Immunological Considerations of Implantation Failure and Treatment

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• Takes average 25 eggs to make a baby
• 50% of pregnancies are lost before missing a menstrual period
• Pregnancy loss due to chromosomal abnormalities and implantation failure
• Implantation is endometrium and related cellular and molecular changes encouraging tolerance
• Implantation failure when embryos and maternal environment do not fit
IMPLANTATION

• A complex process where the interplay of various factors resulting in the host (endometrium) to accept a semi-allogenic embryo to develop and grow within it. These factors include cellular changes, hormones, vascular adaptation, as well as the interplay of cytokines, growth factors, mRNA, as well as gamete and embryo quality.
• 75% conception loss is due to failure of implantation

WILCOX NEJM 1988
Implantation depends on the synchronization of factors:

- quality of embryos
- optimal culture conditions
- receptivity of the endometrium
- maternal immune system
IMPLANTATION FAILURE

• Failure to achieve a pregnancy after >5 transfers of at least 10 good quality embryos

• Nowadays, more than 3 transfers is indication for investigations
RECURRENT IMPLANTATION FAILURE

- Gamete And Embryo Factors
- Endometrial Factors
- Obesity
- Thyroid
- Uterine Factors
- Stimulation, Culture, Transfer
- Immunological Factors
Failed implantation is a major limiting factor in assisted reproduction.

Why high quality embryos failed to implant?

Is it the endometrium?

Is it lack of tolerance – immunology?
Molecules taking part in the dialogue

Hormones
Cytokines/Chemokines
Integrins
Growth Factors
Enzymes/proteases

Dimitriadis et al. Hum Reprod Update 2005:11;613-630
Cellular factors playing part in the dialogue

• NK cells:
  – role of pNK cells
  – role of uNK cells
• NK cells induced cytokine changes
  – +56, +19, +7
• Treg cells
Role of Plasma factors in the dialogue

- Antiphospholipid antibodies
- Autimmune antibodies
  - ANA, LE, Antithyroid
- Interferon
- Interleukins
- Plaminogen Activator Inhibitor
- Tumour Necrotising Factor
Role of the immune system in pregnancy

• Pregnancy is a state of immunologic tolerance

• In a normal pregnancy:
  – Regulatory T cells increased, suppressing T cell activation
  – Predominantly secrete anti-inflammatory cytokines (Th2 response) compared with increase pro-inflammatory cytokines (TH1 response)
It is of utmost importance to understand how the initial inflammatory response during the implantation period is controlled to protect the semi-allogenic fetus.
Immunological blood tests

1. Anti-phospholipid antibodies (APA)
2. Natural killer (NK) cells
3. Th1 and Th2 cytokines
4. Anti-nuclear Antibodies (ANA)
5. Plasminogen Activator Inhibitor (PAI)
6. Antithyroid antibodies
7. Lupus-like anticoagulant
Immunological tests

8. HLA-G
9. Sperm DNA integrity assay
10. Thrombophilia panel
    factors II,V,VIII
    b-fibrinogen
    methylenetetrahydrofolate reductase (MTHFR)
    Protein S deficiency
11. Y-Chromosome deletion assay
# Immunology report

![Image of a laboratory report](image)

## Anti-phospholipid Antibody Panel

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<thead>
<tr>
<th>Test Name</th>
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<tbody>
<tr>
<td>IgM Cardiolipin</td>
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**Notes:** BORDERLINE has an approximate titer of 1:50 and should be considered as an ANA of 1:40, that is suspicious but not clearly positive. POSITIVE results have titer equal to 1:100 to 1:200. HIGHLY POSITIVE results have an equivalent titer of 1:400 or greater and like titer of 1:320 or 1:640 in the ANA test are indicative of a frank disease process.

This test was developed by the Clinical Immunology Laboratory at the RFUMS/The Chicago Medical School. The performance characteristics of this test were determined and are monitored by the Clinical Immunology Laboratory. However, the use of this test has not been cleared or approved by the U.S. FDA.
Anti-phospholipid antibodies (APA)

Phospholipids act like a glue that holds the dividing cells together, which are necessary for growth of the placenta into the wall of the uterus, filter nourishment from the mother’s blood to the baby, and wastes from the baby.

Though in themselves they don’t cause miscarriage, their presence indicates that their ability may be compromised. One of the mechanism is activation of the complement cascade.

