ORDINE MEDICI CHIRURGHI E ODONTOIATRI DELLA PROVINCIA DI BRESCIA

EPILESSIA: ATTENZIONE AL GENERE

EPILESSIA E GRAVIDANZA

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ASST degli SPEDALI CIVILI DI BRESICA

U.O. Neurofisiopatologia

EPILESSIA E GRAVIDANZA

- Counceling preconcepimeto e programmazione gravidanza
- Acido folico
- Aderenza alla terapia
- Adeguamenti terapeutici durante la gravidanza
- Teratogenicità/ritardo cognitivo
- Espletamento del parto
- Allattamento al seno
- Depressione post-partum

EPIDEMIOLOGIA

- Over 1 million women with epilepsy in the USA are of reproductive age
- These women give birth to approximately 20,000 infants every year

TERATOGENICITA’

Congenital defects		General population	Timing of malformations (postconceptional age) [39]
Congenital heart defects	1.5–2%	0.5%	42 days (VSD)
Cleft lip/palate	1.4%	0.15%	36/47–70 days
Neural tube defect	1–3.8% (VPA)	0.06%	28 days
	0.5–1% (CBZ)		
Urogenital defects	1.7%	0.7%	

Major congenital malformations in infants of women with epilepsy.

	Lamotrigine	Carbamazepine
With valproic acid	9.1	15.4
With other AEDs	2.9	2.5

Risk of major congenital malformations in polytherapy with and without valproic acid.

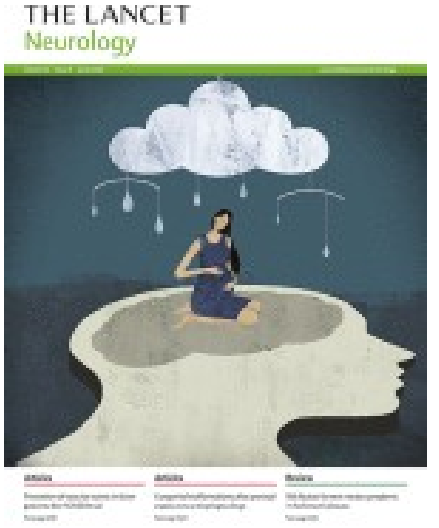
GRAVIDANZA E RISCHIO DI CRISI

Seizures pose a risk to the developing fetus, especially if generalized tonic clonic convulsions. They can cause direct injuries from a fall, compromise the blood supply to the fetus, cause postictal hypoxia and lactic acidosis

GRAVIDANZA E RISCHIO DI CRISI

Andamento degli episodi critici in gravidanza
(Battino et al. 2013)

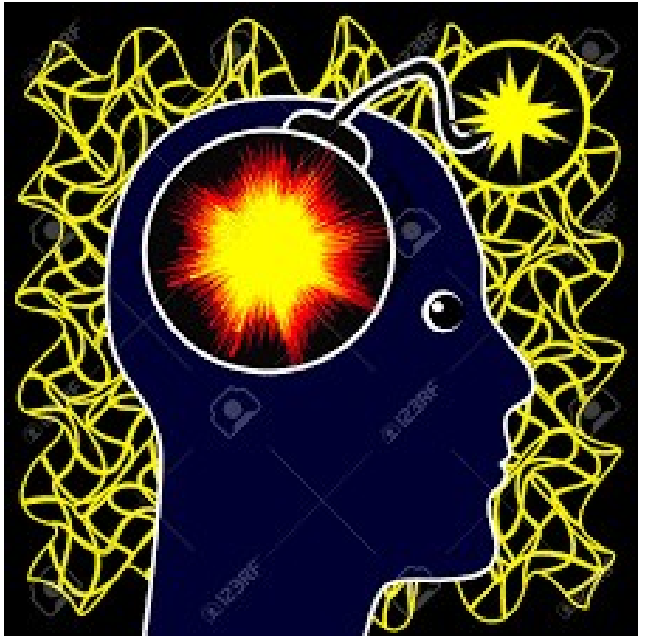
- 70,5% frequenza invariata
- 12% riduzione di frequenza
- 15,8% incremento frequenza
- 32% durante II trimestre
- 39% durante III trimestre
- 29% durante II e III trimestre.



