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Surgery for Ovarian Cysts and Infertility

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Surgery for Ovarian Cysts and Infertility

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An abstract of
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Abstract

Surgery for Ovarian Cysts and Infertility

By Banna Hussain

Background:
Ovarian cysts occur commonly among women of reproductive age. Some cysts become large enough to cause problems and require surgical removal. About 8% of premenopausal women develop ovarian cysts that require surgical treatment. Laparoscopic removal of ovarian cysts has been shown to affect ovarian reserve; however, little is known about the association between ovarian cysts that require surgery and infertility. This study aims to examine this association.

Methods:
We used data from the FUSCHIA Women's Study, a study of reproductive age women (22-45 years old) living in Georgia. All women completed an interview about reproductive health, including whether they had ever had surgery to remove ovarian cysts. Infertility was assessed based on two definitions: 1) experiencing a period of 12 months or more of unprotected sex not resulting in pregnancy after age 20 (infertility) and 2) experiencing a period of 12 months or longer when attempting to get pregnant after age 20, not resulting in pregnancy (infertility while attempting pregnancy). We fit Cox proportional hazard models to quantify the association between surgery to remove ovarian cysts and infertility.

Results:
This study included 2,125 reproductive age women with 36% reporting infertility and 7% reporting having had surgery to remove ovarian cysts. Women who had surgery to remove ovarian cysts had an increased hazard of ever experiencing infertility [hazard ratio (HR) = 1.25, 95% CI: 0.94, 1.64] and of experiencing infertility while trying to get pregnant [HR= 1.36, 95% CI: 0.93, 1.97] compared with women who did not have surgery.

Conclusion:
Having a history of surgery for ovarian cyst removal was associated with a history of infertility. However, it is unclear whether this is due to the surgery or to a factor that puts women with cysts at risk for experiencing infertility.

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Chapter 1:

Ovarian cysts occur in women of all reproductive ages (1). The incidence rate for ovarian cyst occurrence is hard to determine because cysts do not necessarily require medical attention. In some women, ovarian cysts develop then disappear without any or with few signs and symptoms. However, some ovarian cysts are severe enough to require surgical removal. About 8-10% of premenopausal women develop large ovarian cysts that need treatment (2). Because the surgical treatment is invasive, there has been concern regarding the association between surgical removal of ovarian cysts and infertility. It is also unclear whether women who develop ovarian cysts that require surgery are at greater risk of experiencing infertility in general than women who do not develop ovarian cysts.

Infertility

Clinical infertility among couples is described as a period of 12 months or more of unprotected, timed and regular intercourse not resulting in a pregnancy (2). Although this is the most commonly used definition to assess infertility, it misses women who are not attempting to get pregnant. There are several other definitions of infertility that have been assessed for efficacy in research. The definition of infertility used affects research findings regarding who is classified as infertile, age at infertility classification and probability of future conception (2). When restricting the definition to women who were trying to get pregnant, data captured a more specific sample of women who were infertile than when using other definitions (2).

Infertility based on the clinical definition is estimated to affect about 10-15% of couples in industrialized nations (3, 4). According to the National Survey for Family

Growth, clinical infertility in the United States was estimated to be 7.4% as of 2002 but decreased to 6.0% in 2006-2010 (5). The survey defined infertility as a period of 12 months or longer of unprotected sexual activity with the same partner (married or cohabitating) that did not result in a pregnancy although these couples were not necessarily attempting pregnancy at time of interview. However, the prevalence of infertility was found to be 15.5% among women who were at risk of getting pregnant and were trying to get pregnant (6, 7).

Infertility can result from male, female, or unexplained factors. No cause of infertility can be identified in 10-15% of couples who undergo diagnostic tests, while male factors account for 45-50% of remaining cases (6). Main factors that influence male infertility include low sperm count and motility, chromosomal mutations, obstruction in the vas deferens, maldescended testes, hypogonadism, idiopathic infertility and disturbance of ejaculation (8).

