Message from the chair

Welcome to the 1st edition of *Femineus*, the twice-yearly newsletter from the University of Iowa Department of OBGYN. Inside this periodical, we will introduce and describe the latest in our recent clinical and research developments. We will also review our progress toward advancing our key mission areas of research, education, clinical excellence and service. Topics outlined in this newsletter are selected based on their interest and relevance to medical professionals.

In this, our first issue, we chose to highlight a broad variety of research topics from cancer to reproductive endocrinology. Research in our department has enjoyed a long tradition. Founded in 1870, this department is believed to be the first combined program of obstetrics and gynecology in the nation and has been led by ten Chairmen to date. Iowa, along with Michigan, was also one of the first departments to initiate the tradition of including reproductive scientists and active bench researchers on the faculty, thereby beginning a new academic era in our field. James T. Bradbury, Sc.D. was hired in 1944 by our fifth Chairman, E. D. Plass. He received his Doctoral of Science degree in 1932 from the University of Michigan, successfully defending a thesis on endocrine factors influencing mammary development and secretion. After moving to Iowa, he played a key role in establishing the Pap smear program and demonstrated for the first time that ovulation could be suppressed by the administration of stilbestrol – presaging the development of oral contraceptives. His description of the high levels of LH characteristic of PCOS remains a landmark discovery which paved the way for the mechanistic understanding of this condition.

Building upon this substantial foundation, I am excited to share current research developments from our department. I would like to dedicate this first issue of *Femineus* to Dr. James T. Bradbury, the first reproductive biologist on our faculty.

Sincerely,

Kimberly K. Leslie, MD

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**Special points of interest**

- Visit us online at: [www.medicine.uiowa.edu/obgyn/](http://www.medicine.uiowa.edu/obgyn/)

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The uterine endometrium is exquisitely sensitive to hormones. These hormones, acting through their cognate receptors, tightly regulate growth, development, and remodeling of reproductive tissues as well as the cyclic changes that occur during the menstrual cycle. In the endometrium, estrogen receptor (ER) and progesterone receptor (PR) are induced in the first half of the cycle and down-regulated in the luteal phase. ERs are expressed in increasing concentrations as the proliferative phase of the cycle progresses. At ovulation, ERs are down-regulated in response to progesterone production from the ovary. PRs are also induced in increasing concentrations during the proliferative phase, in part due to rising estradiol levels that induce PRs through ERs. During the secretory phase of the menstrual cycle, ERs and PRs are gradually down-regulated in the glandular epithelium, but PRs are still expressed in the stroma where progesterone is critical for ongoing proliferation and the secretory response. Androgen receptors (ARs) are in general induced by estrogen during the proliferative phase of the cycle and down-regulated by testosterone in the late secretory phase. Progesterone has also been implicated in the induction of AR in the endometrium, most likely when it is combined with estrogen. Androgen also inhibits the effects of estrogen, limiting proliferation in the epithelium and the stroma.

A careful balance of hormone expression in the endometrium at the distinct stages of the menstrual cycle is critical to prevent oncogenesis. Over 95% of all endometrial cancers express ER, and similar to early breast cancers, the concentration of ER is high - perhaps abnormally high. ER is a marker for differentiation, and PR is generally, but not always, present in endometrial tumors. ARs are expressed in 40-88% of endometrial cancers. In endometrial cancer cell lines, PRA and PRB function to enhance differentiation, with PRA inducing cell senescence and PRB inducing a secretory phenotype. While expression of either isoform in endometrial cancer cells augments sensitivity to apoptosis and inhibition of the G1 to S cell cycle transition, with respect to growth inhibition, PRB appears to be the dominant controller of growth of human endometrial cancer cells. Of note, PRB expression is undetectable in the poorly differentiated endometrial cancer cell lines (e.g., Hec50 and KLE), identifying a role for PRB in maintaining a differentiated phenotype. In accord with that hypothesis, it has been shown that PRA and PRB or only PRA is downregulated in endometrial cancers.
The endometrium is composed of two cell types, the glandular epithelium and the stroma. Endometrial cancers arise most commonly in the glandular epithelium. However, the glands and stroma communicate directly, and it is likely that abnormal interactions between the two tissues may occur in the process of endometrial carcinogenesis. The epithelial glands and the stroma both express ERs and PRs, and expression in both tissue types is likely to be necessary to induce normal growth and differentiation of the glandular epithelium. Therefore, evaluation of receptor expression in the stroma as well as the glands may provide insight into the process of carcinogenesis and to the responsiveness of the tumor to progestin therapy. The most common method to query hormone receptor status in tumors is immunohistochemistry, a well-accepted as a modality to localize and semi-quantitate ERs and PRs in multiple regions (i.e., glands and surrounding stroma) in paraffin-embedded endometrial tumor tissues. Numerous studies support the finding that high ER and PR levels are associated with a well differentiated tumor phenotype, and ER expression positively correlates with response to progestin treatment.

Excess estrogen stimulation of the endometrium, as a result of exogenous administration of estrogen (i.e., hormone replacement therapy [HRT]) or the endogenous production of estrogen (as with obesity), is a well-documented risk factor for endometrial cancer. Obese women demonstrate a greater capacity for the biochemical conversion of peripherally circulating androstenedione to estrone. It has been estimated that over 40% of endometrial cancer incidence can be attributed to excess body weight. A further example of endogenous estrogen production occurs in the polycystic ovarian syndrome (PCOS), which includes an excess of androgens that can be converted to estrone to produce an estrogen-enriched environment. Indeed, PCOS patients have a 5-fold increased risk of endometrial cancer.

The role of progesterone in the glandular epithelium of the endometrium is primarily antagonistic to estrogen-mediated cell proliferation. In the seminal CASH and Million Women studies of contraceptives and HRT, respectively, it was found that progestins reduce the risk of endometrial cancer. Progestins have found a role in the treatment of the premalignant endometrial hyperplasias as well as early invasive endometrial hyperplasias.

