The role of vitamin D in female infertlity
Hope or hype?

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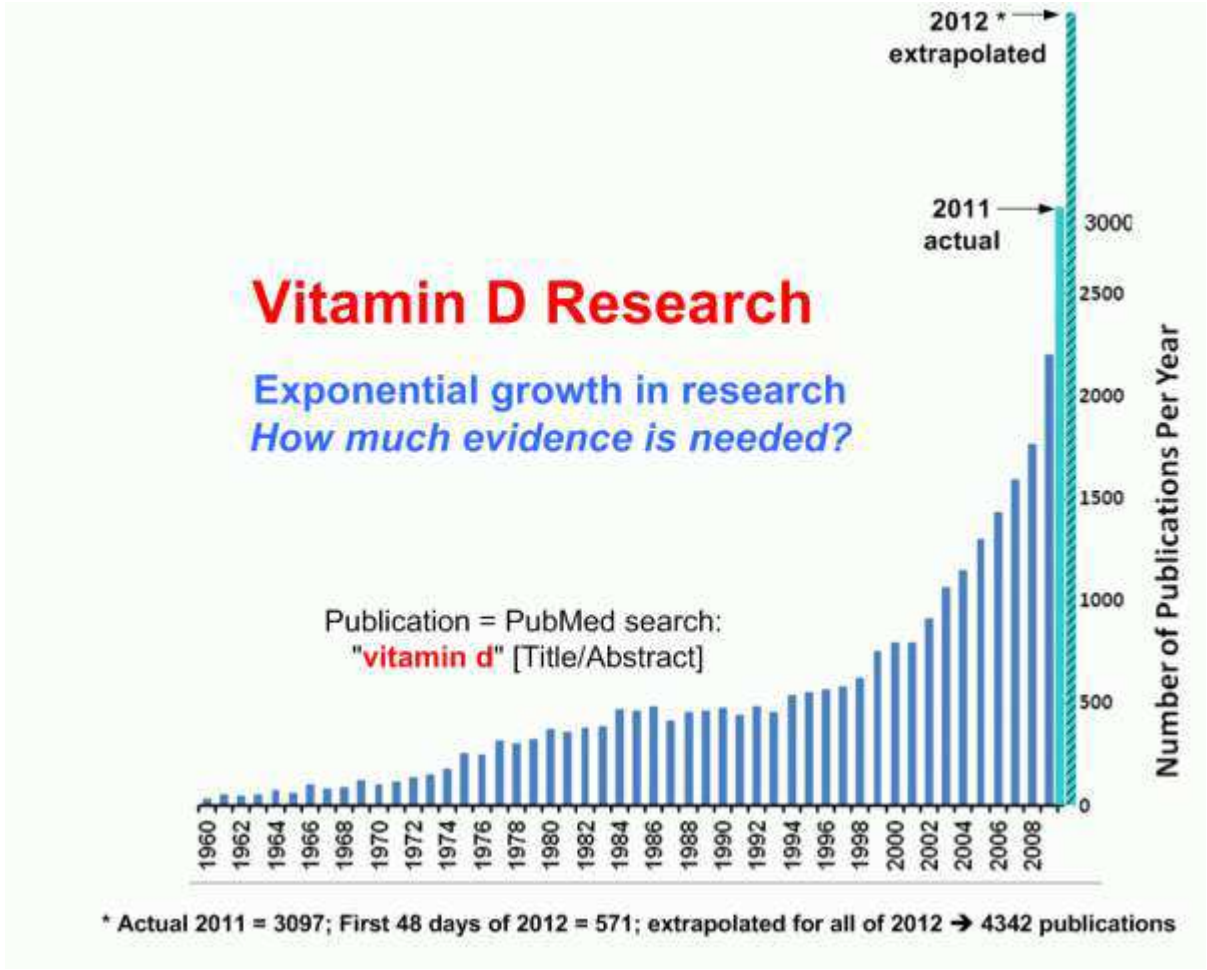
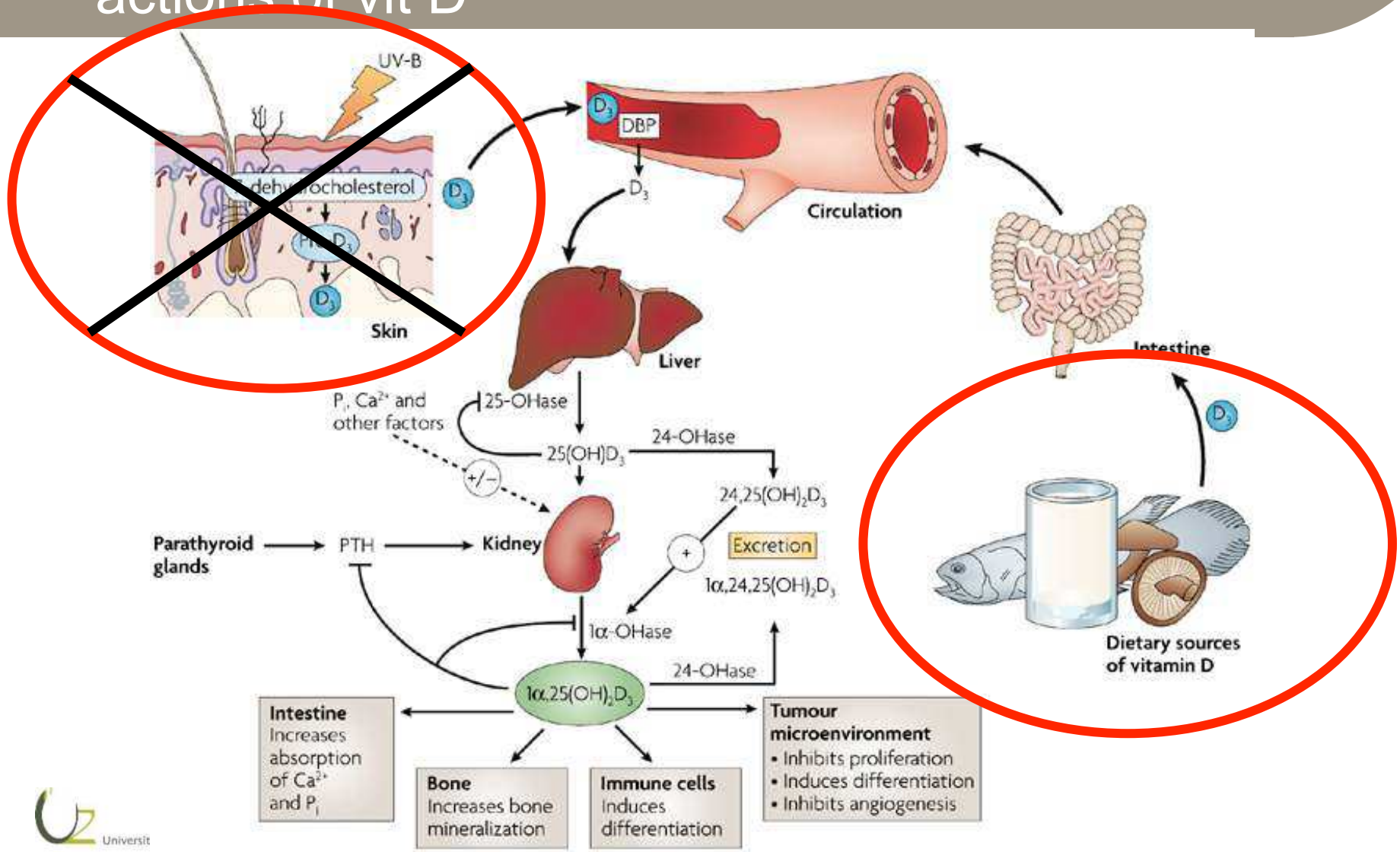
The “trendy” Vitamin D



