Utility of Three-dimensional Ultrasound (3D-US) for Uterine Septum Diagnosis in Women with Arcuate Uteri Scheduled for IVF: A Threshold Analysis

Running Title: *Threshold analysis for the use of 3D-US after HSG*

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Abstract

Background*:* Septate uterus is the most common anomaly in infertile women. Particularly, distinguishing between different anomalies in women for IVF is critical and should be conducted using a superior modality.

Design*:* A theoretical decision/threshold analysis to assess 3D-US utility after hysterosalpingography (HSG) initial diagnosis of arcuate uterus to identify misdiagnosed/subtle uterine septum. Our hypothesis is whether HSG is adequate to conclude arcuate diagnosis in the IVF population.

Patients and Methods*:* A threshold analysis model was constructed for a hypothetical cohort of 100 infertile women indicated for IVF with primary HSG diagnosis of arcuate uterus to compare two 3D-US screening strategies utilized in daily practice. The first strategy (3D strategy) offers 3D-US as the next confirmatory step for HSG uterine indentation concordant with arcuate uterus diagnosis. The second strategy (NO-3D strategy) is the reference standard that adopts proceeding to IVF without 3D-US. Baseline input probabilities were derived by review of the published literature. ASRM criteria for uterine septum were followed to categorize modeled women. Model endpoints were cumulative costs and LB after three successive IVF cycles.

Results: Base-case analysis revealed that the 3D-US strategy was more cost-effective than the NO-3D strategy. After 3 IVF cycles, 3D-US screening resulted in a cumulative LB of 73.2% with $ 2,203,250 total costs compared to 58.9 % cumulative LB and $ 2,255,000 total costs in the NO-3D strategy.

Conclusions*:* Women for IVF with suspected fundal depression on HSG should be examined in advance by 3D-US to minimize hypothetical financial loss from missed septum diagnosis

Keywords: Threshold analysis; Septate uterus; 3D-US ultrasound; HSG; In-Vitro Fertilization.

Introduction:

Congenital uterine anomalies are common in women with infertility and women with recurrent miscarriages. Canalization defects (septate and sub-septate uterus) are the most common reported anomalies in these women. (1) Furthermore, they are also common in infertile women requiring assisted reproductive techniques (ART). (2)

Different modalities have been proposed to diagnose congenital anomalies. Previous studies reported comparable diagnostic accuracy of MRI and 3D-US in detecting uterine anomalies (3, 4); however, in limited resource areas, the utility of MRI for this purpose will be difficult. Moreover, many clinicians are still dependent on HSG as an informative tool to diagnose congenital uterine anomalies.

Arcuate anomaly is considered a variant of the normal uterus (5, 6), and evidence from basic science research suggests that uterine septum could have a deleterious effect on the implantation process. (7, 8)

The only RCTs published after a long period of recruitment (TRUST trial, The Randomised Uterine Septum Trial) and a retrospective study by the same research group found that septum resection does not improve reproductive outcomes. The obvious limitations of these two studies are the different methods for septum diagnosis and the heterogeneous populations with septum. In contrast, observational studies have reported improved reproductive performance after hysteroscopic metroplasty in women with recurrent miscarriages, unexplained infertility, and planned IVF. (9 -14)

Increasing the complexity in clinical practice, different definitions and classification systems; ASRM 2021, CUME of Ludwin 2018/2019, ASRM 2016, ESHRE/ESGE 2015; have been proposed in the last 10 years to identify septate and arcuate uterus, especially the clinical relevance of each definition to the reproductive outcomes have not been examined well. (15 -17).

Thus, using the optimal modality to identify congenital anomalies in IVF women is necessary to provide the definitive diagnosis of the potentially treatable–anomalies that could affect implantation. We hypothesized that 3D-US could be a superior modality to HSG to differentiate between arcuate and septate uterus in infertile women scheduled for IVF. This hypothesis is tested in a hypothetical threshold analysis.

Patients and Methods:

Model Hypothesis:

A theoretical threshold analysis model was performed to determine whether the implementation of 3D-US after HSG in women with arcuate uterus anomaly before IVF treatment could be cost-effective. Furthermore, it evaluates the threshold of different variables that would make 3D-US cost-effective in this HSG group.

