

# PRAMS PERSPECTIVES

A Pregnancy Risk Assessment Monitoring System Report    December 2009

## Infertility Treatments and Pregnancy Outcomes in Utah

### Background

The American Society for Reproductive Medicine (ASRM) defines infertility as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse.<sup>1</sup> The ASRM also notes that earlier evaluation and treatment is warranted after 6 months for women over 35 years of age. Infertility can impact both males and females and causes of infertility are widespread. It is currently unknown what portion of infertility can be prevented.<sup>2</sup>

#### What is PRAMS?

Data in this newsletter were provided by the Utah Pregnancy Risk Assessment Monitoring System (PRAMS). PRAMS is an ongoing, population-based risk factor surveillance system designed to identify and monitor selected maternal experiences that occur before and during pregnancy, as well as experiences of the child's early infancy. Each month, a sample of approximately 200 women, two to four months postpartum, is selected. The sample is stratified based on maternal education and infant birth weight so that inferences and comparisons about these groups can be determined. The results are weighted for sample design and non-response.

PRAMS is intended to help answer questions birth certificate data alone cannot answer. Data will be used to provide important information that can guide policy and other efforts to improve care and outcomes for pregnant women and infants in Utah. Women were asked questions about prenatal care, breastfeeding, smoking and alcohol use, physical abuse, and early infant care.

The PRAMS data reported here represent all live births to Utah residents from 2004-2008. A total of 11,821 mothers were selected to participate in the project and 9,697 mothers responded, for an unweighted response rate of 82.0%. Survey results were weighted for non-response so that analyses could be generalized

In an examination of 2002 National Survey of Family Growth data, Farr et al. found that 9% of women had been to a doctor or other medical care provider to help them become pregnant. Among those women, 59% became pregnant within 2 years of their last infertility visit, resulting in an overall live birth rate of 46%.<sup>3</sup> Another analysis of the same data set found that the most common infertility treatment used was ovulation-enhancing drugs followed by artificial insemination, surgical procedures, and in vitro fertilization (IVF).<sup>4</sup> Women who sought assistance for infertility were more likely to be white, non-Hispanic, college educated and affluent.<sup>5</sup>

Despite the suspected increase in use of infertility treatments, tracking infertility rates and use of infertility treatment other than artificial reproductive technology (ART) is inadequate. The Centers for Disease Control and Prevention (CDC) is contracted by the Society for Assisted Reproductive Technology (SART) to track information about ART procedures in the U.S. SART collects selected data on ART procedures performed by approximately 90% of U.S. providers affiliated with the ASRM. However, the SART data are collected by procedure and not by couple.

There are currently no national data collection systems that track use of artificial insemination procedures or use of fertility enhancing drugs, the most commonly used infertility treatment. The 2003 revision of the

certificate of live birth added use of infertility treatment as an indicated risk factor and separated ART procedures from use of fertility enhancing drugs and artificial insemination. Utah implemented this version of the certificate in 2009; however, it is not yet used in all states.

The research regarding pregnancy outcomes after infertility treatments is expanding. Studies have found that pregnancies conceived with IVF procedures have an increased risk for early pregnancy loss, preterm birth, congenital malformations, low birthweight, multiple gestation, placenta previa, preeclampsia, gestational diabetes, cesarean section, and perinatal mortality.<sup>6</sup> Much of the increase can be attributed to multiple gestations; however, higher rates of these complications have also been observed when singleton pregnancies conceived using IVF are evaluated independently. These elevated risks have not been reported in limited studies examining the use of artificial insemination<sup>7</sup> or fertility-enhancing drugs.<sup>8</sup>

Both the CDC and the World Health Organization (WHO) have recognized infertility as a public health problem. This report looks at the use of infertility treatments and selected outcomes of pregnancies conceived using different infertility treatments among Utah women.

