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Postpartum factors and natural fibroid regression

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Abstract

Objective—Many fibroids regress with pregnancy or postpartum involution. We sought to identify factors that might inhibit or enhance this natural regression.

Study design—We used a prospective cohort of women with fibroids (n=494) determined by ultrasound screening during the early first trimester identified from the *Right from the Start* study. Ultrasounds were repeated three to six months postpartum (n=279). Logistic regression analyses were used to identify factors associated with fibroid regression (>50% reduction in volume).

Results—Postpartum progestin users had significantly less fibroid regression (p=0.01), while there was no association for combined estrogen-progestin use. Cesarean delivery and fever (hypothesized to inhibit regression) and breast feeding (hypothesized to enhance regression) were not associated with fibroid regression.

Conclusion—Progestin use in the postpartum period may limit regression of fibroids, consistent with prior literature on progesterone's role in fibroid development. Research into progestin-only treatments in critical reproductive periods is needed.

Keywords

breastfeeding; leiomyoma; pregnancy; progesterone; ultrasound

Introduction

Fibroids are common in pregnant women and are eliminated or decreased in size over the course of the pregnancy and/or the time of postpartum uterine involution.^{1–2} We previously

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Cities in which study was conducted: Raleigh NC; Nashville TN; Galveston TX; Memphis TN; Chapel Hill NC; Durham NC.

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reported that pregnancy eliminated 36% of fibroids, regardless of the initial fibroid size.² This pregnancy related fibroid regression may account for the inverse association between parity and fibroid risk seen in many epidemiologic studies.^{3–5}

The complex mechanical and cellular mechanisms related to birth and uterine involution may play a role in fibroid elimination and shrinking.⁶ Factors that affect the involution process may limit or enhance natural regression. For instance breast feeding can delay the postpartum return of menstrual cycles; the resulting decrease in ovarian steroids may enhance the regression process. Delivery type (vaginal vs cesarean) may also affect involution as suggested by an ultrasound-based study which found that cesarean delivery is associated with larger uterine size than vaginal delivery at one and three months postpartum.⁷ Thus, we hypothesized that breast feeding would enhance fibroid regression, and that cesarean delivery and postpartum infection would inhibit fibroid regression. We also examined other factors including postpartum hormonal contraception and length of gestation.

Material and Methods

This analysis was conducted as part of an ongoing prospective study of pregnancy, *Right from the Start*. The overall cohort study has collected data in North Carolina, Tennessee and Texas. Methods have been described previously.^{1, 8} Briefly, eligibility criteria included age 18 or older, enrollment before 13 completed weeks gestation by last menstrual period, intention to carry pregnancy to term, fluency in English or Spanish, and plans to remain in the study area for at least 18 months. Women were recruited from the community early in pregnancy or when planning a pregnancy. Institutional review boards at all sites gave approval, and written informed consent was obtained from each participant.

An early pregnancy endovaginal ultrasound screened systematically for uterine fibroids of at least 0.5 cm in largest diameter. Of the 494 study participants with fibroids, 294 participated in the postpartum ultrasound, which was scheduled between three and six months after delivery. Fifteen women not completing the postpartum interview were excluded, leaving 235 women who had a live birth and 44 who had a miscarriage. The primary reason for not completing a postpartum ultrasound was that the postpartum ultrasound was not added to the study until 2002, while enrollment for *Right from the Start* began in 2000. Systematic follow-up with incentive to attend the postpartum ultrasound began in 2005. Women who completed the postpartum ultrasound were on average 1 year older than those who did not complete it, but there was no difference in ethnicity or parity.

The data collection from ultrasounds has been described in detail.² Briefly, fibroid number, type of the largest fibroid (submucous, subserous, intramural or pedunculated) and location (fundus, corpus, cervix) were documented by sonographers.² Triplicate measures of largest diameter in three dimensions were used to estimate fibroid volume using the prolate ellipsoid formula. For more than one fibroid, total fibroid volume was calculated by summing all of the individual fibroid volumes. Fibroid images were saved initially as still photos and later as digital images on CD-ROM for review by study physicians (KH, SL). Body mass index (BMI) was calculated from height and weight measured at the study ultrasound.

