Predicting subsequent ill health from pregnancy

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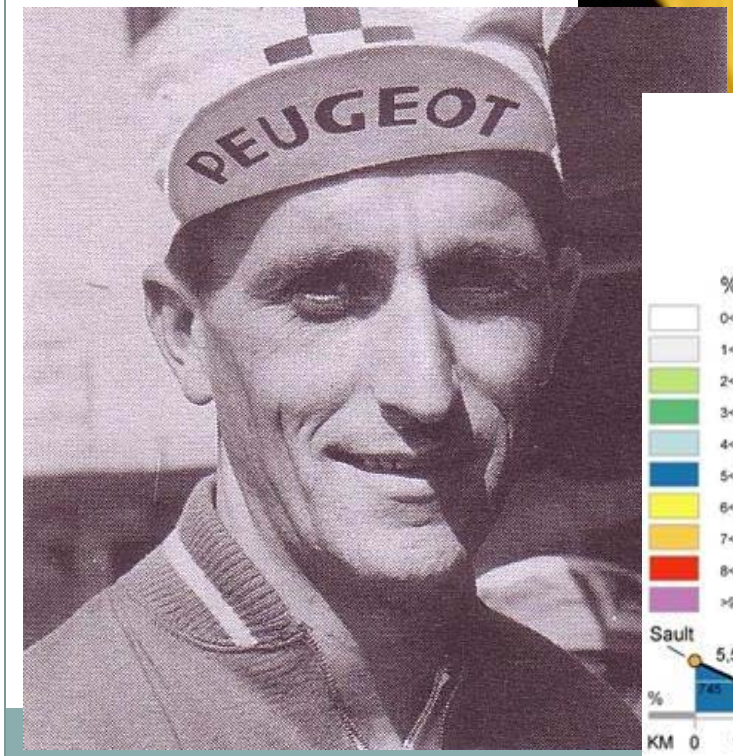
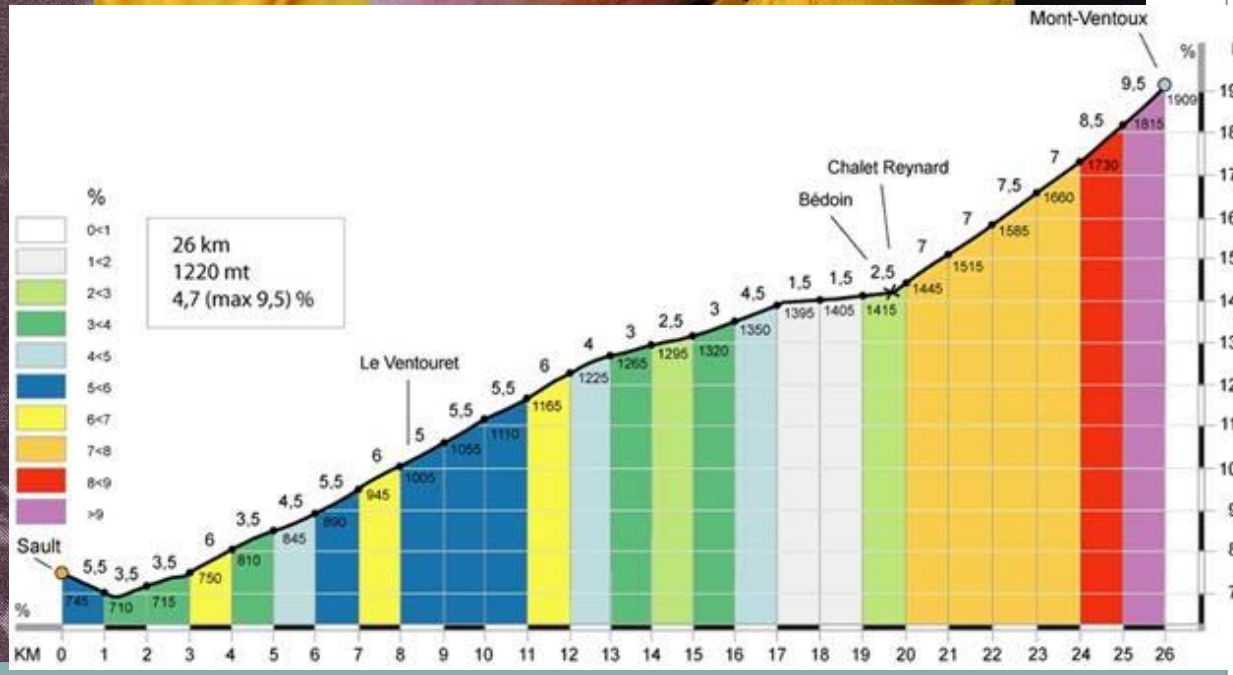
The Tour de France





