Medical Problems of Early Pregnancy
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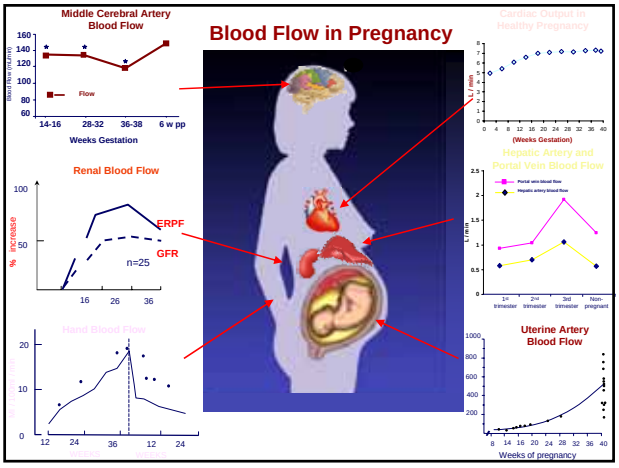
Maternal changes during pregnancy

- Cardiovascular
- Haemostatic
- Renal
- Respiratory
- Hepatic
- Endocrine
- Immunological
- Skin



Epilepsy in the UK

- Epilepsy - most common serious disorder of brain
- Cumulative lifetime incidence - 1 / 20
- Incidence – In UK, 30,000 new cases/year
- Prevalence - 456,000 people in UK
- 2 / 3 - epilepsy controlled with AEDs
- 100,000 - severe epilepsy

Duncan J, 2007

Before Pregnancy Epilepsy can be difficult to manage

- The epilepsies are common
- Heterogeneity
- Serious consequences
- 2/3 treatment is quite easy
- 1/3 refractory
- Range of AEDs
- Many adverse effects
- Need to balance risk-benefit ratio

Morbidity from Epilepsy

- Physical injury and death
- Cognitive impairment
  - Short term memory loss and fine motor dysfunction
  - Damage to pre-exisiting lesion (tumour)
  - Effect of treatment
  - Psycho-social and economic effects
    - Loss of self esteem
    - Stigma
    - Confidence
    - Activities; driving and sport
    - Partners
    - Employment

Confidential Enquiry into Maternal Deaths 1985-99

Years of enquiry	Maternities*	Deaths	Epilepsy
1985–87	2.27m	223	3
1988–90	2.36m	238	9
1991–93	2.32m	228	6
1994–96	2.19m	268	19
1997–99	2.12m	242	9
2000-02			13
2003-05			11

*Number of pregnant mothers in millions

Fetal and Childhood Requirements

In utero:

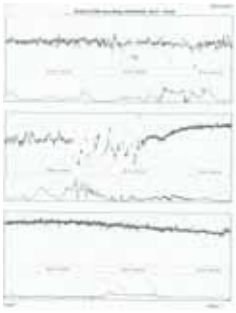
- Absence of teratogenic substances
- Freedom from maternal seizures

After delivery:

- Mother who is seizure-free (applies equally to older children *during* subsequent pregnancies)

CTG during a generalised Convulsion

- A maternal convulsion is not healthy for the fetus
- Infrequent seizures, self limiting seizures are unlikely to have a negative effect on the fetus



Risk of major malformations with AEDs

2-6 fold increase in risk

Spina bifida, cardiac, gastrointestinal, skeletal and urogenital defects

Valproate consistently associated with highest risk

Mechanism of Increased Neural Tube Defect in pregnancy

Teratogenicity demonstrated in animal models

Dose response established

Several mechanisms characterised in animals species

Little direct evidence from humans regarding mechanism

Folate metabolism

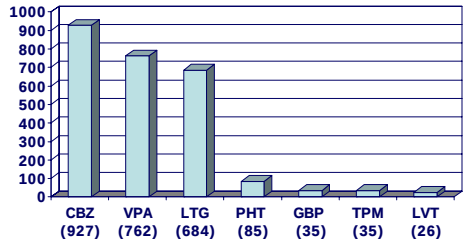
- Meadow (1968)
  - AED malformations in children similar to folic acid antagonist drugs
- Valproate reduces serum folate in patients with epilepsy
- Low folate during pregnancy linked to NTD defects in humans
- Dietary folate can reduce NTD incidence, but not in animals or humans who take AEDs

