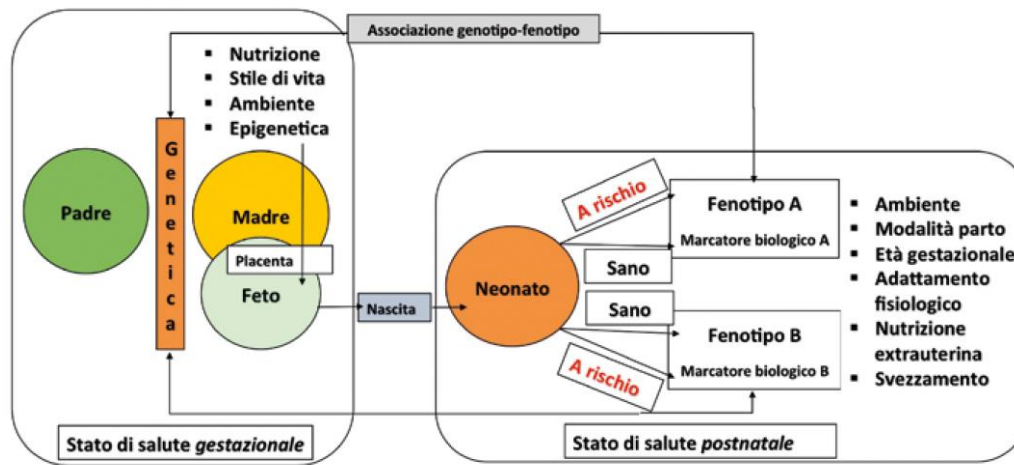
- E' la scienza omica che si basa sull'analisi e l'interpretazione delle funzioni dei metaboliti (molecole di basso peso molecolare) di un determinato sistema biologico (cellula, tessuto, sistema, organismo) sotto l'influenza di una serie di condizioni
- E' considerata quella che si avvicina di più all'espressione definitiva del fenotipo, inteso come risultato dell'interazione tra geni ed ambiente.

La Metabolomica



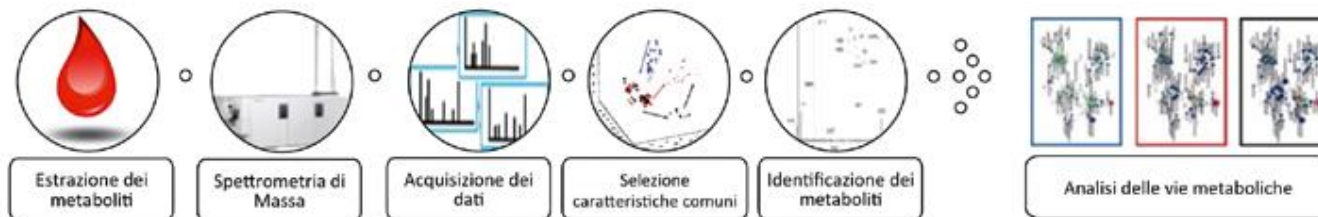
tecnologia più promettente nello studio del fenotipo
complesso di un organismo

La Metabolomica



Influenza dell’**“ambientoma”** materno (es., stile di vita e nutrizione della madre) sul feto e influenza dei fattori ambientali perinatali (es., modalità del parto, età gestazionale, adattamenti fisiologici) sul neonato e interazioni/influenze del patrimonio genetico (paterno/materno).

Sequenza di indagini metabolomiche



Applicazione degli OMICS allo IUGR

Selective Intrauterine Growth Restriction in Monochorionic Twin Pregnancies: Markers of Endothelial Damage and Metabolomic Profile

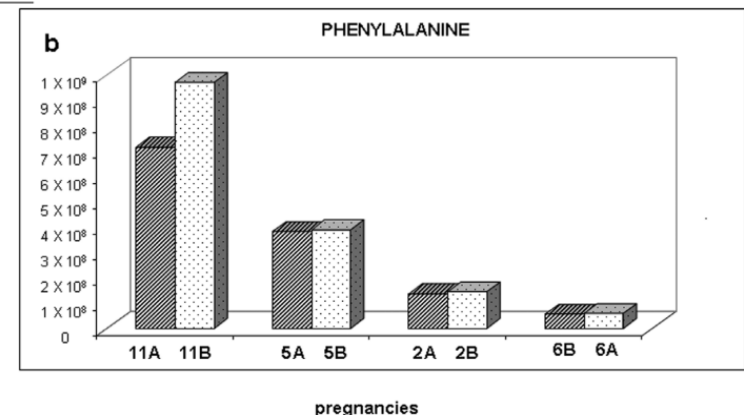
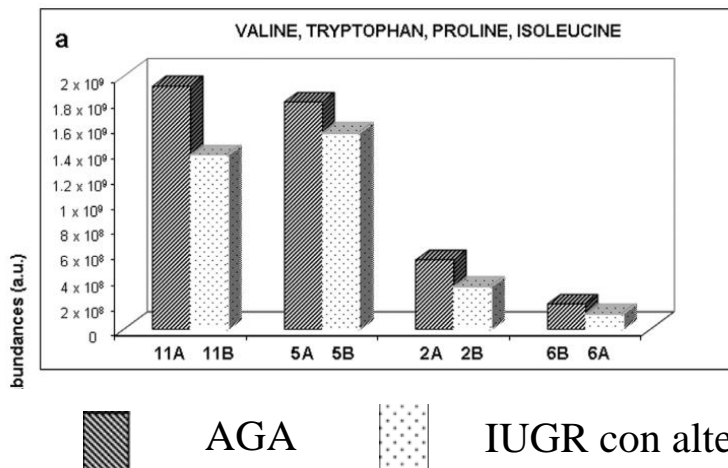
Erich Cosmi,^{1*} Silvia Visentin,^{1*} Donata Favretto,² Marianna Tucci,² Eugenio Ragazzi,³ Guido Viel,² and Santo Davide Ferrara²