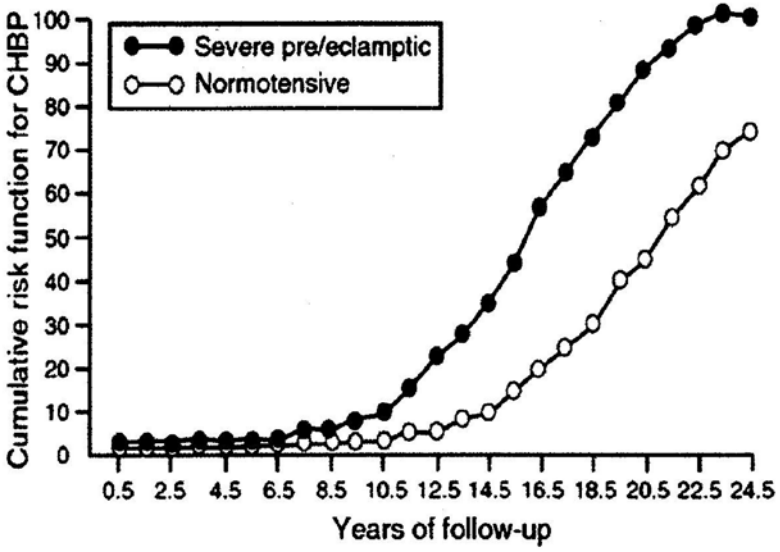
Cardiovascular and Metabolic Changes of Healthy Pregnancy

- Increased Erythropoeitin, cortisol, noradrenaline
- High Cardiac Output (50%)
- Plasma volume expansion
- High cholesterol (50%) and triglycerides (300%)
- Prothrombotic state
- Pro-inflammatory state
- Insulin resistance

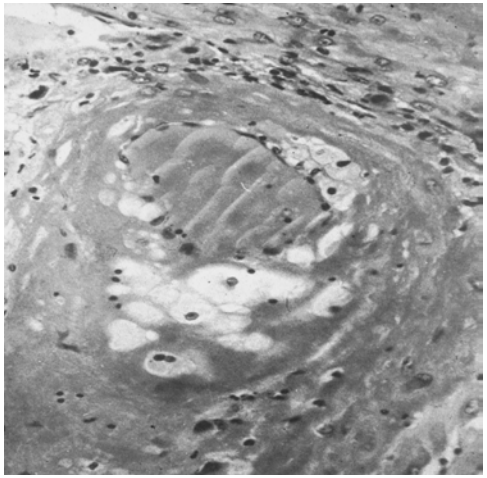
Gestational Syndromes

- **Gestational syndromes appear when maternal adaptation to pregnancy unmasks latent disease**
- **Pre-eclampsia**
- **Gestational Diabetes**
- Obstetric Cholestatsis
- Transient diabetes insipidus
- **Lipid disorders**
- Postnatal Depression
- **Postpartum thyroid disease**
- **Postnatal autoimmune disease**
- Paternal Disease

