

UNIVERSIDADE FEDERAL DE MINAS GERAIS
PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE DA MULHER

Prevalência de alterações histeroscópicas em mulheres submetidas à fertilização *in vitro*: estudo retrospectivo

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BELO HORIZONTE

DEZEMBRO DE 2018

Prevalência de alterações histeroscópicas em mulheres submetidas à fertilização *in vitro*: estudo retrospectivo

Dissertação apresentada ao Programa de Pós-Graduação em Saúde da Mulher da Faculdade de Medicina da
Universidade Federal de Minas Gerais
Área de Concentração: Patologia Ginecológica e Reprodução
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Monteiro, Cecília de Souza.

M775p Prevalência de alterações histeroscópicas em mulheres submetidas à fertilização in vitro [manuscrito]: estudo retrospectivo. / Cecília de Souza Monteiro. - - Belo Horizonte: 2018.

39f.: il.

Orientador (a): Fernando Marcos dos Reis. Coorientador (a): Francisco de Assis Nunes Pereira.

Área de concentração: Patologia Ginecológica e Reprodução. Dissertação (mestrado): Universidade Federal de Minas Gerais, Faculdade de Medicina.

1. Histeroscopia. 2. Fertilização In Vitro. 3. Ultrassom. 4. Dissertações Acadêmicas. I. Reis, Fernando Marcos dos. II. Pereira, Francisco de Assis Nunes. III. Universidade Federal de Minas Gerais, Faculdade de Medicina. IV. Título.

NLM: WQ 205

Agradecimentos

Em primeiro lugar, gostaria de agradecer ao meu orientador, Professor Fernando Marcos dos Reis, pela paciência, empenho e sentido prático com que sempre me orientou neste trabalho e em todos aqueles que realizei durante o percurso do mestrado.

Desejo igualmente agradecer ao meu co-orientador Francisco de Assis Nunes Pereira pela disponibilidade e atenção sempre em todos os momentos.

Desejo também agradecer aos colegas médicos, técnicos, secretárias do Laboratório de Reprodução Humana Aroldo Camargos pelas orientações e assistência sempre que necessário.

Por último, quero agradecer à minha família pelo apoio e carinho durante essa trajetória.

Resumo

Segundo a literatura, ensaios clínicos recentes não demonstraram benefício em realizar histeroscopia como exame de rotina antes do tratamento de fertilização *in vitro* (FIV) em mulheres com exame uterino normal à ultrassonografia. Entretanto, esses estudos encontraram anormalidades histeroscópicas em menos de 13% dos participantes e, portanto, seus achados podem não se aplicar a populações com maior prevalência de distúrbios intrauterinos. Realizamos um estudo transversal retrospectivo incluindo 1141 mulheres submetidas à histeroscopia ambulatorial antes da fertilização *in vitro* no Hospital das Clínicas da Universidade Federal de Minas Gerais, entre janeiro de 2012 e Dezembro de 2017. Destas, 961 participantes tiveram a ultrassonografia transvaginal (USTV) sem alterações da cavidade uterina. Alterações histeroscópicas estavam presentes em 265 das 961 pacientes com USTV negativo (prevalência de 27,6%, intervalo de confiança de 95% [IC] 24,8%–30,5%). Além disso, a prevalência de histeroscopias com leiomioma submucoso não detectado pelo ultrassom aumentou significativamente com a idade ($p = 0,005$, teste do qui-quadrado para tendência linear) e atingiu 7,2% (IC95% 3,5%–14,1%) após os 40 anos. Também observamos que a sensibilidade do USTV variou de 8% (IC95% 2%–20%) para sinéquias uterinas a 41% (IC95% 28%–56%) para o leiomioma submucoso, resultando em baixas razões de verossimilhança para resultados negativos do USTV. Esses achados sugerem uma alta prevalência de alterações insuspeitas encontradas pela histeroscopia de rotina antes da FIV, um aumento dependente da idade na frequência de leiomioma submucoso e uma baixa sensibilidade diagnóstica do USTV em detectar lesões intrauterinas.

Abstract

Recent clinical trials showed no benefit of performing routine hysteroscopy before in vitro fertilization (IVF) in women with normal intrauterine imaging. However, these trials found hysteroscopic abnormalities in less than 13% of the participants and, therefore, their findings might not be applicable to populations with higher prevalence of intrauterine disorders. We carried out a retrospective cross-sectional study of 1141 consecutive women who underwent outpatient hysteroscopy before IVF at a tertiary academic center. Of these, 961 participants had a normal transvaginal sonography (TVS) of the uterine cavity. Hysteroscopic alterations were present in 265/961 of patients with a negative TVS (prevalence 27.6%, 95% confidence interval [CI] 24.8%-30.5%). The prevalence of unsuspected submucous leiomyoma increased significantly with age ($p=0.005$, chi-square test for linear trend) and reached 7.2% (95% CI 3.5%-14.1%) after 40 years. The sensitivity of TVS ranged from 8% (95% CI 2%-20%) for uterine synechiae to 41% (95% CI 28%-56%) for submucous leiomyoma, resulting in low likelihood ratios for negative TVS results. These findings suggest a high prevalence of unsuspected alterations found by routine hysteroscopy before IVF, an age dependent increase in the frequency of submucous leiomyoma and a low diagnostic sensitivity of TVS to detect intracavitary lesions.

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Introdução

Estima-se que haja 72 milhões de casais inférteis em todo o mundo e que 40 milhões de pessoas estejam atualmente em busca de tratamento para infertilidade (Boivin *et al.*, 2007). A definição mais aceita de infertilidade é a da Comissão Internacional de Acompanhamento das Tecnologias de Reprodução Assistida (ICMART) e da Organização Mundial da Saúde (OMS), que descreve a infertilidade como "incapacidade de conseguir uma gravidez clínica após 12 meses ou mais de relação sexual desprotegida regular".

A avaliação do casal infértil se baseia na investigação das etapas participantes do ciclo reprodutivo, desde a produção de gametas até a fecundação e desenvolvimento embrionário no ambiente uterino. Qualidade do embrião, boas condições do ambiente uterino e uso de técnicas laboratoriais adequadas são essenciais para alcançar uma gravidez na fertilização *in vitro* (FIV).

Dentre as etapas acima citadas, inclui-se a avaliação do fator uterino, etapa fundamental da propedêutica da infertilidade, tendo em vista a prevalência elevada de alterações uterinas em mulheres inférteis. Anormalidades na cavidade uterina têm um impacto negativo sobre as chances de fertilidade espontânea, bem como no sucesso de gestação por fertilização *in vitro* (FIV) (Di Spiezio Sardo *et al.*, 2016).

Embora o fator uterino represente apenas 2% a 3% das principais causas de infertilidade, a patologia intrauterina pode estar presente em cerca de um terço das mulheres inférteis submetidas a histeroscopia de rotina antes da fertilização *in vitro* (FIV) (Bakas *et al.*, 2014, Hinckley and Milki, 2004).