What do we know about production and the actions of vit D



Nature Reviews | Cancer

Is it Vitamin D so important?

- Mortality elderly
- Bone health
- Cancer (colon, prostate, breast)
- Cardiovascular disease
- Immune system
- Pregnancy
- Multiple sclerosis

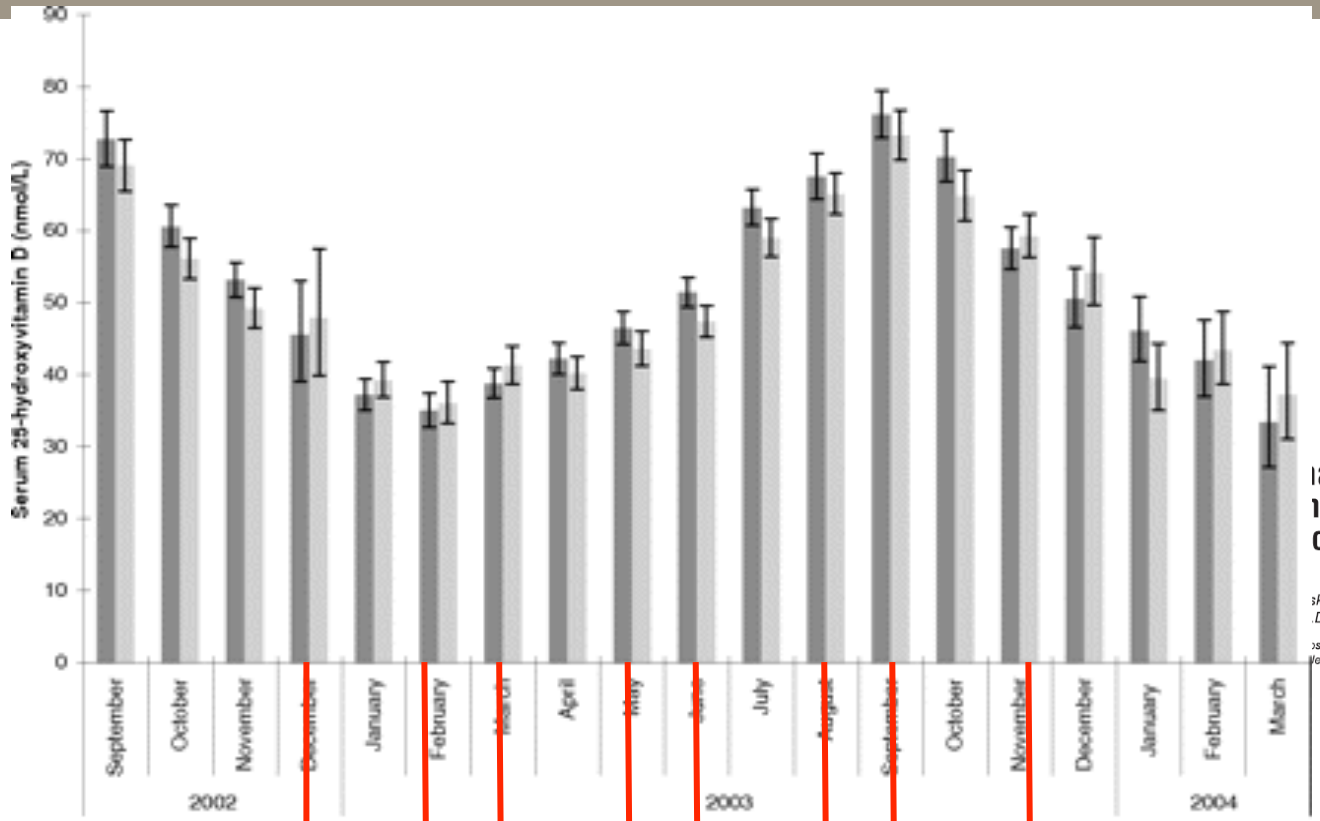
Does Vitamin D have any role in female infertility?

