The 2023 Digital Learning Journey on Diabetes and Thyroid Disorders

Clinical considerations of endocrine disorders in pregnancy: from planning through birth

Endocrinology of fertility and sterility: preparing for a healthy pregnancy

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SCIENTIFIC SEMINARS INTERNATIONAL FOUNDATION

SAEM SOCIEDAD ARGENTINA DE ENDOCRINOLOGÍA Y METABOLISMO

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- Receipt of grants from Merck, Ferring Pharmaceuticals, MSD, IBSA, Theramex, Gedeon Richter, Roche, Beckmann Coulter
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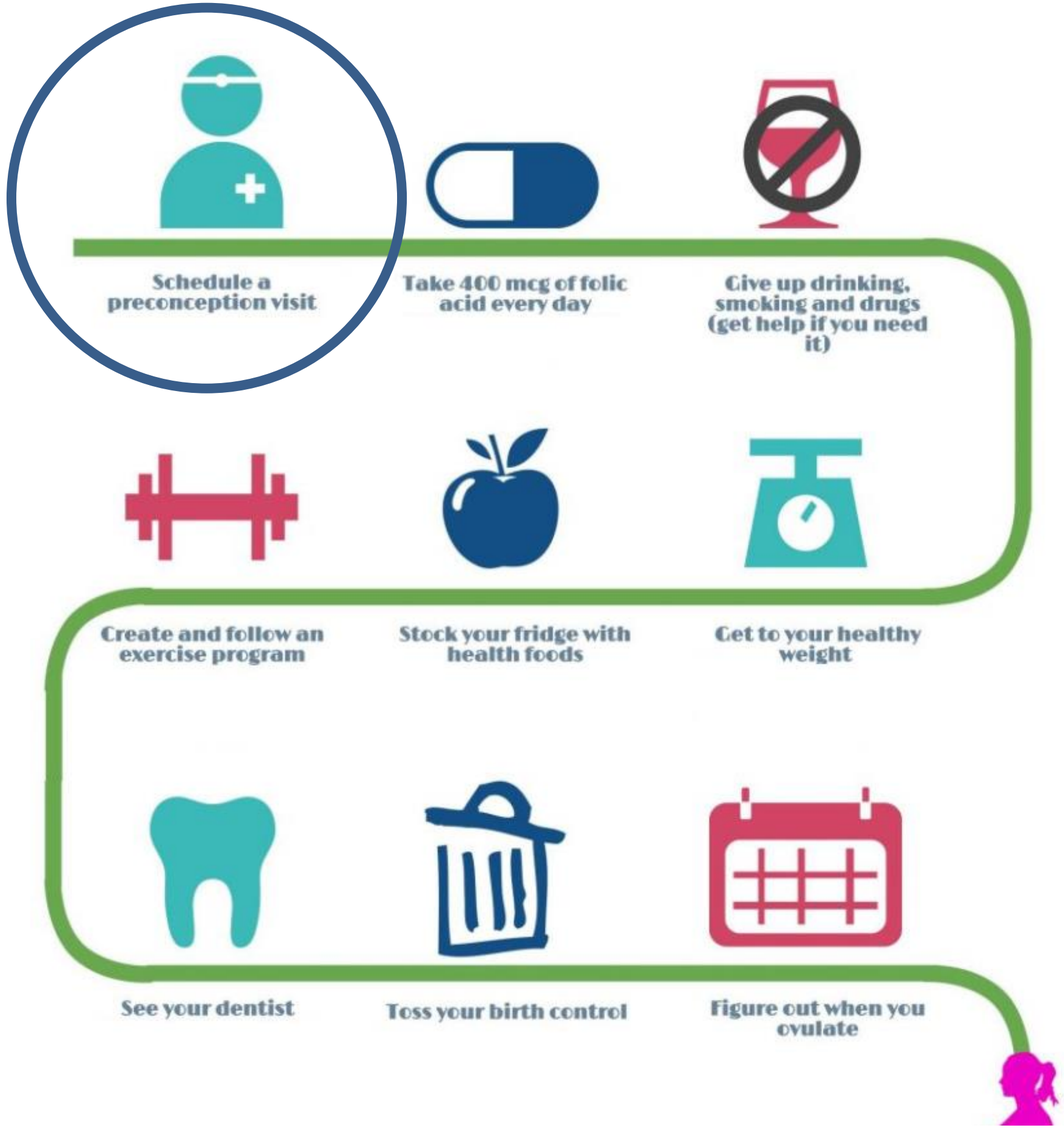
Preconception health refers to the health of people during their reproductive years



the goal of prepregnancy care is to reduce the risk of adverse health effects for the woman, fetus, and neonate by working with the woman to optimize health, address modifiable risk factors, and provide education about healthy pregnancy

What role we have in preconception health care

health history

previous pregnancy outcomes

Vaccinations

Medical conditions (STDs, diabetes, thyroid disease, high blood pressure, any other chronic disease)

Lifestyle and Behaviors (smoke, alcohol, drugs, environment, toxic substances)

Infertile patients are often «âgé» and with co-morbidities

Patients entering IVF program in Modena (n=1000)

	Female	Male
Age (M±SD)	36.4±6.7	38±8.4
Over 40, %	28 %	36 %
BMI	21.5±4.5	24.5±7.3
% obese	18 %	19 %
% smokers	23 %	24 %
Previous uterus/ovarian surgery %	15 %	na
Any chronic disease, %	18 %	15 %