The A and B isoforms of PR arise from alternative promoters from the same gene. The B isoform (upper figure) is identical in sequence to the A isoform (lower figure) with the exception of the first 164 amino acids at the N-terminus, termed the B upstream segment (BUS). The domains are divided into functional units A-E: IF = an inhibitory function area unmasked by the absence of BUS; DBD = the DNA binding domain; Cor = a hinge region known to bind to receptor co-modulators; LBD = the ligand (hormone) binding domain. AF 1-3 = activation functions required for gene transactivation and protein/protein interactions. The numbers noted above indicate the amino acids.
cancer. This therapy has mainly been deemed an option for either younger patients that desire future fertility or patients that are medically compromised. In patients with advanced or recurrent endometrial cancer, oral progestins such as megestrol acetate (MA) and MPA have been reported to demonstrate response rates around 25%. These responses have predominantly occurred in PR-positive tumors, and the duration of efficacy for progestins has been relatively short with progression-free intervals ranging from 2.5 to 8.5 months; longer intervals are associated with low grade tumors that tested positive for estrogen and progesterone receptors. The lack of prolonged responses to progestins is thought to involve progestin receptor downregulation that accompanies continuous progestin therapy. Other hormone receptor antagonists, including tamoxifen (ER) and aromatase inhibitors (AR) have been explored for endometrial cancer therapy. Tamoxifen demonstrated an overall response rate of only 10% when used as a single agent in patients with advanced or recurrent endometrial carcinoma. Administration of tamoxifen daily with alternative MPA increased the response rate to 33%, but the median progression free survival was only 3 months with an overall survival of 13 months. Aromatase inhibitors have yet to prove their efficacy in the treatment of endometrial cancer, with response rates of 9-14%. Gonadotropin-releasing hormone (GnRH) analogues, which stimulate the pituitary to produce gonadotropins and thereby suppress sex steroid hormone production in the ovaries, have also failed to meet the therapeutic bar with response rates of 11% for goserelin.

Despite our current understanding of the dynamic roles of steroid hormones in maintaining endometrial integrity and preventing development of cancer, the current treatment strategies for endometrial cancer are not as effective in promoting disease-free survival and preventing recurrence as in other types of hormone-dependent cancer, such as breast and prostate cancer. Future therapeutic strategies for endometrial cancer should focus on ways to re-establish the hormonal balance.
A major complication of in vitro fertilization treatments for infertile couples remains a high incidence of multiple gestations. Multiple gestations occur in approximately 30% of pregnancies conceived by in vitro fertilization in the United States. This high multiple birthrate can be directly attributed to the practice of transferring more than one embryo to the uterus. Multiple gestations are much riskier with a much higher rate of preterm delivery leading to adverse health consequences for the babies that are delivered.

The University of Iowa has been one of the leading centers in the United States promoting the use of single embryo transfer in IVF cycles. Since 2004, we have established a policy where only a single embryo will be transferred in good prognosis patients. These patients are defined by being age 37 or less, having no previous failed IVF cycles, and having a good quality blastocyst for transfer. Since establishing this policy, we have noted a continued high pregnancy rate for these patients but our multiple birth rate has dropped dramatically. This is directly attributable to the excellent laboratory that we have under the direction of Amy Sparks, Ph.D. For example, in 2010 we performed single embryo transfer in 49% of cycles in women under the age of 35 and 23% of cycles in women between the ages of 35 and 37. In contrast, national averages for the same age ranges were 9.6% and 5.3% respectively. Despite transferring fewer embryos, we were still able to beat national averages for pregnancy rates for these women and also have had half the multiple birth rate experienced by most clinics. We think this has long-term benefits for our patients as their children are born at a later gestational age and have fewer complications of prematurity.

In a recent publication, we evaluated factors that are associated with a live birth after single embryo transfer. We analyzed over 400 single embryos transfer cycles done at our center and found that the live birthrate for the couples who qualify for single embryo transfer was 66.8% per transfer. Patients who were particularly likely to benefit from single embryo transfer included younger females and patients with more advanced blastocyst development. This means that even within a good prognosis group, there is still an advantage to being younger and having the best quality blastocysts in culture. We found that a uterine factor which included mullerian anomalies, uterine fibroids, and endometrial polyps was a negative factor for the outcome of live birth. In many cases, we still transfer a single embryo to women with mullerian anomalies due to the extremely high risk of prematurity in these patients. Nevertheless, miscarriage is more common which reduces the live birthrate in this population of women. Our study confirms the high likelihood of pregnancy after single embryo transfer in selected patients treated with IVF and gives guidance to other clinics who are seeking to identify the best candidates for this practice.
Because GBS infection continues to be a serious concern during pregnancy, the updated guidelines from the Centers for Disease Control continue to recommend universal culture-based screening of all pregnant women at 35–37 weeks gestation.1,2 Recent studies demonstrate that up to 24% of all pregnant women receive antibiotic prophylaxis for Group B Streptococcus (GBS).

Many shortcomings exist in the current therapy of antibiotic prophylaxis. These shortcomings are especially evident in cases in which a woman has a lack of prenatal care, delivers before being screened, delivers before the culture results return, has a rapid labor and does not finish receiving all of the antibiotic dose(s), or is allergic to antibiotics. In addition, the development of antibiotic resistance is an increasing problem. Penicillin-tolerant strains of GBS have been identified and resistance to other antibiotics has been documented.3,4

A GBS vaccine could reduce the development of antibiotic-resistant GBS strains. As recommended by the Centers for Disease Control, the consequences of a GBS infection in pregnancy require that treatment be given. However, this large-scale use of antibiotics is contributing to the development of antibiotic resistance. At the University of Iowa Hospitals & Clinics in 2011, 47% of GBS isolates were resistant to erythromycin and 29% to clindamycin. Without prevention strategies, such as vaccination, our first line antibiotic therapies are going to become useless against GBS. Even with current antibiotic prophylaxis regimens, GBS remains the most frequent pathogen in children born at term.5 Our vaccination could decrease the number of preterm births, the incidence of early and late onset sepsis, and the development of antibiotic-resistant strains of bacteria.
The heart of our unique approach to GBS immunization is encapsulating antigen within polymeric microspheres (Figure 1). Antigens are more immunogenic in particulate form than in solution. By trapping lyophilized protein within microspheres, we can induce a strong protective immune response. Furthermore, the microparticles can be engineered to degrade in “bursts” at different rates. The PLGA microparticles themselves act as an adjuvant and increase the immune response.