Demographics including race/ethnicity, age, parity, education, income, and smoking status were gathered during a screening interview and first trimester computer assisted telephone interview. Pregnancy and postpartum factors were assessed by postpartum computer assisted telephone interview performed between 3 and 6 months postpartum. Variables, such as

menses, gestational age, and breastfeeding duration were categorized for analysis so that extremes of the distribution could be included

Gestational age at the time of delivery was categorized into 4 levels (<37 weeks, 37–<39 weeks, 39–<41 weeks, and 41+ weeks), calculated from last menstrual period adjusted by early ultrasound if dates were inconsistent. Delivery route (cesarean or vaginal) was self-reported. Intrapartum or postpartum fever was assessed by self-report on postpartum questionnaire. Antibiotic use at the time of delivery or in the postpartum period was asked as two separate questions and combined for data analysis.

The participants were asked about the duration of regular breastfeeding defined as suckling or pumping at least 4 times per day. A 3-level variable was created (0–29 days, 30–89 days, and 90 days or longer). Women who were breastfeeding at 90 days but less than four times per day were put into the second category. The information on timing of the return of menses was categorized into ≤60 days postpartum, 61–90 days and >90 days. Lastly, participants were asked about up to three types of contraception they used postpartum. We created mutually exclusive variables for progestin-only use (including mini-pill, Mirena IUD and Depo-provera), estrogen-progestin combined (including the contraceptive ring and patch) and non-hormonal contraception. The reference group for all three was no contraception. Eleven percent of women had more than one type of contraception within the first 90 days. For users of both non-hormonal and hormonal agents (n=23), the contraceptive method assigned was the hormonal one. If both progestin and combined hormone use were used (n=2), the category assigned was progestin use since it was used first, and dropping those two had little effect on results.

The outcome variable was defined by a > 50% decrease in total fibroid volume. This cutoff was chosen because it is above expected measurement error or likely first trimester growth.^{9–10} Fibroids that were no longer detectable on the postpartum ultrasound contributed zero postpartum volume giving a 100% decrease in volume. Volume reduction of ≤ 50% or volume increase at the postpartum ultrasound were combined as the referent.

Data analysis was performed using Stata 10.0 (College Park, TX). Logistic regression models were used to evaluate the associations of demographic, fibroid, pregnancy and postpartum factors of interest with fibroid regression. Each pregnancy and postpartum factor of interest was examined separately controlling for black ethnicity and presence of any submucosal fibroid (the only demographic or fibroid characteristic significantly related to fibroid regression). We used two-sided p-values with an alpha equal to 0.05. The primary analysis was based on the 235 women with live births. An additional analysis also included the 44 women who had an ultrasound 3–6 months after a miscarriage in order to compare fibroid regression for miscarriages to live births.

Results

Live birth cohort

The majority of the cohort was white; 31% were black. Nearly half were between 30 and 35 years old and just under half were nulliparous (Table 1). Most had only one fibroid (n=166, 71%). Seventy-two percent of the women (n=168) showed fibroid regression >50%. Twelve percent (n = 29) had fibroid volume changes of 50% or less. The rest (n=38) showed an increase in fibroid volume with ten percent showing more than a 50% increase.

Black, non-Hispanic women were less likely to have fibroids regress (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.25, 0.88) than white women (Table 1). Submucous fibroids had an increased likelihood of regressing compared to the most common type (subserosal)

(OR 3.13, 95% CI 0.98, 10.0). None of the other demographic or fibroid characteristics (age, parity, BMI, education, income, smoking status, fibroid number, fibroid location or total fibroid volume) was associated with fibroid regression (Table 1).

The association of postpartum factors with fibroid regression is shown in Table 2. Thirty-four percent had a cesarean birth and though fewer of these women had their fibroids regress than those with vaginal births (OR=0.83, 95% CI 0.45, 1.52), the two groups were not statistically different. Gestational age at birth was not an important factor except that women with births at ≥ 41 weeks gestation were less likely than the women giving birth at 39 to <41 weeks to exhibit fibroid regression (OR 0.36, 95% CI 0.15, 0.87) There was no clear trend across gestational ages.

Fever was reported by 19%; women reporting a fever showed a non-significant trend towards decreased regression than those without fever (OR 0.54, 95% CI 0.26, 1.11). Antibiotics were reported by 43% of women and had no association with regression.