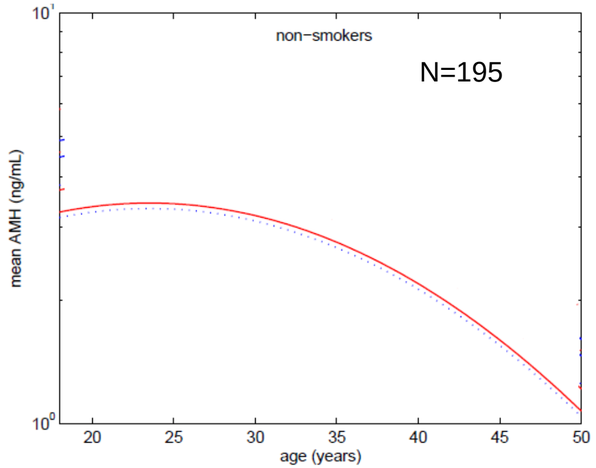
Preconception counselling as a great opportunity to improve patients' health

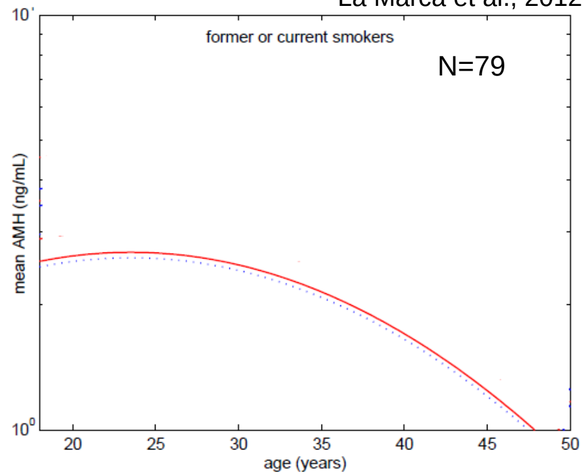
La Marca et al., 2020

Smoking is a cause of infertility and poor obstetric outcome

Reduced AMH levels in smokers

La Marca et al., 2012





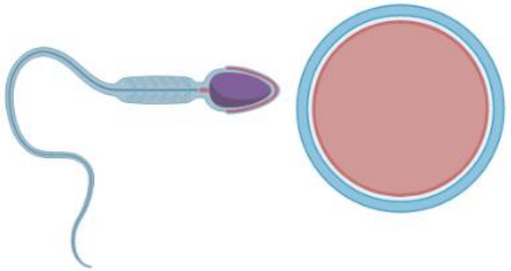
Marker for anticipated menopause

Adena M, 1982	n=15464	Age of menopause	**1.3 years** lower for smokers than non-smokers
Kinney et al., 2006	n=494		**2.2 years**
Cooper GS 1999	n=543		**0.8 years**

Smokers are more often infertile (O.R 1.6)	*Augood et al., 1998*
Smoking is associated to delayed conception	*Hull et al., 2000*
Smoking is associated to 5-fold increase in ectopic pregnancy	*Hull et al., 2000*
Smoking increases the proportion of aneuploid oocytes	*Zenzes et al., 1995*
Increase risk of trisomy 21 resulting from maternal meiotic nondisjunction	*Yang et al., 1999*
Reduced clinical pregnancy rate in IVF (OR: 0.56)	*Waylen et al., 2009*
Increased miscarriage rate (OR: 2.65)	*Waylen et al., 2009*

Air pollution and human reproduction

Reduced fertility



- Reduced sperm quality
- Luteal phase defects
- Reduced Female fecundability
- Increased risk of infertility
- Reduced embryo implantation rate
- Reduced chance of LB in IVF

(Legro et al., 2010; Slama et al 2013; Nieuwenhuijsen et al., 2014, Choe S 2018;)

Obstetrics complications

- Miscarriage
- IUGR
- Preterm birth

(Bobak et al., 2000; Stieb et al. 2012)

The OORExPO study

Retrospective, observational, cohort study

in the **Province of Modena** (Italy)

- Area: 2688 km^2
- 702,364 habitants

assessing the effect of air polluttants on ovarian reserve as measured by serum AMH

