“Effect of Air Quality on Assisted Human Reproduction” (2010), by Richard Legro, Mark V. Sauer, Gilbert L. Mottla, Kevin S. Richter, Xian Li, William C. Dodson, and Duanping Liao

In the early 2000s, Richard S. Legro, Mark V. Sauer, Gilbert L. Mottla, Kevin S. Richter, William C. Dodson, and Duanping Liao studied the relationship between air pollution and reproductive complications. In the United States, Legro’s team tracked thousands of women undergoing in vitro fertilization, or IVF, along with the air quality of both the IVF clinics and patients’ home locations. IVF is a reproductive technology during which a physician obtains mature eggs from a patient’s ovaries and fertilizes them with sperm in a lab setting outside of the body, after which the physician transfers the fertilized eggs into the patient’s uterus. As stated in Legro’s publication, Legro suspected that poor air quality would adversely affect live birth rates during IVF, so he compiled and analyzed the various types of pollutants that IVF patients were naturally exposed to in their homes and clinics. Legro’s experiment led to an increased awareness among patients about the dangers of conceiving via IVF in highly polluted areas.

The authors of “Effect of Air Quality on Assisted Human Reproduction” investigated the impacts of air pollution on the assisted reproductive technique, in vitro fertilization, or IVF. According to the World Health Organization, air pollution is a large contributing source of death and disease around the world. As of 2021, they claim that air pollution causes over 4.2 million premature deaths each year, and label four pollutants as providing the most significant contributions. Those pollutants are nitrogen dioxide, sulfur dioxide, ozone, and particulate matter. Generally, all of those pollutants enter the body through the respiratory tract, where they can diminish lung function, aggravate asthma or lung infections, and in the case of particulate matter especially, penetrate into the bloodstream to cause negative effects on the heart and lungs. Additionally, previous to the study, other researchers had performed experiments indicating a connection between increased levels of pollutant exposure and adverse pregnancy outcomes. Thus, Legro and his team designed their study to assess that relationship.

Using data from the US Environmental Protection Agency, or EPA, they analyzed average measures of the air quality around the study participants’ homes and IVF clinic center locations. Legro and colleagues then compared that pollution data with different variables to assess the impact of air pollution on the participants’ IVF cycles. Those variables included the total numbers of successful embryo transfers into the participant’s uterus, of positive pregnancy tests, of confirmed intrauterine pregnancy visualized with an ultrasound, and of live births. Legro and colleagues’ overall hypothesis was that increased air pollution would be correlated with lower rates of live births among IVF pregnancies.

At the time of the article’s publication, Legro was a researcher at the Pennsylvania State University College of Medicine in Hershey, Pennsylvania, who focused on improving methods for the diagnosis and treatment of infertility, as well as genetic and environmental causes of polycystic ovary syndrome, or PCOS. PCOS is a condition characterized by several cyst-like follicles on the ovaries in addition to characteristics associated with elevated levels of testosterone in women, which can contribute to infertility issues. After Beate Ritz, who studies disease control at the University of California Los Angeles School of Public Health in Los Angeles, California, published an article about air pollution and impaired human reproduction in 2007, Legro designed his study to specifically

focus on air pollution and live birth during IVF.

From 2000 to 2007, Legro collected data from the outcomes of the first IVF cycle of 7403 female patients from three centers in the United States, including the Pennsylvania State College of Medicine, Shady Grove Fertility in Rockville, Maryland, and Columbia University College of Physicians and Surgeons in New York City, New York. Those locations are generally urban, which results in increased levels of air pollution. Legro obtained air pollutant concentration data recorded at monitors located in the three centers from the US Environmental Protection Agency. The data provided location-specific daily mean concentrations of their identified criteria pollutants (particulate matter, sulfur dioxide, nitrogen dioxide, and ozone) at the patient's home locations and IVF clinic centers during the study period. Legro's team used the pollution concentration data to calculate an estimate of exposure each patient had with the pollutants, sulfur dioxide, nitrogen dioxide, ozone, and particulate matter, measured both during the IVF cycle and during the pregnancy itself.