AntiPhospholipid Antibodies (APA)

Anticardiolipin most commonly tested, but negative in 53% of APA positive

A panel of tests for antibodies to six additional phospholipids to determine the presence of APA
Antiphosphotidylserine, antiphosphotidylcholine, antiphosphotidylglycerol, antiphosphotidylethanolamine, antiphosphotidylinositol, antiphosphotidic acid

Testing +ve for one or more kind of antiphospholipid antibodies can cause miscarriages

APA’s target endothelial cells (clotting) trophoblasts, and embryo toxicity
Antiphospholipid Syndrome

- Antiphospholipid syndrome is an autoimmune hypercoagulable state caused by antibodies against cell-membrane phospholipids that provokes blood clots leading to miscarriage or severe preeclampsia
- This is characterised by presence of antiphospholipid antibodies, lupus anticoagulants, and anti-Beta2 glycoprotein plus history of 3 or more repeated pregnancy failures

Carp 2008
Natural killer (NK) cells and inflammation

NK cell cytotoxicity - measures the killing activity within each cell
• NK cells are defined as large granular lymphocytes generating B and T lymphocytes
• NK cells are effectors of innate immunity and also playing a role in adaptive immune response
Lymphocytes in Pregnancy

• NK cells produce a substance called tumor necrosis factor (TNF)

• The proportion of NK cells is determined by a reproductive immunophenotype (RIP) test, which looks for cells that have CD56+ marker, the “uterine NK cells”

• Successful pregnancy requires the mother’s immune system to be suppressed
Lymphocytes in Pregnancy

• NK cells: secretes cytokines, have potent chemicals to kill non-self cells

• T cells: cellular immunity
  – Cytotoxic T – express CD8+, attack
  – Helper T – express CD4, mediates immune response, secret TH1, TH2 responses
  – Regulatory T – express CD8, CD25, suppress activation of immunity

• B cells: humeral immunity
  – secrete antibodies act by complement fixation, neutralization, agglutination and precipitation
TH1 and TH2 immune response

TH1 Cytokines: Pro-inflammatory
• Produce the pro-inflammatory responses for perpetuating autoimmune responses
• TNF and IFG are the main TH1 cytokine

TH2 Cytokines: Anti-inflammatory
• Include interleukin 4, 5, and 13
• Promotion of IgE and eosinophilic response
• Counteract the TH1 mediated microbacteriocidal action
• Balanced Th1 and Th2 is crucial to a successful implantation
Anti-nuclear Antibodies (ANA)

• Also known as anti-nuclear factor (ANF) are autoantibodies against normal components of the cell nucleus
• Can be present in systemic lupus erythematosus, progressive systemic sclerosis, Sjorgen’s syndrome, dermatomyositis
• Presence of ANA indicates an underlying autoimmune process that may affect the development of placenta
• Autoantibodies as predictors of pregnancy complication:
  Decidual inflammation
  Peri villous fibrin deposition
  Thromboembolism in decidual vessels
ANA

• Autoantibodies as predictors of pregnancy complication:
  
  Decidua inflammation
  
  Peri villous fibrin deposition
  
  Thromboembolism in decidual vessels

• Can be present in systemic lupus erythematosus, progressive systemic sclerosis, Sjorgen’s syndrome, dermatomyositis

• Presence of ANA indicates an underlying autoimmune process that may affect the development of placenta
Plasma Activator Inhibitor-1

• Polymorphism of the PAI-1 gene (4G/4G), an inherited thrombophilia's
• A primary inhibitor of plasminogen activates both tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA)
• Reduced plasma fibrinolytic activity
PAI-1

• With a mutated PAI-1 (homogeneous mutated) gene is associated with elevated plasma PAI-1 levels which related to arterial thrombosis and high plasma levels of coagulation and fibrinolytic factor

• Suggested Treatment:

  Metformin therapy:

  • By lowering insulin, reduces the levels of PA-1, reduces the ability of the body to dissolve blood clots (thrombi)
Clinical reviews

• 40 patients treated in 2010-11
• Age ranging from 30-44
• History of repeated failure of IVF
  (2 patients with repeated failure in IUI)
• Immunological blood tests were performed
• Treatment including steroids, anticoagulants and IVIG were prescribed
No. of non-treatment cycles among the 40 patients: Total 104 cycles had been done and failed

