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Intrauterine fluid instillation to confirm tubal occlusion after transcervical permanent contraception: a pilot study

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Abstract

Objectives: To determine if women with tubal patency experience more fluid loss compared to those with bilateral tubal occlusion following intrauterine instillation of fluid via a balloon catheter.

Study Design: In this prospective cohort pilot study, we enrolled women with prior Essure[®] procedures and healthy controls from September 2016–July 2017. We excluded women using an implant or intrauterine device, or with a prior cesarean delivery or permanent contraception procedures other than Essure[®]. An infusion pump delivered saline via balloon catheter under continuous pressure monitoring. After one minute, we withdrew the fluid and recorded volumes in and out. Subjects then underwent hysterosalpingogram for evaluation of tubal patency. We conducted crude analyses with t-tests and sensitivity analyses.

Results: We recruited 23 participants; ten provided analyzable data in each group. Hysterosalpingogram confirmed patency in all control and occlusion in all post-Essure[®] subjects in the analysis group. We found the median volume of saline lost among control subjects [7.8 mL (7.4, 8.4)] larger than post-Essure[®] participants [2.2 mL (2.0, 3.8), $p < 0.01$]. While 50% of control subjects tolerated the full 10mL of fluid instillation, none of the post-Essure[®] subjects tolerated this volume ($p = 0.03$). A combination of saline loss ≥ 4 mL and participant intolerance of the full 10mL volume yielded sensitivity of 0.80 (95% CI: 0.57, 1.00) and specificity of 1.00 for bilateral tubal occlusion.

Conclusion: Instillation of a fixed volume into the uterus may discriminate between women with tubal patency and occlusion following permanent contraception procedures with high specificity

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Clinical Trial Registration:

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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and adequate sensitivity. These findings should be validated in larger, more diverse study populations.

Implications: Confirmation of tubal occlusion following permanent contraception with an office-based approach could improve acceptability of nonsurgical approaches. The recent removal of Essure® from the U.S. market increases the need for novel non-surgical procedures and occlusion verification methods.

Keywords

Nonsurgical permanent contraception; transcervical permanent contraception; tubal occlusion verification; sterilization; intrauterine fluid loss; sensitivity and specificity

1.0 Introduction

Globally, the use of permanent contraceptive methods exceeds that of reversible contraception [1]. For women, surgical options via laparotomy or laparoscopy have traditionally been the most widely available permanent contraceptive methods, but the introduction of Essure® hysteroscopic tubal occlusion in the US in 2002 offered a less invasive, no-incision alternative [2]. While surgical approaches provide immediate permanent contraception, tubal occlusion following placement of Essure® requires the development of a collagen scar which takes several weeks. This necessitates an additional step of verifying bilateral fallopian tube occlusion three months after placement of Essure®. The US Food and Drug Administration (FDA) requires verification of occlusion with hysterosalpingogram or confirmation of correct coil placement with transvaginal ultrasound [3]. While this verification provides evidence of occlusion, failure rates in real world clinical use with Essure® appear higher than in clinical studies. That estimates of actual completion of the verification test vary widely (6-87%) likely explains this difference [4]. This suggests current strategies for confirmation do not meet the needs of clinicians and women. A low-cost, office-based tubal occlusion verification test may increase the accessibility of transcervical permanent contraception methods under development.

Alternative techniques proposed to investigate tubal occlusion include measurement of individual tubal perfusion pressures [5] or ultrasound-based techniques like FemVue® [5]. However, the resources, equipment (e.g. ultrasound), and training required for these techniques would likely preclude their use in low-resource settings [6]. Furthermore, new transcervical permanent contraception methods currently in development do not involve placement of a permanent device viewable by standard radiographs or ultrasound [7].

