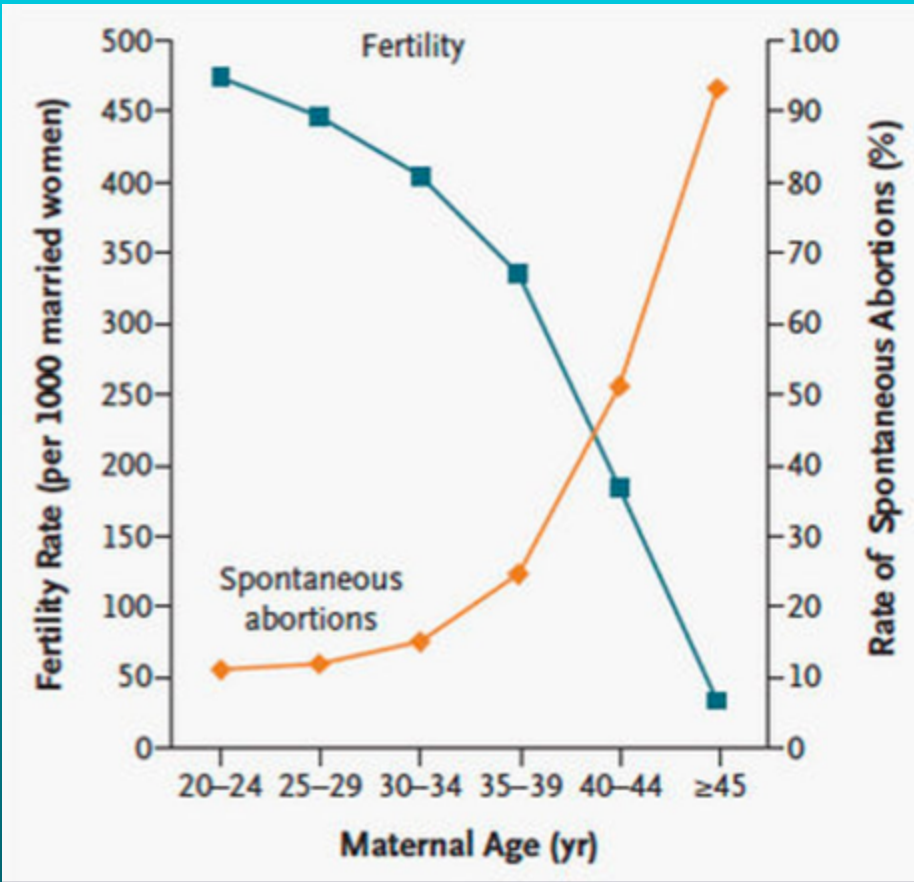


# Integrative Approaches to Recurrent Pregnancy Loss

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# Today:

- Overview of conventional approaches on RPL
- Underlying \*more naturopathic\* & research-informed reasons for pregnancy loss and how we can prevent future losses for our patients



