Effect of intrauterine marijuana exposure on fetal growth patterns and placental vascular resistance

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ABSTRACT

Objective: The recent legalization of marijuana has increased overall use, including in pregnancy. Studies have previously associated marijuana use with adverse fetal neurodevelopmental outcomes. We sought to compare fetal sonographic growth parameters and placental perfusion, as measured by umbilical artery Dopplers, in women using daily marijuana versus nonusers.

Methods: A retrospective cohort study capturing self-identified pregnant daily marijuana users with gestational age matched controls was performed. We compared maternal demographics, fetal biometry, nuchal translucency, and umbilical artery Dopplers in marijuana users versus controls. Intrauterine growth restriction was defined as an estimated fetal weight <10th %.

Results: In 55 first trimester ultrasounds, there were no differences in crown rump lengths or nuchal translucencies between the groups. Likewise, in 195-second trimester ultrasounds, no differences were noted in biometry. Second trimester umbilical artery systolic to diastolic ratios were higher in marijuana users compared to nonusers (4.02 versus 3.92, \(p = .024\)). In the third trimester, 26 of 192 marijuana exposed fetuses were growth restricted compared to 6 of 192 controls (\(p = .002\), and umbilical artery systolic to diastolic ratios were higher (3.52 versus 3.12, \(p = .0001\)). Four cases of absent and reversed end diastolic flow were observed in marijuana users, while no cases were observed in controls.

Conclusions: Our data shows that daily marijuana use is associated with impaired fetal growth and increased placental vascular resistance. Marijuana consumption in pregnancy should be avoided until further studies delineate its exact potential for fetotoxicity.

Introduction

Marijuana, the most common illicit drug consumed in society, has been associated with alterations in sensation, hallucinations, loss of IQ points, increased appetite, and subsequent use of additional illicit substances. Approximately 20 million Americans currently report using marijuana with the incidence on the rise [1]. Perhaps owing to the increased widespread legalization of marijuana, utilization in pregnancy has also increased in recent years. Current reports estimate daily use occurs in approximately 16% of pregnant women. Alarmingly, 70% of women believe there is minimal or no harm from using marijuana in pregnancy [2].

Marijuana crosses the placenta, and its use has been associated with long term impaired fetal neurodevelopment, the etiology of which is poorly understood [3]. Prior studies on marijuana’s effects on fetal growth have been limited and conflicting. One large meta-analysis demonstrated no increased risk of birth weight less than 2500 g in marijuana users, while in another recent study, marijuana users had an increased risk of birth weight less than the 10th percentile for gestational age [4,5]. The primary objective of the present study is to compare fetal sonographic growth parameters and placental perfusion as measured by umbilical artery (UA) Dopplers in women using daily marijuana versus nonusers.

Materials and methods

We performed a retrospective cohort study over a 4-year period from January 2013 to January 2017. Patients who self professed daily marijuana use on their prenatal questionnaire were captured, and matched to gestational age controls. Additional inclusion criteria were age greater than 18 years and less than 52 years, as well as confirmed viability at the...
time of ultrasound. Patients with apparent risk factors for fetal growth abnormalities were excluded from analysis, including those with diabetes, hypertension, multifetal gestations, and congenital anomalies. Tobacco users were excluded from the control group. Patients with multiple ultrasounds performed at the testing center were not recaptured if they were included in the cohort or control group at an earlier gestational age. IRB approval was obtained prior to study onset.

Maternal demographic information, indication for ultrasound, and presence of concomitant tobacco use were collected for both groups of patients. The first trimester was defined as 0–13 weeks 6-day gestation, the second trimester as 14 weeks 0 days to 27 weeks 6 days gestation, and the third trimester as 28 weeks 0 days to 42-week gestation. Intrauterine growth restriction (IUGR), was defined as an estimated fetal weight (EFW) less than the 10th percentile.