Mesmo pequenas anormalidades da cavidade uterina, tais como os pólipos endometriais, pequenos leiomiomas submucosos, aderências e septos podem ter um impacto negativo sobre a possibilidade de engravidar através da FIV (Smit *et al.*, 2016). Por isso, tem sido sugerido que essas alterações devam ser diagnosticadas e tratadas, a fim de otimizar a condição do ambiente uterino e, assim, o resultado do tratamento de FIV (Carneiro, 2014, Elsetohy *et al.*, 2015).

A técnica mais completa para avaliação da cavidade uterina é a histeroscopia, pois permite a visualização direta das lesões e o tratamento das principais alterações encontradas, em comparação a outros exames de imagem, como a ultrassonografia endovaginal (Di Spiezio Sardo *et al.*, 2016).

Recentemente, a relevância da realização da histeroscopia no mês anterior à FIV em mulheres com anatomia uterina normal à ultrassonografia tem sido questionada, uma vez que dois ensaios clínicos randomizados não evidenciaram nenhum benefício em se realizar a histeroscopia de rotina para melhorar as taxas de nascidos vivos (Di Spiezio Sardo *et al.*, 2016, El-Toukhy *et al.*, 2016). No entanto, ambos os estudos encontraram anormalidades intracavitárias em menos de 13% dos pacientes investigados e, portanto, seus resultados podem não ser aplicáveis a outras populações com maior prevalência de alterações uterinas insuspeitas.

Já que a frequência de achados de anormalidades intra-uterinas em pacientes que se submeterão a FIV varia de acordo com as características da população e os critérios de diagnóstico (Bakas *et al.*, 2014, Fatemi *et al.*, 2010), ainda é importante analisar grandes séries de pacientes submetidas a procedimentos de diagnóstico homogêneos, a fim de esclarecer o impacto da histeroscopia de rotina em revelar alterações uterinas antes da FIV.

Justificativa do Estudo

O papel da histeroscopia como parte da propedêutica para fertilização *in vitro* em mulheres sem diagnóstico prévio de lesões intrauterinas ainda é objeto de debate entre os estudiosos.

Uma meta-análise de 2016 incluiu 16 grandes estudos e encontrou um efeito benéfico da histeroscopia ambulatorial no aumento da taxa de gravidez, com evidências de qualidade moderada, para as mulheres com uma ou mais falhas de implantação após FIV e também para mulheres submetidas a sua primeira FIV (Di Spiezio Sardo *et al.*, 2016). Uma possível explicação para as conclusões acima se baseia na hipótese de que a histeroscopia poderia revelar uma anormalidade intrauterina insuspeita em pacientes com um exame de ultrassonografia prévio normal, contribuindo para melhora das taxas de fertilização neste grupo de pacientes (Di Spiezio Sardo *et al.*, 2016).

Já o estudo randomizado controlado denominado “inSIGHT trial”, investigou os efeitos da histeroscopia na taxa de nascidos vivos, antes da primeira tentativa de fertilização *in vitro*, com seguimento de 18 meses, na Holanda. A conclusão foi que a histeroscopia de rastreamento não melhorou as taxas de nascidos vivos em mulheres com ultrassonografia transvaginal normal que estão programando o seu primeiro ciclo de fertilização *in vitro* (Smit *et al.*, 2016).

Com resultados semelhantes, o estudo multicêntrico randomizado controlado denominado “TROPHY trial”, realizado no Reino Unido, Bélgica, Itália e República Checa concluiu que a histeroscopia ambulatorial em mulheres com ultrassonografia normal e com história de ciclos de tratamento de FIV sem sucesso não melhora a taxa de nascidos vivos (El-Toukhy *et al.*, 2016).

Essa ampla variedade de achados torna difícil definir a frequência das anormalidades da cavidade uterina não visualizadas à ultrassonografia e diagnosticadas por histeroscopia de rotina em pacientes que se submeterão à FIV e que podem causar um impacto negativo nos desfechos do tratamento de reprodução assistida.

Portanto, mais estudos em pacientes candidatas a FIV e sem evidência prévia de lesão intrauterina são necessários a fim de melhor delinear o papel da histeroscopia nesse grupo de pacientes, o que justifica a escolha desse tema para a pesquisa.

Objetivos

O objetivo principal foi verificar a prevalência de anormalidades da cavidade uterina não visualizadas à ultrassonografia e diagnosticadas por histeroscopia ambulatorial de rotina em mulheres que seriam submetidas à FIV.

Dentre os objetivos secundários foi avaliada a correlação entre a prevalência das alterações histeroscópicas e a idade das pacientes investigadas.

Também foi definida a acurácia do exame de ultrassonografia transvaginal (USTV) em detectar as mais freqüentes alterações na cavidade uterina.

Artigo

1

2 **Uterine alterations in women undergoing routine hysteroscopy before in vitro fertilization:**
3 **high prevalence of unsuspected lesions**

4

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21 **Abstract**

22 **Objective:** The aim of this study was to verify the prevalence of uterine cavity abnormalities
23 diagnosed by routine office hysteroscopy in women preparing to IVF.

24 **Methods:** We carried out a retrospective cross-sectional study of 1141 consecutive women who
25 underwent outpatient hysteroscopy before IVF at a tertiary academic center. Of these, 961
26 participants had a normal transvaginal sonography (TVS) of the uterine cavity. The prevalence of
27 hysteroscopic alterations in successive age strata was submitted to Mantel-Haenzsel Chi-square
28 test for linear trend. The diagnostic accuracy of TVS using hysteroscopy as reference was
29 assessed by calculating the sensitivity, specificity, positive and negative likelihood ratios.

30 **Results:** Hysteroscopic alterations were present in 265/961 of patients with a negative TVS
31 (prevalence 27.6%, 95% confidence interval [CI] 24.8%-30.5%). The prevalence of unsuspected
32 submucous leiomyoma was higher among older women ($p=0.005$, chi-square test for linear trend)
33 and reached 7.2% (95% CI 3.5%-14.1%) after 40 years. The sensitivity of TVS ranged from 8%
34 (95% CI 2%-20%) for uterine synechiae to 41% (95% CI 28%-56%) for submucous leiomyoma,
35 resulting in low likelihood ratios for negative TVS results.

36 **Conclusions:** These findings suggest a high prevalence of unsuspected alterations found by
37 routine hysteroscopy before IVF, an age-dependent increase in the frequency of submucous
38 leiomyoma and a low diagnostic sensitivity of TVS to detect intracavitary lesions.

39

40 **Key words:** hysteroscopy, IVF, endometrial polyp, submucous leiomyoma, transvaginal
41 ultrasound, accuracy

42

43 Introduction

44 It is estimated that 72.4 million couples are infertile worldwide and that 40.5 million of them
45 are currently seeking treatment for infertility (Boivin *et al.*, 2007). Although uterine factors represent
46 only 2% to 3% of the primary causes of infertility, intracavitary pathology may be present in
47 approximately one third of infertile women submitted to routine hysteroscopy before *in vitro*
48 fertilization (IVF) (Bakas *et al.*, 2014; Boivin *et al.*, 2007; Carneiro, 2014). Even minor uterine cavity
49 abnormalities, such as endometrial polyps, small submucous leiomyomas, adhesions, and septa
50 are considered to have a negative impact on the chance to conceive through IVF (Smit *et al.*,
51 2016). Therefore, it has been suggested that these abnormalities should be diagnosed and treated
52 to optimize the condition of the uterine environment and thus, the outcome of IVF treatment
53 (Elsetohy *et al.*, 2015).

