BRAVERMAN
IVF & Reproductive Immunology, P.C.
Answers for Infertility & Recurrent Pregnancy Loss

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Pregnant Patient Report

- Report date is 6-28-16 (~17.5 weeks pregnant)
- 6-1-16 (~14 weeks pregnant)
- 5-2-16 (~10.5 weeks pregnant)
- 4-4-16 (~6 weeks pregnant)
- 2-15-16 (not pregnant)

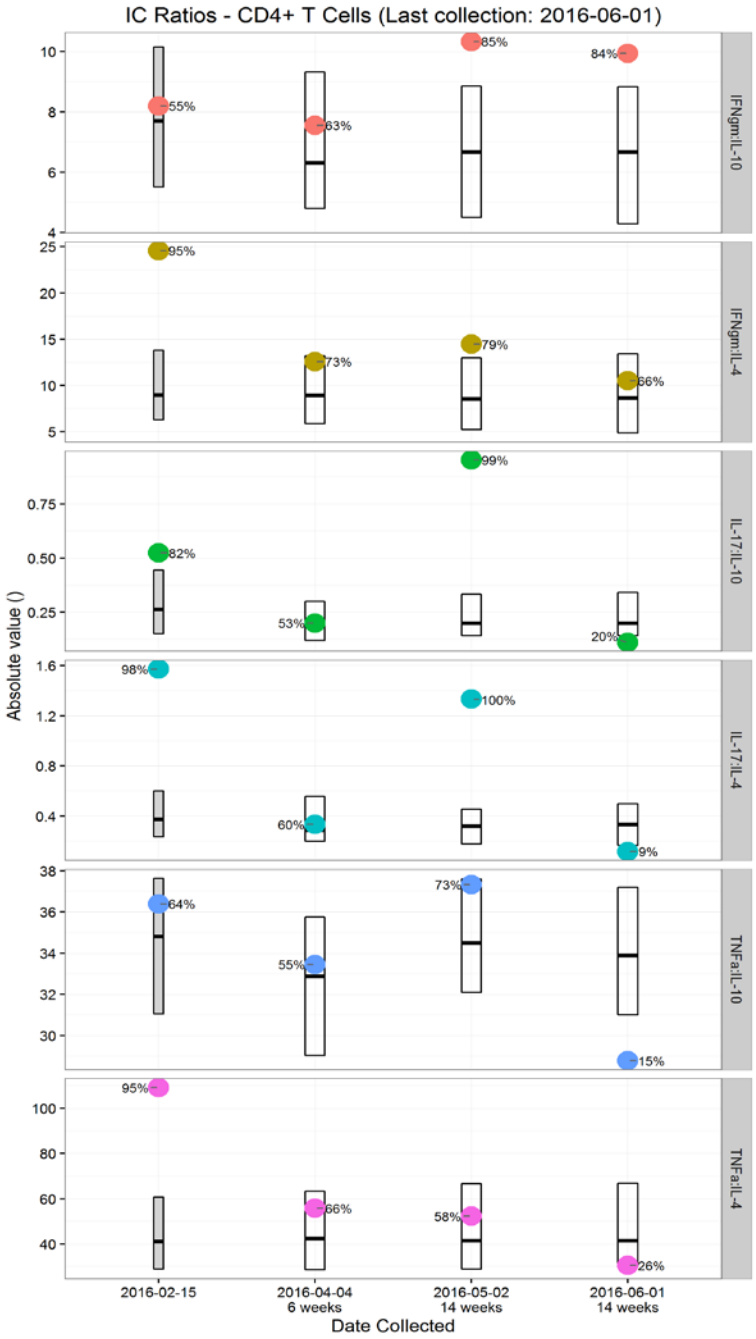
Clinical History

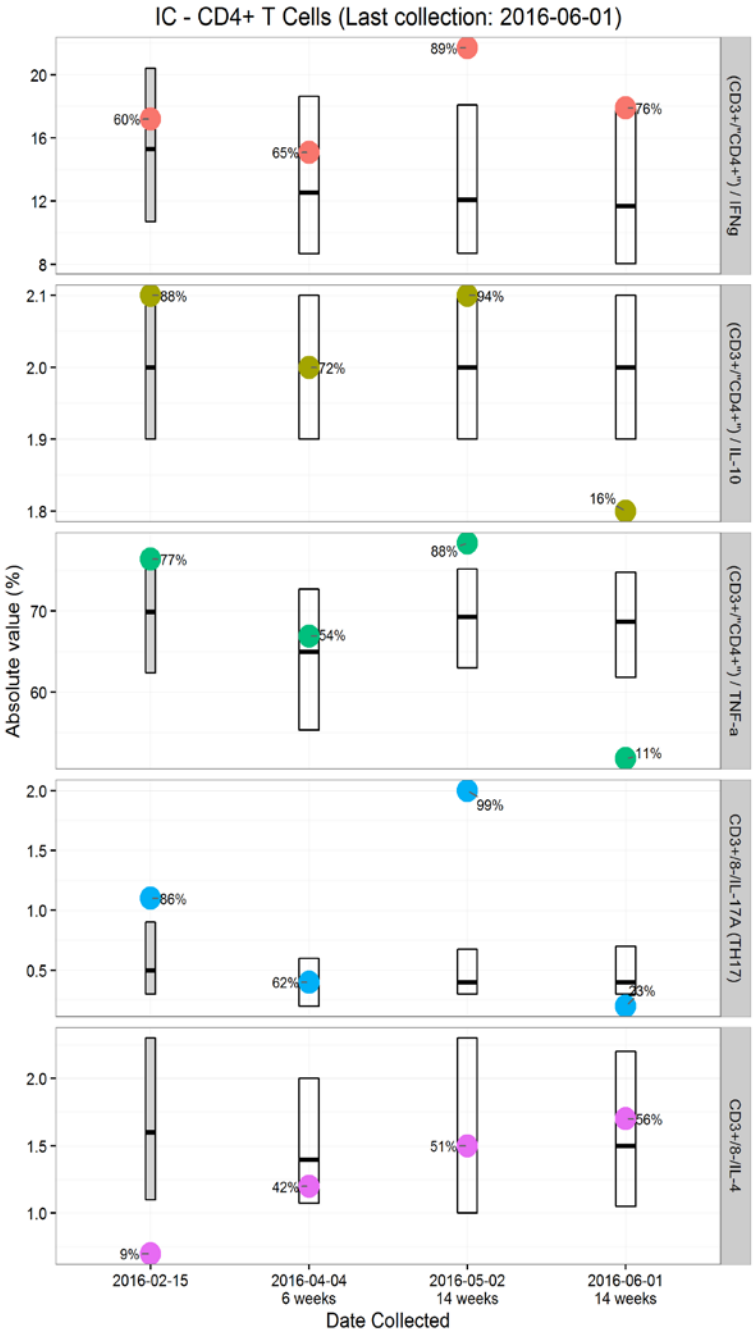
- Currently 35 years old
- History of 3 losses at 10 (spontaneous pregnancy), 7 (monitored cycle), and then 6 weeks (FET cycle)
  - 10 week loss was trisomy 21
  - 7 week loss was trisomy 15
  - 6 week loss tested karyotypically normal
  - Also multiple negative pregnancy tests with IUI cycles and FET cycles
- History of PCOS
  - History of irregular menstrual cycles
    - Average about 2-3 months between periods, but up to 8 months
  - History of 25 and 30 eggs produced with IVF
  - History of AMH = 3.9
- History of flu-like symptoms with conception
- History of Factor V Leiden mutation
- History of multiple environmental and food allergies
- History of tonsillectomy and adenoidectomy
  - Enlarged lymph node in neck removed and found to be benign hyperplasia
- Family history of miscarriages
- Partner with history of prostatitis treated with a course of antibiotics