## Methods

This report is derived from PRAMS data from 2004–2008. PRAMS respondents include Utah women who delivered a live birth. For this report, women are included if they indicated they were trying to get pregnant when they conceived (60% of all respondents). The PRAMS respondents who indicated they were trying to get pregnant were then asked, “Did you receive treatment from a doctor, nurse, or other health care worker to help you get pregnant with your new baby? (This may include infertility treatments such as fertility-enhancing drugs or assisted reproductive technology.)”

Specific treatment types were also self-reported in response to the following question:

“Did you use any of the following treatments during the month you got pregnant with your new baby?  
Check all that apply

- “ Fertility-enhancing drugs prescribed by a doctor (fertility drugs include Clomid®, Serophene®, Pergonal®, or other drugs that stimulate ovulation)
- “ Artificial insemination or intrauterine insemination (treatments in which sperm, but NOT eggs, were collected and medically placed into a woman’s body)
- “ Assisted reproductive technology (treatments in which BOTH a woman’s eggs and a man’s sperm were handled in the laboratory, such as in vitro fertilization [IVF], gamete intrafallopian transfer [GIFT], zygote intrafallopian transfer [ZIFT], intracytoplasmic sperm injection [ICSI], frozen embryo transfer, or donor embryo transfer)
- “ Other medical treatment, please tell us \_\_\_\_\_”

Treatment types were analyzed as five mutually exclusive categories: 1) use of ART with or without any other treatment, 2) insemination with fertility-enhancing drugs (as there were only 10 cases where insemination was performed without drugs, they were included in this category), 3) fertility-enhancing drugs only, 4) other medical treatment only, and 5) none. The authors assumed that if no boxes were checked, this indicated that the woman used infertility treatments, but not during the month of conception.

Data were analyzed using chi-square tests to detect differences in use of infertility treatments and birth outcomes. SAS-callable SUDAAN was used for analysis.

## Results

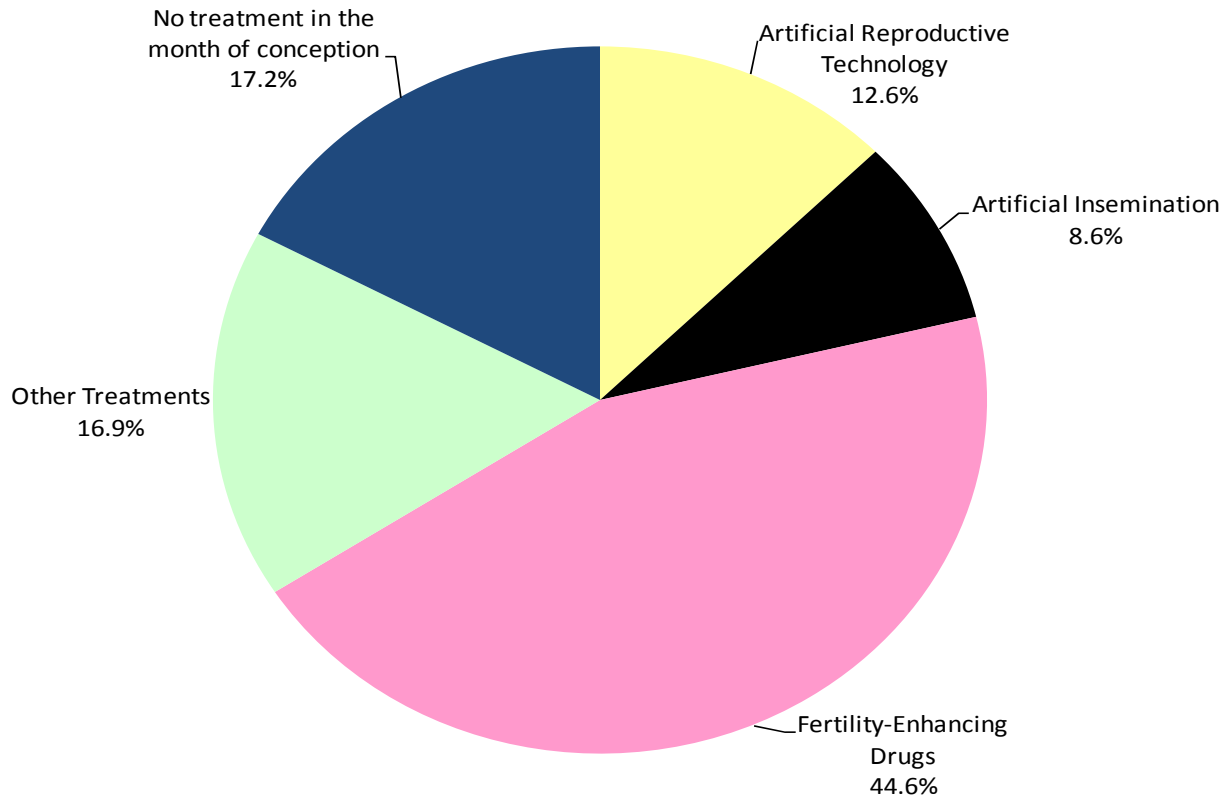
From 2004 to 2008, 9.5% of women who indicated they were trying to get pregnant said they received treatment to help them get pregnant. Table 1 shows that higher rates of treatment were found among women who were older, of higher education levels, married, non-Hispanic, of higher income levels, insured prior to pregnancy, had higher body mass indexes, and did not consume alcohol in the three months prior to pregnancy.

