The Use of Transcranial Magnetic Stimulation for Pregnant Women with Depression

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Disclosures

- Neuronetics, Inc., Malvern, PA
  - Device support only, not involved with study design
- NIMH
  - K23 MH092399

Objectives

- Describe the risks of antidepressant use during pregnancy
- Review the current data regarding transcranial magnetic stimulation (TMS) and antenatal depression
- Discuss risks, benefits and future directions for the use of TMS for antenatal depression

Stress and Health

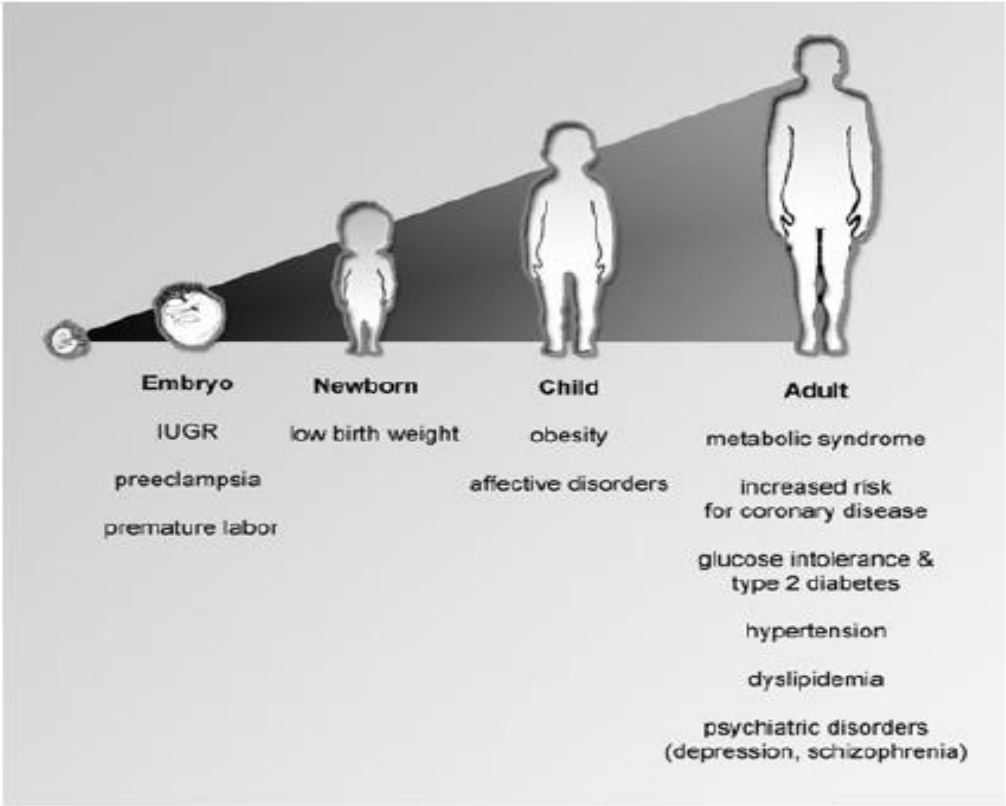


Figure 2. Effects of adverse intrauterine phenomena (of either maternal or fetal origin) in the development of the offspring: from the embryo to adult life.

Antenatal Depression

- Course of antenatal depression usually similar to course outside of pregnancy
  - Depressive symptoms: 15-20%
  - MDD 8-10%
- 2.6% of pregnant women report suicidal ideation

Gavin et al. *Arch Womens Ment Health* 2011 Jun;14(3):239-46

Prevalence of Major Depressive Disorder During Pregnancy

Trimester:	1st Trimester	2nd Trimester	3rd Trimester
% (95% CI)	7.4 (2.2, 2.6)	12.8 (10.7,14.8)	12.0 (7.4,16.7)

Bennett HA et al. *Obstet Gynecol.* 2004;103(4):698-709

Risk of Relapse of Antenatal Depression

- 201 women
- **43%** relapsed with MDD during pregnancy
- Maintained their medication = **26%** relapse rate (21/82)
- Discontinued medication = **68%** relapse rate (44/65)
- Women who discontinued medication relapsed significantly more frequently over the course of their pregnancy compared with women who maintained their medication (hazard ratio, 5.0; 95% confidence interval, 2.8-9.1; P<.001)

Cohen, L. S. et al. *JAMA* 2006;295:499-507

Risks of Untreated Antenatal Depression

- Both maternal and fetal risks
- Meta-analysis included 29 studies
  - Risks of PTB (< 37 wks), LBW (< 2500 g) and IUGR (<10th %ile) were increased in women with antenatal depression by 39%, 49%, and 45% respectively