We collected sonographic parameters for both groups, including first trimester nuchal translucency (NT), first trimester crown rump length (CRL), second trimester head circumference (HC), second trimester abdominal circumference (AC), second trimester EFW, and second trimester umbilical artery systolic to diastolic (S/D) ratios. Third trimester fetal biometry and umbilical artery S/D ratios were also obtained. Hadlock growth curves were utilized for ultrasound measurements. We compared measurements in the marijuana without tobacco group, and marijuana with tobacco group to those of gestational age matched controls.

We captured IUGR fetuses as well as gestations with absent and reversed end diastolic flow in the umbilical artery. A sub analysis was then performed comparing umbilical artery S/D ratios in marijuana users without tobacco use to S/D ratios in the umbilical artery of marijuana users with concomitant tobacco use in the second and third trimester. Statistical analyses were performed using SPSS software, and a p < .05 was considered statistically significant.

Results

Demographics and indications for ultrasound

We had 442 pregnant women with singleton, non-syndromic fetuses and selfreported daily marijuana exposure in our cohort. There were 55 first trimester daily marijuana users, 195-s trimester daily marijuana users, and 192 third trimester daily marijuana users analyzed. The control group consisted of an equal number of patients of the same gestational age. The average age of marijuana users was 28.5 and the average age of the control group was 26.0. Average gravidity and parity of the marijuana users was 4.29 and 2.38, whereas average gravidity and parity of the control group was 3.67 and 2.89. The marijuana users consisted of 61.9% Hispanics, 20.1% Caucasians, 15.1% African Americans, and 2.7% Asians. The control group consisted of 56.1% Hispanics, 27.3% Caucasians, 11.9% African Americans, and 4.5% Asians.

Indications for ultrasound were varied and were similar in the marijuana users and the control group. These indications included, in addition to marijuana and/or tobacco use, first trimester aneuploidy screening, dating ultrasound, family history of birth defects, cystic fibrosis carrier, routine level two anatomy ultrasound, placenta previa, low lying placenta, third trimester bleeding, previous preterm birth, preterm contractions, adnexal cysts in pregnancy, history of prior uterine surgery, decreased fetal movement, and fetal arrhythmia.

Nuchal translucency, and biometry

The mean nuchal translucency, as measured in mm, in first trimester daily marijuana users was 1.78 ± 0.46 in comparison to 1.81 ± 0.45 in the control group (p = .35). In the subset of first trimester patients that used marijuana without concomitant tobacco (n = 40), the mean nuchal translucency was 1.77 ± 0.49 in comparison to 1.84 ± 0.42 in the control group (p = .23). When analyzing patients who used marijuana and tobacco (n = 15), the mean nuchal translucency was 1.81 ± 0.44 in comparison to 1.73 ± 0.51 in the control group (p = .33).

The mean crown rump length, as measured by percentile, in first trimester daily marijuana users was 50.46 ± 24.24 in comparison to 50.34 ± 24.3 in the control group (p = .49). First trimester fetuses exposed to marijuana without concomitant tobacco (n = 40), had a mean crown rump length of 47.60 ± 24.58 in comparison to 48.15 ± 22.39 in the control group (p = .46). When analyzing patients who used marijuana and tobacco (n = 15), the mean crown rump length was 58.09 ± 22.28 in comparison to 56.18 ± 24.58 in the control group (p = .42).

The average estimated fetal weight in all second trimester daily marijuana users, as measured by percentile, was 50.58 ± 23.54, in comparison to an average of 50.52 ± 23.2 in the control group (p = .49). There were a total of 145 patients who utilized marijuana without tobacco, and the average estimated fetal weight in this group of patients was 51.73 ± 23.85 compared to
Table 1. Estimated fetal weight (%ile) in all marijuana users, marijuana without tobacco users, and marijuana with tobacco users compared to matched controls.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Users</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MJ</td>
<td>36.04 ± 22.48</td>
<td>51.07 ± 25.42</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>MJ only</td>
<td>35.61 ± 21.93</td>
<td>52.52 ± 24.41</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>MJ + tobacco</td>
<td>37.52 ± 24.48</td>
<td>46.02 ± 28.39</td>
<td>.070</td>
</tr>
</tbody>
</table>

