

REI Clinical Trials Workshop Information

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At the NICHD Young Investigators Meeting, there is a Clinical Trials Workshop. In this activity, we will be discussing and designing a clinical trial. Prior to the workshop there will be a presentation on the topic to set the stage. In addition, the material below will help you to prepare for the workshop – you will be expected to have reviewed this material and the suggested reading to actively participate in the workshop.

Clinical Question: How to achieve lifestyle modification and weight loss in obese women seeking pregnancy and explore its perinatal effects?

Scope of clinical issue:

Over 30% of women in the U.S. are obese, and unlike in men and children, the rate of extreme obesity continues to increase among women. Female obesity is associated with reproductive impairment and failure. Women who are obese are more likely to experience delayed time to conception, ovulatory dysfunction, pregnancy loss and most major morbidities of pregnancy including higher rates of preterm labor and delivery, gestational hypertension including pre-eclampsia, gestational diabetes and operative delivery and pelvic floor trauma. Additionally there are increased fetal risks of prematurity higher rates of the extremes of birth weight, i.e. SGA and LGA, birth trauma, and congenital anomalies. This has led to widespread, common sense recommendations to seek preconception weight loss in obese women, prior to conceiving or prior to infertility treatment.

However most current treatments of obesity have only marginal success at achieving significant weight loss, many are contra-indicated in women seeking pregnancy, and the most effective treatment, i.e. bariatric surgery is only utilized by a small fraction of eligible women and requires a substantial time period of recovery after surgery before attempting pregnancy. Current evidence also suggests that bariatric surgery is not a panacea for obesity related reproductive dysfunction. Thus both the short and long term effects of these interventions on maternal, fetal and infant health are poorly understood. There are few randomized studies exploring the risk benefit ratio of a preconception lifestyle intervention in obese women seeking fertility.

How to develop an RCT

When addressing the need and design of a randomized clinical trial care should be taken to address the following:

- Background and importance
 - Before doing an RCT, is there a need for additional studies (a) descriptive epidemiology; (b) observational study(ies) to determine if there are associated morbidities and assess the effectiveness and safety of treatment (c) review of current trials? Are these studies possible?

- What is the quality of evidence for an intervention achieving meaningful weight loss? What interventions would be acceptable in a woman seeking pregnancy? What interventions would you avoid? What would you do with the intervention when the woman seeks pregnancy or undergoes infertility treatment? How would you maintain weight (or weight loss) during such treatment?
 - *Quality of Evidence:
 - I - RCT
 - II-1 Controlled Trials / No randomization
 - II-2 cohort (case control studies)
 - II-3 multiple time series / dramatic effect
 - III Opinion of experts / descriptive studies, expert committees

- General goal – what is the hypothesis?

- Outcomes: Primary – What is the primary outcome? Is it maternal or fetal or both (i.e. composite outcome)? What secondary outcomes in mother (father?), fetus, and infant would it be important to track?

- Population of study – who to target: should there be a lower limit or upper limit of BMI? Should the population include all women with infertility or subgroups (such as women with PCOS?) or should it be obese women at risk for pregnancy, since infertility only affects a fraction of obese women?

- Inclusion and exclusion criteria. Is there an age limit to participation? Should ovarian reserve testing, such as FSH or AMH levels be incorporated? Are there some medical conditions or confounding medications or treatments that should be excluded?

- Study design and overview
 - In development of the study design, what treatment regimens should/can be compared? What is the comparator to lifestyle modification/weight loss???
 - How many treatment/control groups should the study have?
 - Can you single or double blind any of the interventions?
 - Do the interventions have to begin and end concurrently for all treatment groups?

- Interventions
 - How should treatment be administered and followed?
 - For disparate treatments, how should study visits be conducted?
 - What key information: medical, biometric, biochemical, etc. should be conducted at each visit? i.s. what should the study visit table look like?
 - What is the treatment duration? Does intervention change or extend into and through pregnancy?

- Randomization
 - What is the best randomization method?
 - How to preserve allocation concealment?

- Sample size

- What sample size is reasonable for NIH (RO1, U10 level resources)
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- Safety analysis – how to define AE's
 - How to collect AEs during different phases of the study, i.e. pre-conception and post conception
 - Who to collect AEs on- I.e. male partner, infant
 - What is a SAE in non-primary participants, i.e. male or infant?
- Analysis plan –
 - Should you examine rates per group or Kaplan Meier Curves? What prespecified subgroup analyses do you want to conduct? How do you incorporate lost to follow up into an intention to treat design
- Compliance with protocol and protocol violations:
 - What do you do with patients who are blatantly non-compliant with lifestyle modification?
 - How do you follow up patients who drop out to seek more immediately effective infertility treatment options?
 - How do you handle drop out due to loss of partner?

Suggested Reading:(1-9)

1. Harbin Consensus Conference Workshop G. Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): modifying the CONSORT statement. *Fertility and sterility*. 2014;102(4):952-9 e15.
2. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2013.
3. Legro RS, Dodson WC, Kunselman AR, Stetter CM, Kris-Etherton PM, Williams NI, et al. Benefit of Delayed Fertility Therapy with Preconception Weight Loss over Immediate Therapy in Obese Women with PCOS. *The Journal of clinical endocrinology and metabolism*. 2016;jc20161659.
4. Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, et al. Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome. *The Journal of clinical endocrinology and metabolism*. 2015;100(11):4048-58.
5. Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA, et al. Randomized Trial of a Lifestyle Program in Obese Infertile Women. *The New England journal of medicine*. 2016;374(20):1942-53.
6. Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. 2014;15(10):839-50.
7. Sim KA, Dezarnaulds GS, Denyer MR, Skilton MR, Carterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. *Clinical Obesity*. 2014;4(2):61-8.

8. Johansson K, Cnattingius S, Naslund I, Roos N, Trolle Lagerros Y, Granath F, et al. Outcomes of pregnancy after bariatric surgery. *The New England journal of medicine*. 2015;372(9):814-24.
9. Legro RS, Dodson WC, Gnatuk CL, Estes SJ, Kunselman AR, Meadows JW, et al. Effects of gastric bypass surgery on female reproductive function. *The Journal of clinical endocrinology and metabolism*. 2012;97(12):4540-8.