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BESINS HEALTHCARE SCIENTIFIC LITERATURE REVIEW – April 2021

Must Read Articles in Women's Health

Pregnancy maintenance (TM & RM)

Sporadic pregnancy loss and recurrent miscarriage. Devall A.J. PhD., Coomarasamy A. MD.

Best Practice & Research Clinical Obstetrics and Gynaecology 69 (2020) 30-39

Pubmed Link: 10.1016/j.bpobgyn.2020.09.002

Menopause Hormone Therapy (MHT)

Lessons from KEEPS: the Kronos Early Estrogen Prevention Study. Miller V.M. *et al.*

Climateric 2021, 24 (2), 139-145

Pubmed Link: 10.1080/13697137.2020.1804545

Other Articles of Interest - Women's Health

Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials	The EPPIC Group Lancet 2021; 397: 1183–94	See full comments provided by Paul in email from April 6th 2021
Sporadic Miscarriage – evidence to provide effective care	Coomarasamy A *et al* The Lancet 397: 1668 - 1674	High-quality evidence that vaginal micronised progesterone increases livebirth rates in women with early pregnancy bleeding and a history of miscarriage

Must Read Articles in Men's Health

Testosterone Replacement Therapy (TRT)

Erythrocytosis in a large cohort of trans men using testosterone: a long term follow-up study on prevalence, determinants and exposure years. Madsen M.C. *et al*.

Journal of Clinical Endocrinology and Metabolism. 2021

Pubmed Link: 10.1210/clinem/dgab089

Other Articles of Interest Men's Health

YouTube as a Patient Education Resource for Male Hypogonadism and Testosterone Therapy	Warren CJ *et al* Sex Med 2021 9	Discusses the unreliable information on hypogonadism and TRT that patients are accessing on Youtube and the importance of accurate patient education being made available to patients by doctors and through academic societies
Testosterone Therapy and Cardiovascular Risk: A Critical Analysis of Studies Reporting Increased Risk	Khera M *et al* J Sex Med 2021 18(1):83-98.	This review article looks at the studies published since 2013 that suggest an association between TRT and increased CV risk. The authors critically appraise these articles and indicate that many were not well designed CT's but rather Post -hoc analysis of cohort data. Caution is advised when selecting patients and emphasis placed on the importance of measuring pre -treatment T levels and continuous monitoring.

Title	Authors	Journal and Issue	Article Type
Sporadic pregnancy loss and recurrent miscarriage	Devall A.J. PhD., Coomarasamy A. MD.	Best Practice & Research Clinical Obstetrics and Gynaecology 69 (2020) 30-39	Review

What this review brings: While PRISM and PROMISE Trials are well cited within medical plans for Utrogestan, this review reinforces the important evidence to support the use of vaginal micronised Progesterone (P4) in the threatened and recurrent miscarriage (TM & RM) patient population.

Background:

- ~15% of Clinically recognised Pregnancies end in a miscarriage.
- Miscarriage has a negative impact on psychological and physical wellbeing.
- Important to note is that half of all miscarriage including those of a recurrent nature are due to chromosome abnormalities (aneuploid).
- ~140,000 women miscarry in the UK per year.
- ~ Economic burden miscarriage in the UK is £471 million (€547 million).
- Risk factors for miscarriage include Demographic, Lifestyle, Clinical and Environmental.
- Well identified major risk factor is the number of previous miscarriages and vaginal bleeding.
- P4 is essential to the establishment and maintenance of Pregnancy.
- Luteal Phase Defect (LPD), a Progesterone related problem is thought to be one of the main causes of a genetically normal (euploid) miscarriage.