What do we already know about fertility? Basic science

- Vitamin D receptor null mice express uterine hypoplasia and impaired folliculogenesis *(Yoshizawa T, et al. Nat Genet 1997)*

- Vitamin D receptor is present and differentially expressed in endometrium throughout the estrous cycle *(Zarnani et al., Fertil Steril 2010)*

Seasonality in live births and vitamin D levels



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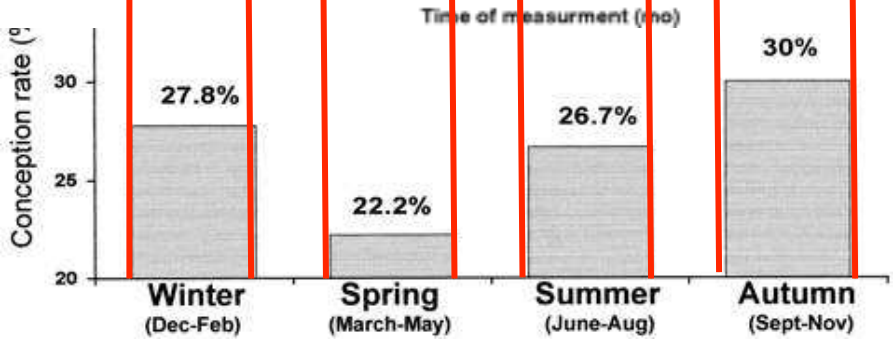
al variability in fertilization
mbryo quality rates in women
oing IVF

sky, M.D., Abraham Benshushan, M.D., Samuel Meirsdorf, M.D.,[a]
.D., Neri Laufer, M.D., and Anat Safran, Ph.D.

stetrics and Gynecology, the IVF Unit, Hadassah Ein-Kerem Hospital, Hebrew University
lerusalem, Israel



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How can it affect fertility?

- Affecting genes involved in steroidogenesis and follicular development
- Affecting of vitamin D on markers of ovarian reserve
- Affecting endometrial receptivity

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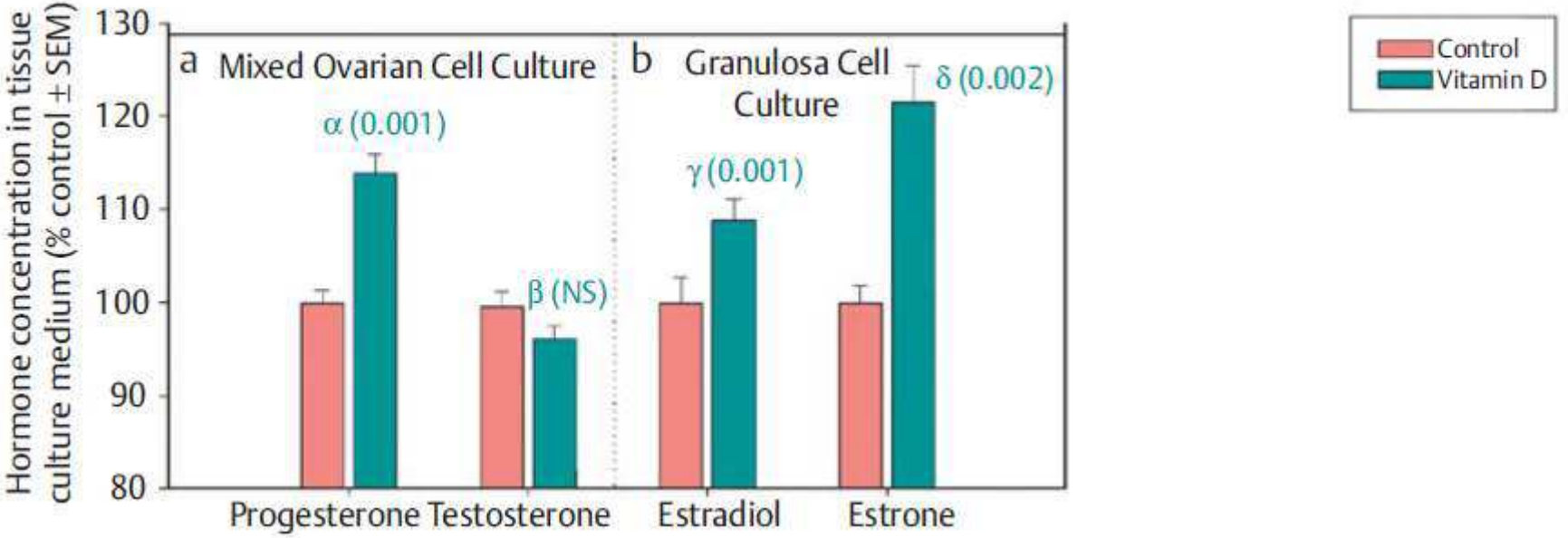
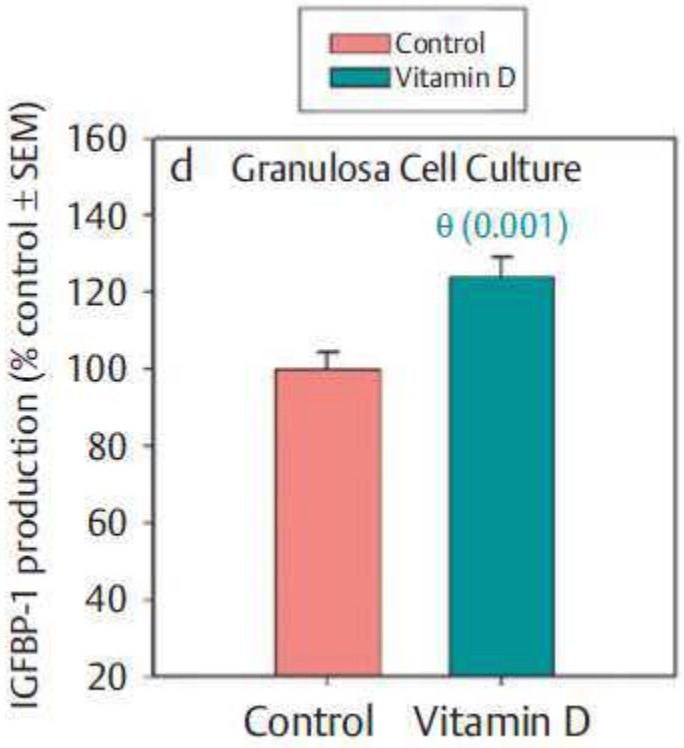
Effect of Vitamin D deficiency on steroidogenesis and follicular development (1)