54 More recently, the usefulness of performing hysteroscopy in the month preceding IVF in
55 women with normal uterine imaging has been challenged by two randomized clinical trials that
56 showed no benefit of routine hysteroscopy to improve livebirth rates (El-Toukhy *et al.*, 2016; Smit
57 *et al.*, 2016). However, both trials found intracavitary abnormalities in less than 13% of the
58 screened patients and, therefore, their findings might not be applicable to other populations with
59 larger prevalence of unsuspected uterine alterations. Because the frequency of intrauterine
60 pathology in IVF candidates varies depending on the population characteristics and the diagnostic
61 criteria (Bakas *et al.*, 2014; Fatemi *et al.*, 2010), more data from different populations is needed to
62 clarify the impact of routine hysteroscopy in revealing uterine alterations before IVF.

63 The aim of this study was to verify the prevalence of unsuspected uterine cavity
64 abnormalities diagnosed by routine office hysteroscopy in women preparing to IVF. We also
65 assessed the age-related prevalence of lesions and the accuracy of transvaginal sonography
66 (TVS) to detect the most frequent hysteroscopic alterations. We believe that this study adds to the
67 current literature by evaluating a large sample of women undergoing both ultrasound and
68 hysteroscopy in a single setting using a standardized protocol, which allow us to estimate the
69 actual prevalence of unsuspected intrauterine lesions in a typical group of Brazilian women
70 preparing to IVF in a tertiary teaching hospital.

71 **Materials and methods**

72 We carried out a single center, retrospective cross-sectional study of 1141 consecutive
73 women who underwent outpatient hysteroscopy in preparation to an IVF cycle at a tertiary
74 academic center of Belo Horizonte, Brazil, between January 2012 and December 2017. Of these,
75 961 participants had a negative TVS, defined as absence of visible intracavitary abnormal
76 structures, thickening, malformation or distortion. For the purpose of this study, adnexal masses
77 and subserous/intramural fibroids not distorting the uterine cavity were not considered as positive
78 TVS findings. All TVS examinations were performed by a staff of 4 certified specialists during the
79 patient's proliferative phase of menstrual cycle. The time interval between TVS and hysteroscopy
80 ranged from 0 to 60 days.

81 The study was approved by the Research Ethics Committee of Universidade Federal de
82 Minas Gerais (protocol number CAAE59731016.90000.5149) and was exempted from informed
83 consent due to the retrospective design and anonymization of the participants.

84 The only inclusion criterion of the study was having undergone a complete hysteroscopy in
85 preparation to IVF (Figure 1). The total number of IVF cycles performed in our center during the
86 study period was 914, which is inferior to the number of hysteroscopies because some women did
87 not return after the hysteroscopy to start the IVF cycle.

88

89 **Hysteroscopic examination**

90 Hysteroscopy examination was performed using the vaginoscopic approach, without
91 previous anesthesia or cervical dilatation, and was scheduled for the follicular phase of the
92 menstrual cycle (up to the 10th day of the cycle). Patients were instructed to take oral
93 antispasmodic medication 30 minutes before the procedure.

94 The examinations were performed by in training physicians under direct supervision of 3
95 experienced gynecologic endoscopists. The equipment used was a rigid Karl Storz Telescope with
96 30-degree oblique view, 2.9 mm inner diameter and a 4.1mm outer sheath. The uterine cavity was
97 distended with 0.9% saline and a maximal pressure of 70 mmHg. The cervical canal, uterine
98 cavity, tubal ostia and endometrial surface were inspected methodically and the findings were

99 recorded on a standardized form.

100

101 **Statistical Analysis**

102 Categorical data (primary vs. secondary infertility, main cause of infertility, prevalence of
103 lesions) were summarized as simple or relative frequencies and tested with Chi-square or Fisher's
104 exact test, as appropriate. Continuous variables (age, length of infertility, menstrual cycle day)
105 were submitted to Shapiro-Wilk normality test and departed significantly from normal distribution,
106 therefore the inter-group differences were analyzed with the non-parametric Mann-Whitney test.
107 The prevalence of hysteroscopic alterations in successive age strata was submitted to Mantel-
108 Haenzel Chi-square test for linear trend. The diagnostic accuracy of TVS using hysteroscopy as
109 reference was assessed by calculating the sensitivity, specificity, positive and negative likelihood
110 ratios with their respective 95% confidence intervals (CI). We used the statistical software package

111 SPSS version 22 (IBM, Armonk, NY, USA).

112

113

115 The study flow is depicted in Figure 1. A total of 1151 hysteroscopy reports were initially
116 available. Two cases were excluded because the examination had been cancelled before starting
117 and 8 cases had incomplete examination due to patient intolerance and/or technical difficulties,
118 e.g. cervical stenosis with failed access and excess bleeding or mucus. The final sample
119 comprised 1141 completed hysteroscopies of which 180 were associated with a positive TVS and
120 961 with a negative TVS (Figure 1). The two groups had similar age, length of infertility and
121 proportion of primary to secondary infertility (Table 1).

122 Uterine alterations were found by hysteroscopy in 351/1141 patients of the whole cohort
123 (prevalence 30.7%, 95% CI 28.2%-33.5%) and in 265/961 patients with a negative TVS
124 (prevalence 27.6%, 95% CI 24.8%-30.5%, Table 2). These included 126 cases of endometrial
125 polyp (13.1% [95% CI 11.1% to 15.4%]), 24 cases of submucous leiomyoma (2.5% [1.7% to
126 3.7%]), 30 cases of uterine synechiae (3.1% [2.2% to 4.4%]), and 37 cases of uterine
127 malformations such as septate, arcuate and bicornuate uterus (3.9% [2.8% to 5.3%]; Figure 2A
128 and Table 2). In addition, there were 41 cases of suspected endometritis (4.3%) and 33 cases of
129 nonspecific endometrial "thickening" (3.4%), defined by elevated endometrial surface upon contact
130 with the hysteroscope (Table 2). The number of hysteroscopies needed to detect one unsuspected
131 lesion in this population was 3.6 (95% CI 3.3 to 4.0).

132 The prevalence of uterine cavity abnormalities in the group with a negative TVS changed
133 according to the woman's age, as shown in Figure 2B. Older women had non-significant increases
134 in the frequency of endometrial polyp ($p=0.133$) and uterine synechiae ($p=0.083$) and decrease in
135 uterine malformation ($p=0.237$). However, the prevalence of submucous leiomyoma increased
136 significantly with age ($p=0.005$, Chi-square test for linear trend) and reached 7.2% (95% CI 3.5%-
137 14.1%) after 40 years, whereas that of endometritis decreased ($p=0.044$, Figure 2B). A similar age
138 trend was seen in the group with a positive TVS (not shown).