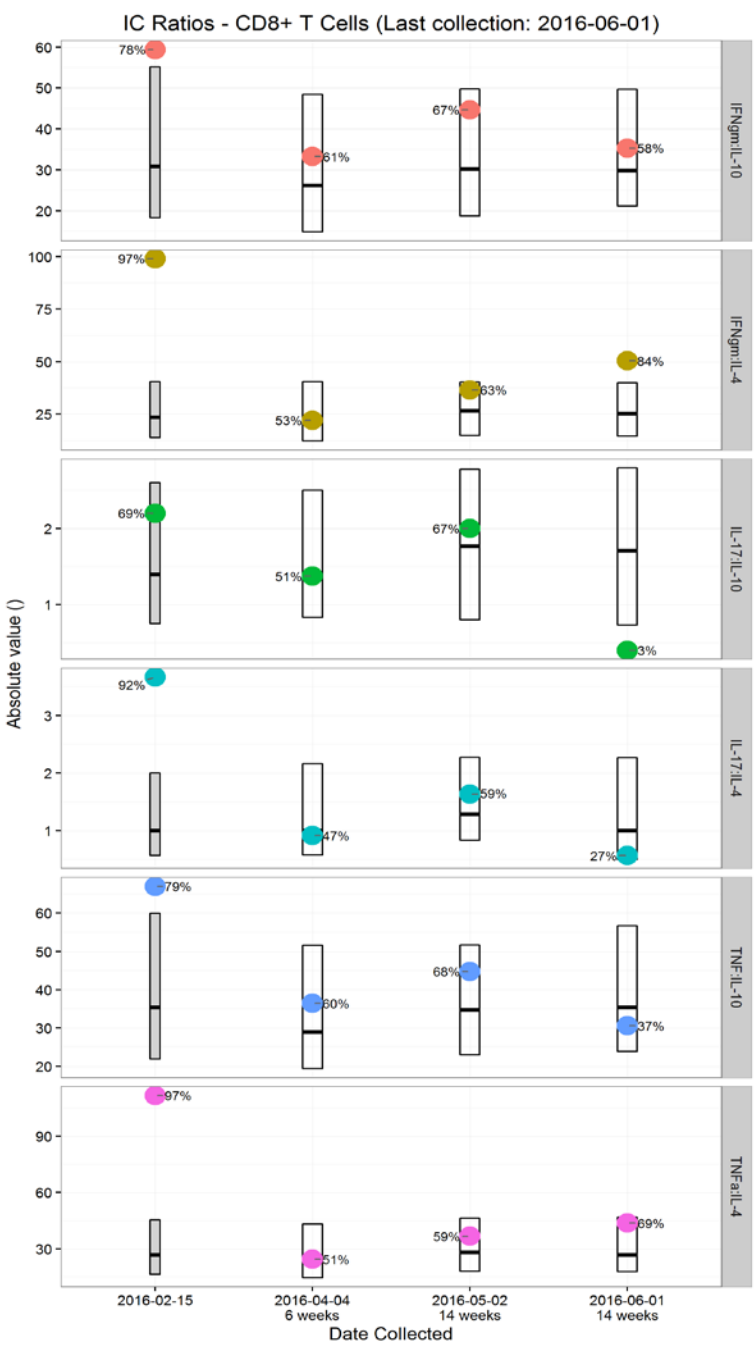
Treatments

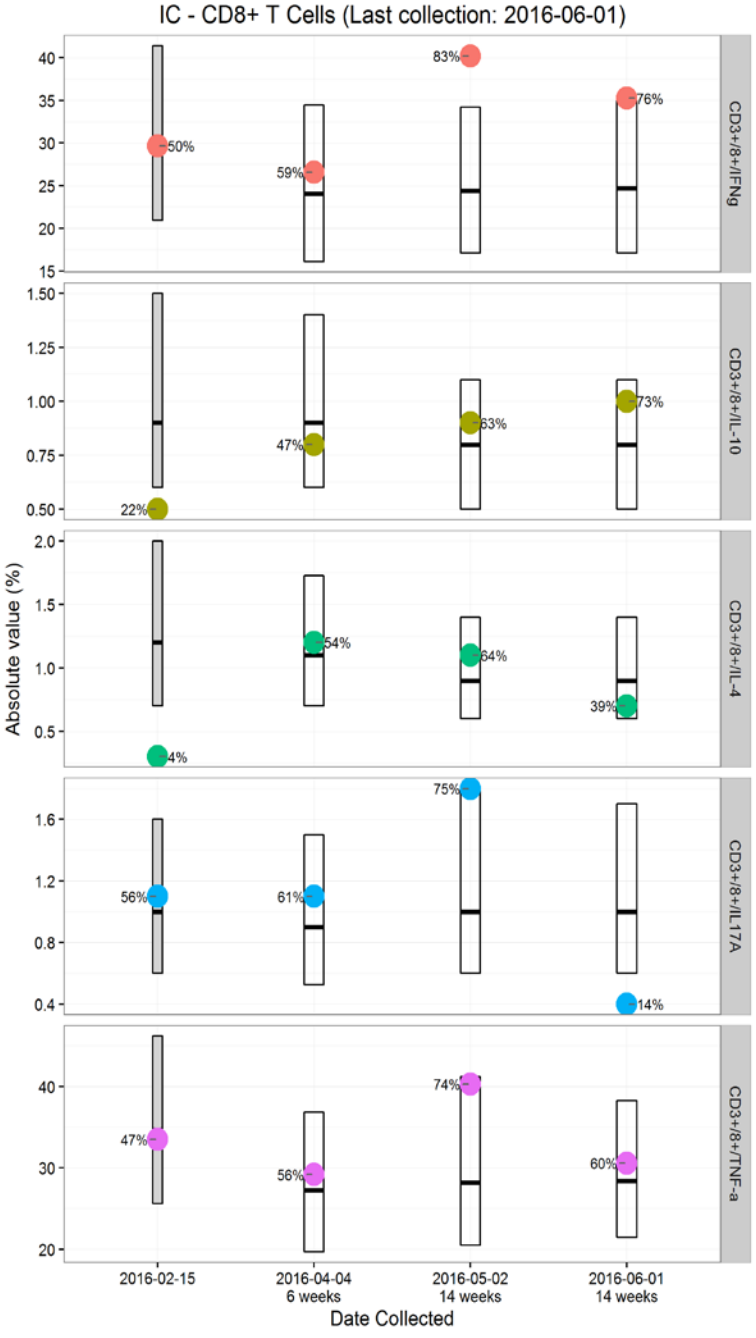
- Prednisone
  - 10 mg BID – increased to 30 mg QD around 4-16-16 – increased to 20 mg BID around 4-19-16 – started tapering around 6-17-16 (~16 weeks pregnant)
- Intralipid
  - 100 ml every 4 weeks – discontinued around 6-15-16
- Lovenox
  - 40 mg QD