GRAVIDANZA E RISCHIO DI CRISI

Rischio di crisi dipende da (Reisinger et al. 2013)

- Crisi nell’anno precedente la gravidanza
- Epilessie focali sintomatiche
- Politerapia



GRAVIDANZA E RISCHIO DI CRISI

Il miglior predittore del rischio di recidive critiche in corso di gravidanza sembra essere la

FREQUENZA DI CRISI NELL'ULTIMO ANNO PRECEDENTE LA GRAVIDANZA
(Reisinger et al. 2013)

COUNCELING PRECONCEZIONALE

Preconceptual counseling should aim to raise awareness among women with epilepsy that the best outcome for any pregnancy may be secured if the pregnancy is planned in advance. This will allow the necessary time for any changes or discontinuation of antiepileptic treatment to be carried out, or, if necessary, for seizure control to be optimized prior to pregnancy.

COUNCELING PRECONCEZIONALE

Abrupt cessation of AED therapy should be avoided at all costs because of the risk of uncontrolled epileptic seizures (Samuels MA et al 2009)

In some cases, **drug withdrawal may be considered** as a proportion of women with epilepsy who have been seizure free for 2 years on medication could successfully withdraw from treatment without relapse. (Chadwick D et al. 2013)

If during the reassessment of the epilepsy, the risk of complete drug withdrawal is considered too high it may still be possible to **reduce the drug load and in particular to reduce the number of AEDs that are prescribed**.

COUNCELING PRECONCEZIONALE

The **dose of individual AEDs may also be considered** as there is some evidence to suggest that there is an association with dose and congenital malformation with all of the commonly prescribed AEDs. (EURAP registry. Epilepsia 2009).

The effect of dose for sodium valproate in particular, may be of clinical importance in determining the size of the teratogenic risk, with the highest risk in those taking over 1000 mg per day. (Guthrie E et al. 2006).

NELLA POPOLAZIONE GENERALE

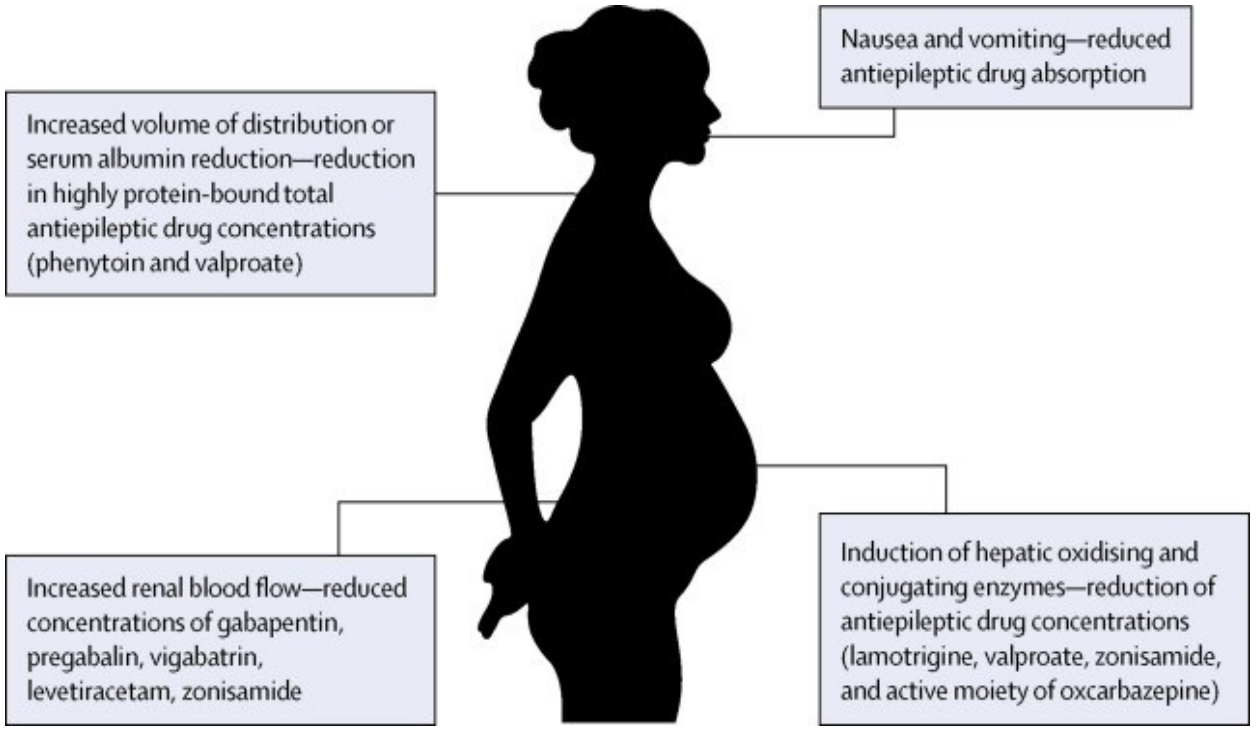
Deficit folati → Difetti del tubo neurale

