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

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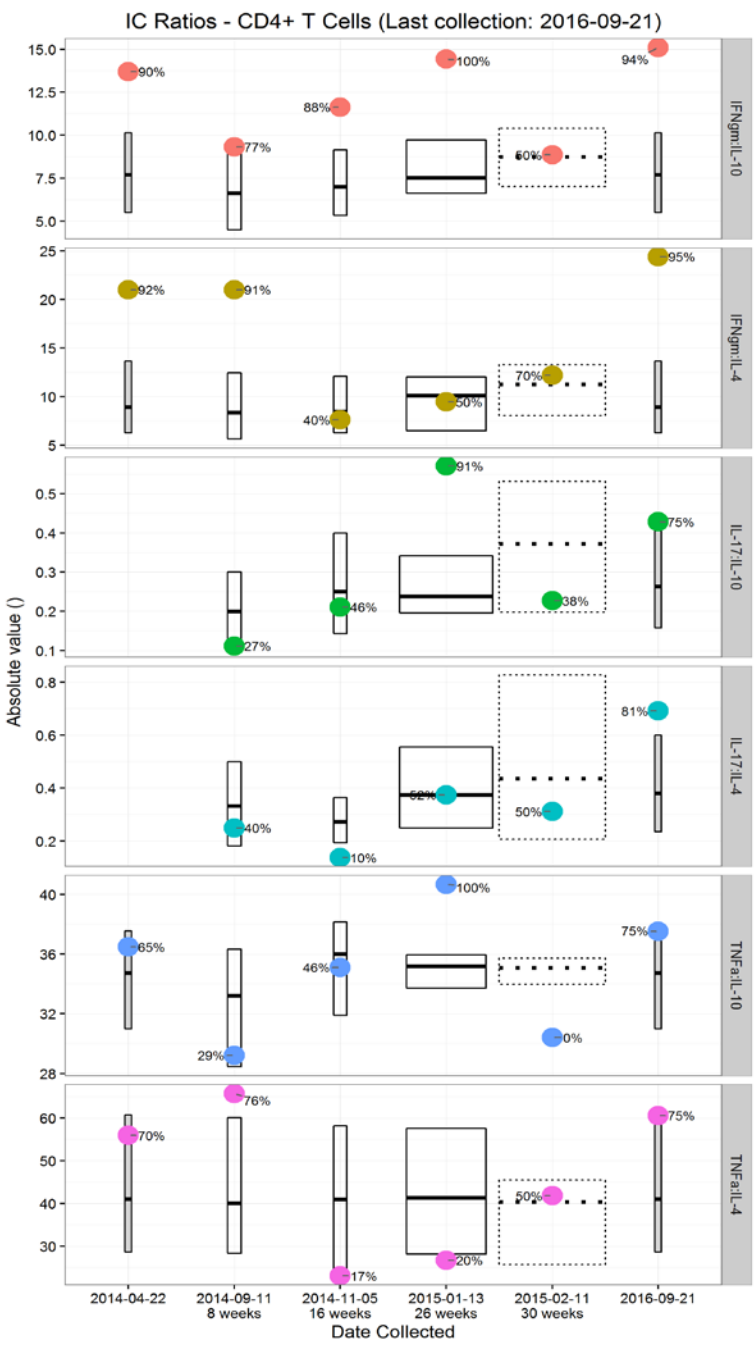
**New Consult Report**

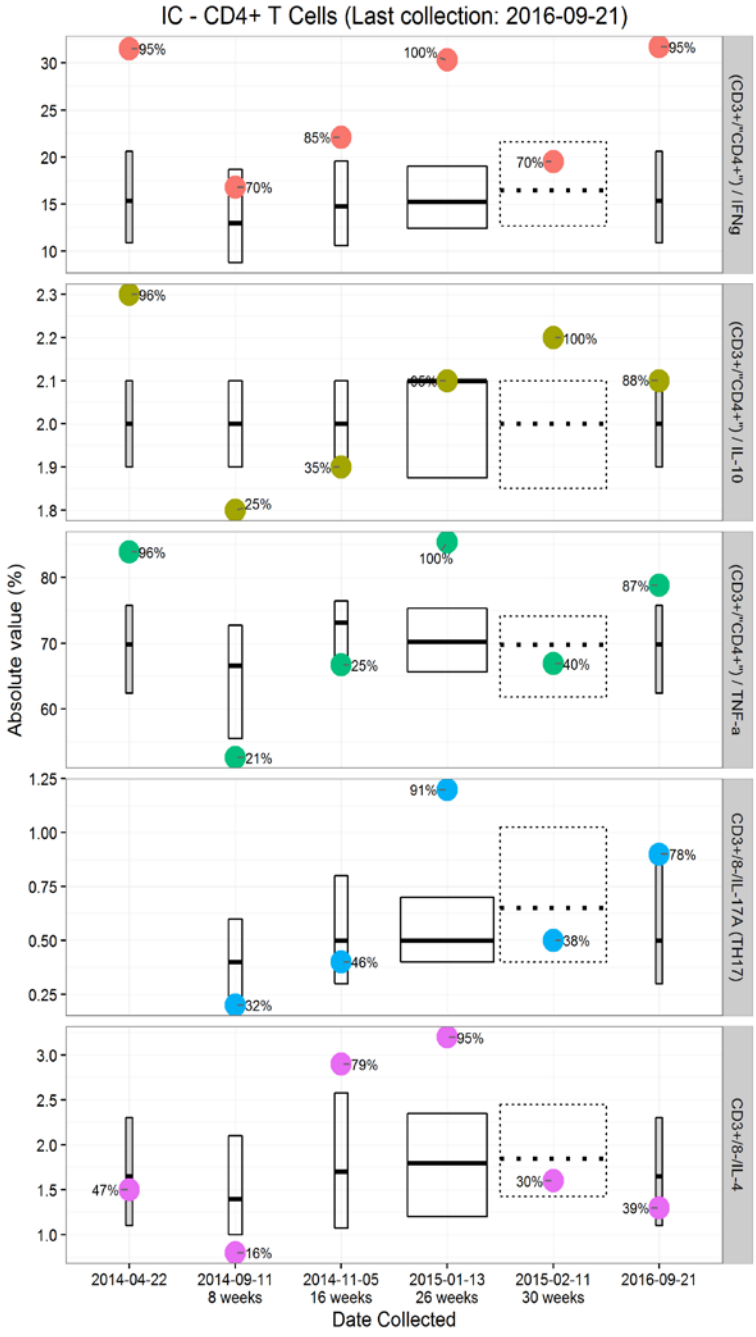
- 9-21-16 (not pregnant)
- 2-11-15 (30 weeks pregnant)
- 1-13-15 (~25.5 weeks pregnant)
- 11-5-14 (~14.5 weeks pregnant)
- 9-11-14 (~6.5 weeks pregnant)
- 4-23-14 (not pregnant)