# No. of treatment cycles: Total 54 cycles received IVIG treatment, 22 patients got pregnant
Immunology compromised patients

- Series II 2012-2013  N=136
- All patients referred for repeated IVF or very early pregnancy failures
- Age 35-47
- All have at least 3 failures, and more than 8 embryos replaced
- All underwent the same group of immunological tests done by the Rosalind Franklin Reproductive Centre laboratory
Immunology compromised patients

- All had at least one failed IVF treatment in our own center
- Acting as their own control, all had IVF treatment with the same protocol before (without) and with immuno-suppression treatments
- A no selection prospective study, only entry point was same immunologic test panel
Immunological blood tests taken

1. Anti-phospholipid antibodies (APA)
2. Natural killer (NK) cells
3. Th1 and Th2 cytokines
4. Anti-nuclear Antibodies (ANA)
5. Plasminogen Activator Inhibitor (PAI)
6. Antithyroid antibodies
7. Lupus-like anticoagulant
Composition of patient immunological blood test results n=136

- **POSITIVE IMMUNO BLOOD TEST RESULT**
- **NEGATIVE IMMUNO BLOOD TEST RESULT**

87%

13%
Pregnancy Rate: Patients with Abnormal Blood Test Results who received treatment

- **70%** Successfully Pregnant
- **21.82%** of Pregnant Patients miscarried
- **30%** Not Pregnant
Immunology study report

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NORTH CHICAGO, IL 60064

CLIA ID# 14D0646416
Kenneth Beaman, Ph.D., D(ABMLI)

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### Immunology report

#### NK Assay Full Panel

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<th>RESULT</th>
<th>UNITS</th>
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<td>50:1</td>
<td>27.1</td>
<td>%</td>
<td>10.0-40.0</td>
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<td>25:1</td>
<td>23.4</td>
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<td>5.0-30.0</td>
</tr>
<tr>
<td>12:5:1</td>
<td>21.3 (H)</td>
<td>%</td>
<td>3.0-20.0</td>
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<td>IVIG 12.5 mg/ml, 50:1**</td>
<td>28.0</td>
<td>%</td>
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<td>IVIG 12.5 mg/ml, 25:1**</td>
<td>29.1</td>
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<td>IVIG 6.25 mg/ml, 50:1**</td>
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<tr>
<td>IVIG 6.25 mg/ml, 25:1**</td>
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<td>60.0-85.0</td>
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<td>%CD19</td>
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<td>%</td>
<td>2.0-12.0</td>
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<td>%CD56</td>
<td>25.9 (H)</td>
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<tr>
<td>%CD19+cells,CD5+</td>
<td>21.7 (H)</td>
<td>%</td>
<td>5.0-10.0</td>
</tr>
</tbody>
</table>

**Notes:** **> 10% reduction in killing at each effector/target ratio.

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#### TH1/TH2 Intracellular Cytokine Ratios

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<tr>
<th>Cytokine Ratio</th>
<th>RESULT</th>
<th>RATIO</th>
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<tbody>
<tr>
<td>TNF-α:IL-10 (CD3+CD4+)</td>
<td>45.5 (H)</td>
<td>13.2-30.6</td>
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<tr>
<td>IFN-γ:IL-10 (CD3+CD4+)</td>
<td>22.1 (H)</td>
<td>5.8-20.5</td>
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# Immunology report

## Anti-Nuclear Antibodies (by IFA) 抗核因子

**Reference range:**
Healthy adults (95 percentiles)

**Note:** Reference values updated Sept 5, 2011

**Reference values:**
Guideline to ANA prevalence in autoimmune disease:
- Systemic lupus erythematosus: Active (95% - 100%), Inactive (80% - 100%)
- Drug induced lupus erythematosus: 100%
- Mixed connective tissue disease (MCTD, Scleroderma): 100%
- Rheumatoid arthritis: 20 - 40%
- Other rheumatic diseases: 20 - 50%
- Progressive systemic sclerosis: 85 - 95%
- Polymyositis and dermatomyositis: 30 - 50%
- Sjogren's syndrome: 70 - 80%
- Chronic active hepatitis: 30 - 40%
- Ulcerative colitis: 26%