Pre-eclampsia and risk of future cardiovascular disease



Sibai BM et al Am J Obstet Gynecol 1986; 155: 1011-1016



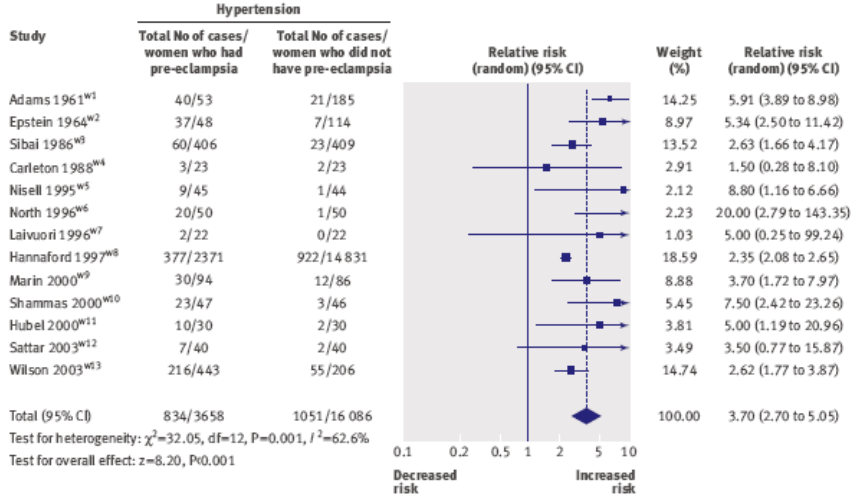


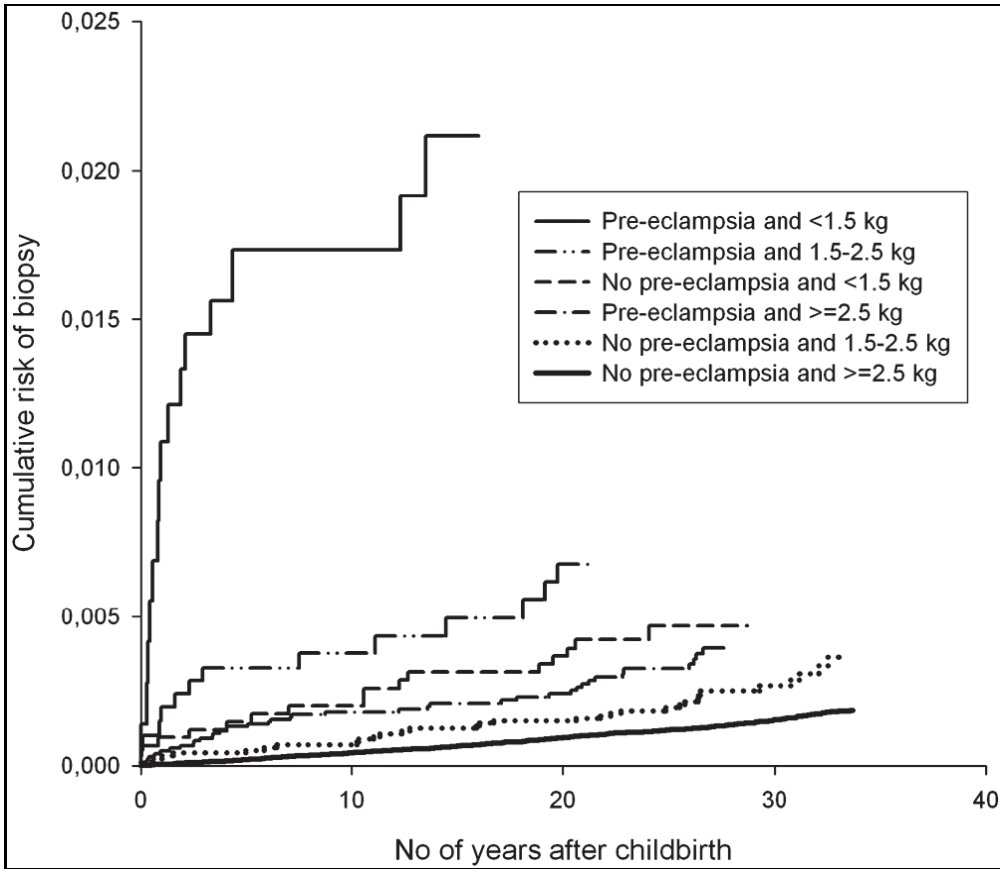
Fig 2 | Pre-eclampsia and risk of hypertension in later life

Bellamy L et al BMJ 2007; 335: 974-77

What should we tell women who have had pre-eclampsia about their future risk of cardiovascular disease?

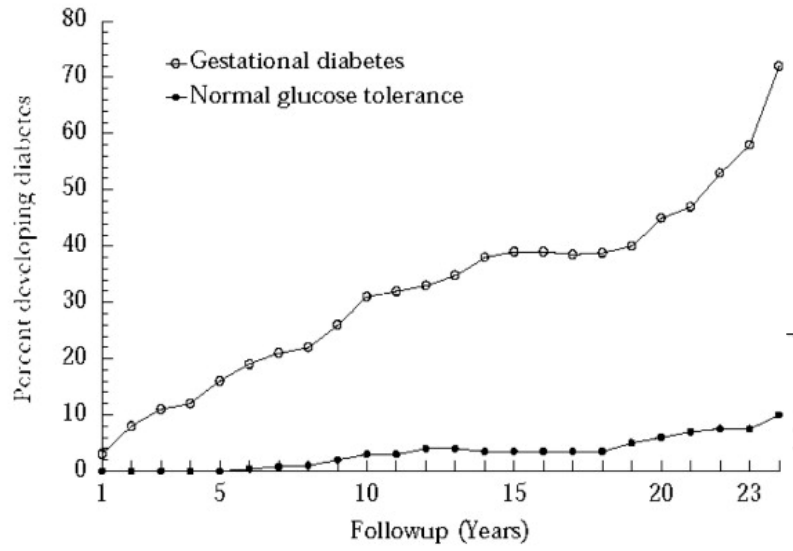
- Who should be screened?
- How should they be screened?
- How often should they be screened?
- Who should pay for the screening?
- What can we do to prevent future disease?
- Will primary prevention work?