Ninety-four percent of women breastfed for at least one day; 63% breastfed four times a day for at least 90 days post-delivery. Breastfeeding was not associated with fibroid regression. Return of menses was delayed for more than 90 days for the majority of women, but menses delay was not significantly associated with fibroid regression.

Postpartum contraceptive use was common with 65% of women using some means of contraceptive by the time of their interviews. Most of these women used condoms, but combined estrogen and progestin methods as well as progestin-only were also used. The use of progestin-only contraception was associated with a significantly lower likelihood of fibroid regression compared with those not using any contraception (OR 0.33, 95% CI 0.14, 0.79). Use of combined estrogen and progestin pills was not associated with fibroid regression.

Miscarriage and fibroid regression

Of the 44 women with miscarriages, most were white, 45% were 35 years or older and 60% were nulliparous. Thirty-five percent (n=15) exhibited a decrease in total fibroid volume $>50\%$ at the post miscarriage ultrasound, while twenty-five percent (n=11) had an increase in total fibroid volume $>50\%$. The rest had minimal change in size. Compared with women who had live births these women were significantly less likely to exhibit fibroid regression (OR = 0.19, 95% CI 0.09, 0.39). Pregnancy loss occurred at a median of 8 weeks (range 5–22 weeks). Miscarriages before 8 weeks had less fibroid regression (OR 0.09, 95% CI 0.03, 0.27) than miscarriages after 8 weeks (OR 0.35, 95% CI 0.14, 0.89) when compared with live births.

Comment

Fibroid regression was common with over 70% of women with live births having fibroids shrink more than 50% in volume between early gestation and 3–6 months postpartum. We found an association between fibroid regression and postpartum progestin use, with users showing significantly less regression, but no associations were found between fibroid regression and use of other hormonal contraceptives, cesarean delivery, fever, or breastfeeding. We also found that miscarriages were associated with a decrease in fibroid regression, and the later the miscarriage the greater the regression. Gestational age was not important among live births.

Our study has the advantage of systematic ultrasound screening for fibroids that was conducted very early in pregnancy; studies based on self-reported fibroid status have too

much misclassification of case status to assess fibroid regression. Once the protocol was fully implemented, we also had a high retention rate for women into the postpartum period, including women returning after miscarriage, so that selection issues are less likely to bias our results. Timing of the ultrasound in early pregnancy and postpartum period did not differ between contraceptive groups nor affect the outcome of regression. As the first large prospective study to follow fibroids through pregnancy, our findings provide an investigation of factors that may affect the inverse relationship between parity and fibroids that has been reported for decades.³⁻⁵ We had small numbers for examining some of the postpartum factors. Additionally, while we collected infection data proximal to the events, more severe infections around delivery (chorioamnionitis and endometritis) are subject to poor recall during a stressful time. Ideally, we would capture infections around the time of birth either prospectively or through medical record review.

The timing of fibroid regression (during pregnancy, at birth, or during the postpartum period) and the mechanisms involved are not known. Fibroid shrinkage during pregnancy is difficult to study. As the fetus develops, it is more difficult to measure fibroids. Burbank suggested that birth and placental delivery, with its associated hypoxia, would induce regression.⁶ Mechanical changes during the delivery and the following three months may also play a role. Negishi found a difference in the amount of uterine involution between cesarean and vaginal deliveries.⁷ Thus, we anticipated differences in fibroid regression between those with cesarean and those with vaginal delivery, but we did not see any. Marginally fewer of those with cesarean deliveries exhibited fibroid regression compared with those having vaginal deliveries (68% vs 74%), but this difference is not significant.

Baird and Dunson (2003) suggested that the postpartum processes involved with uterine involution would induce fibroid regression. Many mechanisms are involved in uterine involution including mechanical forces, vascular changes, hormonal changes, hypoxia, apoptosis, and tissue development. The factors we examined were possible modulators of these biological processes. However, only progestin use was significantly associated with fibroid regression.