Malformation risks of anti-epileptic drugs in pregnancy: A prospective study from the UK Epilepsy and Pregnancy Register (31 March 2005)

- Number of reports 4,414
- Number with full outcome data 3,607
- AED details
  - No AED (n=239) 6.7%
  - Monotherapy (n=2,598) 72.0%
  - Polytherapy (n=770) 21.3%
- Lost to follow up (n=356) 8.1%
- Ongoing pregnancies (n=451) 10.2%

Morrow et al; Journal of Neurol, Neurosurg & Psych 2006;77: 193 -198

Exposure to Monotherapy

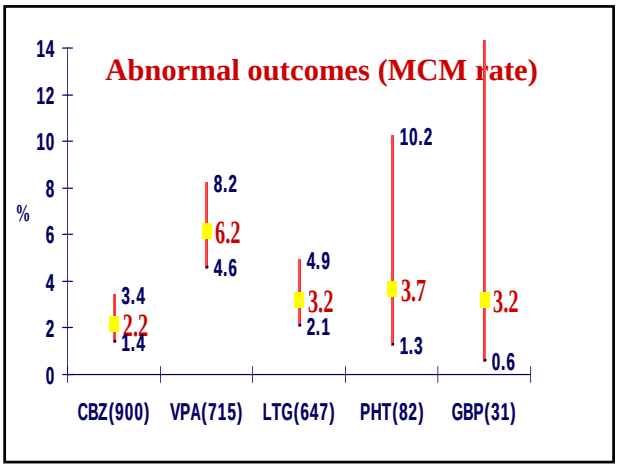


Morrow et al; Journal of Neurol, Neurosurg & Psych 2006;77: 193 -198

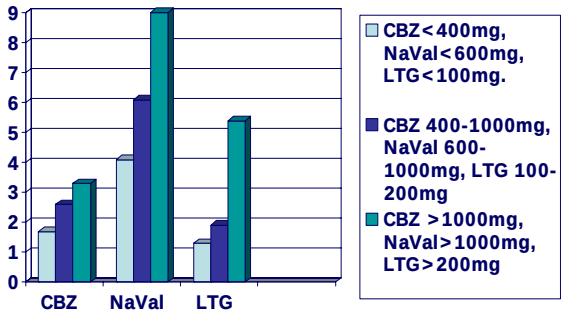
Risk of Major Congenital Malformation for the fetus exposed to AED during Pregnancy

	number	%	(95% C.I.)
No AED	227	3.5	(1.8% – 6.8%)
Monotherapy	2468	3.7	(3.0% – 4.5%)
Polytherapy	718	6.0	(4.5% – 8.0%)
Total Exposed Group	3176	4.2	(3.6 – 5.0%)

Morrow et al; Journal of Neurol, Neurosurg & Psych 2006;77: 193 -198



MCM rate (%) by dose.



AED Polytherapy

(126 different combinations recorded)

MCM rates for any combination INCLUDING:.

CBZ (n=388): 4.1 % (95% CI. 2.5 – 6.7)

LTG (n=430): 4.8% (95% CI. 3.1 - 7.3)

Na Val (n= 304): 9.0% (95% CI. 6.3 – 12.8)

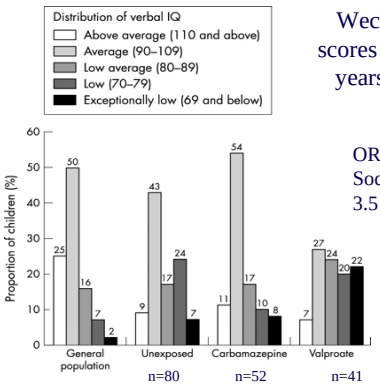
- Those polytherapy regimes containg NaVal had a significantly higher rate of MCM compared to those without NaVal