Maternal and Neonatal Data

Parameters	Group 1	Group 2	Group 3	Overall p value
Twins (no.)	4	4	16	
Maternal age (years)	31 (24-37)	33 (32-35)	29 (24-37)	.26
Primiparous (%)	50%	100%	75%	.18
aIT (mm)	0.9 (0.8-1.0)**	0.8 (0.7-0.9)**	0.5 (0.4-0.6)	.0002
Aortic diameter (mm)	3.5 (2-4.1)	3.2 (2.7-4)	4.1 (2.9-4.9)	.20
Umbilical artery Doppler waveforms (no.)				
Normal	0**	4†	16	.0002
PI > 2 SD	4**	0†	0	.0002
AEDF/ARED UA	3*	0	0	.004
Presence of A-wave in DV	4	4	16	1
Mode of delivery (no.)				
Cesarean	4	4	16	1
Vaginal	0	0	0	1
Gestational age at delivery (wk)	33 (28-36)	33 (33-36)	35 (28-36)	.47
Birth weight (g)	1,480 (870-1,725)*	1,970 (1,680-2,260)	2,315 (1,210-3,030)	.01
Birth height (cm)	39.5 (35-41)*	43 (42-45)†	45 (37-47)	.006
Apgar at 5 minutes	9 (8-9)	9 (9-10)	9 (6-10)	.42
pH cord blood at delivery	7.1 (7.1-7.2)*	7.2 (7.2-7.3)	7.3 (7.2-7.3)	.004
BE cord blood	3.7 (1.6-6.2)	4.7 (3.2-8.5)	4.3 (1.6-6.7)	.54

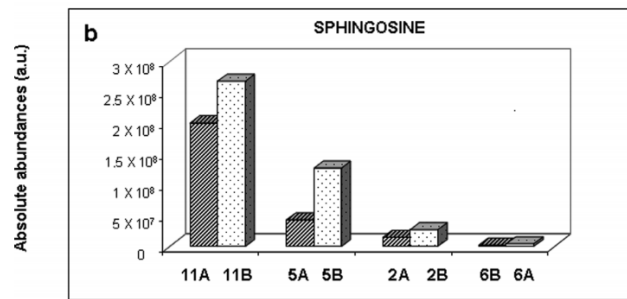
Ionic Species Identified in the LC-HRMS Spectra		
Metabolites	Elemental composition	Label, according to XCMS output
Valine	C ₅ H ₁₁ NO ₂	M118T101
Tryptophan	C ₁₁ H ₁₂ N ₂ O ₂	M205T241
Proline	C ₅ H ₉ NO ₂	M116T100
Isoleucine	C ₆ H ₁₃ NO ₂	M132T103
Phenylalanine	C ₉ H ₁₁ NO ₂	M166T141
Choline	C ₅ H ₁₃ NO	M104T79
Glycerophosphocholine	C ₂₆ H ₅₂ NO ₇ P	M522T2096
		M544T2098
		M520T2032
		M518T2071
		M544T2032
		M496T2071
Sphingosine	C ₁₈ H ₃₇ NO ₂	M300T1683

Alterato trasporto transplacentare degli aminoacidi nei feti IUGR con alterazioni flussimetriche



pregnancies

Applicazione degli OMICS allo IUGR



AGA



IUGR con alterazioni
flussimetriche

Sfingosina: messaggero secondario presente sulla superficie cellulare coinvolto nei processi di crescita, differenziazione e migrazione cellulare



Sfingosina 1 fosfato è espresso nel sistema cardio vascolare ed è coinvolto nella fisiopatologia delle problematiche legate a disfunzione endoteliale

Proprietà vasoattive degli sfingolipidi



Elevato rilascio di Trombossano e sostanze infiammatorie



IPERTENSIONE

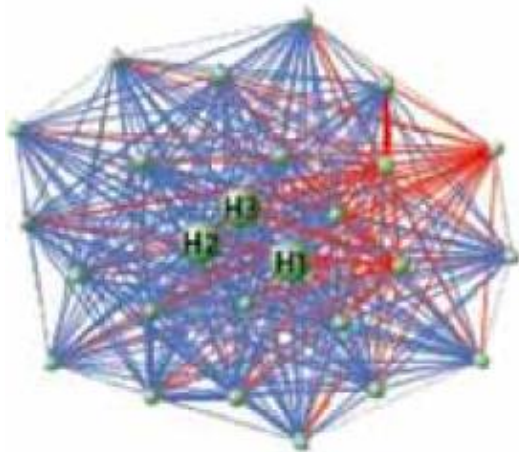
Glicerofosfolina: messaggero secondario presente sulla superficie cellulare coinvolto nei processi di crescita, differenziazione e migrazione cellulare

Take Home message

- ❑ Importanza della corretta diagnosi di IUGR
- ❑ Correlazione fra IUGR con alterazioni dei flussi e disfunzione endoteliale precoce
- ❑ Utilità dell'ecografia nell'identificazione dei cambiamenti a livello cardiovascolare
- ❑ Importanza del follow up dopo la nascita
- ❑ Utilizzo delle tecnologie omiche per intervenire precocemente e bloccare l'avanzamento delle patologie

GRAZIE

Networks



New Developments



F. Z. Kuppelje-L.

And this is the latest breakthrough: 5D ultrasound.. with 95% accuracy this is a realistic representation of your cute little baby 20 years from now..