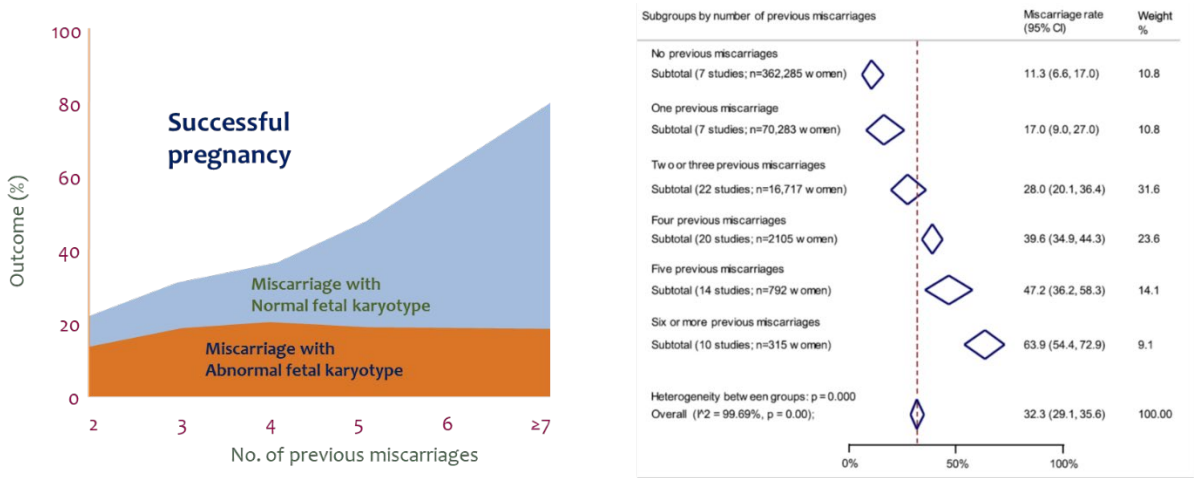

Figure 1: Risk of miscarriage by the number of previous miscarriages: a meta-analysis

Effectiveness of progesterone treatment in recurrent miscarriage:

- 8 studies examined the effectiveness of Progestogens in women with a history of recurrent miscarriages, examining live birth rate (LBR) outcomes or ongoing pregnancy rate (OPR).
- 6 of these trials were of a small sample size and 1 low quality.
- Largest, High Quality Trial: PROgesterone in recurrent MIScarriage (PROMISE), a double blind, randomized, placebo-controlled study of 836 subjects.

- Women were randomized to either vaginal Progesterone 2 x 200mg (Utrogestan) twice daily (800mg per day) or placebo from positive pregnancy test until **12 weeks** of pregnancy.
- Primary outcome was LBR ≥ 24 weeks.
- Primary analysis found LBR was 66% (262/398) in the P4 group versus 63% (271/428) in the placebo group. (RR 1.04, 95% CI 0.94 -1.15). The 3% higher life birth rate was reported as not statically significant due to a large P values (P=0.45).
- A pre-defined subgroup analysis was completed consisting of 2 groups of women: Group 1: 3 miscarriages and Group 2 ≥4 miscarriages.
- A further analysis for women with 3, 4, 5 and ≥ 6 miscarriages was analysed for hypothesis generation to determine if a biological gradient existed within these groups. **The analysis appears to suggest a trend towards increased benefit with increasing numbers of miscarriages.**

Effectiveness of progesterone treatment in threatened miscarriage:

- 8 clinical trials have been conducted looking at the effects of progestogens on the outcome of LBR or OPR in women with threatened miscarriage.
- A meta-analysis of these trials indicated a benefit for progestogens in the improvement of live birth or ongoing pregnancy.
- Important to note is the quality and size of the trials was variable with 6 trials have less than 150 women.
- **2 studies looked at the effects of dydrogesterone but the evidence of their effectiveness cannot be considered reliable due to low quality study design (Single centered, open label, no placebo control).**
- The largest trial was **PR**ogesterone **I**n **S**pontaneous **M**iscarriage (PRISM): a double blind, placebo controlled trial with excellent follow up.
- 4153 women were randomized to the trial.
- Treatment was 2x200mg of vaginal progesterone twice daily (800 mg/day) or placebo from the time of presentation with early pregnancy bleeding during the first 12 weeks of pregnancy to **16 weeks** of pregnancy.
- Primary endpoint was LBR at ≥ 34 weeks.
- LBR in the progesterone group was 75% (1513/2025) versus 72% (1459/2013) in the placebo group. (RR 1.03, 95% CI 1.00-1.07).
- A number of other pre-defined sub analysis were examined.
- The subgroups showing the most benefit from Progesterone use were as follows:
    - ✓ Women with ≥ 1 miscarriage and current pregnancy bleeding, live birth rates of 75% (689/914) with progesterone versus 70% (619/886) placebo.
      (**RR 1.09, 95% CI 1.03 -1.15**)
    - ✓ Women with ≥ 3 miscarriages and current pregnancy bleeding had a live birth rate of 72% (98/137) with progesterone versus 57% (85/148) with placebo.
      (**RR 1.28, 95% CI 1.08-1.51)**
    - ✓ Both pre-defined and post-hoc analysis indicate a relationship between the number of miscarriages and the beneficial effects of progesterone.

