Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format.

1. **Grantee Institution:** The Pennsylvania State University

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 - 12/31/2013

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** John Anthony, MPA

4. **Grant Contact Person's Telephone Number:** 814 935 1081

5. **Grant SAP Number:** 4100050904

6. **Project Number and Title of Research Project:** 19. A Multi-Center Randomized Single-blind Trial of Intravenous Fluids During Labor

7. **Start and End Date of Research Project:** 4/21/2010 - 6/30/2013

8. **Name of Principal Investigator for the Research Project:** Richard Legro, MD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 38,771

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Kunselman, Allen	Biostatistician	4.9%	$4,050
Stetter, Christy	Biostatistician	9.6%	$4,417

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Legro, Richard	Principal Investigator	5
Smulian, John	Lead Protocol Investigator	5
Rochon, Meredith	Co-Investigator	2
Repke, John	Co-Investigator	2
Neubert, George	Co-Investigator	2
Schnatz, Peter	Co-Investigator	2
Airoldi, James	Co-Investigator	2
Eyer, Sandy	Research Coordinator	2

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No_____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____) ☐ Nonfederal source (specify:_)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____X____ No_____

If yes, please describe your plans:

We plan to apply to a nonprofit funding agency for a multicenter clinical trial in gynecology. We are still discussing projects.

12. Future of Research Project. What are the future plans for this research project?

An abstract has been accepted at the 2014 Annual Meeting of the Society for Maternal Fetal Medicine. A manuscript has been prepared and will be submitted to an Ob/Gyn journal.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes____X_____ No_____

The 7 summarized below include the residents in ob/gyn who worked on the project.

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				7
Unknown				
Total				**7**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				2
Non-Hispanic				5
Unknown				
Total				**7**

	Undergraduate	Masters	Pre-doc	Post-doc
White				6
Black				
Asian				1
Other				
Unknown				
Total				**7**

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

    Yes_____ No_____X_____

    If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. **Impact on Research Capacity and Quality**. Did the health research project enhance the quality and/or capacity of research at your institution?

    Yes____X_____ No_____

    If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

    Penn State Hershey served as the Data Coordinating Center for the project. It also established a precedent of multi-center clinical trial collaboration between our medical centers.

16. **Collaboration, business and community involvement.**

    16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes___X_____ No_____

If yes, please describe the collaborations:

We established a clinical trial network with three other medical centers: Reading Hospital, Lehigh Valley Hospital, and St. Luke's University Hospital. York Hospital elected not to participate in the project once enrollment began.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No_____ X _____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No_____X____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project

work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

This will be a multi-center, prospective, single-blind randomized trial of two types of IV fluids for maintenance hydration during labor to determine if intrapartum use of a glucose-containing solution will improve the outcome of labor. This study will randomize 1524 women at greater than or equal to 36 weeks in spontaneous labor attempting vaginal delivery and will be conducted at 4 sites: Reading (Reading Hospital), Allentown (Lehigh Valley), Hershey (Penn State College of Medicine), and York (York Hospital). The primary analysis will use an intent-to-treat approach to examine differences between the two IV fluid treatments in the proportion of deliveries requiring cesarean section. We assume the proportion of deliveries requiring cesarean section will be 0.24 in the arm receiving the non-glucose-containing (i.e., lactated Ringer's) solution and 0.18 in the arm receiving the glucose-containing (i.e., D_5 lactated Ringer's) solution (i.e., a 25% relative reduction in the proportion of cesarean deliveries). We anticipate a 5% dropout rate for this study. Secondary efficacy parameters will include incidence of ketosis and influence of ketonuria on the primary outcome, incidence of prolonged labor, need for oxytocin augmentation, incidence of operative vaginal delivery, incidence of chorioamnionitis, indications for cesarean birth, maternal nausea/vomiting in labor, reduced umbilical artery pH/fetal acidemia, increased umbilical artery CO_2/fetal hypercarbia, neonatal hypoglycemia, neonatal intensive care unit admission, and difficulties with initiating breast feeding. A total of 28 months will be required to complete the study. This will be accomplished by enrolling 15 women per center per month over the two-year enrollment period, and for 3 months to clean and analyze the final data.

Specific Aim 1: To determine the effects of glucose containing IV fluids during labor on operative delivery

The primary research hypothesis is that intravenous hydration during labor with a glucose-containing fluid will lead to more efficient uterine contractility and will lead to a reduction of cesarean delivery.

Specific Aim 2: To determine the effects of glucose containing IV fluids during labor on other maternal and fetal parameters related to dysfunctional labor

Secondary Research Hypotheses are that the use of glucose-containing solutions will be associated with:

a. lower rates of labor augmentation,
b. shorter time to vaginal delivery,
c. lower incidence of chorioamnionitis,
d. reduced umbilical cord acidemia and fetal hypercarbia,
e. reduced neonatal hypoglycemia and need for NICU admission, and higher rate of lactation initiation.

Summary of Results

Abstract:
Objective: To determine if the intrapartum use of a 5% glucose-containing intravenous solution decreases the chance of a cesarean delivery for women presenting in active labor.
Methods: This was a multi-center, prospective, single (patient) blind, randomized study design implemented at 4 obstetric residency programs in Pennsylvania. Singleton, term, consenting women presenting in active spontaneous labor with a cervical dilation of <6cm were randomized to lactated Ringer's with or without 5% glucose (LR versus D5LR) as their maintenance intravenous fluid. The primary outcome was the cesarean birth rate. Secondary outcomes included labor characteristics, as well as maternal or neonatal complications. Log-binomial regression was used to assess risk ratios (RR) and 95% confidence intervals (CI) after adjusting for participating center.

Results: There were 309 women analyzed from 4 hospital sites. Demographic variables and admitting cervical dilation were similar among study groups. There was no significant difference in the cesarean delivery rate for the D5LR group (23/153 or 15.0%) versus the LR arm (18/156 or 11.5%), [RR (95%CI) of 1.32 (0.75, 2.35), P=0.34]. There were no differences in augmentation rates or intrapartum complications. The postpartum hemorrhage rate was 6.0% in the LR arm and 1.3% in the D5LR arm, P=0.05). There also was a marginally higher rate of neonatal hypoglycemia (glucose < 40 mg/dL) and 5 minute Apgar scores <7 in the D5LR group versus the LR group.

Conclusions: The use of intravenous fluid containing 5% dextrose does not lower the chance of cesarean delivery for women admitted in active labor.

