Answering Health Care’s Challenges
Each year, as we transition from one year to the next, we have the opportunity to look back at the important initiatives in which the Division of Research played a part. And in 2018, the Division was instrumental in a number of significant changes that allow us to advance our core mission of delivering research that both informs and improves health care.

Perhaps the biggest transition for us in 2018 was a redesign of Kaiser Permanente Northern California clinical trials. Historically, the Division of Research’s Comprehensive Clinical Research Unit assisted in planning and conducting a number of clinical trials across the region. In August, this unit was folded into a new, larger, effort now called the Clinical Trials Program. This program will guide and support all Northern California Kaiser Permanente clinical trials, with leadership from our regional director for clinical trials Alan Go, MD, new managing director Victor Chen, and myself.

The new program will continue to reside at the Division of Research and provide strategic leadership and increased coordination and support for our clinical trial groups, providing the best experience for our physicians and members.

Another notable change came in July, when Doug Corley, MD, PhD, of the Division of Research took on a newly created regional role as medical director of delivery science and applied research for The Permanente Medical Group. The term “delivery science” means evaluating the effectiveness of clinical practices and systems for delivering care at scale. In his new role, Doug will be bridging research and implementation to optimize care across Kaiser Permanente Northern California. TPMG’s support for the growth of our work in delivery science has led to increasing opportunities for physicians to partner with researchers in operationally relevant studies.

Related to these efforts, our Delivery Science Fellows program continues to grow, with the inclusion of 3 new fellows for the 2018-2020 term. These early-career investigators cover a broad range of work, from looking at how technology and data can enhance care, to the best ways to improve cardiovascular and related health services. They complement 2 other fellows currently in their final year as Delivery Science Fellows. Combined with 6 other postdoctoral researchers, these emerging investigators comprise our contribution to growing the next generation of health care researchers.

Adding to that in 2018 was a first — both for Kaiser Permanente and the Division of Research: the award of a T32 grant from the National Institute of Diabetes and Digestive and Kidney Diseases. The grant will train young scientists to translate research into practice, specifically, for people with type 2 diabetes and prediabetes. T32 training grants are much more commonly awarded to universities, and this marks the first time any Kaiser Permanente research institution has been the prime recipient.

Needless to say, this hasn’t distracted us from our core mission of conducting top-quality research. In 2018, our research appeared on 4 “Most Talked About Articles” lists from the Journal of the American Medical Association’s publications: JAMA Cardiology, JAMA Internal Medicine, JAMA Oncology and JAMA Pediatrics. It’s worth noting that the Division was the only institution that had studies on all 4 of those lists.

All this puts the Division of Research in a unique place: as a leading institution dedicated to understanding the health care challenges of our times and training those who will one day find answers to those challenges. No small task, but one I’m confident we’re capable of.

Tracy A. Lieu, MD, MPH
Director, Division of Research
The Division of Research (DOR) is currently home to approximately 59 investigators and staff scientists, 11 research fellows, and nearly 600 employees. The DOR also has 40 adjunct investigators from within Kaiser Permanente and other academic institutions. DOR scientists are involved in 393 ongoing research projects and 400 clinical trials. Since its founding in 1961, DOR researchers have published nearly 4,500 peer-reviewed articles including 441 papers in 2018 alone.
Projects from across the Division of Research made a splash in 2018. Here are some of the year’s attention-grabbing stories:

<table>
<thead>
<tr>
<th>Research Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children With Autism and Their Younger Siblings Less Likely to Be Fully Vaccinated</strong></td>
</tr>
<tr>
<td>More from TIME</td>
</tr>
<tr>
<td><strong>Expensive Insulin Analogs Perform No Better Than Human Insulin for Type 2 Diabetes</strong></td>
</tr>
<tr>
<td>More from HealthDay</td>
</tr>
<tr>
<td><strong>30-Year National Study Shows Women Who Breastfeed for 6 Months or More Reduce their Diabetes Risk by 50%</strong></td>
</tr>
<tr>
<td>More from The New York Times</td>
</tr>
<tr>
<td><strong>First Genetic Risk Factor for Erectile Dysfunction Identified</strong></td>
</tr>
<tr>
<td>More from Newsweek</td>
</tr>
<tr>
<td><strong>Men and Women with Pregnancy-related Nausea and Vomiting Use Marijuana More</strong></td>
</tr>
<tr>
<td>More from ABC News</td>
</tr>
<tr>
<td><strong>Pregnancy and Reproductive History May Impact Dementia Risk</strong></td>
</tr>
<tr>
<td>More from Washington Post</td>
</tr>
<tr>
<td><strong>Follow-up Interval After Colonoscopies Associated with Reduced Risk of Colorectal Cancer and Mortality</strong></td>
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<tr>
<td>More from Healio</td>
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<tr>
<td><strong>Partners of Newly Diagnosed Diabetes Patients More Likely to Adopt Healthy Behaviors</strong></td>
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Genomic Link to Glaucoma
A genetic analysis of nearly 65,000 Kaiser Permanente Northern California patients uncovered 9 specific positions across the human genome that are associated with variations in the risk of the most common form of glaucoma. The findings appeared in *Nature Communications*. “Glaucoma is a leading cause of blindness worldwide,” said lead author Hélène Choquet, PhD. “By identifying new genetic loci associated with glaucoma risk, our study provides important insights into the pathogenesis of this progressive condition.”

