

SITAGLIPTIN FOR RECURRENT MISCARRIAGE

? Light At The End Of The Tunnel



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Overview

- **Implantation**
 - Endometrial Receptivity and Selectivity
 - Endometrial Mesenchymal Stem Cells
- **Sitagliptin**
 - DPP4 Inhibitor
 - Role in Implantation
- **SIMPLANT**
 - RCT

Implantation

Abnormal Decidualisation

- ↓ eMSC's
- Cellular senescence
- Disordered inflammation

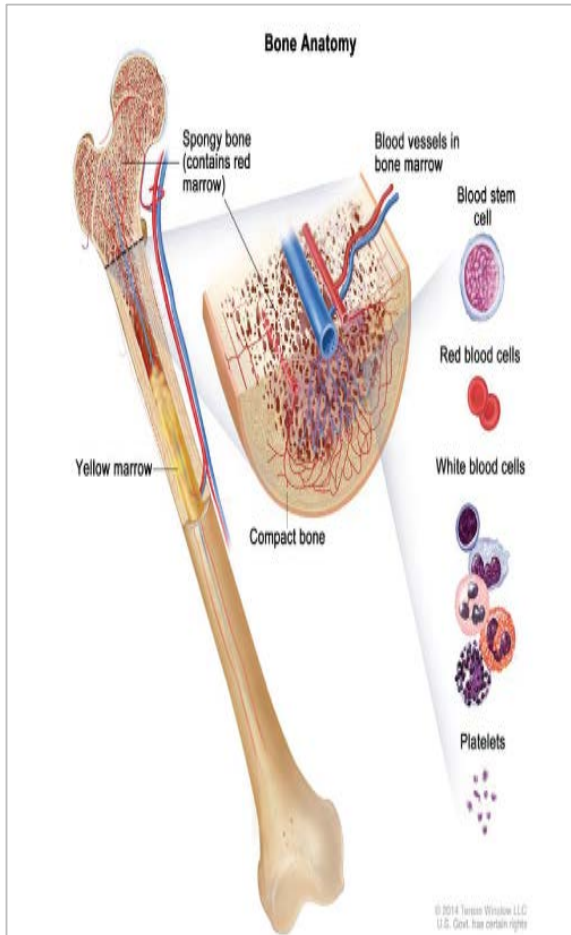
Recurrent miscarriage

↓ Selectivity
↑ Receptivity

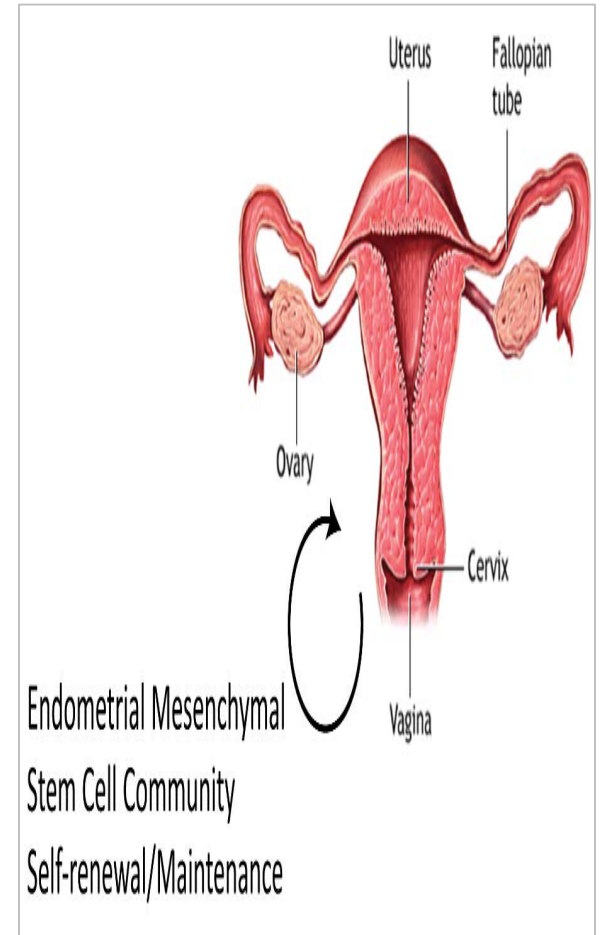
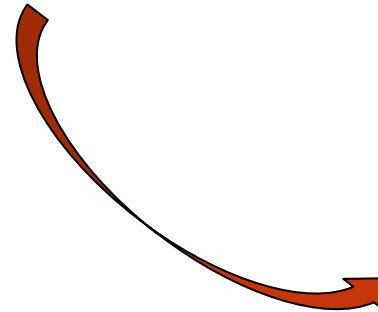
Subfertility

