Pathological Pregnancies

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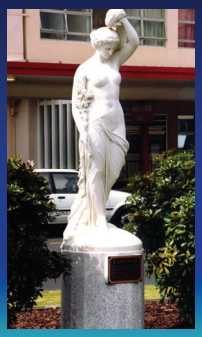

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Objectives

- To understand the pathogenesis and consequences of maternal mal-adaptation to pregnancy – disorders of pregnancy
  - Preeclampsia
  - Intrauterine growth restriction

Scenarios

- Late pregnancy complications (preg 04)
- Fetal Health (preg 07)
- Secondary hypertension (endo 07)
- Stroke / TIA / sudden onset unilateral weakness

What are the **major** complications of pregnancy?

- 1)
- 2)
- 3)
- 4)
- 5)

Maternal adaptations to pregnancy- Maladaptation leads to disease

Changes occur in

- **Most systems of the body including**
- **The maternal cardiovascular system**
- **The haematological system**
- **The maternal immune system**

Haematological Changes

Increased blood volume

Plasma volume and blood volume increase at different rates.

Thus the haematocrit declines in pregnancy as plasma volume increases at a higher rate than cell mass

Plasma volume increases by 1250 mls by 30 weeks and thereafter remains stable.

Haematological Changes in pregnancy

	Non Pregnant	Pregnant
Blood volume	4L	6L
Plasma volume	2.6L	4.2L
Haematocrit	35% - 47%	30 – 40%
Haemoglobin	115 – 165 g/L	100 – 140 g/L

Cardiovascular adaptations

Most important changes are

- Increased cardiac output
  - Caused by a 10% increase in stroke volume and 10-15% increase in pulse rate.
  - 50% increase in blood volume
- Reduced peripheral vascular resistance

Pregnancies complicated by preeclampsia are characterised by higher than "normal" peripheral resistance.

Maternal cardiovascular adaptations to pregnancy

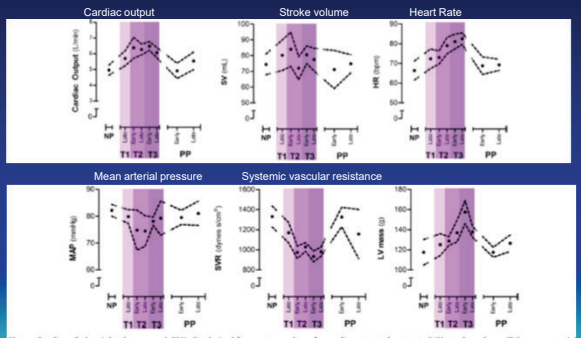


Figure 3 Compiled weighted mean and 95% CIs derived from meta-analyses for cardiac output, heart rate (HR), stroke volume (SV), mean arterial pressure (MAP), systemic vascular resistance (SVR) and left ventricular (LV) mass at each gestational age. Coloured bars represent the first, second and third trimester of gestation. NP, non-pregnant; T1, trimester one; T2, trimester two; T3, trimester three; PP, postpartum.

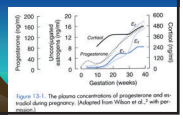
Meah et al. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. Heart 102 (7), 518-26. PMID 26794234

Cardiovascular

- Most of the cardiovascular/heamodynamic changes necessary for normal pregnancy commence early in pregnancy
- What causes the changes?

Cardiovascular

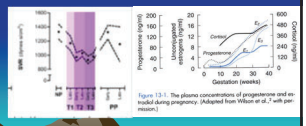
- Oestrogen and CV changes?
- Can reduce vascular resistance
- Increases expression of NO synthetase
- Can alter the ratio of type I /type III collagen in the vessel wall
- High levels of oestrogen are not reached until 9 weeks when fetal adrenals induce synthesis.



From Gynaecology and Obstetrics: a longitudinal approach. Editors Moore T, Reiter R, Rebar R and Baker V. Churchill Livingstone 1993 ISBN 0-443-08811-X.

Cardiovascular

- Progesterone and CV changes?
- Progesterone may induce vascular relaxation in the uteroplacental circulation but does not appear to have a systemic effect.
- Progesterone levels also are not markedly elevated until 10 weeks



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Angiotensin and CV changes?