# Age Related Incidence

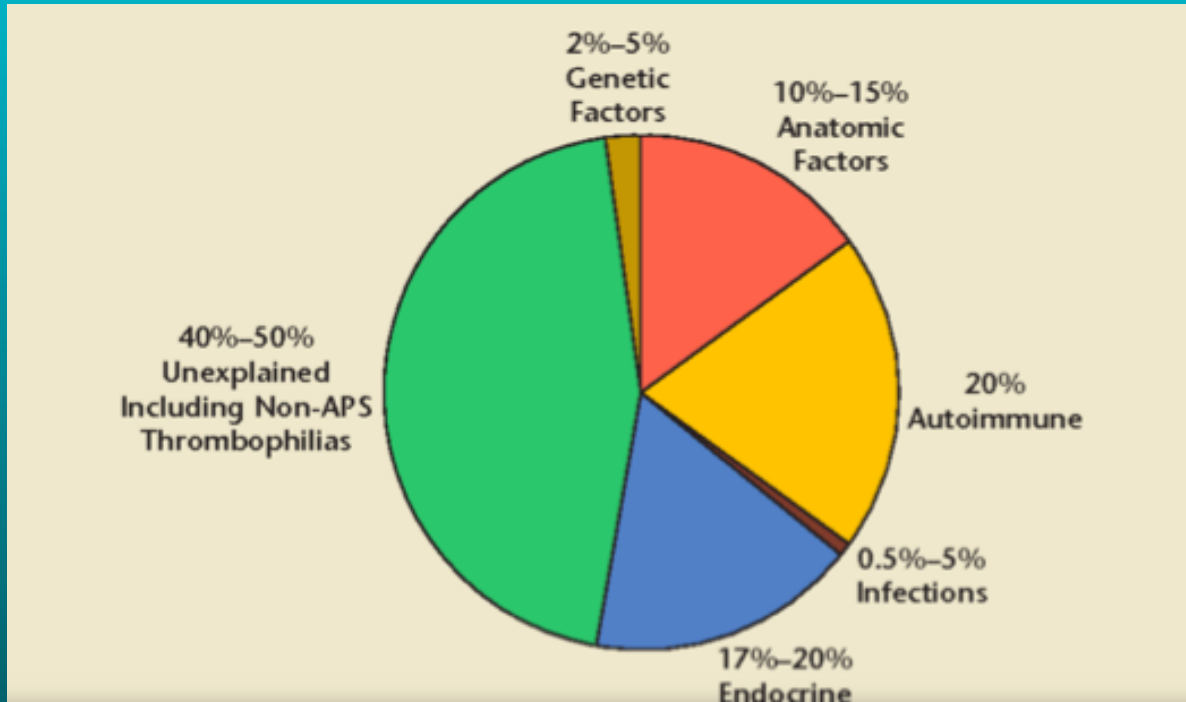
Maternal Age	Incidence of RPL
20	1/85
25	1/70
30	1/45
35	1/16
40	1/4
45	1/2

# What is RPL?

- Recurrent pregnancy loss is defined as 3 or more consecutive losses
- 2-5% of women are affected
- Usually after 2 losses, OBGYNs will generally initiate further investigation for underlying etiology

- Parental chromosomal abnormalities and anti-phospholipid syndrome are the only undisputed causes of RPL

# Most Common Causes



# Anatomic Factors

- Mullerian anomalies: septate, unicornuate, or bicornuate uterus
- Asherman's syndrome: scar tissue or adhesions in uterus
  - Intrauterine surgeries or IUDs
- Leiomyomas



# Genetic Factors

- Balanced translocations
  - Usually no signs/symptoms in the parent
  - Egg/sperm can end up with extra or missing genetic material which results in M/C
  - Solution: Keep trying or PGD test embryos

# Inherited Thrombophilias

- Factor V leiden
- Protein C/S
- MTHFR
- Homocysteine

# Autoimmune

- Anti-phospholipid syndrome
  - testing: lupus anticoagulant + anticardiolipin antibodies + anti- $\beta_2$  glycoprotein

# Infections

- Endometritis
- Other bacterial/viral/fungal/parasitic infections

# Endocrine Factors

- PCOS
- Hypothyroidism
- Luteal phase defects
- Diabetes mellitus

# Hypothyroidism

- RPL associated with a TSH > 2.5 mIU/L
- Study found 69% higher rates of miscarriage in women with TSH 2.5-5mIU/L
- Endocrinology society accepts and actively treats TSH above 2.5 in pregnancy (I suggest starting in preconception period!)

# In a test group of 100 women:

- TSH levels were significantly higher in the first trimester in women who had spontaneous abortion as compared to pregnant women who had successful pregnancies
- Hypothyroidism is associated with increased TRH production and hyperprolactinemia
  - This further leads to delayed luteinizing hormone response and inadequate corpus luteum formation
- By affecting the peripheral estrogen metabolism and decreasing SHBG production, hypothyroidism may affect fertility

# Hyperthyroidism

- Both early (miscarriage) and late (stillbirth) pregnancy loss were more common in women suffering from hyperthyroidism
- Inadequately treated hyperthyroidism in early pregnancy may have been involved in spontaneous abortion and undetected high maternal thyroid hormone levels present in late pregnancy may have attributed to an increased risk of stillbirth