For these reasons, our team continues to explore ways to confirm tubal occlusion after transcervical permanent contraception in an office setting with low-cost and low-technology needs. Our initial study explored the measurement of intrauterine pressure as a way to differentiate between women with patent and occluded fallopian tubes [8]. While we did not demonstrate a difference in peak intrauterine pressure between women with occluded and patent tubes (292.7 mmHg vs 293.8 mmHg, $p=.95$) [8], we did notice a small difference in the amount of contrast used between participants with open (6.9 ± 1.9 mL) and blocked (5.2 ± 2.7 mL, $p<.01$) fallopian tubes. Based on this observed difference, we selected 10 mL

as a sufficient and practical volume to study whether fluid instilled into the uterus may be lost to the peritoneal cavity in women with open fallopian tubes, and whether the amount of fluid recovered after infusion of a standard volume into the uterine cavity might be predictive of tubal occlusion. We hypothesized that recovered fluid volume from participants with bilateral tubal occlusion would exceed that of fluid volume recovered from women with tubal patency.

2.0 Materials and methods

We conducted a prospective cohort pilot study at Womens Imaging and Intervention (WI&I) in Lake Oswego, OR. Study procedures occurred between September 2016 and July 2017 after approval by the Institutional Review Board of Oregon Health & Science University (OHSU). All participants signed an IRB-approved written consent.

We recruited women with either a history of Essure[®] transcervical permanent contraception or healthy control participants without history of a permanent contraception procedure. Other inclusion criteria for both groups included general good health, age 18-50 years, at least one prior full-term vaginal delivery, no history of infertility, regular menstrual cycles occurring every 24-37 days, and willingness to undergo a washout period of either one month (if using the pill, patch, or ring) or three months (if using depo-provera). Exclusion criteria included prior cesarean sections, female sterilization procedures other than Essure[®], current use of an IUD or contraceptive implant, hypersensitivity to radio-opaque contrast, or history recognized as clinically significant by the investigator, such as symptoms of untreated or recent pelvic infection. We employed strict inclusion and exclusion criteria for this initial proof-of-concept study with the intent of verifying generalizability in future studies.

We recruited participants using email and mailing lists coordinated by the Women's Health Research Unit at OHSU, as well as by direct phone and email contact with women who had undergone Essure[®] between 2010 and 2016 at OHSU. Participants were scheduled according to WI&I's routine including scheduling procedures in the follicular phase. Once enrolled, participants provided sociodemographic data and health history via questionnaire. The study coordinator measured vital signs including height and weight. Given that functional tubal patency may fluctuate with the menstrual cycle, participants provided a serum sample for hormonal analysis to confirm cycle stage [9]. One non-blinded board-certified radiologist who specializes in women's imaging conducted all study procedures. We used the same equipment and settings as described in our prior study [8]. In the present study, after placement of the hysterosalpingogram catheter (5-Fr balloon catheter (MM1154; Monarch Medical, Cumming, GA, USA)), we used an infusion pump to deliver normal saline under continuous pressure monitoring until we reached one of the following endpoints: delivery of the entire volume of 10mL; a peak pressure of 450mmHg; or the participant requested the infusion to stop due to intolerable discomfort. After one minute, we withdrew the delivered fluid through the hysterosalpingogram catheter and recorded the volume instilled and recovered. We then repeated the procedure using contrast under fluoroscopy to confirm tubal patency or occlusion as previously described [8]. We did not place a tenaculum or other instrument on the cervix during the procedure.

We used an inline pressure monitor (DPT-100, Utah Medical, Midvale, UT) and the PressureMAT™ (PendoTech, Princeton, NJ) system and software to record pressure through an intrauterine balloon catheter as previously described [8], and stored data on a secure, encrypted laptop. To manage data from participant questionnaires and the radiologist's procedure notes we used the REDCap™ electronic data capture tool [10]. The Oregon National Primate Research Center Endocrine Technologies Core Lab analyzed the serum samples for estrogen and progesterone levels as described previously [8].

An *a priori* sample size calculation showed that a total of 24 participants divided evenly would provide 80% power at the 0.05 level of significance to detect a 3mL difference between participants with tubal patency and bilateral fallopian tube occlusion, allowing for the possible exclusion of two participants in each group following consent. We selected 3mL as a significant amount for this pilot study as a first measure. We planned to exclude results obtained when technical challenges interfered with accurate data collection including fluid leaked around the catheter.