↑ Selectivity
↓ Receptivity

Stem Cell Recruitment

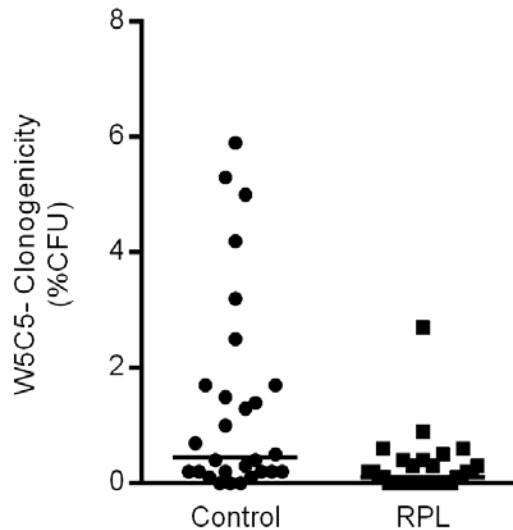


- Low levels eMSCs
- ↓
- Abnormal decidualisation

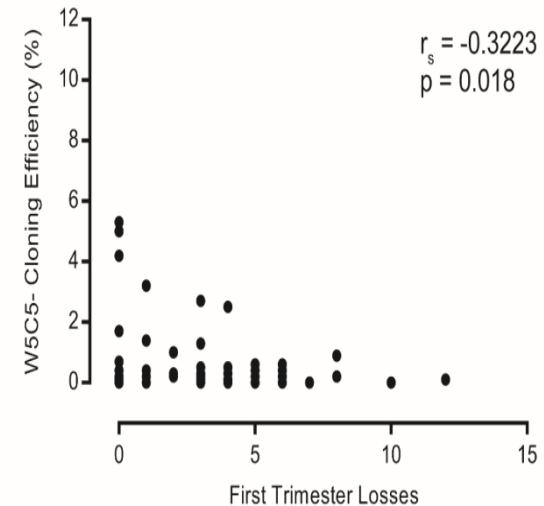


Endometrial Cells Derived From Donor Stem Cells in Bone Marrow Transplant Recipients. AMA 2004, July. 292:81-85

Endometrial mesenchymal stem cells



RM patients have lower number of endometrial mesenchymal stem cells (assessed by clonogenic assay) compared to control patients



The stem cell-ness of the endometrium decreases with increasing number of miscarriages.

Sitagliptin

- Type 2 Diabetes
 - Enhances stem cell recruitment at site of injury (menstruation)
- CXCR4 and CXCL12 pathway
 - Chemoattraction of stem cells to all peripheral tissues

CXCR4	CXCL12
Expressed on BMDSC's Modulates migration of SC's	Chemokine recruiting SC's Expressed on endometrial stromal cells

- Sitagliptin enhances this process
- DPP4 expression higher in RM

1. Du H, Naqvi H, Taylor HS. Ischemia/Reperfusion Injury Promotes and Granulocyte-Colony Stimulating Factor Inhibits Migration of Bone Marrow-Derived Stem Cells to Endometrium. Stem Cells Dev. 2012 Aug 16;21(18):3324–31.
2. Castilla DM, Liu Z-J, Tian R, Li Y, Livingstone AS, Velazquez OC. A novel autologous cell-based therapy to promote diabetic wound healing. Ann Surg. 2012 Oct;256(4):560–72.