Sexual Assault’s Physical and Mental Toll
In the year after a sexual assault, women had significantly greater increases in psychiatric disorders, stress-related medical conditions, and use of psychiatric and gynecological services compared to women without a sexual assault, according to research led by Kelly Young-Wolff, PhD, MPH, and published in *Medical Care*. “It is imperative that health care settings ensure that women who experience sexual assault are offered caring and effective services,” said study co-author Brigid McCaw, MD, medical director of Kaiser Permanente’s Family Violence Prevention Program.

Brain Injuries and Dementia in Diabetics
A study in *Neurology* found a significant increase in the risk of dementia among people with type 1 diabetes who experienced a traumatic brain injury. Falls are the most common cause of traumatic brain injuries, and older people with type 1 diabetes have an elevated risk of falling, possibly due to diabetes-related complications. “It’s really important to understand this association because people with type 1 diabetes are living longer than ever before and are entering an age group at risk for dementia,” said lead author Paola Gilsanz, ScD.

Depression Screening in the Doctor’s Office
Findings published in in the *Journal of American Board of Family Medicine* suggest that primary care doctors have a chance to identify depressive symptoms in at-risk patients through a simple questionnaire that can be combined with alcohol abuse screening. A study led by Stacy Sterling, DrPH, identified at-risk populations for which screening for depression and hazardous alcohol use could catch depressive symptoms that might otherwise go untreated. “Many people already have a strong relationship with their primary care provider, so it may actually be the perfect environment for behavioral health intervention,” Sterling said.

Morning Sickness and Marijuana
Women with severe nausea and vomiting in pregnancy were nearly 4 times more likely, and those with mild nausea and vomiting were more than twice as likely, to use marijuana during pregnancy than pregnant women without nausea and vomiting. A study in *JAMA Internal Medicine* of more than 220,000 pregnancies in Northern California found “important evidence to a small but growing body of research suggesting that some pregnant women may use marijuana to self-medicate morning sickness,” said lead author Kelly Young-Wolff, PhD, MPH.

Genetic Risk Factor for Erectile Dysfunction
For the first time, researchers found a specific place in the human genome that raises a person’s risk of erectile dysfunction. Published in *Proceedings of the National Academy of Sciences*, the study found that variations near the SIM1 gene were significantly associated with an increased risk of erectile dysfunction. “Identifying the first genetic risk factor for erectile dysfunction is an exciting discovery because it opens the door for investigations into new, genetic-based therapies,” said the study’s lead author Eric Jorgenson, PhD.
Block-by-Block Pollution
The Division of Research joined forces with the Environmental Defense Fund and the University of Texas at Austin to leverage data collected by Google’s Street View mapping cars, creating a block-by-block map of air pollution in 3 Oakland neighborhoods. Led by Stacey Alexeeff, PhD, the study found that elderly people living on a street with higher levels of traffic-related pollutants had a higher risk of cardiovascular events, such as heart attacks, than did elderly people living on less-polluted streets. The findings appeared in Environmental Health.

Benefits of Pokémon Go
In July 2016, the smartphone game Pokémon Go rose to record-breaking popularity. Kaiser Permanente researchers, including Diane Carpenter, MPH, of the Biostatistical Consulting Unit, have now reported in Games for Health that patients treated at Kaiser Permanente Northern California between July and November of 2016 reported more benefits than injuries from playing the game, which encourages walking. “The game may be reaching a population that needs increased physical activity,” said lead author Erika Barbero, MD.