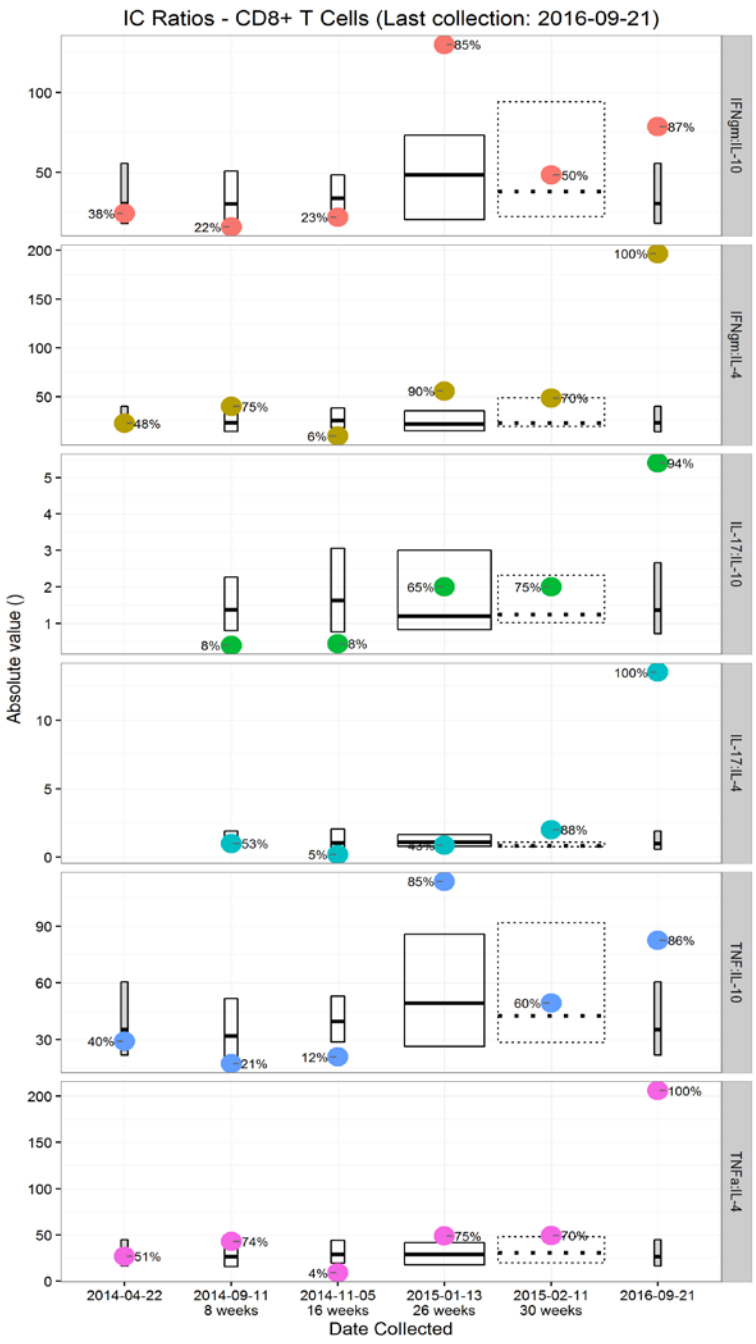
Clinical History

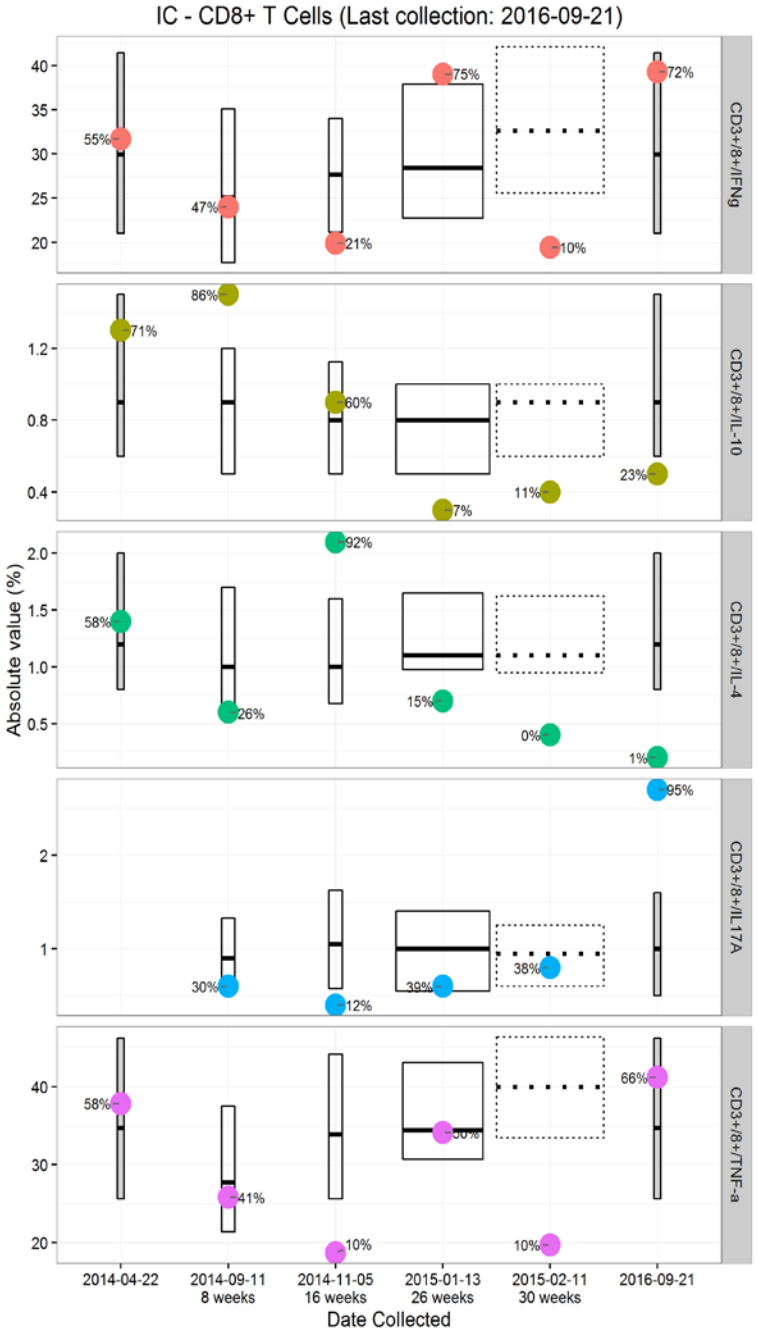
- Currently 37 years old
- Two miscarriages following IVF cycles with PGD followed by successful treatment by Dr. Braverman using Neupogen (1 mcg/kg/day), Intralipid (100 ml every 2 weeks), and Lovenox (30 mg QD)
- Protein S deficiency
- History of blood clots
- Family history of miscarriages
- Endometrial polyp removed in June, 2013