Grote et al. *Arch Gen Psychiatry*. 2010 Oct;67(10):1012-24

Risks of Antenatal Depression

Logistic Regressions of Risk Factors for Preeclampsia, Low Birth Weight, and Preterm Birth

	Preeclampsia			LBW			PTB			IUGR < 10%		
	β	OR	95% CI	β	OR	95% CI	β	OR	95% CI	β	OR	95% CI
Age	-0.03	0.97 ns	0.89-1.06	0.00	1.00 ns	0.92-1.09	0.00	1.00 ns	0.92-1.08	0.03	1.03 ns	0.95-1.11
Parity	-0.50	0.61 ns	0.23-1.62	-0.10	0.90 ns	0.29-2.83	-0.50	0.61 ns	0.20-1.86	-0.48	0.62 ns	0.22-1.73
EPDS ≥ 10	1.08	2.95*	1.26-6.89	1.07	2.90*	1.18-7.13	0.85	2.34*	1.03-5.36	1.07	2.91*	1.26-6.72
Thyroid disease during preg.							2.05	7.79*	1.52-39.99			
History of PTB							1.21	3.35*	1.29-8.73			
Constant	-1.65			-2.60			-2.46			-2.72		

Note. *OR* = odds ratio, 95% *CI* = 95% confidence interval for odds ratio
ns $p > 0.05$. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$

Kim et al. *Arch Womens Ment Health* 2013 Dec;16(6):475-82

Risks of Antenatal Depression

- Prematurity, low birth weight, and intrauterine growth restriction
- Increased risk of developing postpartum depression and suicidality
- More likely to engage in high-risk health behavior. Some examples include smoking, illicit substance and alcohol abuse, and poor nutrition.

Chan et al. *Can Fam Physician*. 2014

From: **Maternal Depression During Pregnancy and the Postnatal Period: Risks and Possible Mechanisms for Offspring Depression at Age 18 Years**

JAMA Psychiatry. 2013;70(12):1312-1319. doi:10.1001/jamapsychiatry.2013.2163

Table 2. Odds Ratio for Offspring Depression According to Antenatal or Postnatal Depression and Stratified by Maternal Education Using Continuous Measures of Antenatal and Postnatal Depression as Exposure Variables[a]

Timing of Maternal Depression	Exposure Measure[b]	Entire Sample (N = 3335)		High Maternal Education (n = 1644)		Low Maternal Education (n = 1691)		Interaction Term		Test for Interaction[c]	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	χ^2	*P* Value
Antenatal	5	1.28 (1.08-1.51)	.003	1.27 (1.02-1.57)	.03	1.34 (1.12-1.60)	.001	0.96 (0.90-1.11)	.18	0.62	.43
Postnatal	5	1.24 (1.03-1.49)	.02	1.09 (0.88-1.36)	.42	1.26 (1.06-1.50)	.01	0.93 (0.88-0.99)	.04	4.52	.03

Abbreviation: OR, odds ratio.

[a] Results are for those with complete data for both timings of depression and maternal education.

[b] Mean Edinburgh Postnatal Depression Scale continuous score.

[c] Using the likelihood ratio test for the model with and without interaction.

Figure Legend:

Odds Ratio for Offspring Depression According to Antenatal or Postnatal Depression and Stratified by Maternal Education Using Continuous Measures of Antenatal and Postnatal Depression as Exposure Variables[a,]

Consensus Guidelines for the Treatment of Depression During Pregnancy

- Jointly published by the APA and ACOG
- Psychotherapy for mild to moderate depression
- Antidepressants for moderate to severe depression
- *Data not from prospective RCTs but from retrospective case control, observational and database studies*

Yonkers KA et al *Obstet Gynecol* 2009;114:703-713

Antidepressants and Pregnancy

- 4-8% of pregnant women on SSRIs, increased significantly since 1990
  - 1/10 of pregnant women with MDD receive medications at adequate doses

Peterson et al. *J Clin Psychiatry* 2011
Alwan et al. *J Clin Psychopharm* 2011

Risk of Antidepressants In Pregnancy

- Poor Neonatal Adaptation Syndrome
  - Occurs in 10-30% of infants
  - Resolves by day 5 in most cases
- Meta-analysis showed higher risk of respiratory distress in exposed neonates compared to unexposed (13.9% compared with 7.8%;p=.001) but no difference in risk of neonatal convulsions (0.14% compared with 0.11%; p=5.64)
- PTB – conflicting data, some studies suggest increase from baseline 12% to 15-20%, some studies show no association