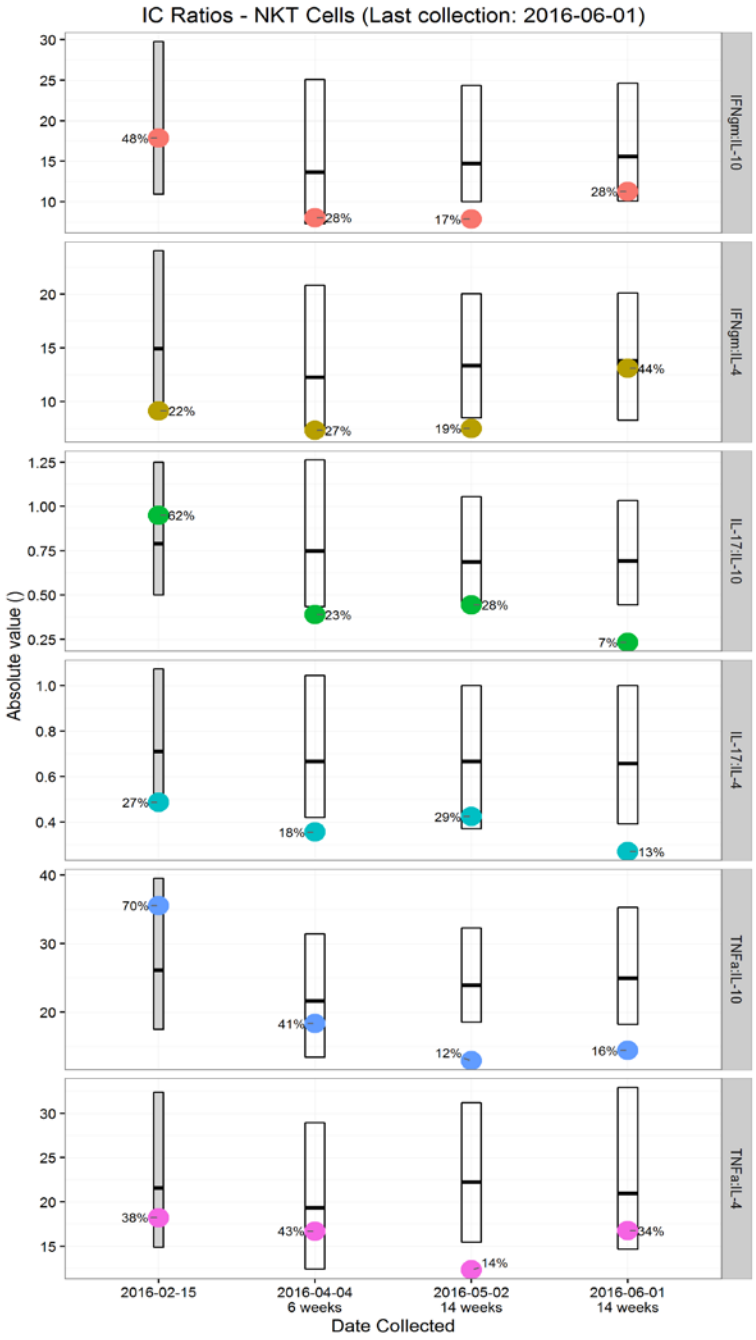
Summary of 6-1-16 Data

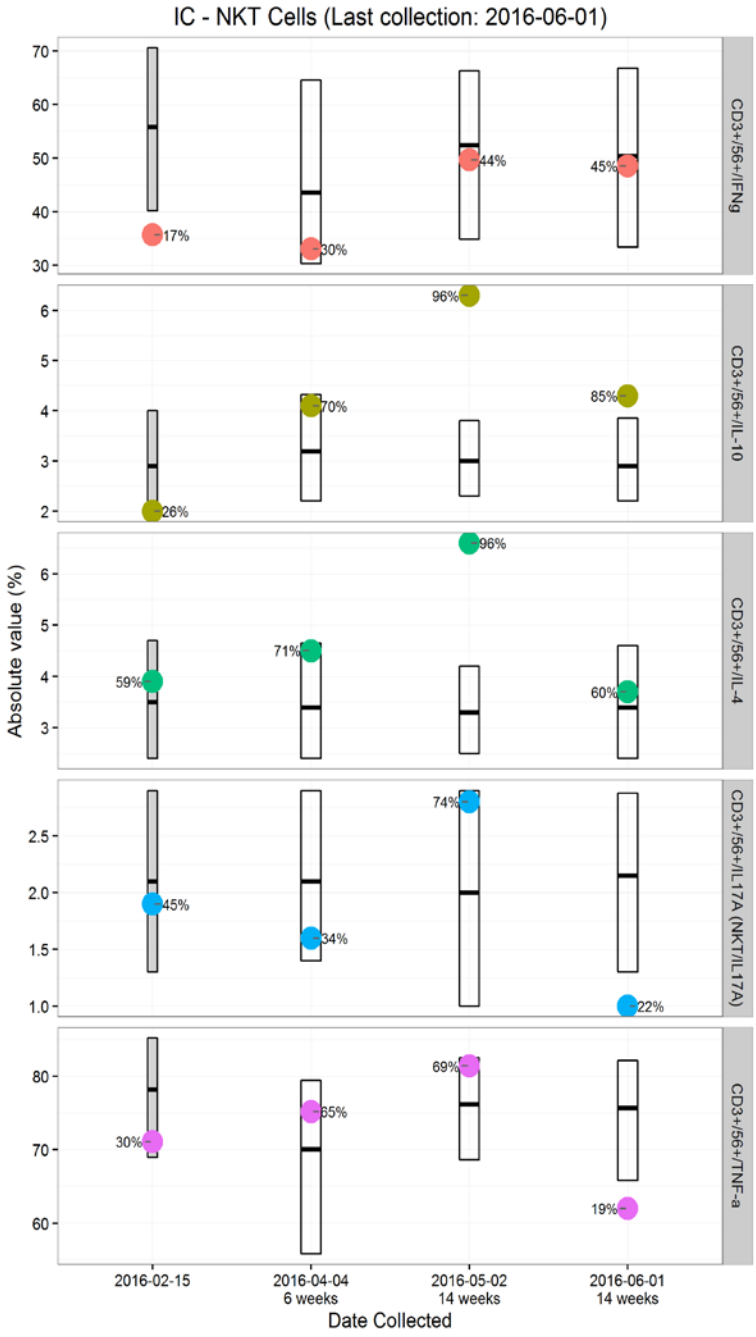


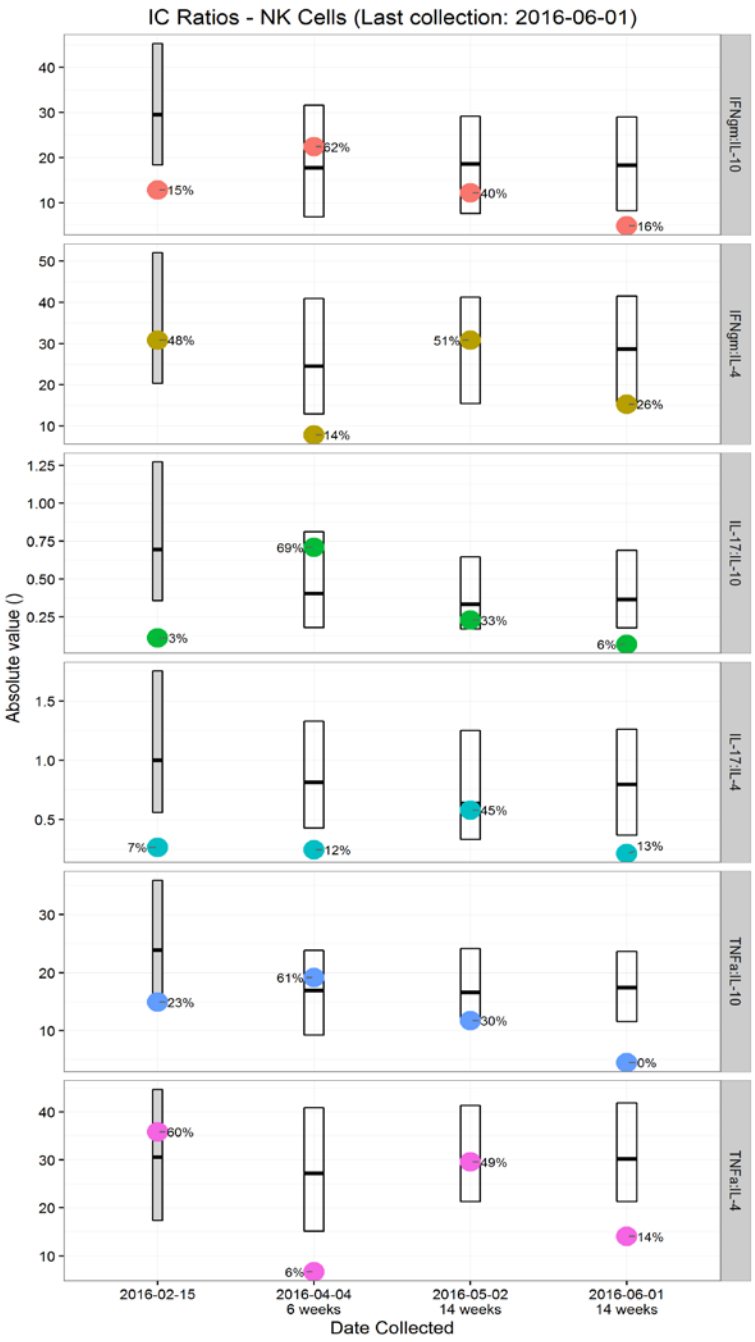


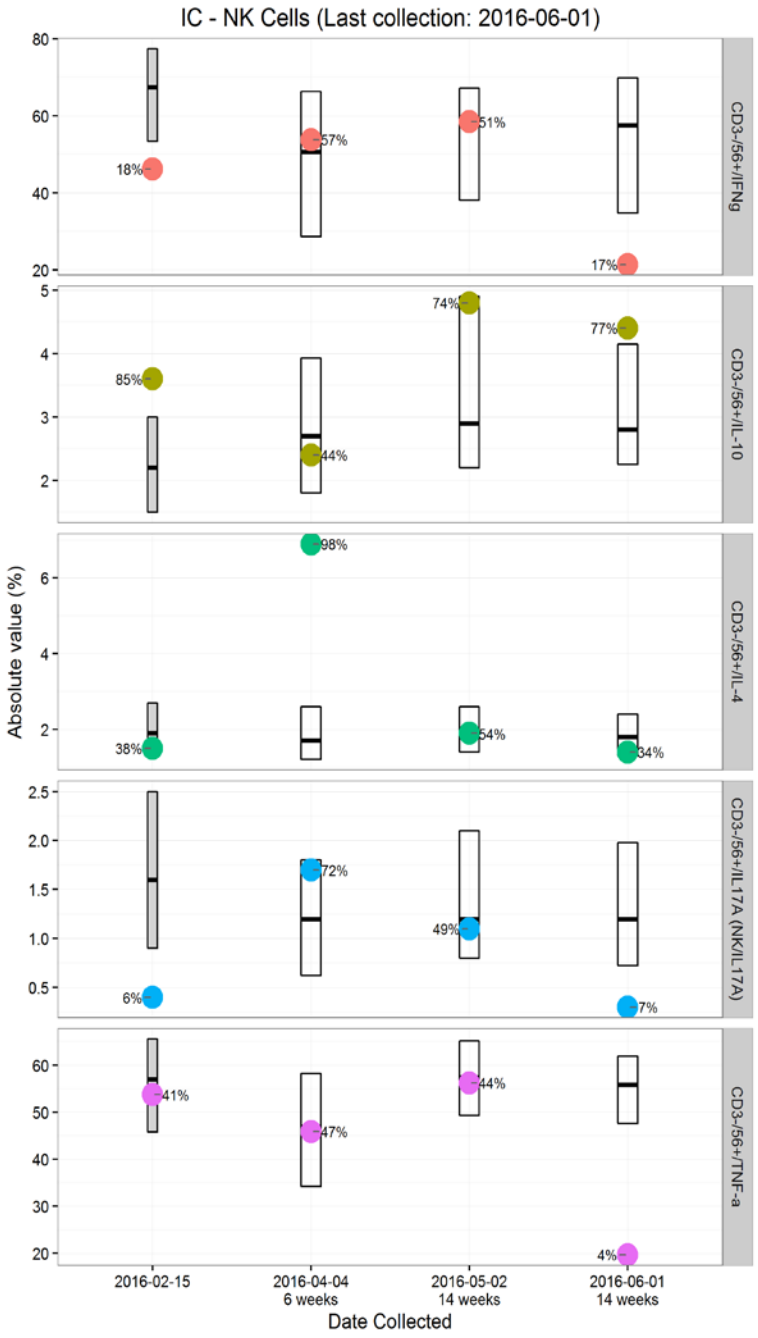

IC Ratios - CD8+ T Cells (Last collection: 2016-06-01)
Absolute value ()
IFNgm:IL-10
IFNgm:IL-4
IL-17:IL-10
IL-17:IL-4
TNF:IL-10
TNFa:IL-4
78%
61%
67%
58%
97%
53%
63%
84%
69%
51%
67%
3%
92%
47%
59%
27%
79%
60%
68%
37%
97%
51%
59%
69%
2016-02-15
2016-04-04
6 weeks
2016-05-02
14 weeks
2016-06-01
14 weeks
Date Collected


IC - CD8+ T Cells (Last collection: 2016-06-01)
Absolute value (%)
CD3+/8+/IFNg
CD3+/8+/IL-10
CD3+/8+/IL-4
CD3+/8+/IL17A
CD3+/8+/TNF-a
50%
59%
83%
76%
22%
47%
63%
73%
4%
54%
64%
39%
56%
61%
75%
14%
47%
56%
74%
60%
2016-02-15
2016-04-04
6 weeks
2016-05-02
14 weeks
2016-06-01
14 weeks
Date Collected