INFLUENCE OF PRE-ECLAMPSIA AND BIRTH WEIGHT ON CUMULATIVE RISK OF KIDNEY BIOPSY



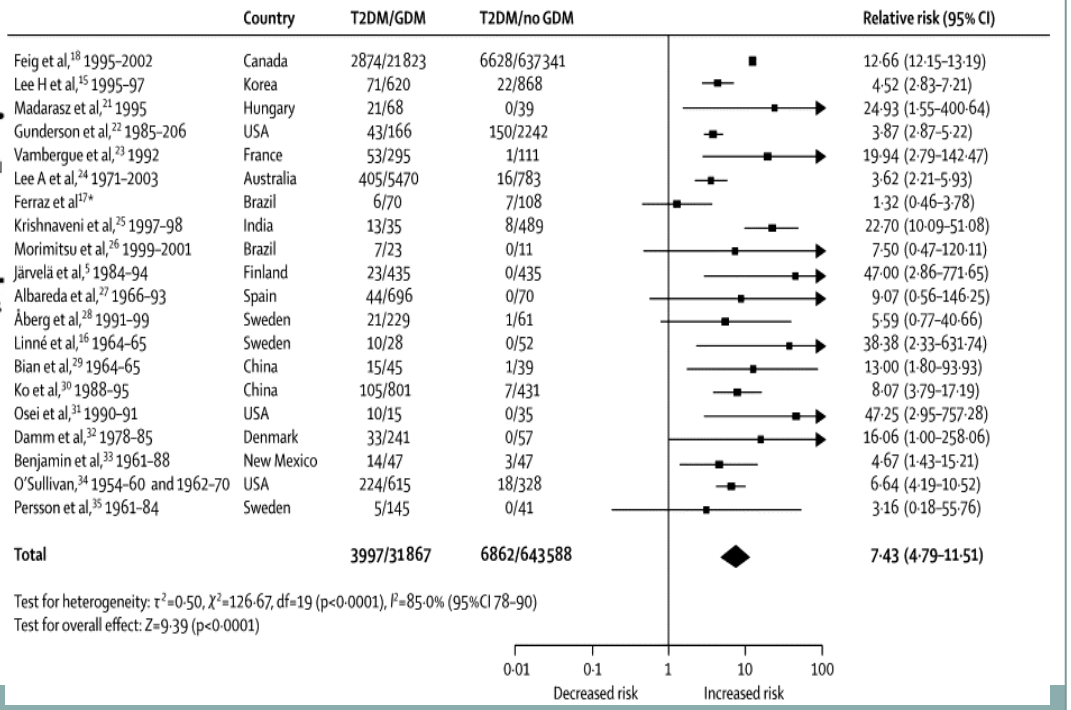
Vikse et al JASN 2006; 17: 837-845

Gestational Diabetes Mellitus and Future Risk of Type 2 Diabetes Mellitus



United States Public Health Service criteria were used to diagnose diabetes during the followup.

O'Sullivan et al, 1984



	Country	T2DM/GDM	T2DM/no GDM	Relative risk (95% CI)
Feig et al,[18] 1995–2002	Canada	2874/21823	6628/637341	12·66 (12·15–13·19)
Lee H et al,[15] 1995–97	Korea	71/620	22/868	4·52 (2·83–7·21)
Madarasz et al,[21] 1995	Hungary	21/68	0/39	24·93 (1·55–400·64)
Gunderson et al,[22] 1985–206	USA	43/166	150/2242	3·87 (2·87–5·22)
Vambergue et al,[23] 1992	France	53/295	1/111	19·94 (2·79–142·47)
Lee A et al,[24] 1971–2003	Australia	405/5470	16/783	3·62 (2·21–5·93)
Ferraz et al[17]*	Brazil	6/70	7/108	1·32 (0·46–3·78)
Krishnaveni et al,[25] 1997–98	India	13/35	8/489	22·70 (10·09–51·08)
Morimitsu et al,[26] 1999–2001	Brazil	7/23	0/11	7·50 (0·47–120·11)
Järvelä et al,[5] 1984–94	Finland	23/435	0/435	47·00 (2·86–771·65)
Albareda et al,[27] 1966–93	Spain	44/696	0/70	9·07 (0·56–146·25)
Åberg et al,[28] 1991–99	Sweden	21/229	1/61	5·59 (0·77–40·66)
Linné et al,[16] 1964–65	Sweden	10/28	0/52	38·38 (2·33–631·74)
Bian et al,[29] 1964–65	China	15/45	1/39	13·00 (1·80–93·93)
Ko et al,[30] 1988–95	China	105/801	7/431	8·07 (3·79–17·19)
Osei et al,[31] 1990–91	USA	10/15	0/35	47·25 (2·95–757·28)
Damm et al,[32] 1978–85	Denmark	33/241	0/57	16·06 (1·00–258·06)
Benjamin et al,[33] 1961–88	New Mexico	14/47	3/47	4·67 (1·43–15·21)
O'Sullivan,[34] 1954–60 and 1962–70	USA	224/615	18/328	6·64 (4·19–10·52)
Persson et al,[35] 1961–84	Sweden	5/145	0/41	3·16 (0·18–55·76)
Total		**3997/31867**	**6862/643588**	**7·43 (4·79–11·51)**

Test for heterogeneity: τ^2=0·50, χ^2=126·67, df=19 (p<0·0001), I^2=85·0% (95%CI 78–90)
Test for overall effect: Z=9·39 (p<0·0001)

Bellamy L, et al Lancet 2009; 373: 1773-79

Risk Factors for Developing Type 2 Diabetes after Gestational Diabetes

- Increased maternal weight
- Early gestation of onset
- Use of insulin in pregnancy

