Uterine Fibroids and Risk for Complications Following Second-Trimester Amniocentesis

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OBJECTIVE: To compare the abortion rate and preterm premature rupture of membranes (PPROM) after amniocentesis in women who have undergone antibiotic prophylaxis with uterine fibroids and control.

STUDY DESIGN: Retrospective study using the Antibiotic Prophylaxis before Second-Trimester Genetic Amniocentesis trial database carried out between January 1999 and December 2005 at the Artemisia Fetal-Maternal Medical Center (Rome, Italy). All women underwent antibiotic prophylaxis before amniocentesis. A follow-up within 4 weeks from the procedure was available.

RESULTS: A total of 2,497 of 21,219 (11.8%) women with uterine fibroids were identified. The rate of abortion was 2 of 2,497 (0.08%) in women with fibroids and 4 of 18,722 (0.03%) in women without fibroids ($p = 0.42$). The rate of PPROM was 4 of 2,497 (0.16%) in women with fibroids and 10 of 18,722 (0.05%) in women without fibroids ($p = 0.12$).

CONCLUSION: The risk for abortion and PPROM does not increase in the presence of uterine fibroids in women who have undergone antibiotic prophylaxis. (J Reprod Med 2011;56:0000–0000)

Keywords: amniocentesis, fetal loss, premature postpartum rupture of membrane, uterine fibroids.

Our study data showed that the presence of uterine myomas does not modify the rate of complications during second-trimester genetic amniocentesis.

Since Steele and Breg[1] demonstrated the possibility that amniotic fluid could be cultured for fetal karyotype in 1966, amniocentesis has represented the most widespread invasive prenatal test used for prenatal diagnosis of fetal aneuploidies and genetic disorders. In fact, in 2003 ~70,000 amniocenteses were performed in the United States,[2] and in Italy during recent decades, the use of second-trimester amniocentesis for genetic purposes in pregnancy has significantly increased, despite the introduction of screening tests for aneuploidy.[3]

Many retrospective studies or small casistic trials try to better define the rate of abortion after second-trimester amniocentesis, and their results range from 0.06% to 2.9%.[4-12] This wide range is probably

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Financial Disclosure: The authors have no connection to any companies or products mentioned in this article.

0024-7758/11/5600-0000/$18.00/0

related to the influence of many factors, some of which have been scientifically proven. Only a few of these have been indicated as possible determinants of fetal loss after amniocentesis.[13] Recently, we demonstrated the protective action of antibiotic prophylaxis that reduces both fetal losses and preterm premature rupture of membranes (PPROMs) by ~80%.[14]

The incidence of uterine fibroids is quite high in pregnant populations, ranging from 2.6% to 25%, but their effects on pregnancy outcomes and complications are far from being understood.[15] Even the risk for miscarriages cited in many manuscripts concerning the presence of fibroids (from a series of reports reviewed in 1981)[16] were biased by the small series and low clinical evidence.[15]

The role of fibroids in prenatal diagnosis is still unclear, and to our knowledge only a small retrospective case control study[17] has so far analyzed the relationship between leiomyomas and amniocentesis outcome, concluding that women with leiomyomas are at increased risk for second-trimester spontaneous abortion but mid-trimester amniocentesis does not further increase this risk.

Based on the lack of data concerning the role of fibroids during amniocentesis, in the present study we attempted to evaluate whether the presence of uterine fibroids increases the abortion rate or PPROM after second-trimester genetic amniocentesis in women who had undergone antibiotic prophylaxis and entered the Antibiotic Prophylaxis before Second-Trimester Genetic Amniocentesis (APGA) trial.[14]

Materials and Methods

We compared the rates of spontaneous pregnancy loss and PPROM within 4 weeks of the procedure in women with fibroids and in women without fibroids who received antibiotic prophylaxis before the amniocentesis and entered the APGA trial.

The APGA trial was an Italian Society of Prenatal Diagnosis and Fetal Maternal Medicine (S.I.Di.P.)–sponsored single-center randomized controlled trial that demonstrates the role of antibiotic prophylaxis before amniocentesis in protecting against fetal loss and PPROM.[14] The APGA trial was carried out between January 1999 and December 2005 at the Artemisia Fetal-Maternal Medical Center, Rome, Italy.