Types and safety of progesterone used in early pregnancy:

PROMISE and PRISM trials used vaginal micronized progesterone and the safety profiles observed in these studies are not applicable to all progestogens such as dydrogesterone or 17-hydroxyprogesterone.

PROMISE Trial: No difference was seen between the treatment and placebo group for the outcomes of any genetic anomaly and genital congenital anomaly.

PRISM Trial: No difference was seen between women treated with vaginal micronized progesterone and those receiving placebo for the outcome of congenital, familial and genetic disorders and no difference in the number of terminations.

Summary:

- **Current evidence indicates a positive effect of vaginal progesterone supplementation in early pregnancy that seems to be dependent on the number of miscarriages (see Fig 2.)**
- No benefit has been seen for women with early pregnancy bleeding without history of previous miscarriage
- **Early pregnancy bleeding with a previous history of ≥ 1 miscarriage identifies high risk women that could benefit from vaginal micronized progesterone therapy.**

Suggested therapy for high-risk pregnant women, is 2 x 200mg (400mg) of vaginal micronized progesterone twice daily (800 mg/day) initiated at presentation of vaginal bleeding and continued for 16 weeks of gestation.

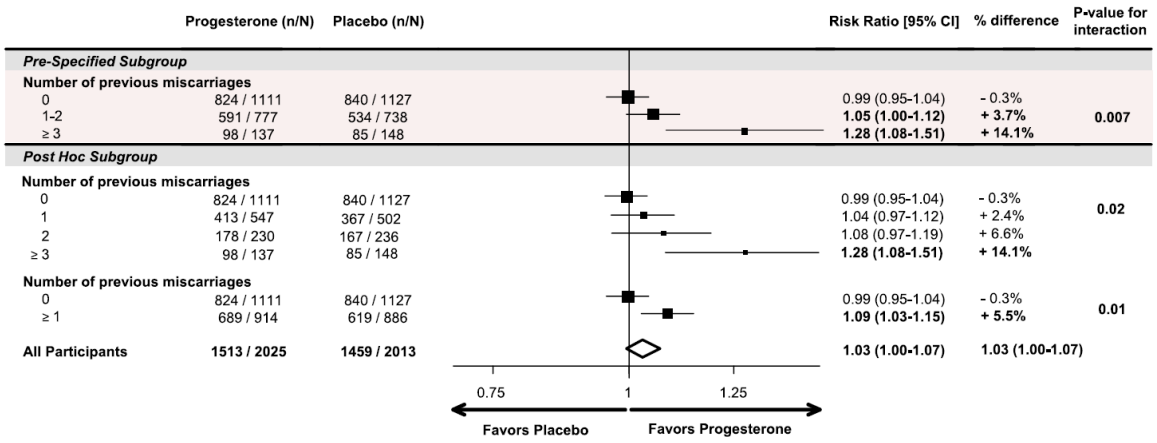

Figure 2: PRISM Trial subgroup analysis by number of previous miscarriages on the outcome of live birth ≥ 34 weeks.