Model Population:

The hypothetical patient population consisted of 100 infertile women indicated for IVF with HSG diagnosis of arcuate uterus.

Benchmarking:

The recent ASRM description of the congenital uterine anomalies 2021 and the diagnostic criteria applied in 3D-US to differentiate between the arcuate, septate, and bicornuate uterus were followed to categorize the modeled women (15-17). For diagnosis of a congenital uterine anomaly, outer and inner uterine fundal contours and the length of the fundal indentation were the key elements of analysis.

The arcuate uterus is diagnosed if the external contour is convex or depressed to less than 10 mm and the internal contour is depressed to less than 10 mm. The septate uterus is diagnosed if the external contour is convex or depressed by less than 10 mm and the internal contour is depressed by 10 mm or more. This recent ASRM 2021 classification addressed the gap caused by

the prior 2016 defining criteria; this gap concerns 1-1.5 cm internal fundal indentations with angles < 90 degrees that were left unclassified by the prior ASRM 2016 classification system.

Model Assumptions:

We assumed that live births improved after resection of internal depressions more than 1 cm, depicting the clinical relevance of ASRM-2021 and CUME-2018. After restoring uterine cavity normality through septum resection, such uteri will behave the same as normal after IVF and the same as the arcuate uteri in terms of live birth.

Model Strategies

The model was constructed to compare two screening strategies based on 3D-US utility. The first strategy (3D strategy) offers 3D-US screening of subtle septum in IVF women with arcuate uterus diagnosis based on initial HSG. The second strategy (NO-3D) is the reference standard that adopted proceeding to IVF without 3D-US screening in a similar cohort (see ***Figure 1: Model Flowchart)*.**

Model Inputs (see Table 1)

- Effect of surgical treatment of septate uterus before IVF therapy on IVF outcome: The probability data of the decision model were obtained from observational studies.
- Live birth rate per transfer cycle in normal IVF population that represents the LB in women with truly arcuate uteri. We used the USA population-based live birth per transfer cycle 2017. for this assumption. (Centers for Disease Control and Prevention. 2017; Assisted Reproductive Technology Fertility Clinic Success Rates Report).
- Prevalence of missed septum in a population of the arcuate uterus: For this probability input, we utilized a probability of 25%, representing an average value between the published prevalence by Moini et al. in 2013 and our assumption (21).
- The following costs were included in their average value. Each cost included both the technical and professional costs for each procedure. We utilized documented costs in the USA. Medicare national fee estimates were utilized for the hysteroscopic septal resection cost input and 3D-US. Average costs in the last years reflect the physician and hospital payments that were used. The lowest reported cost for the IVF cycle among USA IVF registries was also used. (www.verywellfamily.com, www.sart.org, www.asrm.org). Costs were reported in US dollars.

Model Endpoints

The Cumulative Live Birth Rate (LBR) over 3 IVF cycles, costs spent in each strategy, costs per infertile couple, and costs per one live birth (LB). The incremental cost-effectiveness ratio (ICER) was calculated to determine the extra costs required for achieving an additional live birth. Analysis was done using Microsoft Excel 365.