Introduction:
Factors that influence the ability of women to have a successful vaginal delivery have been studied extensively. However, most studies have focused primarily on maternal and fetal characteristics that predict successful labor.(1) Other than uterotonic agonists (mainly oxytocin), few studies have examined specific interventions that would enhance the likelihood of a vaginal delivery in laboring women. There are data generated through studies using intrauterine pressure catheter monitoring of labor that demonstrate the importance of effective myometrial contractility for the adequate progress of labor.(2) Exercise physiologists have shown that increased fluid intake and carbohydrate replacement improve skeletal muscle performance in prolonged exercise. (3, 4)

Although the uterus is a muscle that is undergoing work during labor, little attention has been paid to the impact that intrapartum fluid management and caloric supplementation might have on labor.(1) Adequate supplies of glucose are needed to maintain exercise tolerance and muscle efficiency, which are important factors in the progress of labor. Physiological requirements for glucose during labor are estimated to be around 10 grams per hour. We propose that even in the presence of adequate hydration, inadequate carbohydrate replacement in labor may contribute to prolongation of labor and an increased need for operative delivery. There are 2 studies that have examined the impact of adding glucose to the intravenous fluid solution for laboring women. Both studies suggested a shorter duration of labor in nulliparous women when glucose was added to the intrapartum IV fluids, although neither study demonstrated a reduction in the cesarean delivery rate.

Because the cesarean delivery rate may be a more important clinical outcome than duration of labor, we designed this study to determine if adding 5% dextrose to a lactated Ringer's (D5LR) solution as the maintenance intravenous (IV) fluid in active labor was associated with a lower cesarean delivery rate compared to lactated Ringer's (LR) as the maintenance IV fluid. We hypothesized that IV hydration during labor with a glucose-containing fluid will lead to more efficient uterine contractility and will lead to a reduction of cesarean delivery and improved labor characteristics in women presenting in active labor. We further hypothesized that any effect of adding glucose to the maintenance fluids would be modified by the presence of ketonuria as a surrogate measure of glycemic and hydration status.

Material and methods:

This was a multi-center, prospective, single (patient) blind randomized trial comparing LR versus D5LR as the maintenance IV fluid during the intrapartum period. This study was conducted by a consortium of 4 institutions: Lehigh Valley Health Network (Allentown, PA), Pennsylvania State University, College of Medicine (Hershey, PA), Reading Hospital (Reading, PA) and St. Luke's University Hospital (Bethlehem, PA). This consortium was developed from a concept linking together junior residents from selected regional residency programs to allow them to perform a prospective research study. The educational goal was to provide these residents the experience in developing, implementing, conducting and reporting prospective research in Obstetrics and Gynecology. Pennsylvania State University, College of Medicine (Hershey, PA) served as the data coordinating center for this study. The protocol for this effort was submitted and approved at each hospital's individual institutional review board (IRB). Subjects were candidates for participation if they were pregnant at or above 36 weeks gestation in spontaneous labor, less than 6 cm dilated, and were eligible for a vaginal delivery. Note that the initial cervical dilation inclusion criteria was specified to be less than 5 cm dilation, but this was increased by 1 cm due to the difficulty with recruiting women in active labor unless they were more dilated. Exclusion criteria included: inability to have a vaginal delivery, multiple gestation, history of prior cesarean delivery, need for induction of labor, diabetes mellitus or another glucose dysregulation condition, concurrent use of steroids, active labor with cervical dilation of $\geq$6 cm, or participation in another research study.

Subjects in spontaneous labor were screened for eligibility upon admission to labor and delivery for anticipated delivery. Screen eligible subjects were provided information about study participation after the care providers made the decision for admission for delivery. Recruitment

at each site was performed by residents who were approved to obtain informed consent by their respective institutional review boards. Informed consent training was specific to each site and was the responsibility of the site faculty and resident principal investigators. After written informed consent was obtained, subjects were randomized to one of the two maintenance IV fluids, LR or D5LR. Randomization was stratified by clinical site and a random number generator was used to create permuted blocks of size (n=6) within each stratum, so that the treatment allocation ratio was 1:1 within each clinical site. Numbered opaque envelopes containing the randomization assignment were provided by the data coordinating center to each site and were chosen in sequence to determine the treatment assignment. Given that potentially large number of residents from each clinical site could be involved in the randomization process, we believed the simple opaque envelope method would serve the study best. Subjects were not informed of their specific treatment group assignment in an attempt to keep them blind to their assigned IV fluid. However, complete blinding could not be guaranteed during the entire labor course.

By protocol, the assigned IV fluid was used throughout labor as the maintenance fluid. LR was used for IV fluid boluses for all clinical indications such a pre-epidural volume expansion. No minimum or maximum infusion rate was specified in the protocol, although the maintenance infusion rate was expected to be 125 mL/hr per usual practice at all participating sites. Sites were encouraged to perform an initial urine dipstick analysis for urinary ketones on admission, as well as an umbilical artery blood gas immediately after delivery when feasible. Medical records were reviewed to obtain information about labor course and complications for mother, fetus, and infant. Primary data sources included the prenatal record, intrapartum and delivery record, and the neonatal inpatient record.

The primary outcome of this study was cesarean delivery. Secondary outcomes included: the duration of labor, need for oxytocin augmentation, incidence of operative vaginal delivery, incidence of chorioamnionitis, umbilical artery blood gases, neonatal hypoglycemia (serum glucose <40mg/dL), need for neonatal special care nursery, and difficulties with initiating breast feeding. Infant glucose levels were checked for symptomatic infants or with high risk conditions such as small or large for gestational age. Breastfeeding success was measured using the LATCH score, which is a 5 component assessment using scores of 0, 1 or 2. (LATCH score components include: Latch, Audible swallowing, Type of nipple, Comfort, and Hold or positioning.) Other maternal or neonatal complications noted in the records were collected. The presence of ketonuria was assessed in order to assess its impact on outcomes.

Data were recorded at each site on Clinical Report Forms developed specifically for this project. Data were then entered into a Web-based Universal Questionnaire Data Entry System (WebUQ). The WEBUQ application is a password-protected online data entry system developed by the Department of Public Health Sciences at Penn State University. Study personnel used unique user IDs and passwords to protect access to the system. All analyses were performed from data entered into the WebUQ system.