Practice points:

- **At present, the usefulness of tests to detect luteal phase defect is uncertain.**
- **We recommend that women with vaginal bleeding and a history of one or more previous miscarriage(s) are offered a course of treatment with 400mg of vaginal micronized progesterone twice daily, started at the time of presentation with vaginal bleeding and continued to 16 completed weeks of gestation.**

Title	Authors	Journal and Issue	Article Type
Lessons from KEEPS: the Kronos Early Estrogen Prevention Study	Miller V.M. *et al*	Climateric 2021, 24 (2), 139-145	Review

What this review brings: KEEPS trial was the first double-blind RCT in MHT after WHI comparing the positive benefits/risks balance of a continuous sequential **standard dose of transdermal estradiol** (therapeutically equivalent to Oestrogel 2 Pumps actuation [1.5 mg E2]/day) in association with oral micronised P4 (Prometrium® 200 mg 14 days/28) versus a **low dose oral Conjugated Equine Estrogen** (CEE 0.45mg/day).

The KEEPS trial was initiated after the publication of the Women's Health Initiative (WHI) study and was designed to address some of the limitation of the WHI study which were criticized and considered irrelevant to medical practice. e.g. age distribution of women, years post menopause, underlying risk of CVD.

KEEPS Trial:

- Randomized, Double Blind, Placebo Controlled Trial
- Women were treated with either oral Conjugated Equine Estrogen (oCEE; 0.45mg/day) or transdermal 17β-estradiol (Climara®, tE2; 50µg/day), both with oral progesterone (Prometrium®, 200mg/day) for 12days/month, or placebo pills and patches for 4 years.
- 728 women, 3 years post menopause enrolled across 9 centers.
- CVD or CVD risk factors were exclusion criteria.
- KEEPS examined the effects of MHT on CVD and other physiological systems.

Results:
The following schematic summarizes the effects of KEEPS hormonal treatment on recently menopausal women. This schematic has been taken directly from the publication.

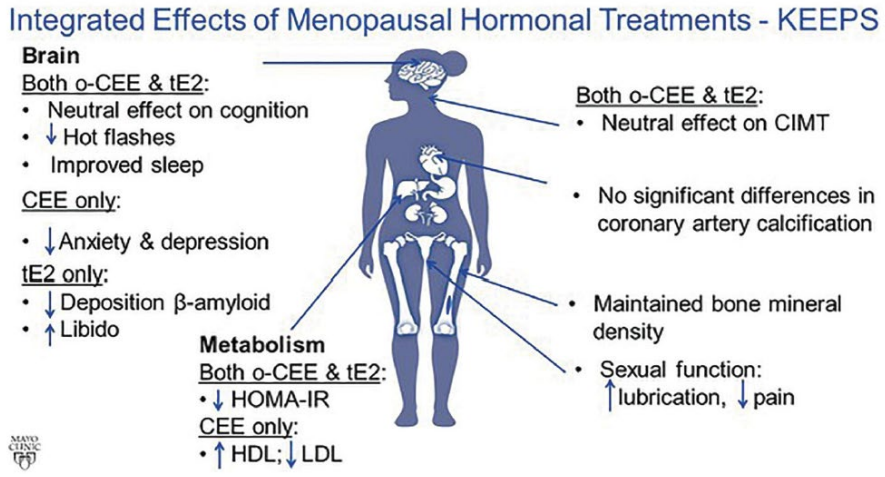

Figure 3: Schematic summary of the effects of Kronos Early Estrogen Prevention Study (KEEPS) hormonal treatments in recently menopausal women. CIMT, carotid intima-medial thickness; HDL, high density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein cholesterol; oCEE, oral conjugated equine estrogens; tE2, transdermal 17β-estradiol.

Summary:

KEEPS Trial included a well characterized group of recently menopausal women with low risk for CVD.

- 2 types of MHT were studied on multiple systems.
- No major cardiovascular or cognitive events were identified.
- No differences in Breast Cancer incidences were identified between groups.

Important to note is that the trial involved low number of participants, relatively healthy at baseline and the trial was of short duration.

- Overall, the KEEPS study provides reassurance regarding the efficacy and safety of these specific doses (oral CEE (0.45mg/day) or transdermal 17β-estradiol (tE2; 50µg/day), both with oral progesterone (200mg/day) for 12days/month) for women considering MHT for postmenopausal symptoms.