The diagnostic value of autoantibodies against cell nuclei (ANA) is proven for many autoimmune diseases, above all, but not exclusively, those of the rheumatic forms. Interference includes patients having high mitochonrdial antibody levels that may mask the pattern and titer of ANA. Positive ANA testing may be more meaningful when interpreted with additional tests, such as ANEs (SLE) and ENA antibodies for the differentiation of different illnesses.
Treatment

• All patients were treated with prednisolone from the time when follicles respond
• IVIG infusion, 40mg, given 1 week prior to egg collection, and then at embryo transfer
• Low dose aspirin given the next day of egg collection, as well as clexane, 40mg sc qd
• Luteal support was by suppository and IMI Progesterone
Treatment

• Progesterone, PT, APTT monitored regularly
• Another dose of IVIG at time of first (6 wk) ultrasound, and if FHM observed; and then 4 weeks later
• All medication tapered off after 10 weeks and when fetus appeared normal
• Patients homozygous for PAI-I pretreated with metformin from 1 cycle prior to IVF, and continued to 10 weeks
Treatment

• Beginning of 2013, started using intralipid 300ML 10% infusion
• Schedule of infusion the same as IVIG
• ** Same treatment for FET which is usually done using estradiol (oral) for preparing the endometrium, and HCG trigger 2 days before starting progesterone
• Intravenous Immunoglobulin
  – To suppress elevated circulating levels of NK cells and NK cell killing activity and embryotoxins
  – To suppress elevated levels of antiphospholipid antibodies and antithyroid antibodies
  – To enhance regulatory T cell activity and suppress B cells production of antoantibodies
INTRALIPID

Content
Intralipid 10%: 1000ml contain purified soybean oil 100g, purified egg phospholipids 12g, glycerol anhydrous 22g, water for injection. It is composed of 10 percent soybean oil, 1.2 percent egg yolk phospholipids, 2.25 percent glycerine and water.

Dosage:
2g of fat/kg body weight/day (20ml, 10ml and 6.7ml/kg of intralipid 10%, 20% and 30% respectively)

Infusion rate:
The drip rate is about 2 to 3 ml/min for intralipid 10%. It should be started at half the infusion rate during the first 30mins under supervision.

IVF protocol:
7-14 days prior to ET
Repeated on the day of ET
Repeated again with a positive pregnancy test and administer every month until the 20th week

## It is a safe and inexpensive alternative to IVIG therapy. It is not a blood product and is without significant side effect
Pregnancy Outcome and Rate Comparison

Not Pregnant
- Abnormal (Treated) 69.62%
- Abnormal (Not Treated) 20.83%
- Negative 0.00%

Pregnant
- Abnormal (Treated) 66.67%
- Abnormal (Not Treated) 0.00%
- Negative 10.00%

Miscarriage
- Abnormal (Treated) 0.00%
- Abnormal (Not Treated) 20.00%
- Negative 30.00%

Number of patients

Rate
Pregnancy Analysis of Abnormal Blood Test
Result Patients Treated VS Not Treated

- Patient not pregnant
- Patient miscarriage
- Live birth/ ongoing pregnancy

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<tr>
<th>Test</th>
<th>Received Treatment</th>
<th>Not Received Treatment</th>
<th>Received Treatment</th>
<th>Not Received Treatment</th>
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Pregnancy Rate of patients with positive immunological blood test results - Treated

- 1 Positive
- 2 Positive
- 3 Positive
- 4 Positive
- 5 Positive

Legend:
- Blue: not pregnant
- Light Gray: Pregnant
- Light Blue: Miscarriage
- Black: Total
Single Abnormality

• To be able to apply some algorithm and may be test for validity, there has to be special cases. We had in this series two: Th1/Th2 ratio raised only.

• We decided to treat with humira without IVIG
Immunology report

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PAI-1 4G/5G Gene Polymorphism

PAI-1 4G/5G Mutation Detection  NORMAL

Note: Plasminogen activator inhibitor-1 (PAI-1) is an essential regulatory component of fibrinolytic pathway. A common guanosine (G) insertion/deletion gene polymorphism at 675 bp is related to levels of PAI-1 protein. Homozygosity for the deletion genotype (4G/4G) is associated with higher levels of PAI-1 protein and increased risk for thrombosis. NORMAL represents a 5G/5G genotype; HETEROZYGOUS MUTATED represents a 4G/5G genotype; HOMOZYGOUS MUTATED represents 4G/4G genotype.