Fetuses exposed to marijuana in the third trimester (n = 192) had a smaller head circumference, measured in percentile, than controls of the same gestational age (37.15 ± 21.89 versus 51.49 ± 26.36, p < .0001). Additionally, fetuses exposed to daily marijuana in the third trimester had smaller abdominal circumferences, also measured in percentile, than controls of the same gestational age (36.78 ± 24.82 versus 50.43 ± 26.34, p < .0001). Both the third trimester head circumference and abdominal circumference remained statistically significantly smaller than the control group when tobacco users were excluded from the analysis. Estimated fetal weights in the third trimester, as predicted by ultrasonography and measured in terms of percentile, were smaller in marijuana users when compared to estimated fetal weights in the control group (36.04 ± 22.48 versus 51.07 ± 25.42, p < .0001). A further breakdown of this comparison is depicted in Table 1. Additionally, third trimester marijuana users had a higher incidence of intrauterine growth restriction (estimated fetal weight less than 10th percentile) than controls (26/192 versus 6/192, p = .002).

Umbilical artery Doppler measurements

When analyzing placental vascular resistance as measured by systolic to diastolic ratio (S/D) in the umbilical artery, there was a higher S/D ratio in the 195-s trimester marijuana users compared to gestational aged matched controls (4.02 ± 0.115 versus 3.92 ± 0.086, p = .024). Further analysis of the subset of patients that used marijuana without concomitant tobacco demonstrated a persistently higher umbilical artery S/D ratio in comparison to controls (3.99 ± 0.137 versus 3.90 ± 0.103, p = .043). There was a trend towards higher umbilical artery S/D ratio in the group of second trimester patients that used marijuana and tobacco when compared to controls (4.09 ± 0.044 versus 3.98 ± 0.034, p = .18), although this did not approach statistical significance likely owing to a smaller sample size. When examining third trimester placental resistance, there were higher umbilical artery S/D ratios in all marijuana users versus controls (3.52 ± 0.09 versus 3.12 ± 0.160, p = .0001), and in marijuana users without concomitant tobacco use versus controls (3.51 ± 0.102 versus 3.1 ± 0.179, p = .0004). Similarly, there was a nonstatistically significant trend towards a higher umbilical artery S/D ratio in users of both marijuana and tobacco when compared to controls (3.57 ± 0.053 versus 3.18 ± 0.087, p = .067). There were three cases of absent end diastolic flow and one case of reversal of end diastolic flow in the umbilical artery in marijuana users, and no cases in the control group. A sub analysis, which is further depicted in Table 2, demonstrated a higher umbilical artery S/D ratio in both the second and third trimester of fetuses exposed to marijuana and tobacco compared to the S/D ratios of fetuses exposed to marijuana alone.

Table 2. Mean umbilical artery S/D ratios in the second and third trimester of marijuana only users versus marijuana and tobacco users.

<table>
<thead>
<tr>
<th>Groups</th>
<th>MJ Only users</th>
<th>MJ + Tobacco users</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd trimester</td>
<td>3.99 ± 0.137</td>
<td>4.09 ± 0.044</td>
<td>.000007</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>3.51 ± 0.102</td>
<td>3.57 ± 0.053</td>
<td>.011</td>
</tr>
</tbody>
</table>

Discussion

We report on selfidentified daily marijuana using pregnant patients over all three trimesters. While no significant findings were obtained in the first trimester and second trimester, our study demonstrated that fetuses exposed to marijuana had statistically significant smaller third trimester head circumferences, abdominal circumferences, and estimated fetal weights than controls of the same gestational age, as well as a higher incidence of third trimester intrauterine growth restriction. Umbilical artery Doppler studies were also more likely to be abnormal in the marijuana group. These findings were still statistically significant when concomitant tobacco use was excluded from the analysis suggesting an independent impact of marijuana on fetal growth.

