The challenge of making obstetric medicine evidence-based

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Evidence-based medicine

- **Evidence-based medicine is the care of patients using the best available research evidence to guide clinical decision making**
  [Sackett DL - BMJ. 1996;312(7023):71]
- **Care for the individual patient includes the best research evidence as a benchmark, with evidence then tailored to individual circumstances that may include genetic makeup, past and concurrent illnesses, health-related behaviours, and personal preferences**

The method

- **Define our clinical question**
  - **e.g., teratogenicity of a medication following inadvertent first trimester exposure?**
  - **e.g., fetotoxicity potentially associated with initiating therapy at 16 weeks?**
- **Access high quality *syntheses* of the evidence**
  - **e.g., UpToDate, Cochrane Database of Systematic Reviews, Clinical Practice Guidelines**
  - **Otherwise, we turn to more labour-intensive sources, such as Medline**
- **Judge credibility of the results**
  - **In terms of rigour and their applicability to our patients**
- **Apply evidence to our practice**

When is there ENOUGH evidence to change practice and use a medication?

- When it is EFFECTIVE?
  - In an individual trial? By meta-analysis?
  - According to evidence outside pregnancy? in pregnancy?
- When it is 'SAFE'? By which standard?
  - Teratogenicity
  - Fetotoxicity
  - Neonatal side effects
  - Long-term paediatric adverse effects
- When there are no proven ALTERNATIVES?

Hydroxychloroquine for SLE

- **Effectiveness**
  - **1970s, there was growing evidence of effectiveness in treatment of SLE & discoid lupus** [*Br J Dermatol* 1975;2:323]
- **Safety**
  - **Late 1980s, small case series were reporting "…clinically healthy normal babies."** [*J Rheumatol* 1988;15:607]
    - **"…prudent to stop using these agents as soon as pregnancy is diagnosed."** [*Am J Reprod Immunol* 1992;28:148]
    - **Growing understanding that discontinuation of antimalarial therapy can precipitate a flare of disease** [*Lupus* 1993;2:S21; *Lupus* 2001;10:401]
    - **"…it is our opinion that these drugs should not be discontinued during pregnancy…"** [*Drug Saf* 2001;24:1055]

Hydroxychloroquine for SLE

- By 2005, reports of more than 250 pregnancies ending in live births without malformations [*Autoimmun Rev* 2005;4:111]
  - As well as reassuring studies of eye and ear defects (N=182) [*Can Fam Phys* 1999;45:2870; *Lancet* 2001;358:813; *Arthritis Rheum* 2003;48:3207; *J Perinatol* 2005;25:86]
- By 2009, systematic review of controlled studies reached reassuring conclusions about fetal safety [*Ped Rheum* 2009;7:9]

Challenges of EBM in obstetric medicine

- **All too often we are faced with limited evidence**
  - **Without RCTs in pregnancy to rate effectiveness**
  - **Without observational studies throughout pregnancy and postpartum to rate safety**
- **May be useful to reflect on different approaches to the same evidence**

eVIDENCE – *BMJ* 1999

- Vehemence*
- providence
- Diffidence*
- Eminence*
- Nervousness
- Confidence
- Eloquence*