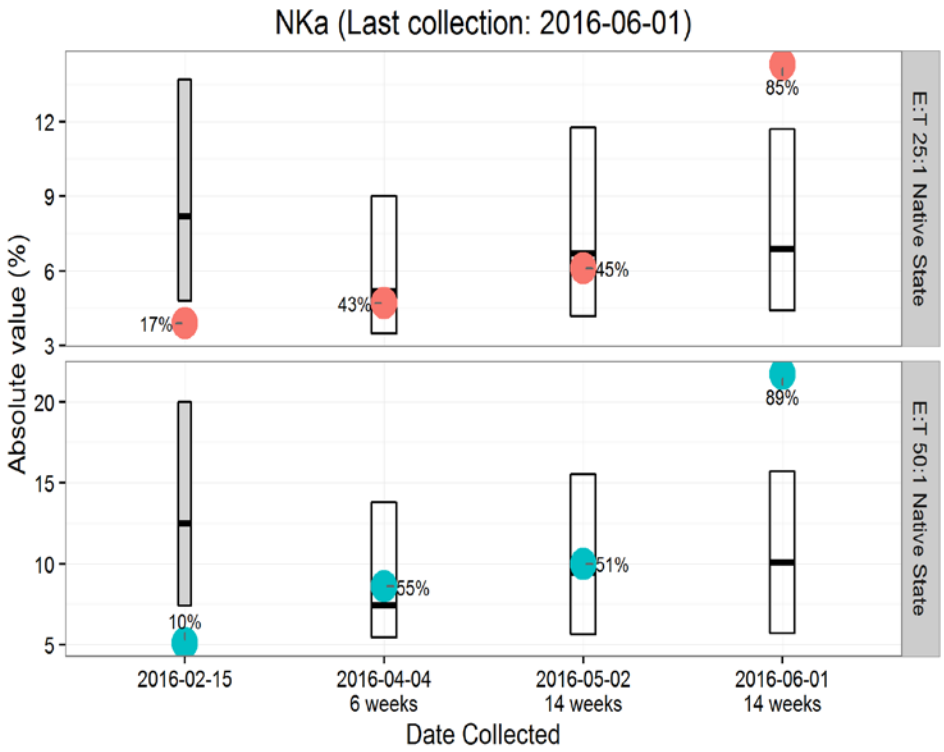

IC Ratios - NKT Cells (Last collection: 2016-06-01)
IFNgm:IL-10
IFNgm:IL-4
IL-17:IL-10
IL-17:IL-4
TNFa:IL-10
TNFa:IL-4
Absolute value ()
48%
28%
17%
28%
22%
27%
19%
44%
62%
23%
28%
7%
27%
18%
29%
13%
70%
41%
12%
16%
38%
43%
14%
34%
2016-02-15
2016-04-04
6 weeks
2016-05-02
14 weeks
2016-06-01
14 weeks
Date Collected


IC - NKT Cells (Last collection: 2016-06-01)
CD3+/56+/IFNg
CD3+/56+/IL-10
CD3+/56+/IL-4
CD3+/56+/IL17A (NKT/IL17A)
CD3+/56+/TNF-a
Absolute value (%)
17%
30%
44%
45%
26%
70%
96%
85%
59%
71%
96%
60%
45%
34%
74%
22%
30%
65%
69%
19%
2016-02-15
2016-04-04
6 weeks
2016-05-02
14 weeks
2016-06-01
14 weeks
Date Collected

