AN OBSERVATIONAL STUDY OF TREATMENT OUTCOMES OF UTERINE MYOMA AMONG CLIENTS WHO HAD UNDERGONE INVITRO FERTILIZATION AT A PUBLIC CENTER IN ADDIS ABABA, ETHIOPIA

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ABSTRACT

BACKGROUND: For clients undergoing invitro-fertilization (IVF), there is no consensus regarding the management of non-cavity-distorting intramural myoma.

BACKGROUND: To assess the prevalence and treatment outcomes of IVF clients with uterine myoma.

METHODS: A 2-year (April 1, 2019–April 1, 2021) chart review was conducted for 1300 infertile women who had undergone IVF. Categorical data were summarized in proportion, and continuous data were summarized using the mean, median, and standard deviation where appropriate. Bivariate logistic regression was conducted to assess the association between predictor variables and the outcome variable (clinical pregnancy). P-values of 0.05 were considered significant.

RESULTS: Of the total 1,300 IVF clients, 282 (21.7%) cases were diagnosed as having myoma. Among the 13 cases of cavity-distorting intramural myomas who underwent IVF without myomectomy, all were negative for clinical pregnancy, whereas among the 60 cases of cavity-distorting myomas who had pre-IVF myomectomy followed by IVF, 16 (26.7%) were positive for clinical pregnancy. This difference was not statistically significant (P = 0.160).

38 (27.5%) of 138 cases of non-cavity-distorting intramural myoma who underwent IVF without pre-IVF myomectomy had clinical pregnancy. In contrast, among the 19 cases who had undergone pre-IVF myomectomy followed by IVF, only 2 (10.5%) had a clinical pregnancy. This difference was not statistically significant (P = 0.160).

CONCLUSION: While not statistically significant, conducting a pre-IVF myomectomy for cavity-distorting myomas improves the clinical pregnancy, whereas a pre-IVF myomectomy does not improve the clinical pregnancy for women with non-cavity-distorting myomas. We recommend further research with a larger sample size.

KEYWORDS: Myoma; infertility; invitro fertilization; myomectomy; treatment outcomes

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INTRODUCTION

Invitrofertilization (IVF) is a multifaceted series of procedures used to help with fertility and assist with the conception of a child. IVF begins with ovarian stimulation with exogenous gonadotropins, followed by the picking of oocytes from the ovaries under transvaginal ultrasound guidance, fertilization, embryo culture, and finally the transfer of embryos into the uterus. Myoma-related infertility has been linked to various factors, including cervix displacement, which reduces sperm exposure; uterine cavity enlargement or deformity, which interferes with sperm transport; obstruction of the interstitial segment of the fallopian tubes; distorted adnexal anatomy, which interferes with ovum capture; distortion of the uterine cavity; increased or abnormal myometrial contractions, which inhibit sperm or embryo transport and impair uterine blood flow; and chronic endometritis, or decreased endometrial receptivity, interfering with implantation. Uterine myomas are benign smooth muscle neoplasms arising from a single smooth muscle cell of the myometrium.

Myomas are the most prevalent tumors, affecting 30% of reproductive age women, and at least half of those who have them have no symptoms. Myomas are seen in five to ten percent of infertile women. Additionally, myomas are the only abnormal finding in one to two percent of women with infertility.

There is clear unanimity that submucous myomas have a substantial adverse effect on clinical pregnancy rates. Existing data also support the conclusion that submucous myomas increase the risk for miscarriage by more than threefold. However, the impact of non-cavity distorting myoma on the possibility of abortion is unclear. Studies regarding the effect of intramural myomas on IVF success were found to be conflicting, with some reporting less favorable outcomes and others not. The accrued body of evidence shows that submucous myomas reduce IVF success rates by 70%, intramural myomas by 20-40%, and subserosal myomas have no adverse effect on outcomes. It is clear that submucous myomas have important adverse effects on pregnancy and pregnancy outcomes and that myomectomy improves both.

Evidence for the benefits of myomectomy in women with non-cavity distorting intramural myomas is less compelling, probably because their effect on fertility is not as great. Decisions regarding the management of infertile women with asymptomatic intramural myomas are among the most challenging clinical judgments. There is no agreement regarding the management of intramural myoma that is not distorting the endometrial cavity. As the results of the existing studies regarding the management of intramural myomas for IVF clients are inconsistent, there is no clear guideline. Therefore, this study aims to assess the management of myomas in general and intramural myomas in particular and their pregnancy outcomes among IVF clients at our clinical site in Addis Ababa, Ethiopia.