  Odds ratio : 2.49 (95% CI. 1.3 – 4.7)

Increased risk for non-syndromic cleft palate among infants exposed to lamotrigine during pregnancy[1]

- North American Registry for Epilepsy and Pregnancy
  - 564 first trimester lamotrigine monotherapy exposures
    - 3 cases isolated, non-syndromic cleft palate
    - 2 cases isolated, non-syndromic cleft lip without cleft palate
    - 8.9/1000 (cf 0.37/1000 local population [RR 24; 95% C.I. 10.0 – 57.4])

1.Homes LB, Wyszynski DF, Baldwin EJ et al. Birth Defects Research Part A: Clinical and Molecular Teratology 2006;75(5): 318



n=80 Mean 90.9 n=52 Mean IQ 94.1 n=41 Mean IQ 83.6

Wechsler Intelligence scores for children aged 6 years or older by drug exposure

OR for VIQ >69
Sodium Val v unexposed
3.5 (95% CI 1.1-10.6)

Adab et al,
JNNP 2004; 75: 1575-1583

Conclusions – Pregnancy registries

- Results are generally reassuring – overall low rates of MCMs.
- If need to continue on AED treatment then monotherapy should be the preferred practice.
- Women taking VPA appear to carry higher relative risk (particularly, as part of a polytherapy regime) (UK, N.American, Australian ?GSK).
- Safety in pregnancy CBZ and LTG reassuring. (Data lacking for other agents).

Current Usual Practice

- Advise women of risk of seizures in pregnancy and potential effect on the fetus
- Aim for lowest effective dose pre-pregnancy to control symptoms
- High dose folate 5mg, until we know better
- Review symptom control during pregnancy
- Vitamin K in those at additional risk of neonatal haemorrhage of newborn.

Hyperemesis Gravidarum and Biochemical Thyrotoxicosis

- Hyperemesis Gravidarum affects 1% of pregnancies
- Transient thyroxaemia occurs in 2/3 women with hyperemesis
- Pathophysiology of hyperemesis unclear
- Elevated HCG, but not correlated with thyroxaemia
- Increased TSH receptor sensitivity to HCG

Hyperemesis Gravidarum and Biochemical Thyrotoxicosis

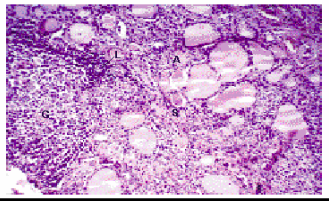
- NOT CLINICALLY HYPERTHYROID
- Free T4 normal by 15 weeks
- TSH suppressed until 19 weeks
- Vomiting and nausea can persist throughout pregnancy
- Treat with anti-emetics, NOT thyroxine

Ranges for thyroid function tests during pregnancy

	Not Pregnant	First Trimester	Second Trimester	Third Trimester
Free thyroxine (pmol/L)	11-23	11-22	11-19	7-15
Free triiodo-thyronine (pmol/L)	4-9	4-8	4-7	3-5
Thyroid Stimulating Hormone (mIU/L)	0.2-4.2	0.2-1.6	1-1.8	0.7-7.3

Hypothyroidism during Pregnancy

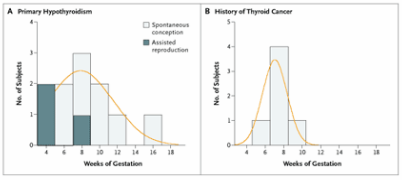
- Hypothyroidism affects 2.5% of pregnancies
- Hypothyroidism associated with reduced fertility and raised prolactin
- Hypothyroidism usually autoimmune
- Thyrotropin receptor blocking antibodies rarely cross placenta to cause transient neonatal hypothyroidism in < 5%



Chronic Autoimmune Thyroiditis

Thyroxine Replacement for Hypothyroidism during Pregnancy

- Increase in thyroid replacement in 25-50% of hypothyroid women
- **BUT**, in one study, 17/19 increased thyroxine by almost 50%



Alexander et al NEJM 2004: 241

Targeted Screening for Subclinical Hypothyroidism in Pregnancy?