240 - 1200 inhabitants

180 . 240 inhabiants

50 - 180 inhabitants

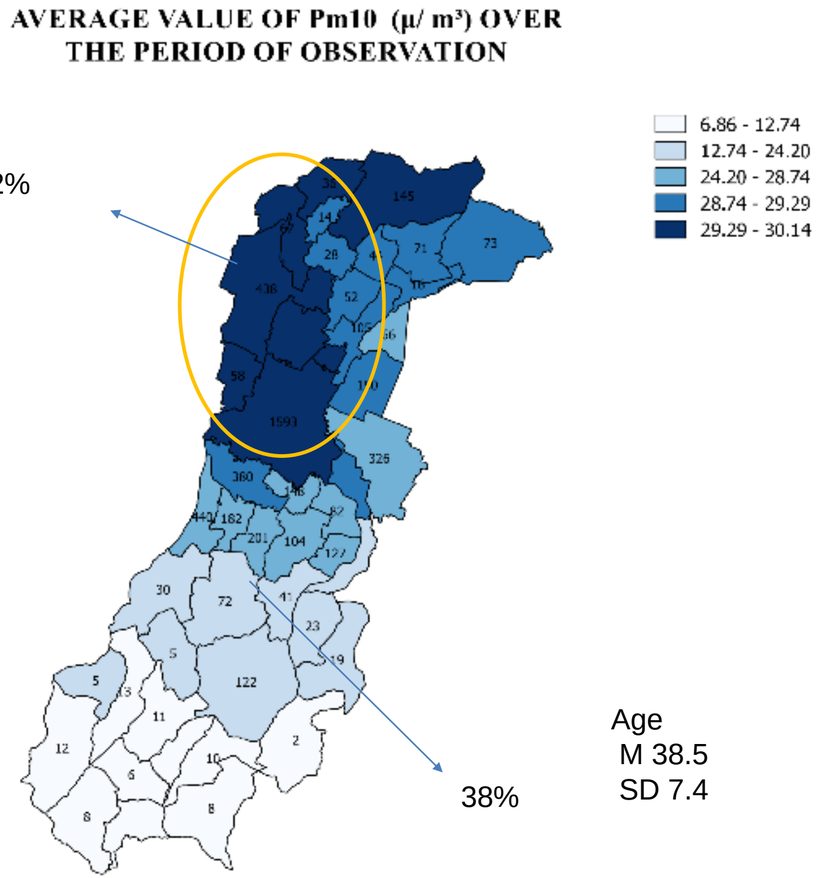
0 - 50 inhabitants

La Marca et al., Hum Reprod 2020

Low ovarian reserve was more frequent in areas with high levels of polluttants

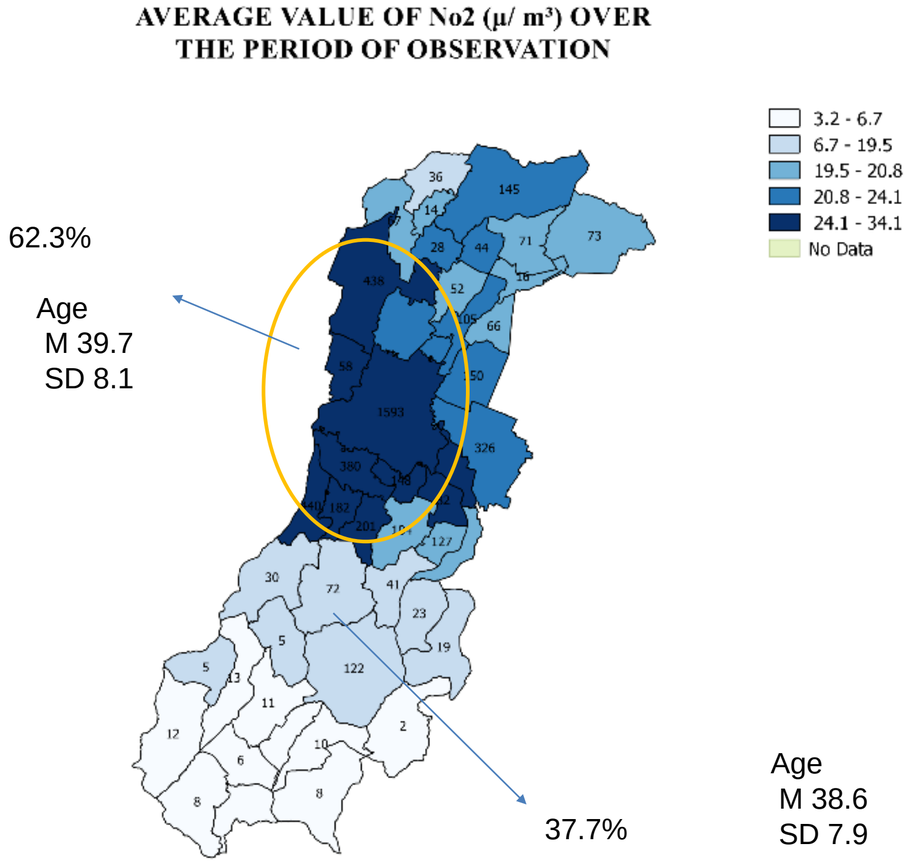
Low ovarian reserve: AMH < 1 ng/ml

PM10



relative risk 3.2±0.24, p=0.001

NO2



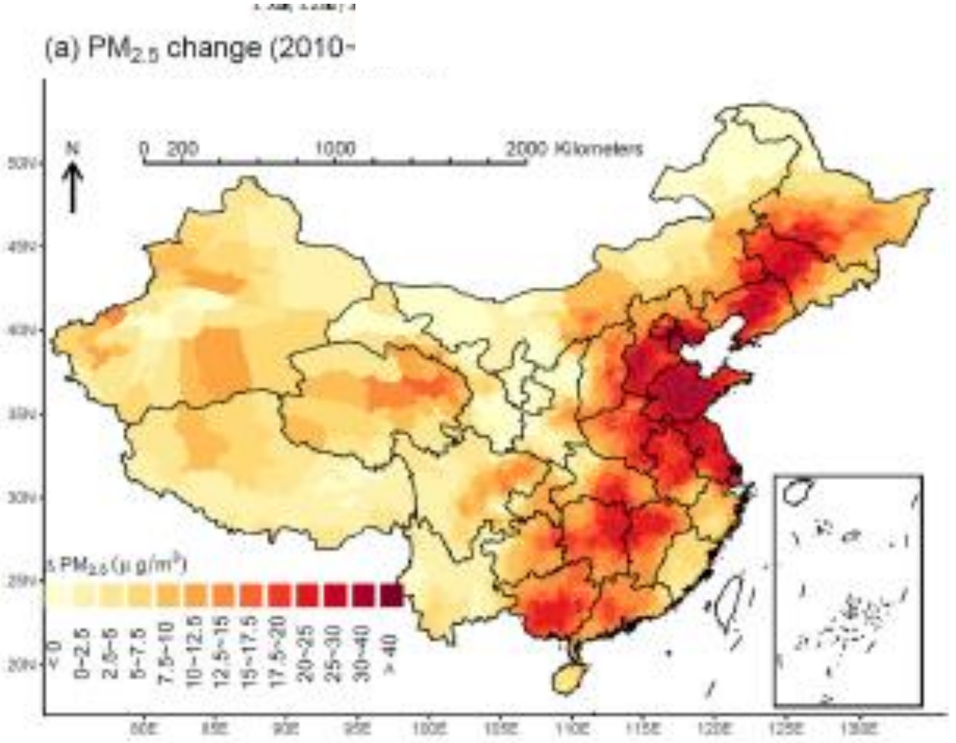
relative risk 3.31±0.24, p=0.001

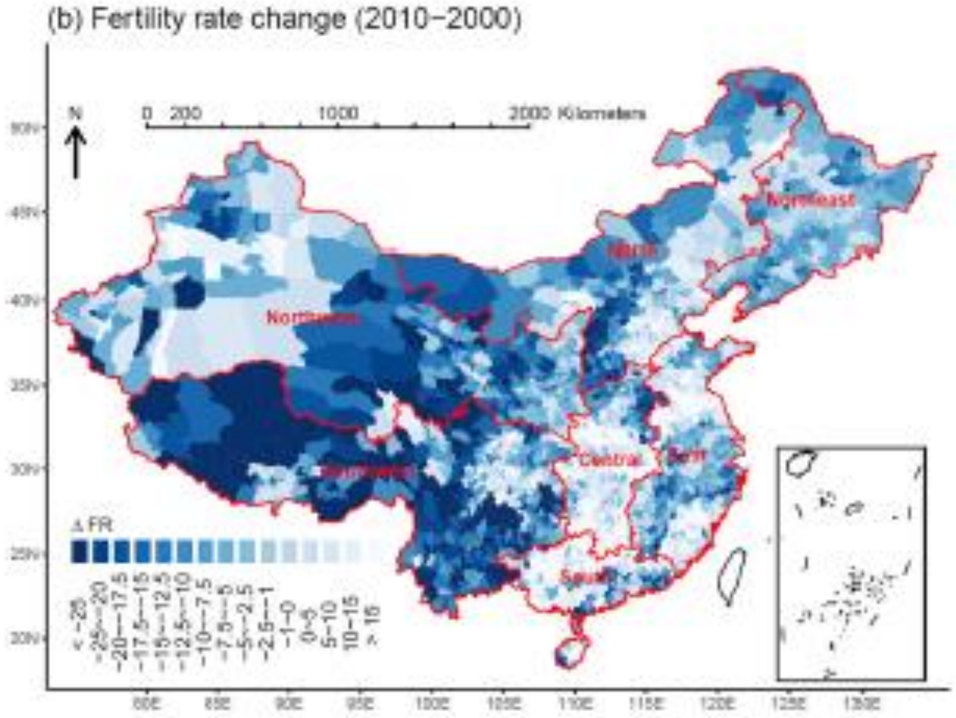
La Marca A, Hum Reprod 2020

Reduced fertility rate in areas with an increase in air pollution

Average $PM_{2.5}$ was 32 μg/m_3 in 2000 and 48 μg/m_3 in 2010

2000	13 million newborns and 308 million women aged 15-44
2010	13 million newborns and 328 million women aged 15-44





Increment in PM2.5 of 10 mcg/m3

Reduction in FR by 3.3%

Increase in PM2.5 from 2000-2010

-2.5 newborns / 1000 women

Xue et al., 2018

Increasing patient demand for testing the ovarian function

Ovarian reserve

- Hormonal assesment (day3FSH, AMH)
- TV ultrasound (AFC)

Ovulation

- Menstrual cycle logbook
- Urine LH assay