Understanding IUD Risks
Although complications are rare, intrauterine devices (IUDs) carry some risks, including perforation of the uterine wall and expulsion from the body. With funding from Bayer AG, a major IUD manufacturer, Mary Anne Armstrong, MA, is leading two studies that use electronic health records to examine how often IUD perforation and expulsion occur, and which factors, such as breastfeeding status, affect the risk of these complications. This project is a collaboration with RTI International, a nonprofit that coordinated earlier work validating the use of electronic health records for these kinds of studies.

Drug Refill Behavior and Chronic Disease
Management of chronic conditions, such as type 2 diabetes, requires long-term treatment, but medication nonadherence is widespread. Romain S. Neugebauer, PhD, is leading the development of causal inference methods to evaluate or account for the effect of drug refill behaviors in comparative effectiveness research, based on electronic health records. The work, funded by the Patient-Centered Outcomes Research Institute, aims to address the limitations of existing statistical methods.

Large Air Pollution Study
A retrospective study of more than 5 million Kaiser Permanente Northern California members will investigate associations between exposure to pollutant particles less than 2.5 micrometers in diameter (PM2.5) and the risk of cardiovascular disease events, such as heart attacks. Led by Stacey Alexeeff, PhD, the project will employ a state-of-the-art model that incorporates meteorological, land-use, and satellite data, and will examine factors, such as socioeconomic status, that might confer elevated risk to the effects of PM2.5.

Research Consultations
Under the direction of Mary Anne Armstrong, MA, in 2018 the Biostatistical Consulting Unit provided support for 216 resident and fellow research projects, 17 funded projects, and 8 unfunded consultations (via funding from the Clinical Trials Program); and helped clinical partners develop 46 Community Benefit grant proposals. The unit also provided intensive consultations on 22 Community Benefit projects that were funded in 2018. Throughout the year, unit staff contributed to 32 publications and 54 conference presentations for their clients.
Leading in Colorectal Cancer Screening

Ten years after a colonoscopy with no cancer found, Kaiser Permanente members were less likely to develop or die from colorectal cancer than those not screened, according to research led by Jeffrey Lee, MD, MAS. Another study led by Theodore R. Levin, MD, and Douglas A. Corley, MD, PhD, found a 52 percent decline in colorectal cancer deaths among Northern California members in the 15 years since a new screening program launched. Also, the National Cancer Institute awarded $16 million to the Division of Research and 3 collaborating institutions to evaluate how colorectal cancer screening can be most effective.

Life’s Work

In 2018, Division of Research scientists shared how their lives inspire their cancer research. Candyce Kroenke, ScD, MPH's early fascination with sociology and psychology now informs her work on how social ties affect life after breast cancer. Marilyn L. Kwan, PhD, who leads the largest study of bladder cancer survivors, is a certified CrossFit Level 1 trainer; “Some day I hope to conduct lifestyle research involving CrossFit in cancer survivors,” she says. Ai Kubo, MPH, PhD, benefitted from mindfulness early in her career, setting her on a path to make the practice feasible for cancer patients.

Muscle, Fat, and Mortality

Body mass index (BMI), a measure of body fat, can affect cancer survival. However, traditional BMI measurements suffer from errors and a lack of information on muscle, posing risks in using BMI to inform treatment. In a study of nonmetastatic breast cancer patients published in *JAMA Oncology*, Bette Caan, DrPH, and colleagues found that measures of muscle and fat composition gleaned from CT scans outperformed BMI as predictors of mortality. “Radiologists should think about incorporating this information into clinical care,” Caan said.

Body Composition and Cancer

Body composition can affect cancer survival and aid screening and treatment decisions. New work led by Elizabeth C. Feliciano, ScD, and supported by the National Cancer Institute, is leveraging Kaiser Permanente’s extensive electronic health records to rapidly assess body composition from computed tomography (CT) scans of colorectal cancer and breast cancer patients, and present risk information to clinicians.

The Lowdown on Low-Dose Screening

A new study led by Lori Sakoda, PhD, will examine factors that influence patient adherence to follow-up recommendations after low-dose computed tomography (CT) screening for lung cancer. Sakoda is also leading an evaluation of whether a computational model that predicts lung cancer risk can be enhanced to help clinicians weigh the potential benefits of low-dose computed tomography, such as earlier detection and reduced mortality, against potential harms, such as false-positives and radiation exposure.