The Oncologist®
Humor Rounds

* = characteristics of the messenger

† = characteristics of the recipient

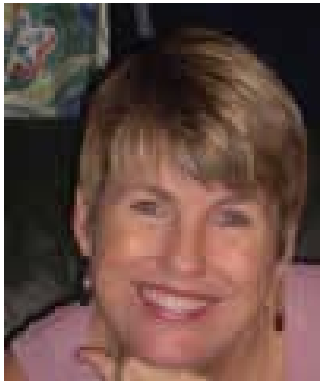
eVIDENCE - Vehemence

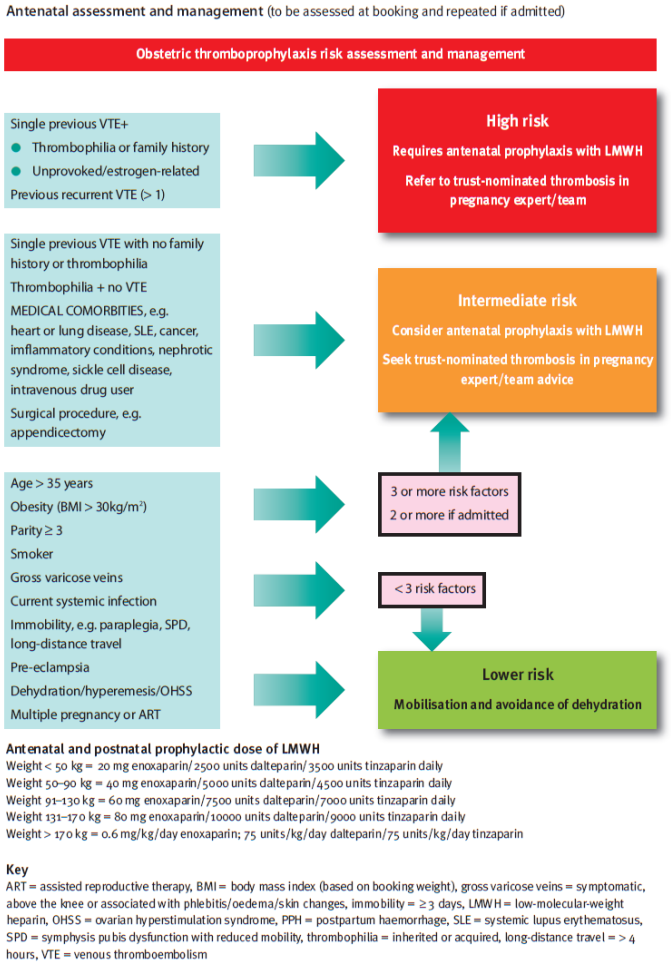
- For pre-existing or gestational hypertension, maternal and perinatal complications are not fully accounted for by the incidence of superimposed pre-eclampsia
- Pre-existing hypertension, pre-eclampsia accounts for:
  - <50% of preterm birth
  - <50% of SGA infants
  - <50% of high level neonatal care

- Gestational hypertension:
  - Many complications occur more commonly with severe hypertension (without proteinuria) vs. non-severe hypertension with proteinuria
    - Abruption, preterm delivery, perinatal death, SGA infants, and RDS

AJOG 1994;171:410 - *BJOG* 2007;114:e13 - *BJOG* 1996;103:123 - *NEJM* 1998;339:667 – *Hypertens* 2008;51:1002 - AJOG 2000;183:S1 - AJOG 2002; 186;66 – Obstet Gynecol 2000;95:24

eVIDENCE - Eminence





- **Clear guidance on a *reasonable approach* to antenatal and postnatal VTE risk assessment and thromboprophylaxis**
- **Standardisation of practice enables audit and quality improvement activities**

eVIDENCE – Eloquence

Williams and Davison. *BMJ* 2008;336:211-5

Summary of the literature from 1985-2007 for pregnancies attaining at least 24 weeks

Risks for the mother of ~ 25%

Long-term prognosis for mother excellent

Survival of the baby very high

Table 3 | Estimated effects of prepregnancy renal function on pregnancy outcome and maternal renal function. Values are the estimated percentage of women or neonates affected

Mean (SD) prepregnancy serum creatinine value (μmol/l)	Effects on pregnancy outcome				Loss of >25% renal function		
	Fetal growth restriction	Preterm delivery	Pre-eclampsia	Perinatal deaths	During pregnancy	Persists postpartum	End stage renal failure after 1 year
<125	* 25	30	22	1	2	0	0
125-180	40	60	40	5	40	20	2
>180	65	>90	60	10	70	50	35
On dialysis	>90	>90	75	50*	N/A	N/A	N/A

N/A=not applicable.
Estimates are based on literature from 1985-2007, with all pregnancies attaining at least 24 weeks' gestation.[1-4 7 8 w8-w16]
*If conceived on dialysis, 50% of infants survive; if conceived before introduction of dialysis, 75% of infants survive.