- Serum Progesterone
- Follicular Ultrtasound tracking

Anovulation and luteal phase defect may occurr in all women

The BioCycle Study (n=259)

- Women with regular cycles
- Aged 18-44, from the general population

LPD: luteal phase < 10 days or P < 10 ng/ml (d+6/+8)

2.7% of cycles were **anovulatory cycle**

8.9% of cycles showed **clinical LPD** (short cycles)

8.4% of cycles showed **biochemical LPD** (low P)

3.4% of women had **recurrent LPD**

	Total
No. of participants [*n* (%)]	259
Age (y)	27.3 ± 8.2[4]
Race [*n* (%)]	
White	154 (59.5)
Black	51 (19.7)
Asian	37 (14.3)
Other	17 (6.6)
BMI (kg/m^2)	24.1 ± 3.9
Biomarkers	
Total E2 (pg/mL)	
Follicular[5]	67.0 (40.0–142.0)[6]
Luteal[7]	107.0 (66.0–160.5)
Free E2 (pg/mL)	
Follicular[5]	1.05 (0.64–2.27)
Luteal[7]	1.63 (1.03–2.38)
Progesterone[8] (ng/mL)	7.0 (2.0–11.3)
LH[9] (ng/mL)	8.7 (5.5–17.4)
FSH[9] (mIU/mL)	6.5 (4.6–9.6)
Insulin resistance (mmol/L)	1.5 (1.1–2.1)

Schliep et al., JCME 2014

Obesity may increase the risk of anovulation

Paediatr Perinat Epidemiol. 2021 March ; 35(2): 174–183. doi:10.1111/ppe.12726.