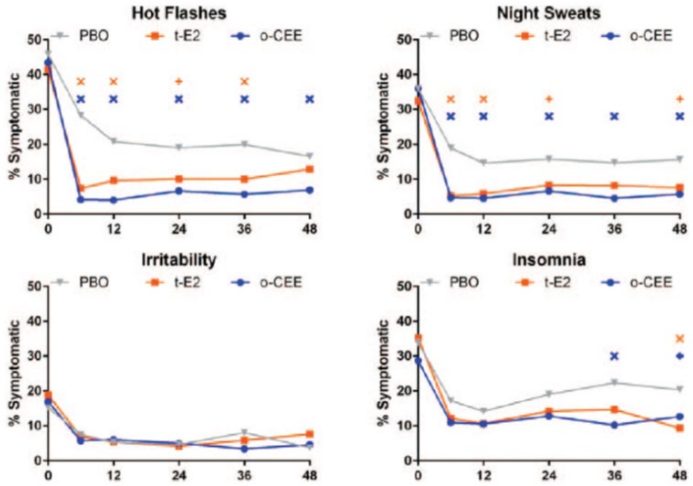

Figure 4: Unadjusted cross-sectional prevalence of symptoms over time. The proportion of women reporting moderate to severe symptoms is shown at each assessment. The x axis indicates the month of study. Significant differences from PBO indicated by additional symbol: (X) P<0.01 and (þ)0.01<P<0.05. o-CEE, oral conjugated estrogens; PBO, placebo; t-E2, transdermal estradiol. *from* **Santoro N,** *et al*. *Menopause* 2017; **24 (3)**: 238-246.

- The generally favorable data from the KEEPS trial appears to be supported by additional data using these 2 formulations and doses from clinical practice, when the MHT is initiated within 3 years of menopause.
    - Favorable outcomes included reduction in post-menopausal symptoms, improved bone health and sexual function.
- Neoplasia/hyperplasia numbers were low and did not differ among treatment groups.
- Dose, formulation, outcome of interest and CVD risk of women all need to be considered when choosing an MHT.

Practice points:

- **No effect on Blood Pressure (unlike WHI)**
- **No effect on $_{us}$CRP / Triglycerides / SHBG with Transdermal E2 on the contrary of oral CEE**
- **Transdermal E2, but not oral was associated with improvement in the overall Female Sexual Function Inventory score and libido (no increase in SHBG)**
- **Transdermal E2 appeared to improve insulin sensitivity (both routes of administration)**
- **Decrease in β-amyloid deposition with Transdermal E2**

From Santoro N, *et al.* Menopause 2017; **24 (3)**: 238-246; **Kantarci K**, *et al*. Journal of Alzheimer's Disease 2016; **53**: 547–556.

Title	Authors	Journal and Issue	Article Type
Erythrocytosis in a large cohort of trans men using testosterone: a long term follow-up study on prevalence, determinants and exposure years.	Madsen M.C. *et al*	Journal of Clinical Endocrinology and Metabolism 2021	Long term follow up study

What this review brings: This study confirms in a gender dysphoria patient population that long acting testosterone replacement therapy (i.e. Nebido®) increases significantly hematocrit levels above the upper limit of 0.50 l/l in a significant % of patients. A treatment-limiting increase in hematocrit to 54% or higher, a prespecified safety trigger, was flagged in 106 (22%) of 491 participants treated with testosterone in T4DM study (Wittert G, *et al*. Lancet Diabetes Endocrinol 2021; 9: 32–45)

Background:

- Gender dysphoria patients wishing to be identified as Trans Men are treated with Testosterone therapy to induce virilization.
- Physical, phycological and sexual changes occur as well as Hematological and Biochemical changes, therefore regular blood monitoring is recommended.
- Studies using testosterone for hypogonadal cis men have demonstrated a dose dependent stimulating effect on erythropoiesis leading to an increase in hematocrit levels.
- Increased hematocrit levels can lead to an increase in blood viscosity and increased risk of coronary heart disease and unprovoked venous thromboembolisms.
- Prevalence of erythrocytosis (hematocrit >50 l/l) in testosterone treated hypogonadal cis men has been described between 5% and 66% (depending on study cut-off value) and 11.5% in Testosterone treated trans men.
- **Higher risk has been seen with testosterone injections (short acting esters and long acting undecanoate) compared to gel in trans men especially in first 3 -12 months.**