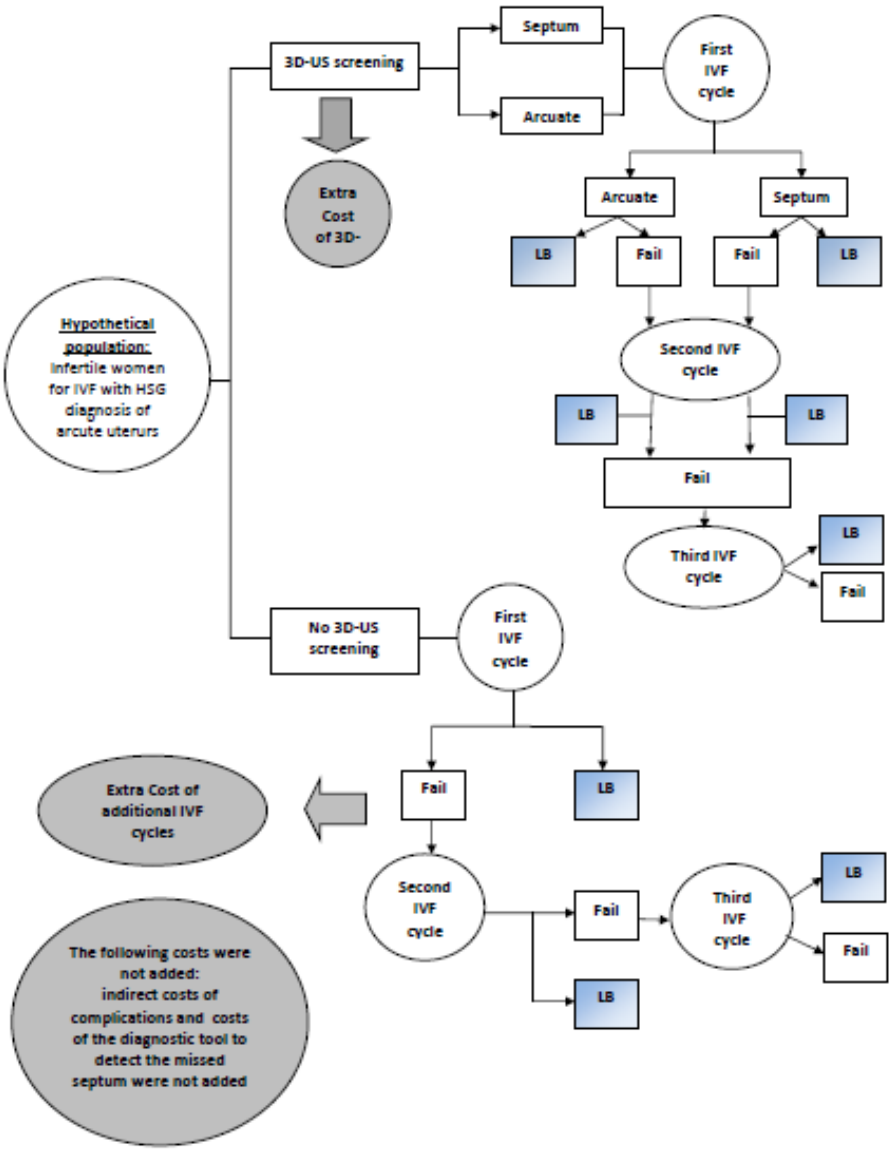

Figure 1: The model flowchart for a timeframe of 3 cycles

Blue boxes were used for the calculation of the cumulative live birth rate, while white boxes were used for calculating costs

LB; live birth, 3D-US; three-dimensional ultrasound, IVF; In-vitro fertilization, HSG; hysterosalpingography.

Results:

Base-case analysis using the average estimates revealed that the 3D-US screening strategy before IVF was more cost-effective than the NO-3D strategy. After 3 IVF cycles, 3D-US screening resulted in a cumulative LB of 73.2 % with $ 2,203,250 total costs compared to 58.9 % cumulative LB and $ 2,255,000 total costs in the NO-3D strategy.

In base-case analysis, 3D-US implementation would cause initial costs of $142,250 for diagnosis of missed septae and their accompanying metroplasty procedure; however, this would yield cost savings of $ 3620 per live birth gained after 3 IVF cycles. The higher the probability of missed septum detection in the arcuate IVF population and the higher the increase in LB after septum resection, the more cost-effective the 3D strategy would be.