- Angiotensin II (AII) is basically a vasoconstrictor which causes the arterioles to contract and thereby increases BP – its levels increase in pregnancy
- The uteroplacental unit produces large amounts of the RAS
- The effects of AII appear to be blunted in normal pregnancy
  - possibly due to receptor changes: increase in ACE2/MAS receptor system (ligand Ang1-7)

Cardiovascular

- Nitric Oxide and CV changes?
- NO is produced by vascular endothelial cells by nitric oxide synthetase in response to the shear stress of blood flowing over the vessel surface.
- Nitric oxide has a ½ life of 6 seconds and causes arterial wall relaxation and dilation.
- The activity of nitric oxide synthetase in some tissues is increased in pregnancy.

Cardiovascular

- Do we really know what causes the cardiovascular adaptations of normal pregnancy?
- Who cares anyway?

Preeclampsia

- "Preeclampsia is a multi-system disorder unique to human pregnancy characterised by hypertension and involvement of one or more other organ systems and/or the fetus. Raised blood pressure is commonly but not always the first manifestation. Proteinuria is the most commonly recognised additional feature after hypertension but should not be considered mandatory to make the clinical diagnosis."

Lowe et al (2014) The SOMANZ guideline for the management of hypertensive disorders of pregnancy. https://www.somanz.org/documents/HTPregnancyGuidelineJuly2014.pdf.

Preeclampsia- clinically

- hypertension arises 20+ weeks gestation accompanied by one or more of
- Renal involvement
- Disseminated intravascular coagulation
- Severe epigastric and/or right upper quadrant pain.
- Neurological involvement headache visual disturbances
- Stroke
- Pulmonary oedema
- Fetal growth restriction (FGR/IUGR)

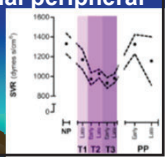
Lowe et al (2014) The SOMANZ guideline for the management of hypertensive disorders of pregnancy. https://www.somanz.org/documents/HTPregnancyGuidelineJuly2014.pdf.

Preeclampsia

- 3-8 % of all pregnancies
- Approx 60,000 maternal deaths/year world wide
- 3000 New Zealand women annually
- 3000 New Zealand fetuses/babies annually
- Only cure is delivery of the placenta

Preeclampsia failed maternal adaptation

- **Triggered by something from the placenta**
- **An exaggerated inflammatory response leading to vascular dysfunction**
- **Failure of the normal cardiovascular adaptations to pregnancy.**
- **Loss of the normal decrease in maternal peripheral vascular resistance**



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Early and Late onset preeclampsia

- There are subgroups of preeclampsia
- Early onset, 20-34 weeks at diagnosis
- Late onset 34+ weeks
- Distinction important - usually but NOT always, late onset is less severe
- The pathogenesis of early and late onset is increasingly thought to be different –
- Potential treatments may differ

How to cure preeclampsia

- There is only one cure for preeclampsia
  - –Delivery of the fetus to prevent progression of maternal signs/symptoms
  - –The hypertension may be managed pharmacologically

Lowe et al (2014) The SOMANZ guideline for the management of hypertensive disorders of pregnancy. https://www.somanz.org/documents/HTPregnancyGuidelineJuly2014.pdf.

Cardiovascular Mortality

- Cardiovascular disease (CVD) is a leading cause of death in New Zealand …..Coronary heart disease and cerebrovascular disease combined accounted for 8889 (8041 in 2009[2]) deaths in New Zealand in 2003 compared to 7932 (8437 in 2009[2]) deaths related to cancer.[1]
- In New Zealand, longstanding ethnic and socioeconomic disparities have been well documented for CVD mortality. Chan et al., (2008) Ethnic and socioeconomic disparities in the prevalence of cardiovascular disease in New Zealand. Journal of the New Zealand Medical Association, Vol 121 No 1285

[1] New Zealand Health Information Service. Mortality and Demographic Data 2002 and 2003. Wellington: Ministry of health; 2006.
[2] New Zealand Health Information Service. Mortality and Demographic Data 2009. Wellington: Ministry of health.