Female fertility peaks between the ages of 18-24 years and begins to decline after age 27, with this decline becoming more apparent after age 35 (9-11). Female infertility can result from fallopian tube abnormalities, which account for 30-40% of cases, endometriosis, intrauterine filling defects, uterine contour irregularities, cervical abnormalities, and ovarian abnormalities (10). Polycystic ovarian syndrome (PCOS), a type of ovarian abnormality associated with infertility, was found to be the most common cause of infertility in women (12). PCOS results in increased production of androgens, insulin resistance and causes anovulatory cycles (12), which in turn results in infertility.

Lifestyle factors contributing to female infertility include smoking, alcohol consumption, body mass index (BMI) and socioeconomic status (9, 13). Approximately

30% of women of reproductive age in the United States smoke cigarettes (14). Although smoking has been tied to several adverse reproductive health outcomes, its association with infertility is not very well established. A meta-analysis conducted to assess whether smoking is associated with infertility concluded that up to 13% of female infertility could be related to smoking (14), but this estimate may be biased. Studies have been conducted to determine the relationship between alcohol consumption and infertility. One study reported that high alcohol consumption was associated with an increased risk of infertility RR=1.59 (95% confidence interval (CI): 1.09–2.31) compared to women who drank moderate amounts of alcohol (15). Although a weak association had been suggested, it is not clear what the threshold for alcohol consumption is before it can result in infertility (10, 16). A BMI greater than 27 may cause ovarian dysfunction and lead to infertility (9, 17). Being underweight and having low amounts of body fat are also associated with ovarian dysfunction (17). Prevalence and clinical expression of PCOS are also strongly influenced by weight (18). Obesity worsens reproductive and metabolic features of PCOS, while additionally worsening fertility outcomes independent of PCOS (9).

Infertility has important implications for individuals and public health, as the physical, psychological and financial costs resulting from infertility issues can be substantial (19). Parenthood is a major transition in adult life for both men and women. Thus, the stress of not being able to conceive a child has been associated with anger, depression, anxiety, and marital problems as couples experience stigma, a sense of loss and diminished self-esteem (20). A longer time to pregnancy is also reported to be associated with risk of adverse pregnancy outcomes such as preeclampsia, unintended cesarean sections, preterm birth, small for gestational age and poor neonatal health (21,

22). This in turn may influence onset of disease during adulthood in babies born to mothers who who have had trouble conceiving (21, 23).

Ovarian cysts

Ovarian cysts are sacs or pouches filled with fluid or other tissue that form on or in an ovary. They usually develop as a result of oocyte production during the menstrual cycle. Around the midpoint of the menstrual cycle, an egg bursts out of its follicle and travels down the fallopian tube. Cysts can occur when the follicle doesn't rupture or release its egg but continues to grow although there are other types of cysts unrelated to the menstrual cycle. Many ovarian cysts develop and disappear without any intervention and in some cases, women do not develop any symptoms. Incidence rates for ovarian cyst occurrence is hard to determine because cysts do not necessarily require medical attention. Most U.S data suggest a prevalence of spontaneous ovarian cysts ranging between 3% and 15%, while worldwide, the reported prevalence of spontaneous ovarian cysts is 7% (16, 24).

Cysts smaller than 6 cm in size are classified as mild and may display symptoms such as abdominal distension, nausea and vomiting, but they typically resolve without treatment. Cysts between 6-12 cm are classified as moderate and may cause ascites if they rupture. It is recommended that patients follow-up to ensure the cysts have resolved with no complications. Cysts greater than 12 cm in size are classified as severe and are associated with more serious symptoms such as coagulation disorder and shock. Severe cysts typically require surgical removal (25). It has been estimated that ovarian cysts that require surgical removal affect about 10% of women in the United States (10). The first-

line of treatment for benign ovarian cysts or tumors requiring treatment is laparoscopic ovarian cystectomy (26, 27). Surgery for ovarian cysts is recommended based on the size of the cyst and severity of its symptoms (28).

Although laparoscopy is considered the gold standard procedure for management of ovarian cysts (27), recent research has suggested that laparoscopic cystectomy for benign ovarian masses causes postoperative decrease in serum anti-mullerian hormone (AMH), which is an indicator of ovarian reserve (27). These results were based on measuring ovarian reserve markers before and 3 months after operation. AMH levels in women of reproductive age were also measured before cyst removal surgery and 6-weeks and 6-months post-surgery (4, 29). AMH levels were found to decrease from levels at baseline at both post-surgery time points although the difference was more noticeable 6-months post-surgery (30). Finally, a single-center retrospective study of nonendometriotic ovarian cyst excisions also found that after excision, ovarian reserve decreased in volume by 40%, and levels remained low 6-12 months after surgery (31). However, women with low ovarian reserve may still conceive. AMH is a good marker of time to menopause but not necessarily of ability to get pregnant (31).

