PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
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PROTOCOL TITLE
Predictors of Postoperative Pain Following Oocyte Retrieval for Assisted Reproduction

FUNDING
Departmental/Internal Funding

VERSION DATE
9/13/2010

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

The central objective of this study will be to evaluate the relationship between estrogen levels and the pain following oocyte retrieval in women undergoing in vitro fertilization.

Our primary hypothesis is that higher estrogen levels will result in greater postoperative pain. Thus, our primary outcome will be :

- The amount of discomfort following oocyte retrieval with a standardized anesthetic regimen, as measured by verbal analogue scoring and the amount of postoperative pain medications required.

Secondary outcomes will be:

- The identification of other possible predictors of postoperative pain, including:
  - pre-procedure oocyte count,
  - actual oocyte count,
  - pre-oocyte retrieval verbal analogue score for pain, or
  - other co-morbid conditions (e.g. anxiety, depression, pelvic inflammatory disease, inflammatory bowel disease, endometriosis).

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Pain perception is modulated by hormones. The in-vitro fertilization process raises a unique opportunity to investigate the effect of estrogen, as it is the

predominant hormone manipulated, and through the course of the IVF cycle, undergoes dramatic changes from almost complete suppression to supraphysiologic levels. Previously, our group has demonstrated that estrogen levels, as a result of hormonal stimulation for oocyte retrieval, are correlated to an increased sensitivity to a cold thermal, but not pressure, noxious stimuli. Clinically, we would like to determine if the estrogen level is a principle factor in modulating, and more specifically predicting, postoperative pain following occyte retrieval. Such a study could promote a greater understanding of pain mechanisms, identify elements responsible for greater discomfort or pain, and potentially offer strategies for postoperative pain management following oocyte retrieval.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

The study will enroll 100 subjects. There is only one study group. The patient's estrogen levels, pain ratings and pain medication consumption will be recorded.
Inclusion criteria will be American Society of Anesthesiologists (ASA) I to III health status (moderate systemic disease), age between 18 and 50 yrs, undergoing oocyte retrieval under intravenous general anesthesia.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Subject will undergo standard clinical protocols for the entire oocyte stimulation cycle and all assisted reproductive procedure decisions and algorithms will be decided entirely independent of this study. Pre and post oocyte retrieval estrogen levels are part of the standard clinical care, and the data will be abstracted from the existing laboratory record.

The anesthetic and postoperative pain regimens will use the same agents (fentanyl and propofol for anesthesia; fentanyl, acetaminophen and Percocet for postoperative analgesia) and dose ranges used in clinical standard practice; however, the regimens will be standardized, so as to limit confounding variables. The study regimen for anesthesia will differ from the current, clinical standard by the mandated use of **actual** body weight (in current practice, actual, adjusted ideal, or ideal body weights are used), the use of fentanyl 1 mcg/kg IV (instead of 100 mcg for everyone), and the standardization of postoperative analgesia (noted below). The total amount of fentanyl, propofol, and postoperative drugs will be recorded.

Postoperative analgesia will be standardized based on the subject's self reported verbal analogue score (VAS) and the timing of the report. The agents and timing used below differ from the current clinical standard by assessing VAS and responding with a certain regimen. Although the same agents are used in clinical practice and the response is similar and guided by VAS, the nurse and anesthesiologist of the day are at their own discretion as to what is given; there is no regimented algorithm. As such, there is variability in the response. The study doses noted below were derived from a concensus of nursing and anesthesia practitioners.

PACU Arrival	VAS 1-2	VAS 3-4	VAS 5-7	8-10
≤30 min	Heating Pad	Fentanyl 0.5 mcg/kg	Fentanyl 1 mcg/kg	Fentanyl 1 mcg/kg + Tylenol 1 gm
	Heating Pad	Acetaminophen 1 gm	Percocet 1-2 tab	Percocet 1-2 tab + Fentanyl 1 mcg/kg

The verbal analogue score (VAS) will be used to assess baseline and postretrieval discomfort. Post-procedure assessments will occur in the postoperative anesthesia care unit (PACU) on arrival (time 0) and at 15, 30, 60, and 120 minutes. The patients will be told that VAS corresponds to 0 (no pain) to 10 (worst pain imaginable). Patients will be administered the analgesic agents in accordance to the table noted above. No more than acetaminophen 1 gm **and** Percocet 2 tablets will be given during the entire study period. Following the provision of pain medications, a period of 15 min will be given before additional medications can be given. The VAS scores and the total amount of analgesic agents provided will be recorded.

Prior to discharge from PACU, the recovery room nurse will give the patient discharge instructions in accordance to IVF protocol. Patients will be instructed to write the time, dose and type of analgesic drugs, and how much pain they are experiencing immediately prior to taking the medication, on a "postoperative pain medication record". **Patients will also be reminded that no more than 4 gm Acetaminophen (as labeled tablets, or contained in Percocet) should be taken within each 24 hr period.** In addition, they will be requested to bring this medication record with them at the time of their embryo transfer (almost always on post-oocyte retrieval day 3) or their next IVF clinic visit.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

The anesthetic and postoperative pain regimens will use the same agents and dose ranges used in clinical standard practice; however, the regimens will be standardized, so as to limit confounding variables. No alternative or study-only drugs will be administered. Please note the discussion immediately above, which indicates specifically how the clinical and study regimens differ.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The risks in this study are minimized by the use of standard of care anesthetic and obstetric interventions.