We used R version 3.4.1 (R Core Team, Vienna, Austria) to perform statistical analysis. We compared baseline descriptive and procedure characteristics of participants with tubal patency and bilateral tubal occlusion using Student's t-test (two-sided), Wilcoxon rank-sum test, and Fisher's exact test, as appropriate. To evaluate the primary outcome of volume of fluid lost between the two groups, we conducted a crude analysis within each fluid type, using a series of two-sample t-tests. Since data were not normally distributed, we compared medians using the Wilcoxon test.

For adjusted analysis, we constructed a linear mixed-effects model with a random effect for participant identifier and fixed effects for fluid type (contrast versus saline), tubal occlusion, 17 β -estradiol, and progesterone. To evaluate the capacity of fluid volume loss and participants' ability to tolerate 10mL of infused fluid to discriminate between patency and occlusion, we calculated sensitivity and specificity with bootstrapped 95% confidence intervals. To identify optimal cut-points of volume lost, we used Youden's criterion, which defines the threshold that maximizes the sum of sensitivity and specificity [11]. To assess the influence on the results of two participants in whom the balloon was expelled during the procedure, we conducted a sensitivity analysis (including t-tests, linear mixed-effects models, and discrimination statistics).

3.0 Results

We recruited 23 women: 11 parous control participants, 11 post-transcervical permanent contraception participants, and one woman who participated as a control immediately prior to her Essure® procedure and again as a post-transcervical permanent contraception participant three months after undergoing the Essure® procedure. Hysterosalpingogram confirmed bilateral tubal occlusion for all post-Essure® participants. We excluded from analysis one participant from each group noted by the radiologist to have fluid leak around the hysterosalpingogram catheter. One control participant's hysterosalpingogram did not demonstrate tubal contrast fill so she was also excluded. The participant who enrolled both in control and post-transcervical permanent contraception groups had her data from the post-

Essure[®] procedure excluded to preserve statistical independence. This left 10 participants in the control group and 10 in the post-transcervical permanent contraception group included in the statistical analysis (Figure 1).

Participant characteristics and baseline hormone levels are presented in Table 1. No enrolled participants had a history of cesarean delivery, ectopic pregnancy, pelvic infection, endometriosis, uterine anomalies or uterine fibroids. We successfully placed the HSG catheter in the uterus at the internal os for all subjects except one control participant who had intracervical placement.

Table 2 details the fluid measurements, as well as the participants' tolerance of 10mL infusion. With regards to our primary outcome of intrauterine fluid volume lost, we noted differences between the control and post-transcervical permanent contraception participants with both saline [median 7.8 mL (interquartile range 7.4, 8.4) in the control group, versus 2.2 mL (2.0, 3.8) in the post-transcervical permanent contraception group, $p<0.01$] and contrast [5.9 mL (4.6, 6.9) in the control group, versus 0.0 mL (0.0, 1.9) in the post-transcervical permanent contraception group, $p<0.01$]. This difference remained when we eliminated stratification between saline and contrast [6.7 mL (5.8, 7.9) in the control group, vs 1.8 mL (0.6, 2.9) in the post-transcervical permanent contraception group, $p<0.01$]. For both saline and contrast, 50% (5/10) of control participants tolerated the full 10mL of fluid instillation, compared to 0% (0/10) in the post-transcervical permanent contraception group ($p=0.03$). Table 3 provides data on intrauterine pressure. Although we measured higher maximum pressures with both saline and contrast in the transcervical permanent contraception group, the magnitude of the difference in mean pressures during infusion between the groups differed by only 10 mmHg with each fluid.

In a linear mixed-effect model of volume of intrauterine fluid loss, post-Essure[®] tubal occlusion was associated with 4.0mL less fluid loss (95% CI: 2.0, 6.0 mL) after adjusting for type of fluid (contrast vs saline) and serum estradiol and progesterone levels. Tubal occlusion status was the only significant predictor of fluid loss in this model (Table 4).