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# Immunology study report

## Clinical Immunology Lab

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CLIA ID# 14DO664616  
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<td>NEGATIVE</td>
<td></td>
<td></td>
<td>NEGATIVE</td>
</tr>
</tbody>
</table>

Notes:  
BORDERLINE has an approximate titer of 1:50 and should be considered as an ANA of 1:40, that is suspicious but not clearly positive.  
POSITIVE results have titers equal to 1:100 to 1:200.  
HIGH POSITIVE results have an equivalent titer of 1:400 or greater and like titers of 1:320 or 1:640 in the ANA test are indicative of a frank disease process.  

This test was developed by the Clinical Immunology Laboratory at the RFUMS/The Chicago Medical School. The performance characteristics of this test were determined and are monitored by the Clinical Immunology Laboratory. However, The use of this test has not been cleared or approved by the U.S. FDA.
# Immunology study report

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3333 Green Bay Road
NORTH CHICAGO, IL 60064

**CLIA ID# 14D0646416**
Kenneth Beam, Ph.D., D(ABMLI)

<table>
<thead>
<tr>
<th>TEST NAME</th>
<th>IN RANGE</th>
<th>RESULT</th>
<th>OUT OF RANGE</th>
<th>UNITS</th>
<th>REFERENCE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK Assay Full Panel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50:1</td>
<td></td>
<td>12.8</td>
<td></td>
<td>%</td>
<td>10.0-40.0</td>
</tr>
<tr>
<td>25:1</td>
<td></td>
<td>10.8</td>
<td></td>
<td>%</td>
<td>5.0-30.0</td>
</tr>
<tr>
<td>12.5:1</td>
<td></td>
<td>8.0</td>
<td></td>
<td>%</td>
<td>3.0-20.0</td>
</tr>
<tr>
<td>IVIG 12.5 mg/ml, 50:1**</td>
<td></td>
<td>9.3</td>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>IVIG 12.5 mg/ml, 25:1**</td>
<td></td>
<td>6.7</td>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>IVIG 6.25 mg/ml, 50:1**</td>
<td></td>
<td>9.7</td>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>IVIG 6.25 mg/ml, 25:1**</td>
<td></td>
<td>8.6</td>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>%CD3</td>
<td></td>
<td>78.3</td>
<td></td>
<td>%</td>
<td>60.0-85.0</td>
</tr>
<tr>
<td>%CD19</td>
<td></td>
<td>9.3</td>
<td></td>
<td>%</td>
<td>2.0-12.0</td>
</tr>
<tr>
<td>%CD56</td>
<td></td>
<td>11.7</td>
<td></td>
<td>%</td>
<td>2.0-12.0</td>
</tr>
<tr>
<td>%CD19+cells,CD5+</td>
<td></td>
<td>6.0</td>
<td></td>
<td>%</td>
<td>5.0-10.0</td>
</tr>
</tbody>
</table>

**Notes:** > 10% reduction in killing at each effector/target ratio.

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**TH1/TH2 Intracellular Cytokine Ratios**

<table>
<thead>
<tr>
<th>Cytokine Ratio</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α:IL-10 (CD3+CD4+)</td>
<td>39.8 (H)</td>
</tr>
<tr>
<td>IFN-γ:IL-10 (CD3+CD4+)</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>ratio</td>
</tr>
</tbody>
</table>
Immunology study report

Anti-Nuclear Antibodies (by IFA) 抗核因子

Reference range:
Healthy adults (95 percentile)

Note: Reference notes updated Sept 5, 2011

Reference notes:
Guideline to ANA prevalence in autoimmune disease:
- Systemic Lupus erythematosus: Active
  - 95 - 100%
  - 80 - 100%
  - 100%
- Drug induced lupus erythematosus
  - 100%
- Mixed connective tissue disease (MCTD, Sharp Syndrome)
  - 100%
- Rheumatoid arthritis
  - 20 - 40%
- Other rheumatic diseases
  - 20 - 50%
- Progressive systemic sclerosis
  - 85 - 95%
- Polymyositis and dermatomyositis
  - 50 - 80%
- Sjogren’s syndrome
  - 70 - 85%
- Chronic active hepatitis
  - 30 - 40%
- Ulcerative colitis
  - 25%