There is a potential for less or more postoperative discomfort than usual care, because instead of having the intraoperative fentanyl and the postoperative pain medications administered by each individual practitioner, a standardized approach based on the verbal analogue pain scores will be used.

The risks associated with opioids include nausea and vomiting, sedation, and respiratory depression. Given the limited duration of surgery and typically limited amounts of additional opioids administered in the postoperative period, it would be uncommon for these side effects to occur to any significant degree. Acetaminophen (e.g. Tylenol) can cause increased levels of liver enzymes, however, this is unlikely due to the limited doses (up to two tablets) provided.

No additional inpatient hospital time is anticipated by participating in this study.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Safety of the subjects will be ensured by the inclusion of two early endpoints (drop criteria):

1) Subject decision for withdrawal from participation at any time.
2) Any operative or medical condition changes prior to or during the entire study period deemed unacceptable by the obstetrician, anesthesiologist, or physician investigator.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for

research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

The risks and discomforts to the mother should be minimal. No new drugs/devices/procedures are being studied or administered soley for research purposes.

There is a potential for less or more discomfort than usual care, because instead of having the postoperative pain medications administered by each individual practitioner, a standardized approach based on the verbal analogue pain scores will be used.

All data collected in the study will be considered confidential with procedures in place to limit access to subject charts and information from the study.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

No benefits may be seen in the participants in this study. However, the identification of predictor factors for post-operative pain could generate an individualized approach and a better management of post-operative pain.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The study will only be conducted in women. Non-English speaking subjects will be approached with the use of translators.

No other vulnerable populations will be specifically targeted, nor will any one group bear a disproportionate share of the burdens or the benefits of the research.

Women undergoing oocyte retrieval as part of the Assisted Reproduction Cycle are included in the study, but the potential benefit of better understanding the estrogen association with post-operative pain and identifying predictors for post-operative pain extends to all women undergoing surgery.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

NA

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Prior to approaching a potential subject, the subject's reproductive endocrinologist will be contacted. Subjects will be approached when they are admitted for a preoperative reproductive endocrinology and anesthetic assessment for their oocyte retrieval. Typically, this preoperative assessment occurs approximately 7 days prior to their oocyte retrieval. The reproductive endocrinologist will ask the potential subject's permission to be approached by a physician investigator. If the response is affirmative, a physician investigator will then approach the potential subject.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

The study is not anticipated to cause any additional inconvenience to patients.

There will be no costs to the subjects related to the conduct of this study, as there are no additional medications or tests that are not already the routine standard of care at Brigham and Women's Hospital.

For guidance, refer to the following Partners policies:
Recruitment of Research Subjects
http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects
http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Informed consent will be obtained from all subjects prior to enrollment after a thorough explanation and discussion of the study plan with the physician investigator. Subjects will be approached at their preoperative reproductive endocrinology and anesthetic asessement, which typically occurs approximately 7 days prior to oocyte retrieval.

Subjects will be given the opportunity to ask questions and discuss their decision to participate with the treating physicians. Following satisfactory completion of the recruitment procedures, subjects will be consented by the principal investigator or physician co-investigator.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The principal investigator will review all forms and data with every 5th subjects to ensure accuracy, adherence and completeness of the protocol. An independent data monitor will not be used, as all agents and dose ranges used in this study are part of standard practice.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

All adverse events will be recorded on the Adverse Experience Form within the Case Report Forms (CRFs). The study investigators will follow Food and Drug Administration (FDA) regulations requiring rapid reporting of any adverse event that is Serious, Unexpected, and Associated with the use of the study drug. **Adverse events and unanticipated problems involving risks to subjects or others will be reported to the HRC in accordance to HRC adverse event and unanticipated problem guidelines.**

The investigators will notify the principal investigator immediately of any serious adverse events. All adverse events will be reported to the IRB as per the HRC guidelines.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The principal investigator will be responsible for validating and ensuring the integrity of the data, and will do so by examining the data sheets and the

primary documents (medical and anesthetic record) of the case. Such a review will occur with every 5th completed subject. Moreover, the PI will be in the first case of each of the co-investigators and will be available for consultation throughout the study. Finally, an initial training session and regular investigator meetings will occur to review the study progress, and adherence to the IRB/HRC approved protocol and guidance (for study conduct and reporting of adverse events).

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/datasafe.htm

Adverse Event Reporting Guidelines
http://healthcare.partners.org/phsirb/adverse_events.htm

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All clinical and other data obtained during this study will be considered confidential. Individually identifiable information will be stored in binders in the locked office of the primary investigator. The names of study participants will be known only to the investigators. The database established for this study will use the patient's initials and last 4 digits of the MRN, and will be kept on a password protected computer which is secured to the desk within the locked office of the prinicipal investigator.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

NA

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

NA

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

NA