Adiposity is associated with anovulation independent of serum free testosterone: A prospective cohort study

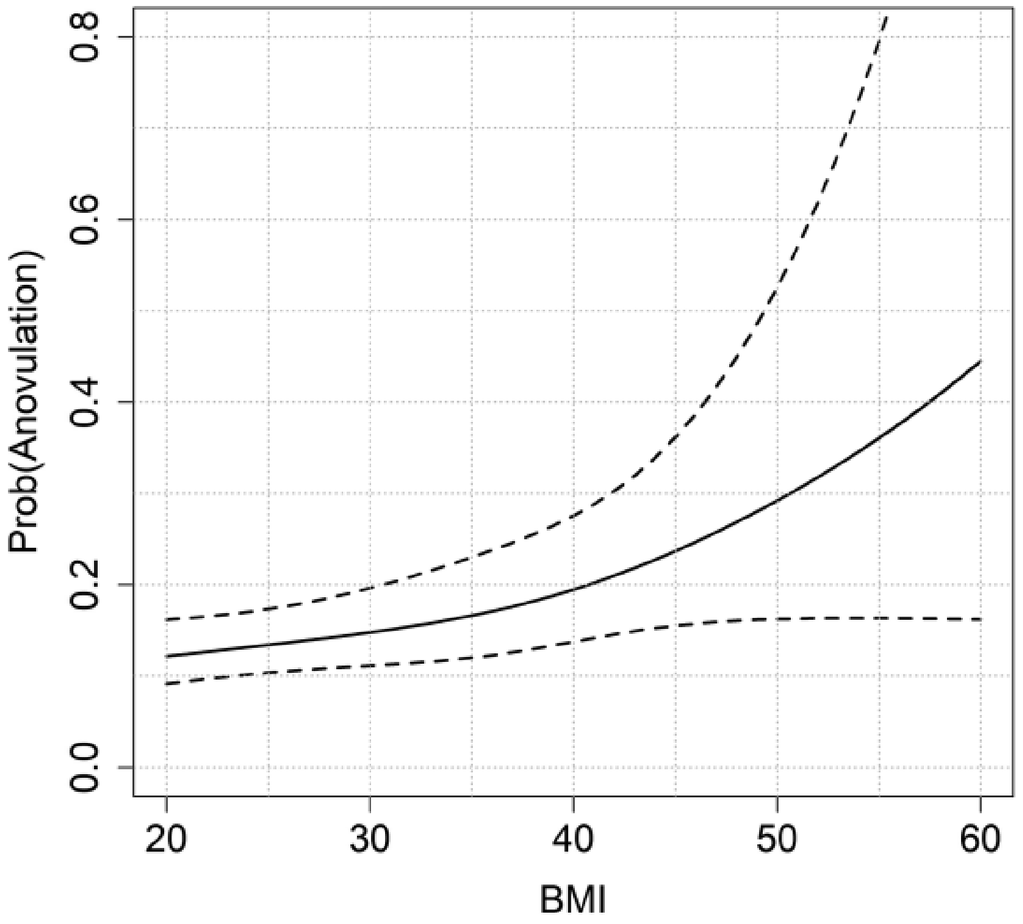
Michael S. Bloom[1,2], Neil J. Perkins[3], Lindsey A. Sjaarda[3], Sunni L. Mumford[3], Aijun Ye[3], Keewan Kim[3], Daniel L. Kuhr[3,4], Carrie J. Nobles[3], Matthew T. Connell[3], Enrique F. Schisterman[3]

the **EAGeR trial** (n=1200)

Women used fertility monitors for up to six consecutive menstrual cycles (3784 cycles)

Mean age: 28.4 (±4.8)

28.3% of women had at least one anovulatory cycle



Is ovarian reserve related to the probability of spontaneous pregnancy?