METHODS

This study was conducted at the Center for Reproductive Medicine (CFRM) clinic. The CFRM was established on April 1, 2019, and is a branch of Saint Paul’s Hospital Millennium Medical College (SPHMMC). This clinic provides all reproductive health, endocrinology, and IVF services in a dedicated building. There are four outpatient clinics: two of them are for reproductive health services, and the other two are for the evaluation of infertile couples and endocrinology clients. On average, 100 infertile clients visit the CFRM clinic on working days, and the clinic is open from 2:30–6:30 am and 1:30–5:30 pm, seven days per week. The service is run by Reproductive Health and Endocrinology (REI) fellows and specialists.

Ethical approval was obtained before the start of the data collection from the Institutional Review Board of St. Paul’s Hospital Millennium Medical
College. The ethical approval ID is PM23/280. A chart review of those infertile women who had undergone IVF in the past 2 years (April 1, 2019–April 1, 2021) was done. All charts of women diagnosed with myoma were taken for further data abstraction using the Open Data Kit (ODK). The charts of all women diagnosed with myoma were complete with the information that we required. The data collection tool in the Open Data Kit (ODK) was tested on 5% of the study population and the validity checked before the start of data collection. The data was entered into ODK, cleaned, and then exported to Stata 14 for analysis. Summarization using frequency distribution was done for the clients’ socio-demographic characteristics. The mean and median were calculated for the clients’ ages. A Chi-square test was used to test associations between categorical variables and outcome variables. The intention was to do bivariate analysis followed by multivariate analysis for those factors that have significant association with outcome variable, but we found no significant association between the predictor variables and outcome variable so only a bivariate logistic regression model was fitted to identify predictors of the outcome variable. A p-value of less than 0.05 is considered statistically significant, with a 95% confidence interval. The outcome variable is a clinical pregnancy (ultrasound-confirmed pregnancy), which is dichotomized as “yes” or “no.” The predictor variables are the type of myoma treatment (myomectomy versus no myomectomy), the location of the myoma (intramural cavity distorting, intramural non-cavity distorting, and submucous), the age of the woman, dichotomized as “<=35” and “>35,” and the type of protocol for IVF. Intramural myomas are myomas that are located in the uterine muscle, and they are classified as cavity-distorting and non-cavity-distorting. Submucous myomas are myomas that are located in the uterine cavity. There are two main types of protocols based on the type of gonadotropin-releasing hormone (GnRH) analogue used: agonist and antagonist protocols. During the long protocol, GnRH agonists are given during the luteal phase of the menstrual cycle, and ovarian stimulation using gonadotropins is started on days 2 or 3 of the menses. For the antagonist protocol, ovarian stimulation is started using gonadotropins on days 2 or 3 of menses, and the GnRH antagonist will be started when the dominant ovarian follicle reaches a size of 14 mm. Mild stimulation is a modification of the antagonist protocol where the ovarian stimulation is started on the 2nd day of menses using an oral aromatase inhibitor (Letrozole) and stimulation with gonadotropins is initiated on the 4th day. The woman will be started on antagonist medication when the dominant follicle reaches a size of 14 mm. Long protocols are used for young women with good ovarian reserve, whereas antagonist and mild stimulation protocols are used for women with poor ovarian reserve, previous poor responses to long protocol stimulation, and women over the age of 35. RESULTS Among the total of 1,300 women who underwent IVF during the study period, 282 (21.69%) were diagnosed with myoma. Socio-demographic characteristics and profiles of women who have undergone IVF treatment are shown in Table 1. The mean age of the women was 34.1 years, with a standard deviation of 4.2 years. The majority (62.8%)—177 (62.8%)—of the 282 cases of myoma are 35 years old or younger. Most women, 254 (90.1%), were nulliparous, and the majority, 246 (87.2%), had no history of abortion. As shown in Table 1, the majority, 230 (81.6%), were diagnosed with intramural myoma. The majority of the 230 intramural myoma cases—157 (68.3%)—were non-cavity distorting. Among the 85 cases who had undergone pre-IVF myomectomy, most—57 (67.1%)—were done for cavity-distorting myomas. The majority, 74 (87.1%) of women had undergone laparotomy for myomectomy. For most women, a 69.9% mild stimulation protocol was used.
Table 1 Sociodemographic characteristic and profiles of women who have undergone In vitro-fertilization treatment at Saint Paul’s Hospital Millennium Medical College, Addis Ababa, Ethiopia (n= 282 unless otherwise specified)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=35</td>
<td>177</td>
<td>62.8</td>
</tr>
<tr>
<td>&gt;35</td>
<td>105</td>
<td>37.2</td>
</tr>
<tr>
<td>Number of children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>254</td>
<td>90.1</td>
</tr>
<tr>
<td>Primiparous</td>
<td>28</td>
<td>9.9</td>
</tr>
<tr>
<td>Number of abortions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>246</td>
<td>87.2</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
<td>6.4</td>
</tr>
<tr>
<td>≥2</td>
<td>18</td>
<td>6.4</td>
</tr>
<tr>
<td>Submucous Myoma</td>
<td>14</td>
<td>5.0</td>
</tr>
<tr>
<td>Intramural Myoma</td>
<td>230</td>
<td>81.6%</td>
</tr>
</tbody>
</table>