Supplementazione con acido foico (0,36-4,0 mg)
riduce rischio di NTD del **60-86%**

...E NELLA DONNA AFFETTA DA EPILESSIA?

In one study, preconception use of folic acid (**5 mg per day**) in WWE resulted in no MCM, whereas no folic acid use was associated with 23% fetal abnormalities (Betts and Fox, 1999). Some studies have found high dose folic acid (≥5 mg per day) may be associated with enhanced vocabulary development, communicational skills and verbal comprehension at 18 months of age (ROTH et al. 2011; Chatzi et al. 2012). Low serum folate concentrations (<4.4mmol/l) have been associated as an independent risk factor for the occurrence of MCM in WWE (Kaaia et al. 2003). In the NEAD study, children born to women taking periconception folate had a higher IQ.

AED: concentrazione plasmatica



La variazione della concentrazione plasmatica è differente a seconda del farmaco utilizzato

METABOLISMO AED

Hepatic CYP450 †
- Phenytoin†
- Phenobarbital†
- Carbamazepine†
- Zonisamide

Renal excretion‡
- Levetiracetam
- Pregabalin
- Vigabatrin
- Topiramate

Glucuronidation (most affected during pregnancy)‡
- Valproate (and beta oxidation)†
- Lamotrigine
- Oxcarbazepine (MHD)

†Highly protein bound.
‡Main route of metabolism.
MHD: Monohydroxy dervative of oxcarbazepine, the active metabolite of oxcarbazepine

Antiepileptic drug primary routes of elimination

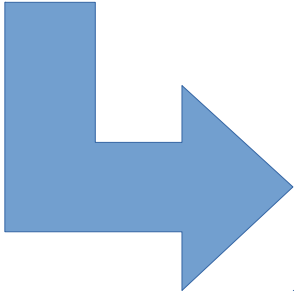
AED: concentrazione plasmatica

Una riduzione del 35% dei livelli plasmatici del farmaco rispetto alla baseline è associato a maggior rischio di recidiva (Reisinger et al. 2013)

Individuare un livello plasmatico “target” da mantenere durante tutta la gravidanza

AED: concentrazione plasmatica

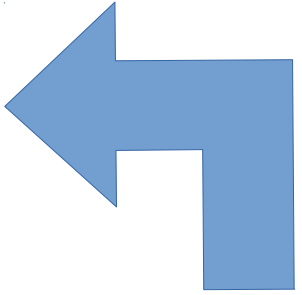
RISCHIO TERATOGENO MINORE



LAMOTRIGINA

LEVETIRACETAM

OXCARBAZEPINA



CLEARANCE MAGGIORE

MAGGIOR VARIAZIONE LIVELLI PLASMATICI

AED: concentrazione plasmatica

LAMOTRIGINA *(Pennel et al 2008)*

- Aumento clearance 94% durante III trimestre
- Riduzione concentrazione plasmatica 65% durante II trimestre