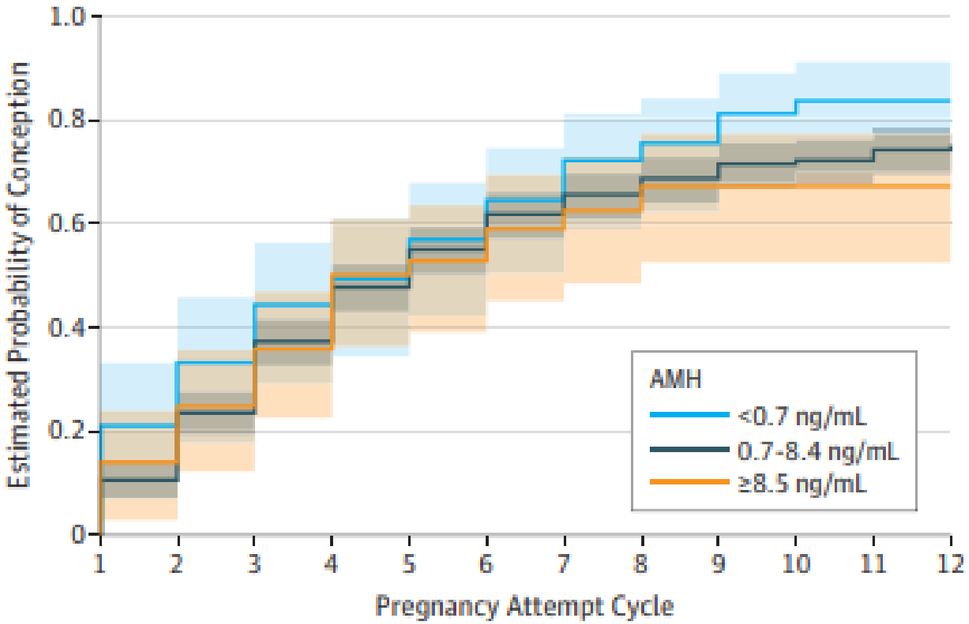
JAMA | Original Investigation

Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age

Anne Z. Steiner, MD, MPH; David Pritchard, MS; Frank Z. Stanczyk, PhD; James S. Kesner, PhD; Juliana W. Meadows, PhD; Amy H. Herring, ScD; Donna D. Baird, PhD, MPH

Prospective study on 750 women aged 30-44
Main outcome measure: AMH and d3FSH
Primary outcome: probability of positive urine pregnancy test at 12 months

A Cumulative probability of conception stratified by AMH levels



No. at risk by serum AMH level, ng/mL

<0.7	39	49	59	51	45	37	30	19	14	8	6	5
0.7-8.4	309	405	404	340	277	221	170	133	104	83	70	58
≥8.5	33	52	52	43	32	27	20	14	10	8	6	6

- “biomarkers indicating diminished ovarian reserve compared with normal ovarian reserve were not associated with reduced fertility”
- “These findings do not support the use of AMH or FSH tests to assess natural fertility for women”

Miscarriage risk increses with decreasing AMH

Antimüllerian hormone as a risk factor for miscarriage in naturally conceived pregnancies

533 pregnant women
24% miscarried

Variable	Total (N = 460)	No. of miscarriages (%) (n = 111)	No. of live births (%) (n = 349)	*P* value[a]
AMH (ng/mL)				.006
≤ 0.4	26	13 (50)	13 (50)	
>0.4 and <1	46	11 (24)	35 (76)	
≥1	388	87 (22)	301 (78)	
Age (y)				.09
30–34	342	76 (22)	266 (78)	
35–37	80	23 (29)	57 (71)	
38–40	29	7 (24)	22 (76)	
>40	9	5 (56)	4 (44)	

Risk of miscarriage for women with AMH < 0.4 ng/ml (age-independent)

RR 2.2; 95%CI 1.5,3.3

Age adjusted geometric mean AMH stratified by pregnancy outcome among women with known pregnancy outcome (*P*= .01).

		Geometric mean AMH,
Live birth/multiple live birth	349 (76)	2.6 (2.4, 2.9)

While AMH may not be an independent marker of fecundability, low AMH or diminished ovarian reserve may be a marker of reduced reproductive potential due to its association with pregnancy loss.

Schumacher & Steiner, Fertil Steril, 2018

Thyroid may largely affect ovarian function and fertility

Hypothyroidism & infertility (Ovulatory disturbances)

The prevalence of infertility is estimated to range 10% - 15%

- Hypothalamo-pituitary changes in Hypothyroidism → **impair LH response To GnRH-stimuli**
- **↑ TSH** (analogy to FSH)→**Pseudo-Feed back inhibition of FSH/LH**
- **High TRH→ Hyper-prolactinemia**
- **↓SHBG pool— Androgen Clearance ↓**
- **Ovulatory disturbance**
- **↑ Ovarian Vol**
- **↑ Stromal Depots**

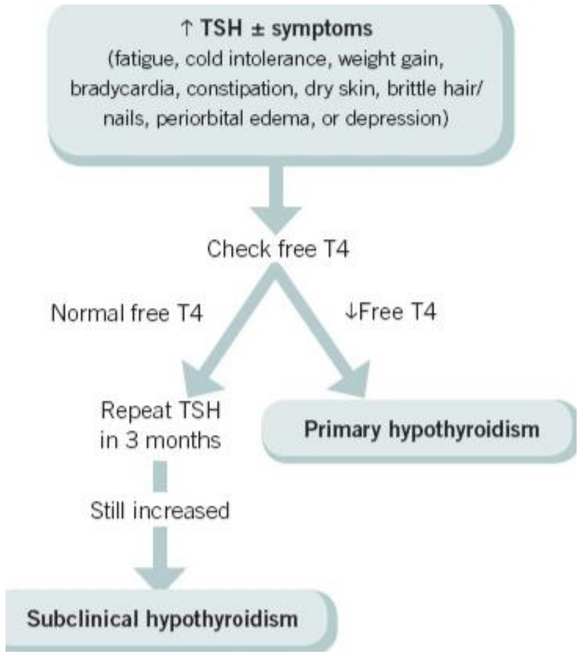
Kris Poppe et al.; Thyroid Disease and Female Reproduction; Clin Endocrinol. 2007;66(3):309-321.