Scanning electron microscopy of microspheres containing antigen demonstrates that the microparticles are a consistent size and shape (Figure 1). Further, the microspheres are less than 10 microns making them easily processed by antigen presenting cells.

For our vaccine, C5a peptidase serves as the vaccine antigen. C5a peptidase is a highly conserved multifunctional surface protein on the surface of both group A streptococcus (GAS) and group B streptococcus tested. We have previously shown that encapsulating C5a peptidase within microspheres composed of a co-polymer of lactic and glycolic acids, poly(lactide-co-glycolide (PLGA) was able to induce systemic and mucosal immune response in mice. Because PLGA degrades through bulk erosion to produce lactic and glycolic acid, it is safe for use in humans and has been used for many years in resorbable sutures, bone plates, and drug delivery formulations.

In this study, we tested whether PLGA formulation (50:50 and 75:25 lactic acid: glycolic acid) and route of vaccine administration (intramuscular and intranasal) affect the immune system response. Additionally, we tested whether the PLGA-C5a microsphere vaccine affords protection from vaginal colonization against multiple GBS serotypes.

Methods
Administration of vaccine
Female ICR mice (5–7 weeks old) were vaccinated either through an intramuscular or intranasal route. For all doses of the intramuscular vaccine, the vaccine was administered in 100µl into the right upper leg. For all doses of the intranasal administration, 50ul of vaccine was administered into each nostril (100ul total volume). Booster doses were administered in the same manner as the initial vaccination and were given at weeks 4 and 8.

Determination of Immune Response
Mice were bled via the submandibular route at weeks 4, 8, 11, and 40. Serum was isolated using serum separator tubes (Becton Dickinson) per the manufacturer’s
recommendations, frozen and stored at -80°C. Concurrently, vaginal washes were obtained by pipetting 100ul of Phosphate Buffered Saline (PBS) 40–50 times. Washes were frozen and stored at -80°C. Colormetric enzyme linked immunosorbent assay (ELISA) was used to measure the C5a peptidase-specific IgG and IgA antibody responses in serum and vaginal washes as described previously. Samples producing a significant difference when further diluted are considered to have a larger immune response than samples in which a significant difference was observed in only smaller dilutions. The OD405 reading for each dilution was compared between each vaccine formulation group and the empty microsphere control. The largest dilution that remained statistically significant in the OD405 comparisons was considered the titer. The largest dilution tested was 1:100,000. Animals were housed at the University of Iowa and all experiments were performed according to IACUC-approved protocols.

Vaginal Colonization Studies
At 12 weeks, 1 x 10^6 colony forming units of GBS Serotypes Ia, III, and V were pipetted into the vagina of 5 mice of each vaccination group. After 48h, vaginal washings were obtained and 2 dilutions were plated on blood agar plates. Plates were incubated for 24 at 37°C with 5% CO2. After 24 and 48h, plates were assessed for growth of GBS. The presence of at least 1 GBS colony on a plate was counted as a positive plate. Results of each vaccine group were compared against the group of mice receiving empty microspheres (75:25 0µg).

Results
To compare the strength and duration of C5a peptidase specific IgG and IgA immune responses of mice vaccinated with various microspheres formulations and doses of encapsulated C5a peptidase, an ELISA was performed on serum and vaginal mucosal samples. When average titers were calculated regardless of route of administration, the 30µg doses of the 75:25 and 50:50 formulations elicited the highest titers at 4 weeks for C5a peptidase specific IgG responses in serum and in vaginal washes. The 75:25 30µg dose lead to the highest C5a peptidase specific IgA titer at 40 weeks in serum and vaginal washes.

When we analyzed the C5a peptidase-specific antibody titers with respect to route of vaccine administration, we found that the same results were achieved for mice vaccinated via the intramuscular route.

When we analyzed the C5a peptidase-specific antibody titers with respect to route of vaccine administration, we found that the same results were achieved for mice vaccinated via the intramuscular route. Titers of 1:100,000 were achieved by both 75:25 30µg and 50:50 30µg PLGA microspheres by 4 weeks and were sustained through 40 weeks for serum C5 peptidase specific IgG whereas 75:25 10µg titer dropped to 1000 at 40 weeks. In serum, C5a-IgA response was not detectable for the 75:25 30µg dose until 8 weeks; by 11 weeks both the 75:25 30µg and 50:50 30µg doses were 1:100,000. By 40 weeks these serum titers were reduced to 1:10,000 for the 30µg doses and were not detectable for the 10µg dose. The vaginal C5a specific titers were inconsistent. The vaginal washes of mice inoculated with the 50:50 30µg and 75:25 30µg vaccines had C5a-IgG titers of 1:100,000 at 40 weeks despite titers of 1:10,000 and 1:100 at 11 weeks, respectively. C5a peptidase specific IgA antibodies were not detectable after 8 weeks in mice vaccinated with 75:25 10µg. However at 40 weeks, the vaginal washes had titers of 1:100,000 and 1:10,000 with 75:25 30ug and 50:50 30ug, respectively.

Each intranasal vaccine was able to generate a 1:100,000 C5a-IgG titer in serum by 4 weeks and sustain this titer through 11 weeks. However, all of the titers dropped by 40
weeks. Also in serum, the C5a-IgA titer reached the maximum dilution tested at 1:100,000 for all vaccines at week 8 and then dropped to 1:10,000 by week 11. In the vaginal washes, C5a-IgG titers of 1:100,000 were measured for each of the vaccine formulations at weeks 8 and 11; whereas the maximal 1:100,000 C5a-IgA titer was only found at week 8 in the vaginal wash samples.