# Hashimoto's

- Thyroid autoimmunity was higher in pregnant women with a history of RPL compared with healthy pregnant control population
- Following T4 treatment, there was no difference in prevalence of miscarriage between hypothyroid and euthyroid individuals with TPO Ab+

# Even when TSH is normal

- anti-TPO positive euthyroid females had a higher prevalence of infertility, anemia and preterm delivery
- Pre-pregnancy anti-TPO screening may aid in early identification of women at risk

# Hashimoto's

meta-analysis of 17 studies:

- Most studies (14 out of 17) showed double the rate of miscarriage in euthyroid women with TPO antibodies vs euthyroid women without antibodies

Unexplained

- The negative influence of age on oocyte quality may lead to a difficulty in conceiving for many couples
- Lifestyle factors: low body fat, excessive exercise, increasing prevalence of STIs, and smoking all have significant negative impacts on fertility
- Other factors: polycystic ovary syndrome, presence of uterine fibroids, and endometriosis
- Genetic influences that may limit the number of oocytes within the ovary
- Potentially reduced reproductive life-span due to postponing childbearing
- Environmental influences on reproduction are under increasing scrutiny
  - Dioxin exposure may be linked to endometriosis
  - Phthalate exposure may influence ovarian reserve
  - Bisphenol A may interfere with oocyte development and maturation

MTHFR?

# MTHFR

Fifty-seven of the total 173 (32.9%) patients were heterozygous for the MTHFR mutation, 14/173 (8.1%) were homozygous (allele frequency of 0.25). The prevalence of the MTHFR mutation in these women did not differ significantly from that in the control group of various women with uneventful pregnancies, where 30/67 (44.8%) were heterozygous and 6/67 (9.0%) were homozygous for the mutation (allele frequency 0.31; odds ratio for homozygous T/T 0.90, 95% CI 0.30-2.4).

There was no association between the trimester of pregnancy loss and MTHFR genotype. We conclude that the C677T MTHFR mutation is not a risk predictor in women with a history of early or late recurrent miscarriage.

# MTHFR Links to Homocysteine

OBJECTIVE: to investigate the association between the C677T polymorphism of the 5,10-methylenetetrahydrofolate reductase gene (MTHFR), serum homocysteine levels, and idiopathic recurrent miscarriage in a Middle-European white population.

CONCLUSION: Carriage of the mutant allele of the MTHFR C677T polymorphism is associated with elevated serum levels of homocysteine and idiopathic recurrent miscarriage.



# Genetic Factors

The aim of this study was to evaluate the effect of treatment in patients analyzed for recurrent spontaneous miscarriage with a diagnosis of a hereditary thrombophilia, the presence of antiphospholipid and/or autoimmune antibodies, and/or hyperhomocysteinemia (HHC) with/without methylenetetrahydrofolate reductase (MTHFR) polymorphisms. In total, 76 women with 2 or more embryonic or fetal losses were analyzed.

Of these, 49 (64.4%) women were found to have one or more thrombophilias and/or autoimmune antibodies and 33 (43.4%) women were found to have a MTHFR polymorphism and/or HHC. Since completion of the recurrent miscarriage analysis, 39 women conceived again.

All women with a thrombophilia were treated with low-dose aspirin plus low molecular weight heparin.

All women with previously diagnosed HHC and/or MTHFR polymorphisms were treated with folate and vitamin B(6) and B(12) supplementation.

In the thrombophilia group, 27 women conceived resulting in 20 successful pregnancies (74.1%) and 7 pregnancy losses (2 trisomy 16, 1 ectopic pregnancy and 4 unexplained miscarriages), i.e. an unexplained pregnancy loss rate of 14.8%.

In the HHC/MTHFR group 22 women conceived, resulting in 17 successful pregnancies (77.3%) and 5 pregnancy losses (1 trisomy 16, 1 Turner syndrome and 3 unexplained miscarriages), i.e. an unexplained pregnancy loss rate of 13.6%.