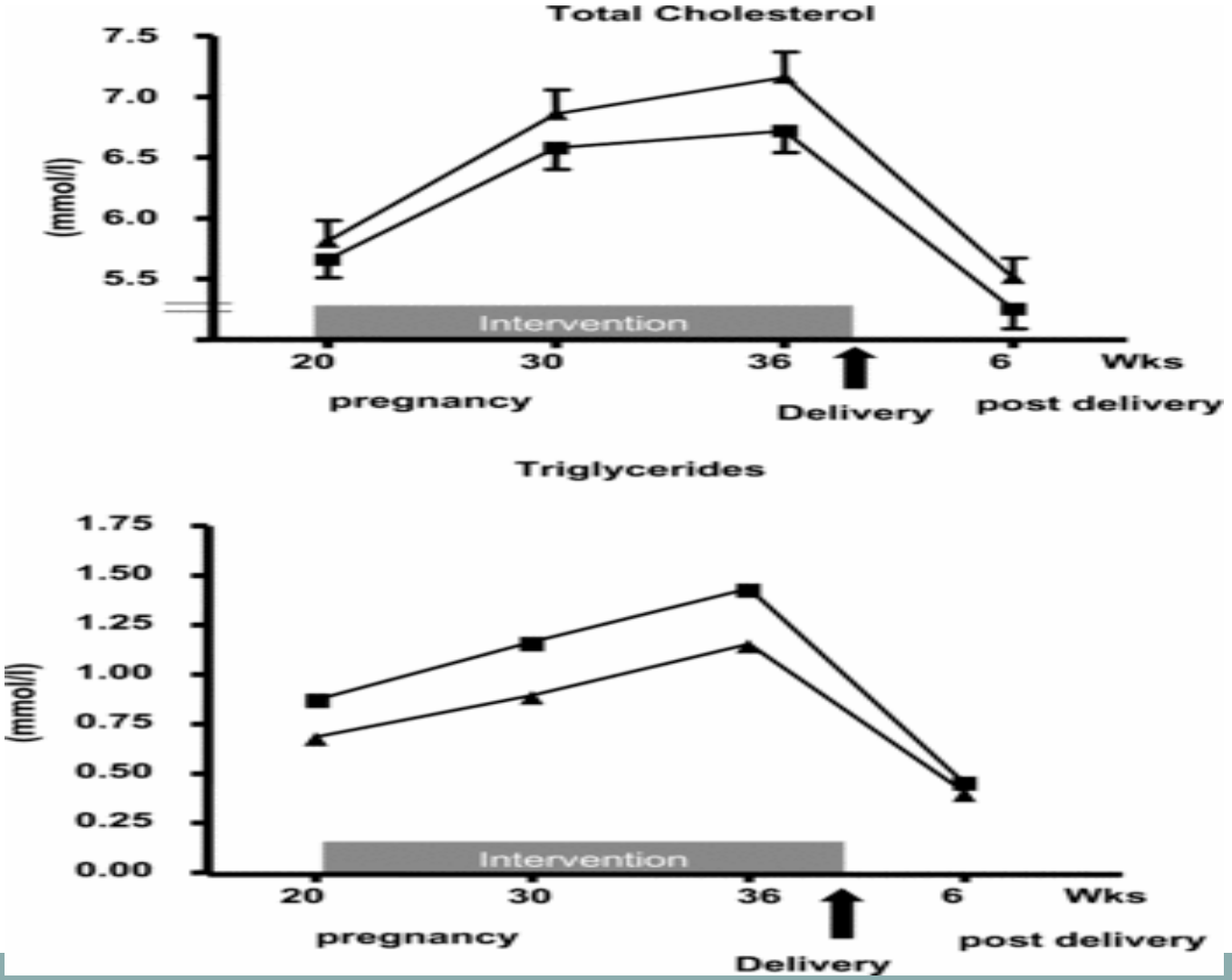
(K Baptiste-Roberts et al Am J Med 2009)

But, when and how and how often should we screen women who have had GDM for type 2 diabetes?

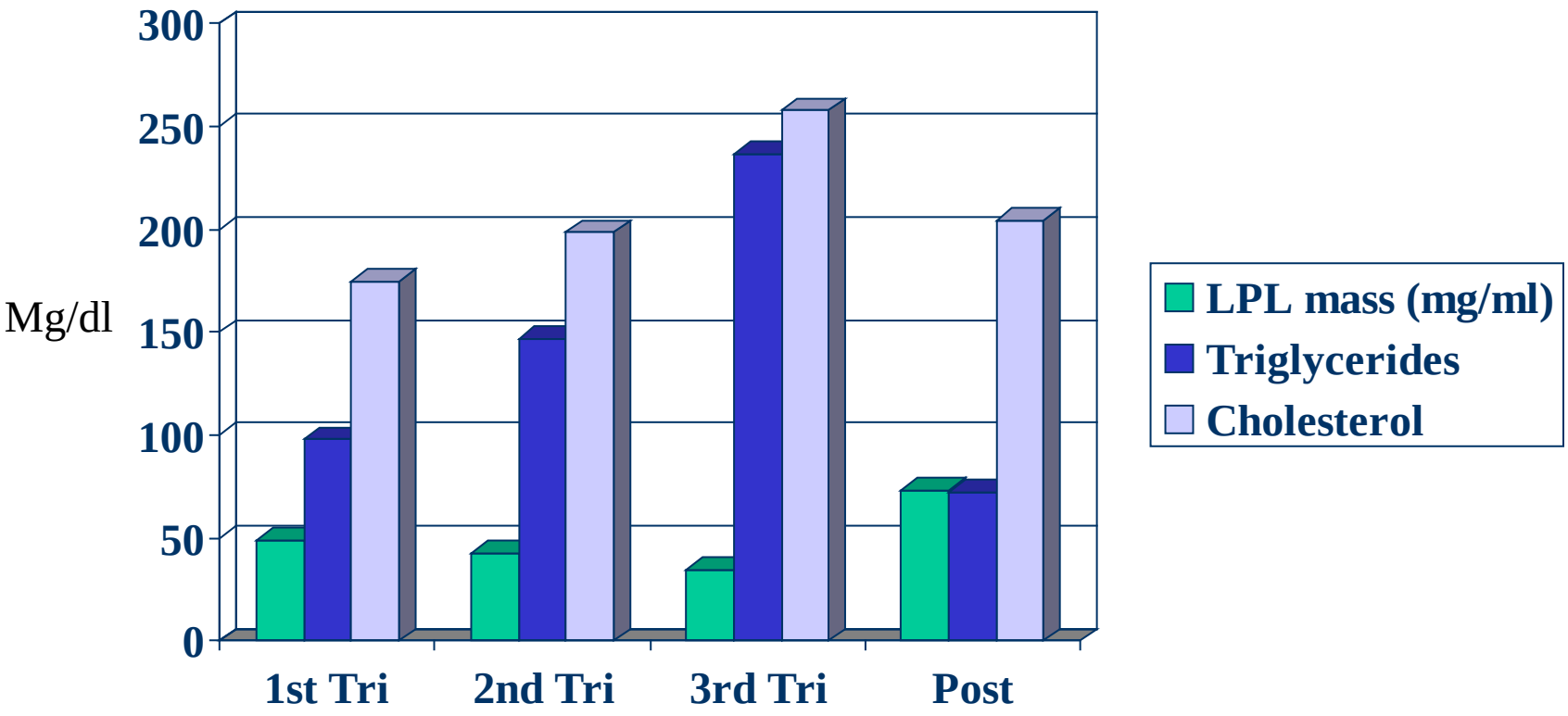
Who should do this screening and who should fund it?