Several assumptions were made in order to estimate the sample size for this trial. We estimated a baseline cesarean delivery rate for women in labor of approximately 24% based on a consensus among the participating institutions after scheduled repeat cesarean deliveries were excluded. We

decided a priori that a 25% reduction in the cesarean delivery rate to 18% due to the use of D5LR would be a clinically meaningful effect on the primary outcome. In order to have a two-sided test with a significance level of 5% and a power of 80% we estimated that 723 subjects in each arm would be needed to detect this difference in cesarean delivery rates. We added an additional 5% to each arm as a buffer against potential loss of subjects to achieve a final sample size estimate of 762 per study arm, or a total of 1524 subjects.

Statistical analyses were performed using an intent-to-treat paradigm where randomized subjects were included according to their treatment assignment regardless of actual treatment received. All tests were two-sided and all analyses were adjusted for clinical site, except where noted, and were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC) or S-Plus software, version 8.1 (TIBCO, Palo Alto, CA).

A risk ratio (RR) and 95% confidence interval for comparing the treatment arms with respect to the primary outcome of cesarean delivery proportions was estimated from a log-binomial regression model. (7) In randomized clinical trials, estimation of the risk difference is more appropriate, and easier to interpret, than an odds ratio. A log-binomial regression model having one two-level factor (i.e., treatment) is asymptotically equivalent to a chi-square test and the model allowed adjustment for potentially confounding covariates such as site of recruitment. The primary outcome of cesarean delivery proportions was also compared between the two treatment arms adjusting for the presence of maternal ketonuria and the clinical site using a log-binomial regression model. Log-binomial regression models were used to compare the treatment arms in secondary analyses for binary outcomes. Continuous outcomes were analyzed using parametric (i.e., analysis of covariance models) or non-parametric (i.e., Cochran-Mantel Haenszel mean score tests based on rank scores) methods as appropriate based on normalcy distributions. A Cox proportional hazards model was used to compare the time from admission to delivery between the treatment arms where a cesarean delivery was considered a censored observation.

A Data Safety Monitoring Committee (DSMC) was created that consisted of representatives of each medical center (not involved in the study) and one independent member for a total of 5 members. Although an interim analysis was not planned, the DSMC periodically reviewed enrollment progress, outcomes, and safety data by treatment arm. All adverse events were reported to the IRBs and the DSMC. Data from these subjects were analyzed utilizing the intent-to-treat approach. The DSMC recommended discontinuing enrollment in the study in April 2013 given the lack of difference between treatment groups in the primary outcome of operative delivery.

Results:

A total of 318 subjects were randomized for the study between May 2010 and April 2013, 161 (50.6%) for LR and 157 (49.4%) for D5LR. Nine subjects were excluded from analysis: 3 were deemed ineligible, 5 did not have adequate documentation of informed consent, and 1 subject withdrew consent. Of the subjects, 54% were recruited with the initial cervical dilation requirement of <5 cm and 46% after the change to <6 cm, with approximately equal numbers randomized to both arms for both study periods. Importantly, the trial was stopped short of the targeted sample size based on the recommendations of the DSMC after carefully considering the

slower-than-expected recruitment rate and the lower-than-predicted rate of cesarean delivery as the primary outcome.

Outcome data was available for 309 subjects, 156 from the LR arm and 153 from the D5LR arm. (Figure 1) Subject characteristics are reported in Table 1. There were no statistically significant or clinically important demographic or pregnancy differences noted between the 2 study groups. Characteristics that could influence labor progress and route of delivery were also similar including: cervical dilation on admission, rates of hypertensive disorders, and medical conditions. (Table 2)

For the primary outcome, there was no difference in the cesarean delivery rate after adjusting for recruiting site for the D5LR arm (23/153 or 15.0%) versus the LR arm (18/156 or 11.5%), [RR (95%CI) of 1.32 (0.75, 2.35), P=0.34]. Adjusting for the presence of ketonuria on admission did not change these results significantly with a cesarean rate for the D5LR arm versus the LR arm, RR (95%CI) of 1.37 (0.78, 2.41), P=0.27. Using a Cox proportional hazards model adjusted for clinical site, there was no evidence of a statistical difference in the time from the onset of labor to delivery (i.e., whether vaginal or cesarean section) between the D5LR and LR arms (hazard ratio: 1.00; 95% CI: (0.80, 1.26); p-value=0.99).

There were no differences in augmentation rates, overall operative delivery rates (cesarean, vacuum and forceps) and selected intrapartum or postpartum complications other than a slightly higher rate of identified postpartum hemorrhage in the LR arm (6.0%) versus the D5LR arm (1.3%). Umbilical artery blood gas results were similar between study arms. There was only 1 case of a gas pH of <7.00, in the D5LR arm. There were more cases of Apgar scores <7 (N=4), of which all were in the D5LR group. However, the overall Apgar scores were similar. There was a lower rate of neonatal hypoglycemia (glucose <40 mg/dL) in the LR arm versus the D5-LR arm (7/50 (14%) versus 18/55 (32.7%), p = 0.05). LATCH scores were also similar between study arms. There were 5 cases (4 infant) of serious adverse events (1 in D5LR arm and 4 in LR arm), which were considered as not related to the study treatment (right foot polydactyly, tracheomalacia, trisomy 21, congenital heart defect, placental sulfatase deficiency and maternal right ovarian torsion).

In order to examine whether nulliparas represented a different responder population we analyzed this group separately for the primary outcome. The cesarean delivery rates for the nulliparas only subset were LR 18/86 (20.9%) vs. D5LR 20/83 (24.1%); p= 0.56. Additional analyses were performed to examine the effect of cesarean delivery on the obstetric outcomes based on whether the cesarean was performed at a cervical dilation of <4cm or ≥4cm using this variable as both a direct and interaction term. The results remained unchanged after this adjustment was applied. (Results are not shown.)

Discussion:

This trial was designed to assess whether the addition of glucose to maintenance IV fluids for women in spontaneous active labor would lead to a lower cesarean delivery rate without significantly increasing complications. Although the trial was stopped prior to reaching the targeted sample size, there was no suggestion that this population benefited from the addition of glucose to the intravenous fluids. The cesarean delivery rates, labor augmentation rates and

duration of labor were similar. Even after adjusting for the presence of ketonuria at the time of admission, there was no identified benefit from using a glucose solution. There were no significant differences in any of the potential complications other than a marginally higher rate of neonatal hypoglycemia and 5 minute Apgar scores <7among those receiving D5LR. The lack of a difference in neonatal admission to a special care nursery suggests that the glucose and Apgar differences may not have been clinically important. Our results indicate that for women in active labor, the choice of whether to add 5% dextrose to the IV fluids does not significantly impact the likelihood of a vaginal delivery, but may have a modest effect on postpartum hemorrhage, neonatal hypoglycemia rates and low Apgar scores.