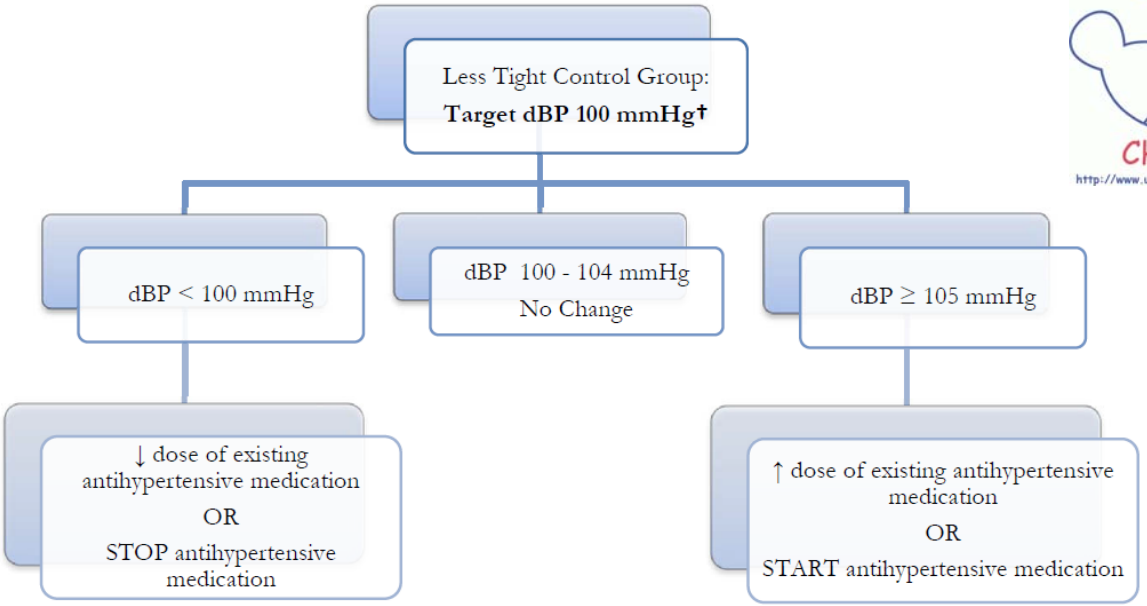
eVIDENCE – Diffidence

"hesitant in acting or speaking through lack of self-confidence"

- **"It is unclear whether the benefits outweigh the risks of …"**
- **"We just don't know but it is likely that….."**

eVIDENCE – Providence

"the foreseeing care and guidance of nature"



- **Watching non-severe hypertension (as opposed to normalising with antihypertensive therapy) may be associated with better uteroplacental perfusion and better perinatal outcomes**

eVIDENCE - Nervousness

Malik et al. *Interactive Cardiovascular and Thoracic Survey* 2012;1-5

(8 observational studies)

- No ideal approach to anticoagulation for women with mechanical heart valves in pregnancy
- For the mother
  - Warfarin (vs. heparin) is associated with fewer thromboembolic events: 0-10% (vs. 4-48%)
- For the baby
  - Congenital anomalies in up to 6.4%
  - Stillbirth 1.52 – 76%

eVIDENCE - Confidence

WHO recommendations for

Prevention and Treatment of Pre-eclampsia and Eclampsia

World Health Organization

Box 1: Interventions that are recommended for prevention or treatment of preeclampsia and eclampsia