Summary

Research has been conducted to understand the effect of having surgery for ovarian cysts on ovarian reserve, but little is understood about the relationship between invasive surgical procedures for ovarian cyst removal and its effects on infertility. Additionally, there are gaps in evidence regarding whether women who develop ovarian cysts that require surgical removal are more likely to experience infertility in general than

women who do not develop ovarian cysts. The aim of this study is to assess the association between developing ovarian cysts that require surgical removal and experiencing a period of infertility in a population of reproductive age women.

Chapter 2

Ovarian cysts occur in women of all ages. Most ovarian cysts develop and disappear without any or few signs and symptoms, making it difficult to determine their incidence in the population. Cysts that require medical attention are typically easier to detect. About 8-10% of premenopausal women develop large ovarian cysts that need treatment (4). However, there has been concern regarding the association between surgical removal of ovarian cysts and infertility. It is unclear whether women who develop ovarian cysts that require surgery are at a greater risk of experiencing infertility in general than women who do not develop ovarian cysts. Infertility has a large public health impact, and because there is little to no information about the effect of ovarian cyst removal procedures on long-term reproductive outcomes, it is important to assess this association.

Recent research has suggested that laparoscopic cystectomy for benign ovarian masses causes postoperative decrease in serum anti-mullerian hormone (AMH), which is an indicator of ovarian reserve (29, 32). These results were based on measuring ovarian reserve markers before and 3 months after operation. AMH levels in women of reproductive age were also measured before cyst removal surgery and 6-weeks and 6-months post-surgery (4, 33). AMH levels were found to decrease from levels at baseline at both post-surgery time points although the difference was more noticeable 6-months post-surgery (34). Finally, a single-center retrospective study of nonendometriotic ovarian cyst excisions also found that after excision, ovarian reserve decreased in volume by 40%, and levels remained low 6-12 months after surgery (3, 4). Although AMH is a good predictor of time to menopause, women with low ovarian reserve may still conceive

(30). Therefore, it is still unclear whether surgical treatment for ovarian cysts causes infertility and whether women who develop cysts that require surgery are more likely to experience infertility in general. We evaluate whether women who report having surgery for ovarian cysts are more likely to have also experienced a period of infertility than women who have not had surgery for ovarian cysts.

Materials and methods

This study used data from the Further Understanding of Cancer, Health, and Survivorship in Adult (FUSCHIA) Women's Study, a research study originally aimed at understanding the effect of treatment for cancer on reproductive health outcomes. Cancer survivors were identified in the Georgia Cancer Registry (GCR). The GCR is a statewide population-based tumor registry that includes all reportable malignant cancers diagnosed among Georgia residents (31). In order to participate in the FUSCHIA Women's Study, women had to be diagnosed with their first primary cancer between the ages of 20 and 35 years and be between the ages of 22 and 45 at the interview. Women also had to be diagnosed with a reportable cancer at least 2 years before participating in the study between the years 1990-2009. Eligible women were identified and contacted by the GCR and asked for permission to be contacted by the study. Women who agreed were called, introduced to the study and asked if they would be willing to participate. Informed consent was obtained over the phone from women who agreed to participate. The initial study included 1,282 participants who were diagnosed with cancer as young adults, and 1,073 women who had never had cancer. Cancer free women were identified using a list purchased from Info USA and frequency matched to cancer survivors on 5-year age

groups and Georgia region of residence. We restricted our analysis to white and African American women due to the small number of women reporting other races and ethnicities. The Institutional Review Boards of Emory University and the Georgia Department of Health approved this study.

The interview was administered via phone and collected information on demographics, cancer diagnosis and treatments, menstrual function, pregnancy history, contraception, desire for children, general reproductive health and reproductive surgeries. Among women who answered the question regarding reproductive surgeries, we compared women who reported having surgery to remove ovarian cysts to women who did not report having surgery.