Previous literature evaluating intravenous fluid interventions for improving labor outcomes is limited. In a randomized controlled study of 2000 subjects comparing IV fluid rates, Garite et al (5) showed a lower proportion of prolonged labor, and possibly a decreased need for oxytocin, with higher IV fluid rates (up to 250 ml/hr) in labor suggesting that inadequate hydration may contribute to dysfunctional labor and possibly an increased rate of cesarean section. Several smaller studies have not consistently confirmed these findings. (Direckvand, Kavitha, Coco) IV infusion rates were not specifically controlled in our protocol, but the overall infusion amounts were not expected to differ between groups. The subanalyses using ketonuria status does provide some insight that the presence of ketonuria as a surrogate measure of both hydration and caloric balance, does not affect labor success in our study population. Fisher and Huddleston (6) demonstrated that adding 5% glucose to intrapartum IV fluid of lactated Ringer's solution reduces umbilical cord acidemia and hypercarbia without changing the cord levels of glucose or base excess. Sharma, et al also found slightly higher umbilical artery pH values with a 5% dextrose solution. We were unable to confirm these findings.

There are only 2 published trials of glucose containing solutions to improve the success of labor. Both of these trials were confined to nulliparous women. Sharma, et al (10) randomized 250 women to either normal saline (NS) or NS alternated with NS plus 5% dextrose at 175 ml per hour. They found no difference in the cesarean rate between groups, although labor was shorter with fewer prolonged labors in women delivering vaginally. Shrivastava, et al (11) randomized 289 women to either NS without dextrose, NS with 5% dextrose or NS with 10% dextrose. They noted shorter durations of the second stage and total labor in both groups receiving dextrose. There were no differences in the cesarean rates among the 3 groups. Our trial was not confined to nulliparous women, which reflects a representative group presenting in active labor. We had equal representation of nulliparous women in both groups. Our subanalysis of just the nulliparous women showed no difference in the cesarean rate or the duration of labor.

Several aspects of this study warrant comment. Strengths include a randomized trial that produced appropriately similar subjects between both study arms. The primary outcome of cesarean delivery was a fixed endpoint and not vulnerable to the subjectivity of determining the time of onset of labor, which can occur when using the outcome of duration of labor. The implementation of the protocol in multiple obstetric units reflects a broad and representative obstetric experience making this more generalizable.

Weaknesses of the study include study closure before reaching the estimated sample size. This was done on the recommendation of the DSMC who based their decision on the slow recruitment

rate and the much lower than estimated cesarean delivery rate (13.2% versus 25%). We found it unexpectedly difficult to find women admitted in active labor with cervical dilation of <6cm. Most of the labor units were unlikely to admit women in early labor with intact membranes due to efforts to reduce cesarean delivery rates. Therefore, a significant portion of women admitted in active labor had more advanced cervical dilation, which is a group that is most likely to deliver vaginally. Additionally, residents found it somewhat difficult to maintain consistent recruitment efforts due to multiple time demands while on the labor unit and the frequent changes in assigned rotations. Nevertheless, if we used the actual cesarean rate in the LR group of 11.5% with an expected 25% reduction in the cesarean rate due to D5LR to recalculate the sample size (two-sided test, significance level of 0.05 and a power of 80%), we would need 3374 total subjects to complete the objectives, which is not practical or feasible. We cannot exclude the potential for bias in assessing neonatal hypoglycemia due to participation in the study, but the labor nurses and physicians were instructed to not provide information to the nursery staff on the specific fluids infused which would have limited any bias effects. Previously undiagnosed maternal glucose intolerance could also have affected neonatal outcomes, but there is no reason to expect that situation to favor one group over the other. Finally, we did not evaluate women having an induction of labor, which may be a group more vulnerable to prolonged restriction of caloric intake through intravenous dextrose solutions and, therefore, might benefit more from caloric supplementation.

One last aspect of this study deserves a special comment. The development of a consortium of residency programs to provide a meaningful research experience to promising young physicians was very successful in a number of areas. It exposed them to the process of protocol development for a prospective trial in a mentored environment. It demonstrated the strengths and weaknesses of collaborating with multiple sites needed for a multi-center study. It provided leadership experience in taking responsibility (with guidance) for managing a prospective trial at the respective sites, including the need to maintain regulatory requirements. It also allowed the residents to perform a meaningful research study that focused on a practical question that was directly related to improving the practice of obstetrics. These benefits have resonated with the residents who participated and should provide lasting effects throughout their careers.

Table 1: Demographic and labor characteristics compared between treatment arms of lactated Ringer's (LR) solution and D5 lactated Ringer's (D5LR) solution.

	LR (N=156)	D5LR (N=153)	P
Maternal age (years)	26.8 ± 4.9 [156]	26.7 ± 4.9 [153]	0.87
Nulliparity	86/156 (55.1%)	83/151 (55.0%)	0.99
Hispanic	12/156 (7.7%)	21/152 (13.8%)	0.09
Race			0.19
Caucasian	127/156 (81.4%)	129/151 (85.4%)	
African American	11/156 (7.1%)	4/151 (2.7%)	
Other	18/156 (11.5%)	18/151 (11.9%)	
Private Insurance	116/153 (75.8%)	111/152 (73.0%)	0.57
> 12th Grade Education	93/136 (68.4%)	89/133 (66.9%)	0.84
Tobacco use	17/153 (11.1%)	15/152 (9.9%)	0.72
Alcohol use	4/153 (2.6%)	9/145 (6.2%)	0.13
Initial BMI (kg/m^2)	26.5 ± 5.8 [148]	26.1 ± 6.5 [147]	0.63
Initial weight (kg)	69.8 ± 15.1 [152]	69.5 ± 17.5 [148]	0.87
Weight gain (kg)	12.0 ± 6.6 [150]	13.5 ± 9.9 [148]	0.14
Hypertensive disorders	2/156 (1.3%)	0/153 (0%)	0.17
Ketonuria on admission	15/106 (14.2%)	8/103 (7.8%)	0.23
Admission dilation (cm)	4.0 (3.0, 4.0) [156]	4.0 (3.0, 4.0) [152]	0.92

BMI-Body Mass Index

Data reported as mean ± SD [n] for continuous variables and proportion (%) for categorical variables, with the exception of admission dilation (cm) which is reported as median (25th, 75th percentile) [n] due to non-normally distributed data. P-values adjusted for recruitment site.