↓

AUMENTO RISCHIO CRISI

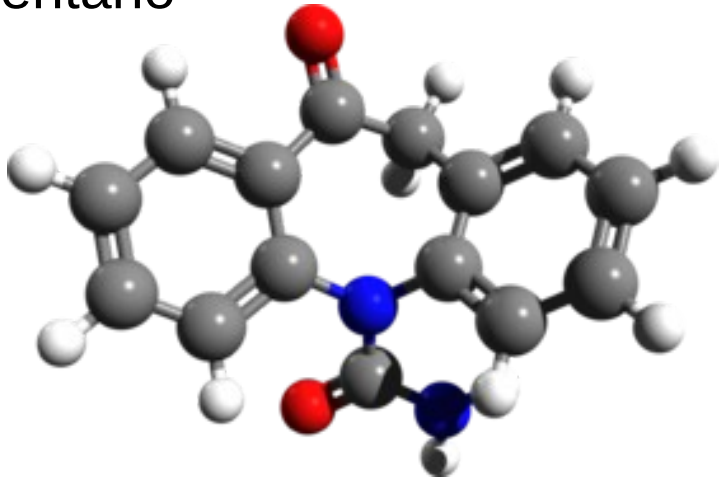
LEVETIRACETAM *(Tomson and Battino 2007)*

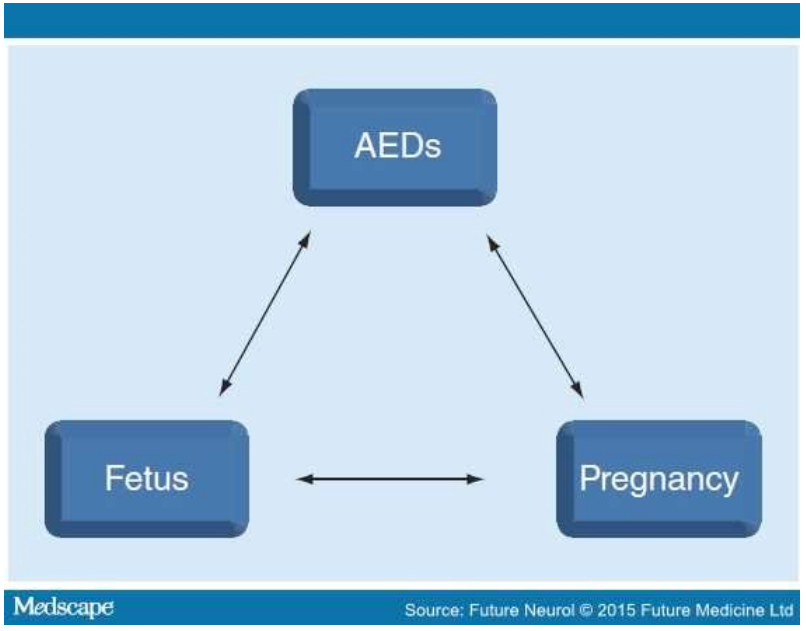
- Aumento clearance 243% durante III trimestre
- Riduzione concentrazione plasmatica 60% nel III trimestre

AED: concentrazione plasmatica

OXCARBAZEPINA *(Petrenaite et al 2009)*

- Riduzione concentrazione plasmatica 26,2% I trimestre, 36,5% ii trimestre, 38,2% III trimestre
- Peggioramneto crisi in quasi il 64% delle pazienti
- 58,5% delle pazienti che assomono OXC presentano crisi durante gravidanza/parto*(EURAP, 2006)*
- Aumentato rischio di crisi di tipo
- generalizzato (OR: 5,4) *(EURAP, 2006)*




AEDs
Fetus
Pregnancy
Medscape
Source: Future Neurol © 2015 Future Medicine Ltd

COSA FARE

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili
U.O. Servizio di Neurofisiopatologia
Centro Regionale per l'Epilessia dell'età adulta (CRE)

Dal 2014 è in atto una collaborazione tra U.O. Neurofisiopatologia e Dipartimento di Ostetricia e Ginecologia della ASST Spedali Civili Brescia per la gestione integrata della paziente gravida, affetta da epilessia

Presidio Ospedaliero di Brescia
Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Dipartimento Ostetrico-Ginecologico
ASST Spedali Civili Brescia

PROTOCOLLO MONITORAGGIO

- PRIMO ACCESSO: 11-13 settimane
  - Visita neurologica ed EEG
  - Prelievo ematico (AED)
  - Ecografia ostetrica II livello ed eventuale NT