Chabarría et al. performed a retrospective analysis examining multiple antenatal variables and pregnancy outcomes in 146 pregnant marijuana users. Although the authors found that marijuana alone was not
associated with impaired fetal growth, when used with tobacco, fetuses had smaller head circumferences as well as a smaller birth weight in comparison to controls [6]. Findings in our analysis examining 442 marijuana users echoed these results in the third trimester in women using tobacco and marijuana. The difference in our findings about impaired fetal growth is likely explained by our study’s larger sample size with a greater power to detect such a difference. Hatch et al. retrospectively examined 367 fetuses exposed to marijuana using mothers at Yale New Haven Hospital, and stratified the pregnancies by occasional marijuana exposure (<two times per month) and frequent (>two times per month) marijuana exposure. Findings were remarkable for a higher incidence of low birth weight infants in fetuses exposed to frequent marijuana exposure, and no difference in the incidence of low birth weight infants in those pregnancies affected by occasional marijuana exposure [7]. Our study, which studied daily marijuana users, is consistent with these findings.

The exact mechanism by which tobacco smoke impairs fetal growth has yet to be fully elucidated, but numerous studies have identified multiple substances present in the smoke with a known association with IUGR, including polycyclic aromatic hydrocarbons (PAHs), lead, and cadmium. These substances are present in other types of air pollutants as well [8]. Interestingly, marijuana has been found to contain PAHs, with some studies showing a higher concentration of these substances in secondhand marijuana smoke when compared to tobacco smoke [9]. The presence of these toxic substrates may explain the fetal growth abnormalities seen in fetuses exposed to marijuana and tobacco. It is likely that the exposure to the smoke, and not necessarily to the nicotine or tetrahydrocannabinol (THC), is what results in IUGR.

Our finding that marijuana exposure is associated with increased umbilical artery S/D ratios suggests that placental vascular resistance is increased in these patients. Increased placental vascular resistance may disrupt the necessary flow of oxygen rich blood through the placenta and ultimately result in IUGR [10]. This may be an important part of the pathophysiology that explains the association between daily marijuana use and IUGR seen in our study. In extreme cases, absence or reversal of umbilical artery end diastolic flow is seen in IUGR fetuses, suggesting a more immediate risk to the fetus than seen with IUGR alone. Although not statistically significant, marijuana users in our study had these worrisome findings. While prior studies demonstrate that tobacco use increases placental vascular resistance, we could not find studies that looked at the impact of marijuana on S/D ratios in the umbilical artery [11]. Chatterjee examined the effect of polysubstance abuse on umbilical artery Doppler blood flow and described the mean S/D ratio as being mildly elevated, ranging from 2.36 to 4.30 [12]. However, only 14 mothers were assessed, and marijuana use was not isolated with sufficient power to draw conclusions on its effect on placental vascular resistance.

There were many strengths present in our study. We had a large sample size that included 442 daily marijuana using pregnant patients, and we isolated the effect of marijuana in each trimester. There is a paucity of prior studies examining the effect of marijuana use on placental vascular resistance, which we found to be affected by marijuana use in a worrisome way. Most importantly, data stratification in our analysis assisted in controlling for tobacco use, a significant confounder present in many prior studies on marijuana in pregnancy.

Our study results and interpretation are limited by the pitfalls inherent with a retrospective study design. For example, we relied on patients to self-report their marijuana use and do not have an objective assessment of the frequency or amount of use. Additionally, there is a possibility of poly drug use confounding our results. Our control group included low risk patients, but these patients were not completely risk free as all patients analyzed were from an antenatal testing center. These limitations, however, would likely minimize any association between marijuana and adverse outcomes. That is to say, if marijuana use was under reported, poly substance abuse was present, or if there were absolutely no risk patients in the control group, the findings would be more pronounced.

In conclusion, our study adds to the literature that daily marijuana use is associated with unfavorable fetal outcomes, including an increase in third trimester growth restriction and increased second and third trimester placental vascular resistance. Our findings support marijuana use in pregnancy should be discouraged due to its association with harmful effects on the pregnancy. Patients should be screened throughout pregnancy for marijuana use and counseled appropriately on its potential effects as well as on strategies for cessation. Continuing study on marijuana use during pregnancy is needed to delineate its exact potential for fetotoxicity.

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Disclosure statement

No potential conflict of interest was reported by the authors. At this time.

References