# Luteal Phase Defects

# Progesterone

## *Pro-gestation*

- Helps implantation of the embryo
- Plays a role in maintaining the pregnancy
- Inadequate secretion of progesterone in early pregnancy has been linked to miscarriage
- Progesterone supplementation has been used as a treatment for threatened miscarriage to prevent spontaneous pregnancy loss

# E & P

- Progesterone and estrogen have a great role along with other hormones
- Progesterone has been shown to stimulate the secretion of TH2 and reduces the secretion of TH1 cytokines which maintains pregnancy
- Supportive care in early pregnancy is associated with a significant beneficial effect on pregnancy outcome. Prophylactic hormonal supplementation can be recommended for all assisted reproduction technique cycles.
- Preterm labor can be prevented by the use of progesterone. The route of administration plays an important role in the drug's safety and efficacy profile in different trimesters of the pregnancy.
- Thyroid disorders have a great impact on pregnancy outcome and needs to be monitored and treated accordingly.

# Progesterone for ART VS Natural

- Progesterone production from the corpus luteum is critical for natural reproduction
- Progesterone supplementation seems to be an important aspect of any assisted reproductive technology treatment
- Luteal phase deficiency in natural cycles is a plausible cause of infertility and pregnancy loss

# Meta-Review

Purpose of Review: Progesterone is an essential hormone in the process of reproduction. Although the pharmacokinetics and pharmacodynamics of progesterone have been well studied, its use in the pathophysiology of pregnancy remains controversial. One of these concerns is the way in which the hormone is administered.

Recent Findings: in obstetrics, the most frequent uses of progesterone are in the treatment of threatened abortion, prevention of recurrent miscarriage, or in the support of the luteal phase in assisted reproduction programs, and in threatened preterm labor.

Randomized, control trials showed that women who received progesterone were statistically significantly less likely to have recurrent miscarriages.

There is currently, however insufficient information to allow recommendations regarding the optimal dose, route and timing of administration of progesterone supplementation.

Summary: Progesterone has been shown to be efficacious when continuation of pregnancy is hampered by immunological factors, luteinic and neuroendocrine deficiencies and myometrial hypercontractility. This may explain the reduction in the incidence of preterm birth in high-risk pregnant women using high-dosage prophylactic progesterone.

There is no evidence that first-trimester progesterone therapy improves outcomes in women with a history of unexplained pregnancy loss.

# Progesterone in Natural Pregnancy

BACKGROUND: Progesterone is essential for the maintenance of pregnancy. However, whether progesterone supplementation in the first trimester of pregnancy would increase the rate of live births among women with a history of unexplained recurrent miscarriages is uncertain

METHODS: double-blind, placebo-controlled, randomized trial to investigate whether treatment with progesterone would increase the rates of live births and newborn survival among women with unexplained recurrent miscarriage. 400 mg of progesterone administered no later than 6 weeks into pregnancy.

RESULTS: 836 women who conceived naturally within 1 year were randomly assigned to receive either progesterone (404 women) or placebo (432 women). The follow-up rate for the primary outcome was 98.8% (826 of 836 women). In an intention-to-treat analysis, the rate of live births was 65.8% (262 of 398 women) in the progesterone group and 63.3% (271 of 428 women) in the placebo group.

CONCLUSIONS: Progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with a history of unexplained recurrent miscarriages.