Parikh et al., Horm Metab Res. 2010

Vitamin D supplementation increases E2 and P production in ovarian cells

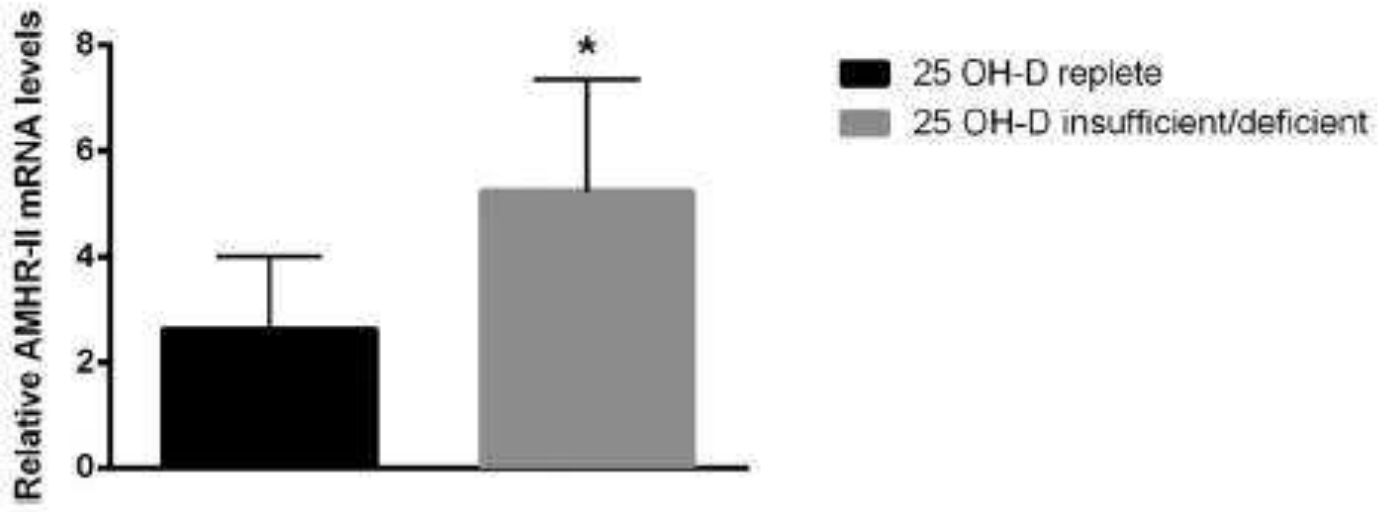
Effect of Vitamin D deficiency on steroidogenesis and follicular development (2)



Parikh et al., Horm Metab Res. 2010

Vitamin D supplementation increases IGFBP-1 production in ovarian cells

Effect of Vitamin D deficiency on steroidogenesis and follicular development (3)



Vitamin D sufficient women have a
2-fold decrease in AMHRII m RNA levels

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Merhi Z et al JCEM. 2014

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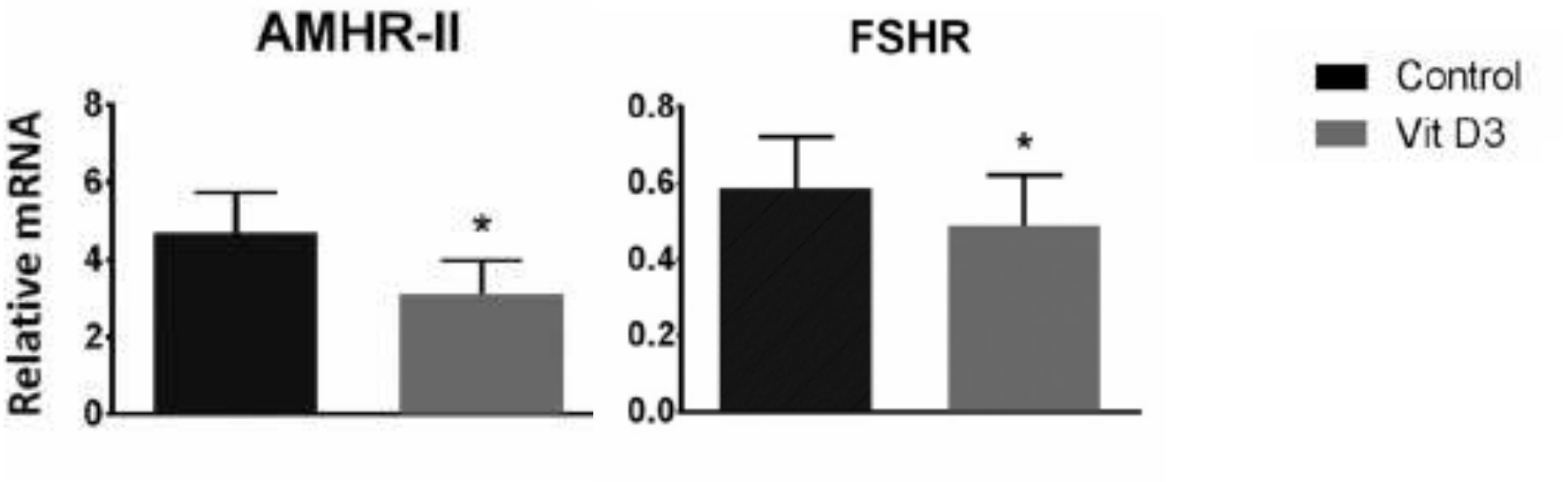
Effect of Vitamin D deficiency on steroidogenesis and follicular development (4)