**Table 1. Percentage of Women Who Reported Trying to Become Pregnant Who Received Infertility Treatment by Selected Maternal Characteristics, 2004–2008 Utah PRAMS Data**

<b>Characteristics</b>	<b>Percent</b>	<b>+ 95% CI%</b>	<b>P-Value</b>
<b>Among all women</b>	9.5%	± 0.9%	
<b>Maternal Age</b>			<0.0001
≤ 19	~	~	
20 - 24	6.3%	± 1.5%	
25 - 29	10.2%	± 1.5%	
30 - 34	11.1%	± 2.1%	
35 - 39	12.1%	± 3.8%	
40+	16.2%*	± 9.6%	
<b>Education Level</b>			<0.0001
Less than High School	6.0%	± 1.6%	
Completed High School	8.3%	± 1.5%	
Some College	10.4%	± 2.0%	
College Graduate	10.3%	± 1.7%	
<b>Marital Status</b>			<0.0001
Married	9.9%	± 1.0%	
Unmarried	4.2%	± 1.9%	
<b>Ethnicity</b>			<0.001
Hispanic	5.8%	± 1.8%	
Non-Hispanic	10.0%	± 1.0%	
<b>Race</b>			NS
White	9.4%	± 0.9%	
Other than White	11.6%	± 5.6%	
<b>Federal Poverty Level (FPL)</b>			<0.0001
<100%	6.2%	± 1.9%	
101 - 133%	2.8%*	± 1.7%	
134 - 185%	6.3%	± 2.0%	
185%+	11.6%	± 1.3%	
<b>Insurance Before Pregnancy</b>			<0.0001
Yes	10.7%	± 1.1%	
No	4.8%	± 1.3%	
<b>Medicaid Before Pregnancy</b>			NS
Yes	5.9%	± 4.0%	
No	9.6%	± 1.0%	
<b>Prepregnancy Body Mass Index</b>			<0.001
Underweight	8.1%	± 4.0%	
Normal	8.7%	± 1.2%	
Overweight	10.3%	± 2.1%	
Obese	13.6%	± 3.0%	
<b>Alcohol Use Before Pregnancy</b>			<0.05
Yes	7.6%	± 2.0%	
No	9.9%	± 1.0%	
<b>Smoked Before Pregnancy</b>			NS
Yes	7.9%	± 3.4%	
No	9.6%	± 1.0%	
<b>Urban/Rural</b>			NS
Urban	9.9%	± 1.1%	
Rural	7.9%	± 1.8%	
~ numerator is less than 5, not reported			
*Use caution in interpreting, the estimate has a relative standard error greater than 30% and does not meet Utah Department of Health standards for reliability.			