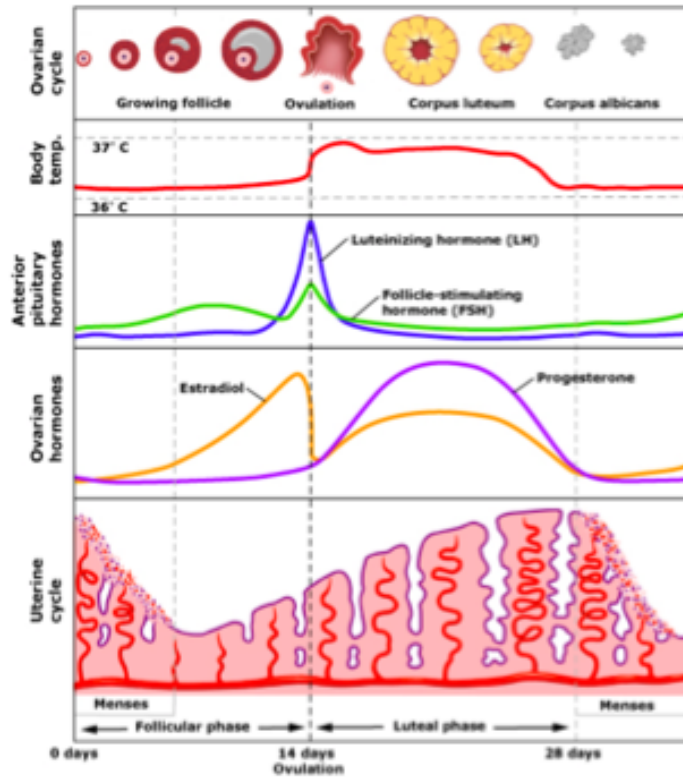
# Summary

- Progesterone may be useful in cycles of assisted reproduction
- Progesterone may not serve a purpose in natural cycles of TTC. Instead, it would be more beneficial to support egg quality
- In women who have immunological imbalances, luteal phase defects, neuroendocrine factors, and myometrial hypercontractility, progesterone may be beneficial

# Egg Quality Comes First!

Even before considering supplementing progesterone

# Review



# Egg Quality Cheat Sheet

- CoQ10 - 200 mg BID
- Acetyl L - Carnitine - 1500 mg QD
- Alpha Lipoic Acid - 600 mg QD
- Melatonin - 3-10 mg QD
- Resveratrol - 200 mg QD
- Green tea - 2-4 cups a day (same tea bag, and organic of course, ideal to avoid the bag)
- Turmeric (contradictory studies, different opinions)
  - stabilize immune function

Is the Uterus Sterile?

# Uterus

- Previously considered sterile
- Evidence that the origin of the endometrial microbiome might happen via seeding by vaginal microbes

# Vaginas

- In general, a lactic-acid driven environment (highly acidic) inhibits the growth and colonization of other pathogenic species
- Lactic acid can suppress the production of inflammatory mediators in the vagina

# Decrease Biodiversity

- Turns out that the optimal vaginal environment is not increased but actually limited biodiversity
- Increased colonization by potential pathogens like Streptococcus, Prevotella, Peptoniphilus, Ureaplasma and Dailister spp. Unregulated pro-inflammatory cytokines



# Lactobacillus Spp

- Miscarriage is associated with decreased prevalence of Lactobacillus spp in the upper reproductive system
  - Increased inflammation (untimely activation of pro-inflammatory pathways)
  - May impact implantation
  - May cause placental trophoblast invasion

# Group B Strep (GBS)

- Shown to be mediated by  $\beta$ -catenin-induced loss of vaginal epithelial barrier function and cellular detachment leading to exfoliation and subsequent bacterial ascension
  - Increased rates of miscarriage, stillbirth, and preterm labor

# E. coli (animal study)

- Ascending infection into the uterine cavity
- Activated intrauterine inflammation and subsequent preterm birth and neonatal brain injury

# What about the men?

Role of paternal DNA

# Sugar intake & Sperm motility

SSB intake was inversely related to progressive sperm motility. Men in the highest quartile of SSB intake ( $\geq 1.3$  serving/day) had 9.8 (95% CI: 1.9, 17.8) percentage units lower progressive sperm motility than men in the lowest quartile of intake ( $< 0.2$  serving/day) ( $P$ , trend = 0.03). This association was stronger among lean men ( $P$ , trend = 0.005) but absent among overweight or obese men ( $P$ , trend = 0.98). SSB intake was unrelated to other semen quality parameters or reproductive hormones levels.

- \* The more acidic your sperm is, the lower the motility
- \* When blood sugar levels surge, this causes destructive free radicals to surge in the bloodstream.
- \* Sperm are very susceptible to free radical cell damage, which creates fragmented DNA. This can cause infertility or abnormalities in the fetus which can lead to miscarriage or birth defects.
- \* There is no mechanism to repair this damage, so the damage is permanent until the sperm renew themselves, which takes about 3 months.