The diagnostic value of autoantibodies against cell nuclei (ANA) is proven for many autoimmune diseases, above all, but not exclusively those of the rheumatic forms. Interference includes patients having high mitochondrial antibody levels that may mask the pattern and titre of ANA. Positive ANA testing may be more meaningful when interpreted with additional tests, such as Anti dsDNA (SLE) and ENA antibodies for the differentiation of different illnesses.
Case 1 Treatment

32 YO G3P0A3 PCO
1 egg collection and 3 FET
1 biochem and 2 <8 wks abortions
Immunological screening showed only Th1/Th2 abnormality
Using Humira during treatment cycle for FET
1st cycle – Biochemical Pregnancy
2nd cycle – On going pregnancy
delivered normal male
Case 2  Treatment

- 29 yo G3P0A3
- One spontaneous abortion
- 2 IVF successes from 4 transfers with 2 empty gestational sac and 2 with FHM at week 6 but no growth or FHM by week 8
- IVF plus treatment with Humira
- Success with on going pregnancy now 35 weeks with normal growth
Single Abnormality

- Humira (Adalimumab) is a TNF inhibiting anti-inflammatory agent which will down regulate the inflammatory reactions associated with autoimmune diseases.
- We chose a dose of 40mg sc q7-10 days from day 7 and continue when pregnancy test positive till 8 weeks.
Luteal phase support

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; cycle</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA, Vit E Viagra</td>
<td>ASA, Vit E, Viagra</td>
</tr>
<tr>
<td>Clexane</td>
<td>Clexane</td>
</tr>
<tr>
<td>Crinone</td>
<td>Crinone</td>
</tr>
<tr>
<td>Estrofem</td>
<td>Estrofem</td>
</tr>
<tr>
<td>Humira</td>
<td>Humira</td>
</tr>
<tr>
<td>Steroid</td>
<td></td>
</tr>
</tbody>
</table>
Why When What and How

- Why is immunological causes for implantation failure known by most but accepted by so few? Why do we have to “pour” in drugs instead of rationalisation?
- When should we use the different drugs and for how long? When will we know whether specific drugs can be selectively use?
- What is the specific mechanism of action, and what we can do to categorise and design specific tests and treatment?
- How can we obtain enough data to convince clinicians to face this problem? It may be 2-5% of population, but 50-70% of RIF patients. How can we collect enough data so the a more logical algorithm for different diseases be treated with different protocols effectively?
Conclusion

• Human reproduction is inefficient, implantation rate is low.
• Causes are multiple and interlinked
• Application of basic science findings to clinical treatment may appear empirical because studies not easy to set up or conduct.
• Role of inflammation and implantation as an inflammation process may be the cause of “unexplained” implantation failure
• Induced inflammation seems to improve implantation
• Immunotherapy works but more needs to be done to clarify the specific relationship between different findings and clinical entity
PIF - PreImplantation Factor

- Small 15AA peptide
- (MVRIKPGSANKPSDD)
- Detected in human circulation and placenta
- Detected in viable embryos, but not in non-viable ones

- Barnea et al 1994, 2004
- Coulam et al 1995
Function of PIF

- Shows activities of cytokines
- Modulates peripheral immune cells
- Creates a Th2/Th1 cytokines bias
- Binds to myelomonocytic cells
- Up regulating T cells and B cells
Functions of PIF in blood

Decreases lymphoctic action by 70%

- Blocks CD3 stimulated monnuclear cells 80%
- Decreases IL10, IL12
- Increases IL4, IL5, TNF-alpha, IGN-gamma, GM-CSF
- Anti-inflammatory effect on activated immunene celld in non-pregnant state
Functions of PIF

- Regulates natural killer cell toxicity in vivo
- Inhibits circulating NK cells, reduces CD69 expression

- Barnea 2009
- Pomponas 2009
- Roussev 2013
PIF now

- A FDA approved phase I studies fast tracked and will start Spring Summer 2014
Conclusion

• Multiple tests, limited test resources, means lack of uniform results
• Multiple abnormal results = confusion
• => multiple drugs = further confusion
• Results clear cut and encouraging
• Needs some type of algorithm and system so further evaluation possible
Acknowledgement

• My patients who made me a believer, and looked into this enigma
• The Rosalind Franklin Laboratory for supporting our requests
• My colleagues Dr Alexander Doo and Dr Bernard Chan for treating patients, and their intellectual stimulation
• Miss Joanne Hung, and Miss Christina Ngai for help in preparing data and slides