Intramural Myoma (n=230)
- Not cavity distorting: 157 (68.3%)
- Cavity distorting: 73 (31.7%)
- Subserous: 38 (13.5%)

Pre-IVF Myomectomy
- No: 197 (69.9%)
- Yes: 85 (30.1%)

Location of myoma<sup>a</sup> (n=85)
- Submucous: 10 (11.8%)
- Intramural cavity distorting: 57 (67.1%)
- Intramural not cavity distorting: 16 (18.8%)
- Subserous: 2 (2.4%)

Type of Myomectomy (n=85)
- Laparotomy: 74 (87.1%)
- Laparoscopic: 6 (7.1%)
- Hysteroscopic: 5 (5.9%)

Type of IVF protocol
- Long: 73 (25.9%)
- Ministim/Mildstimulation: 197 (69.9%)
- Antagonist: 11 (3.9%)
- Other: 1 (0.4%)

<sup>a</sup> for which the woman had undergone Pre-IVF myomectomy

As shown in Figure 1, the majority, 142 (50.32%) of women, were diagnosed to have tubal factor infertility; 45 (14.18%) were diagnosed to have both tubal factors and decreased ovarian reserve (DOR); 41 (14.54%) were diagnosed to have male factor; 22 (7.8%) were diagnosed to have tubal factor and male factor; and 15 (5.32%) of them were diagnosed to have unexplained infertility. Among the 230 women diagnosed with intramural myoma, 56 (24.3%) were pregnant, and among these 56 pregnant women, the majority, 38 (67.9%), did not undergo pre-IVF myomectomy compared to 18 (32.1%) who had undergone pre-IVF myomectomy. Among the 13 cases of cavity-distorting intramural myoma who have undergone in vitro fertilization without myomectomy, all 13 cases were negative for clinical pregnancy. Whereas, among 60 cases of cavity-distorting myomas who have undergone pre-in vitro fertilization myomectomy followed by in vitro fertilization, 16 (26.7%) were positive for clinical pregnancy. Among a total of 14 cases of submucous myoma, 12 (85.71%) cases had undergone pre-IVF myomectomy and 2 (15.38%) had not. The 2 cases of submucous myoma who tried IVF without Myomectomy both were negative for clinical pregnancy whereas among the 12 cases who had undergone Pre-IVF myomectomy, 3 (25%) had a clinical pregnancy. There were 38 (27.5%) clinical pregnancies among 138 cases of non-cavity-distorting intramural myomas that had undergone in vitro fertilization without pre-invitro fertilization myomectomy. Among the 19 cases who had undergone pre-IVF myomectomy followed by IVF, only 2 (10.5%) of them had a clinical pregnancy.

As shown in Table 2, women over the age of 35 have an 80% lower likelihood of clinical pregnancy than women under the age of 35 (COR 0.2; 95% C.I. 0.10-0.42; P = 0.000). Women who received a mild stimulation protocol had a 78% lower chance of achieving pregnancy than women who received a long stimulation protocol (COR 0.22; 95% C.I. 0.12-0.39; P = 0.000).
As shown in Table 2, women who had undergone pre-IVF myomectomy for cavity-distorting intramural myoma had no statistically significant association with clinical pregnancy compared to women with cavity-distorting myoma without pre-IVF myomectomy (COR 3.10; 95% C.I. 0.64-14.9; P = 0.160). Additionally, women who had undergone pre-IVF myomectomy for non-cavity-distorting myoma had no statistically significant association with clinical pregnancy compared to women who had not undergone pre-IVF myomectomy for non-cavity-distorting myoma (COR 0.32; 95% C.I. 0.10-1.56; P = 0.160).

