



VITAMIN D AND MATERNAL HEALTH

Studies linking vitamin D with maternal complications

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VITAMIN D AND MATERNAL HEALTH

Studies linking vitamin D with maternal complications

Link between low 25-OHD and adverse pregnancy outcomes

- o gestational diabetes
- o pre-eclampsia
- o infections
- o caesarean section
- o pre-term delivery
- o low birthweight



VITAMIN D AND MATERNAL HEALTH

Studies linking vitamin D with maternal complications

Link between low 25-OHD and adverse pregnancy outcomes

Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM *University of Calgary, Canada*

"Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies
BMJ 27 March 2013



VITAMIN D AND MATERNAL HEALTH

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Link between low 25-OHD and adverse pregnancy outcomes

3357 studies identified between 1966 and 2012
Medline, PubMed, Embase, CINAHL, Cochrane database of
systematic reviews and of registered clinical trials

31 studies in final analysis

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Studies linking vitamin D with maternal complications

Link between low 25-OHD and adverse pregnancy outcomes

Cochrane database of systematic reviews

Four trials (414 women) showing

Women who receive vitamin D – higher concentration of vitamin D at term than women who did not / receive placebo (*low quality*)

Pre-eclampsia	1 trial
Gestational diabetes	0
Preterm birth	0
Caesarean section	0
Low birthweight	3

*Vitamin D supplementation for women during pregnancy
The Cochrane Collaboration 2012*



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Cochrane database of systematic reviews

Low birthweight 3

Three trials (463 women) suggesting women taking vitamin D supplementation during pregnancy less frequently had a baby with birthweight <2.5kg than women who did not / placebo (*low quality*)
Borderline statistical significance

Vitamin D supplementation for women during pregnancy
The Cochrane Collaboration 2012



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Cochrane database of systematic reviews

Conclusions

- o Vitamin D supplementation during pregnancy
Use of intervention as part of routine antenatal care, clinical significance and safety to be determined
- o Evaluation of vitamin D supplementation in pregnancy
need for further rigorous randomised trials

*Vitamin D supplementation for women during pregnancy
The Cochrane Collaboration 2012*

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VITAMIN D AND MATERNAL HEALTH

Association between Fertility and 25-OHD insufficiency

Ozkan et al 2010

84 women, measured serum and follicular fluid levels of 25-OHD
<50 vs 75 nmol/l and above

Low 25-OHD levels associated with
reduced pregnancy rates after IVF embryo transfer

Blomberg et al 2011

300 men, compared serum 25-OHD levels <25 vs >75 nmol/l
reduced proportion of motile and morphologically normal
spermatozoa with lower 25-OHD serum levels



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Association between Bacterial Vaginosis (BV) and 25-OHD insufficiency

3 studies

Increased risk of BV in pregnant women with low 25-OHD levels

Bodnar et al 2009

469 pregnant women n=192 with BV, control group 277 without BV

Linear increase

25-OHD <50 nmol/l 26% increased prevalence of BV

25-OHD <20 nmol/l 65% increased prevalence of BV

BV associated with pre-term delivery

No existing data to support

Increased odds of pre-term delivery with 25-OHD insufficiency

... apart from 1 Japanese study (*Shibata et al 2011*)



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Association between Pre-eclampsia and 25-OHD insufficiency

9 studies

OR of 1.79 (CI 1.25 – 2.58)

Overall meta-analysis showed a significant association between pre-eclampsia and 25-OHD insufficiency

1 RCT excluded from analysis

Marya et al (1987)

Women who took

1200iu Vitamin D + 375mg calcium supplementation/day
were as likely to develop pre-eclampsia as
women who received no supplementation

Protective effect of vitamin D?



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Association between Pre-eclampsia and 25-OHD insufficiency

Protective effect of vitamin D?

Vitamin D deficiency associated with ↑ inflammatory response

$1,25(\text{OH})_2\text{D}_3$ regulates transcription and function of genes associated with placental invasion, normal implantation and angiogenesis

Pre-eclampsia: reduced placental perfusion secondary to abnormal implantation



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Association between Pre-eclampsia and 25-OHD insufficiency

Protective effect of vitamin D?

Hypponen E et al

Does vitamin D supplementation in infancy reduce the risk of pre-eclampsia? Eur J Clin Nutr 2007; 61:36-9

1966, babies received 2000iu vitamin D/day first year of life
vs no supplementation

Subsequent risk of pre-eclampsia was halved

An example of

Early programming of immune system against pre-eclampsia!



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Association between low birthweight and 25-OHD insufficiency

3 RCTs

Trend for women taking vitamin D supplementation during pregnancy to have a baby with birthweight <2.5kg than women who did not / placebo

Borderline statistical significance

10 studies

OR of 1.85 (CI 1.52 – 2.26)

Overall meta-analysis showed a significant association between small for gestational infants and 25-OHD insufficiency



VITAMIN D AND MATERNAL HEALTH

Association between low birthweight and 25-OHD insufficiency

10 studies

OR of 1.85 (CI 1.52 – 2.26)

Overall meta-analysis showed a significant association between small for gestational infants and 25-OHD insufficiency

BMJ meta-analysis excluded one of the Cochrane database RCT

Brooke et al 1980 Vitamin D supplementation in pregnant Asian women

Results 29% v 15% - nearly twice as many SGA infants in the control group



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Association between primary CS and 25-OHD insufficiency

Overall meta-analysis showed no significant association between delivery by CS and 25-OHD insufficiency

Some studies have shown a link

Scholl et al 2012

Women with 25-OHD <37.5 nmol/l twice as likely to have a CS than women with 25-OHD >80 nmol/l

Merewood et al 2012

Women with 25-OHD <37.5 nmol/l nearly 4x as likely to have a CS than women with 25-OHD 37.5 nmol/l and above (OR 3.84, CI 1.71-8.62)

No control group though! n=253 women with 43 CS



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Association between primary CS and 25-OHD insufficiency

Possible link between delivery by CS and 25-OHD insufficiency

Vitamin D required for calcium homeostasis

Calcium has a role in

- smooth muscle function in early labour
- skeletal and smooth muscle strength

Studies have shown women achieving vaginal delivery have higher calcium levels than women delivered by CS



VITAMIN D AND MATERNAL HEALTH

Association between primary CS and 25-OHD insufficiency

Possible link between delivery by CS and 25-OHD insufficiency

The way forward ...