Youden's criterion for volume of fluid loss to discriminate between patent and occluded tubes was 4mL for saline and 3mL for contrast (Figure 2). The 4mL cut-point for saline yielded sensitivity of 0.8 (95% CI: 0.0, 1.0) and specificity of 0.90 (95% CI: 0.5, 1.0). The 3mL cut-point for contrast completely separated the sample into patent and occluded groups. Using a combination of saline loss 4mL and inability of the participant to tolerate the full 10mL of saline yielded the same sensitivity (0.80) as the 4mL cut-point, but it slightly tightened the bootstrapped confidence interval (0.57, 1.00); this combination also boosted specificity to 1.00 (we could not calculate a confidence interval due to complete separation). In two participants, the balloon was expelled during the procedure; excluding these two participants from crude and multivariable comparisons of volume of fluid loss by occlusion status and from calculations of discrimination statistics did not appreciably change the results (Table 5).

4.0 Discussion

We hypothesized that after instilling a standard volume of fluid in the uterus, the volume lost to the peritoneal cavity would be less in women with blocked tubes after Essure[®] compared to women with patent fallopian tubes. Our data demonstrate a higher volume of fluid lost from control participants compared to post-Essure[®] participants, using both saline and contrast. Using Youden's criterion to identify a cut-point of volume of fluid loss to confirm tubal occlusion, a loss of 4mL of saline or less had the highest sum of sensitivity (80%) and specificity (90%) for predicting bilateral tubal occlusion. The higher viscosity of contrast resulted in similar trends in fluid loss with higher pressure than saline.

Prioritizing specificity over sensitivity is important when considering a confirmatory test for tubal occlusion after transcervical permanent contraception. Women who have undergone a tubal occlusion procedure are more likely to have tubal occlusion compared to the general population. However, mis-classifying a woman with tubal occlusion when she instead has continued tubal patency after a permanent contraception procedure (e.g. false negative) puts her at risk for unintended pregnancy. In contrast, women with blocked tubes classified as patent (false positive) would be advised to continue contraception and undergo the current gold standard test of hysterosalpingogram or have a repeat transcervical permanent contraception procedure. Based on our results, we estimate that 2 of 10 women would require referral for additional testing.

Validation in a larger data set will be important to address the strict inclusion and exclusion criteria used to assess proof-of-concept in as homogenous population as possible. Regional population trends limited the ethnic diversity of our study population. These findings are intended to be explored in a larger, more heterogenous study population to verify generalizability.

Another important limitation of our study is the wide confidence interval for both sensitivity and specificity: indeed, the confidence interval for sensitivity spans the entire range (0.0 to 1.0). While the sensitivity and specificity point estimates suggest a 4mL volume of saline loss could be used as a cut-point for evaluating tubal occlusion status after transcervical permanent contraception, this cut-point is based on training data, so our estimates of classification error may be underestimated. We were able to obtain 100% sensitivity using a cut point of 7.75mL; however, this cut point yields only 50% specificity. Validation in a new, larger data set will be necessary to obtain a more realistic estimate of the discriminative capacity of volume of saline loss prior to implementation of this technique.

Our data also suggest that combining the volume of fluid lost with the ability to tolerate a full 10mL intrauterine instillation may improve the specificity of volume of saline loss as a diagnostic tool for occlusion status. Given that there were two post-Essure[®] participants in whom the hysterosalpingogram catheter expelled from the uterus during fluid instillation who were categorized as unable to tolerate 10mL fluid instillation in the initial analysis, participant tolerance of intrauterine volume also warrants further validation with a larger sample size.

Although we planned a sample size of 12 per group, our final analysis included only 10 subjects in each cohort. We excluded two participants, one control and one post-Essure[®], due to spillage of saline and contrast into the vagina noted by the radiologist, precluding accurate measurement of volume instilled and volume recovered. We excluded another control participant, as we could not confirm tubal patency status during hysterosalpingogram using the 10mL volume of contrast. A final subject participated in both cohorts, but contributed data only as a control to preserve independence. Of interest, this woman tolerated the full 10mL infusion of saline during her pre-Essure[®] hysterosalpingogram showing bilateral patency, with only 2mL recovered and no pain. Following the permanent contraception procedure, the cervical balloon expelled during infusion of both saline and contrast causing leakage of fluid into the vagina invalidating our measurement of fluid loss. The hysterosalpingogram confirmed bilateral tubal blockade.