Subclinical hypothyroidism: definition and prevalence

Subclinical hypothyroidism is much more common than overt hypothyroidism affecting at least 4.3% of the population, compared with 0.3% who are affected by overt hypothyroidism.

Subclinical hypothyroidism is primarily a laboratory diagnosis, and most patients have no symptoms or very mild ones

Diagnosis is based on clinical assessment, TSH measurement and if needed T4 and anti-TPO test



Chelsea S et al., 2020

Guidelines suggest the treatment of subclinical hypothyroidism in subfertile women

European Thyroid Journal

Guidelines

Eur Thyroid J 2020;9:281–295
DOI: 10.1159/000512790

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Accepted: November 4, 2020
Published online: January 21, 2021

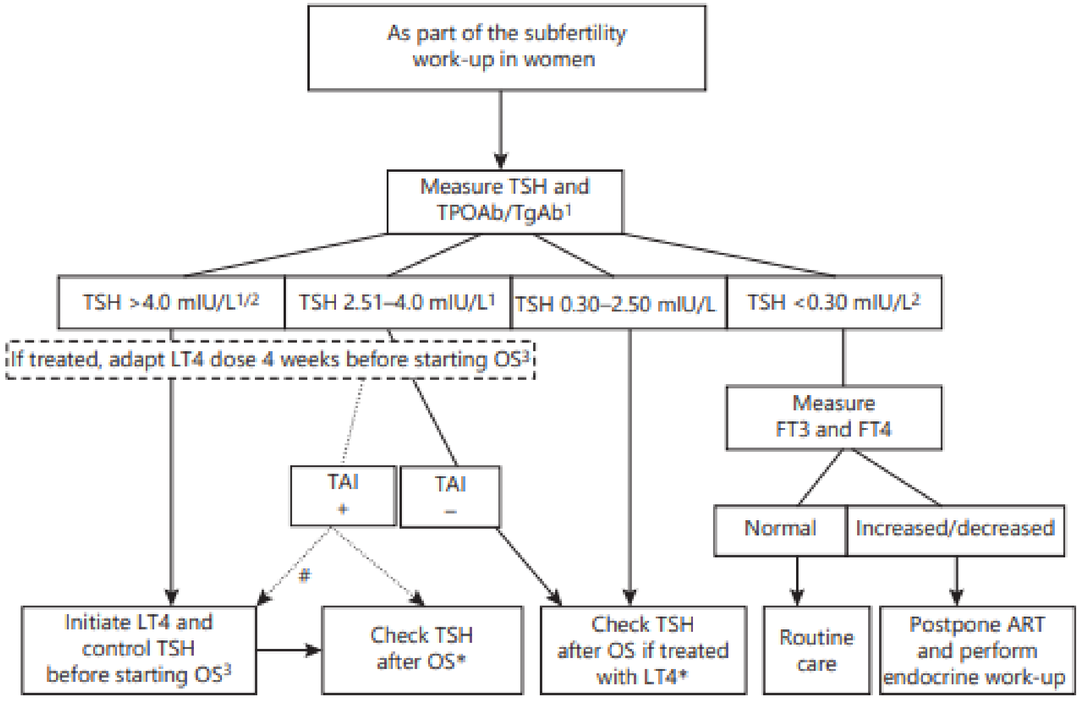
2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction

Kris Poppe[a] Peter Bisschop[b] Laura Fugazzola[c] Gesthimani Minziori[d]
David Unuane[e] Andrea Weghofer[f]

Women with serum TSH >4.0 mIU/L and overt hypothyroidism should be treated with LT4 independently of the presence of TAI.

In women with TSH levels >2.5 mIU/L and TAI, treatment with LT4 could be initiated in a case-by-case manner taking into account among other causes of female subfertility and clinical history

Eur Thyroid J 2021 Feb; 9(6): 281–295.



Recommended for:

- Subfertile women
- Infertile women
- Over 35y women
- Women with recurrent abortion
- Women undergoing IVF

Preparing for a healthy pregnancy: the reproductive endocrinologist point of view

Folic acid, healthy food and excercise should be recommended for women planning a pregnancy

Protection from infection and promotion of vaccination

A menstrual cycle logbook may be useful for understanding how regular is the ovulation, and ovulation tests may be considered if risk factors for anovulation (i.e. obesity)

Other than stop smoking, avoid harmful chemicals, metals, and other toxic substances around the home and in the workplace.

Ovarian reserve testing and spontaneous fertility is an understudied topic. While the possibility of having a positive pregnancy test seems not to be dependent on ovarian reserve, the miscarriage risk is higher when ovarian reserve is low

The screening of all women for thyroid abnormalities is not supported by strong evidence, but subfertile women may benefit from a prompt recognition of sublicinical hypothyrodism if associated to thyroid autoimmunity