Cardiovascular disease mortality in women

- Globally leading cause of death of women
  - – Usually considered to be a male problem
- 2,850 women died from heart disease in New Zealand in 2016

Preeclampsia predisposes to early cardiovascular mortality

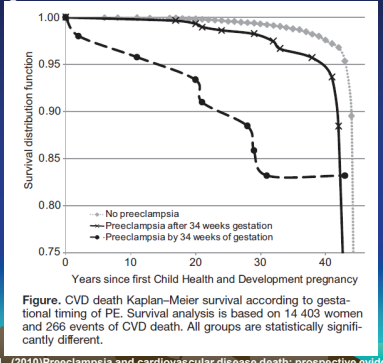


Figure. CVD death Kaplan–Meier survival according to gestational timing of PE. Survival analysis is based on 14 403 women and 266 events of CVD death. All groups are statistically significantly different.

Mongraw-Chaffin et al., (2010)Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. Hypertension;56(1):166-71.

Guidelines for Prevention of Stroke in Women

Table 6. Adverse Pregnancy Outcomes and Risk for Stroke

Study Date and Author	Total No. of Subjects	Study Design	Pregnancy Outcome	Cerebrovascular Outcome	Follow-up, y	HR or OR for Outcome (95% CI)
Mannisto et al, 2013[173]	10 314	Prospective cohort study	Gestational hypertension	Ischemic cerebrovascular disease	40	1.67 (1.13–2.45)
Bonamy et al, 2011[174]	923 686	Retrospective cohort study	Preterm birth; SGA	Cerebrovascular events (infarction, hemorrhage, subarachnoid hemorrhage, TIA, other stroke)		Preterm birth 2.41 (1.4–4.17); SGA birth 1.68 (1.46–2.06); preterm and SGA birth 3.11 (1.91–5.09)
Irgens et al, 2001[175]	626 272	Retrospective cohort study	Preeclampsia	Stroke mortality		Term preeclampsia 0.98 (0.5–1.91); preterm preeclampsia* 5.08 (2.09–12.35)
Wilson et al, 2003[176]	1312	Retrospective cohort study	Preeclampsia	Stroke mortality	32	3.60 (1.04–12.4)
Ray et al, 2005[176]	1 026 265	Retrospective cohort study	Maternal placental syndrome	Cerebrovascular disease		1.90 (1.42–2.54)
Funai et al, 2005[177]	37 061	Retrospective cohort study	Preeclampsia	Stroke		3.07 (2.18–4.33)
Kestenbaum et al, 2003[178]	124 141	Case–control study	Preeclampsia	Cerebrovascular disease		2.53 (1.70–3.77)
Lykke et al, 2009[179]	782 287	Retrospective cohort	Gestational hypertension, mild preeclampsia, severe preeclampsia	Stroke	12.9–14.6	Gestational hypertension 1.58 (1.32–1.89); mild preeclampsia 1.50 (1.36–1.66); severe preeclampsia 1.66 (1.29–2.14)

CI indicates confidence interval; HR, hazard ratio; OR, odds ratio; SGA, small for gestational age; and TIA, transient ischemic attack.
*Defined as preeclampsia between 16 and 36 weeks.

Bushnell et al (2014) Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 45(5):1545-88.

Preeclampsia Foundation

Box 2: Prevention of Stroke in Women with a History of Preeclampsia
Because of the increased risk of future hypertension and stroke 1 to 30 years after delivery in women with a history of preeclampsia *(Level of Evidence B)*, it is reasonable to (1) consider evaluating all women starting 6 months to 1 year post partum, as well as those who are past childbearing age, for a history of preeclampsia/eclampsia and document their history of preeclampsia/eclampsia as a risk factor, and (2) evaluate and treat for cardiovascular risk factors including hypertension, obesity, smoking, and dyslipidemia. *(Class IIa; Level of Evidence C)*.

http://www.preeclampsia.org/research/research-news/325-preeclampsia-doubles-womens-stroke-risk accessed 8/5/2016

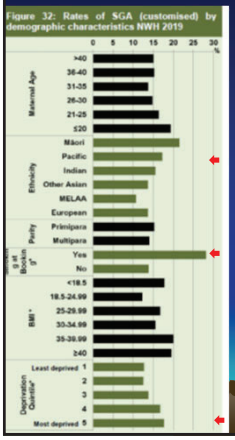
SGA verses FGR/IUGR

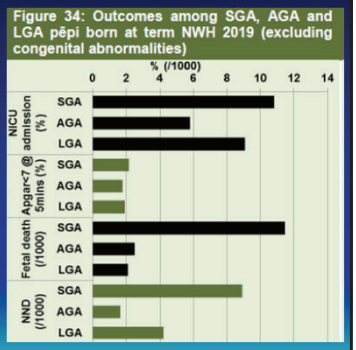
- SGA- small for gestational age
  - compared to averages usually <10 centile
  - includes constitutionally small babies
  - easy and consistent to measure
- FGR fetal growth restriction –always pathologic
  - A fetus that has not reached it growth potential
- IUGR intrauterine growth restriction=FGR