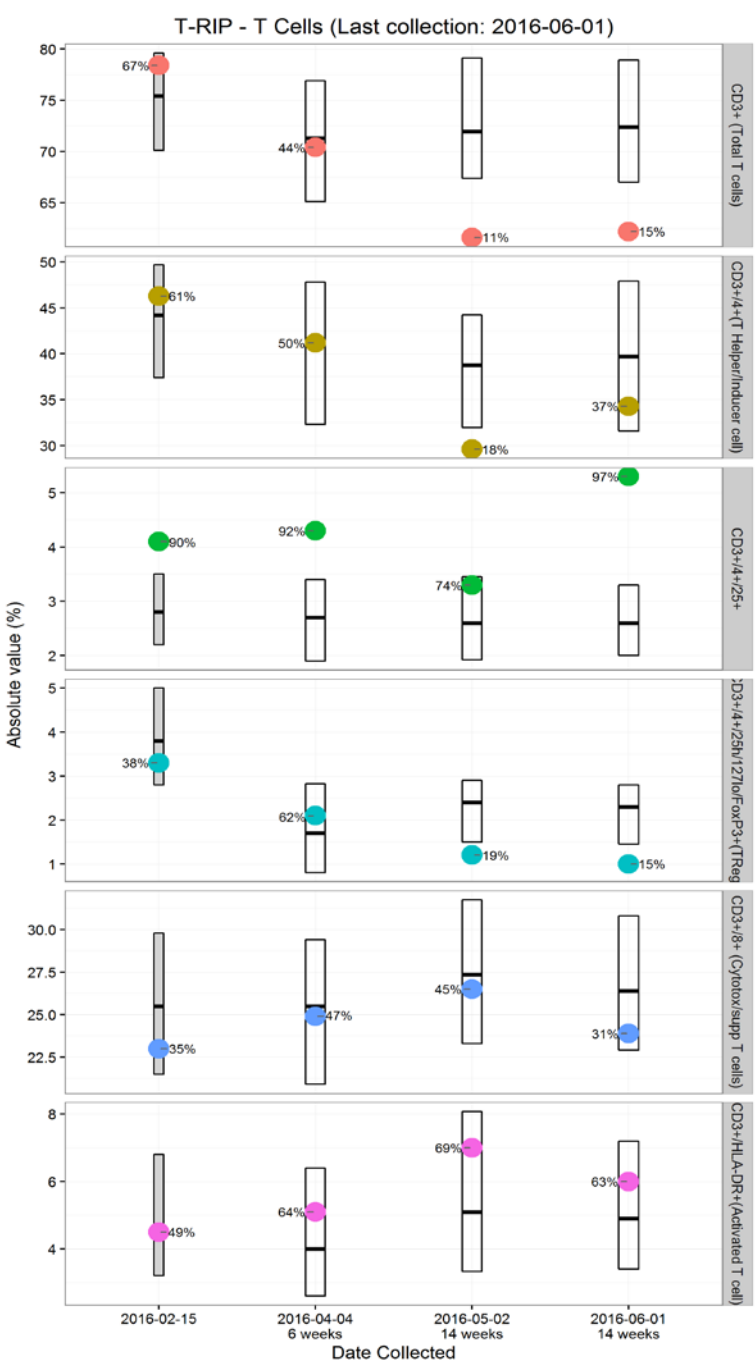


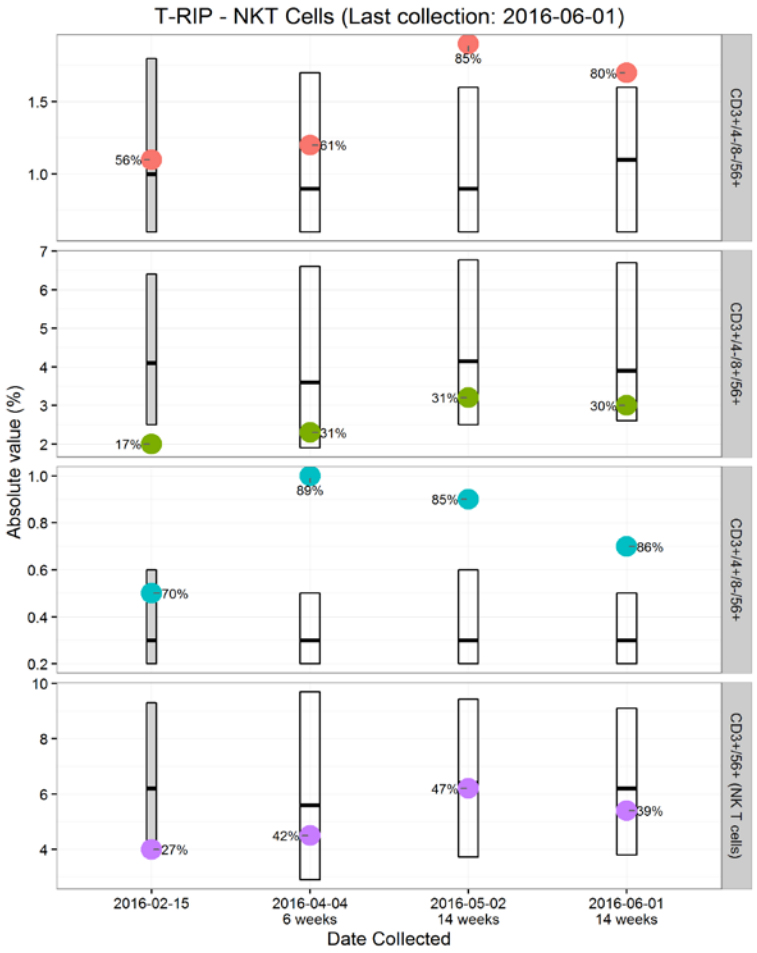


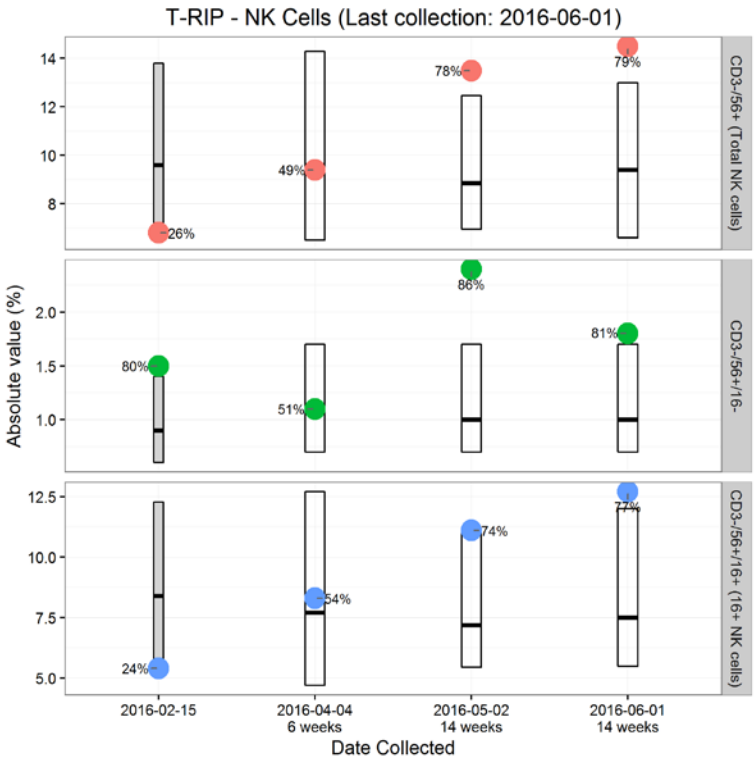
- Compared with results of testing performed on blood from 5-2-16 (~10.5 weeks pregnant), levels of TNFα positive, IFNγ positive, and IL-17 positive cells decreased for all tested cell types (CD4+ T cells, CD8+ T cells, NKT cells, NK cells). This included a decrease in TNFα positive and IL-17 positive CD4+ T cells, CD8+ T cells, and NKT cells from elevated to normal or low levels, although IFNγ positive CD4+ and CD8+ T cells remained mildly elevated. IL-4 positive CD4+ T cells increased, while IL-4 positive CD8+ T cells, NKT cells, and NK cells decreased. These changes to levels of individual intracellular cytokine (IC) positive cells resulted in a Th2 shift from a Th1 bias to Th1/Th2 neutrality. Together with the Th2 shift, there was a decrease in all CD4+ T cell and NK cell IC ratios, as well as your CD8+ T cell TNFα:IL-10 and IFNγ:IL-10 ratios and all CD8+ T cell and NKT cell IL-17 IC ratios. This included a decrease in your CD4+ T cell IL-17 IC ratios from elevated to low levels.

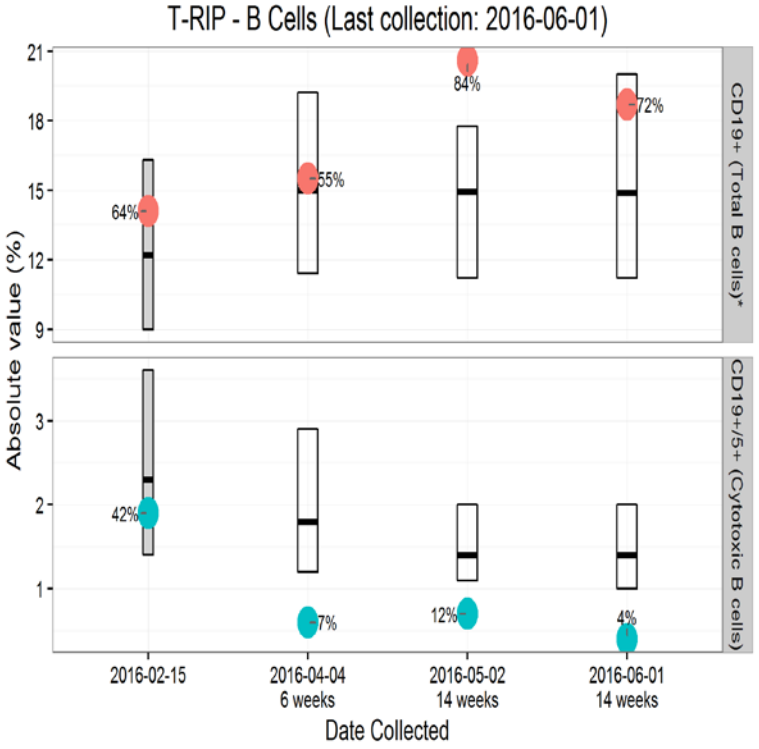


- Your NK cell cytotoxic activity (NKa) increased from normal to elevated levels.