In previous work, we demonstrated that the 50:50 30µg dose administered intranasally was able to prevent GBS colonization of the vaginal vault by serotype III. For this study, we hypothesized that the 30ug doses of the 75:25 and 50:50 PLGA microspheres formulations would be able to protect against multiple serotypes of GBS. We used 15 mice from each group and inserted 1x10^6 CFU of serotypes Ia, III, and V (n=5 per serotype per vaccine group). Results were compared against those from mice vaccinated with empty microspheres.

Without regard to which encapsulated vaccine the mice received, the mice that received a vaccine were significantly protected against colonization (27 of 90 positive) in comparison to mice that received the empty microspheres (18 of 30 positive) (P = 0.005). The intramuscular 30ug doses of the 75:25 and 50:50 PLGA microspheres formulations trended toward significantly inhibited vaginal colonization in mice (P = 0.06). We also tested mice that were vaccinated with unencapsulated antigen and this vaccine did not significantly impede vaginal colonization. Of note, most blood agar plates from mice that were colonized demonstrated colonies that were too numerous to count, often even in the smallest dilution plated; whereas in mice that were protected, the plates showed no evidence of GBS growth.

**Discussion**

In our previous work, we demonstrated that by encapsulating C5a peptidase within microspheres composed of PLGA, we were able to elicit antibody responses in serum and in the vagina of mice against GBS and that these responses were sufficient to protect against vaginal colonization by serotype III. This protection was also conferred to pups of vaccinated dams. In this study, our primary objective was to determine the duration of the immune response to various vaccine formulations and doses. In addition, our secondary goal was to determine if this univalent vaccine was able to protect against vaginal colonization...
The 30µg doses of the 75:25 and 50:50 PLGA microsphere formulations generate the highest and most sustained C5a peptidase-specific IgG and IgA antibody responses.

colonization by multiple serotypes of GBS. Furthermore, we wanted to compare whether different formulations of the PLGA microspheres vaccine (75:25 and 50:50) and different doses (0, 10, and 30µg) were more effective in protecting from vaginal colonization by GBS.

In conclusion, we have demonstrated that, in general, the 30µg doses of the 75:25 and 50:50 PLGA microsphere formulations generate the highest and most sustained C5a peptidase specific IgG and IgA antibody responses. At weeks 4, 8, and 11, we did not detect any significant differences in the IgG or IgA titers between the PLGA 75:25 and 50:50 microsphere formulations at the 30µg dose. At week 40, there were also no differences in the C5a peptidase specific IgG responses. The titers were higher at week 40 for the 75:25 30µg vaccine compared to the 50:50 30µg vaccine. Furthermore, we found that mice receiving the encapsulated C5a peptidase (including 75:25 10µg, 75:25 30µg, and 50:50 30µg) were significantly protected from vaginal colonization compared to mice that receive empty microspheres (75:25 0µg).

Now that we have identified the most optimal formulation for a PLGA C5a peptidase vaccine against GBS, we can work to compare this vaccine to other potential GBS vaccines as well as the ability of our vaccine to prevent GBS-related preterm birth and sepsis in a mouse model.


References
The Maternal Fetal Tissue Bank at University of Iowa Hospitals and Clinics is helping researchers at the University of Iowa and their collaborators across the country learn more about pregnancy-related problems and their causes. The Obstetrics and Gynecology Department at the University of Iowa has been at the forefront of storing samples from gynecologic cancers for decades and the department has recently expanded its tissue banking efforts. These samples have been critical to the research done by many faculty members both at the University of Iowa and at research centers across the country.

“It has become evident that samples from patients can play a critical role in research,” says Donna Santillan, PhD, Assistant Research Scientist in Maternal Fetal Medicine at UI Hospitals and Clinics. “From patient samples we are able to learn more about markers of disease, pathways involved in disease development and other issues related to pregnancy and genetics.”

Santillan and her husband, Mark Santillan, MD, associate professor of maternal fetal medicine in the Department of Obstetrics and Gynecology at UI Hospitals and Clinics, coordinate the Women's Health Tissue Repository, a tissue bank designed to help researchers study a variety of issues affecting women's health. There are four banks within the repository: A maternal fetal tissue bank; a reproductive endocrinology and infertility tissue bank; a well women's tissue bank; and the long-standing oncology tissue bank coordinated by the Gynecologic Oncology Division.

The goal of the Women's Health Tissue Repository (WHTR) is to collect, bank, characterize, and distribute high quality human biological specimens related to the needs of investigators within our department. This umbrella biobank encompasses four tissue repositories: 1) Maternal-Fetal Tissue Bank 2) Reproductive Endocrinology and Infertility Tissue Bank 3) Gynecologic Oncology Tissue Bank and 4) Well-Woman Bank (Figure 1). The objective of each repository is to collect longitudinal samples from women at different stages of their lives and health.

**Figure 1: The WHTR Biobank**
The goal of the Women’s Health Tissue Repository is to collect, bank, characterize, and distribute high-quality human biological specimens related to the needs of investigators within our department.

Each bank has been approved by the Institutional Review Board at the University of Iowa. No “extra” procedures are required of consenting patients; instead, samples are collected during regular doctor’s appointments. Specimens and corresponding clinical information are stored with a coded number to protect patient privacy, and no protected health information is ever given to researchers.

Pregnant women are recruited from the beginning of their prenatal care. Women who enroll into the Maternal Fetal Tissue Bank provide maternal and fetal samples for research at the same time certain procedures are done throughout their pregnancy. Sampling includes blood, amniotic fluid, urine, fetal cord blood, and placental tissue samples. Short and long term clinical information regarding the health of the mother and child are also extracted to correlate with the samples.

“Approximately 75% of women who are asked agree to participate in one or more of the tissue banks,” says Mark Santillan. “It’s hard to overstate the benefits this level of participation has for researchers. It helps keep research on women’s health topics moving forward.”