IUGR/FGR

- Intrauterine growth restriction/Fetal growth restriction (IUGR/FGR)
  - Associated with 65% of cases of still-birth
  - Long term consequences for survivors
  - Difficult to detect *in utero*
    - Abnormal doppler waveforms of the uterine and umbilical arteries.

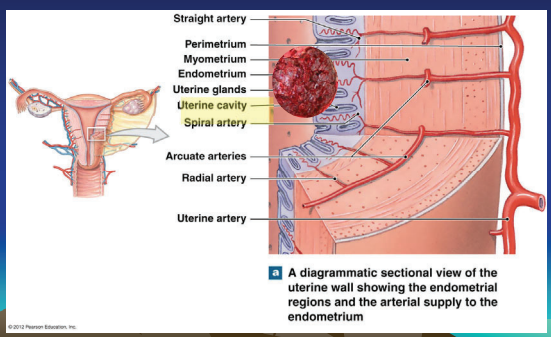
SGA/IUGR/FGR





National Women's Hospital Annual Clinical Report 2019 ISSN1175-6667 https://nationalwomenshealth.adhb.govt.nz/healthprofessionals/annual-clinical-report/national-womens-annual-clinical-report/

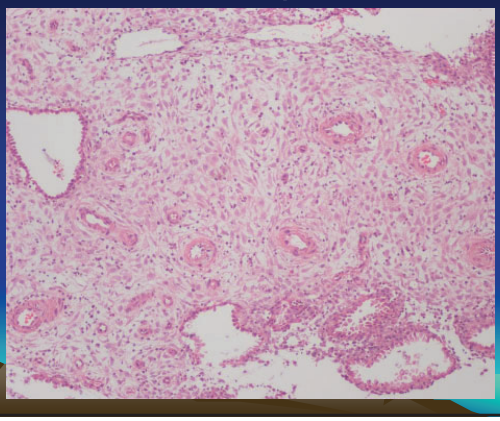
SGA/IUGR/FGR pathophysiology



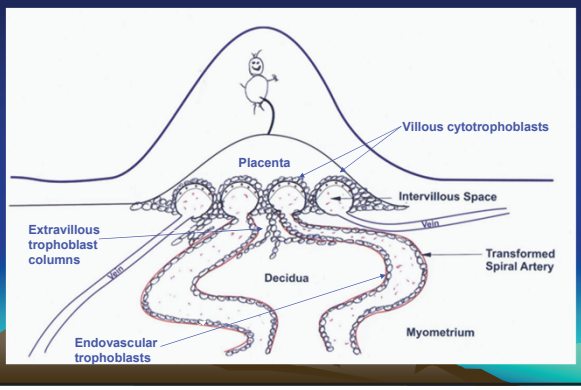
a A diagrammatic sectional view of the uterine wall showing the endometrial regions and the arterial supply to the endometrium

Martini FH, Timmons MJ and Tallitsch RB. (2012) Human Anatomy 7th edition. Benjamin Cummings 10 0-321-68815-5

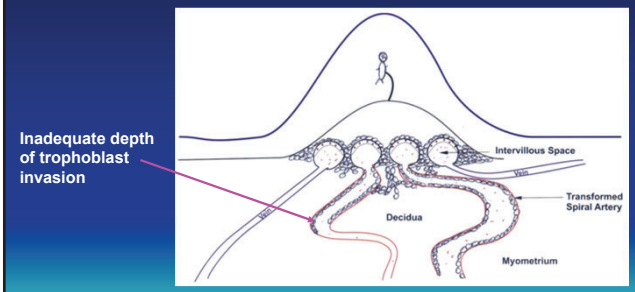
Untransformed spiral arteries



Normal "physiological changes"
(mid gestation)



Inadequate "physiological changes"