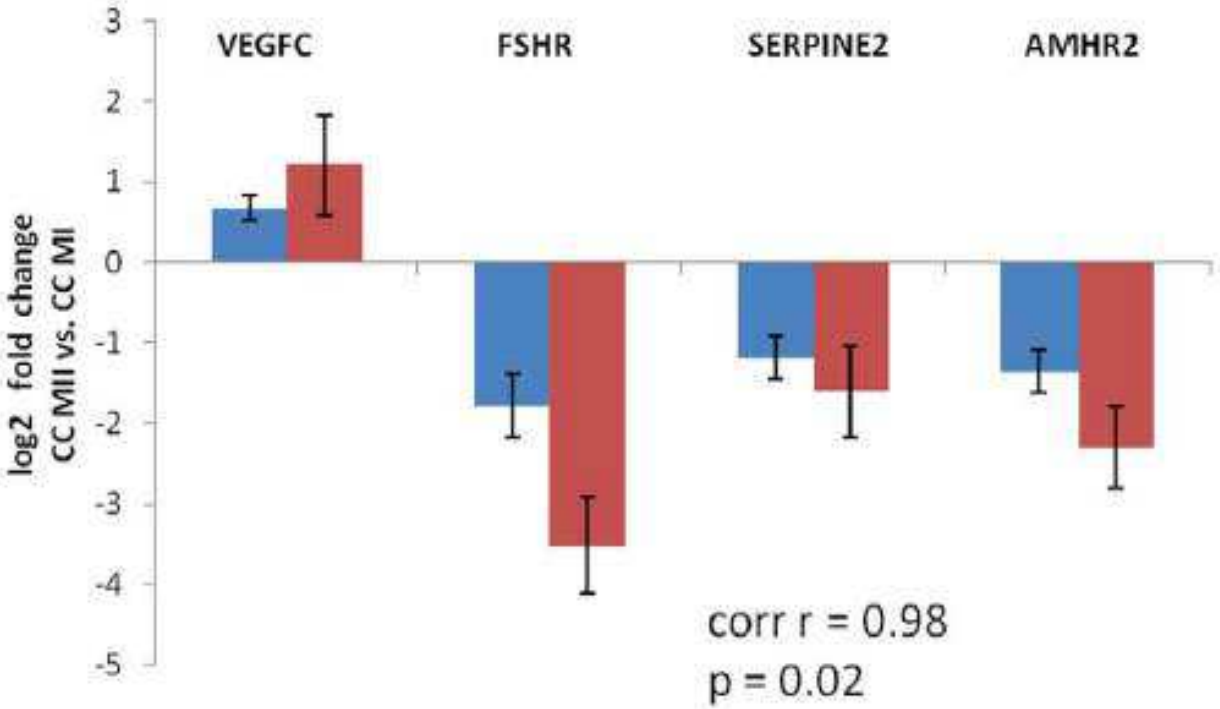


Merhi Z et al JCEM. 2014

Vitamin D supplementation reduced AMH-RII and FSH-R concentrations

Effect of Vitamin D deficiency on steroidogenesis and follicular development (5)

The role of AMHRII and FSHR in oocyte maturity



AMHR2 and FSHR are the most differentially expressed genes between MI and MII oocytes

Devjak R PLoS One. 2012;7(10):e47106.

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- Affecting endometrial receptivity

Effect of vitamin D on markers of ovarian reserve (1)

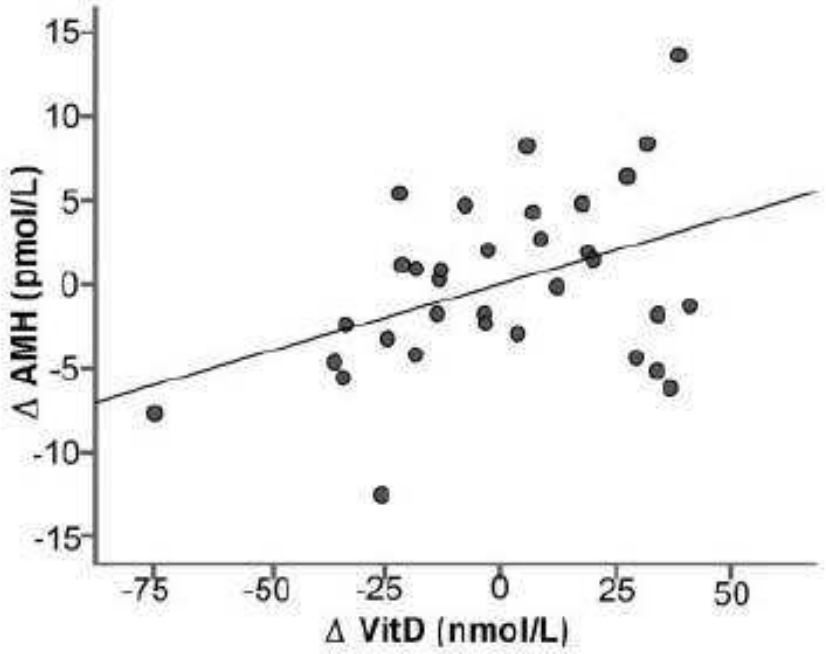

TABLE 2. The change in the level of AMH correlates with seasonal change in 25(OH)D levels of 33 women

	Model		Predictor	Partial	
Model no.	R	*P*	of ΔAMH	R	*P*
1	0.60	0.002	ΔVitD	0.38	0.030
			Initial AMH level	−0.53	0.002
2	0.62	0.007	ΔVitD	0.45	0.014
			Initial AMH level	−0.52	0.003
			Initial vitamin D level	0.21	0.271
			Age	0.20	0.297