The Maternal Fetal Tissue Bank began enrolling women and their babies in March of 2010. As of Oct 15, 2012, 1280 women have enrolled into MFTB, an average of 39 women per month (Figure 2). Additionally, 923 babies have been delivered at the University of Iowa Hospitals & Clinics and there are 166 consented women with pending deliveries. Therefore, we retain 87% of women consented into the MFTB. Participation is very simple for women. If after hearing about the biorepository women provide informed consent for themselves and their child(ren), then they are enrolled. At times when patients are providing medically indicated maternal blood or amniotic fluid samples, an extra 10mL can be collected for research. Additionally, excess urine from clinical tests can be stored. After birth, cord blood and placental tissue that would normally be discarded are also processed and stored. No extra needlesticks or procedures are ever performed on women or their babies. Medical information is extracted from the electronic medical record and stored de-identified using the coded sample number.

Figure 2: Maternal Fetal Tissue Bank Enrollment
We have collected 8873 aliquots of maternal plasma samples, 2411 cord blood serum aliquots, 2455 cord blood plasma aliquots, 1307 vials of viable mononuclear cord blood cells, and 2175 aliquots of placenta materials (Figure 3).

The Women’s Health Tissue Repository is an incredibly powerful research tool that has stimulated many projects and will allow us to explore genetic factors, environmental factors, health risk factors, and other variables in relation to the outcomes of pregnancy including short and long-term maternal health, length of gestation, and short and long-term child health outcomes.

Earlier this year, maternal blood samples from the Maternal Fetal Tissue Bank were used to sequence a baby’s entire genome as part of a study involving researchers from the University of Washington. Though the tests are still in the research phase, they demonstrate the possibility of reducing the use of invasive fetal testing through the use of the testing maternal-fetal tissue.

“The biorepositories at the University of Iowa were critical to this research,” says Jay Shendure, M.D., Ph.D., associate professor of genome sciences at the University of Washington.

Shendure’s study was published in the June 6, 2012, issue of *Science Translational Medicine*, a journal for the American Association for the Advancement of Science. An abstract describing the University of Iowa Department of Obstetrics & Gynecology’s tissue banking efforts was presented at the Society for Gynecologic Investigation 59th Annual Meeting San Diego, CA in March 2012.
Surgical site infections (SSI)* and wound cellulitis† are significant causes of morbidity, prolonged hospital stays, readmissions, and unscheduled outpatient clinic visits after hysterectomies. Abdominal incisions for hysterectomy are considered to be “clean-contaminated” wounds and have an expected infection rate between 2.4 and 7.7%.

The hospital epidemiology service at the University of Iowa Hospitals and Clinics (UIHC) has consistently monitored rates of SSI and cellulitis after hysterectomies since 2007. In addition to the recommended prophylactic antibiotics for surgery, in late 2007 pre-operative showers with Hibiclens were initiated on the evening before surgery and the morning of surgery. These were replaced by the pre-operative use of chlorhexidine wipes in early 2010. As infection rates were considered to be higher than desired despite these measures, we held a half-day symposium in February, 2011 during which we reviewed aspects of pre-operative, intra-operative, and post-operative care that could be modified to reduce the likelihood of post-operative infections.

We identified the following pre-operative factors that might affect SSI rates:
- Minimizing corticosteroid use peri-operatively,
- Smoking cessation (ideally two months or more prior to surgery),
- Using cefazolin preferentially as a prophylactic antibiotic,
- Redosing cefazolin for procedures that last over 3 hours or for estimated blood loss of more than 1500 milliliters,
- Using 3 grams of cefazolin for individuals who weigh 120 kilograms (kg) or more, and
- Adding metronidazole in the perioperative period to reduce the incidence of SSI in women with bacterial vaginosis.

*Surgical site infections are defined by the Center for Disease Control (CDC) as organ space or superficial or deep wound infections that occur within 30 days after surgery if no implant is in place and within one year after surgery if an implant is in place.

†Cellulitis is defined as erythema about a wound that a physician attributes to cellulitis and treats with antibiotics.
We identified the following environmental factors that could affect the rate of SSIs:
- Ensuring appropriate air flow: vertical laminar flow from ceiling to floor, 15 air exchanges per hour, 3 of which are with fresh air,
- Keeping the operating room (OR) doors closed to allow the air handling system to work properly,
- Using ORs with a minimum of 400 square feet of open floor space with 20 feet between fixed cabinets; 360 square feet is considered to be acceptable for remodeled operating rooms,
- Minimizing the number of people in the OR as well as traffic into and out of the OR,
- Clipping hair as opposed to shaving,
- Using chlorhexidine and alcohol rather than povidone-iodine alone for abdominal skin preparation, and
- Using a vapor-permeable dressing material.

Factors that have been helpful in reducing SSI rates after other surgical procedures include:
- Using subcutaneous sutures for wounds greater than two to three centimeters in depth, and
- Using a disposable wound vacuum.

While several of the factors, such as the use of cefazolin for antibiotic prophylaxis, clipping of hair, and the use of vapor-permeable dressings, were already standard practice for abdominal hysterectomies at UIHC, we identified several factors that could be altered:
- In March, 2011 chlorhexidine and alcohol was implemented as the standard abdominal preparation,
- We encouraged surgeons to use subcutaneous sutures,
- Between October and December, 2011, open cases were discontinued in six operating rooms that were older and had less than 400 square feet of floor space,
- Disposable wound vacuums were used for some patients in 2012,
- We monitored door openings and fed the data back to staff.

The SSI rate for all abdominal hysterectomies done between December, 2011 and July, 2012 was 8.9% lower and the cellulitis rate was 75.6% lower than the baseline rates obtained between July, 2006 and November, 2007. As the surgeons performing these procedures have changed over time and because laparoscopic and robot-assisted hysterectomies became more common over time, we compared SSI rates for procedures done between December, 2011 and July, 2012 with the rates for procedures done during the time period immediately before implementation of the chlorhexidine and alcohol preparation, May, 2010 – March, 2011. The SSI rate was 36.6% lower and the cellulitis rate was 73.6% lower than those in May, 2010 – March, 2011.