Table 2: Obstetric outcomes compared between treatment arms of lactated Ringer's (LR) solution and D5 lactated Ringer's (D5LR) solution.

	LR (n = 156)	D5LR (n=153)	Risk Ratio (95% CI)	P
Cesarean delivery	18/156 (11.5%)	23/153 (15.0%)	1.3 (0.7, 2.3)	0.34
Cesarean delivery (adjusted for ketonuria)			1.4 (0.8, 2.4)	0.27
Time to delivery (hours)	12.1 (8.4, 18.0) [150]	12.8 (7.6, 18.3) [150]		0.69
Augmentation	88/156 (56.4%)	92/153 (60.1%)	1.1 (0.9, 1.3)	0.40
Any Operative Delivery (C/S, Forceps, Vacuum)	25/156 (16.0%)	31/153 (20.3%)	1.3 (0.8, 2.1)	0.31
Intrapartum fluids (ml)				
Randomized fluid	2058 ± 1176 [109]	1472 ± 998 [115]		<0.01
Total fluids	2086 ± 1263 [110]	2043 ± 1378 [115]		0.89
Meconium	5/152 (3.3%)	4/150 (2.7%)	0.8 (0.2, 3.0)	0.75
Chorioamnionitis	6/152 (3.9%)	5/150 (3.3%)	0.8 (0.3, 2.7)	0.78
Postpartum hemorrhage	9/151 (6.0%)	2/149 (1.3%)	0.2 (0.0, 1.0)	0.05
Shoulder dystocia	5/152 (3.3%)	5/150 (3.3%)	1.0 (0.3, 3.4)	0.98
Umbilical artery (UA) gases				
pH	7.24 ± 0.07 [48]	7.22 ± 0.08 [59]		0.67
pH ≤7.15	7/48 (14.6%)	12/59 (20.3%)	1.0 (0.5, 2.3)	0.96
UA pCO2	54.8 ± 11.1 [49]	55.0 ± 11.4 [59]		0.55
Base deficit >12	3/48 (6.3%)	6/58 (10.3%)	1.7 (0.4, 6.3)	0.46

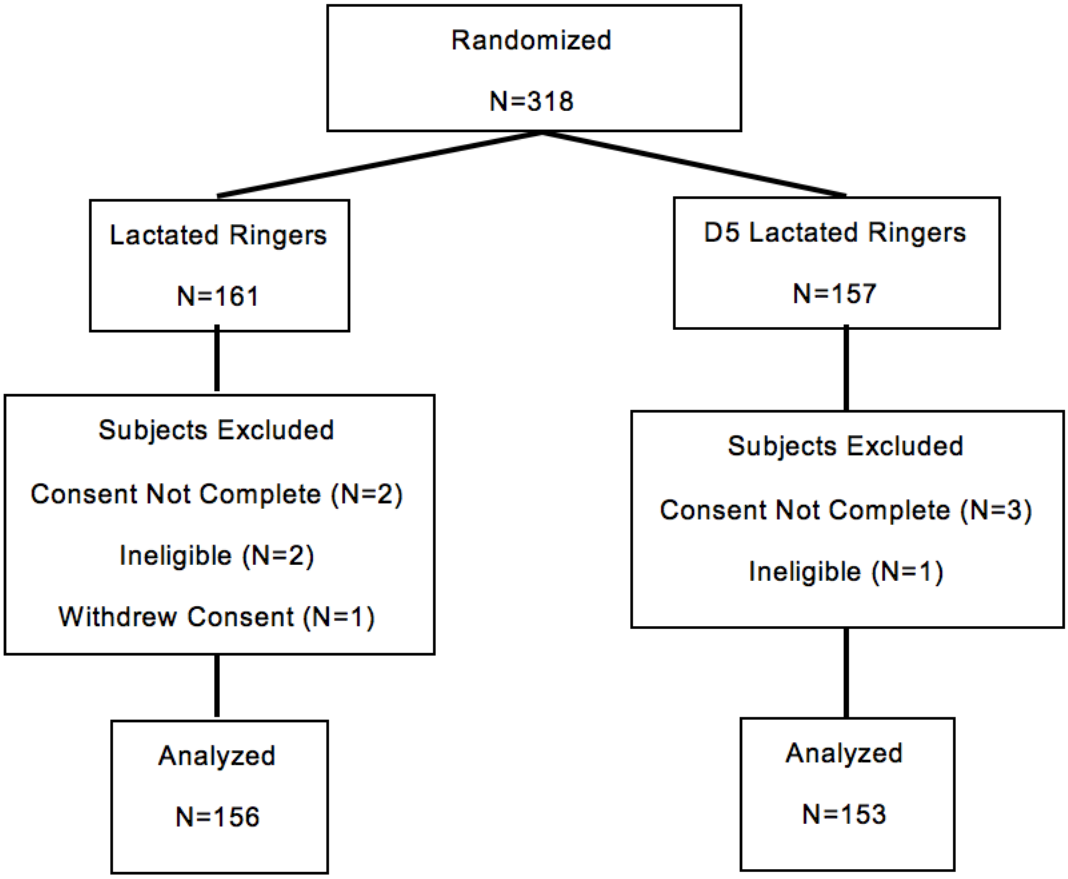
Data reported as mean ± SD [n] for continuous variables and proportion (%) for categorical variables, with the exception of time to delivery (hours) which is reported as median (25th, 75th percentile) [n] due to non-normally distributed data. P-values adjusted for recruitment site except for chorioamnionitis, meconium, shoulder dystocia, postpartum hemorrhage, and base deficit. Analyses were not adjusted by clinical site of recruitment for these 5 outcomes due to sparse numbers which led to model convergence issues.

Table 3: Neonatal outcomes compared between treatment arms of lactated Ringer's (LR) solution and D5 lactated Ringer's (D5LR) solution.