Several lifestyle factors often occur together

Negative variables

Age >35

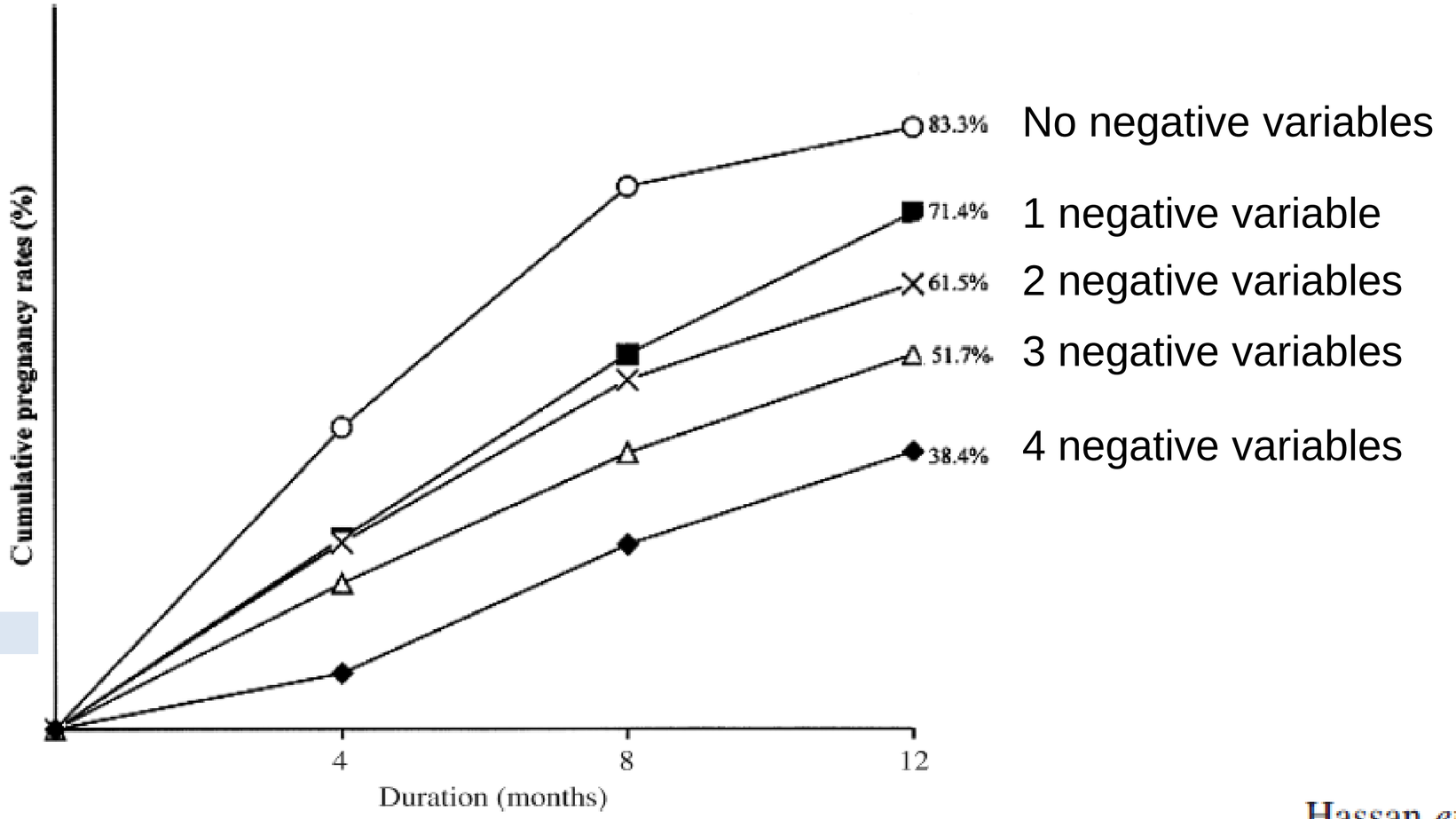
Smoking

Coffee, alcohol intake

High BMI

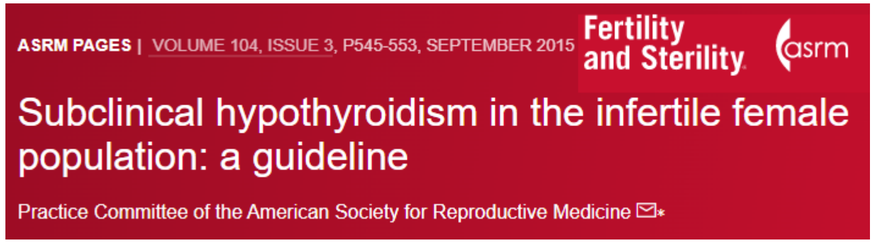
Cumulative negative impact on fecundity

Evidence for a negative synergistic effect



Hassan *et al.* (2004)

Guidelines suggest the treatment of subclinical hypothyroidism in subfertile women



There is evidence to suggest that inadequate treatment of subclinical hypothyroidism (SCH) can lead to infertility, miscarriage, and adverse obstetrical and neurodevelopmental outcomes

Haddow J.E.*N Engl J Med.* 1999; **341**: 549-555
Negro R.*J Clin Endocrinol Metab.* 2006; **91**: 2587-2591
Abalovich M.*Thyroid.* 2002; **12**: 63-68
Poppe K. *Hum Reprod Update.* 2003; **9**: 149-161
Arojoki M.*Gynecol Endocrinol.* 2000; **14**: 127-131

A. Nonpregnant women. Despite the findings that TSH levels are skewed in the general population, current evidence does not support treating nonpregnant women for subtle thyroid abnormalities (TSH <5 mIU/L).

B. Pregnant women. reference range of TSH in pregnancy is to be dependent on the trimester: 2.5 is the recommended upper limit of normal in the first trimester

C. Women attempting pregnancy. Because the reference range of TSH changes when a woman becomes pregnant, some advocate using pregnancy thresholds for the treatment of women attempting conception

THANK YOU

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