These results suggest that the changes we implemented were associated with decreased SSI and cellulitis rates after abdominal hysterectomies at our institution. However, we view this as an ongoing project and we are evaluating additional measures currently. For example, two OR nurses developed an intervention to reduce the number of door openings during cases related to nursing staff. We will continue to follow our SSI and cellulitis rates and implement additional evidence-based changes as needed to minimize infection risks.
Obesity as defined in Table 1 is a chronic disease, which is now considered a global epidemic, with increasing prevalence in adults, adolescents, and children. In the United States, where more than one third of adults (35.7%) and approximately 17% of children and adolescents are obese, the lifetime risk of becoming overweight and obese is approximately 50% and 25% respectively.

Although energy intake needs to be higher than energy expenditure for an increase in body fat, feedback mechanisms that exist in biological systems and are affected by several factors including intrauterine environment, various growth and reproductive hormones modulate energy utilization proving the first law of thermodynamics an oversimplification. Therefore, organisms seem to have a mechanism that tries to maintain body weight, indicating that behavior may not be the sole determinant of obesity.

Obesity has many causes with variable genetic components. Several genetic disorders also present with obesity; Prader-Willi and Bardet-Biedl syndromes are the best known examples. However, genetic disorders that lead to obesity are relatively a rare cause. Major categories of risk factors for obesity are metabolic and socioeconomic. Metabolic factors include a low metabolic rate, increased carbohydrate oxidation, insulin resistance, and low sympathetic activity. Socioeconomic factors include a lower socioeconomic class, a lower education level, and cessation of smoking.

<table>
<thead>
<tr>
<th>WHO Class</th>
<th>Popular Description</th>
<th>BMI (kg/m²)</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>Thin</td>
<td>&lt;18.5</td>
<td>Other clinical problems</td>
</tr>
<tr>
<td>Normal range</td>
<td>Normal</td>
<td>18.5–24.9</td>
<td>Average</td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-obese</td>
<td>Overweight</td>
<td>25.0–29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese Class I</td>
<td>Obese</td>
<td>30.0–34.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Obese Class II</td>
<td>Obese</td>
<td>35.0–39.9</td>
<td>Severe</td>
</tr>
<tr>
<td>Obese Class III</td>
<td>Morbidly obese</td>
<td>&gt;40.0</td>
<td>Very severe</td>
</tr>
</tbody>
</table>
There are several predictors of obesity starting from prenatal period to adulthood. Infants born to women with diabetes and infants born to women who smoked during pregnancy are at greater risk of obesity later in life. Similarly, both infants born small for gestational age and those in the top 10th percentile of birth weight are at greater risk of obesity. Breastfeeding for 3 or more months seems to be a good preventive strategy to prevent obesity later in life (Table 2).

**Table 2. Risk factors for development of obesity**

- Infants born to women who smoked during pregnancy
- Infants born to women with diabetes
- Multiple births
- Premature births
- Small for gestational age infants
- Large for gestational age infants
- Recent marriage
- Smoking cessation
- Parental overweight
- Lower socioeconomic status
- Overweight during childhood or adolescence
- Lack of maternal knowledge of child's sweet-eating habits
- Low level of physical activity
- High intake of dietary fat
- Breastfed for less than 3 months
- Pregnancy
- Menopause

There are several clinical entities that may result in obesity without producing distinctive phenotypes. Some of these conditions are listed in Table 3.

**Reproductive Performance**

Obesity is associated with infertility, most commonly through ovulatory dysfunction. Infertility treatment is more challenging in obese women, associated with either poorer outcomes or similar outcomes with higher doses of medications used. Obesity increases risk of miscarriage, gestational and overt diabetes, pregnancy associated hypertension, preterm delivery, post-term pregnancy, urinary tract infections, and sleep apnea during pregnancy. Obese women endure longer labor by prolongation of the active phase, are more likely to have labor induction, fail vaginal birth attempt after
C-section with an increased risk of uterine dehiscence/rupture, have macrosomic infants with associated intrapartum complications. There are many intra- and postoperative concerns surrounding cesarean delivery with obese women, including emergency delivery, prolonged incision-to-delivery interval, blood loss >1 liter, longer operative times, among others. Complications due to anesthesia are more common. Obese women are at higher risk for postpartum infection, regardless of the mode of delivery and despite the use of antibiotic prophylaxis.

### Conditions Causing Obesity

1. **Neuroendocrine Obesity**
   - a) Hypothalamic Obesity
   - b) Cushing's syndrome
   - c) Hypothyroidism
   - d) Polycystic Ovary Syndrome
   - e) Growth Hormone Deficiency

2. **Drug Induced Weight Gain**

3. **Cessation of Smoking**

4. **Sedentary Life Style**

5. **Dietary Factors**
   - a) Overeating
   - b) Fat Intake
   - c) Carbohydrate and Fiber Intake
   - d) Calcium Intake
   - e) Frequency of Eating
   - f) Restrained Eating
   - g) Binge Eating Disorder
   - h) Night-Eating Syndrome

6. **Psychological and Social Factors**

7. **Socioeconomic and Ethnic Factors**

### Conditions Associated with Obesity

1. **Morbidity Related to Adipose Tissue Hyperplasia /Hypertrophy**
   - Metabolic syndrome
   - Cardiovascular disease
   - Cancer (uterine, breast, colon, gall bladder)
   - Diabetes
   - Hypertension
   - Gall bladder disease

2. **Morbidity Attributed Directly to Fat Tissue**
   - Obstructive sleep apnea
   - Social stigmatization
   - Degenerative osteoarthritis

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Obese women are at higher risk for postpartum infection, regardless of the mode of delivery and despite the use of antibiotic prophylaxis.
Update on Treatment of Nausea and Vomiting of Pregnancy (assumes other causes ruled out)

Jennifer R. Niebyl, MD

Start with Vitamin B6 (pyridoxine), 25 mg (1/2 tablet) po tid
Add Doxylamine (Unisom sleep tabs), 12.5 mg po am and pm (1/2 tab) + 25 mg po q hs

If no improvement switch to Metoclopramide (Reglan) 10 mg q 6-8 hr orally

If no improvement switch to Promethazine (Phenergan), 25 mg po or rectally, q 4-6 hr
OR
Dimenhydrinate (Dramamine) 50 to 100 mg every 4-6 hr orally or rectally, maximum 400 mg/day
OR
Prochlorperazine (Compazine) orally or rectally, 25 mg bid