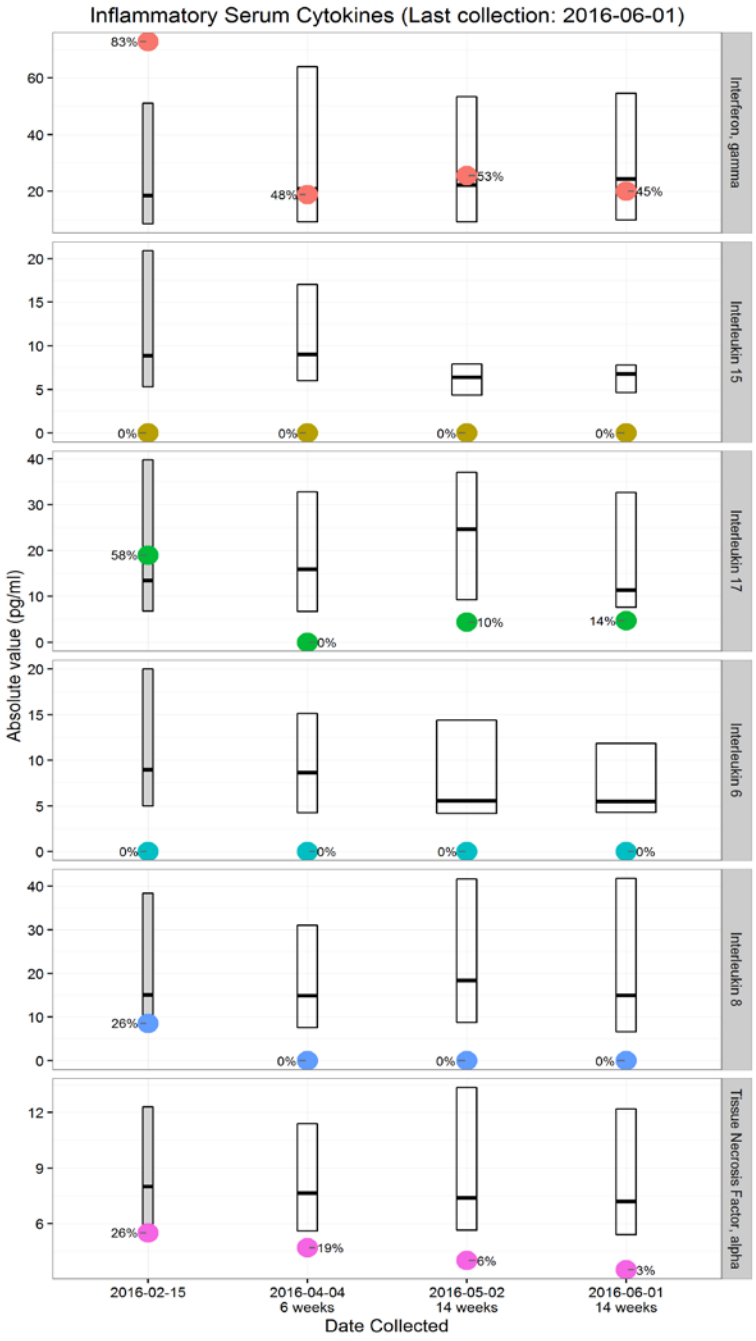

T-RIP - T Cells (Last collection: 2016-06-01)
CD3+ (Total T cells)
CD3+/4+(T Helper/Inducer cell)
CD3+/4+/25+
CD3+/4+25hi127lo/FoxP3+(TReg
CD3+/8+ (Cytotox/supp T cells)
CD3+/HLA-DR+(Activated T cell)
Absolute value (%)
2016-02-15
2016-04-04
6 weeks
2016-05-02
14 weeks
2016-06-01
14 weeks
Date Collected

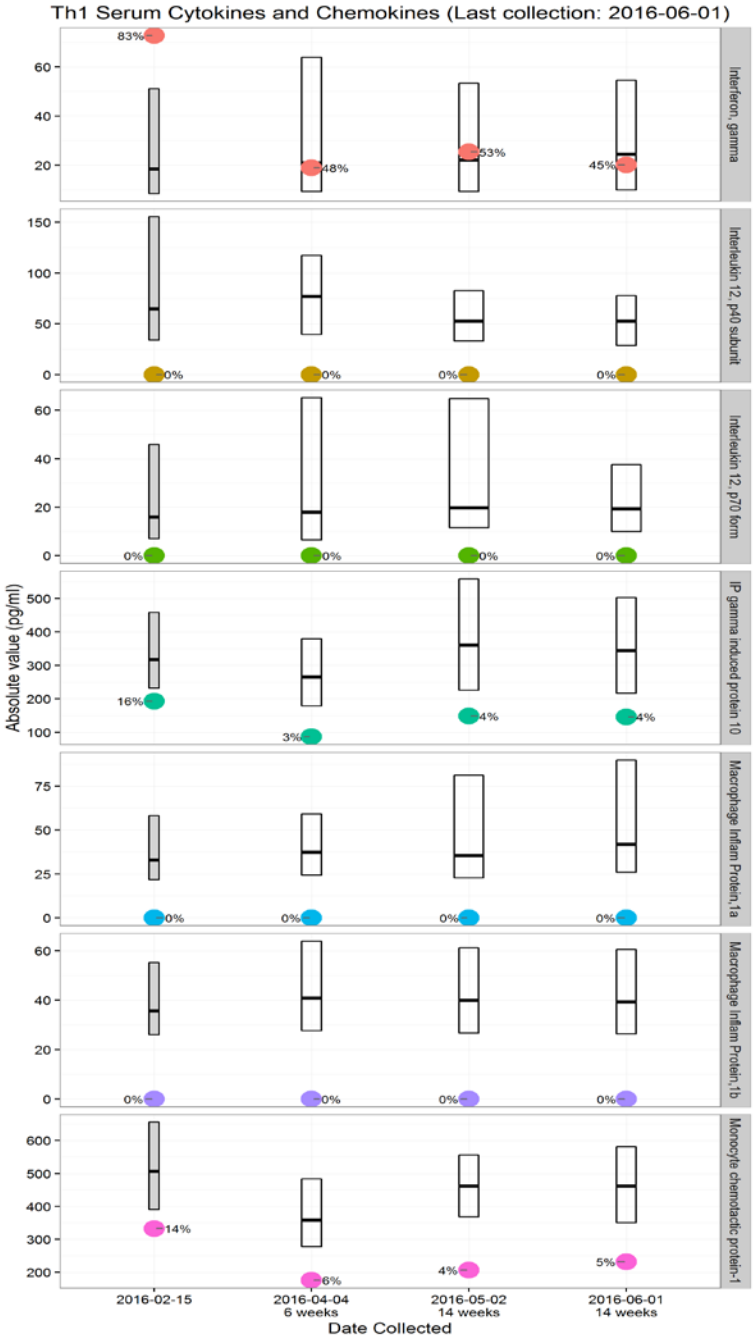

T-RIP - NKT Cells (Last collection: 2016-06-01)
CD3+/4+/8+/56+
CD3+/4+/8+/56+
CD3+/4+/8+/56+
CD3+/56+ (NK T cells)
Absolute value (%)
2016-02-15
2016-04-04
6 weeks
2016-05-02
14 weeks
2016-06-01
14 weeks
Date Collected