	LR (N=156)	D5-LR (N=153)	P
Birth weight (g)	3428 ± 404 [156]	3408 ± 417 [153]	0.64
Male sex	83/156 (53.2%)	83/153 (54.3%)	0.88
Apgar at 5min	9.0 (9.0, 9.0) [155]	9.0 (9.0, 9.0) [153]	0.64
Apgar at 5min, <7	0/155 (0.0%)	4/153 (2.6%)	0.06
Respiratory difficulty	4/153 (2.6%)	6/150 (4.0%)	0.52
Suspected sepsis	3/151 (2.0%)	2/144 (1.4%)	0.69
Neonatal hypoglycemia	7/50 (14.0%)	18/55 (32.7%)	0.05
Hyperbilirubinemia with phototherapy	3/154 (1.9%)	1/146 (0.7%)	0.36
NICU/special nursery admission	19/156 (12.2%)	17/153 (11.1%)	0.79
LATCH Scores	8.0 (7.0, 9.0) [90]	8.0 (7.0, 9.0) [87]	0.15

Data reported as mean ± SD [n] for normally distributed continuous variables, median (25th, 75th percentile) [n] for non-normally distributed variables or ordinal variables, and proportion (%) for binary variables. P-values adjusted for recruitment site.

Figure 1**:** Randomization scheme



References:

1. Toohill J, Soong B, Flenady V. Interventions for ketosis during labour. Cochrane Database Syst Rev:CD004230; 2008.

2. Brown FB. Manometric evaluation of labor. Obstet Gynecol 1975; 45:473-5

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4. Hawley JA, Tipton KD, Millard-Stafford ML. Promoting training adaptations through nutritional interventions. J Sports Sci 2006;24:709-12.

5. Garite TJ, Weeks J, Peters-Phair K, Pattillo C, Brewster WR. A randomized controlled trial of the effect of increased intravenous hydration on the course of labor in nulliparous women. Am J Obstet Gynecol 2000;183:1544-8.

6. Fisher AJ, Huddleston JF. Intrapartum maternal glucose infusion reduces umbilical cord academia. Am J Obstet Gynecol 1997;177:765-9.

7. Wacholder S. Binomial regression in GLIM: estimating risk ratios and risk differences. Am J Epidemiol 1986;123:174-84.

8. Little RR, Nonignorable Missing-Data Models. In: Statistical Analysis with Missing Data. 2nd ed. New York, NY: Wiley; 2002:15

9. Jamal A, Choobak N, Tabassomi F. Intrapartum maternal glucose infusion and fetal acid-base status. Int J Gynaecol Obstet 2007;97(3):187-9

10. Sharma C, Kalra J, Bagga R, Kumar P. A randomized controlled trial comparing parenteral normal saline with and without 5% dextrose on the course of labor in nulliparous women. Arch Gynecol Obstet. 2012;286(6):1425-30.

11. Shrivastava V, Garite T, Jenkins S, Saul L, Rumney P, Preslicka C, Chan K. A randomized, double-blinded, controlled trial comparing parenteral normal saline with and without dextrose on the course of labor in nulliparas. Am J Obstet Gynecol. 2009;2004 (4):379. e1-e6.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

__X__Yes
_____No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

___X_Yes
_____No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

___19___Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

__1524_ Number of subjects originally targeted to be included in the study
___318**__Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

**We failed to reach our subject recruitment goals for several reasons. One is that fewer subjects met our inclusion criteria than we projected. This is likely due to the fact that the majority of deliveries begin as scheduled c-sections, scheduled inductions, or have some contraindication to our goal of studying normal laboring patients (i.e. a high risk pregnancy, a preterm delivery, multiple pregnancies, etc.). Some sites recruited better than others, that may reflect more interest or more resources devoted to the trial. Finally the study was stopped prematurely by the DSMB, because our projected difference in operative deliveries was not met. We address this issue in the draft manuscript which is attached.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
318___Females
_____Unknown

Ethnicity:
___33_Latinos or Hispanics
__274_Not Latinos or Hispanics
___11_Unknown

Race:
_____American Indian or Alaska Native
___36_Asian
___15_Blacks or African American
_____Native Hawaiian or Other Pacific Islander
__256_White
_____Other, specify:_____
__11_Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was

conducted.)

Dauphin, Berks, Lehigh, and Northampton Counties

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X_ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed

acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. A multi-center randomized trial of two different intravenous fluids during labor	Lisa Dapuzzo, M.D., John C. Smulian, M.D., M.P.H., Meredith L. Rochon, M.D. Luisa Galdi, D.O., Jessika Kissling, M.D., Peter Schnatz, D.O., George Neubert, M.D., Angel Gonzalez Rios, M.D. , James Airoldi, M.D. , Mary Anne Carrillo, M.D., Jaimie Maines, M.D., Allen R. Kunselman, M.S., John Repke, M.D., Richard S. Legro, M.D.	American Journal of Obstetrics and Gynecology	April 2014	X Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____ No____X_____

If yes, please describe your plans:

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The use of intravenous fluid containing 5% dextrose does not lower the chance of cesarean delivery for women admitted in active labor. There may be some transient fetal effects of D5 containing intravenous solutions (such as lowered Apgar scores and increased neonatal hypoglycemia).

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention,

diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No____X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Legro, Richard S.	Professor of Obstetrics and Gynecology and Public Health Sciences
eRA COMMONS USER NAME (credential, e.g., agency login) RLEGRO	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Middlebury College, Middlebury, VT	B.A.	05/1979	English
University of Munich, Munich, Germany	--	1982-1985	Medicine
Mount Sinai School of Medicine, New York, NY	M.D.	05/1987	
Magee-Women's Hospital, University of Pittsburgh, Pittsburgh, PA	Residency	1987-1991	Obstetrics & Gynecology
Univ. of Southern California, Los Angeles, CA	Fellowship	1991-1993	Reproductive Endocrinology

A. Personal Statement

I have had extensive experience in designing, implementing, and completing clinical trials across the full spectrum of women's health. My leadership and accomplishments in clinical research resulted in my selection as the Key Function Leader of the Clinical Services Core (CSC) section of our recently funded Penn State Clinical and Translational Science Institute. My interest in improving treatment for women has extended from participating in or leading multiple clinical trials of insulin sensitizers(U10-PPCOSI), or oral contraceptives(RO1HD43332)), as well as studying lifestyle interventions for these indications(U54 HD044315, RO1HD056510). I have extensive experience in building and leading multi-disciplinary clinical trials within a variety of U54 grants and participating for over 13 years as a PI of the U10 Reproductive Medicine Network, including initiating and leading as PI two multi-center trials of medication to treat PCOS (PPCOS I and II trials). Within the framework of these previous studies, we pioneered following women through pregnancy after conception in infertility trials to determine maternal and fetal outcomes. I have acquired the skills to lead this project including: heading and serving on a steering committee, forming a democratic mode of governance, administrating the monies, and overseeing the ever increasing regulatory burden of a clinical trial. I have a track record of completing tasks in a timely fashion, motivating and energizing team members, disseminating and publishing results, and innovating in the face of the inevitable roadblocks that accompany the conduct of a clinical trial.