If no improvement add Zofran 4mg-8mg q 6-8 hr

IF DEHYDRATION

Give IV fluids with intravenous multivitamins
Add 100 mg thiamine per day IV for 3 days if patient has vomited for more than 3 weeks to prevent Wernicke's encephalopathy

Add Metoclopramide (Reglan) 10 mg IV q 8 hr

If no improvement add:
Promethazine (Phenergan) 25 mg q 4 hr deep IM (not IV or SC)
OR
Compazine 5-10 mg q 4 hr, IM max 40 mg/day
OR
Dimenhydrinate (Dramamine) 50 mg IV in 50 ml saline, over 20 min q 4-6 hr

If no improvement add:
Ondansetron (Zofran) 8 mg over 15 minutes IV, q 8-12 hr

Alternative therapies can be added at anytime—ginger capsules 250 mg qid are effective. P6 acustimulation with the Relief Band has been helpful.

With persistent weight loss, enteral feedings should be attempted before parenteral nutrition due to risk of line sepsis (25%).

References
MicroRNAs (miRNAs) are very small pieces of RNA that are encoded in the DNA of nearly every species of plant and animal on Earth. Since these 21-23 nucleotide (nt) RNA fragments were first discovered in the worm Caenorhabditis elegans in the early 1990s, they have been found to be involved to varying degrees in regulating virtually all cellular processes through controlling gene expression. Gene expression control by miRNAs takes place in the cells either by inhibiting the transcription of RNA from DNA or by blocking the translation of RNA into protein (Figure 1).

Since miRNAs function to aid in the regulatory control of normal cellular processes, it was quickly suspected that abnormal production of certain miRNAs in cells would aid in producing and maintaining abnormal cellular processes. The first place where this suspicion was confirmed was in cancer where it was found that specific miRNAs were significantly over-produced or under-produced compared with normal cells. Some of the genes that were regulated by these miRNAs were found to be cancer producing (oncogenes) or cancer inhibiting (tumor suppressors). When a miRNA that normally inhibits an oncogene is under-produced in a cell, that oncogene is free to carry out its cancer-causing program. Similarly, if a miRNA that would inhibit a tumor suppressor is over-produced, the normal brakes are removed from the cancer process.

We wanted to know how many miRNAs are abnormally expressed in endometrial cancers and which ones these were so we carried out two extensive surveys of miRNA expression using primary endometrial tumors and comparing those data with miRNA expression in benign endometrial tissues1,2. What we discovered from our expression surveys was that many miRNAs are aberrantly expressed in endometrial cancers compared with benign endometrium. We also saw that, when we compared endometrial cancer types, endometrioid adenocarcinomas and serous adenocarcinomas shared a number of
aberrantly expressed miRNAs in common but that carcinosarcomas displayed an almost unique pattern of aberrantly expressed miRNAs (Figure 2).

When we looked at the identity of aberrantly expressed miRNAs in our tumors and compared them to those found by other groups to be aberrantly expressed in their endometrial cancers we discovered that there were 16 miRNAs that were reported in multiple studies\(^1\). One of these, \(miR-133\), is consistently under-produced in endometrial cancers while the other fifteen, \(miR—10a, -31, -106a, -107, -141, -155, -182, -183, -200a, -200b, -200c, -203, -205, -210, -429\), are all consistently over-produced in endometrial cancers. Moreover, we found that all of these miRNAs are members of ancient miRNA families dating back hundreds of millions of years. One of these families, containing \(miR-10a\), is one of the two oldest known miRNA families dating from around 700,000,000 years ago. Another family, containing \(miR—31\), is only slightly younger at around 680,000,000 years old. These miRNAs are known to be involved in regulating some very basic, crucial cellular functions. One of our groups, containing all five members of the 500,000,000 year old \(miR—200\) family (\(miR-R-200a, miR—200b, miR—200c, miR—141, and miR—429\), is intimately involved in the endothelial-mesenchymal transition known to be a central process in development and cancer. Others, like \(miR—210\), are involved in cell cycle control and DNA repair mechanisms. Also, \(miR—210\), whose origin has been traced back more than 670,000,000 years, is linked to the hypoxia-inducible factor Hif1α and is the most hypoxia-responsive miRNA known.

The miRNAs commonly expressed abnormally in endometrial cancers form a core group of regulatory elements that point to important processes shared by these cancers. These processes include DNA damage repair, regulation of cellular transitions, and the cell cycle itself. Indeed, most of the “core miRNAs” are known to be abnormally produced in other cancers as well, including leukemia, ovarian, lung, prostate, colorectal, pancreatic and brain. Other miRNAs that are found to be abnormally expressed in only certain types of tumor, such as adenocarcinomas, or are unique to only one type of tumor, such as uterine carcinosarcoma, also point to important processes that may be unique to that type of cancer and must be explored for clues to both origin and treatment of these tumors.

References


Pregnant women are at increased risk of morbidity and mortality during pregnancy. Historically, during the influenza pandemics in 1918 and 1957, there were a large number of deaths due to influenza in pregnant women. The observational reports from these pandemics also report increased incidence of spontaneous abortion and preterm labor. More recently, in the spring of 2009, there was an outbreak of influenza A (H1N1) in the United States which led to increased hospital and intensive care unit admissions and increased mortality for pregnant women.

Since 2004, the American College of Obstetricians and Gynecologists (ACOG) has recommended inactivated influenza vaccine for all women who are pregnant during influenza season, regardless of trimester. In a 2011 Morbidity and Mortality Weekly Report (MMWR) it is reported that vaccinating pregnant women for influenza can protect both the women and their infants aged >6 months who are not old enough to receive influenza vaccination. During the 2009 influenza outbreak, the vaccination coverage of pregnant women was 50 percent. In 2011, the Centers for Disease Control and Prevention (CDC) performed an analysis on data from an internet panel survey for pregnant women. In this survey, there were 1457 respondents and 49 percent of the respondents reported that they had received influenza vaccination. Women who were offered the vaccination by a healthcare provider (62%) were more likely to be vaccinated (71%) than other women (14%). This analysis emphasized the critical role of health care providers in promoting influenza vaccination in pregnant women. ACOG and the CDC have recommended strategies for health care providers to use for the prevention and treatment of influenza in pregnant women.