139 Table 3 shows that TVS had low sensitivity in diagnosing the main intrauterine alterations
140 detected by hysteroscopy. The sensitivity of TVS ranged from 8% (95% CI 2%-20%) for uterine
141 synechiae to 41% (95% CI 28%-56%) for submucous leiomyoma, resulting in low likelihood ratios

142 for negative TVS results. Conversely, TVS findings had very high specificity in all types of lesion
143 evaluated, ranging from 95% specificity (95% CI 93%-96%) for submucous leiomyoma to 100%
144 (95% CI 99%-100%) for uterine malformation. This specificity translated into high likelihood ratios

145 for positive TVS results (Table 3).

146

147

149 The gold standard technique for evaluating the uterine cavity is hysteroscopy, since it
150 allows direct visualization of the lesions and treatment of the main abnormalities found, in contrast
151 to other diagnostic methods such as TVS (Di Spiezio Sardo *et al.*, 2016). In the present study, the
152 overall prevalence of uterine abnormalities found by hysteroscopy after a negative TVS in IVF
153 candidates was 27.6%. The prevalence of intrauterine abnormalities identified in hysteroscopy in
154 cases of previous normal findings in TVS has been estimated to vary from 11% (Fatemi *et al.*,
155 2010) to 32% (Bakas *et al.*, 2014), a broad range of prevalence that may translate differences in
156 participants' age, ethnicity, anthropometry and general health. In addition, the prevalence of
157 unsuspected lesions may vary depending on the diagnostic performance of TVS. Therefore, the
158 TVS sensitivity in our hands might have been lower than in other studies, resulting in a higher
159 prevalence of hysteroscopic findings not detected by a previous TVS.

160 In the present study we detected endometrial polyps more often in women older than 40
161 compared to the younger age strata, although the prevalence did not increase as a linear function
162 of age. Confirmatory diagnosis of endometrial polyp in women in preparation for IVF is important
163 because of its possible association with implantation failure (Perez-Medina *et al.*, 2005). Moderate
164 quality evidence from a single clinical trial suggests that hysteroscopic polypectomy increases the
165 odds of pregnancy following intrauterine insemination (Bosteels *et al.*, 2015; Perez-Medina *et al.*,
166 2005).

167 The prevalence of hysteroscopic images compatible with submucous leiomyoma
168 increased significantly with increasing age suggesting that older women, particularly after 40 years,
169 are more likely to have this lesion detected by hysteroscopy despite a negative TVS. Considering
170 that IVF success rates are low in women over 40 due to oocyte/embryo factors, detecting
171 submucous leiomyoma may be an opportunity to act on a modifiable risk factor that contributes to
172 IVF failure (Ezzati *et al.*, 2009). Based on consistent findings of cohort studies, an American
173 Society of Reproductive Medicine (ASRM) expert group found grade B evidence that performing
174 myomectomy of submucosal leiomyoma improves clinical pregnancy rates (Medicine, 2017). In this
175 study, TVS detected only 41% of the cases in whom hysteroscopy eventually identified a

176 submucous leiomyoma, suggesting that TVS missed most of the possible cases; on the other
177 hand, the 95% specificity of TVS means that in 5% of the cases where hysteroscopy was negative
178 for submucous leiomyoma there was a previous TVS indicating the presence of this lesion. This
179 inconsistency between the two methods suggests that many true fibroids may have escaped from
180 TVS view (false negatives), while some TVS images recorded as possible submucous leiomyomas
181 were actually false positives. However, we cannot rule out the possibility that some true
182 submucous fibroids have been overlooked at hysteroscopy.

183 Uterine malformations (such as septate uterus) and uterine synechiae were found in more
184 than 3% of our study population with a negative TVS. Both conditions are associated with a high
185 risk of miscarriage (Cholkeri-Singh & Sasaki, 2015; Medicine, 2016; Tomazevic *et al.*, 2010).
186 However, hysteroscopy alone is not able to evaluate the external format of the uterus and therefore
187 it does not allow the differential diagnosis between a septate and a bicornuate uterus and thus the
188 best approach for this differentiation is hysteroscopy associated with laparoscopy (Medicine,
189 2016). According to a Cochrane review, high quality evidence is still needed to support the surgical
190 treatment of septate uterus (Rikken *et al.*, 2017), but a current ASRM guideline concludes, based
191 on Grade C evidence, that it is reasonable to consider septum incision in infertile women
192 (Medicine, 2016). Treating uterine synechiae may also reduce the risk of miscarriage in women
193 with recurrent abortions (Goldenberg *et al.*, 1995).

194 We also found hysteroscopic signs of endometritis in 4% of the patients. While diagnosis is
195 made by histology, endometritis can be suspected by TVS based on endometrial thickening,
196 presence of free fluid in the pelvis and painful uterine mobilization during imaging, or at
197 hysteroscopy by the presence of edema and focal or diffuse hyperemia. Chronic endometritis is
198 often asymptomatic and some studies have shown an association with implantation failure and
199 recurrent miscarriage (Cholkeri-Singh & Sasaki, 2015). Another uncommon hysteroscopic finding
200 in our patients was nonspecific endometrial "thickening", which had similar prevalence in the
201 positive and negative TVS groups, suggesting no association with the endometrial thickness
202 objectively measured by TVS.

203 The value of hysteroscopy as a routine investigation in the management of infertile women
204 is a matter of debate. There is evidence that performing hysteroscopy prior to initiating IVF
205 treatment may increase the chances of pregnancy in the subsequent IVF cycle in women who had
206 one or more unsuccessful treatment cycles (Fatemi *et al.*, 2010). A systematic review with meta-
207 analysis including seven studies and 2545 women found moderate quality evidence of a beneficial
208 effect of routine hysteroscopy on the IVF pregnancy rate, but the same review found only very low-
209 quality evidence that such procedure increases the live birth rate (Di Spiezio Sardo *et al.*, 2016).
210 Afterwards, two randomized clinical trials were concluded and showed no benefit of routine
211 hysteroscopy to improve the live birth rate among women undergoing their first IVF cycle (Smit *et*
212 *al.*, 2016) or with a history of IVF failure (El-Toukhy *et al.*, 2016). However, the prevalence of
213 hysteroscopic alterations in these two clinical trials was low (<13%) compared to our study
214 population (27.6%). This suggests that in our population the potential benefit of performing
215 hysteroscopy before IVF might be underestimated by extrapolating the last clinical trial results.

216 The main methodological strengths of this study are the large number of participants, which
217 allowed us to calculate the prevalence of uterine abnormalities with narrow confidence intervals,
218 and the standardized hysteroscopic procedures performed with the same equipment and
219 interpreted by the same staff, which reduced the risk of performance bias. Data accuracy was
220 improved by using only standardized medical reports from a single center. The hysteroscopies
221 were interpreted considering the clinical history and imaging findings of the patients, which is a
222 more realistic scenario than if they had been performed blindly.

223 Some limitations of our research should also be noted. This is a retrospective study, which
224 limits the quality and amount of data and increases the risk of selection bias. It was not possible to
225 obtain data from the histological analysis of the lesions identified. Therefore, the main evaluation of
226 the lesions was based on visual findings in hysteroscopy. Another limitation of the study is that the
227 inter-operator variation of the diagnostic performance could not be measured retrospectively.
228 Finally, our evaluation of TVS sensitivity to detect intrauterine lesions was based only on the record
229 of ultrasound images compatible with the hysteroscopic aspect of the uterine cavity. The
230 complexity of information used in clinical decision is difficult to address in a retrospective study.