B. Positions and Honors

Positions and Employment

1980-1982	Teacher and Houseparent, Ecole d'Humanite, Hasliberg-Goldern, Switzerland
1993-1999	Assistant Professor, Department of Obstetrics and Gynecology, The Milton S. Hershey Medical Center, The Pennsylvania State University College of Medicine, Hershey, PA
1999-2003	Associate Professor with Tenure, Dept. of Ob/Gyn, Penn State College of Medicine

2003-	Professor with Tenure, Dept of Ob/Gyn, Penn State College of Medicine
2010-	Professor, Department of Public Health Sciences, Penn State College of Medicine
2011-2014	Longjiang Scholar, Chair Professorship, Heilongjiang University of Chinese Medicine, Harbin China
2011-2016	Co-Leader, Clinical Services Core (CSC), Penn State Clinical and Translational Science Institute

Certifications

1994	Diplomate, Obstetrics and Gynecology, The American Board of Obstetrics and Gynecology
1996	Diplomate, Obstetrics and Gynecology, The American Board of Obstetrics and Gynecology

Honors

1979	Magna Cum Laude, Phi Beta Kappa, Highest Honors in English, Middlebury College
1985	Bavarian Scholarship for Foreigners, University of Munich
1991	Senior Resident Research Award, Magee Womens Hospital, Pittsburgh
1993	Serono Symposia USA, In-Training Research Award, USC Women's Hospital
1998	APGO/Abbot Medical Education Award, Penn State
1999	Polycystic Ovary Syndrome Association Physician Service Award
2000	Presidential Achievement Award-Society for Gynecologic Investigation
2007	Member, Alpha Omega Alpha Medical Society, Eta Chapter of Pennsylvania
2003-2011	Named to Best Doctor's in America
2003-2011	Named to Top Doctor's in America
2012-13	President, Androgen Excess-PCOS Society

Professional Associations and Service

2002-	Reviewer, PO1 grants, National Institutes of Health -NICHD
2003-2007	Member, NIH Study Section (RAGS-Reproduction, Andrology, Gynecology)
2005-2010	Editorial Board, *Journal of Clinical Endocrinology and Metabolism*
2005-2008, 2010-	Member, Clinical Research and Clinical Practice Committees, Endocrine Society
2006-present	Editorial Board, *Endocrine Reviews*
2007-present	Subspecialty Board Examiner, The American Board of Obstetrics and Gynecology
2008-present	Reviewer, NIH Loan Repayment Applications
2008-2012	Member, NIH Study Section (Obstetric and Fetal-Maternal Biology)
2008- present	Associate Editor, *Human Reproduction*
2009- present	Associate Editor, *Fertility and Sterility*
2010	Speaker/Participant, Pediatric Adolescent Gynecology NICHD Research Think Tank Panel
2010-present	Associate Editor, *Seminars In Reproductive Medicine*
2011	Breakout Leader, NICHD Vision Workshop on Reproduction
2011	Program Director, Annual Meeting of the American Society of Reproductive Medicine
2011	Special Government Employee, Advisory Committee for Reproductive Health Drugs, FDA
2012-15	Member, Board of Directors, American Society of Reproductive Medicine

C. Selected Peer-reviewed Publications (Selected from 201 peer-reviewed publications)

Most relevant to the current application

1. **Legro RS**, Pauli JG, Kunsleman AR, Meadow JW, Kesner JS, Zaino RJ, Demers LM, Gnatuk CL, Dodson WC. (2008). Effects of continuous versus cyclic oral contraception on vaginal bleeding. *J Clin Endocrinol Metab,* Feb;93(2):420-429. Epub 2007 Dec 4. PMCID: PMC2243231
2. **Legro RS**, Roller R, Stetter CM, Kunselman AR, Dodson WC, Dunaif A. (2010). Associations of birthweight and gestational age with reproductive and metabolic phenotypes in women with polycystic ovary syndrome and their first-degree relatives. *J Clin Endocrinol Metab*, 95(2):789-799. PMCID: PMC2840854
3. Dmitrovic R, Katcher HI, Kunsleman AR, Dodson WC, **Legro RS**. (2011). Continuous glucose monitoring in pregnant women with polycystic ovary syndrome. *Obstet Gynecol,* 118(4):878-885. PMCID: PMC3642370
4. Dmitrovic R, Kunselman AR, **Legro RS**. (2012). Continuous compared to cyclic oral contraceptives for the treatment of primary dysmenorrhea: a randomized controlled trial. *Obstet Gynecol,* 119(6):1143-1150. PMCID: PMC3631421
5. Dmitrovic R, Kunselman AR, **Legro RS**. (2013). Slidenafil citrate in the treatment of pain in primary dysmenorrhea: a randomized controlled trial. *Hum Reprod*, 2013 Aug 28 (Epub ahead of print). PMCID: PMC Journal in Process.

Additional publications of importance to the field:

1. **Legro RS**, Barnhart HX, Carson SA, Diamond MP, Carr BA, Schlaff WD, Coutifaris C, Mcgovern PG, Cataldo N, Giudice L, Steinkampf MP, Nestler JE, Gosman G, Leppert PC, and Myers ER for the Cooperative Multicenter Reproductive Medicine Network. (2007). Clomiphene, Metformin, or Both for Infertility in Polycystic Ovary Syndrome. *N Engl J Med,* 356:551-624.
2. Katcher HI, **Legro RS,** Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain enriched hypocaloric diet on cardiovascular disease risk factors in men and women with metabolic syndrome. Am J Clin Nutr. 87:79-90, 2008.
3. Kent SC, Gnatuk CL, Kunselman AR, Demers LM, Lee PA, **Legro RS**. (2008). Hyperandrogenism and Hyperinsulinism in Children of Women with Polycystic ovary syndrome: A Controlled Study. *J Clin Endocriol Metab*, 93(5):1662-1669. PMCID: PMC2386683
4. Trussel J, Baxter C, Kunselman AR, **Legro RS**. Epinephrine is associated with both Erectile Dysfunction and Lower Urinary Tract Symptoms. Fertil Steril. 2010 Feb;93(3):837-42. Epub 2008 Dec 4. 5. Ladson G, Dodson WC, Sweet SD, Archibong AE, Kunselman AR, Demers LM, Williams NI, Coney PJ, **Legro RS**. (2011). The Effects of Metformin with Lifestyle Therapy Polycystic Ovary Syndrome: A Randomized Double Blind Study. *Fertil Steril,* 95(3):1059-1066.e1-7. Epub 2010 Dec 30. PMCID: PMC3073705
6. Williams NI, Reed JL, Leidy HJ, **Legro RS**, DeSouza MJ. Exercise combined with caloric restriction reduces estrogen and progesterone exposure is reduced in response to energy deficiency in women aged 25-40 years. Hum Reprod. 2010 Sep;25(9):2328-39. Epub 2010 Jul 6. *PMCID: PMC2922999*
7. Raja-Khan N, Kunselman AR, Hogeman CS, Stetter CM, Demers LM, **Legro RS**. (2011). Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: a double blind, randomized placebo-controlled trial. *Fertil Steril,* 95(5). 1849-1852. Epub 2010 Dec 8. PMCID: PMC3062732
8. Booker CJ, Dodson WC, Kunselman AK, Repke JT, **Legro RS**. (2011). 24-hr Ambulatory Blood Pressure Monitor Heart Rate is a Marker for Gestational Hypertension in at Risk Women. *Am J Perinatol,* Dec 6. PMCID: PMC3649547