Figure 1 illustrates the types of infertility treatments women reported using in the month they became pregnant. The most commonly reported treatment was fertility-enhancing drugs (FDs), followed by no treatment in the month of conception, other treatments, ART, and artificial insemination with fertility-enhancing drugs (AI). Procedures noted in the other category included use of medications such as Metformin, Glucophage, and progesterone, surgical procedures such as laparoscopy and other procedures like hysterosalpingogram.

**Figure 1. Type of Treatment Used During the Month of Conception Among Women Using Infertility Treatment, Utah PRAMS 2004–2008.**



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Pregnancy outcomes were examined and Table 2 presents rates of these outcomes by infertility treatment types. Using women who said they were trying to become pregnant and who did not use infertility treatment as a comparison group, significantly higher rates of multiple gestations, hospital visits during pregnancy, low birthweight, preterm birth, preterm rupture of membranes (PROM), and infant neonatal intensive care unit (NICU) admission were found in women who used ART. Women using ART also had significantly lower rates of vaginal delivery. Women who reported receiving AI with FD had significantly higher rates of multiple gestations, low birthweight, and preterm birth. Women who reported using FDs had significantly higher rates of multiple gestations, low birthweight, preterm birth, and infant NICU admission. No significant differences were noted among women who reported use of other treatments or no treatment in the month of conception. Many outcomes, such as pregnancy-induced hypertension or placental abruption, were not able to be examined due to small numbers.

In this sample of women who were trying to become pregnant, the 9.5% of women who received treatment delivered 41% of the twins and triplets. While it is assumed that many of these adverse outcomes can be attributable to multiple gestations, the small numbers in several of the treatment groups make stratification by or adjustment for multiple gestations unfeasible.

**Table 2. Selected Outcomes by Infertility Treatment Type, 2004–2008 Utah PRAMS Data**

	ART	Artificial Insemination and Drugs	Drugs Only	Other Treatments	None checked	Trying – No Infertility Treatments <sup>^</sup>
Multiple Gestation	40.4% (27.0, 53.8)	12.6% (1.5, 23.7)*	6.5% (3.5, 9.5)	~	1.4% (0.5, 2.3)*	1.3% (1.0, 1.6)
Hospital Stay of 1–7 Days	39.6% (22.1, 57.1)	27.0% (7.3, 46.7)*	12.6% (7.5, 17.7)	10.2% (2.7, 17.7)*	11.7% (7.0, 16.4)	12.9% (11.5, 14.3)
Low Birthweight	21.0% (14.0, 28.0)	12.1% (6.1, 18.1)	9.9% (7.7, 12.1)	4.6% (2.2, 7.0)	4.9% (3.7, 6.1)	5.0% (4.8, 5.2)
Preterm	30.3% (19.2, 41.4)	21.2% (8.7, 33.7)	12.3% (8.5, 16.1)	7.5% (2.6, 12.4)*	7.8% (5.2, 10.4)	7.2% (6.5, 7.9)
PROM	4.0% (1.7, 6.3)	2.4% (0.4, 4.4)*	2.3% (0.5, 3.9)*	1.5% (0.2, 2.8)*	1.4% (0.2, 2.6)*	1.2% (0.9, 1.5)
Vaginal Delivery	55.8% (30.4, 69.6)	59.8% (42.6, 77.0)	73.7% (67.3, 80.1)	67.0% (55.2, 78.8)	79.1% (74.5, 83.7)	77.4% (76.0, 78.8)
Infant NICU Admission	25.1% (14.4, 35.8)	20.7% (7.6, 33.8)*	15.7% (10.8, 20.6)	9.7% (3.3, 16.1)*	10.6% (7.3, 13.9)	9.5% (8.6, 10.4)

~ numerator is less than 5, not reported

<sup>^</sup> Trying–No Infertility Treatments as Comparison Group

Blue shading denotes statistical significance

\* Use caution in interpreting, the estimate has a relative standard error greater than 30% and does not meet Utah Department of Health standards for reliability.

