Not all progestogens are the same

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Disclosures

I have done sponsored clinical research for

- Eli Lilly, Novo-Nordisk, Astellas, Zafgen, Genkyotex, Merck Sharpe Dohme, Trimel, Medpace, Takeda
- I have received speaker's fees from Sanofi, Novo-Nordisk, Abbott
- I have been on the advisory board for Menarini

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What is the ideal progestogen?

- ❖ Reliable delivery to the endometrium
- ❖ Does not antagonise oestrogen benefits
- ❖ Does not initiate mood disturbance
- ❖ Does not promote androgenic effects
- ❖ Does not increase breast cancer risk

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Why use a progestogen?

Oestrogen-only HRT
- ❖ lowers risk of cardiovascular disease
- ❖ prevents bone loss
- ❖ not associated with increased risk of breast cancer
  BUT
- ❖ increases risk of endometrial cancer when used alone

Addition of a progestogen
- ❖ lowers risk of endometrial cancer
  BUT
- ❖ attenuates cardiovascular disease benefit
- ❖ increases breast cancer risk

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What makes progestogens different?

1. Progestogen class
2. Interaction with other members of the nuclear receptor superfamily
3. Mode of delivery
4. Dose
5. Duration

Why does this matter?
- endometrium
- breast
- lipids

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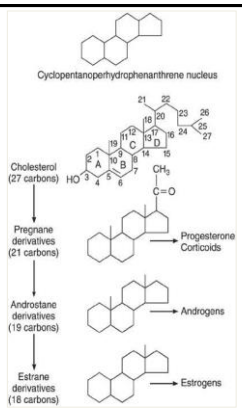
Basic 4-ring structure

Begin with cholesterol



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1. Progestogen classes

Derived from progesterone	Derived from testosterone
17 OH Progesterones	**Estranes**
Medroxyprogesterone acetate	Norethisterone
Cyproterone acetate	Dienogest (non ethyl estrane – anti androgenic)
Megestrol	**Gonanes**
	Norgestrel, levonorgestrel
19 nor progesterones (pregnanes)	Desogestrel
Nomegestrol acetate	Etonorgestrel
Trimegestone	Gestodene
	Norgestimate

Spironolactone
Drospirenone

Retro-progesterone
Dydrogesterone

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The steroid receptor superfamily

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2. Steroid binding within the steroid receptor superfamily

- Steroids and their synthetic analogues can bind to receptors in the steroid receptor superfamily, other than their own receptor
  - Cyproterone acetate binds to androgen receptor
  - Spironolactone binds to mineralocorticoid receptor, androgen receptor and progesterone receptor
  - CPA and MPA bind to glucocorticoid receptor, in high dose can lead to glucorticoid effect

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Biological activities of progesterone and progestins

Progestogen	Anti E	E	A	Anti A	Gluco	Anti min
Progesterone	+	-	-	±	+	+
Dydrogesterone	+	-	-	±	-	±
17α-OH-derivatives						
Cyproterone acetate	+	-	-	++	+	-
MPA	+	-	±	-	+	-
Spironolactone derivatives						
Drospirenone	+	-	-	+	-	+
19-nortestosterone derivatives						
Norethisterone	+	+	+	-	-	-
Levonorgestrel	+	-	+	-	-	-
Dienogest	±	±	-	+	-	-

Schindler Maturitas 2003

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3. Progestogen delivery systems

- Oral
  - Progesterone not well absorbed orally
    - except micronised progesterone (not available in Australia)
- Transdermal
  - Only norethisterone
    - not progesterone cream
- Troches
  - Balance between oestrogen and progestogen is not reliable. Endometrial cancer and hyperplasia reported
- Intravaginal
  - Not available for longterm HRT
- Intra-uterine
  - Levonorgestrel
    - Systemic absorption does happen

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First pass hepatic effect

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4. and 5. Dose and duration

- Progestogens “undo” the effects of oestrogen in the endometrium and elsewhere
- The ideal combination will minimise the antagonism to the oestrogen effect whilst still protecting the uterus
- This depends upon class, delivery, dose and duration of the progestogen

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Cardiovascular implications

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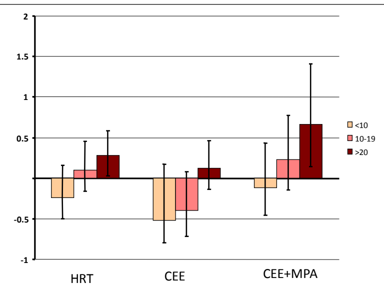
WHI - hazard ratio for cardiovascular disease by year of initiation and +/- progestin