Women who were placed in the treatment group were given 500 mg of oral azithromycin at 24-hour intervals for 3 days before amniocentesis. Before each amniocentesis and on the same day, a detailed ultrasound study of fetal anatomy and placental and uterine structures was performed by an expert fetal ultrasound sonographer. Presence and dimensions of any fibroid bigger than 20 mm in maximal diameter were recorded in the database. We did not consider the type or the location of the myomas. The ultrasound diagnosis of myomas was based on the presence of a spherical mass with a different acoustic structure compared to the surrounding myometrium. In order to distinguish myomas from uterine contractions we used color Doppler imaging. In women with myomas, we observed circumscribed vessel patterns around the mass, whereas in women with contractions, there was no vessel displacement in the area of the local myometrial thickening. The same operator performed all of the amniocenteses under continuous ultrasound guidance using a 21-gauge, 20-cm needle. An ultrasound scan was performed after the amniocenteses; women were discharged 30 minutes after the procedure, and in this phase further control of the myomas was carried out in order to confirm the diagnosis. Patients were told that bed rest was not necessary.

Participation in the APGA trial was approved by the institutional ethics committee responsible for human experimentation.

A χ^2 square test for comparison of proportions was used. RR between the two groups and 95% CI were calculated.

Results

A total of 34,923 women were initially enrolled in the APGA trial. After exclusion of women who did not receive amniocentesis, spontaneous abortion before amniocentesis, major fetal abnormalities, termination of pregnancy after amniocentesis, protocol violation, and loss to follow-up, 21,219 cases were analyzed per protocol in the antibiotic group.

A total of 2,497 (11.8%) women with uterine fibroids were identified. Table I shows the baseline characteristics for women with and without fibroids. The potential confounders were similar for all groups.

No differences in complications between women with and without fibroids were found (Table II).

Discussion

In this study, we demonstrate that in patients who have undergone second-trimester amniocentesis following antibiotic prophylaxis, there is no differ-

Table I *Demographic and Baseline Characteristics*

Variables	Fibroids group (n = 2,497)	No fibroids group (n = 18,722)
Mean age (years)	33.6 (3.88)	33.4 (3.88)
White	2,487 (99.6%)	18,668 (99.7%)
Chronic hypertension	23 (0.92%)	168 (0.9%)
Smoker during pregnancy	217 (8.7%)	1,586 (8.4%)
Primipara	1,141 (45.7%)	8,619 (46%)
Multipara	1,336 (53.5%)	10,123 (54%)
Gestational age, weeks	16.7 (1.035)	16.6 (1.035)
Indication for procedure		
Age ≥ 35	1,226 (49.1%)	9,171 (49%)
Anxiety	924 (37%)	6,927 (37%)
Positive screening for fetal chromosomal abnormalities	147 (5.9%)	1,083 (5.8%)
Family history of genetic disorder	25 (1%)	165 (0.88%)
Personal[a] history of risk	364 (14.6%)	2,712 (14.5%)

Data are median (IQR), number (%), or mean (SD).
[a]Ultrasound markers, infection, previous chromosomal abnormality, previous genetic disorders, assisted reproductive technologies, previous exposure to teratogens.

ence between women with and women without fibroids in terms of miscarriages or PPROM.

The effects of fibroids on pregnancy outcome and complications remain unclear. Myomas have been associated with an increased risk for fetal malpresentation (OR 2.9; 95% CI 2.6–3.2), cesarean section (OR 3.7; 95% CI 3.5–3.9), and preterm delivery (OR 1.5; 95% CI 1.3–1.7).[18,19] The rate of spontaneous miscarriage in pregnant women with fibroids has been investigated by several authors. The largest study was carried out by Benson et al,[20] who reported a nearly 2-fold increase in abortion rate among 143 women with fibroids compared with 715 age-matched controls (14% vs. 7.6%). Furthermore, Feinberg et al[21] also showed an increased risk for miscarriage if fibroids were present (25% vs. 16.6%). It is obvious that the inherent risk for pregnancy loss in the first trimester of gestation can complicate identification of any deaths that might be caused by fibroids. However, all of these studies were biased by small sample sizes or low clinical evidence, making the outcome and complications related to uterine fibroids during pregnancy unclear.