McDonagh et al *Obset Gyn* 2014

TABLE 5.
The PAES

Neonatal Symptoms	*Birth and Pregnancy Complications*
Neurological symptoms	**Prematurity**
Jitteriness	
Irritability	
Lethargy	
Sleep disturbances	
Changes in muscle tone	
Tremors	
Abnormal movements	
Myoclonus	
Seizures	
Gastrointestinal symptoms	**Low birth weight**
Poor feeding	
Vomiting	
Necrotizing enterocolitis*	
Metabolic symptoms	**Low Apgar scores**
Hypoglycemia	
Hyponatremia	
Respiratory symptoms	
Tachypnea	
Apnea	
Respiratory distress	
PPHN*	
Cardiac symptoms	
Tachycardia	
Bradycardia	
Decreased heart rate variability	
QTc prolongation	
Arrhythmia	
Body temperature instability	
Hyperthermia	
Hypothermia	

* Untoward events not definitively attributable to iatrogenic adverse effects

PAES=prenatal antidepressant exposure syndrome; PPHN=persistent pulmonary hypertension in newborn

Gentile S. *CNS Spectr.* Vol 15, No 3. 2010.

Controversial Risk of Antidepressants

- Cardiac malformations – particularly septal defects
- Persistent Pulmonary Hypertension of the Newborn
  - Marked pulmonary hypertension that causes hypoxemia and right-to-left extrapulmonary shunting of blood
  - Severe PPHN has been estimated to occur in 2 out of 1000 live-born term infants

Association with SSRIs controversial

In Dec 2011, FDA issued a revision of their warning stating that it is premature to reach a conclusion about the link between SSRIs and PPHN

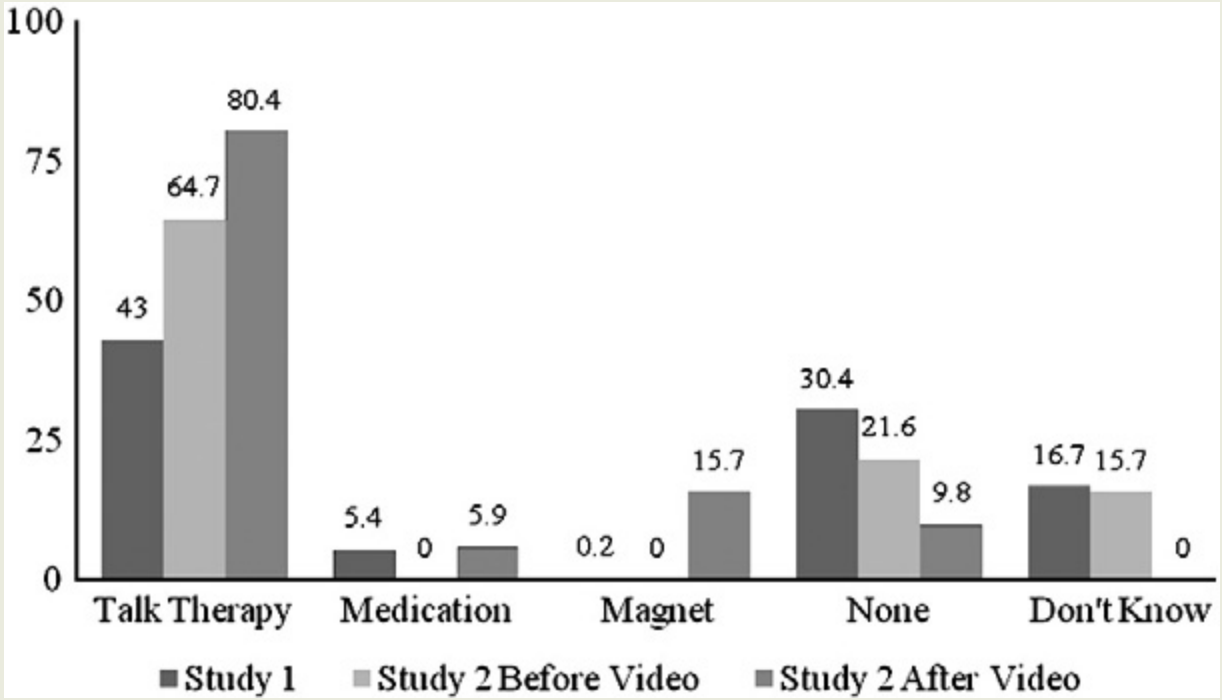
Occhiogrosso M et al. *Am J Psych* 2011

- Autism
  - Some studies demonstrate an association but the absolute risk small
  - A recent study found that there is an increased risk in women taking an antidepressant for depression but not for women taking an antidepressant for another indication