231 Since we had no access to the full medical history of the patients, we did not calculate the
232 predictive value of TVS in this context because this would only be informative if we knew the
233 expected prevalence of each lesion according to the patient's signs and symptoms.

234 In conclusion, our findings suggest a high prevalence of unsuspected alterations found by
235 routine hysteroscopy before IVF, an age-dependent increase in the frequency of submucous
236 leiomyoma and a low diagnostic sensitivity of TVS to detect intracavitary lesions. International
237 guidelines do not recommend hysteroscopy as first line method to assess uterine abnormalities in
238 infertile women (Practice Committee of the American Society for Reproductive, 2015), but they do
239 not make specific recommendations for women preparing to IVF. We therefore believe that
240 additional high quality evidence is needed to define whether there are any clinical or demographic
241 groups that might benefit from routine hysteroscopy before IVF.

243 **Funding and Conflict of Interest**

244 This study received no funding and the authors report no conflicts of interest.

246 **References**

- 247 Bakas P, Hassiakos D, Grigoriadis C, Vlahos N, Liapis A, Gregoriou O. Role of hysteroscopy prior
248 to assisted reproduction techniques. *J Minim Invasive Gynecol.* 2014; 21:233-7. PMID:
249 24067621 10.1016/j.jmig.2013.07.023: 10.1016/j.jmig.2013.07.023
- 250 Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and
251 treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod.* 2007;
252 22:1506-12. PMID: 17376819 10.1093/humrep/dem046: 10.1093/humrep/dem046
- 253 Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BW, D'Hooghe TM. Hysteroscopy for treating
254 subfertility associated with suspected major uterine cavity abnormalities. *Cochrane Database*
255 *Syst Rev.* 2015; Cd009461. PMID: 25701429 10.1002/14651858.CD009461.pub3:
256 10.1002/14651858.CD009461.pub3
- 257 Carneiro MM. What is the role of hysteroscopic surgery in the management of female infertility? A
258 review of the literature. *Surg Res Pract.* 2014; 2014:105412. PMID: 25374944
259 10.1155/2014/105412: 10.1155/2014/105412
- 260 Cholkeri-Singh A, Sasaki KJ. Hysteroscopy for infertile women: a review. *J Minim Invasive*
261 *Gynecol.* 2015; 22:353-62. PMID: 25553895 10.1016/j.jmig.2014.12.163:
262 10.1016/j.jmig.2014.12.163

263 Di Spiezio Sardo A, Calagna G, Laganà AS, Vitale SG, Catena U, Scutiero G, Nappi C. Is
264 Hysteroscopy Better than Ultrasonography for Uterine Cavity Evaluation? An Evidence-Based
265 and Patient-Oriented Approach. *Journal of Endometriosis and Pelvic Pain Disorders*. 2016;
266 8:87-93. PMID: 10.5301/je.5000252: 10.5301/je.5000252

267 Di Spiezio Sardo A, Di Carlo C, Minozzi S, Spinelli M, Pistotti V, Alviggi C, De Placido G, Nappi C,
268 Bifulco G. Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a
269 systematic review and meta-analysis. *Hum Reprod Update*. 2016; 22:479-96. PMID:
270 27008893 10.1093/humupd/dmw008: 10.1093/humupd/dmw008

271 El-Toukhy T, Campo R, Khalaf Y, Tabanelli C, Gianaroli L, Gordts SS, Gordts S, Mestdagh G,
272 Mardesic T, Voboril J, Marchino GL, Benedetto C, Al-Shawaf T, Sabatini L, Seed PT, Gergolet
273 M, Grimbizis G, Harb H, Coomarasamy A. Hysteroscopy in recurrent in-vitro fertilisation failure
274 (TROPHY): a multicentre, randomised controlled trial. *Lancet*. 2016; 387:2614-21. PMID:
275 27132053 10.1016/s0140-6736(16)00258-0: 10.1016/s0140-6736(16)00258-0

276 Elsetohy KA, Askalany AH, Hassan M, Dawood Z. Routine office hysteroscopy prior to ICSI vs.
7 ICSI alone in patients with normal transvaginal ultrasound: a randomized controlled trial. *Arch*
278 *Gynecol Obstet*. 2015; 291:193-9. PMID: 25082070 10.1007/s00404-014-3397-z:
279 10.1007/s00404-014-3397-z

280 Ezzati M, Norian JM, Segars JH. Management of uterine fibroids in the patient pursuing assisted
281 reproductive technologies. *Womens Health (Lond)*. 2009; 5:413-21. PMID: 19586433
282 10.2217/whe.09.29: 10.2217/whe.09.29

283 Fatemi HM, Kasius JC, Timmermans A, van Disseldorp J, Fauser BC, Devroey P, Broekmans FJ.
284 Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior
285 to in vitro fertilization. *Hum Reprod*. 2010; 25:1959-65. PMID: 20570971
286 10.1093/humrep/deq150: 10.1093/humrep/deq150

287 Goldenberg M, Sivan E, Sharabi Z, Mashiach S, Lipitz S, Seidman DS. Reproductive outcome
288 following hysteroscopic management of intrauterine septum and adhesions. *Hum Reprod*.
289 1995; 10:2663-5. PMID: 8567788

290 Medicine PCotASfR. Uterine septum: a guideline. *Fertil Steril*. 2016; 106:530-40. PMID: 27235766
291 10.1016/j.fertnstert.2016.05.014: 10.1016/j.fertnstert.2016.05.014

292 Medicine PCotASfR. Removal of myomas in asymptomatic patients to improve fertility and/or
293 reduce miscarriage rate: a guideline. *Fertil Steril*. 2017; 108:416-25. PMID: 28865538
294 10.1016/j.fertnstert.2017.06.034: 10.1016/j.fertnstert.2017.06.034

295 Perez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, Engels V.
296 Endometrial polyps and their implication in the pregnancy rates of patients undergoing
297 intrauterine insemination: a prospective, randomized study. *Hum Reprod*. 2005; 20:1632-5.
298 PMID: 15760959 10.1093/humrep/deh822: 10.1093/humrep/deh822

299 Practice Committee of the American Society for Reproductive M. Diagnostic evaluation of the
300 infertile female: a committee opinion. *Fertil Steril*. 2015; 103:e44-50. PMID: 25936238
301 10.1016/j.fertnstert.2015.03.019: 10.1016/j.fertnstert.2015.03.019

302 Rikken JF, Kowalik CR, Emanuel MH, Mol BW, Van der Veen F, van Wely M, Goddijn M. Septum
303 resection for women of reproductive age with a septate uterus. *Cochrane Database Syst Rev*.
304 2017; 1:Cd008576. PMID: 28093720 10.1002/14651858.CD008576.pub4:
305 10.1002/14651858.CD008576.pub4

306 Smit JG, Kasius JC, Eijkemans MJC, Koks CAM, van Golde R, Nap AW et al. Hysteroscopy before
307 in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial. *Lancet*. 2016;
308 387:2622-9. PMID: 27132052 10.1016/s0140-6736(16)00231-2: 10.1016/s0140-
309 6736(16)00231-2

310 Tomazevic T, Ban-Frangez H, Virant-Klun I, Verdenik I, Pozlep B, Vrtacnik-Bokal E. Septate,
311 subseptate and arcuate uterus decrease pregnancy and live birth rates in IVF/ICSI. *Reprod*
312 *Biomed Online*. 2010; 21:700-5. PMID: 20864409 10.1016/j.rbmo.2010.06.028:
313 10.1016/j.rbmo.2010.06.028

314

315 **Figure Legends**

316

317 **Figure 1:** Study flow chart.