Vitamin D levels correlate with AMH in women

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Dennis et al, JCEM 2012

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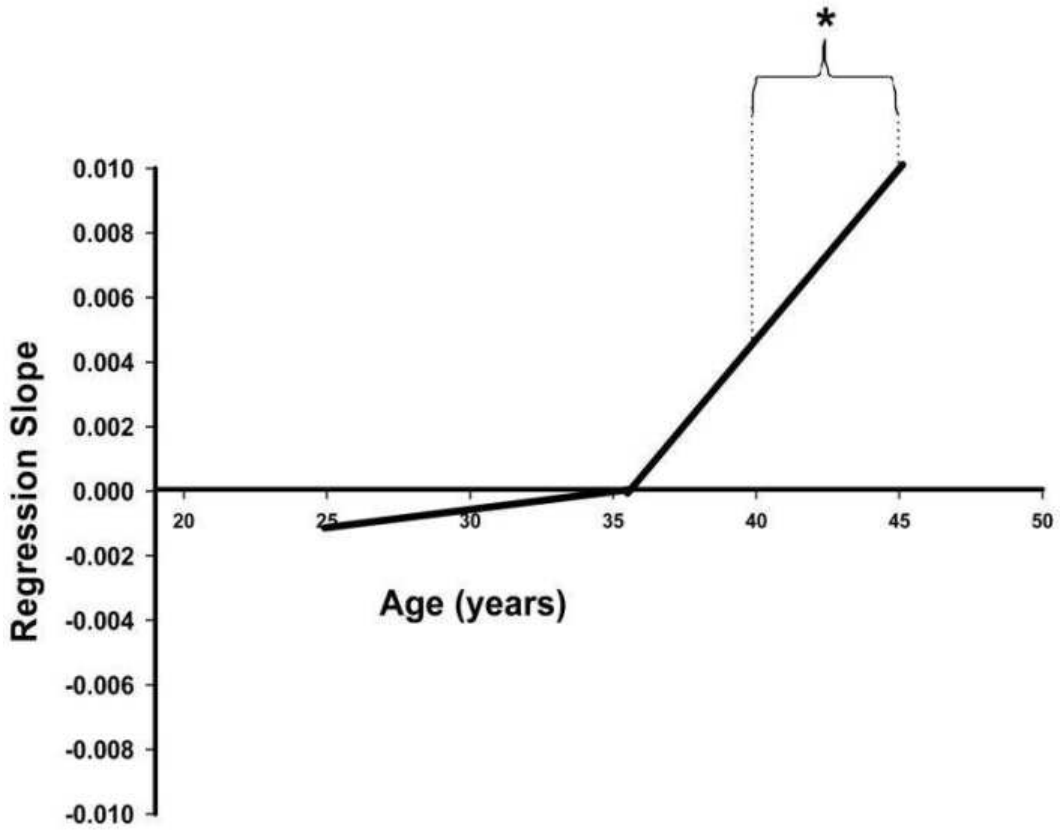
Effect of vitamin D on markers of ovarian reserve (1)



Vitamin D levels correlate with AMH only in women of advanced reproductive age

Merhi et al, Fertil Steril 2012

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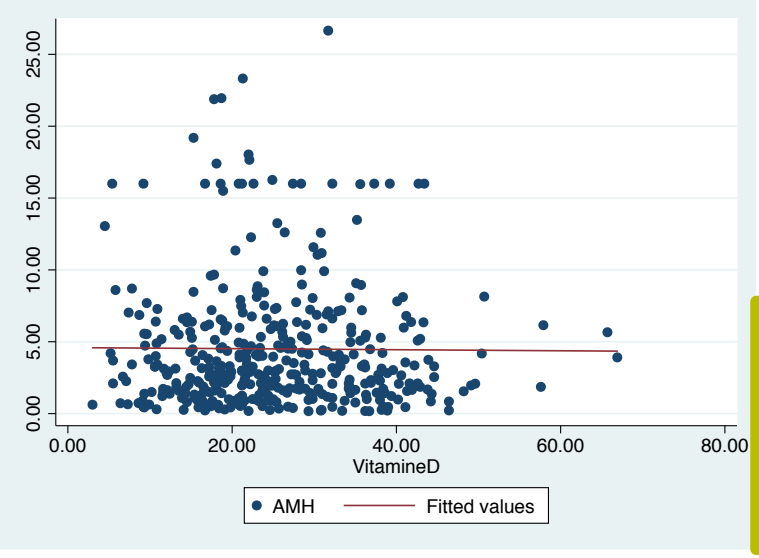
Vitamin D and ovarian reserve UZ Brussel

- ~400 women attending the unit
- AMH and 25-OH vitamin D measured on the same day



Source	SS	df	MS
Model	252.381715	2	126.190857
Residual	8784.60028	382	22.9963358
Total	9036.982	384	23.5338073

Number of obs	385
F(2, 382)	5.49
Prob > F	0.0045
R-squared	0.0279
Adj R-squared	0.0228
Root MSE	4.7954

AMH	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
VitDcat	.5740401	.513993	1.12	0.265	-.4365696	1.58465
AGE	-.1594923	.0509497	-3.13	0.002	-.2596693	-.0593154
_cons	9.289139	1.656239	5.61	0.000	6.032652	12.54562

Vitamin D levels do not correlate with AMH

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Vitamin D and endometrial receptivity (1)

The elective single embryo transfer (eSET) model

- 368 women with SET
- Age 18-36
- Evaluation of Vitamin D levels in relation to pregnancy rates

Polyzos et al, Hum Reprod 2014

Vitamin D and endometrial receptivity

The eSET model

	Vitamin D <20ng/mL	Vitamin D ≥20ng/mL	P value
	239	129	
Positive hCG, n(%)	124 (52)	86 (67)	**0.006**
Clinical pregnancy, n(%)	98 (41)	70 (54)	**0.015**
Live birth, n(%)*	78 (35)	61 (48)	**0.015**

Vitamin D deficient had 40% lower odds for pregnancy compared with normal levels

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Polyzos et al, Hum Reprod 2014

Vitamin D and endometrial receptivity

The frozen embryo transfer model

- Prospective cohort
- 280 women
- Frozen ET
- Measurement of Vitamin D levels on the day of ET and correlation with pregnancy rates

Polyzos et al, NCT01985672

Vitamin D and endometrial receptivity

The frozen embryo transfer model

	Vitamin D <20ng/ml	Vitamin D ≥20 ng/ml	P value
Number of patients	127	153	
Positive hCG	52 (41.3%)	74 (58.7%)	0.2[b]
Clinical pregnancy	41 (32.2%)	58 (37.9%)	0.3[b]

Polyzos et al. NCT01985672

Vitamin D levels do not affect pregnancy rates if FET cycles

Vitamin D and endometrial receptivity

The oocyte acceptor model

	Normal, >30 ng/mL	Insufficient, 20–30 ng/mL	Deficient, <20 ng/mL	*P*trend
Clinical pregnancy rate, %				
Unadjusted	74	42	35	.002
Adjusted	79	36	32	.001
Live-birth rate, %				
Unadjusted	57	34	31	.03
Adjusted	59	30	31	.04