Rossouw JAMA 2007

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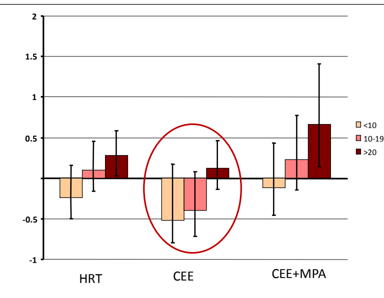

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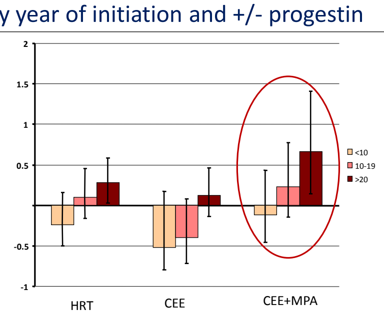

Rossouw JAMA 2007

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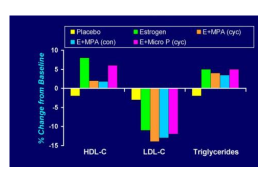
Progestogens and lipids

- Oral oestrogen raises HDL, lowers LDL, lowers total cholesterol
- Oral progestogen antagonises this effect
  - Especially androgenic progestins
- Progesterone and dydrogesterone have relatively neutral effect on lipids

First pass effect



Rosano G et al. Maturitas 2003; 46S1: S17-29

Sitruk-Ware R, Nath A. Rev Endocr Metab Disord 2011

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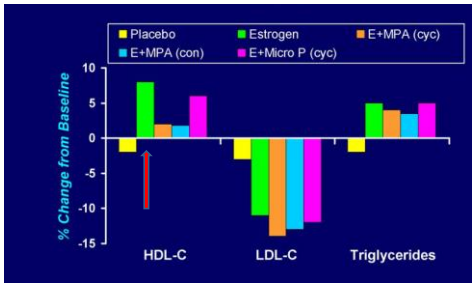
Progestogens and lipids



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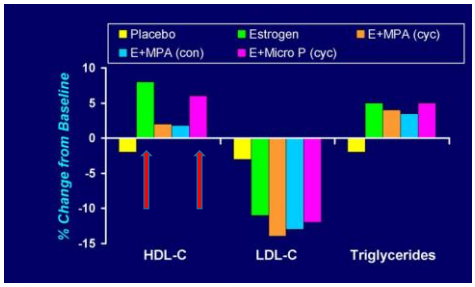

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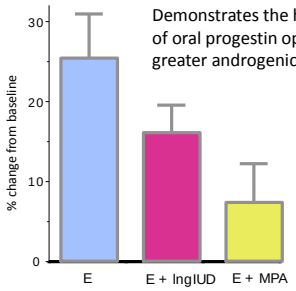
Effect of oral oestrogen on HDL/Chol ratio - a) alone, b) with LNG IUD, c) with oral MPA



Demonstrates the hepatic first pass effect of oral progestin opposing oestrogen despite greater androgenicity of the IUD progestin

LNG = levonorgestrel

Stuckey et al unpublished data

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Genomic and non-genomic effects

- Lipid changes, breast and endometrial proliferation are through the interaction of oestrogen at the genome
- Non-genomic effect are very rapid and occur via receptor on the cell surface

ANGELS

Activators of Non-Genomic Estrogen-Like Signalling

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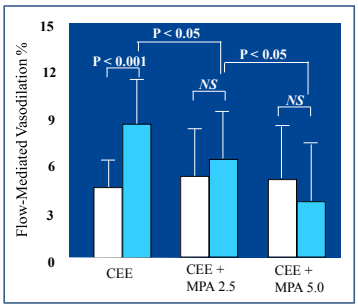
Effects of CEE ± MPA on arterial dilatation



CEE promotes and MPA antagonises flow-mediated vasodilation

Demonstrates dose-effect of 5mg v 2.5 mg MPA

Adams M, Arterio Thromb Vasc Biol 17: 217, 1997

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Progestins and insulin sensitivity

Injectable progestin-only contraception

- 2 epidemiological studies = increased incidence of DM2.
- 7 of 8 studies using OGTT = approx 2 x insulin excursion at 2 or 3 h
- 3 studies of IVGTTs = increased early-phase insulin response.
- 1 study using glucose clamps showed reduced total-body glucose uptake per unit of insulin