318

319 **Figure 2:** Prevalence of hysteroscopic alterations with 95% confidence interval (**A**) and according
320 to age (**B**) in women with normal TVS imaging of the uterine cavity (n=961).

321

322 **Table 1:** Characteristics of the study participants.

	All (n=1141)	TVS positive (n=180)	TVS negative (n=961)	P value
Age (years)	35.4 ± 4.7	36.1 ± 4.9	35.3 ± 4.7	0.031
Length of infertility (years)	7.7 ± 4.2	7.5 ± 4.7	7.7 ± 4.1	0.611
Menstrual cycle day	8.7 ± 1.9	8.7 ± 2.2	8.7 ± 1.9	0.221
Infertility				
Primary	613/901 (68%)	85/134 (63%)	528/767 (69%)	0.255
Secondary	288/901 (32%)	49/134 (37%)	239/767 (31%)	
Main Cause*				
Male factor	290 (25%)	28 (16%)	262 (27%)	0.000
Tubal	97 (9%)	11 (6%)	86 (9%)	
Endometriosis	90 (8%)	12 (7%)	78 (8%)	
PCOS	30 (3%)	1 (1%)	29 (3%)	
Unexplained	627 (55%)	126 (70%)	501 (52%)	
Other	7 (1%)	2 (1%)	5 (1%)	

323 Continuous variables are shown as mean ± standard variation. P values refer to the comparison
 324 between TVS positive and TVS negative groups (Mann-Whitney test for continuous variables and
 325 Chi-square test for categorical variables).

326 *according to annotations in the hysteroscopy report.

327

328 **Table 2:** Hysteroscopic findings

329

All (n=1141)		TVS positive (n=180)	TVS negative (n=961)	P value
Any alteration	351 (30.7%)	86 (47.8%)	265 (27.6%)	0.000
Endometrial Polyp	170 (17.9%)	44 (24.4%)	126 (13.1%)	0.000
Submucous Leiomyoma	44 (3.9%)	20 (11.1%)	24 (2.5%)	0.000
Uterine Synechiae	39 (3.4%)	9 (5.0%)	30 (3.1%)	0.260
Uterine Malformation	53 (4.6%)	16 (8.9%)	37 (3.9%)	0.006
Suspected Endometritis	42 (3.7%)	1 (0.6%)	41 (4.3%)	0.009
Endometrial "thickening"	42 (3.7%)	9 (5.0%)	33 (3.4%)	0.285
Other	15 (1.3%)	1 (0.6%)	14 (1.4%)	0.490

330 The sum of all alterations is higher than the number of hysteroscopies with "any alteration"
 331 because some patients had more than one type of lesion.

332 P values refer to the comparison between TVS positive and TVS negative groups (Chi-square or
 333 Fisher's exact test, as appropriate).

334

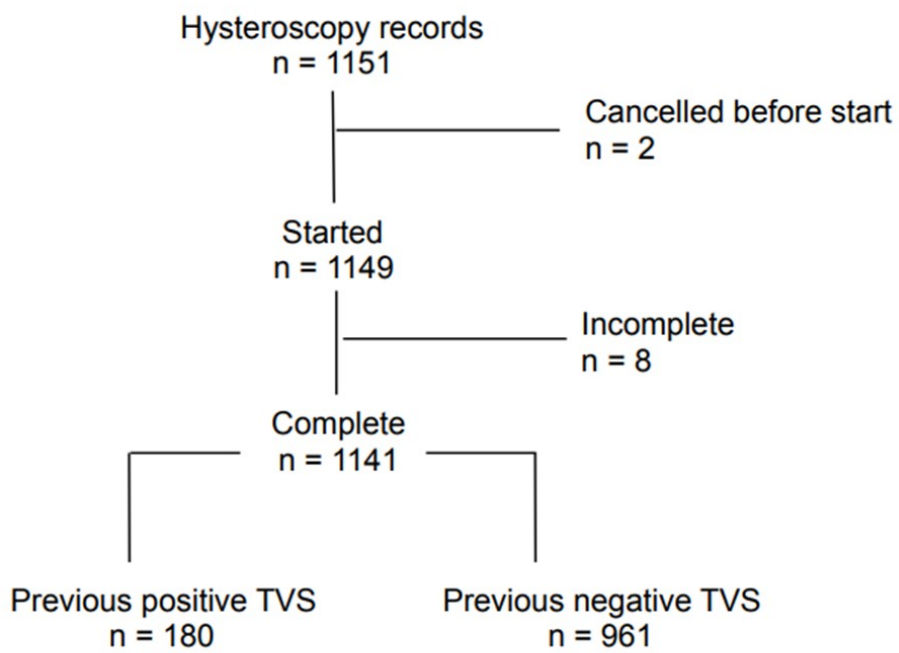
335 **Table 3:** Diagnostic accuracy of transvaginal sonography to detect uterine lesions using
 336 hysteroscopy as reference.

Endometrial Polyp	Submucous Leiomyoma	Uterine Synechiae	Uterine Malformation	
Sensitivity	15 (11-21)	41 (28-56)	8 (2-20)	17 (9-29)
Specificity	97 (96-98)	95 (93-96)	99 (99-99)	100 (99-100)
LR+	4.8 (2.9-7.9)	7.5 (4.9-11.5)	10.6 (2.9 (38.4)	36.9 (12.8-106.4)
LR-	0.9 (0.8-0.9)	0.6 (0.5-0.8)	0.9 (0.8-1.0)	0.8 (0.7-0.9)