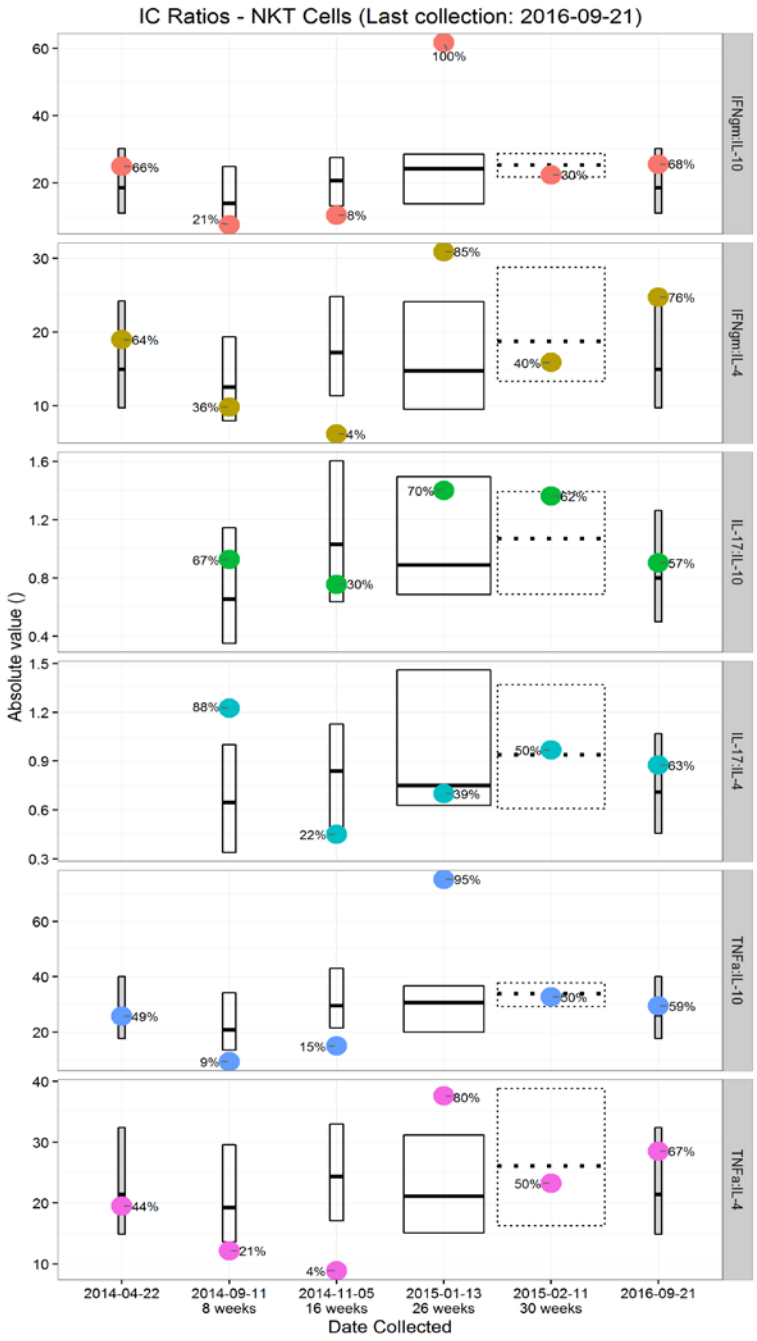
Summary of 9-21-16 Data

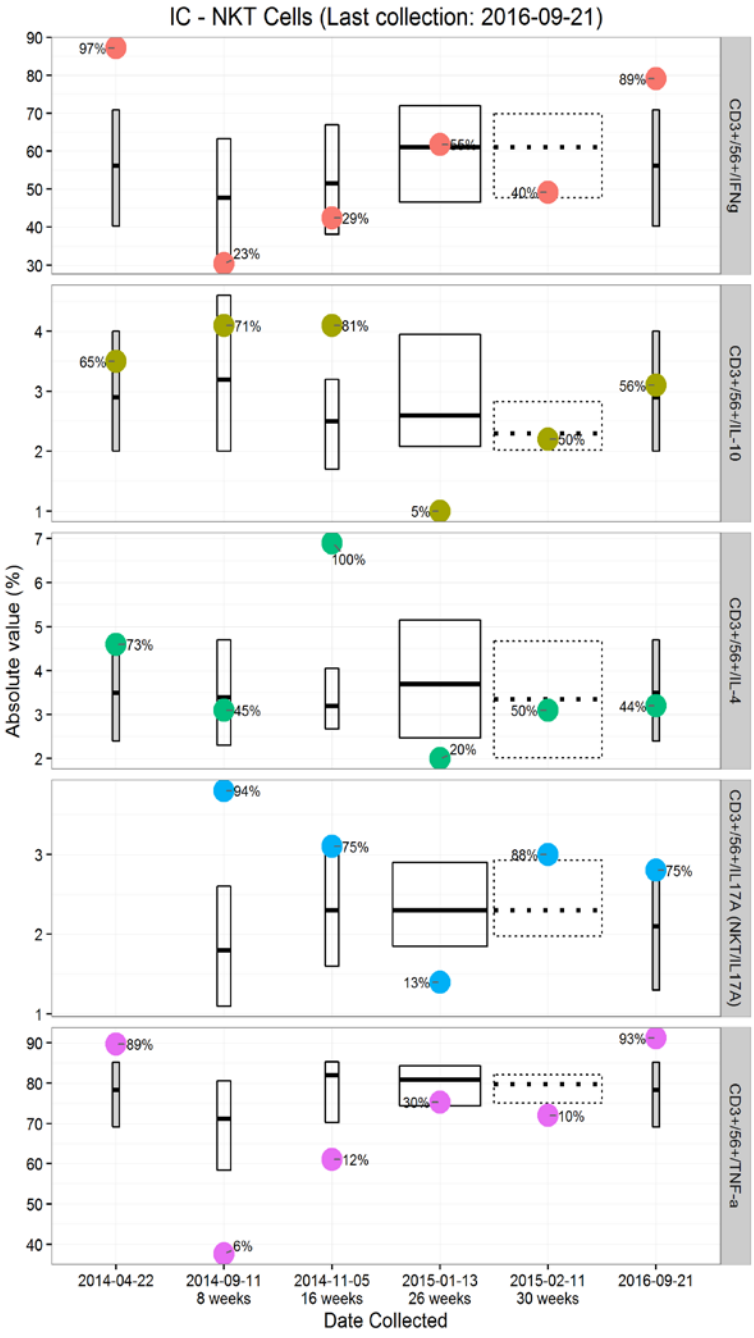


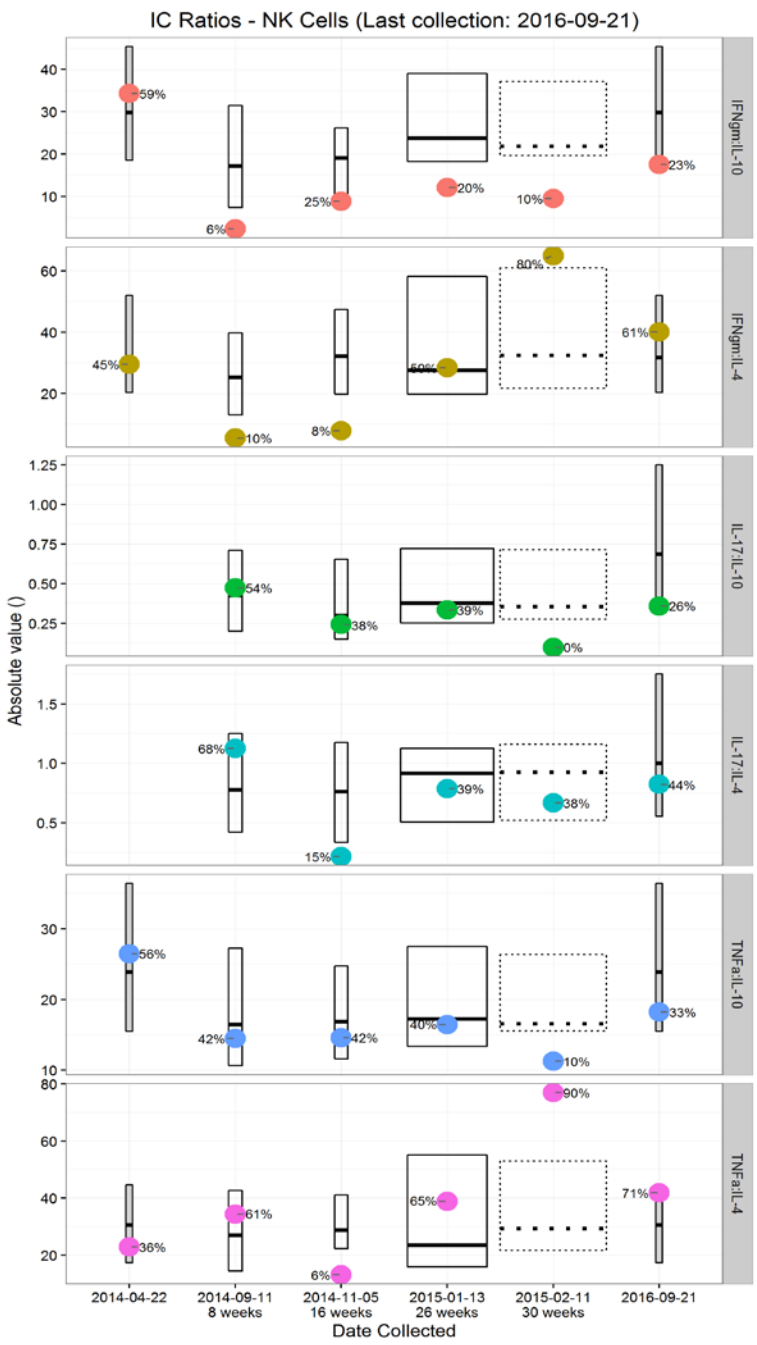



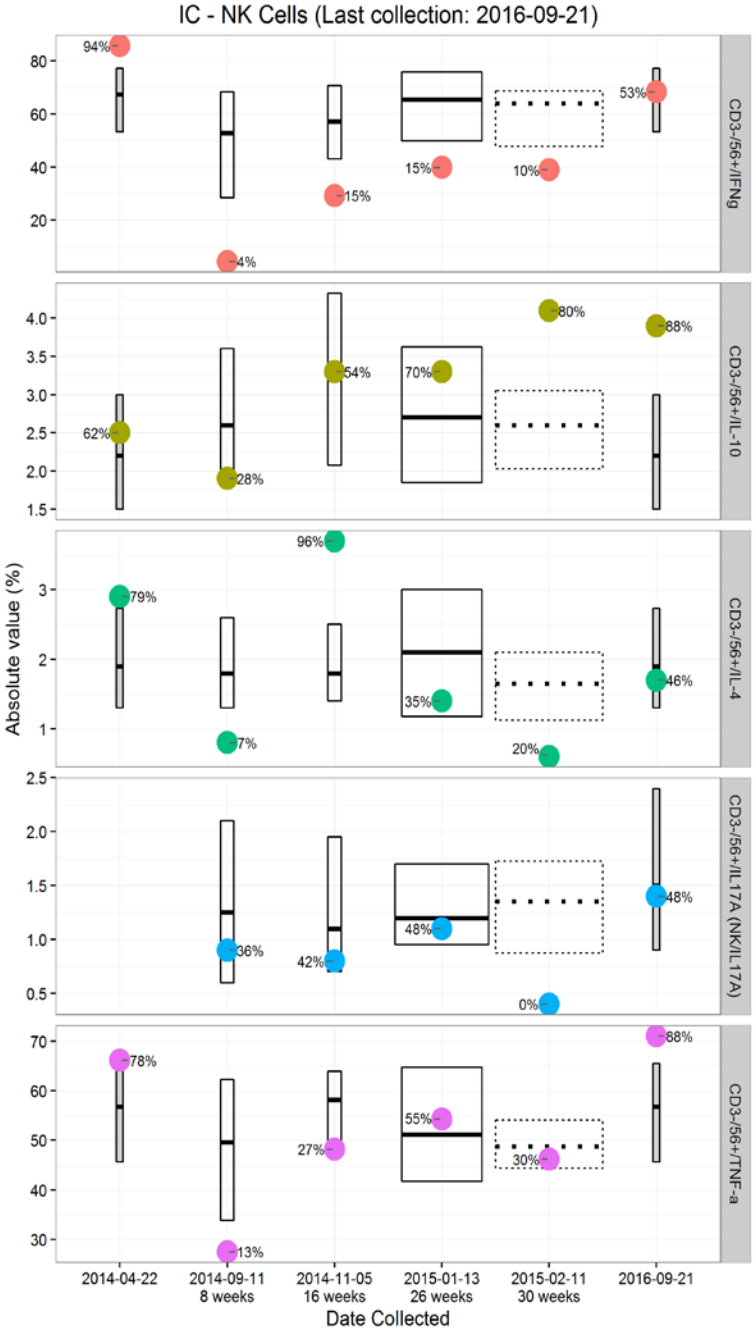

IC Ratios - CD8+ T Cells (Last collection: 2016-09-21)
IFNgm:IL-10
IFNgm:IL-4
IL-17:IL-10
IL-17:IL-4
TNF:IL-10
TNFa:IL-4
Absolute value ()
2014-04-22
2014-09-11 8 weeks
2014-11-05 16 weeks
2015-01-13 26 weeks
2015-02-11 30 weeks
2016-09-21
Date Collected


IC - CD8+ T Cells (Last collection: 2016-09-21)
CD3+/8+/IFNg
CD3+/8+/IL-10
CD3+/8+/IL-4
CD3+/8+/IL17A
CD3+/8+/TNF-a
Absolute value (%)
2014-04-22
2014-09-11 8 weeks
2014-11-05 16 weeks