Strengths of our study include a well-matched cohort of participants and rigorous procedural methodology to explore a novel association between the volume of fluid lost after intrauterine instillation and tubal occlusion status. Consistently similar results using contrast fluid provides internal validity for saline data, with saline being the most practical fluid for a tubal occlusion verification test used in the field. Furthermore, we saw a difference in peak intrauterine pressure between controls and post-Essure[®] participants correlating with the trend toward different peak intrauterine pressure in parous women seen in our original study [8].

Although we found peak pressure predictive in this study, we have less confidence in this result due to sampling variance. We have higher confidence in our findings of intrauterine fluid volume loss and the ability to tolerate 10mL of intrauterine fluid as predictive of tubal patency. Future research should endeavor to combine these three measures in a larger sample such that a predictive model can be constructed and validated in test data as a possible alternative tubal occlusion verification test. With the recent removal of the Essure[®] device from the U.S. market, women are left without an FDA-approved transcervical permanent contraception option. This greatly increases the importance of and need for novel transcervical permanent contraception and tubal occlusion verification methods so women can continue to access safe and effective permanent contraceptives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1: Flowchart of participant enrollment in control and post-Essure[®] groups, participant exclusion, and final participants for analysis

Figure 2: Receiver-operator curves for cut-offs of 3 or 4 mL of intrauterine fluid loss to predict bilateral tubal occlusion

Sens - sensitivity

Spec - specificity

Table 1:**Baseline Characteristics.**

Participant demographic characteristics and ovarian hormonal profile at the time of the procedure by transcervical permanent contraception status.

	Control group (n=10)	TCPC group (n=10)	p-value
Age	38.4 ± 6.1	39.3 ± 4.5	0.71 ^a
BMI (kg/m²)	29.8 ± 6.9	27.5 ± 5.3	0.41 ^a
Race			1.00 ^b
Non-Hispanic White	8 (80)	8 (80)	
Hispanic	1 (10)	1 (10)	
Asian	1 (10)	1 (10)	
Insurance type			1.00 ^b
Private	7 (70)	8 (80)	
State Medicaid	1 (10)	2 (20)	
No insurance/Other	2 (20)	0	
Gravidity			0.72 ^b
1	3 (30)	2 (20)	
2	3 (30)	2 (20)	
3+	4 (40)	6 (60)	
Prior vaginal deliveries			0.40 ^b
0	0	0	
1	4 (40)	3 (30)	
2	5 (50)	3 (30)	
3+	1 (10)	4 (40)	
Estradiol 17β (pg/mL)	132.1 ± 61.8	174.3 ± 100.7	0.30 ^a
Progesterone (ng/mL)	0.3 ± 0.2	0.5 ± 0.8	0.51 ^a

Data are presented as n(%) or mean ± standard deviation

TCPC – transcervical permanent contraception

BMI - Body mass index

^aStudent's t-test (two-sided)

^bFisher's exact test

Table 2:
Results of transcervical fluid administration.

Main results of transcervical fluid (saline or contrast media) administration in control participants and those with a transcervical permanent contraception procedure. Volumes of fluid administered and recovered during the procedure, with net loss and proportion that tolerated the entire 10 mL infusion.

	Control group (n=10)	TCPC group (n=10)	p-value
Saline infused (mL)	9.8 (9.5, 10.0)	5.5 (4.0, 7.5)	<0.01 ^a
Saline recovered (mL)	2.0 (1.1, 2.0)	2.0 (1.5, 3.8)	0.76 ^a
Saline net loss (mL)	7.8 (7.4, 8.4)	2.2 (2.0, 3.8)	<0.01 ^a
Contrast infused (mL)	9.8 (9.5, 10.0)	5.5 (4.2, 6.0)	<0.01 ^a
Contrast recovered (mL)	3.5 (3.0, 5.2)	4.5 (3.6, 6.8)	0.31 ^a
Contrast lost	5.9 (4.6, 6.9)	0.0 (0.0, 1.9)	<0.01 ^a
Contrast net loss (mL)	6.7 (5.8, 7.9)	1.8 (0.6, 2.9)	<0.01 ^a
Tolerated 10 mL saline ^c	5 (50%)	0 (0%)	0.03 ^b
Tolerated 10 mL contrast ^c	5 (50%)	0 (0%)	0.03 ^b

Values reflect medians with inter-quartile ranges unless noted.