Kahn, HS; DIABETES CARE 2003 Review

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Breast cancer implications

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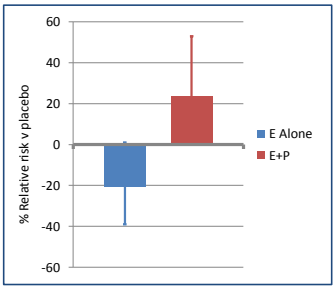
Women's Health Initiative – breast cancer risk e v E+P



Progestin changes breast cancer risk in HRT

Manson JAMA 2013

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Nurses Health Study – Chen 2006

Oestrogen only analysis - baseline mammogram

	All tumours	ER+/PR+ only
Duration of oestrogen use	**RR (95% CI)**	**RR (95% CI)**
< 5 yrs	1.06 (0.76-1.47)	1.04 (0.64-1.70)
5-9.9	0.91 (0.68-1.21)	1.08 (0.72-1.62)
10-14.9	1.11 (0.85-1.44)	1.29 (0.89-1.86)
15-19.9	1.19 (0.89-1.58)	1.50 (1.02-2.21)
≥ 20 yrs	1.58 (1.20-2.07)	1.83 (1.25-2.68)

Conclusion – oestrogen does not significantly increase risk of breast cancer until >15 years of use.

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Results of studies of HRT post breast cancer

HABITS study - used continuous combined oestrogen + progestin

Stockholm study – investigators had a policy of progestin minimisation (3 monthly cyclical)

HABITS

relative risk of recurrence = 3.3 (95%CI, 1.5-7.4)

Stockholm

relative risk of recurrence = 0.82 (95%CI, 0.35-1.9)

Chlebowski JCNI 2007

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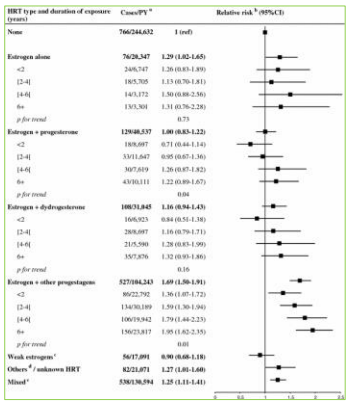

Increased incidence of breast cancer with addition of progestin

Possible influence of type of progestin

Note "dose effect" difference between different formulations

Fournier Breast Cancer Res Treat 2008

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Progestogens and the breast

- The effects of progestogens alone, or in combination with estradiol, on breast cell lines in vitro are markedly different
- Some progestogens inhibit sulfatase activity (eg nomegestrol, tibolone)
- Some progestogens stimulate sulfatase activity (eg MPA)
- Overall the effects appear dependent on dose, hormonal environment, duration of therapy, growth factors and oncogenes
- Data suggest that progesterone and dydrogesterone, in combination with oestradiol, may have less impact on the breast

Pasqualini J et al. J Steroid Biochem Mol Biol. 1998;65:225-235
Fournier A et al. Breast Cancer res treatment. 2008;107:103-111

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Mode of delivery implications

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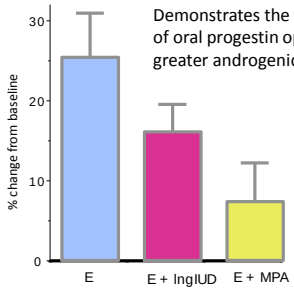
Effect of oral oestrogen on HDL/Chol ratio - a) alone, b) with LNG IUD, c) with oral MPA



Demonstrates the hepatic first pass effect of oral progestin opposing oestrogen <u>despite</u> greater androgenicity of the IUD progestin

LNG = levonorgestrel

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What if we combine transdermal oestrogen with oral progestin

	Transdermal E	Oral P	Combined effect
HDL Cholesterol	Neutral	Suppresses	Unfavourable
LDL Cholesterol	Neutral	Neutral	Neutral
Vasodilatation	Improves	Suppresses	Unfavourable
Thrombosis	Neutral	Neutral except MPA	Neutral
Breast cancer	Combination increases risk		Unfavourable

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Conclusions

- "HRT" is not one entity but a summation of the components used e.g. E vs E+P, oral vs non-oral, high vs low dose, continuous progestogen v cyclical
- the effect of HRT may be different for one progestogen v another
- the effect of HRT may be different for different components in different tissues e.g. bone vs liver
- extrapolation from observations on the effects of unopposed E use may not be valid for combined E+P

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Do we have the ideal progestogen?

- ❖ Reliable delivery to the endometrium
- ❖ Does not antagonise oestrogen benefits
- ❖ Does not initiate mood disturbance
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- ❖ Does not increase breast cancer risk

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