2015-01-13 26 weeks
2015-02-11 30 weeks
2016-09-21
Date Collected

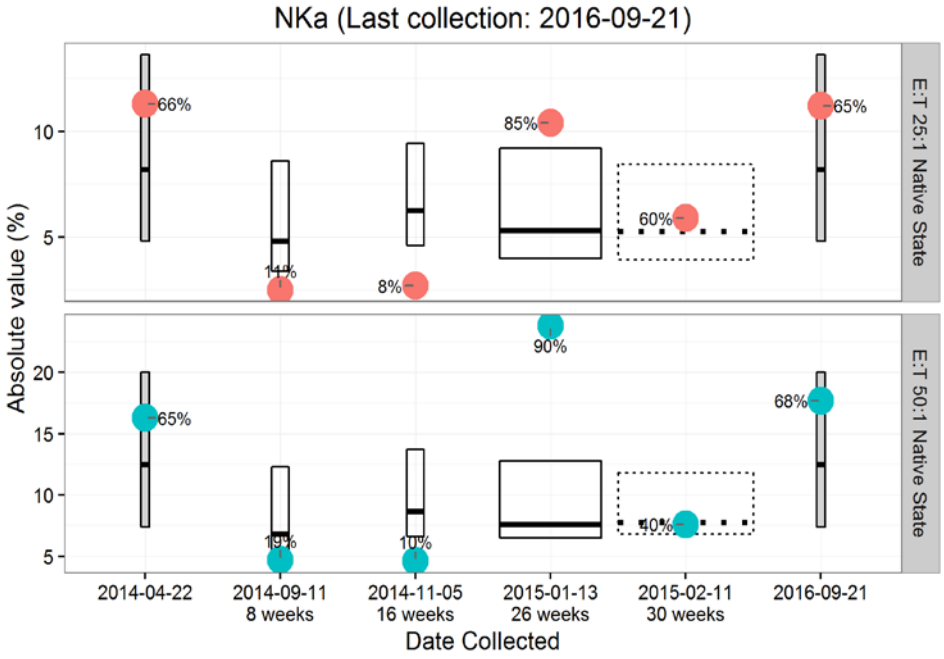

IC Ratios - NKT Cells (Last collection: 2016-09-21)
IFNgm:IL-10
IFNgm:IL-4
IL-17:IL-10
IL-17:IL-4
TNFa:IL-10
TNFa:IL-4
Absolute value ()
Date Collected
2014-04-22
2014-09-11 8 weeks
2014-11-05 16 weeks
2015-01-13 26 weeks
2015-02-11 30 weeks
2016-09-21


IC - NKT Cells (Last collection: 2016-09-21)
CD3+/56+/IFNg
CD3+/56+/IL-10
CD3+/56+/IL-4
CD3+/56+/IL17A (NKT/IL17A)
CD3+/56+/TNF-a
Absolute value (%)
Date Collected
2014-04-22
2014-09-11 8 weeks
2014-11-05 16 weeks
2015-01-13 26 weeks
2015-02-11 30 weeks
2016-09-21