## Limitations

In this study, infertility treatment is self-reported and there may be some over/underreporting of procedures. This analysis includes data on live births only. Therefore, the incidence of conception with infertility treatments may be underestimated as it does not include miscarriages, stillbirths, or women who received infertility treatment but never conceived. Lastly, PRAMS does not sample higher order multiples (quadruplets or higher), which may also lead to some underestimation.

## Conclusion/Recommendations

Researchers continue to evaluate the effects of infertility treatments on pregnancy. As the risks regarding increases in birth defects, multiple gestations, preterm birth, and other adverse outcomes are known, women contemplating infertility treatment should be counseled thoroughly about these risks before undergoing treatment.

Multiple gestations are considered an undesirable outcome of infertility treatments and multifetal pregnancies are the major contributor to adverse pregnancy outcomes. Single embryo transfers with ART have been found to produce lower rates of preterm birth and low birthweight compared to double embryo transfers resulting in either single or multiple births.<sup>9</sup> Women undergoing treatment with fertility-enhancing drugs should be advised to use a barrier contraceptive if more than three follicles greater than 15 mm are found with ultrasound.<sup>10</sup>

However, the best option for reducing adverse pregnancy outcomes due to infertility treatments is to reduce the incidence of infertility. How can public health and clinicians impact infertility? The following are known factors that contribute to infertility and can be impacted by education efforts:

**Obesity:** In Utah 17.7% of reproductive-age women reported their BMI as obese during the 2008 Behavioral Risk Factor Surveillance System (BRFSS) survey. Fertility is decreased in women who are obese, related mainly to ovulatory dysfunction, and obesity adversely affects spontaneous conception.<sup>11, 12</sup> Many obese women with infertility problems are diagnosed with Polycystic Ovarian Syndrome (PCOS). PCOS has been shown to be reduced with a loss of body weight as low as 5–10%.<sup>11</sup> Knowing the increased risks for adverse pregnancy outcomes among women who are obese prior to pregnancy, as well as the risks to fertility, reproductive-age women who are obese should be counseled to achieve a healthy weight. The American College of Obstetricians and Gynecologists (ACOG) recommends that weight loss should be attempted before use of FDs.<sup>10</sup>

**Smoking:** Women who smoke are more likely to be infertile. Smoking has been found to accelerate follicular depletion and shorten menstrual cycle length. In addition, menopause occurs one to four years earlier among smokers.<sup>13</sup> The ASRM reports that up to 13% of female infertility may be caused by smoking.<sup>13</sup> The 2008 BRFSS found that 8.9% of women aged 18-49 in Utah reported being a current smoker. Women of reproductive-age who are smoking should be counseled about the risks to their fertility. There are many tools available to assist women with smoking cessation, as well as tools for health care providers. Visit the Utah Tobacco Prevention and Control Program's website at <http://www.tobaccofreeutah.org/> for resources.

**Maternal age:** There is wide acceptance of the fact that women’s fertility declines with age. There have been many reports that the age of first childbearing in the U.S. is increasing. A review of 10 years of birth certificate data reveals that the percentage of women having a first pregnancy at ages 30 or older has remained relatively steady in Utah (3.6% in 1999 and 3.9% in 2008). Reproductive-age women should be educated on the decline in fertility with age.

**Sexually Transmitted Infections:** Untreated STIs can lead to infertility through the development of pelvic inflammatory disease. An analysis of reported cases of chlamydia and gonorrhea in Utah from 2003–2007 found that chlamydia rates increased nearly 50% and gonorrhea rates increased 99%. During this time period, Utah women ages 15–24 accounted for 51% of chlamydia and 64% of gonorrhea cases.<sup>14</sup> Information on the prevention of STIs for young adults, parents, and health care providers can be found at <http://www.catchtheanswers.net/>.

Because of the adverse outcomes associated with infertility treatment, questions about the duration of treatment beyond the conception cycle, and because it is not known how many more women in Utah had fertility treatment but did not have a live birth, ongoing and better surveillance of infertility treatments is warranted. The Utah Department of Health will continue monitoring the use of and outcomes associated with infertility treatments via the revised birth certificate, as well as expanding PRAMS data collection to address duration of treatments.

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