Pancreatic Cancer Prediction

Kaiser Permanente is a founding site of the Consortium to Study Chronic Pancreatitis, Diabetes and Pancreatic Cancer, funded by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Cancer Institute. Stephen K. Van Den Eeden, PhD, leads the Division of Research's contributions to the consortium, which examines relationships between the 3 conditions. As part of this work, Dr. Van Den Eeden and colleagues will prospectively follow a cohort of patients at high risk of pancreatic cancer.

Family History

About 1 in 10 people in the United States develops cancer due to a hereditary condition, but information on a patient’s family history of cancer is difficult for physicians to collect and act on. The Patient-Centered Outcomes Research Institute awarded $7 million for a study led by Douglas A. Corley, MD, PhD, to assess 3 different methods for using family history to improve patient care. “Knowing family history is crucial for knowing how to best care for patients,” Corley said.

Assessing Ovarian Cancer Risk

Ovarian cancer is difficult to treat successfully in its later stages, but outcomes are good when it is found early. An original new process for reading ultrasound scans, developed by Elizabeth (Betty) Suh Burgmann, MD, and Kaiser Permanente gynecology and radiology physician leaders, allows them to categorize ovarian masses into different risk groups based on the size of the mass and the presence of blood flow and solid areas. These new radiology guidelines, which were validated in a research study, allows women at higher risk for ovarian cancer to be promptly referred for surgical evaluation while women at low risk can safely avoid surgery.
Outpacing the Nation

Death rates from heart disease and stroke in adults under age 65 are lower for Kaiser Permanente Northern California (KPNC) members than for patients in the rest of the United States, according to research led by Stephen Sidney, MD, MPH. Another study led by Jamal S. Rana, MD, PhD, found that control of 3 key cardiovascular risk factors improved faster over a 10-year period for KPNC diabetes patients than for patients in the rest of the country. Both studies appeared in the American Journal of Medicine.

Breastfeeding and Diabetes Risk in the CARDIA Study

Breastfeeding for 6 months or longer cut the risk of developing type 2 diabetes nearly in half for women throughout their childbearing years, according to study led by Erica P. Gunderson, PhD, MS, MPH, and published in JAMA Internal Medicine. Researchers analyzed data during the 30 years of follow up from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a national, multicenter investigation of cardiovascular disease risk factors that originally enrolled about 5,000 adults aged 18 to 30 in 1985 to 1986, including more than 1,000 members of Kaiser Permanente Northern California.

AFib Stroke Risk

Anti-blood-clotting drugs can dramatically reduce stroke risk in people with atrial fibrillation. However, research led by Alan S. Go, MD, and published in Annals of Internal Medicine found wide variations in how the initial risk of stroke is estimated, meaning that for some patients, these drugs may not be worth the risk of brain hemorrhage. Dr. Go also led a JAMA Cardiology study that points to the potential for continuous heart monitoring to help identify atrial fibrillation patients at higher risk of stroke and other blood clots.

Kidney-Heart Connections

A study of almost 150,000 Kaiser Permanente Northern California patients found that those who experienced acute kidney injury while hospitalized faced a 44 percent greater risk of heart failure during their first year after discharge. That work was led by Alan S. Go, MD, who was also senior author of a JAMA Internal Medicine study linking implantable cardioverter defibrillators (ICDs) to increased risk of hospitalization in people with kidney disease and heart failure. “Clinicians should carefully consider the risks and benefits of ICDs when recommending them for this subset of patients,” Dr. Go said.

A Heart-to-Heart for Researchers

In March, speakers at the second Cardiovascular Research Symposium shared innovative research on population-based heart care, specialty care, emergency medicine, and more. Convened at the Division of Research, the event drew about 80 cardiovascular researchers, subspecialty physicians, quality and operational staff, and others from across Kaiser Permanente Northern California. It provided “opportunities to engage about how to use research to improve our practice and expand our collaborations to take on the next challenges,” said Alan S. Go, MD.
To Tolerate or Transfuse?
Anemia, a shortage of healthy red blood cells, can be treated with red blood cell transfusions. However, transfusions have risks, and tolerating moderate anemia instead of receiving transfusions carries few short-term risks. Tolerating moderate anemia is also safe in the long-term, according to an analysis of records from 400,000 Kaiser Permanente Northern California members led by Nareg Roubinian, MD, MPH. The study appeared in *Annals of Internal Medicine*, with Gabriel Escobar, MD, as senior author.