- SECONDO ACCESSO: 19-20,6 settimane
  - Visita neurologica ed EEG
  - Prelievo ematico (AED)
  - Ecografia ostetrica morfologica ed ecocardiogramma fetale

PROTOCOLLO MONITORAGGIO

- TERZO ACCESSO: 28-32 W
  - Visita neurologica ed EEG
  - Prelievo ematico (AED)
  - Ecografia ostetrica del III trimestre (accrescimento fetale)
- QUARTO ACCESSO: 35-36 w
  - Visita neurologica ed EEG
  - Prelievo ematico (AED)
  - Ecografia ostetrica accrescimento
  - Valutazione anestesiologica partoanalgesia

MANAGMENT DEL PARTO

- Il parto per via vaginale è consigliato.
- Non vi sono controindicazioni all’induzione del travaglio con prostaglandine.
- L’analgesia epidurale può esercitare un effetto protettivo sul rischio di crisi, pertanto va consigliata.
- Non vi sono controindicazioni specifiche all’utilizzo dell’analgesia con protossido d’azoto

PUERPERIO/ALLATTAMENTO

Infant exposure to AEDs in breast milk varies depending on multiple factors such as maternal plasma drug concentration, the milk/plasma ratio of the drug, the milk volume ingested by infant, and the absorption, metabolism and excretion of the drug in the infant. Even though an AED may appear in the breast milk, **the degree of medication exposure to the newborn is still likely to be less than the degree of exposure during gestation** (Pennel et al. 2016)

Some AEDs such as PRM, LVT, GBP, LTG and TPM penetrate into breast milk in relatively high enough concentrations with the potential for clinical effects on the newborn (Harden et al. 2009a). Other AEDs that are highly protein bound, such as VPA, PB, PHT and CBZ, do not to penetrate into breast milk in substantially high concentrations (Harden et al. 2009a).

PUERPERIO/ALLATTAMENTO

The NEAD study investigated the effects of breastfeeding on child cognitive development (*n* = 195 mother–child pairs). They found **there was no significant difference in the IQs of children tested at age 3 years old** of children who were breast fed by mothers taking AEDs (CBZ, LTG, PHT or VPA monotherapy) compared with children who were not breastfed [Meador *et al.* 2010].

A follow-up 6-year study found similar results, but also found that breastfed children had a **higher IQ (by 4 points) and increased verbal abilities (by 4 points)** even after adjusting for confounding variables such as maternal IQ, AED dose and periconception folate use [Meador, 2014]. Another prospective population-based study found breastfed children of mothers taking AEDs had **no adverse development at ages 6 and 16 months**, and continuous breastfeeding was associated with less impaired development. Children who were continuously breastfed had **favorable outcomes**, despite maternal use of AEDs [Veiby et al. 2013]

PUERPERIO/ALLATTAMENTO

With recent data from breastfeeding women on AEDs and their children, we can state that **the benefits of breastfeeding outweigh the risks to the infant.**

WWE taking AEDs should be encouraged to breast feed their baby if they choose, although many will supplement with 1–2 bottles per 24 hours to allow 1 period of more sustained sleep.

PUERPERIO/ALLATTAMENTO

INSONNIA

DEPRESSIONE
POST-PARTUM

PUERPERIO/ALLATTAMENTO

- Eviatare privazioni di sonno
- Aiuto al partner e alla famiglia oppure a persona qualificata

CONCLUSIONI

- Le donne affette da epilessia DEVONO continuare ad assumere la terapia antiepilettica in gravidanza per ridurre il rischio di traumi materni e fetali secondari alle crisi
- OBIETTIVO: massimo controllo delle crisi con minimo dosaggio dei farmaci
- Supplementazione con acido folico 5 mg/die
- Stretto monitoraggio livelli plasmatici: evitare una riduzione >35% baseline
- Va incoraggiato il parto vaginale e l’uso della parto-analgesia
- Va incorraggiato l’allattamento al seno

GRAZIE PER L'ATTENZIONE

SPEDALI CIVILI DI BRESCIA
AZIENDA OSPEDALIERA

MIA

Regione Lombardia

ORDINE
MEDICI CHIRURGHI
E ODONTOIATRI
DELLA PROVINCIA
DI BRESCIA