337 Data are presented as percentage with 95% confidence interval

338 LR+: positive likelihood ratio; LR-: negative likelihood ratio

Figure 1



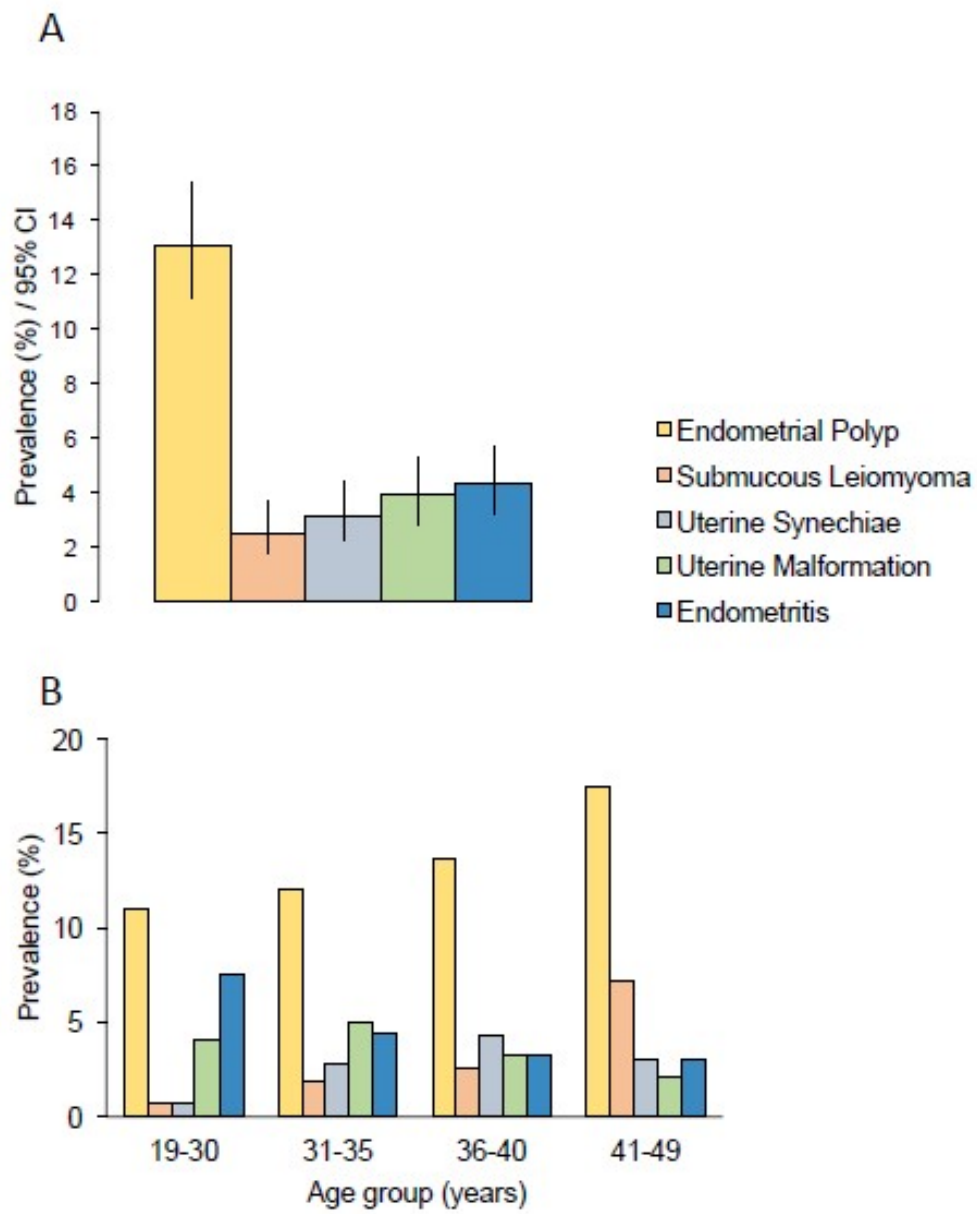


Figure 2

Considerações Finais

O papel da histeroscopia de rotina no manejo das mulheres inférteis com indicação de FIV é uma questão em debate.

Há evidências na literatura de que a realização de histeroscopia de rotina pode aumentar as chances de gravidez em mulheres com uma ou mais falhas de implantação após FIV e também em mulheres submetidas a sua primeira FIV (Di Spiezio Sardo *et al.*, 2016, Fatemi *et al.*, 2010).

Por outro lado, estudos mais recentes (El-Toukhy *et al.*, 2016, Smit *et al.*, 2016) não demonstraram benefício da histeroscopia de rotina para melhorar a taxa de nascidos vivos entre as mulheres que se submeteriam à FIV. Entretanto, a prevalência de alterações histeroscópicas nesses dois estudos foi baixa (<13%) em comparação com a população estudada no presente estudo (27,6%), podendo sugerir que na nossa população o benefício potencial da realização da histeroscopia de rotina antes da FIV poderia ser subestimado se extrapolarmos as conclusões dos ensaios clínicos feitos em população com menor prevalência de lesões.

Nosso estudo encontrou uma alta prevalência de alterações intra-uterinas insuspeitas diagnosticadas pela histeroscopia de rotina antes da FIV nas pacientes em tratamento no Hospital das Clínicas da Universidade Federal de Minas Gerais. Detectamos baixa sensibilidade diagnóstica da ultrassonografia transvaginal para diagnosticar lesões intra-uterinas que poderiam comprometer a eficiência do tratamento em reprodução assistida.

Acreditamos que ensaios clínicos randomizados controlados adicionais de alta qualidade sejam necessários para definir com precisão se há algum perfil de pacientes do ponto de vista clínico ou demográfico/etário que possa se beneficiar da histeroscopia de rotina antes da fertilização *in vitro*.

Referencias Bibliográficas

- Bakas P, Hassiakos D, Grigoriadis C, Vlahos N, Liapis A and Gregoriou O. Role of hysteroscopy prior to assisted reproduction techniques. *J Minim Invasive Gynecol* 2014; **21**: 233-237.
- Boivin J, Bunting L, Collins JA and Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod* 2007; **22**: 1506-1512.
- Carneiro MM. What is the role of hysteroscopic surgery in the management of female infertility? A review of the literature. *Surg Res Pract* 2014; **2014**: 105412.
- Di Spiezio Sardo A, Calagna G, Laganà AS, Vitale SG, Catena U, Scutiero G and Nappi C. Is Hysteroscopy Better than Ultrasonography for Uterine Cavity Evaluation? An Evidence-Based and Patient-Oriented Approach. *Journal of Endometriosis and Pelvic Pain Disorders* 2016; **8**: 87-93.
- Di Spiezio Sardo A, Di Carlo C, Minozzi S, Spinelli M, Pistotti V, Alviggi C, De Placido G, Nappi C and Bifulco G. Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis. *Hum Reprod Update* 2016; **22**: 479-496.
- El-Toukhy T, Campo R, Khalaf Y, Tabanelli C, Gianaroli L, Gordts SS, Gordts S, Mestdagh G, Mardesic T, Voboril J *et al*. Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial. *Lancet* 2016; **387**: 2614-2621.
- Elsetohy KA, Askalany AH, Hassan M and Dawood Z. Routine office hysteroscopy prior to ICSI vs. ICSI alone in patients with normal transvaginal ultrasound: a randomized controlled trial. *Arch Gynecol Obstet* 2015; **291**: 193-199.
- Fatemi HM, Kasius JC, Timmermans A, van Disseldorp J, Fauser BC, Devroey P and Broekmans FJ. Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. *Hum Reprod* 2010; **25**: 1959-1965.
- Hinckley MD and Milki AA. 1000 office-based hysteroscopies prior to in vitro fertilization: feasibility and findings. *Jsls* 2004; **8**: 103-107.

Smit JG, Kasius JC, Eijkemans MJC, Koks CAM, van Golde R, Nap AW, Scheffer GJ, Manger PAP, Hoek A, Schoot BC *et al.* Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial. *Lancet* 2016; **387**: 2622-2629.