After analyzing the data from the seven-year period, Legro noted a consistent negative effect of elevated levels of nitrogen dioxide on the odds of live birth throughout the entire duration of an IVF cycle, including time at home and at the IVF lab. That means that higher levels of nitrogen dioxide correlated with a higher chance of a stillbirth, or nonviable neonate. According to the authors, nitrogen dioxide most critically impacted the time period between when the physician transferred the embryo into the participant's uterus until the confirmation of pregnancy. The authors noted that there were no statistical correlations between sulfur dioxide and IVF outcomes, except that they had found a weak correlation between increased sulfur dioxide exposure and lower live birth outcomes. Legro also noticed that ozone caused both negative and positive effects. Higher levels of ozone during the period of oocyte maturation were associated with increased chance for a live birth, but they were associated with lower odds of live birth after embryo transfer in the uterus.

According to Legro, increasing particulate matter concentrations had no measurable effect on IVF pregnancy outcomes. However, as particulate sizes became smaller, the authors observed an association between exposure to those particles and decreased rates of conception. Live birth outcome had no clear association with particulate matter throughout the entire duration of the IVF cycle. Legro and colleagues also stated there were no significant associations between pregnancy or live birth with sulfur dioxide or particulate matter at the IVF lab during the period of embryo culture, nor did they claim any significant associations between particulate matter at the patients' homes and those outcomes during the same period.

During their analysis, Legro and colleagues discuss how fluctuations in certain air pollutants have varying effects on assisted reproduction outcomes. Legro found that there was a positive association between ozone levels and live birth rates, but he claims that those findings are most likely misleading. According to Legro, the data suggests that a high level of ozone is indicative of lower nitrogen dioxide. The researchers claimed that increases in nitrogen dioxide concentration at the patient's address and at the IVF lab were significantly associated with a lower chance of pregnancy and live birth during all phases of an IVF cycle. Finally, the authors concluded that some pollutants such as sulfur dioxide or particulate matter had no recognizable effects on pregnancy throughout the duration of the experiment. Legro and colleagues claim that the effects of air quality changes have a clinically significant impact in pregnancy outcomes. According to the authors, air pollution negatively affects the chances of women using IVF to carry a fetus to term.

Legro noted the most consistent negative associations and pregnancy after IVF with nitrogen dioxide, which is a gas produced by combustion at high temperatures, originating primarily from motor vehicles and trucks. It also comes indoors with combustion from gas stoves, vented appliances with defective installations, and tobacco smoke. Researchers previously had correlated human exposure to nitrogen dioxide with negative respiratory symptoms and toxicity, especially to the heart. According to the authors, women undergoing IVF could have increased exposure to nitrogen dioxide during a cycle if they must frequently commute to and from medical care because of recurring monitoring visits and procedures. If a woman has to travel to her physician's office each week for monitoring appointments, whereas the majority of other women only visit their doctors once a month, she would likely already have an elevated risk of adverse pregnancy outcomes. That means there was no reliable means of measuring and incorporating increased or decreased amounts of pollutant exposure based on the participants' activity levels. Due to that design error in the exper-

iment, they conclude that it is not possible to conclusively single out one of the pollutants as the cause.

Legro and colleagues have shown that women undergoing IVF may have effects on the conception and success of any pregnancies based on exposure to a range of air pollutants. As fertility rates continue to fall in developed countries, assisted reproduction makes up a larger percentage of the birth rate. For example, in Denmark, IVF results in up to seven percent of births in the country. In Massachusetts, 6.1 percent of births were a result of IVF according to a 2005 study. The authors note also that IVF success rates in the United States have continually improved since the first annual reporting of results. The authors speculate that the increased focus on bettering air quality in the US may have been a factor in those improvements. However, researchers continue to refine reproductive technology, which may also account for the rising successful outcomes. Legro's findings may therefore hold particular relevance to developing countries where the utilization of IVF is steadily growing, while the urban air quality continues to decline. As of 2021, the World Health Organization notes an association between elevated pollutant exposure and adverse birth outcomes, including low birth weight and pre-term birth.

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