Infertility was defined based on questions which was also identified from the interview. Women were asked if there had ever been a period of time during which they had unprotected sex with a male partner for 6 months or longer but did not get pregnant, counting only times when they had sex at least 3 times a month. Those answering yes were also asked their age when they experienced this, how long the period lasted, whether they were actively trying to get pregnant, and whether it ended with a pregnancy. This information was used to create 2 infertility definitions: 1) experiencing a period of 12 months or more of unprotected sex not resulting in pregnancy (infertility) and 2) experiencing a period of 12 months or longer when attempting to get pregnant, not resulting in pregnancy (infertility while attempting pregnancy). We also only included infertile periods lasting for 12 months after age 20.

Co-variates identified from the interview included race, education, age, income, parity, menopause, history of hysterectomy or oophorectomy, hormonal contraceptive use,

and body mass index (BMI) based on weight in kg/height in meters squared. Cancer status was based on information from the cancer registry. Cutpoints for BMI were coded as <18.5 for underweight, 18.5-25 for normal, 25-30 for overweight and >30 for obese. Based on the literature, BMI, parity, race and cancer survivor status were included in a directed acyclic graph (DAG) and determined to be confounders. These were adjusted for in our models.

Statistical Analysis

We fit Cox proportional hazard models to assess whether women who had surgery for an ovarian cyst were more likely to ever experience a period of infertility than women who did not have surgery to remove ovarian cysts. Time to infertility was defined as the first age at which a woman reported experiencing infertility. Women who did not report infertility were censored at their age at interview or the age at which they had a hysterectomy or double oophorectomy. We repeated the analysis for infertility while attempting pregnancy. For both infertility definitions, we fit unadjusted and adjusted models.

All statistical analyses were performed using SAS version 9.4 (SAS institute).

Results

Participant demographics

Of 2,355 women who completed the survey, women who reported races other than white or black were dropped (n=120). In addition, women who had missing data on infertility were not included (n=110), leaving 2,125 (90.3%) women to be included in our study. Of remaining women, 150 (7.1%) had surgery to remove ovarian cysts. The median

age at surgery was 26 years (IQR = 13) .There was no meaningful difference in race, education, income level, hormonal contraceptive use, or BMI between women who had surgery and women who did not (Table 1). Women who did not report surgery for ovarian cysts were more likely to be less than 35 years old than women with surgery (29% vs. 18%). Women who had surgery were more likely to be nulliparous than women without surgery (21.3% vs. 13.7%). Additionally, women who had surgery to remove ovarian cysts were also more likely to have had a history of hysterectomy or oophorectomy (36.0% vs. 15.9%). There was a greater proportion of women who had surgery who were cancer survivors (66.7%) compared to women who never had surgery (53.5%).

Approximately 46.o% of the women who had surgery for an ovarian cyst and 35.3% of women who did not have surgery reported ever experiencing infertility. Of women who had ovarian cyst surgery, 37 women reported experiencing infertility after they had surgery to remove ovarian cysts (23.4%), while 26 women experienced any infertility before their surgery (16.5%). The average age at infertility for women who had infertility before surgery was 36.8 ± 5.0.and was 37.4 ± 5.1 for women who had infertility after surgery. The proportions decreased to 24.7% of women who had cysts removed and 17.2% of women who did not have surgery reporting infertility while attempting pregnancy. The average age at infertility when trying to get pregnant before surgery was 38.3 ± 4.6 years and was 38.0 ± 4.6 years when trying to get pregnant after surgery.

Women reporting any infertility were more likely to be black than those without a history of infertility, but when the definition was restricted to those attempting pregnancy, the distribution of races was similar to women who never reported infertility (Table 2). Women who never reported infertility were more likely to have a graduate education than

women meeting either definition of infertility. Women who experienced any infertility were older (34.8%) compared to women who did not (30.3%). Women who ever experienced a period of infertility had lower income than women with infertility while trying to become pregnant and women who did not experience infertility (36.9% vs. 24.3% and 25.8% respectively). Women who ever had a period of infertility and who had infertility while trying to get pregnant were more likely to be nulliparous (18.4% and 19.2%) compared to women who never had a period of infertility (11.9%). Women who ever had a period of infertility and women who had infertility when trying to get pregnant were more likely to have had a history of hysterectomy or oophorectomy (21.1% and 18.9% respectively) compared to women who did not have infertility (15.2%). Women with any infertility were less likely to use hormonal contraceptives (76.1%) than women who experienced infertility while trying to get pregnant and women who did not experience infertility (81.9% and 84.1% respectively). Women who ever reported infertility were more likely to be obese (34.9%) than women who did not experience a period of infertility (19.7%) as were women who experienced a period of infertility when trying to get pregnant (30.1%).