- 1560 first trimester women (9 week)
- 2.6% (40) of all women had raised TSH >4.2mU/L
- 6.8% high risk v 1% low risk (RR 6.5 95% CI 3.3-12.6 p<0.0001)
- PH thyroid disease RR 12.2 (6.8-22 p<0.0001)
- PH autoimmune disease RR 4.8 (1.3-18.2 p=0.016)
- FH thyroid disease RR 3.4: (1.8-6.2 p<0.0001)
- TPO antibody RR 8.4: (4.6-15.3: p<0.0001)

- **BUT,** 12/40 (30%) of all women with raised TSH were in the low risk group

Vaidya B et al. J Clin Endocrin Metab 2006

Neuropsychological Test Scores of Children of Women with Hypothyroidism (Haddow et al NEJM 1999

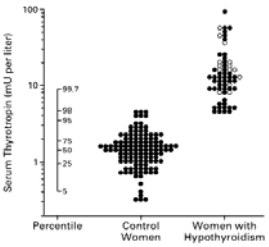


TABLE 2. MEASUREMENTS OF THYROID FUNCTION IN THE STUDY WOMEN DURING PREGNANCY.*

VARIABLE	WOMEN WITH HYPOTHYROIDISM (N=62)	CONTROL WOMEN (N=124)
Serum thyrotropin concentration (mU/liter)	13.2±0.3†	1.4±0.2
Serum thyroxine concentration (μg/dl)	7.4±0.1†	10.6±0.1
Serum free thyroxine concentration (ng/dl)	0.71±0.1†	0.97±0.07
High serum concentrations of anti-thyroid peroxidase antibodies (%)‡	77†	14

*Plus–minus values are geometric means ± the logarithmic SD. To convert values for serum thyroxine and free thyroxine to nanomoles per liter and picomoles per liter, respectively, multiply by 12.87.
†$P<0.001$ for the comparison with the control women.
‡Concentrations of more than 2 U per milliliter were considered high.

Neuropsychological Test Scores of Children of Women with Hypothyroidism (Haddow et al NEJM 1999

TABLE 3. NEUROPSYCHOLOGICAL TEST SCORES AMONG THE CHILDREN OF WOMEN WITH HYPOTHYROIDISM DURING PREGNANCY AS COMPARED WITH THE CHILDREN OF MATCHED CONTROL WOMEN.*

TEST	CHILDREN OF WOMEN WITH HYPOTHYROIDISM (N=62)	CONTROL CHILDREN (N=124)	MEAN DIFFERENCE†	P VALUE
Intelligence				
WISC-III full-scale IQ score	103±15	107±12	−4.1±2.1	0.06
WISC-III full-scale IQ score <85 (%)	15	5	3 (1–8)	0.08
Attention				
WISC-III freedom-from-distractibility score	98±13	102±13	−3±2	0.08
Continuous Performance Test score >8 (%)‡	37	19	3 (1–5)	0.01
Language				
Test of Language Development score				
Word articulation	10.1±2.5	10.2±2.4	−0.2±0.4	0.80
Word discrimination	10.5±2.9	11.4±2.4	−0.9±0.4	0.04
WISC-III verbal IQ score	103±16	107±16	−4.2±2.2	0.06
Reading ability and school performance				
PIAT-R reading-recognition score	96±14	100±16	−3.8±2.5	0.14
PIAT-R reading-comprehension score	98±17	101±17	−3.0±2.6	0.26
School difficulties and learning problems (%)‡	23	11	2 (1–6)	0.06
Repeated a grade (%)‡	8	4	2 (0.6–7)	0.40
Visual–motor performance				
Score on Developmental Test of Visual–Motor Integration	96±13	97±11	−1±2	0.40
WISC-III performance IQ score	101±16	105±13	−4±2	0.08
Pegboard-test score				
Dominant hand‡	86±16	83±15	3±2	0.10
Nondominant hand‡	94±22	89±16	5±3	0.10