The APGA trial[14] is today the biggest randomized controlled trial ever performed in prenatal diagnosis demonstrating with considerable clinical evidence (IB) that antibiotic prophylaxis could prevent abortion and PPROM after amniocentesis. All women came from an unselected population with a normal background risk for abortion (data not shown). Furthermore, considering that fibroids during pregnancy is by no means a rare condition, the results of this investigation could be helpful in decision making for women who have been advised to undergo antibiotic prophylaxis before amniocentesis. In this research we decided to investigate only the antibiotic group because we believe that given its highest clinical evidence, this prophylaxis could become the standard procedure among perinatologists who perform amniocentesis.

To date, the role of fibroids has yet to be established during amniocentesis. Only Salvador et al[17] in a retrospective case control study reported an increased risk for second-trimester spontaneous abortion in women with leiomyomata, concluding that this risk is not increased by genetic amniocentesis. However, as these authors say, the procedure-related risk from amniocentesis in the presence of

Table II *Comparison of Rates of Fetal Death and PPROM After Amniocentesis (Per-Protocol Analysis) in Women with and without Fibroids*

	Fibroids group (n = 2,497)	No fibroids group (n = 18,722)	p Value	Relative risk
Fetal deaths	2 (0.08, 0.00–0.19)	5 (0.03, 0.00–0.05)	0.42	3.0 (0.58–15.45)
PPROM	4 (0.16, 0.00–0.32)	10 (0.05, 0.02–0.09)	0.12	3.0 (0.94–9.56)

Data are number (%, 95% CI), or RR (95% CI).

fibroids could not be investigated in their study because of the limited number of cases presented. For these reasons, we investigated the impact of uterine fibroids on the endpoint considered, namely abortion rate and PPROM, in women who had undergone the antibiotic prophylaxis and had entered the APGA trial. Our study data showed that the presence of uterine myomas does not modify the rate of complications during second-trimester genetic amniocentesis. Pregnancy loss rate or PPROM rate does not significantly increase in pregnant women with sonographically identified fibroids who have undergone amniocentesis in the second trimester.

Our data are not consistent with findings in other studies, in which the incidence of uterine fibroids in the second trimester of pregnancy ranged from 1.6% to 4%.[15] In fact, in our study, in 11.7% of women, a myoma was found. We believe there are several reasons for this. The first is that the majority of studies reporting diagnosis of myomas during the second trimester of pregnancy are all retrospective cohort studies performed in the 1990s, when scanning equipment was less well developed. This could have led to an underestimation of the diagnosis. The second consideration is that the majority of the recent studies are based on a non-European population. Only Vergani et al[22] described, in a recent retrospective paper, the incidence of myomas in an Italian cohort population, with a rate of 3%. However, in this report they considered only myomas with an average diameter >5 cm. Moreover, in our cohort, 49% of the women were older than 35 years[14] and our report is the first in which myomas were recorded prospectively. The strength of the study lies in the large sample size and the study design, which made it possible to demonstrate the harmlessness of fibroids in prenatal diagnosis. This is true for a follow-up period of 4 weeks. In fact, we set our follow-up period to within 4 weeks from the procedure because other studies reported complications mainly within the first and second week following the procedure.[9,11,23,24] The harmlessness of fibroids during amniocentesis indirectly confirms the results arising from the APGA trial, in which the role of infections was suggested to be responsible for adverse outcomes.

In conclusion, we demonstrated that fibroids did not increase complications after amniocentesis in women who received antibiotic prophylaxis.

Acknowledgments

We would like to thank Dr. Francesco Padula of the Department of Prenatal Diagnosis at the Artemisia Medical Center for the critical review of the manuscript for important intellectual content and drafting of the manuscript. We also thank Dr. Alvaro Mesoraca and the staff of the Genetics and Molecular Biology Unit at the Artemisia Medical Center, including Ivan Gabrielli, Domenico Bizzoco, Antonella Cima, Antonietta Viola, Gianluca Di Giacomo and Monica Sarti. We also thank the doctors of the center who took part in the study conducting assessment of the women needing ultrasound scan listed alphabetically by name: Cristiana Brizzi, M.D., Ornella Carcioppolo, M.D., Paolo Gentili, M.D., and Vincenzo Milite, M.D. We thank Dr. Luca Granata and the inspectors of SINCERT and CERMET, heads of quality control whose scrupulous check guaranteed the methodologic correctness of the study. We thank Mr. Michael Kenyon for his assistance in language revision of the manuscript.

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