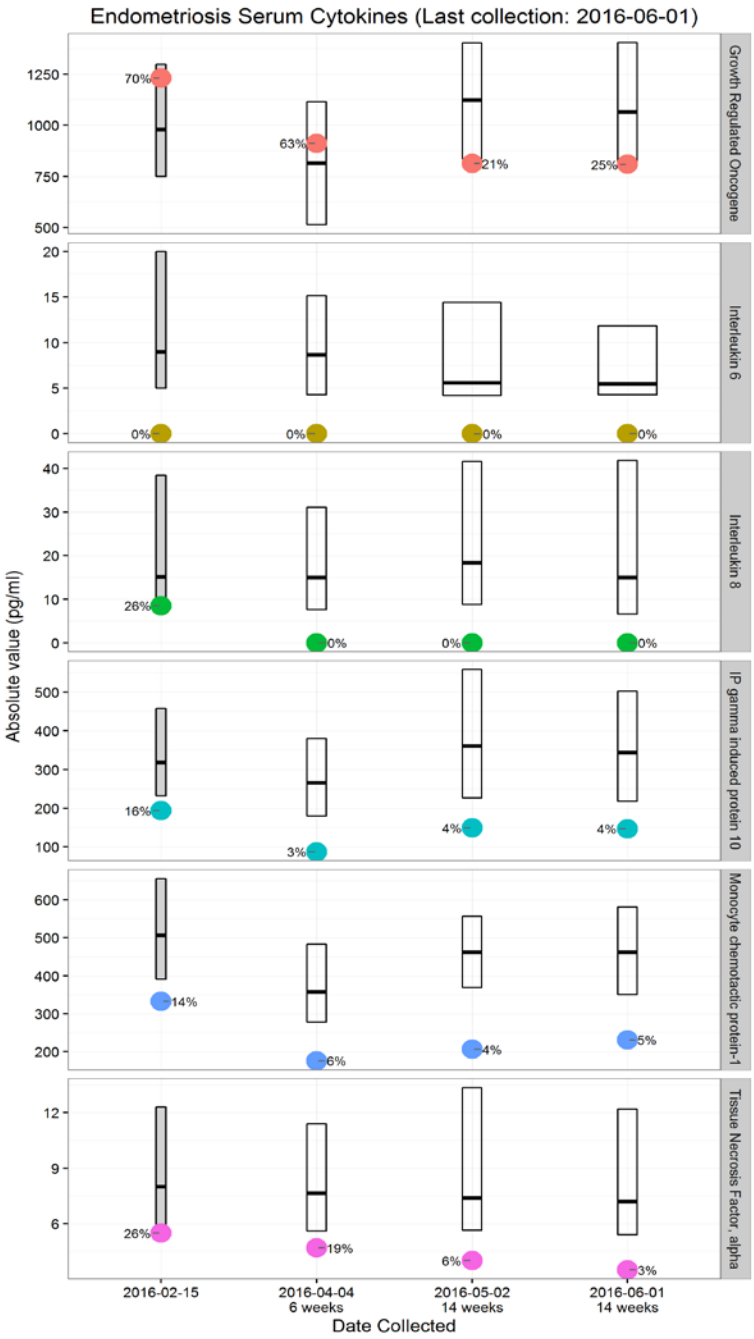




- T-RIP
  - Your total white blood cells (WBCs) decreased slightly from 26.0 to 20.3 although your Treg cells decreased from borderline low to low levels, indicative of further recruitment of these cells to the decidua from the peripheral blood. Your total and CD16+ NK cells increased slightly from borderline elevated to mildly elevated levels.
- CBC
  - Elevated WBCs = 20.3
  - Elevated hematocrit (45.7)
  - Elevated MCV (105.2)
  - Elevated RDW (18.7)
  - Elevated absolute neutrophils (18006)
  - Low MCHC (31.2)


Inflammatory Serum Cytokines (Last collection: 2016-06-01)
Absolute value (pg/ml)
Interferon, gamma
Interleukin 15
Interleukin 17
Interleukin 6
Interleukin 8
Tissue Necrosis Factor, alpha
83%
48%
53%
45%
0%
58%
10%
14%
26%
19%
6%
3%
2016-02-15
2016-04-04
6 weeks
2016-05-02
14 weeks
2016-06-01
14 weeks
Date Collected


Th1 Serum Cytokines and Chemokines (Last collection: 2016-06-01)
Absolute value (pg/ml)
Interferon, gamma
Interleukin 12, p40 subunit
Interleukin 12, p70 form
IP gamma induced protein 10
Macrophage Inflam Protein,1a
Macrophage Inflam Protein,1b
Monocyte chemotactic protein-1
83%
48%
53%
45%
0%
16%
3%
4%
14%
6%
5%
2016-02-15
2016-04-04
6 weeks
2016-05-02
14 weeks
2016-06-01
14 weeks
Date Collected



- Serum levels of cytokines and chemokines remained largely unchanged and within normal ranges or low.

- ANA/APA/ATA
  - Normal C3 complement activity (116)
  - Normal C4 complement activity (23)
  - Negative for anti-TPO/THAB
    - Anti-TPO = 1.0
    - THAB = <1.0
  - Negative for TSH receptor antibody (<6.00)
  - Negative for ANAs
  - Negative for APAs
  - Total 25 Hydroxy Vit D sufficiency (40.5)
    - 25 Hydroxy Vit D2 = <5.0
    - 25 Hydroxy Vit D3 = 40.5
  - Antiphosphatidylethanolamine IgM and antiphosphatidylglycerol IgM antiphospholipid antibodies (APAs) both decreased from indeterminate to negative levels and your C3 and C4 complement activities remained within normal ranges. You remained negative for all tested ANAs and ATAs.
- Summary
  - There was an overall decrease in activation of your immune system at the cellular level, evidenced by a decrease in levels of TNFα positive, IFNγ positive, and IL-17 positive cells for all tested cell types (including a decrease in TNFα positive and IL-17 positive CD4+ T cells, CD8+ T cells, and NKT cells from elevated to normal or low levels); a Th2 shift from a Th1 bias to Th1/Th2 neutrality together with a decrease in all CD4+ T cell and NK cell IC ratios, as well as your CD8+ T cell TNFα:IL-10 and IFNγ:IL-10 ratios and all CD8+ T cell and NKT cell IL-17 IC ratios (including a decrease in your CD4+ T cell IL-17 IC ratios from elevated to low levels).
    - Your Treg cells also decreased slightly from borderline low to low levels, indicative of further recruitment of these regulatory cells to the decidua from the peripheral blood.
  - Serum levels of cytokines and chemokines remained largely unchanged and low although there was an overall decrease in levels of systemic inflammation, evidenced by a decrease in antiphosphatidylethanolamine IgM and antiphosphatidylglycerol IgM APAs from indeterminate to negative levels.
- Conclusions
  - Your 6-1-16 data indicate an overall decrease in activation of your immune system at the cellular level with maintenance of a low level of systemic inflammation. Therefore, no changes to your treatment protocol were made following initial expedited review of these data. Although the current data are not concerning, careful monitoring of your pregnancy for the potential onset of any third trimester complications is warranted.