Association with SSRIs controversial

Antidepressant Acceptability In Pregnancy

- Pregnant women prefer non-medication treatments to medications during pregnancy



Kim et al. *J Affect Disord.* 2011 Mar;129(1-3):385-90

TMS and Antenatal Depression Case Reports

- First reported case -1999
  - 36 yo G1 P0 female, no psychiatric history, refused antidepressants and therapy not helpful, started treatment for MDD with prominent anxiety at 22 weeks gestation (14 sessions of left DLPFC, 5 HZ, 5 sec on, 25 sec off, 20 min at 100% MT), improvement rapid, delivered healthy term infant

Nahas et al. *J Clin Psychiatry*. 1999 Jan;60(1):50-2

Additional Case Reports

- The next 2 cases were reported nearly a decade later in 2008. The first patient received 15 sessions of HFL-TMS starting at 16 weeks of pregnancy. The second patient was treated with 15 sessions of LFR-TMS starting at 31 weeks of pregnancy (300 pulses/session, 60 sec trains, 60 sec intertrain intervals) at 100% MT. *Klirova et al. Neuro Endocrinol Lett. 2008 Feb;29(1):69-70*

- In 2009, an additional 3 cases were reported. No details about the frequency, duration, number of pulses/session were included. The authors provided a general statement that the infant's were born in "good health".

Zhang D, Hu Z . Arch Womens Ment Health. 2009 Jun;12 (3):189-90

UPenn Pilot Study

Subject Entry Criteria

- 18 - 39 years old
- 14 – 34 weeks GA
- DSM-IV diagnosis of MDD in a current MDE
- Medications were allowed as long as doses stable 2 weeks prior to entry
- Entry HDRS-17 ≥ 14, CGI-S ≥ 4

Study Design – Pregnancy Assessments

- Antenatal monitoring at treatments 1, 10 and 20 (uterine tocometry and FHR monitoring)
- Growth ultrasound before treatment 1 and within a week after treatment 20
- Performed in the perinatal evaluation center with access to obstetric physicians, anesthesiologists and emergency equipment

Subject Characteristics

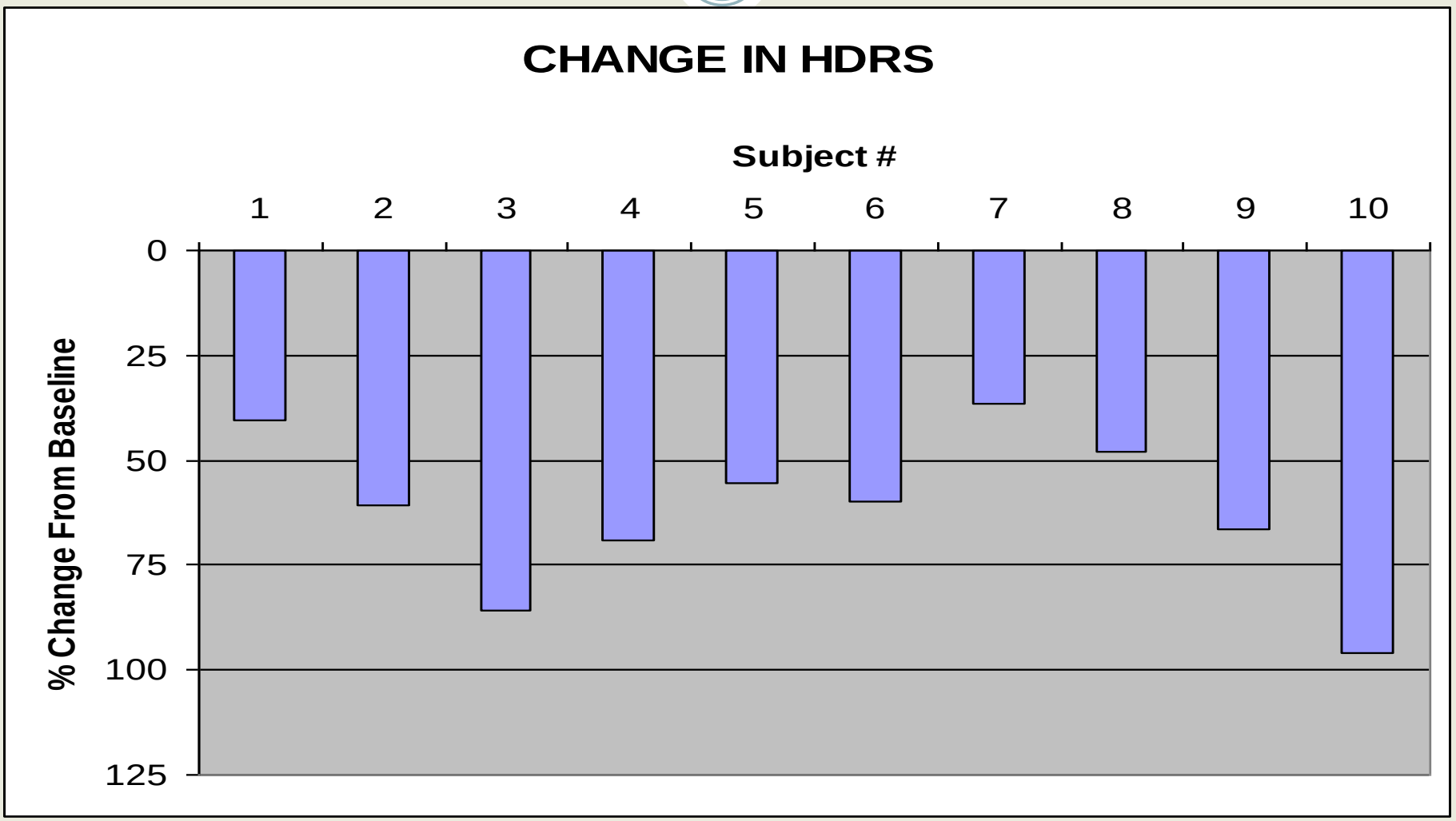
- 7 W, 3 AA
- 50% had co-morbid anxiety disorder
- 90% had a HDRS-17 ≥ 20
- 40% on concurrent AD
  - Subject 2: bupropion SR 300 mg, escitalopram 20 mg, Subject 3: escitalopram 10 mg, Subject 4: sertraline 100 mg, Subject 5: fluoxetine 40 mg