Table 2. Bivariate logistic regression analysis of predictors of clinical pregnancy among clients who have undergone Invitro-fertilization treatment at Saint Paul’s Hospital Millennium Medical College, Addis Ababa, Ethiopia (n= 282)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude Odds Ratio (95% C.I)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;35</td>
<td>0.20 (0.10 - 0.42)</td>
<td>0.000**</td>
</tr>
<tr>
<td>Mild stimulation protocol</td>
<td>0.22 (0.12 - 0.39)</td>
<td>0.000**</td>
</tr>
<tr>
<td>Pre-IVF myomectomy a</td>
<td>0.32 (0.10 -1.56)</td>
<td>0.160</td>
</tr>
<tr>
<td>Pre-IVF myomectomy b</td>
<td>3.10 (0.64 - 14.9)</td>
<td>0.160</td>
</tr>
<tr>
<td>Cavity distorting c</td>
<td>0.82 (0.42 - 1.60)</td>
<td>0.559</td>
</tr>
<tr>
<td>Non-cavity distorting c</td>
<td>1.22(0.63 - 2.36)</td>
<td>0.559</td>
</tr>
</tbody>
</table>

Table 2. Bivariate logistic regression analysis of predictors of clinical pregnancy among clients who have undergone Invitro-fertilization treatment at Saint Paul’s Hospital Millennium Medical College, Addis Ababa, Ethiopia (n= 282)

DISCUSSIONS

In this study, 22% of women were diagnosed with myoma. In the two cases of submucous myoma who tried IVF without myomectomy, both of them were negative for pregnancy, whereas among the 12 cases that had undergone pre-IVF myomectomy for submucous myoma, 3 (25%) had a clinical pregnancy. Among the 13 cases of cavity-distorting intramural myomas who underwent invitro fertilization without myomectomy, all 13 cases were negative for clinical pregnancy. This compares to the 60 cases of cavity-distorting myomas who had pre-IVF myomectomy followed by IVF, where 16 (26.7%) of them were pregnant.

In this study, almost 22% of women were diagnosed with myoma. This is in contrast to other studies which showed myomas in 5–10% of infertile women 4, 5. Further, while only 7 of our participants (0.5%) had myomas as their only abnormal finding, in other studies, this rate is 1-2% 6.

Previous research has consistently shown that submucous myomas have a profound adverse effect on the clinical pregnancy rate6–12. Similarly, in this study, there are 2 cases of submucous myoma who tried IVF without myomectomy; both were negative for pregnancy, whereas, among the 12 cases who had undergone pre-IVF myomectomy for submucous myoma, 3 (25%) had a clinical pregnancy.

Evidence for the benefits of myomectomy in women with intramural myomas (not distorting the uterine cavity) is less compelling, probably because their impact on fertility is not as great1. Similarly, 38 (27.5%) of 138 cases of non-cavity-distorting intramural myomas who underwent in vitro fertilization without pre-in vitro fertilization myomectomy had clinical pregnancy in this study. In comparison, only two (10.5%) of the 19 who had pre-IVF myomectomy followed by IVF had clinical pregnancy. Therefore, there is no benefit in doing a myomectomy for a non-cavity-distorting myoma.

Decisions regarding the management of infertile women with asymptomatic intramural myomas are among the most difficult clinical judgments. There is no consensus regarding the management of intramural myoma that is not distorting the endometrium1. In this study, while doing a pre-IVF myomectomy does not have a statistically significant impact on clinical pregnancy, all 13 cases of cavity-distorting intramural myomas that underwent in vitro fertilization without myomectomy were
negative for clinical pregnancy. This compares to the 60 cases of cavity-distorting myomas that underwent pre-IVF myomectomy followed by IVF, where 16 (26.7%) of them were pregnant. So according to the findings of this study, there is a clear benefit to doing a myomectomy for intramural myomas that distort the uterine cavity.

CONCLUSION
While not statistically significant, conducting a pre-IVF myomectomy for cavity-distorting myomas improves the clinical pregnancy, whereas a pre-IVF myomectomy does not improve the clinical pregnancy for women with non-cavity-distorting myomas. We recommend further research with a larger sample size.

DECLARATIONS
Strengths of this study
• The findings of this study can be generalized to other settings since the patient populations (patients with myoma requiring IVF treatment) are the same worldwide.
• Compared to previous researches, this research has a larger sample size, since most of the existing researches have smaller sample size

Limitation of this study
• The nature of our research being a retrospective can be one limitation but it is unethical to do prospective observational or randomized controlled trial
• While we have collected data over two years, the number of cases with myoma is still small to result in statistical significance

Author contribution
AT contributed to the study planning, design, data collection and analysis, and writing of the manuscript. MN contributed to the study planning, data analysis, and editing of the manuscript. FS contributed to the study planning and editing of the manuscript.

Conflict of Interest
The authors have no conflict of interest

Acknowledgment
We would like to thank Sarah D. Compton for reviewing this manuscript and its language edition.

Funding
The study was funded by the St. Paul’s Institute for Reproductive Health and Rights (SPIRHR), Addis Ababa, Ethiopia.

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