Anexo I

Técnica do exame de histeroscopia ambulatorial

Stefano Bettocchi teve um papel significativo no desenvolvimento e propagação de histeroscopia ambulatorial com o desenvolvimento e a criação de um novo revestimento de 5 mm de diâmetro e uma secção transversal de forma oval. Essas inovações tornaram o instrumento mais ergonômico, contribuindo para a realização de histeroscopia como um procedimento ambulatorial.

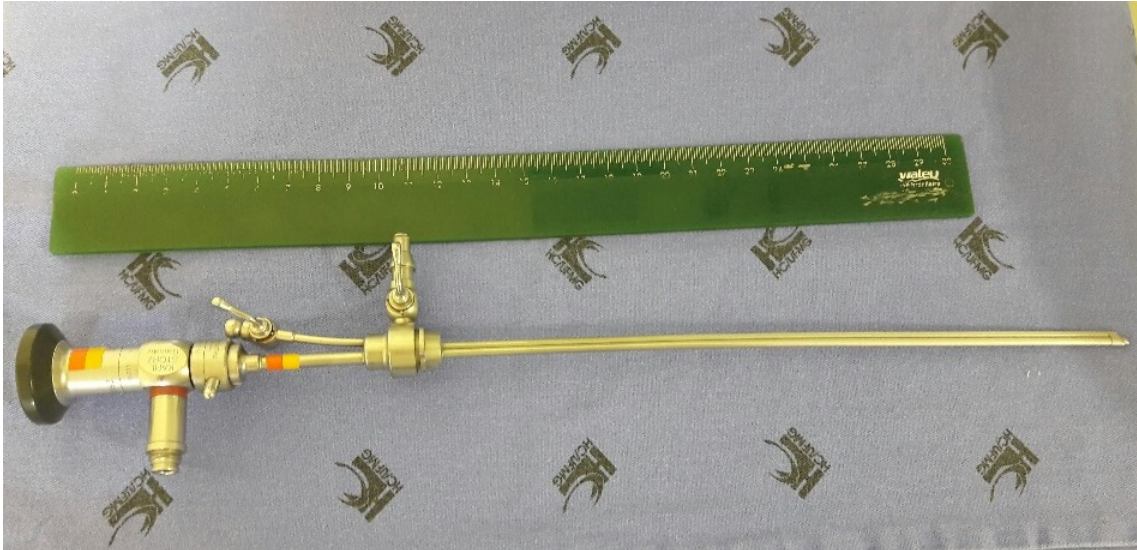
O desenvolvimento da histeroscopia ambulatorial tem permitido uma abordagem minimamente invasiva de lesões intrauterinas por meio da visualização da vagina, da cavidade endometrial, dos óstios tubários e do canal endocervical (Fatemi,*et al*, 2010).

O exame de histeroscopia diagnostica alterações na cavidade uterina, como miomas, pólipos e malformações, que poderão ser corrigidos cirurgicamente, além de permitir a biópsia endometrial (Fatemi,*et al*, 2010).

Os procedimentos de histeroscopia foram realizados em caráter ambulatorial utilizando a abordagem vaginoscópica, sem anestesia ou dilatação cervical prévia, e foram programados para a fase folicular do ciclo menstrual.

A abordagem vagino-histeroscópica consiste em um procedimento menos invasivo e mais acessível, uma vez que evita o uso do espécuro e da pinça de Pozzi para introduzir o histeroscópio, respeitando a anatomia do canal endocervical, reduzindo a dor durante o exame. Além disso, oferece uma avaliação ampliada das paredes vaginais, fundo de saco, e ectocervice, que são áreas anatômicas não adequadamente estudadas pela ultrassonografia e histeroscopia tradicional.

Os exames foram realizados pelos médicos residentes do Hospital das Clínicas sob supervisão direta dos preceptores do Laboratório de Reprodução Humana. Foram usados equipamentos com ótica Storz Telescope 30°, 2,9mm de diâmetro, 30 cm de comprimento, rígida, com camisa de exame de 4,1mm (Figura). A vagina e a cavidade uterina foram distendidas com soro fisiológico 0,9% sob a pressão de 30-40 mmHg. As pacientes foram orientadas a usar 2 comprimidos de analgésico (buscopam, dipirona), 30 minutos antes do exame.



Ótica Storz Telescope 30°, 2,9mm de diâmetro, 30 cm de comprimento, rígida, com camisa de exame de 4,1mm, camisa Bettocchi

Anexo II

Ficha padrão de laudo de Histeroscopia Diagnóstica do Laboratório de Reprodução Humana do Hospital das Clínicas



HISTEROSCOPIA DIAGNÓSTICA - Aparelho: Storz 3 mm

Paciente:

Data:

Data Nascimento:

Idade: anos

DUM:

Médico solicitante:

Resumo do quadro clínico:

HISTEROSCOPIA

Canal Endocervical:

Cavidade uterina:

Istmo:

Morfologia:

Região cornual e orifícios tubáreos:

Mucosa endometrial:

Aspecto ao contato:

Conclusão:

Médico - CRM

Anexo III
Aprovação do COEP



UNIVERSIDADE FEDERAL DE MINAS GERAIS
COMITÊ DE ÉTICA EM PESQUISA - COEP


Projeto: CAAE 59731016.9.0000.5149

Interessado(a): Prof. Fernando Marcos dos Reis
Departamento de Ginecologia e
Obstetria
Faculdade de Medicina -UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 28 de setembro de 2016, o projeto de pesquisa intitulado **"Prevalência de alterações histeroscópicas em mulheres submetidas à fertilização in vitro: estudo retrospectivo"**.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto através da Plataforma Brasil.


Profa. Dra. Vivian Resende
Coordenadora do COEP-UFMG



UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE DA MULHER

UFMG

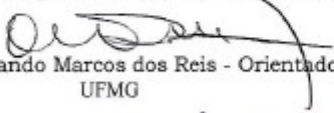
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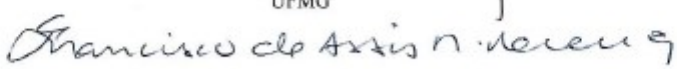
**PREVALÊNCIA DE ALTERAÇÕES HISTEROSCÓPICAS EM MULHERES
SUBMETIDAS À FERTILIZAÇÃO IN VITRO: ESTUDO RETROSPECTIVO**

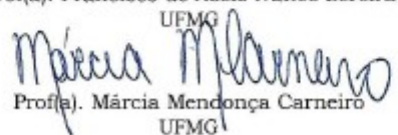
CECILIA DE SOUZA MONTEIRO

Dissertação submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em SAÚDE DA MULHER, como requisito para obtenção do grau de Mestre em SAÚDE DA MULHER, área de concentração PATOLOGIA GINECOLÓGICA E REPRODUÇÃO.

Aprovada em 14 de dezembro de 2018, pela banca constituída pelos membros:


Prof(a). Fernando Marcos dos Reis - Orientador
UFMG


Prof(a). Francisco de Assis Nunes Rereira
UFMG


Prof(a). Márcia Mendonça Carneiro
UFMG


Prof(a). Márcia Cristina França Ferreira
UFMG