Pilot Study Results

Table 1: Subject Characteristics			
	PRE TMS	**POST TMS**	**P-VALUE**
Mean age (SD) in yrs	**31.2 (5.6)**	**N/A**	
Mean gestational age (SD)	**25.8 (5.16)**	**N/A**	
Race	**7 White, 3 African American**	**N/A**	
Marital status	**9 Married, 1 Single**	**N/A**	
Concurrent antidepressant	**4 Yes, 6 No**	**N/A**	
Mean HDRS-17 (SD)	**24.4 (5.6)**	**9.7 (6.1)***	**0.0050**
Mean CGI-S (SD)	**4.6 (0.5)**	**1.7 (0.7)***	**0.0036**
Mean BDI (SD)	**33.2 (9.0)**	**18.7 (11)***	**0.0050**
Mean BAI (SD)	**18.9 (12.5)**	**14.7 (16.3)**	**0.1022**

***Significant**

Change in Depression Scores From Baseline to Session 20



Treatment Response and Feasibility

- Mean HDRS-17 decrease of 60%, p=0.005.
- Seven out of 10 (70%) subjects had ≥ 50% improvement in HDRS-17 scores indicating response
- Three participants (30%) had a post TMS HDRS-17 score < 8 and CGI-S of ≤1 indicating remission
- The BDI decreased by an average of 44% which was significantly improved, p=0.005, while there was little change in the BAI, p=0.10
- For all scales, there was no significant difference in response rates between the 4 participants on antidepressants versus the 6 off antidepressants (p > .05)

Kim et al. *J Womens Health*. 2011 Feb;20(2):255-61

Maternal Safety

- No serious maternal adverse events
- Mild headache was the only common adverse event and was reported by 4/10 (40%) subjects
- One participant had an episode of supine hypotension during her 10th treatment session
- The treatment was stopped and she was repositioned and the hypotension and lightheadedness resolved quickly

Pregnancy Outcomes

- Antenatal monitoring was done with uterine tocodynamometry (to assess uterine contractions) and fetal heart rate monitoring for 20 minutes before, during and 20 minutes after TMS treatments at sessions 1, 10 and 20

- One participant had a uterine contraction followed by a fetal heart rate deceleration at 18 minutes after treatment #20. Uterine tocodynamometry and fetal heart rate monitoring were extended for another hour with no further events