In 2009, Kyser and Andrews reviewed the recommendations for prevention, chemoprophylaxis and treatment of H1N1 in pregnant women.
Prevention
- Vaccination has been shown to be the most effective way to prevent influenza and its complications in pregnant women in all trimesters.
- The Advisory Committee on Immunization Practices recommends that certain high risk groups get vaccinated and pregnant women and persons who live with or provide care for infants aged 6 months make up two of these high risk groups.
- Instruct pregnant women to wash hands frequently; avoid touching eyes, nose and mouth; and avoid close contact with persons with influenza-like symptoms.

Chemoprophylaxis
- Pregnant women who have been in close contact with individuals who have symptoms of an influenza-like illness should receive chemoprophylaxis.
- Oseltamivir (Tamiflu) 75mg orally for 10 days is the recommended chemoprophylaxis medication. Although, Zanamivir (Relenza) can be used if Oseltamivir is unavailable.

Treatment
- All pregnant women with clinical symptoms.
- Rapid influenza testing and PCR testing should be done if available to confirm.
- Antiviral therapy is most effective if started within 48 hours of symptom onset. Do not need to wait for test results.
- Oseltamivir 75mg orally twice daily for five days is the preferred antiviral agent, although zanamivir 5 mg inhaled twice daily for 5 days can be used as an alternative.
- Breastfeeding is encouraged, but infected mothers should express their breast milk and allow a healthy adult to bottle feed the infant the breast milk.

As healthcare providers, we can make the largest impact on influenza vaccination coverage in pregnant women.

The increased morbidity and mortality from influenza in pregnant women can be prevented. The key to prevention is vaccination. The Healthy People 2020 target for influenza vaccination coverage in pregnant women is 80 percent. The CDC study has shown, as healthcare providers, we can make the largest impact on influenza vaccination coverage in pregnant women. Information given to pregnant women should emphasize the safety and effectiveness of maternal influenza vaccination to maximize protection for them and their infants.

References
Rene Genadry, MD
We are pleased to include Rene Genadry, MD among our faculty in the Department of OBGYN at the University of Iowa. Dr. Genadry, a world renowned Urogynecologist, joined Iowa in August 2012, after more than 40 years at the Johns Hopkins Department of Gynecology and Obstetrics, where he had been the director of urogynecology; one of the earliest units of its kind in the US.

“Urogynecology has only recently been recognized as a sub-specialty in obstetrics and gynecology,” Genadry says. “It's taken a great deal of work within the profession but we're seeing a real expansion of interest in urogynecology. That's one of the reasons I came to the University of Iowa.”

Genadry is also co-author of the book “A Woman’s Guide to Urinary Incontinence”, which serves as a primer for women in search of answers to what has become a serious issue for millions of women.

In addition to the book, (co-authored with Jacek L. Mostwin, MD, D.Phil), Genadry has spent a large part of his career researching and teaching about urogynecology. Much of his recent focus has been in the developing world.

“Here in the US, we're very lucky. We have access to good medical care. In places like Southeast Asia and Africa, women face a very different set of issues, many of which can be traced to their lack of accessible care, leading to a high mortality and morbidity including fistula for example. Much of what I do in my research involves gathering and understanding data in order to try to understand the issues.

Genadry joins Catherine Bradley, MD in the urogynecology division at the University of Iowa Hospitals and Clinics.

Jona Conklin, MD
Dr. Conklin was hired following completion of her Maternal-Fetal Medicine Fellowship in the Department of Obstetrics and Gynecology at the University of Iowa in 2013. She joins the Department of Obstetrics and Gynecology as a faculty member in the Maternal-Fetal Medicine Division.
Rebecca Dworkin, MSN, CNM
Rebecca Dworkin, MSN, CNM came to Iowa in July 2012 after completion of her MSN Degree and Certified Nurse Midwife (CNM) from Georgetown University. She joins the Department of Obstetrics and Gynecology as a faculty member in the General Obstetrics and Gynecology Division.

Jessica Kresowik, MD
Dr. Kresowik was hired following completion of her Reproductive Endocrinology and Infertility Fellowship in the Department of Obstetrics and Gynecology at the University of Iowa in 2013. She joins the Department of Obstetrics and Gynecology as a faculty member in the Reproductive Endocrinology and Infertility Division.

Jennifer Krupp, MD
Dr. Krupp came to Iowa in July 2012 after completion of her Maternal-Fetal Medicine Fellowship at the University of Wisconsin School of Medicine and Public Health. She joins the Department of Obstetrics and Gynecology as a faculty member in the Maternal-Fetal Medicine Division.

Rachel Mejia, DO
Dr. Mejia completed her residency in Obstetrics and Gynecology in 2013 at the University of Iowa. She joins the Department of Obstetrics and Gynecology as a faculty member in the General Obstetrics and Gynecology Division.

Henry Edward Reyes, MD
Dr. Reyes came to Iowa in July 2012 after completion of an Obstetrics and Gynecology Residency at the State University of New York, University at Buffalo in 2011 and one year on the faculty in the Department of Gynecology-Obstetrics at the State University of New York, University at Buffalo. He joins the Department of Obstetrics and Gynecology as a faculty member in the General Obstetrics and Gynecology Division.

Divya Shah, MD
Dr. Shah came to Iowa in August 2012 after completion of her Reproductive Endocrinology and Infertility Fellowship at Brigham & Women's Hospital, Harvard Medical School. She joins the Department of Obstetrics and Gynecology as a faculty member in the Reproductive Endocrinology and Infertility Division.

Jennifer Steines Wagemester, MD
Dr. Steines Wagemester came to Iowa in July 2012 after completion of an Obstetrics and Gynecology Residency at the University of Iowa Hospitals and Clinics. She joins the Department of Obstetrics and Gynecology as a faculty member in the General Obstetrics and Gynecology Division.