Screen Time with Doctors
Kaiser Permanente members who chose video visits were overwhelmingly satisfied with this new way to “see” their doctor, Mary Reed, DrPH, and colleagues reported in the *New England Journal of Medicine*. Their survey of nearly 1,300 members who self-scheduled video visits found that 9 out of 10 felt the visit met their health care needs. “Many patients reported that the video visit actually improved the relationship with their clinician,” Reed said.

Diabetes and Partner Habits
A study of more than 180,000 couples found that partners of people with newly diagnosed type 2 diabetes are more likely to improve their health behaviors than partners of people without the disease. This research, led by Julie Schmittdiel, PhD, and published in *Annals of Family Medicine*, suggests that a new diagnosis can be a “teachable moment” for the whole family to improve health habits and reduce diabetes risk.

Testicular Cancer Miniregistry
Kaiser Permanente Northern California’s Testicular Cancer Review Panel unites urologists and medical oncologists to ensure that every patient with testicular cancer receives consistent, expert care. The panel received critical assistance from Lisa Herrinton, PhD, who used natural language processing to create spreadsheets of all new and ongoing testicular cancer cases. Dr. Herrinton said that this “miniregistry” was “exactly what the [panel] needed” to efficiently track treatments and outcomes.

Spotting Sepsis Sooner
Sepsis kills 6 million people worldwide every year. Typically, people with sepsis do not receive treatment until they get to the hospital or emergency department, which is often too late. A new study led by Vincent Liu, MD, MS, is leveraging electronic health records and advanced informatics to identify opportunities to improve care of patients who show worrisome signs of sepsis risk before they get to the hospital. The National Institute of General Medical Sciences is funding this work.

Improving Diabetes Care
Insulin analogs cost more but perform no better than human insulin in patients with type 2 diabetes, according to analysis of records from 25,000 Kaiser Permanente Northern California patients. That research appeared in *JAMA (Journal of the American Medical Association)*, with Andrew J. Karter, PhD, as senior author. Dr. Karter also led work published in *JAMA Internal Medicine* that found a nationwide need for better tracking of severe hypoglycemic events in diabetes patients.

Sharing Health System Knowledge
In July, more than 2,500 people gathered in Seattle for the 35th annual AcademyHealth Annual Research Meeting. Known as the nation’s top meeting for convening health services and policy researchers, the event facilitates the transfer of knowledge about the way the nation’s health system works, what it costs, and how to improve it. “Kaiser Permanente researchers were well-represented at this year’s annual research meeting,” said Alyce Adams, PhD. Division of Research presenters included Alison E. Fohner, PhD, Mary E. Reed, DrPH, Anjali Gopalan, MD, MS, and Julie Schmittdiel, PhD.

Pulmonary Embolism in the Emergency Room
A study by Kaiser Permanente’s Clinical Research on Emergency Services and Treatments (CREST) Network evaluated the implementation of a web-based decision support tool that “helps emergency room doctors to quickly and easily identify which patients with pulmonary embolism can be safely treated at home, thus avoiding costly and inconvenient hospitalization,” said lead author David R. Vinson, MD, an adjunct researcher with the Division of Research.
Hepatitis C Regimen in Black Patients
A study in *Clinical Gastroenterology and Hepatology* found that a treatment regimen of 8 weeks for hepatitis C may be just as effective as the guideline-recommended 12 weeks in black patients. The study also showed that more people overall can take advantage of the shorter treatment durations, which has important implications for access given the medication’s high cost. “The 8-week regimen was also generally underused for all patients, with 26 percent of those eligible for 8 weeks receiving 12 weeks of therapy,” said senior author Michael J. Silverberg, PhD, MPH.

Vaccination in Younger Siblings of Children with Autism
Research in *JAMA Pediatrics*, led by Ousseny Zerbo, PhD, found that children with autism and their younger siblings are significantly less likely to be fully vaccinated than the general population. The study identified large disparities in vaccination rates between children with and without autism spectrum disorders, as well as between their siblings, across all age groups and after adjusting for important

“Catch-up” HPV Vaccination
A study in *Lancet Child and Adolescent Health* led by Michael Silverberg, PhD, MPH, found that catch-up HPV vaccination with 3 doses was associated with a lower risk of pre-cancers or cancers in girls and women ages 14 to 20 at first vaccine dose. However, researchers found no significant associations in women who initiated vaccination at ages 21 to 26 years or in women who received fewer than the full 3 doses.