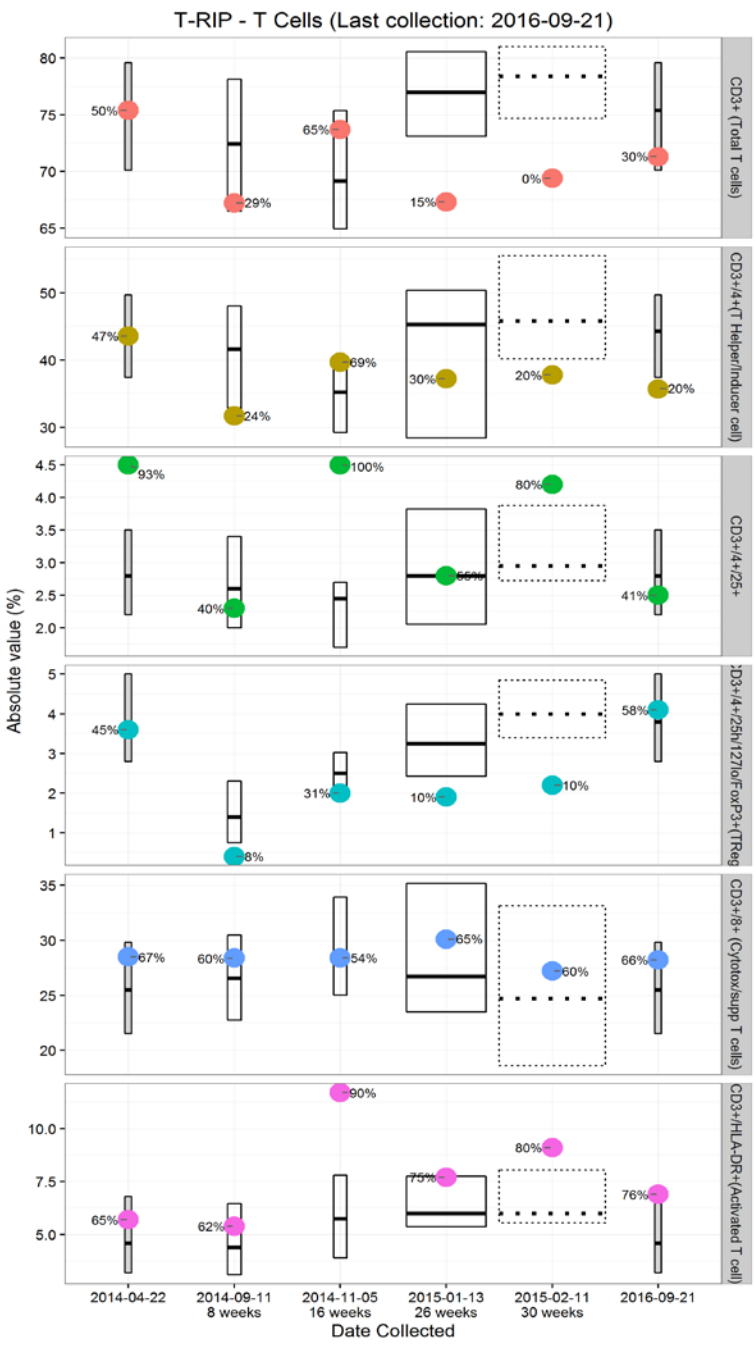


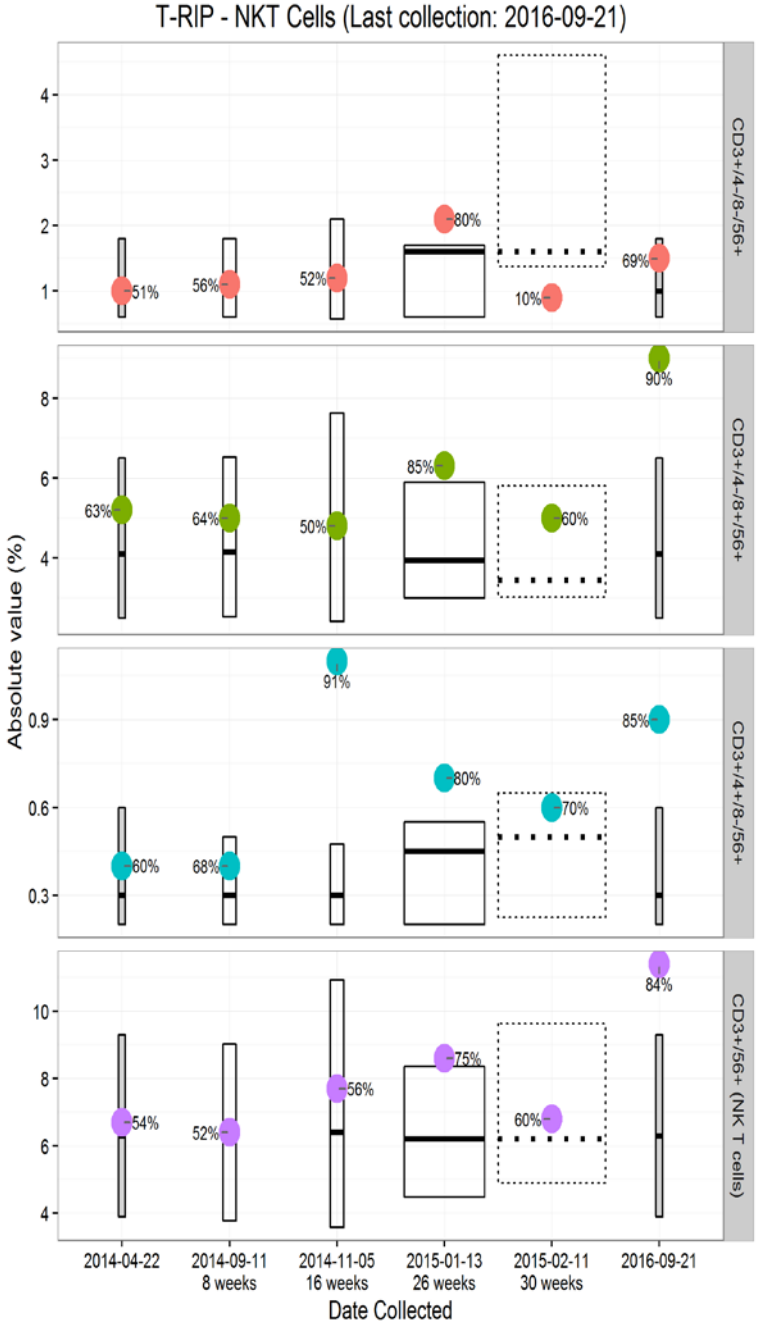



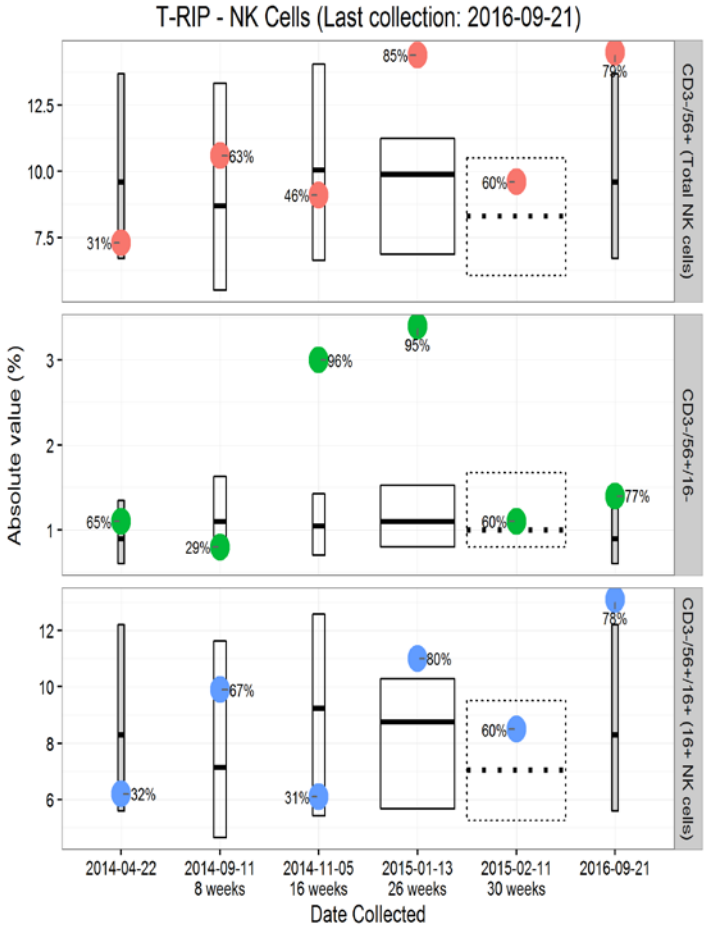

- Compared with baseline testing performed on blood drawn prior to your earlier pregnancy (4-22-14), levels of TNFα positive and IFNγ positive CD8+ T cells increased, as well as TNFα positive NKT and NK cells. IFNγ positive NK cells decreased from elevated to normal levels, and IFNγ positive NKT cells decreased but remained elevated. IL-4 positive cells decreased for all tested cell types. As a result of these changes to levels of individual intracellular cytokine (IC) positive cells, your immune system had a slight Th1 shift to a slightly stronger Th1 bias. Together with the Th1 shift, there was an increase in all CD4+ T cell, CD8+ T cell, and NKT