The hazard ratio for any infertility was 1.2 (95% CI, 0.94-1.6) comparing women who had ovarian cysts removed to those without surgery adjusted for BMI, race, cancer status, and parity (Table 3). The hazard ratio for infertility when attempting pregnancy was 1.4 (95% CI, 0.94-1.9) when adjusted for the same factors.

Discussion

Surgery to remove ovarian cysts was associated with and increased hazard of ever experiencing a period of infertility compared with no surgery. This persisted when restricting to infertility when attempting pregnancy. Further, women with surgery for ovarian cysts were more likely to report infertility after surgery than before. However, this might not be an effect of the surgery. Infertility increases with increasing age for all women, and we were unable to distinguish infertility caused by aging from infertility that might have resulted from surgery. Therefore, it is unclear whether the associations we observed were the result of the effects of surgery on infertility or were because women who experience cysts requiring surgery are at greater risk of infertility in general.

Research has shown that laparoscopic excision of ovarian cysts is associated with decreased AMH levels in the short-term (31). However, there are no long-term follow-up studies to see if AMH levels remained low or whether the decline in ovarian reserve is associated with infertility in these women. Although low AMH does not predict a woman's ability to become pregnant (33), it is predictive of early menopause (34). Our finding that women were more likely to experience a period of infertility after their surgery could be consistent with research on the effects of surgery on ovarian reserve if the lower AMH levels in these studies predict early menopause and our women are experiencing infertility because of early menopause.

A strength of our study was being able to look at the association between surgery and infertility, a clinically relevant outcome, as opposed to AMH. We were also able to use two definitions of infertility. The first definition (women had unprotected intercourse for more than 12 months and did not get pregnant) likely had good sensitivity but may have

included women who were not actually infertile. We addressed this issue by using the more restricted definition (women who had unprotected intercourse for more than 12 months and were trying to get pregnant but did not achieve pregnancy), which likely had better specificity. However, our results were consistent across definitions.

Another strength of our study is that we had a high proportion of African American women who are usually underrepresented in research regarding infertility. Our infertility measure was not limited to people coming into clinics. African American women are less likely to attend fertility clinics than white women (34). Thus, our study is more reflective of the general population. We also had rich data on reproduction because the questionnaire asked extensively about reproductive history.

This study is not without limitations. Although we could identify women who experienced infertility after surgery, we were unable to restrict the risk period for the women without cysts to a comparable time frame. Therefore, we could not draw a clear conclusion about whether the surgery itself was associated with infertility. We also may have included time that women were not at risk of becoming pregnant in the denominator of our calculations because we did not have information about contraceptive use or sexual activity during that period. However, we do not have reason to believe this was differential by surgery. Another limitation is that we had a relatively small sample of women who had surgery (n=150). Finally, in our study, we estimated prevalence of infertility in women. However, infertility is affected by the health of the couple. Some women may have been classified as infertile due to the reproductive health of their partner rather than their own but we were not able to distinguish between causes of infertility.

To our knowledge, our study is the first to look at the association between ovarian cyst removal surgery and infertility. As anticipated, ovarian cyst surgery is associated with an increased hazard of infertility in women of reproductive age. However, further research is needed to assess whether this increase is related to the surgery or is the result of a higher risk of infertility among women who have ovarian cysts that require surgery.