Can women who have had gestational diabetes change their life style and diet to reduce or delay their risk of developing type 2 diabetes?

In healthy pregnancy
maternal blood cholesterol and triglyceride levels go up



In healthy pregnancy: Lipoprotein lipase activity, triglyceride and total cholesterol levels



Kinoshita et al, Clin Chim Acta, 2003

Serum of a woman with hyper-triglyceridaemia secondary to lipo-protein lipase deficiency

Autoimmune conditions improve in pregnancy and… relapse postpartum?

Multiple Sclerosis; relapse rates before during and after pregnancy

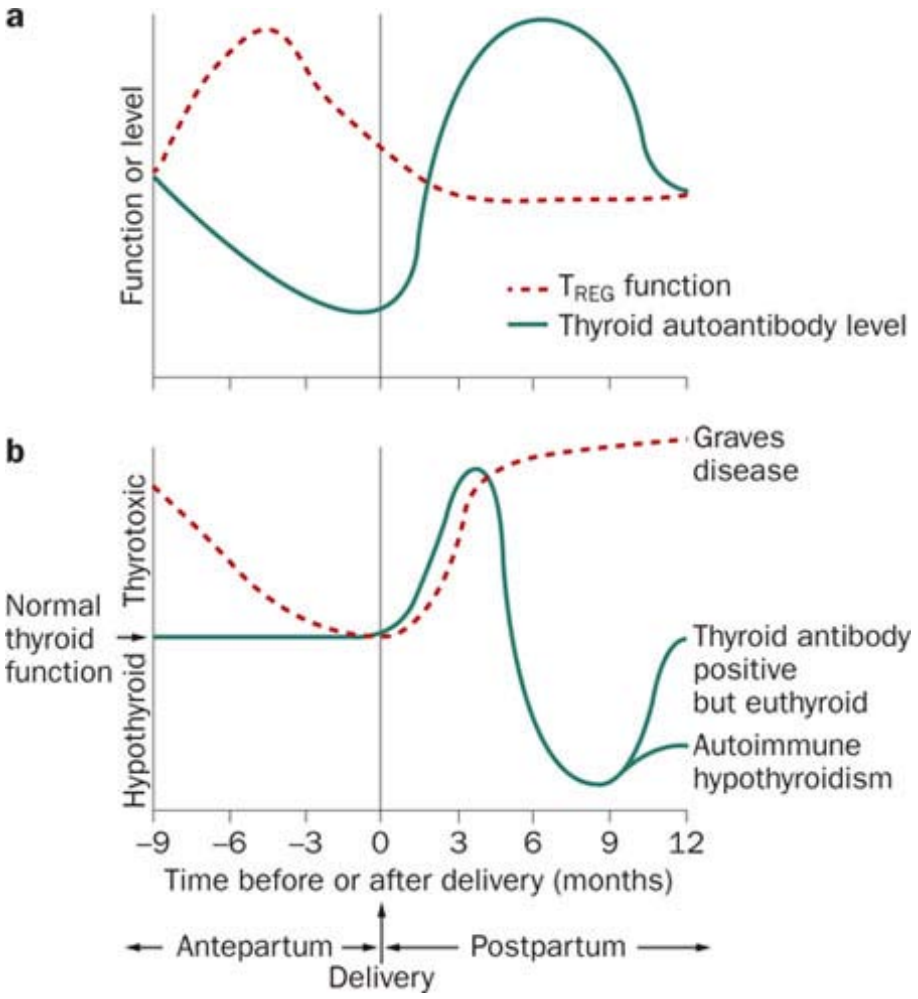
Country	Number	Pre-pregnancy relapse rate	Pregnancy relapse rate ($1^{st}/2^{nd}/3^{rd}$ trimester)	Postpartum relapse rate
Finland	42	1.0	0.5/na/0.2	1.5
12 European	227	0.7	0.5/0.6/0.2	1.2
Spain	74/88	0.61	0.31	0.87
Argentina	81/141	0.22	0.31/0.19/0.04	0.82
Argentina	46/86	1.3	0.7/0.6/0.1	1.2
Brazil	47/49	1.37	0.29	0.86