cell TNFα and IFNγ IC ratios, as well as your NK cell TNFα:IL-4 and IFNγ:IL-4 ratios. This included an increase in all CD8+ T cell TNFα and IFNγ IC ratios from normal to elevated levels, and your NK cell TNFα:IL-4 and IFNγ:IL-4 ratios from normal to borderline elevated levels.

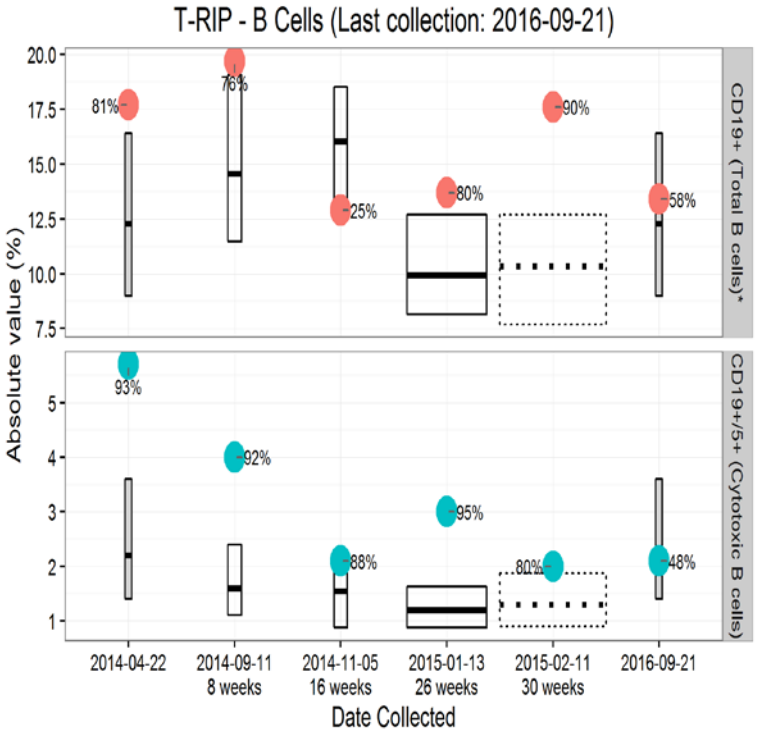



- Your NK cell cytotoxic activity (NKa) remained unchanged and mildly elevated.

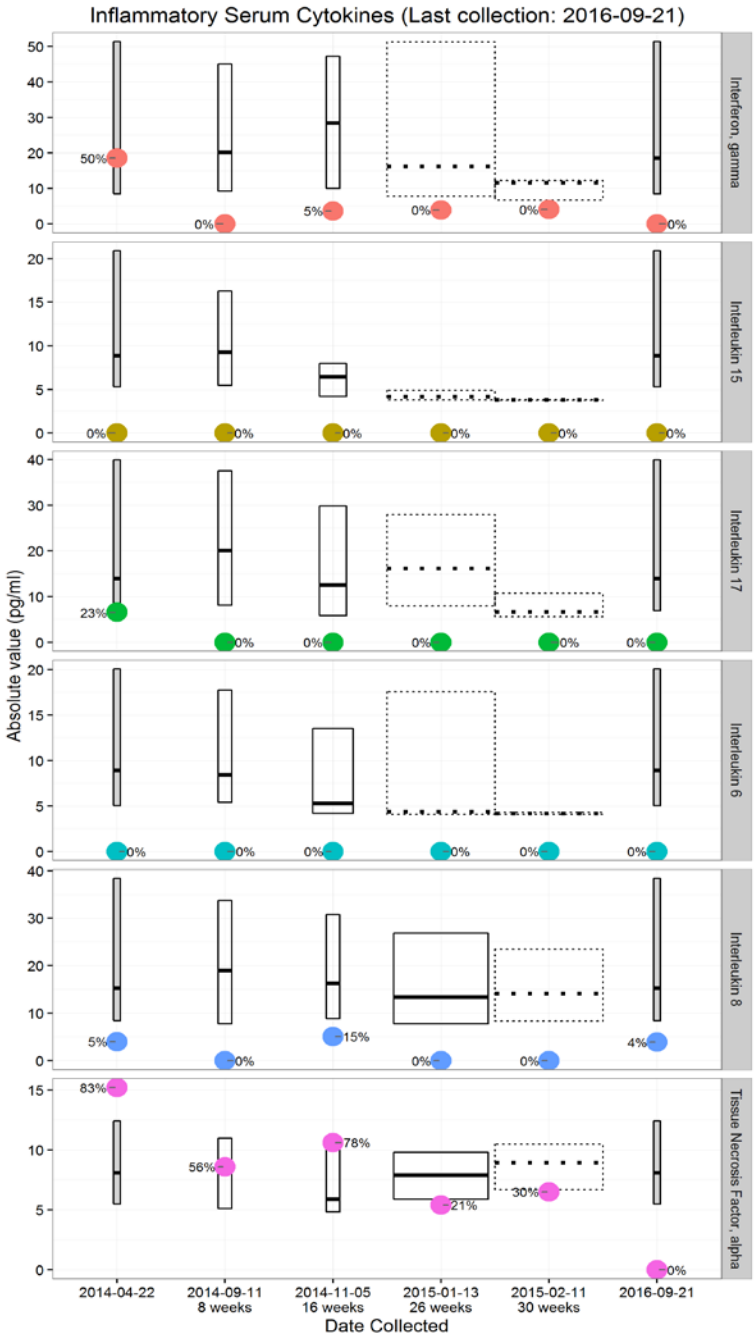

T-RIP - T Cells (Last collection: 2016-09-21)
CD3+ (Total T cells)
CD3+/4+(T Helper/Inducer cell)
CD3+/4+/25+
CD3+/4+/25hi127lo/FoxP3+(TReg
CD3+/8+ (Cytotox/supp T cells)
CD3+/HLA-DR+(Activated T cell)
Absolute value (%)
2014-04-22
2014-09-11 8 weeks
2014-11-05 16 weeks
2015-01-13 26 weeks
2015-02-11 30 weeks
2016-09-21
Date Collected