Fetal Outcomes

- Ultrasounds conducted at baseline and within one week of the end of treatment showed that all fetuses were appropriately grown for gestational age
- All infants were born > 37 weeks GA
- All infants were admitted to the well baby nursery and were discharged with the mother

Table 2: Pregnancy and Fetal Outcomes	
Offspring gender	4 Male, 6 Female
Mean gestational age at delivery (SD)	39 (0.32) wks
Mean birth weight (grams) (SD)	3395.5 (458.98)
Mode of delivery	8 Vaginal, 2 Cesarean
Mean APGAR 1 min (SD)	7.9 (1.36)
Mean APGAR 5 min (SD)	8.75 (0.48)
Major congenital malformations at birth	0/10
NICU admissions	0/10

Another open label pilot study

- 30 pregnant women, TRD, 12 on concurrent SSRI
- 3 weeks of 6 days per week sessions
- 25 Hz, session 1000 pulses at 100% MT
- 41% had a reduction of HAM-D ≥ 50%, 21% achieved remission (HAM-D < 8)
- 23 women had delivered at publication without complication

Sayar et al *Arch Womens Ment Health*. 2014

Right LF versus Left HF TMS

- Left HF TMS over the DLPFC is more common in the field and efficacy is supported with gold standard RCTs.
- Less data for right LF TMS but in some comparative studies efficacy is similar.
- L initially thought to be “excitatory and R “inhibitory” but likely more complicated than that
- We picked right initially because of early concerns about seizure risk with left HF TMS

RCT Preliminary Results

- Sham coil
- Similar study design except less fetal monitoring and increased to 900 pulses per session in a single train (100% MT, 15 minutes)
- Looked at cognitive data and hormone data for first 13 women (5 – active; 8 – sham coil)

Cognition in Pregnancy

- Objectively, the data evaluating memory during pregnancy have been mixed with some studies finding no difference between pregnant women and controls (Logan 2014, Brindle 1991, McDowall 2000) while other studies have found impairment in visual memory, explicit memory, implicit memory and working memory (Farrar 2014, MacBeth 2010, Henry and Rendall 2007, Anderson and Rutherford 2012).
- Other cognitive processes such as attention, psychomotor speed and executive functioning have also been tested during pregnancy with conflicting results (Casey 1999, Logan 2014, MacBeth 2010).
- Cognitive processes, especially memory tasks, tend to worsen as pregnancy proceeds in humans while rodents show enhanced memory suggesting a contradictory effect of increasing neurosteroids on cognition in rodents and humans (MacBeth 2010).

Cognition and TMS

- The effect of TMS on cognition has also been evaluated in some studies. In a meta-analysis of 4 studies (14 experiments) that included both healthy volunteers and schizophrenic subjects, high-frequency left-sided TMS of the DLPFC has been shown to improve working memory. (Brunoni 2014).
- Two recent reviews of TMS in both clinical and non-clinical patients concluded that high-frequency TMS was superior to low-frequency TMS in improving cognition and that clinical populations show the most improvement – possibly because the clinical populations had more impairment at baseline (Guse 2010, Demirtas-Tatlidede 2013).
- These reviews included studies with different methodologies and most results were mixed but, overall, there were improvements in selective and sustained attention, working memory and cognitive flexibility. No consistent improvement in problem solving or psychomotor/processing speed was seen.