*Plus–minus values are means ±SD, except as indicated. WISC-III denotes Wechsler Intelligence Scale for Children, third edition, and PIAT-R Peabody Individual Achievement Test, revised.
†The difference is the value in the case child minus the average of the values in the two control children. The values shown are the means (±SE) of the individual differences in each matched set. For categorical variables, this column provides the odds ratio for the children of the women with hypothyroidism as compared with the control children and (in parentheses) the 95 percent confidence interval.
‡A higher score or percentage indicates more problems.

Conclusions

- Be aware of physiological changes to thyroid function during pregnancy
- Treat biochemical thyrotoxicosis of hyperemesis with anti-emetics
- Supplement hypothyroidism according to TSH – keep TSH 1.0-2.0mu/L

The spectrum of maternal glucose metabolism in pregnancy

- Healthy Pregnancy
- Impaired Glucose Tolerance
- Gestational Diabetes Mellitus
- Pre-existing Type 2 Diabetes mellitus
- Pre-existing Type 1 Diabetes mellitus

Glucose Metabolism in Healthy pregnancy

- The first half of pregnancy is an insulin sensitive state
- The second half of pregnancy is an insulin resistant state
- In the 3rd trimester, insulin levels average 30% higher and last longer

Type 1 Diabetes Mellitus (IDDM)

- **St Vincent Declaration 1990**
  The aim of management of pre-existing diabetes during pregnancy is to achieve the same complication rate as non-diabetic women.
- Increased risk of congenital malformations, obstetric complications, neonatal and maternal morbidity.
- Congenital abnormalities reduced by peri-conceptional euglycaemia and folic acid supplementation (5mg).

Pregnancy complications with Type 1 Diabetes mellitus

- Neonatal morbidity (260; 80.2%)
- Macrosomia (146; 45.1%)
- Congenital malformations (29; 8.8%)
- Caesarean section (139; 44.3%)
- Pre-term delivery (101; 32.2%)
- Pre-eclampsia (40; 12.7%)
- Perinatal mortality (9; 2.8%)
- Maternal mortality (2; 0.6%; hypoglycaemia at 17 weeks and Amniotic fluid embolus)

Pregnancy complications with Type 1 Diabetes mellitus

- Major congenital malformations were less common in planned v unplanned pregnancies. Relative Risk 0.34 (95%CI, 0.13-0.88)
- But, still many complications, especially neonatal hypoglycaemia (64%).
- Quote; 'Near optimal maternal glycaemic control (HbA_{1c} <7.0%) is not apparently good enough'. (Evers et al, BMJ 328; 915-20)

Pregnancy complications with Type 1 Diabetes mellitus

- Severe hypoglycaemia occurred in 116/286 (41%) in the first trimester and in 44/264 (17%) in the third trimester.
- The CEMACH 2004, revealed 4 maternal deaths due to hypoglycaemia in type 1 diabetes.
- Maternal v fetal risks need to be balanced.

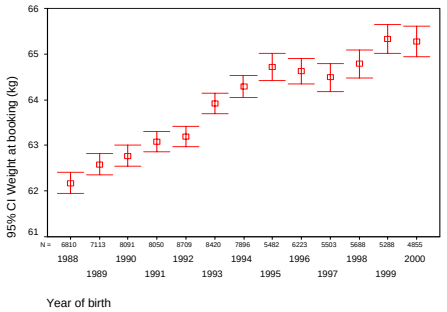
Management of pregnancy with Type 1 Diabetes Mellitus

- Multiple injection therapy or continuous subcutaneous insulin infusion pumps.
- Standard short acting insulin before meals and long acting at night or morning
- Insulin analogues; short-acting lispro (humalog) and aspart (novorapid) safely used in pregnancy.
- Reassuring data on long-acting insulin glargine (lantus).