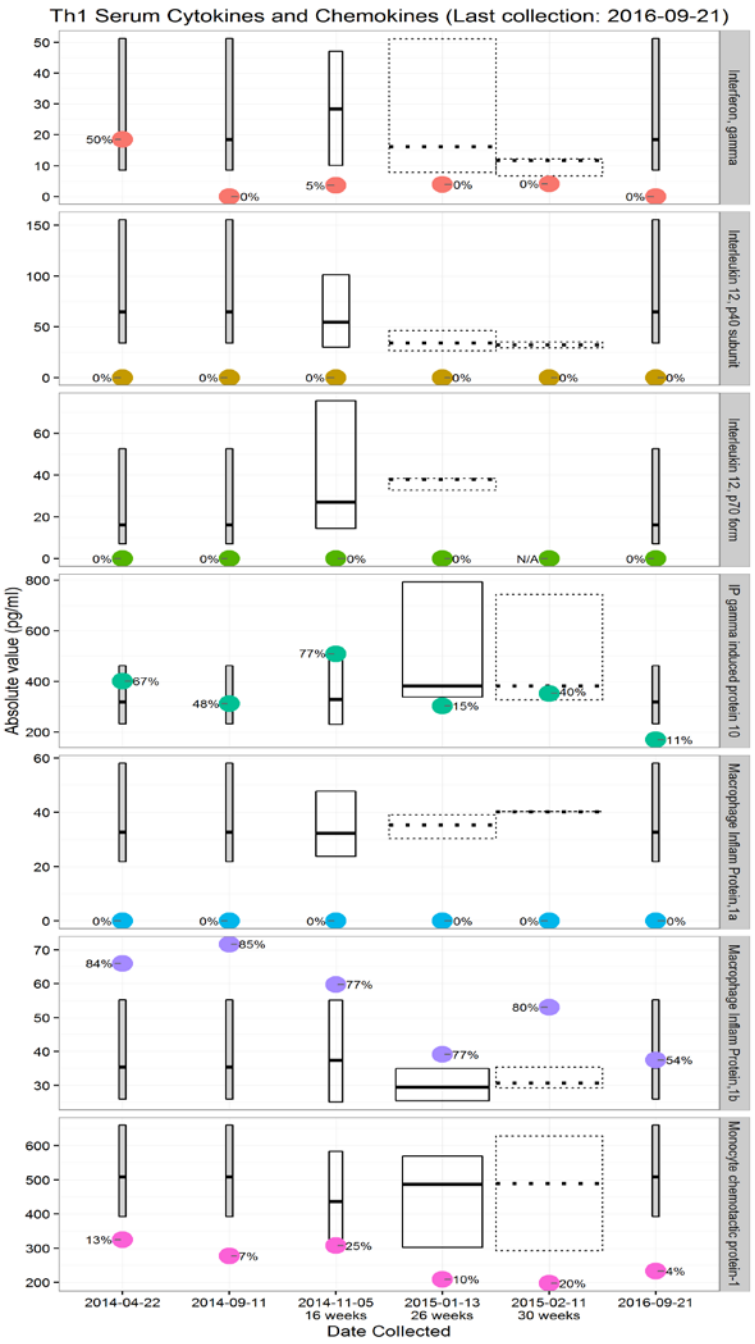

T-RIP - NKT Cells (Last collection: 2016-09-21)
CD3+/4-/8-/56+
CD3+/4-/8+/56+
CD3+/4+/8-/56+
CD3+/56+ (NK T cells)
Absolute value (%)
2014-04-22
2014-09-11 8 weeks
2014-11-05 16 weeks
2015-01-13 26 weeks
2015-02-11 30 weeks
2016-09-21
Date Collected