Tables

Table 1. Characteristics of FUSCHIA participants by ovarian cyst surgeries

Characteristic	Surgery to remove ovarian cyst			
	Ever (n=150)		Never (n=1970)	
	No.	%	No.	%
Race/ethnicity				
White	110	73.3	1425	72.3
Black or African American	40	26.7	545	27.7
Highest education level at interview				
High school graduate or less	13	8.7	121	6.1
Some College	41	27.3	493	25.0
College Graduate	51	34.0	719	36.5
Some graduate school or degree	45	30.0	636	32.3
Participant age, years				
Less than 35	27	18.0	561	28.5
36-40	66	44.0	790	40.1
41-45	57	38.0	619	31.4
Income at interview				
Less than or equal to $50,000	52	34.7	579	29.4
More than $50,000	95	63.3	1375	69.8
Parity				
None	32	21.3	269	13.7
1	28	18.7	464	23.6
2	40	26.7	587	29.8
3	23	15.3	288	14.6
History of a Hysterectomy or Double Oophorectomy				
Yes	54	36.0	313	15.9
No	96	64.0	1657	84.1
Hormonal Contraceptive Use				
Ever	123	82.0	1598	81.1
Never	27	18.0	365	18.5
BMI at interview				
Underweight	2	1.3	28	1.4
Normal	66	44.0	846	42.9
Overweight	40	26.7	534	27.1
Obese	40	26.7	555	28.2
Cancer survivor				
Yes	100	66.7	1054	53.5

No	50	33.3	916	46.5
Ever Infertility				
Yes	69	46.0	695	35.3
No	81	54.0	1275	64.7
Timing of Infertility				
Before surgery	26	17.3		
After surgery	37	24.7		
Never	87	58.0		
Ever Infertility While Trying				
Yes	37	24.7	338	17.2
No	112	74.7	1630	82.7

Table 2. Characteristics of FUSCHIA participants by infertility status

Characteristic	Period of infertility					
	Ever (n=767)		When trying to get pregnant (n=375)		Never (n=1358)	
	No.	%	No.	%	No.	%
Race/ethnicity						
White	512	66.8	291	77.6	1027	75.6
Black or African American	255	33.2	84	22.4	331	24.4
Highest education level at interview						
High school graduate or less	58	7.6	23	6.1	76	5.6
Some College	248	32.3	103	27.5	290	21.4
College Graduate	256	33.4	139	37.1	514	37.8
Some graduate school or degree	204	26.6	110	29.3	478	35.2
Participant age, years						
Less than 35	188	24.5	96	25.6	400	29.5
36-40	312	40.7	160	42.7	547	40.3
41-45	267	34.8	119	31.7	411	30.3
Income at interview						
Less than or equal to $50,000	283	36.9	91	24.3	350	25.8
More than $50,000	474	61.8	280	74.7	999	73.6
Parity						
None	141	18.4	72	19.2	161	11.9
1	201	26.2	97	25.9	291	21.4
2	212	27.6	113	30.1	418	30.8
3	91	11.9	52	13.9	221	16.3
History of a Hysterectomy or Oophorectomy						
Yes	162	21.1	71	18.9	206	15.2
No	605	78.9	304	81.1	1152	84.8
Hormonal Contraceptive Use						
Ever	584	76.1	307	81.9	1142	84.1
Never	179	23.3	68	18.1	213	15.7
BMI at interview						
Underweight	8	1.0	4	1.1	22	1.6
Normal	275	35.9	148	39.5	638	47.0
Overweight	213	27.8	109	29.1	364	26.8
Obese	268	34.9	113	30.1	268	19.7
Cancer survivor						
Yes	437	57.0	190	50.7	719	52.9
No	330	43.0	185	49.3	639	47.1

Table 3. Estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for ovarian cyst surgery according to two definitions of infertility for FUSCHIA participants

			Unadjusted			Adjusted		
	Infertile	**Total**	**HR**	**95% CI**		**HR**	**95% CI**	
Ever infertile[1]								
Surgery for ovarian cysts	69	150	1.3	1.0	1.7	1.2	0.9	1.6
No surgery	695	1970	1.0			1.0		
Infertility while trying to get pregnant[2]								
Surgery for ovarian cysts	37	150	1.4	1.0	2.0	1.4	1.0	2.0
No surgery	338	1970	1.0			1.0		

[1] Ever infertile: Couples who were having regular unprotected sex for a period of 12 months or more without getting pregnant

[2] Infertility while trying to get pregnant: Couples who were having regular, timed and unprotected sex for a period of 12 months or more without getting pregnant

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