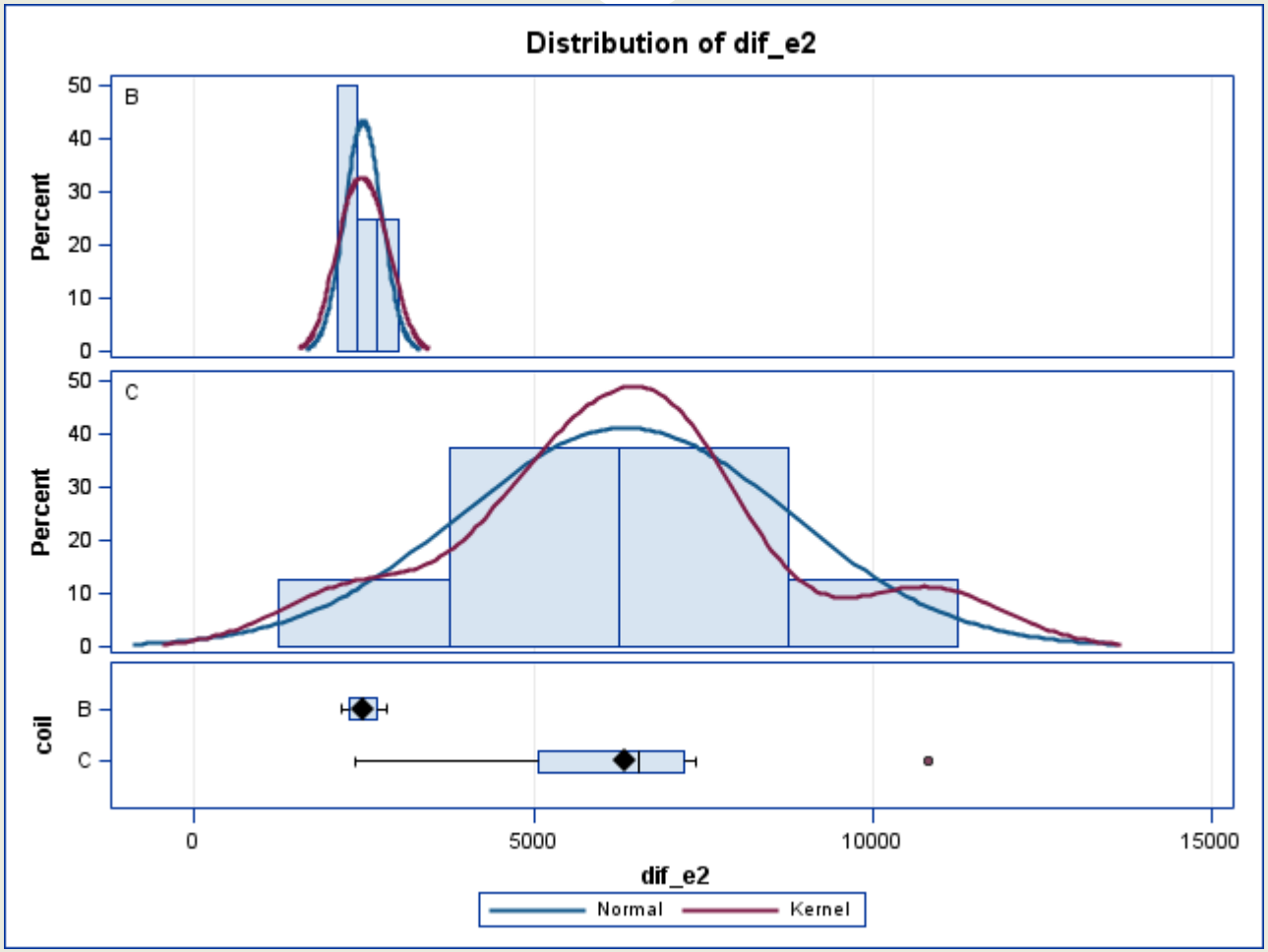
RCT Cognitive Tests

- LNS
- Digit span-forwards/backwards
- Trails A and B
- Stroop

RCT Cognitive Tests

- Depression (as measured by HDRS) has no statistically significant effect on cognition (as measured by Trails A, Trails B, Letter-number-sequencing, and backward digit span.)
- Coil and Cognition: With the current cohort, we see no statistically significant association between coil and cognition (or change in cognition)
  - However, in a prior cohort we DID see a trend toward improved LNS scores with the TMS coil; currently, the p-value for Coil is 0.11 in models adjusted for baseline LNS. We anticipate that this relationship may become significant once we have a larger sample size to work with.

Estradiol and TMS Post-TMS



Baseline Values

Baseline Values	Active Coil (n=11*)	Sham Coil (n=11*)	P value
HDRS	23.5 (3.3)	22.8 (3.0)	0.637
EPDS	17.8 (2.3)	19.7 (3.5)	0.142
BDI	25.9 (6.8)	31.6 (10.1)	0.135
BAI	20.4 (8.6)	19.7 (13.0)	0.894
Estradiol (pg)	9638 (5209)	13,570 (8581)	0.305
Progesterone (ng)	58.3 (27.0)	77.7 (35.6)	0.253

Variable	Active Coil (n=11)	Sham Coil (n=11)	P value
Gestational age at Baseline (weeks)	22.6 (7.5)	26.0 (7.8)	0.313
Maternal age at Baseline	31.1 (6.8)	26.1 (5.0)	0.063
Education :			1.000
HS or less	2 (18%)	2 (18%)	
Some college	3 (27%)	3 (27%)	
4-year degree	3 (27%)	4 (36%)	
Grad/Prof School	3 (27%)	2 (18%)	
Household Income:			0.123
Less than $25K	6 (55%)	9 (82%)	
$25K+ to $100K	4 (36%)	0	
$100K+ to $250K	1 (9%)	2 (18%)	
Race:			1.000
African-American	6 (55%)	7 (64%)	
White/Other	5 (45%)	4 (36%)	
Gravida:			0.035
1	3 (27%)	7 (64%)	
2	3 (27%)	4 (36%)	
3 or more	5 (45%)	0	