Both biochemical and clinical evidence support a role of progesterone in fibroid growth outside of pregnancy.¹¹ High cellularity and mitotic activity were seen in women treated with progestin agents and during the secretory phase of the menstrual cycle when progesterone is highest. Inhibiting progesterone with agents such as RU-486 has shown reduction in size. Thus, inhibition of fibroid regression by progestin-only medication in the postpartum period is plausible. Progestin-only contraception can be used during breastfeeding, so most users also reported breastfeeding. However, a progestin effect remained regardless of breastfeeding level. On the other hand, the breastfeeding results could have been influenced by progestin-only contraceptive effects. However, estimates for fibroid shrinking associated with breast-feeding changed little after excluding the progestin users.

We were surprised that duration of breast feeding, with its suppression of ovarian steroid production, was not associated with fibroid regression and that the direction of effect was opposite of that predicted. However, a lack of protective effect from breastfeeding is consistent with existing epidemiologic data. Studies that have sought to evaluate the effect of breastfeeding on fibroid risk to explain the inverse relationship of parity with fibroids, do not show significant protective effects of breastfeeding.^{3 12} One explanation may be that a recent study demonstrated oxytocin induced fibroid growth, which may counteract the hormonal suppression during breastfeeding.¹³

Our other null findings do not support hypotheses based on analogy with the literature. One study reported that uterine involution was not as complete by 3 months postpartum in women with cesarean deliveries compared to those with vaginal delivery, but as noted above, we found no effect of cesarean delivery on fibroid regression. Similarly, animal studies have shown a delay in uterine involution secondary to subclinical infection and severe endometritis (but not mild endometritis);^{14–15} we found no association with fibroid regression for infections or antibiotic use, while fever appeared to be marginally important. Our infection data was not limited to nor specified endometritis, so more detailed future study is needed. Early onset of ovulation increased involution time in animal studies, but we did not see associations with early return of menses.¹⁵ Small sample size may play a role in our findings.

Among those with live births, post-date delivery was associated with inhibition of fibroid shrinking, but there was no trend across gestational age. However, later miscarriage was associated with greater regression which may indicate greater shift from pregnancy hormone levels to non-pregnancy state when compared with earlier loss. Whether the mechanical changes from a longer, and usually larger, pregnancy directly affect the fibroid regression process or there is a common cause is unknown. Further data would be needed.

There is much we need to learn about the natural history of fibroids, as they are dynamic tumors that grow and shrink in response to events in the reproductive years. The postpartum events hypothesized to affect fibroid regression were not found except for progestin use. The current understanding of progesterone's effects on fibroids support our findings. Further research needs to determine the effect of all progestin treatments, whether for contraception or menorrhagia, on fibroid growth. Given the importance of contraception during the postpartum period, our findings regarding progestin contraception need to be replicated and the length of a vulnerable window elucidated before formal recommendations are formulated.

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Table 1

Demographics of the live birth cohort (n=235) and associations with fibroid regression.

	Number	Percent	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)	P (adj)
Ethnicity ^b					
White	134	57.3	Referent	Referent	Ref
Black	72	30.8	0.50 (0.27, 0.93)	0.47 (0.25, 0.88)	0.02
Hispanic	12	5.1	1.70 (0.35, 8.15)	1.75 (0.36, 8.45)	0.5
Other	16	6.8	4.76 (0.60, 37.6)	5.00 (0.63, 39.5)	0.1
Missing	1				
Age					
<30	68	28.9	Referent	Referent	Ref
30–<35	108	46.0	0.72 (0.36, 1.42)	0.67 (0.33, 1.35)	0.3
≥35	59	25.1	0.98 (0.44, 2.18)	0.93 (0.41, 2.15)	0.9
Missing	0				
Parity ^c					
Nulliparous	112	47.9	Referent	Referent	Ref
Primiparous	86	36.8	0.95 (0.51, 1.76)	1.00 (0.53, 1.87)	1.0
Multiparous	36	15.4	1.01 (0.44, 2.33)	1.17 (0.49, 2.78)	0.7
Missing	1				
Body Mass Index (BMI)					
Under or normal	125	53.2	Referent	Referent	Ref
Overweight	43	18.3	0.52 (0.24, 1.09)	0.60 (0.28, 1.29)	0.2
Obese	67	28.5	0.67 (0.35, 1.30)	0.87 (0.43, 1.78)	0.7
Missing	0				
Education					
≤ High school	20	8.5	Referent	Referent	Ref
Some college	39	16.6	0.67 (0.20, 2.24)	0.85 (0.24, 3.02)	0.8
≥4 yrs college	176	74.9	0.88 (0.30, 2.56)	0.83 (0.27, 2.58)	0.7
Missing	0				
Income					
≤\$40,000	47	20.6	Referent	Referent	Ref