9. **Legro RS**, Dodson WC, Gnatuk CL, Estes SJ, Kunselman AR, Meadows JW, Kesner JS, Krieg, Jr. EF, Rogers AM, Haluck RS, Cooney RN. Effects of Bariatric Surgery on Female Reproductive Function. J Clin Endocrinol Metab 2012 Dec;97(12):4540-8. Epub 2012 Oct 12. PMID: 23066115, PMCID: PMC3513539
10. Polotsky AJ, Allhouse A, Crawford SL, Harlow SD, Khalil N, Santoro N, **Legro RS**. (2012). Relative contributions of oligomenorrhea and hyperandrogenemia to the risk of metabolic syndrome in midlife women. *J Clin Endocrinol Metab,* 97(6):E868-877. PMCID: PMC3387411

D. Research Support

Ongoing Research Support

3U10 HD38992 Legro (PI) 07/31/13-07/31/18
NIH/NICHD
Reproductive Medicine Network
Dr. Legro is the site PI of this multicenter trial network and lead investigator of the protocol Pregnancy in Polycystic Ovary Syndrome II trial. This network conducts multi-center infertility trials

1 R13HD078105 Legro (PI) 09/08/13-08/31/16
NIH/NICHD
Annual Meeting of the Androgen Excess Society
Dr. Legro is the PI of this meeting grant to cover costs related to the Annual Meeting of the Androgen Excess-PCOS society. He has no effort on this grant

1R01HL119245 Downs (PI) 08/15/13-8/14/17
NHLBI
Control Systems Engineering for Optimizing a Prenatal Weight Gain Intervention
This grant will design and test an intervention to prevent excessive prenatal weight gain.
Role: Co-Investigator

CD-1304-6117 Chuang (PI) 10/1/2013-9/30/2016
PCORI
Reducing Unintended Pregnancies through Reproductive Life Planning and Contraceptive Action Planning
The objective of this randomized controlled trial is to determine whether reproductive life planning, with or without contraceptive action planning, can help women formulate and achieve their reproductive goals compared with an information-only control group.
Role: Co-Investigator

UL1RR033184 Sinoway (PI) 06/14/11 - 12/31/16
NIH
Penn State Clinical and Translational Science Institute
The goal of Penn State CTSI is an engaged and responsive health science research and education enterprise that delivers on the promise of improved health.
Role: Key Function Leader of the Clinical Services Core (CSC)

R01 HD056510 Legro (PI) 6/02/08-03/31/14 (No Cost Extension)
NIH/NICHD
Treatment of Insulin Resistance vs. Hyperandrogenism in Infertile PCOS Women (OWL-PCOS)
This is a two center clinical trial testing the efficacy of pretreatment with oral contraceptive pills vs. weight loss on pregnancy outcomes in obese infertile women with PCOS.

U54 HD034449 Nestler (PI) 04/01/08-03/31/14 (No Cost Extension)
NIH/NICHD
Hyperandrogenism and Insulin Resistance in the Ontogeny of PCOS (Project 1)
This is a longitudinal case/control study of reproductive development in pre-pubertal children of PCOS mothers compared to children from control women mothers. We study both mothers and daughters.
Role: PI of Project 1, Co-Investigator Project 3, Member Steering Committee

Completed Research Support:

2U10 HD38992 Legro (PI) 09/01/07 – 07/31/13
NIH/NICHD
Reproductive Medicine Network
Dr. Legro is the site PI of this multicenter trial network and lead investigator of the protocol Pregnancy in Polycystic Ovary Syndrome II trial

Deans Feasibility Grant – 60024317 Legro (PI) 04/21/10-09/30/12
PA-DOH Tobacco Settlement Funds
A Multi-Center, Two Arm, Single Blind Randomized Trial of IV Fluids During Labor. This is a three center ongoing trial of two types of IV fluids during normal labor in healthy women.

ARRA: U10 HD380992-S1 Legro (PI) 10/01/09 – 09/29/12
NIH/NICHD
Assessment of Multiple Intrauterine Gestations From Ovarian Stimulation
This is randomized trial of letrozole, clomiphene, or gonadotropin therapy combined with intrauterine insemination combined with intrauterine insemination for unexplained infertility.
Role: Site PI

ARRA: R01 HD057223 Dunaif (PI) 08/15/08-07/31/12
NIH/NICHD:
Genome-Wide Association Scan of Polycystic Ovary Syndrome Phenotypes
This is a collaborative GWAS to identify genes that contribute to PCOS
Role: Co-Investigator

5 R03 TW007438 Legro (PI) 07/01/06-06/30/11
Fogarty International Center-NIH
The Treatment of Dysmenorrhea: Effects of Slidenafil and Oral Contraceptives
This project involves two separate trials (in Zagreb, Croatia) of these agents to treat dysmenorrhea.

U54 HD044315 Coney (PI) 07/01/03-6/30/10
NIH/NICHD
The Meharry Medical College/Penn State Cooperative Reproductive Science Center
This is a cooperative reproductive science center with a focus on reproductive endocrinology in minorities.
Role: Co-Director of the Center and P.I. at the Penn State site and also PI of Project III- A Randomized trial of metformin and lifestyle interventions in adolescents and adult women with PCOS)