Preliminary Results

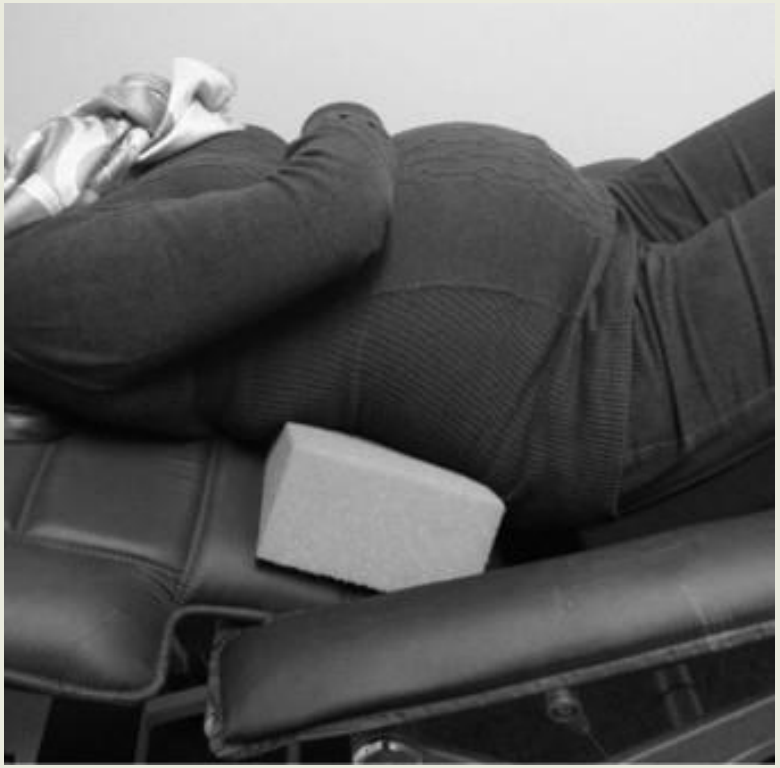
- To date, 21 women have completed the treatment phase
- At enrollment, the mean age of subjects was 28.3 years (SD 5.6) and mean gestational age was 24.5 weeks (SD 7.4)
- 11 subjects were randomized to active treatment and 10 to placebo
- 9/11 (82%) of subjects receiving active TMS responded and 5/10 (50%) of subjects receiving placebo responded.
- 4/11 (36%) active remitted and 2/10 (20%) placebo remitted
- 18 women have delivered and all infants were healthy

Side Effects

Side Effects	Headaches	Site Application Pain	Jaw Pain	Neck Pain	Dizziness	Tooth pain
Active (n=12)	45%	9%	9%	9%	9%	9%
Placebo (n=9)	10%	10%	None	None	None	None

Supine Hypotension

- In women over 24 weeks, recommend a 30% left pelvic tilt (similar to ECT)



Pregnancy-specific Risks/Issues

- Based on the known neurophysiology of the magnetic field induced by the TMS coil there is no reason to believe that there will be any exposure of the fetus. The maximum depth of the magnetic field is believed to be about 5 cm, just sufficient to reach the outer edges of the brain white matter.
- In healthy subjects, neuroendocrine measurements have included cortisol, prolactin, FSH, and TSH. Suprathreshold stimulation showed no deleterious or clinically changes in levels of these hormones (Szuba et al., 2000).
- In pregnancy are there any systemic changes? Estradiol? Oxytocin? Inflammatory cytokines?
- Postural hypotension – published in Psych Res 2014 - pelvic tilt like for ECT
- In epileptic women, 90% have either no change or decreased seizure frequency during pregnancy. L-sided trial warranted.
- Do you have to increase power output as pregnancy progresses? Does allopregnanolone increase cortical inhibition?
- Multi-site study to get power we need to really move the field forward? The regulatory issues involved are complex.
- Would taper and maintenance TMS after acute course prevent PPD?
- Other neuromodulation options - tDCS study in pregnancy just started enrolling July 2014
- High placebo rate

Mentors/Collaborators

- John O'Reardon
- C. Neill Epperson
- Eileen Wang
- Samuel Parry
- Nadav Schwartz
- Lisa Lamprou
- Jessica Snell
- Jeanette Bradley
- Claudia Iannelli