	Number	Percent	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)	P (adj)
	90	39.5	1.15 (0.53, 2.51)	0.90 (0.39, 2.06)	0.8
\$40,001–\$80,000	91	39.9	1.06 (0.49, 2.30)	0.85 (0.37, 1.94)	0.7
>\$80,000	7				
Missing					
Smoking status					
Never	182	77.8	Referent	Referent	Ref
Quit >4 mos prior	38	16.2	1.30 (0.58, 2.93)	1.13 (0.49, 2.61)	0.7
Current/ quit within 4 mos	14	6.0	0.73 (0.23, 2.27)	0.68 (0.21, 2.25)	0.5
Missing	1				
Total fibroid number					
1	166	70.6	Referent	Referent	Ref
2+	69	29.4	0.58 (0.32, 1.07)	0.75 (0.40, 1.42)	0.4
Missing	0				
Total Fibroid Volume					
≤10 cm3	37	15.9	Referent	Referent	Ref
10–30 cm3	117	50.2	1.23 (0.54, 2.78)	1.31 (0.56, 3.04)	0.5
>30 cm3	79	33.9	0.91 (0.39, 2.14)	0.95 (0.39, 2.33)	0.9
Missing	2				
Fibroid type ^d					
Submucous	29	12.6	2.71 (0.86, 8.47)	3.13 (0.98, 10.0)	0.05
Intramura		40.4	1.06 (0.57, 1.98)	1.06 (0.56, 2.01)	0.9
Subserous	96	41.7	Ref	Ref	ref
Pedunculated	12	5.2	0.61 (0.18, 2.07)	0.67 (0.19, 2.35)	0.5
Missing	5				
Fibroid segment					
Cervix	33	14.2	1.86 (0.71, 4.89)	1.84 (0.69, 4.94)	0.2
Corpus	123	52.8	Ref	Ref	Ref
Fundus	77	33.1	0.91 (0.49, 1.70)	0.98 (0.52, 1.85)	0.9
Missing	2				

^aOdds Ratios (OR) for fibroid shrinking greater than 50%: unadjusted and adjusted for ethnicity and submucous fibroid.

^bEthnicity adjusted only for submucous

^cParity at beginning of pregnancy
^dType adjusted only for ethnicity

Table 2

Associations of birth and postpartum factors with fibroid regression

	Number	Percent	Adjusted OR ^a (95% CI)	P-value
Cesarean delivery	81	34.5	0.83 (0.45, 1.52)	0.5
Missing	0			
Gestational age (weeks)				
<37	15	6.4	1.46 (0.37, 5.80)	0.6
37–<39	63	26.8	0.69 (0.34, 1.37)	0.3
39–<41	128	54.5	Ref	Ref
≥41	29	12.3	0.36 (0.15, 0.87)	0.02
Missing	0			
Infection				
Fever	44	18.7	0.54 (0.26, 1.11)	0.09
Antibiotics	98	43.0	0.78 (0.42, 1.44)	0.4
Breastfeeding				
<30 days	43	18.3	Ref	Ref
30–90 days	43	18.3	0.92 (0.33, 2.55)	0.9
4×/day at 90 days	149	63.4	0.63 (0.28, 1.41)	0.3
Missing	0			
Time of postpartum return of menses				
≤60 days	50	21.7	0.61 (0.29, 1.28)	0.2
61–90 days	44	19.1	1.02 (0.44, 2.36)	1.0
>90 days	137	59.3	Ref	Ref
Contraceptive use before day 90				
Progestosterone-only	36	15.3	0.33 (0.14, 0.79)	0.01
Combined	33	14.0	0.88 (0.36, 2.19)	0.8
Non-hormonal	72	30.6	1.30 (0.60, 2.81)	0.5
No contraception	94	40.0	Ref	Ref

^a adjusted for black ethnicity and submucosal type fibroid