Rudick et al., Fertil Steril 2014

Vitamin D status	Normal, >30 ng/mL	Insufficient, 20–30 ng/mL	Deficient, <20 ng/mL	*P*value
Implantation rate (%)	60.9	63.4	65.2	.894
Pregnancy rate (%)	70	69.9	73.9	.787
Ongoing pregnancy rate (%)	55.9	52.7	60.7	.533

Fabris et al., Fertil Steril 2014

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Vitamin D and endometrial receptivity

The euploid embryo and its implantation potential

	Ongoing pregnancy
Deficient <20 ng/mL	131 (63.6)
Insufficient, 20–29.9 ng/mL	133 (61.9)
Replete, ≥30 ng/mL	60 (62.5)

Franasiak et al., AJOG 2015

Vitamin D levels do not correlate with implantation of an euploid embryo

Vitamin D human endometrium or embryo quality

The euploid embryo and its implantation potential

- Retrospective study
- 298 embryos (113 patients)
- Embryo aneuploidy rate (New comprehensive chromosome screening (CCS) platforms)
- Evaluate pregnancy rates after single euploid blastocyst trasfer

Polyzos, Capalbo, Rienzi, Vaiarelli, Ubaldi

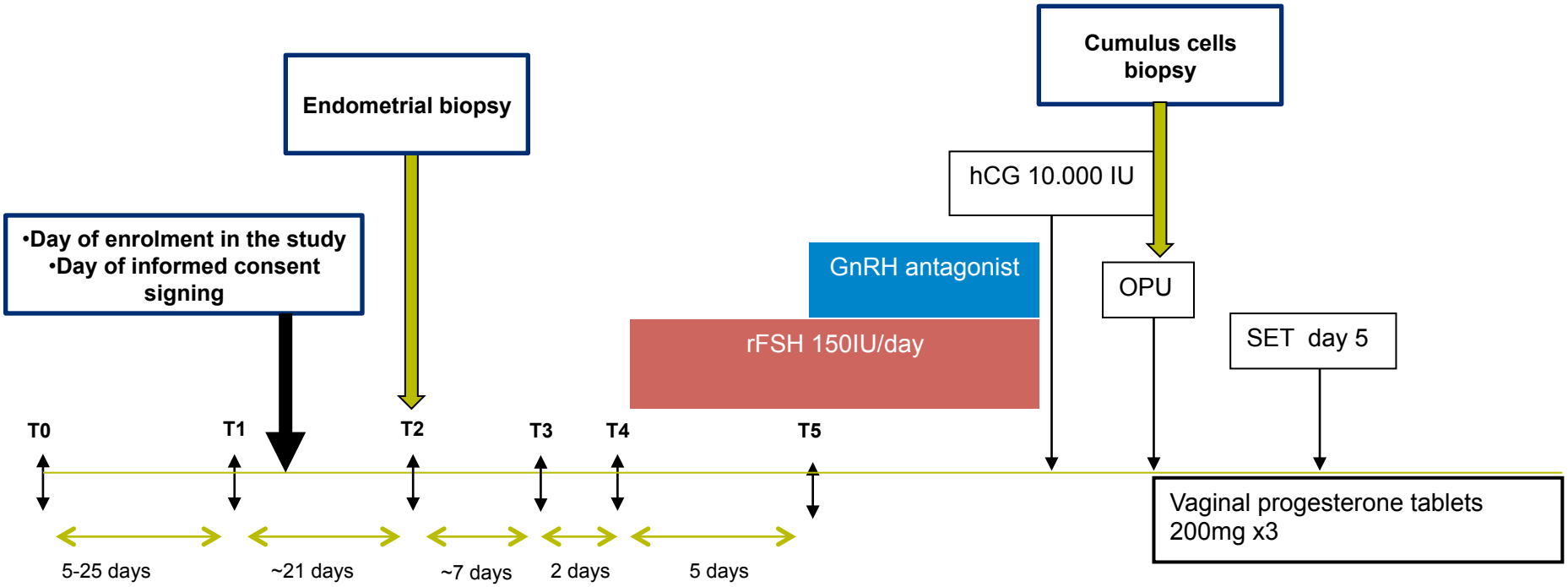
So……..

In which direction should we focus?

Translational research should be the answer to our queries

Translational research study in UZ Brussel

- Case control study (vitamin D deficient women and controls)
  - 36 women undergoing IVF/ICSI
- RNA sequencing from endometrial biopsies and cumulus cell biopsies