Table 1: Model input probabilities

Input probabilities	Out-of-favor of screening	In-favor- of screening	Base-Case	Reference
Cost of IVF	11000	9000	10000	www.verywellfamily.com, www.sart.org, www.asrm.org
Cost of Hysteroscopic Metroplasty	4500	4400	4450	Medicare Reimbursement for Hysteroscopy Procedures (CPT code: 58560).
Cost of 3D-US	350	250	**300**	Medicare Reimbursement Information for Diagnostic Ultrasound Procedures.
% Of missed septum	**5**	49	**25**	References: (21), (24)
% LBR in Resected long indentation > 1.5 cm	**24**	**47**	**35.5**	LBR in normal women per transfer in women <35 and 35-37 years: Centers for Disease Control and Prevention. 2017 Assisted Reproductive Technology Fertility Clinic Success Rates Report. Atlanta (GA): US Dept of Health and Human Services; 2019.
% LBR in Resected short indentation 1 – 1.5 and naturally arcuate uterus	**28**	**47**		
% LBR in Unresected long indentation	**8**	**2**	**5.5**	References: (11), (12), (28), (29), (30), (31)
% LBR in Unresected short indentation	**8**	**3**		

Table 2: The results of the base-case analysis:

Hypothetical cohort of 100 women	3D-US screening strategy	No 3D-US screening strategy
Total costs per strategy	$2,203,250	$2,255,000
Cumulative LBR	73.2%	58.9%
Cost per LB	$30,178	$38,220

Discussion

An optimal diagnostic test for congenital uterine anomalies has been defined as a test that can accurately visualize the external and internal uterine contours. (1)

Wu et al., who evaluated 40 women with suspected uterine anomalies, reported 100% accuracy in detecting anomalies by 3D-US. (18) A similar perfect accuracy was concluded by Bocca et al. when they evaluated 101 infertile women by 3D-US. (19,20). Moini et al. reported that HSG identified only 43 (35.8%) cases correctly and misdiagnosed 16 (13.3%) as arcuate and 36 (30%) as normal. (21). Comparable results for the suboptimal performance of HSG in identifying arcuate, septate, and bicornuate uterus were reported by many investigators. (22, 23)

Studies evaluating the uterine cavity of women with recurrent implantation failure reported subtle septae in 1 - 5% of cases. (24, 25). In one study, all subtle septae appeared as arcuate uteri on previous HSG performed before the first IVF trial. (24)

This raises the question of what an optimal diagnostic test is for a conclusion of an arcuate uterus that behaves benignly from an implantation perspective. (5) Even with the use of MRI, the authors of a recent study found difficulty differentiating between the arcuate uterus and septate uterus, especially when the detected septae were short with a broad base. (3) A similar difficulty was observed for office hysteroscopy; a poor inter-observer agreement was reported among 78 international experts for the differentiation between the arcuate and septate uterus and the need for resection before IVF. (26),(27)

In contrast to the TRUST trial (14), data from observational studies showed improved clinical pregnancy and live birth rates in IVF women after hysteroscopic metroplasty of both small and large septae compared to non-operated women. (11, 12, 28). Tomosevic et al. (12), in their retrospective cross-matched study, found higher clinical pregnancy (32.5 vs. 9.6) and live birth rates (24.4 vs. 1.9) in women who underwent metroplasty compared to those who did not undergo resection of the septum (odds ratio [OR] 2.507, 95% CI 1.539-4.111, 250 P<0.001). A similar trend was observed when they included 13-15 mm fundal indentations as a cutoff point to define a small partial septum (11). Makrakis et al. also found an 84.6 % clinical pregnancy rate in a new IVF cycle after metroplasty for women with recurrent implantation failure and missed septae (24). The recent meta-analysis's conclusion also concurs with this (31). The key limitation of these observations is that they are derived from before-after design studies.

These prior observations triggered the authors to conduct this hypothetical threshold analysis in a simple format, especially in the lack of well-designed randomized controlled trials. The model concluded that 3D-US implementation before IVF in women with fundal depression on HSG could minimize the financial burden that an infertile couple would suffer from a failed cycle due to a missed septum.

This model has key limitations; first, the analysis does not include the indirect costs of IVF and hysteroscopy complications. Second, a dearth of literature tackled the issue of missed septum diagnosis by HSG, rendering the range of our model wide. Third, we followed USA cost and LB registries, although Middle East authors constructed this model due to a lack of documented Middle East registries in this context. Finally, the natural unexplained decline in LB with subsequent cycles is not included as input for resected and unresected uteri.

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