Robust trials are needed

- o Is 25-OHD insufficiency associated with increased CS rates?
- o What is the critical level? < 75 or < 50 nmol/l?
- o Is there a continuum of risk?



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Association between Gestational Diabetes (GDM)
and 25-OHD insufficiency

10 studies

OR of 1.49 (CI 1.18 – 1.89)

Overall meta-analysis showed a significant inverse relation
between serum 25-OHD levels and the incidence of GDM

25-OHD < 50 nmol/l (7 studies)

25-OHD < 75 nmol/l (3 studies)

7 studies from developed countries

2 studies from Iran, 1 study from India



VITAMIN D AND MATERNAL HEALTH

Association between Gestational Diabetes (GDM) and 25-OHD insufficiency

10 studies OR of 1.49 (CI 1.18 – 1.89)

Maghbooli et al (2008)

Lower serum levels 25-OHD in women with GDM than controls

25-OHD < 12.5 nmol/l

Zhang et al (2008)

25-OHD < 50 nmol/l → odds GDM 2½ fold increase

For each 12.5 nmol/l ↓ → odds GDM increased by 29%

Parlea et al (2011)

25-OHD < 73.5 nmol/l → odds GDM doubled

Clifton-Bligh et al (2008)

Borderline inverse correlation between 25-OHD and FBG



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Association between Gestational Diabetes (GDM)
and 25-OHD insufficiency

10 studies OR of 1.49 (CI 1.18 – 1.89)

Baker et al (2012)

No association between first trimester 25-OHD levels and GDM
a small study



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Association between Gestational Diabetes (GDM)
and 25-OHD insufficiency

Other studies

Savvidou et al (2011)

Maternal serum 25-OHD levels at 11+0-13+6 weeks in
pregnant women

50 women with type 2 diabetes

100 women who developed GDM

50 women non-diabetic with LGA babies

1000 control group, non-diabetic, delivered AGA babies

No difference in serum 25-OHD levels between the groups
but small numbers

high number in control group with 25-OHD <30 nmol/l



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Association between Gestational Diabetes (GDM)
and 25-OHD insufficiency

Possible link between GDM and 25-OHD insufficiency

The way forward ...

Clinical trials to study whether vitamin D supplementation improves glycaemic control in women with GDM

✓ Vitamin D increases insulin sensitivity

Pregnancy

- insulin resistant state
- compensating increased insulin secretion

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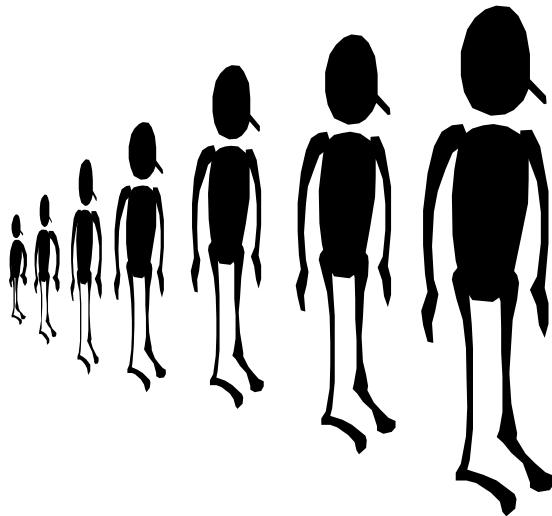
Lots of unknowns ...

- Optimal maternal 25-OHD levels at different gestational age?
<50 nmol/l is common in pregnant women
- Does more severe deficiency have a greater impact?
- Optimal supplementation pre- during and post-pregnancy?
- Do strategies to optimise maternal 25-OHD levels improve pregnancy and neonatal outcomes?

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Do strategies to optimise maternal 25-OHD levels improve pregnancy and neonatal outcomes?



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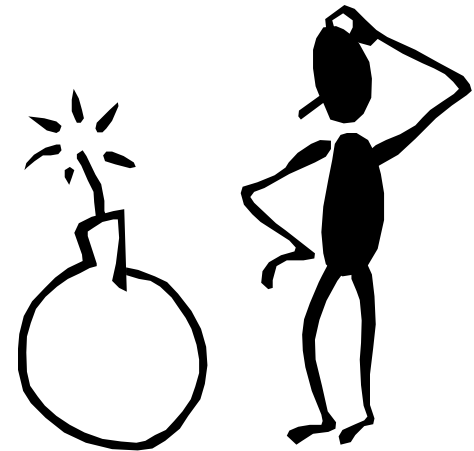
Safety of vitamin D supplementation in pregnancy

In animal studies

Dose-dependent fetal toxicities (skeletal, cardiovascular)

No published reports of teratogenic effects of vitamin D on humans

Probably safe even in very high doses



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Any questions?