Borchers AT et al J Autoimmunity 2010; 34: J287-299

Gestational changes to thyroid autoimmunity, antibody levels and Treg function

a. Changes in thyroid autoantibody levels and Treg cell function

b. Changes in thyroid function in Women with autoimmune thyroid disease



Weetman AP. Nature Reviews Endocrinology 2010; 6: 311-18

Development of autoantibodies before the clinical onset of Systemic Lupus Erythematosus (SLE).

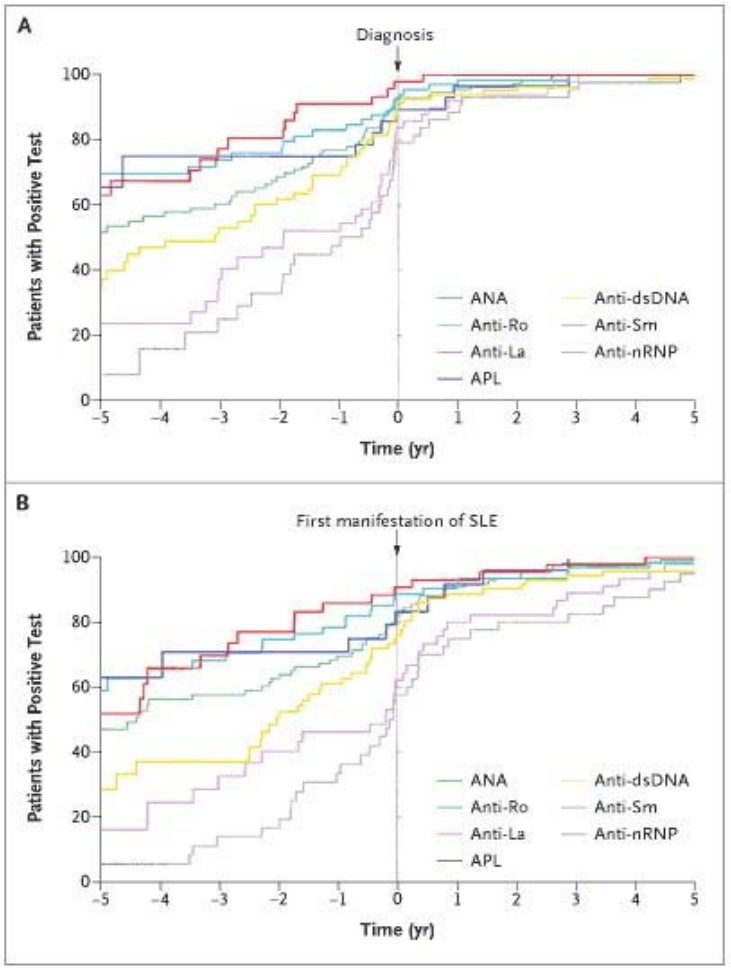
(Arbuckle MR et al N Engl J Med 2003; 349: 1526-1533)

Panel A; Analysis of the time from antibody development to the diagnosis of SLE.

Antinuclear antibodies (ANA) appeared earlier than anti-Sm ab and anti-nRNP but not significantly earlier than anti-Ro, anti-La, APL, or anti–double-stranded DNA antibodies (anti-dsDNA).

Panel B; Analysis of the time from antibody development to the first clinical manifestation.

ANA appeared earlier than anti-Sm antibodies and anti–nRNPab but not significantly earlier than the other autoantibodies, with anti–ds DNA antibodies being intermediate.