Type 2 diabetes in pregnancy

- Insulin resistant phenotype
- Overweight, family history, racial group
- Polycystic ovary syndrome
- Pre-conception, controlled with diet or oral hypoglycaemic agents
- During the second half of pregnancy increased insulin resistance makes glucose control more demanding.

Increase in maternal booking weight in more than 500,000 women over 12 years (1988 – 2000) in London, UK



Glycaemic parameters and neonatal outcome in type 2 diabetes

- Anomaly more common with poorer blood glucose control (major > minor > no anomaly) Fasting blood glucose in second trimester
  8 v 7.3 v 6.3mmol/L (144 v 132 v 114mg/dL)
- It is weakly implied that blood glucose levels were highest in first trimester of women with major anomalies (Schaefer-Graf et al Am J Obs & Gynae 2000; 182: 313-320).

Management of Type 2 Diabetes in Pregnancy

Classes	Generic names	Trade names	Manufacturers	Comments
First-sulfonylureas generation	Chloropropamide	Diabinese	Pharmacia & Upjohn	Neonatal hypoglycemia
	Tolbutamide	Orinase	Pfizer U.S. Pharmaceuticals	Neonatal hypoglycemia
	Tolazamide	Tolinase	Pharmacia & Upjohn	
	Acetohexamide			
Second-sulfonylureas generation	Glipizide	Glucotrol	Pfizer U.S. Pharmaceuticals Allscripts Pharmaceuticals	Minimal placental transfer
	Glyburide	Micronase	Pharmacia & Upjohn Physicians Total Care	Minimal placental transfer; promising results in pregnancy
		Glynase	Pharmacia & Upjohn	
		DiaBeta	Aventis Pharmaceuticals	
	Glimepiride	Amaryl	Aventis Pharmaceuticals	
Biguanides	Metformin	Glucophage	Bristol-Myers Squibb Company	Does not stimulate fetal pancreatic beta cells; promising results in pregnancy
Thiazolidinedione	Rosiglitazone	Avandia	GlaxoSmithKline	Risk of liver toxicity
	Pioglitazone	Actos	Takeda Pharmaceuticals	Risk of liver toxicity
Alpha-glucosidase Inhibitors	Acarbose	Precose	Bayer Corporation Pharmaceuticals	Gastrointestinal discomfort
	Miglitol	Glyset	Pfizer U.S. Pharmaceuticals	Gastrointestinal discomfort
Meglitinides	Nateglinide	Starlix	Novartis Pharmaceuticals	
	Repaglinide	Prandin	Novo Nordisk Pharmaceuticals	

Few of the medications listed in this table have been extensively evaluated for use in pregnancy. The authors advise caution in using these medications unless acceptable safety data are available or use is part of a research protocol.
None of the medications listed in the table have been approved for use in pregnancy by the U.S. Food and Drug Administration.

Metformin in Pregnancy

- Reduces peripheral insulin resistance.
- Assists ovulation induction in PCOS
- Crosses placenta, but not teratogenic
- Used throughout pregnancy in obese women, unable to take insulin or when doses of insulin are high.
- Appears safe, but still subject to large ongoing studies in comparison with insulin

Management of GDM

- Aim for glucose < 5.5mmol/L (100mg/dL) and 1 hour postprandial <8.0mmol/L (144mg/dl)
- Dietary advice
- If 20% or more of readings are more than 20% above target, start insulin or metformin.

Conclusion

- Diabetes in pregnancy is a metabolic syndrome involving many factors
- Pregnancy outcome for mother, fetus and neonate is improved with glycaemic control
- Metformin has a role in glycaemic control throughout pregnancy
- Follow up of women who had GDM is essential for ongoing women's health