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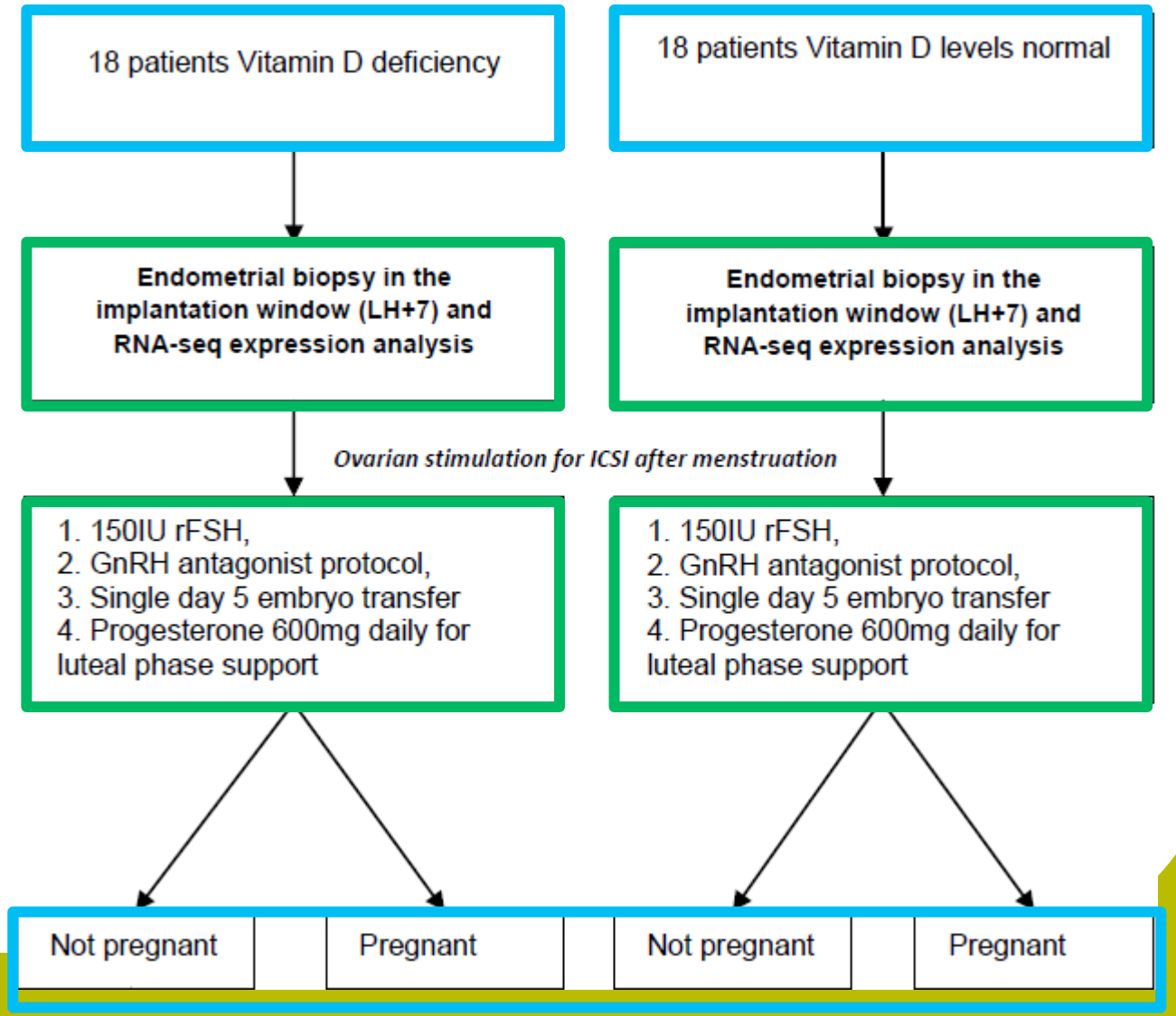
Aims and design

RNA sequencing in endometrial and cumulus cells

AIM 1:
Vitamin D deficient
vs.
controls

AIM 2:
pregnant
vs.
not pregnant



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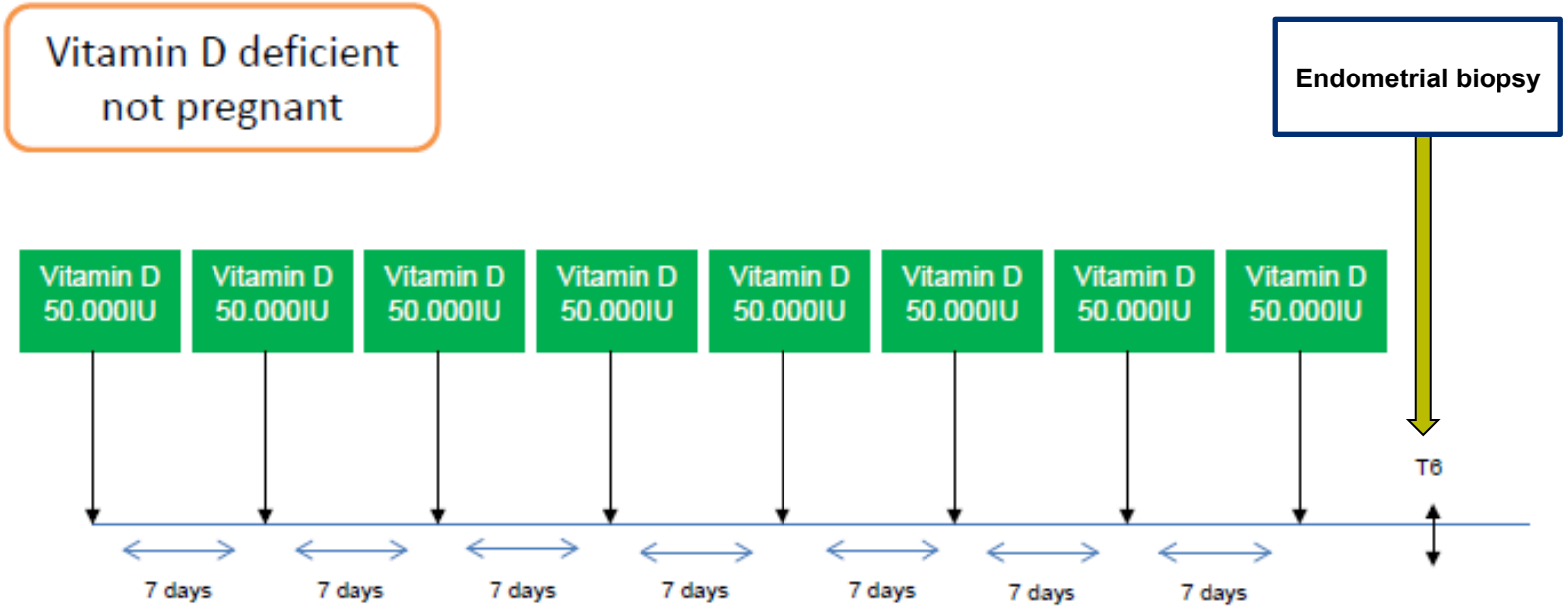
Aims and design

AIM 3:
endometrial gene expression profiling on the day of implantation, *before and after the supplementation of Vitamin D*



Conclusions

- Vitamin D is a trend
- We cannot exclude a link between vitamin D levels and ovarian folliculogenesis
- We should not forget the endometrium
- Ongoing prospective studies and translational research projects will shed light into this field
- Although data should be interpreted with caution research opportunities are excellent

In the meanwhile…..

LET THE SUNSHINE IN …… and maybe you can get easier pregnant