TCPC - Transcervical permanent contraception

^aWilcoxon rank-sum test

^bFisher's exact test

^cValues reflect n(%)

Table 3:
Intrauterine pressure measurements.

Intrauterine pressure measured during saline and contrast administration in control participants and those with a transcervical permanent contraception procedure.

	Control group (n=10)	TCPC group (n=10)	p-value^a
Maximum pressure saline	85.3 ± 30.0	238.1 ± 128.9	<0.01
Minimum pressure saline	1.5 ± 1.8	2.1 ± 5.7	0.74
Mean pressure saline	42.2 ± 10.9	81.9 ± 51.1	0.04
Maximum pressure contrast	284.6 ± 54.7	362.1 ± 71.2	0.01
Minimum pressure contrast	16.7 ± 11.2	10.4 ± 15.8	0.32
Mean pressure contrast	150.1 ± 28.2	160.5 ± 29.2	0.43
Maximum pressure combined	284.6 ± 54.7	381.9 ± 62.1	<0.01

Pressure values reported as mmHg and reflect mean ± standard deviation

TCPC - Transcervical permanent contraception

^aStudent's t-test (two-sided)

Table 4:
Linear mixed-effects models of predictors of intrauterine fluid loss

Fixed effects	Primary analysis		Sensitivity analysis*	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Intercept	7.29 (5.22, 9.36)	<0.01	7.38 (5.30, 9.46)	<0.01
Contrast (vs saline)	-1.15 (-2.51, 0.21)	0.09	-1.15 (-2.61, 0.31)	0.11
Occluded (vs not occluded)	-3.98 (-5.99, -1.96)	<0.01	-4.43 (-6.61, -2.26)	<0.01
Occluded and contrast	0.00 (-0.01, 0.01)	0.51	0.00 (-0.02, 0.01)	0.39
Estradiol 17 β	0.75 (-0.77, 2.28)	0.31	0.95 (-0.57, 2.47)	0.20
Progesterone	-1.41 (-3.38, 0.57)	0.15	-1.49 (-3.77, 0.78)	0.18
Random effects	Variance	SD	Variance	SD
(Intercept)	1.76	1.33	1.44	1.20
Residual	2.08	1.44	2.35	1.53

* Excludes two participants in whom the balloon was expelled during the procedure.

Table 5:
Sensitivity and specificity of measures.

Sensitivity and specificity of intrauterine fluid loss and tolerance to 10mL infusion volume as predictors of bilateral occlusion status.

Fluid	Primary analysis		Sensitivity analysis*	
	Sensitivity	Specificity	Sensitivity	Specificity
Saline loss 4mL	0.80 (0.00, 1.00)	0.90 (0.55, 1.00)	0.88 (0.00, 1.00)	0.90 (0.40, 1.00)
Contrast loss 3mL	1.00	1.00	1.00	1.00
Did not tolerate 10mL contrast	1.00	0.50 (0.23, 0.78)	1.00	0.50 (0.25, 0.78)
Did not tolerate 10mL contrast	1.00	0.50 (0.22, 0.77)	1.00	0.50 (0.23, 0.78)
Saline loss 4mL & did not tolerate 10mL	0.80 (0.57, 1.00)	1.00	0.88 (0.67, 1.00)	1.00
Contrast loss 4mL & did not tolerate 10mL	1.00	1.00	1.00	1.00

Data are presented as AUROC (95% confidence interval).

* Excludes two participants in whom the balloon was expelled during the procedure.