Recommendation	Quality of evidence	Strength
In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5 g–2.0 g elemental calcium/day) is recommended for the prevention of pre-eclampsia in all women, but especially those at high risk of developing pre-eclampsia.	Moderate	Strong
Low-dose acetylsalicylic acid (aspirin, 75 mg) is recommended for the prevention of pre-eclampsia in women at high risk of developing the condition.	Moderate	Strong
Low-dose acetylsalicylic acid (aspirin, 75 mg) for the prevention of pre-eclampsia and its related complications should be initiated before 20 (+0) weeks of pregnancy.	Low	Weak
Women with severe hypertension during pregnancy s… hypertensive drugs.		
The choice and route of administration of an antihyp… during pregnancy, in preference to others, should be …		
For settings where it is not possible to administer the full magnesium sulfate regimen, the use of magnesium sulfate loading dose followed by immediate transfer to a higher level health-care facility is recommended for women with severe pre-eclampsia and eclampsia.	Very low	Weak
Induction of labour is recommended for women with severe pre-eclampsia at a gestational age when the fetus is not viable or unlikely to achieve viability within one or two weeks.	Very low	Strong
In women with severe pre-eclampsia, a viable fetus and before 34 weeks of gestation, a policy of expectant management is recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.	Very low	Weak
In women with severe pre-eclampsia, a viable fetus and between 34 and 36 (plus 6 days) weeks of gestation, a policy of expectant management may be recommended, provided that uncontrolled maternal hypertension, increasing maternal organ dysfunction or fetal distress are absent and can be monitored.	Very low	Weak
In women with severe pre-eclampsia at term, a policy of early delivery is recommended.	Low	Strong
In women with mild pre-eclampsia or mild gestational hypertension at term, induction of labour is recommended.	Moderate	Weak
In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment post partum is recommended.	Very low	Strong
Treatment with antihypertensive drugs is recommended for severe postpartum hypertension.	Very low	Strong

Quality of evidence	Strength
Very Low	Strong

Women with severe hypertension during pregnancy should receive treatment with anti-hypertensive drugs.

Make our decision

- **Honest assessment of the evidence**
  - **"*It can be difficult to modify personal bias despite the evidence*…"** **[S Med J 2012;3:105]**
- **It may be helpful to hear how others are doing things and how others have been influenced**
- **We need COMMUNITY and the strengths that it brings**
  - **UKOSS and associated international endeavours**
  - **OB Medicine ListServe that brings us together**

» ***"I'm able to go to ISOM in Oxford next week, so please introduce yourself if you see me. Would be nice to add some faces to the names."***

» **[Michael Carson, USA]**

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Atrial fibrillation in pregnancy

- **Pre-pregnancy counselling**
  - **Paroxysmal atrial fibrillation (CHADS2 = 0, $CHADS_{VASC}$ = 1)**
  - **No previous TIA/stroke**
  - **Normal echo (except for incidental PFO)**
  - **On long-term aspirin**
- **Evidence**
  - **Stroke (1.05%) on ASA vs. risks of bleeding (1.4-2.4%) on full anticoagulation**
  - **Europace 2010;12:1360 (Guidelines)**
    - **No recommendation for women at low thromboembolic risk**
  - **UpTo Date (accessed 20120411): For CHADS2 <2 with nonvalvular atrial fibrillation, therapy with aspirin may be appropriate.**
  - **Literature review (20120411): 3 case reports in a 2010 review focussed on acute management**

Atrial fibrillation (OB Med ListServe)

	N=16 respondents
ASA only	7
ASA + thromboprophylaxis – low dose	1
Thromboprophylaxis – low dose	2
Thromboprophylaxis – high dose	1
Full anticoagulation	3
Unsure	2

- **QUOTES:**
  - ***"We have encountered this many times."***
  - ***"In this case, you don't want to find out that you didn't do all you could to prevent a stroke, BUT…"***
  - ***"I think that prophylactic [anticoagulation] is basically treating us and not her."***
  - ***"…we certainly don't like to go against each other…"***

Communicating risk - advice

BMJ 2003;327:745

- Best available evidence at the time and evidence does and should change
  - Knowing that there is controversy can be useful
- (Virtually) all options are associated with risk
  - The concept of baseline risk may be new
- Providing information in the appropriate:
  - Amount – essential information
  - Format – NOT descriptive ("low or high risk"), but rather using absolute risks
  - Framing – in a positive or a negative light
- Ensure that woman understands information
- Ensuring that you understand significance to her

Looking beyond Translation — Integrating Clinical Research with Medical Practice

Annetine C. Gelijns, Ph.D., and Sherine E. Gabriel, M.D. *NEJM* 2012;366:18

- **More than 60% of paediatric oncology patients are enrolled in clinical trials**
- **In contrast, there are very low participation rates in clinical trials among adults (5-10%)**
  - **Even lower rates among women (and elderly, minorities)**
  - **This makes the process of generating medical evidence slow and inefficient**
- **WHY is this?**
  - **Separation of medical practice and clinical research into silos without adequate communication**