- **HYPOTHESIS**

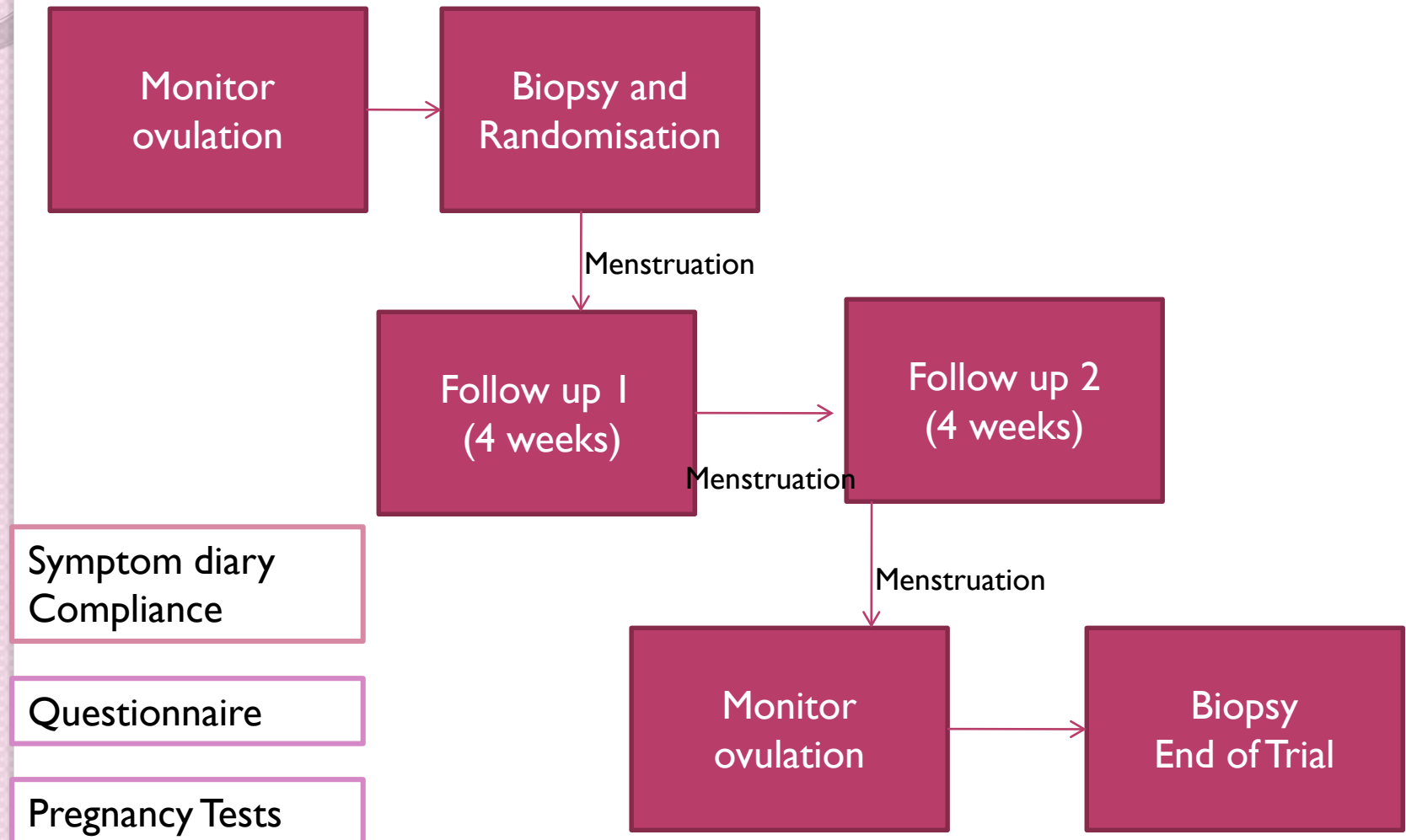
DPP4 inhibition with Sitagliptin given prior to conception will increase eMSC recruitment during menstruation which in turn should prevent repeated miscarriage.

- **PRE-CONCEPTION TREATMENT**

SIMPLANT

- Single centre, pilot study
- Ethical and MHRA approval
- Double blind, placebo controlled
- Planned sample size
 - 34 patients
 - Power 95%, 10% significance level
- Randomisation
 - computerised random number generator

Procedure



Inclusion Criteria

- Age 18 – 42
- 3 or more miscarriages
- Regular menstrual cycle – up to 30/7
- Any BMI
- Consent for study and biopsy
- Negative pregnancy test at randomisation

Exclusion Criteria

- Under 18
- Diabetes – Type I/II
- Pregnancy/Breastfeeding
- Digoxin/Enalapril
- Renal/Hepatic impairment
- Allergy to Sitagliptin
- Unwilling to use barrier contraception through the trial

Outcome Measures

PRIMARY	SECONDARY
<p>Clonogenic Assay The number of colonies per thousand endometrial stromal cells after 3 months of Sitagliptin (100mg) vs. 3 months of placebo</p>	<ol style="list-style-type: none">1. IHC - Change in the expression of DPP4 in endometrium2. RNA sequencing – effect of Sitagliptin on other implantation related genes3. Qualitative analysis<ul style="list-style-type: none">• Adverse events/serious adverse events• Process evaluation questionnaire

Statistical Analysis Plan

- Primary analysis
 - Compare number of colonies/1000 cells between intervention group and control group
- Null hypothesis
 - Mean number of colonies for the control group is equal to that of the intervention group
- Pilot study
 - Hypothesis tested at 10% significance level

Current status

- **Currently**
 - 18 consented
 - 12 randomised
 - 3 completed

Conclusion

- Most current treatment for miscarriage begins once patients are pregnant
- Hope
 - Design pre-conception treatment
 - Large multicentre RCT

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Acknowledgements

- Professor Siobhan Quenby
- Professor Jan Brosens
- Dr Emma Lucas
- Angela Polanco and BRU team
- Dedicated patients

University Hospitals 
Coventry and Warwickshire
NHS Trust

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