# Metabolic Syndrome effects on male fertility

120 participants: 75 male subjects with metabolic syndrome (MS) (38 fertile and 37 infertile), and a control group of 45 fertile males without MS. HOMA-IR, semen analysis, and biochemical measurement of seminal plasma insulin and glucose levels were carried out. Spermatozoal insulin gene and CIDEA gene expressions were performed by the RT-PCR method. The percentage of spermatozoal DNA fragmentation was also estimated.

# Key Take-aways

- The spermatozoal insulin and CIDEA gene expression, as well as the DNA fragmentation were significantly higher in the infertile MS group than the fertile MS group, and significantly higher in both the MS groups than in the control.
- Seminal glucose concentration showed significant positive correlation with seminal insulin level, spermatozoa insulin, CIDEA gene expression, and DNA fragmentation.
- Positive correlation between spermatozoa CIDEA gene expression and DNA fragmentation



# Oxidative stress and affects on sperm

\* Oxidative stress results in generation of ethenonucleoside, an oxidative product which inhibits nucleotide excision repair. Thus sperm DNA damage results in impaired embryonic development and recurrent miscarriages.

\* The role of sperm factor in recurrent assisted and spontaneous conception loss is now being realized. Earlier studies have suggested that pregnancy is unlikely to occur when sperm nuclear DNA fragmentation index values are above certain threshold value. However, a cut-off value for DNA damage in unexplained recurrent miscarriages cases is still not documented.

# DNA & ROS: The chief cause of loss of DNA integrity was oxidative stress.

- \* Smoking has been shown to increase seminal leukocyte concentration by 48% and cause a 107% increase in seminal ROS levels.
- \* Studies documented that extremes of exercise (too little and rigorous exercise) are linked with oxidative stress.
- \* Another group reported that obesity produces oxidative stress as adipose tissue releases pro-inflammatory cytokines that increase leukocyte production of ROS.
- \* Psychological stress results in decline in semen quality. Psychological stress has also been reported to result in poor sperm quality which was mediated by supraphysiological ROS levels and low antioxidant levels

# DNA fragmentation

The percentage of sperm DNA fragmentation and the amount of free radicals in the experimental group were significantly higher than the control group ( $P < 0.001$ ). Antioxidant levels were lower in the experimental group compared to the control. **Spouses of men with lower sperm motility and higher DNA fragmentation had a higher chance of spontaneous miscarriage when compared to the control group.** The results of this study support the hypothesis that sperm DNA fragmentation is a major contributor to spontaneous miscarriage

# Sperm DNA fragmentation

- Study from a private IVF clinic that review 475 cycles
- Groups were divided into SDF <30 or above 30%
- What they found:
  - Fertilization rates were similar between the two groups
  - Lower rates of cleavage speed (how quickly the embryos divided)
  - Lower quality Day 3 embryos
  - Similar pregnancy rates
  - 2.5x miscarriage rate!!!

# Conclusions...

Higher SDF is correlated with poor embryo development, lower implantation rate, and higher miscarriage rate in non-male factor infertility intracytoplasmic sperm injection cycles. Since defects in sperm may be hidden, the SDF test can bring additional information to the sperm quality evaluation of men with unknown infertility history.

# Things that can lead to male factor infertility

Infections

Elevated testicular temperature

Recreational drugs

Smoking

Alcohol

Stress

Diet

Environmental pollutants

Advanced age

Varicocele

# Enhance the sperm

CoQ10 - 400-1200 mg

Vitamin C - 1000-2000 mg

Acetyl-L-carnitine - 100-400 mg

selenium 100-200 mcg

Vitamin E - 200-1200 IUs

Omega 3 - 2000 IUs

Folate - 1-2 mg

Zinc - 10-50 mg

# In conclusion...

- There are many factors related to RPL- Many of which we can address through naturopathic medicine, during pre-conception phase
- Progesterone can be useful in some cases, after you've addressed ALL the underlying causes that can be related to low progesterone levels
- Address and optimize epigenetic factors- not just MTHFR but additional polymorphisms that can cause hyperhomocysteinemia
- Support the vaginal & uterine microbiome which includes less biodiversity, not more
- Make sure to take into equal consideration male factors for early and recurrent pregnancy loss



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