Flu Shot Attenuation
Nicola Klein, MD, PhD, director of the Vaccine Study Center, published a study in *Clinical Infectious Diseases* which found that the flu vaccine’s effectiveness wanes over the course of a flu season. Dr. Klein cautioned that the study doesn’t mean people should delay getting their flu shot and risk not getting it at all; but the evidence will help inform policymakers and scientists to optimize effectiveness of the flu vaccine.

Flu-Related Hospitalizations in Pregnant Women
Kaiser Permanente researchers including Nicola Klein, MD, PhD, collaborated with the U.S. Centers for Disease Control and Prevention to study the effectiveness of flu vaccinations in preventing influenza-associated hospitalizations during pregnancy. The results in *Clinical Infectious Diseases* showed that influenza vaccines reduced a pregnant woman’s risk of being hospitalized from flu by 40 percent on average.

NEW RESEARCHERS
The Division of Research added five new investigators to its ranks in 2018. The Biostatistics Core welcomed Oleg Sofrygin, PhD, as its newest Biostatistician/Research Scientist. Elizabeth Feliciano, ScD, joined the Cancer section as a Research Scientist focusing on identifying, understanding, and intervening on modifiable risk factors for obesity and cancer-related metabolic diseases. Also joining the Cancer section was Jeffrey K. Lee, MD, MAS, a Research Scientist focusing on general gastroenterology, colorectal cancer prevention, and hereditary gastrointestinal cancer syndromes. Joining the Cardiovascular and Metabolic Conditions section was Andrew P. Ambrosy, MD, whose research interests are ischemic heart disease, cardiomyopathy, and heart failure. And, Yeyi Zhu, PhD, joined the Women’s and Children’s Health section as a Research Scientist. Her research interests are at the interface of disease etiology and prevention strategies in the arena of women’s and children’s health across the lifespan.
Personalized Letters and Pregnancy Weight

A study published in *Diabetes Care*, co-led by Monique M. Hedderson, PhD, and Susan D. Brown, PhD, showed that women with gestational diabetes who received a letter with personalized weight-gain recommendations were significantly more likely to meet national weight-gain guidelines. The study analyzed more than 2,000 pregnant women receiving care at Kaiser Permanente facilities in Northern California who received letters automatically generated based on information in their electronic health records, as part of the Gestational Diabetes' Effects on Moms (GEM) cluster-randomized controlled trial led by Assiamira Ferrara, MD, PhD.

Caring for Adults with Autism

Compared to adults with attention deficit hyperactivity disorder (ADHD), those with an autism spectrum disorder had significantly higher utilization of outpatient visits, mental health, and laboratory services, according to a study in *Autism in Adulthood*. “The health care system may need to develop a clinical care path for these individuals that is better suited to their particular needs,” said Autism Research Program director Lisa Croen, PhD, who co-led the work with Ousseny Zerbo, PhD.

Cardiometabolic Conditions and C-section Risk

A study published in *PLOS ONE* and led by Monique Hedderson, PhD, found that elevated maternal body mass index, blood pressure, and blood sugar were all independently associated with increased risk of undergoing a cesarean section. The study suggests that eliminating higher than optimal weight in pregnant women could prevent 17 percent of C-sections, while 20 percent could be eliminated by increasing the proportion of women entering pregnancy at an optimal weight with normal blood pressure and glucose.

Abdominal Obesity and Gestational Diabetes Risk

A study of 1,750 pregnant women published in *Obesity* found that abdominal obesity in early pregnancy was a predictor of gestational diabetes, even when controlling for other conventional risk factors. “Our findings may have significant clinical implications, particularly considering that women with abdominal obesity, but the absence of other risk factors including overall obesity, are not considered a target population for early risk assessment or preventive management of gestational diabetes,” lead author Yeyi Zhu, PhD, said.

Evidence of NSAID Use and Miscarriage Risk

Research published in the *American Journal of Obstetrics & Gynecology*, and led by De-Kun Li, PhD, demonstrates that using non-steroidal anti-inflammatory drugs (NSAIDs) around the time of conception can significantly increase the risk of miscarriage in the first 8 weeks of pregnancy. NSAIDs help to relieve pain and reduce inflammation by inhibiting the production of prostaglandin, a hormone. “It turns out that a sufficient amount of prostaglandin needs to be present for successful embryonic implantation. Thus, a reduced amount of prostaglandin due to NSAID use around the time of conception could lead to difficulties of implantation of the embryo, and miscarriage,” Li told *Reuters Health*. 
Leadership Team

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