Aim:

To study the prevalence and determinants in the development of erythrocytosis in trans men on T therapy over a 20-year period. N = 1073

Methods:

Inclusion criteria – trans men on T therapy with ≥ 1 follow up visit
Exclusion criteria – T therapy discontinued during follow-up, lab results of therapy start date missing
Several other parameters were analyzed including medical history, medication use, BMI, Tobacco use, etc

Results:

1073 trans men met inclusion criteria

- 11% of trans men on Testosterone therapy showed erythrocytosis (2 hematocrit measurements of >50l/l)
- 3.7% (2 hematocrit measurements of >52 l/l)
- 0.5% (2 hematocrit measurements of >0.54 l/l)

Odd's ratio's (OR) for Hematocrit levels >50 l/l:

- Highest OR was seen with long acting undecanoate injections (OR 2.9, 95% CI 1.7-5.0) compared to Testosterone Gel

- Short acting ester injections (0R 1.1, 95% CI 0.7-1.6) and oral formulations (OR 0.4, 95% CI 0.1-1.8) had similar Odd's for hematocrit levels of >50 l/l to Testosterone Gel

Tobacco use, higher BMI, Predisposing Medical History, Older age at Therapy Initiation were all associated with higher hematocrit levels.

Discussion:

- Prevalence of erythrocytosis is similar in this study to previous research in trans men.
- **Long acting undecanoate IM injections had highest odds for hematocrit levels of >50l/l**
- Transdermal Testosterone Gel showed least increase in hematocrit level.
- The data shows a slight increase in the odds of getting hematocrit levels >50 l/l with increased Testosterone Levels.
- 2018 Guidelines for transgender men are based on hypogonadal cis men and state that a hematocrit level of >48 l/l is associated with a moderate to high risk of an adverse event. This is lower than the previous cutoff of >50 l/ l from 2008 guideline.

The author discusses whether Trans men's hematocrit levels should be based on cis women rather than cis men as they are born female.

The largest increase in hematocrit level is seen in the first year after therapy initiation and continues slightly for up to 20 years, therefore regular control of Hematocrit levels is necessary.

Recommendations for Clinical Practice:

- Regular monitoring of hematocrit levels for people on T therapy
- For hematocrit levels of 0.50 to 0.54 l/l the following should be considered.
    - **Switch from injectable testosterone to transdermal administration**
    - For BMI >25 – lose weight
    - Stop smoking
    - Treatment for chronic lung disease or sleep apnea should be investigated

	Hematocrit > 0.50 L/L, crude OR (95% CI)	Adjusted OR (95% CI)[b]	Hematocrit > 0.52 L/L, crude OR (95%CI)	Adjusted OR (95% CI)[b]
Route of testosterone				
T gel	ref	ref	ref	ref
Short-acting im	1.1 (0.7–1.6)	1.1 (0.7–1.7)	1.5 (0.7–3.4)	1.5 (0.6–3.7)
Long-acting im	2.9 (1.7–5.0)	3.1 (1.7–5.6)	1.0 (0.3–3.4)	1.3 (0.4–5.0)
Oral T	0.6 (0.2–1.6)	1.3 (0.4–3.7)	0.2 (0.1–2.4)	0.5 (0.1–5.6)
Unknown	1.2 (0.8–1.7)	1.9 (1.3–2.8)	1.8 (0.9–3.8)	2.9 (1.3–6.6)

Figure 5: Multivariable Analysis: Chance of High Hematocrit for Different Determinants

Practice Points:

- **Regular control of hematocrit seems warranted as long as people use testosterone.**
- **If hematocrit levels are between 0.50 and 0.54 l/l, reasonable first steps to prevent further increase would be to consider switching injectable testosterone therapy to transdermal administration.**