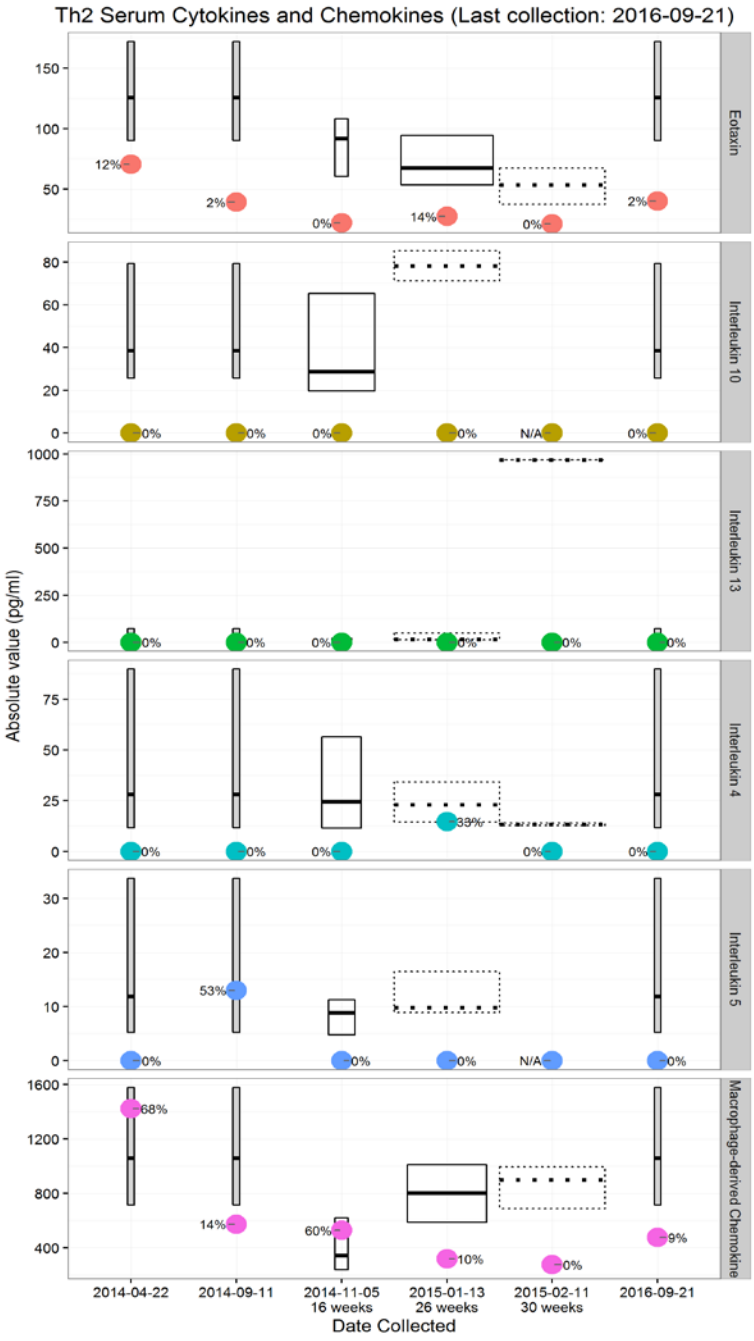


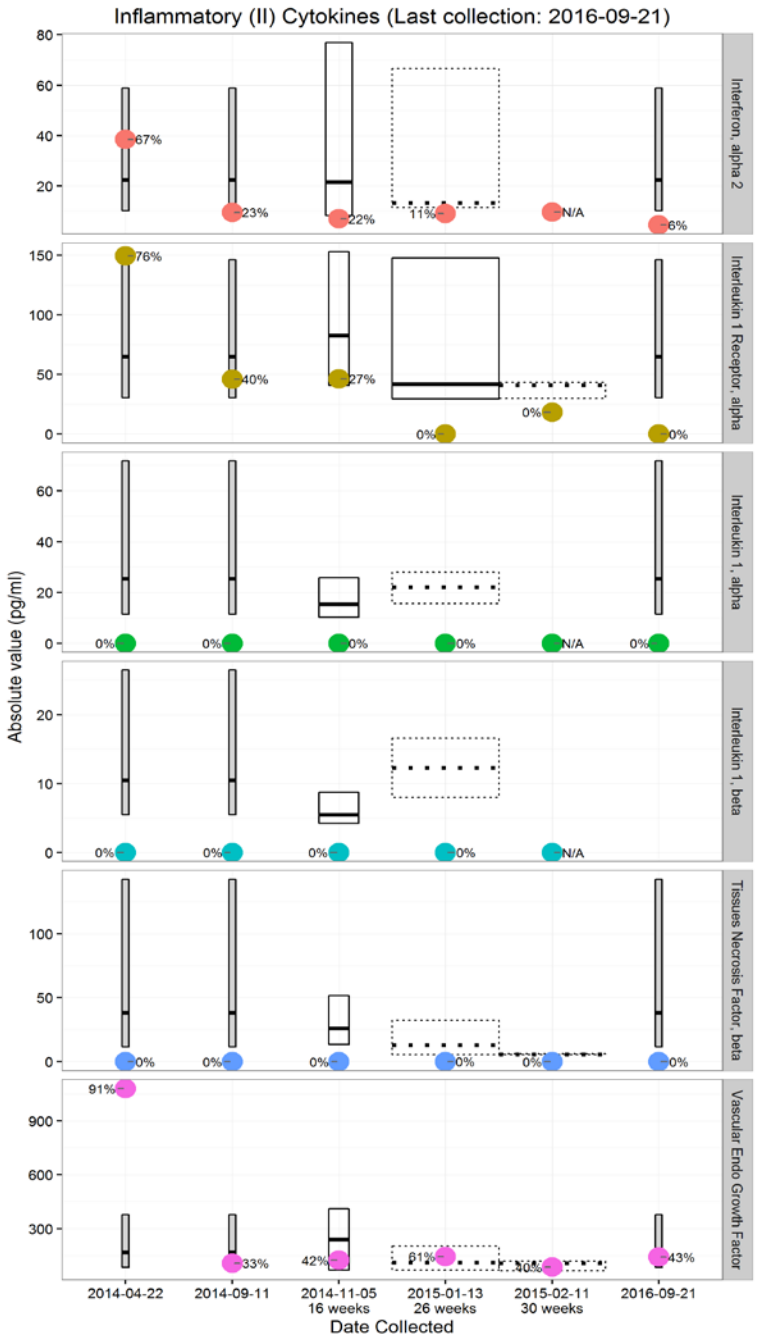




- T-RIP
  - Total and CD16+ NK cells increased from normal to mildly elevated levels, and total, CD4+, CD8+, and CD4-CD8- NKT cells all increased, including an increase in total, CD4+, and CD8+ NKT cells from normal to elevated levels. Total and CD5+ B cells decreased from elevated to normal levels.
- CBC
  - WBCs = 4.0
  - Low absolute monocytes (196)


Inflammatory Serum Cytokines (Last collection: 2016-09-21)
Absolute value (pg/ml)
Interferon, gamma
Interleukin 15
Interleukin 17
Interleukin 6
Interleukin 8
Tissue Necrosis Factor, alpha
2014-04-22
2014-09-11
8 weeks
2014-11-05
16 weeks
2015-01-13
26 weeks
2015-02-11
30 weeks
2016-09-21
Date Collected


Th1 Serum Cytokines and Chemokines (Last collection: 2016-09-21)
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
2014-04-22
2014-09-11
2014-11-05
16 weeks
2015-01-13
26 weeks
2015-02-11
30 weeks
2016-09-21
Date Collected




- Serum levels of several cytokines and chemokines decreased, including IFNγ, TNFα, IP-10, MIP-1β, MCP-1, IL-1Rα, and VEGF. This included a decrease in TNFα, MIP-1β, IL-1Rα, and VEGF from elevated to normal or low levels. Your serum level of GRO increased from low to normal.

- ANA/APA/ATA
  - Weak positive for ANA-Histone (1.1)
  - Indeterminate levels of:
    - Anticardiolipin IgG (10)
    - Antiphosphatidylethanolamine IgM (18)
    - Antiphosphatidic acid IgM (22)
    - Antiphosphatidylglycerol IgG (19)
  - Low C3 complement activity (69)
  - Low C4 complement activity (19)
  - Negative for anti-TPO/THAB
    - Anti-TPO = <1.0
    - THAB = <1.0
  - Negative for TSH receptor antibody (<6.00)
  - Total 25 Hydroxy Vit D sufficiency (50.1)
    - 25 Hydroxy Vit D2 = <5.0
    - 25 Hydroxy Vit D3 = 50.1
  - You were previously negative for all tested ANAs, APAs, and ATAs although you developed positive levels of antiβ2glycoprotein I IgM APAs and indeterminate levels of APhL IgM APAs around week 30 of your pregnancy. You are now weakly positive for ANA-Histone and you have indeterminate levels of anticardiolipin IgG, antiphosphatidylethanolamine IgM, antiphosphatidic acid IgM, and antiphosphatidylglycerol IgG APAs. Your C3 and C4 complement activities are also low suggesting elevated consumption of these factors due to peripheral complement cascade activation.
  -
- Summary
  - Compared with testing performed prior to your earlier pregnancy (4-22-14), there was an overall increase in activation of your immune system at the cellular level, evidenced by an increase in levels of TNFα positive and IFNγ positive CD8+ T cells, and TNFα positive NKT and NK cells. IFNγ positive NK cells decreased from elevated to normal levels, and IFNγ positive NKT cells, a Th1 shift to a slightly stronger Th1 bias together with an increase in all CD4+ T cell, CD8+ T cell, and NKT cell TNFα and IFNγ IC ratios and your NK cell TNFα:IL-4 and IFNγ:IL-4 ratios (including an increase in all CD8+ T cell TNFα and IFNγ IC ratios from normal to elevated levels, and your NK cell TNFα:IL-4 and IFNγ:IL-4 ratios from normal to borderline elevated levels); and an increase in levels of total and CD16+ NK cells (from normal to mildly elevated levels), and total, CD4+, CD8+, and CD4-CD8- NKT cells (including an increase in total, CD4+, and CD8+ NKT cells from normal to elevated levels). Your NKa also remained mildly elevated.
  - There was an overall decrease in levels of systemic inflammation, evidenced by a decrease in serum levels of IFNγ, TNFα, IP-10, MIP-1β, MCP-1, IL-1Rα, and VEGF (including a decrease in TNFα, MIP-1β, IL-1Rα, and VEGF from elevated to normal or low levels).
  - You are newly weakly positive for ANA-Histone and you newly have indeterminate levels of anticardiolipin IgG, antiphosphatidylethanolamine IgM, antiphosphatidic acid IgM, and antiphosphatidylglycerol IgG APAs.
- Conclusions
  - There was an overall decrease in levels of systemic inflammation but an overall increase in activation of your immune system at the cellular level compared with testing prior to your earlier pregnancy. This pattern is consistent with what is observed in our patients with endometriosis and may reflect a decrease in endometriosis-related inflammation resulting from pregnancy and breastfeeding followed by a subsequent activation of cellular mechanisms leading to formation of new ectopic lesions. The increase in TNFα positive NK cells, increase in total and CD16+ NK cells from normal to elevated levels, and maintenance of an elevated NKa are all consistent with this. Additionally, your serum levels of GRO increased despite the overall decrease in

levels of systemic inflammation, and elevated levels of GRO are associated with the presence of endometriosis in our patient population. Weakly positive levels of ANA-Histone and indeterminate levels of APAs are also frequently found in our patients with endometriosis.