Maternal Autoimmune Disease can be identified by Alloimmune Effects of Fetus

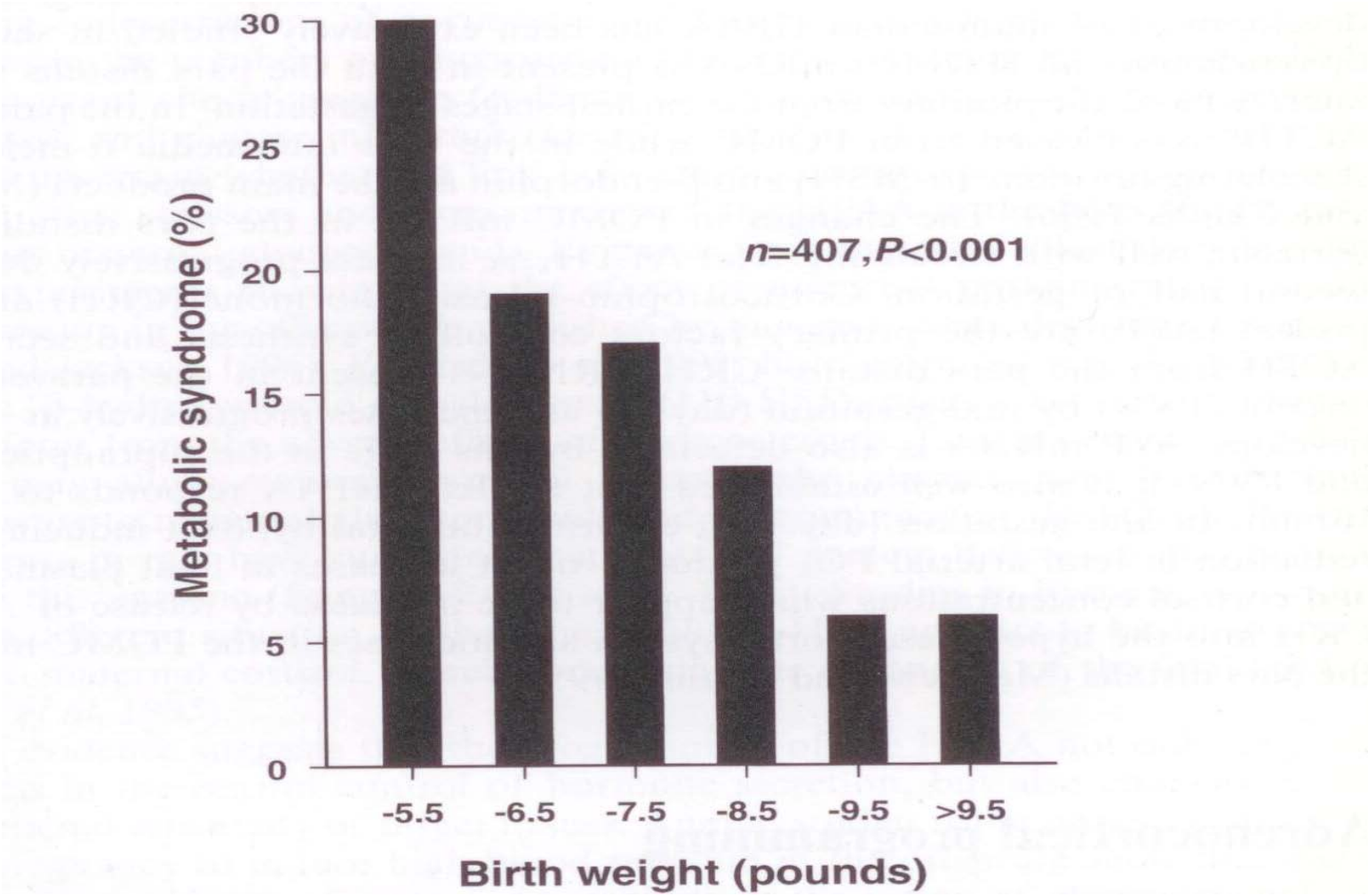
Maternal Disease	Infant Disease	Causative Antibody	% Ab +ve Women	% Affected infants of Ab+ve mothers
SLE, SS, RA & (asymptomatic)	Neonatal Lupus	Anti-SSA/SSB	<0.5%	2%
Immune Thrombocyopaenic Purprura	Neonatal autoimmune thrombocytopaenia	Anti-platelet ab	0.1%	10%
Grave's Disease	Neonatal Grave's Disease	Anti-TSH Receptor ab	0.1-0.4%	1-5%
Pemphigus Gestationis	Pemphigus	Anti-desmoglein	1:50,000	10%
Myasthenia Gravis	Neonatal Myasthenia	Anti-Ach Recptor ab	1:25000	15%
Autoimmune hemolytic anaemia	Autoimmune hemolytic anaemia	Anti-erthyrocyte	1:100000	40%
Hypothyroidism	Neonatal/adolescent onset hypothyroidism	Anti-thyroid (TPO)	10-15%	Rare

Hoftman AC et al Advances in Pediatrics 2008; 55; 271-304

Dutch Famine

Thrifty Phenotype

Prevalence of Metabolic Syndrome in 65 year old Men in Hertfordshire according to Birth weight



Barker D et al Diabetologia 1993; 36: 62-7

Epidemiological Studies

- **Cohort studies from around the world have shown that;**
- Men who father small babies are more likely to be diabetic in later life (Lindsay et al Diabetes 2000; 49:445-9; Hypponen E et al BMJ; 2003; 326: 19-20).
- GWA studies have shown SNPs on genes associated with regulation of glucose that are also associated with birth weight (Freathy et al Nat Genetics 2010; 42: 430-35).

Logistical Regression of Paternal Variables

- For every log unit increase in paternal insulin resistance the OR of fathering a growth restricted offspring is **7.78 (95% CI: 2.63-22.4; p<0.0001)**
- Men who smoked were 3.39 (1.26-9.13; p = 0.016)more likely to father a growth restricted offspring.
- What is the cause of this effect?
- Genetic and/or epigenetic inheritance from father

Conclusions

- Pregnancy outcome;
- 1. predicts the health of all the family
- 2. should be considered an opportunity to screen for future disease
- 3. to initiate changes in lifestyle that might prevent disease in later life