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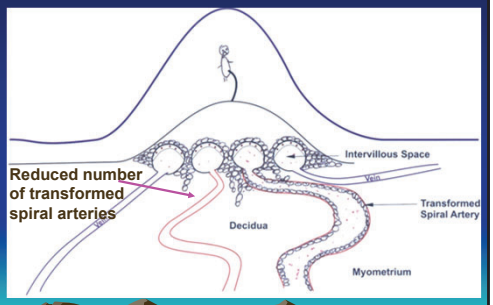
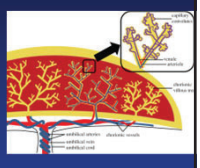


The FGR placenta

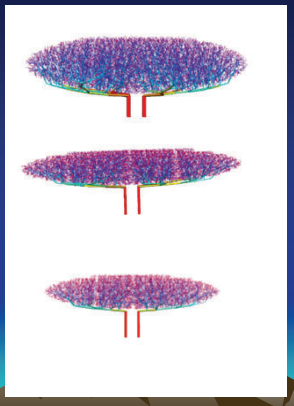
- Smaller – ~29% decrease in volume.
- Thinner – ~21% decrease in thickness.
- Decreased umbilical blood flow (30-50%)
- Inadequately developed vasculature



FGR Normal

Images courtesy of Dr J James, University of Auckland

FGR placental vasculature



Normal

Mild FGR : Thinner placenta with shorter vascular branches

Severe FGR: Placenta is thinner and with a smaller diameter. Vascular branches are shorter and the number of vascular branches is reduced by 36%

Tun et al., Scientific Reports, 9(1):9876. 2019

Immune System

The fetus is genetically half paternal and half maternal!!!!!!!!!!!!!!!!!!!!!!!!!!!

Yet for 9 months the fetal tissue of the placenta and extra-placental membranes survive in intimate contact with the maternal immune system.

Immune System/sperm

Prior to pregnancy sperm must survive in the female genital tract. Sperm are foreign to the mother yet in most cases repeated acts of coitus do not stimulate the maternal immune system to react to sperm.

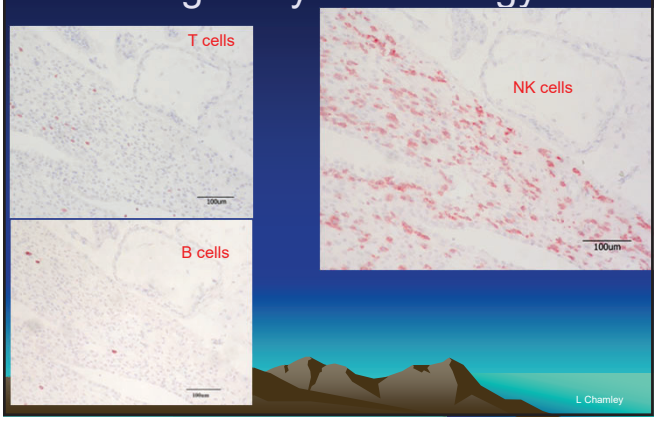
- In fact, repeated exposure to sperm appears to be beneficial protecting against pre-eclampsia.
- Does repeated intercourse tolerise the maternal immune system to paternal/fetal antigens????????

Seminal plasma has been found to be immune suppressive and can reduce the effectiveness of many components of the immune system in vitro.

Immune System

- **The decidua contains**
  - **almost no B cells (no antibody production)**
  - **about 10% of the leuocytes in the decidua are T cells**
  - **70% of the leucocytes are specialised uterine natural killer-like cells.**
- **NK cells in peripheral blood can act by antibody-dependent cell mediated cytotoxicity**
- **But uNK cells lack CD16 the receptor that is required to effect ADCC.**

Pregnancy Immunology



Immune System

Lymphocyte counts do not alter greatly in pregnancy but there is believed to be a bias in the type of T helper (CD4) cells and the cytokines they produce with a tilt in the balance toward Th2 cytokines

Th1 cytokines drive the immune system towards a cell mediated (cytotoxic T cell, ie transplant rejection) response

Th2 cytokines drive the immune system towards an antibody mediated response.

Immune System

There is some evidence for a diminution of the maternal immune response to some organisms in pregnancy.

Some infections if first encountered in pregnancy may be more severe

- The incidence of listeriosis is increased in pregnancy
- Some infections such as leprosy tend to be more severe in later pregnancy.