Is uterine depth measurement by trans-vaginal ultrasound alone as accurate as measurement carried out by trans-abdominal ultrasound-guided trial transfer?

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ABSTRACT

الأهداف: تقييم الاعتماد على فحص عبر المهبل (TVS) في قياس عمق الرحم (UD) بالمقارنة مع تجربة نقل الموجات فوق الصوتية الموجهة (UTT).

الطريقة: أجريت دراسة شاهد استطلاعية اشتملت على 66 مريضه متابع أجري لهن إخصاب في الأنبوب (IVF) ونقل الجنين ET لمدة 3 أشهر خلال الفترة من نوفمبر 2013م حتى 2014م في مركز خاص للإخصاب، المملكة العربية السعودية. خضع المرضى لقياسUD باستخدام TVS وUTT بشكل متتابع. أجريت الفحوصات مخطط واحد للصدى التشخيصي الطبي وأجريت UTT عن طريق طبيب واحد يجهل قياسات TVS.

النتائج: أظهرت النتائج أن متوسط (95% فترة الثقة) قياس UD باستخدام طريقة TVS وUTT كان 6.9 سم (12.5–5) و 7.1 سم (5.9-13.5), (p<0.0001). 15 مريض (22.7%) كان الاختلاف أكثر من 1 سم بين نمط القياسات المختلفة (المجموعة ب). وبالمقارنة مع المرضى الاختلافات أقل من أو يساوي 1 (المجموعة أ) 93.3% من المرضى في المجموعة ب و 9.8% من المرضى في المجموعة أ يبلغ عمق الرحم لديهم أكثر من أو يساوي 8 سم عند قياسهم باستخدام UTT القيمة الإحصائية (p<0.0001). كان تجويف الرحم أعلى بشكل إحصائي عند المجموعة ب عند قياس باستخدام UTT (p<0.0001) واتجاه للقيمة الإحصائية عندما قيس باستخدام TVS (p=0.055). وبشكل عام قياسات TVS خفضت قيم UD بالمقارنة مع UTT.

الخاتمة: أن TVS أقل ثقة من UTT ولا يمكن استخدامه كبديل. نحن بحاجة إلى دراسات بعينات أكثر تشمل على أدوات وأفراد مختلفة.

Objectives: To assess the reliability of trans-vaginal-scan (TVS) in measuring the uterine depth (UD) in comparison with ultrasound-guided trial-transfer (UTT).

Methods: This prospective study was conducted in 66 consecutive patients undergoing in-vitro fertilization and embryo transfer (IVF-ET). The study took place in a private IVF center in Jeddah, Saudi Arabia between November 2013 and January 2014. The patients underwent UD measurements using TVS and UTT, sequentially. All scans were performed by a single sonographer, and all UTT were carried out by a single physician who was blinded to the TVS measurement.

Results: The median (95% confidence interval) UD measurement using the TVS method was 6.9 cm (5.0-12.5) and UTT was 7.1 cm (5.9-13.5), (p<0.0001). Fifteen patients (22.7%) had a difference of >1 cm between the 2 measurement modalities (group-B). When measured by UTT, 93.3% of patients in group-B had UD ≥8cm, compared with 9.8% of patients in group-A, (p<0.0001). Group-B had a significantly longer uterine cavity when measured by UTT (p<0.0001), and a trend towards significance when measured by TVS (p=0.055). The TVS measurements generally underestimated UD when compared with UTT.

Conclusion: Trans-vaginal-scan is less reliable than UTT and should not be used as a substitute. Larger sample-size studies involving different personnel, and equipment is needed.

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There are many factors influencing the overall *in-vitro* fertilization and embryo transfer (IVF-ET) success rate including, but was not limited to patient's age, embryo(s) quality, endometrial receptivity, and other.[1] Placing the embryo(s) at the "right" location within the uterine cavity has been shown to be an important factor that can affect the IVF success rate.[2-4] It has been reported that depositing embryo(s) at 1.5-2 cm away from the uterine fundus, significantly increases the pregnancy rate (PR).[5-8] Historically, ET has been performed blindly without ultrasound (U/S) guidance. However, since multiple studies and meta-analyses have shown a significant improvement of PR when ET was carried out under U/S guidance, most IVF centers are currently using ultrasonic guided ET (UG-ET).[9,10] To measure the uterine depth (UD) accurately, trans-abdominal ultrasound-guided trial transfer (UTT) has been used and was claimed to be the best practice or more accurate method when compared with blind trial transfer (BTT).[11,12] Ultrasound-guided trial transfer did not serve only those clinicians using the blind ET technique, but also helped those using UG-ET, in knowing the actual UD measurement ahead of time, and helped clinicians to decide where to place the "stopper" of the outer ET catheter before they started the ET procedure. It also helped them in deciding where to place the embryo(s) when visualization of the catheter tip by U/S was technically difficult on the day of ET, as in patients with high body mass index (BMI), or those patients with an empty bladder on the day of ET. Though considered a good practice, measurement by UTT entails several disadvantages. These include invasiveness of the procedure, possible risk of infection, endometrial trauma, and patient discomfort. Since trans-vaginal U/S (TVS) measurement lack the potential risks associated with UTT, we compared the reliability of TVS to UTT, in assessing the UD.

Methods. All patients undergoing IVF treatment under the care of a single clinician in a private IVF center in Jeddah, Saudi Arabia between November 2013 and January 2014 were prospectively enrolled in this pilot study. Ethical approval for the study protocol was obtained from the Research Ethical Committee, Umm Al-Qura University. There were no exclusion criteria, as all patients undergoing IVF need UD measurement. All patients underwent UD measurements using both modalities (TVS and UTT techniques). The TVS measurement was performed by a single sonographer using the same U/S machine (Philips iU22, Philips Medical Systems, Bothell, WA, USA). The UTT measurement was performed by a single clinician, using the same catheter (Sperm Trans IUI Catheter, Sperm Processor Pvt. Ltd., Aurangabad, India). A total of 66 patients were recruited for this study. The TVS measurement were recorded before the UTT measurements with patients in the dorsal lithotomy position in stirrups, a 3.5 MHz trans-vaginal probe was used to assess the UD measurement in centimeters. A sagittal plane of the uterus was obtained in which the endometrial lining was visualized from the fundus to the external cervical os. Multiple consecutive cursors were used to measure the UD along the line of the endometrial lining, starting from the highest point of the endometrial cavity all the way to the cervical external os. Most measurements were obtained from a single frame by applying less pressure with the probe (**Figure 1**).

If the whole uterus could not be seen within one frame, the remaining part of the endometrial lining was measured in a second frame, and then the sum of both measurements was calculated and recorded. Care was taken to ensure measuring only the part of the endometrial lining that was not included in the first frame. To do so, the sonographer assessed the uterus as whole in "live" mode, before the picture was "frozen" and the upper part of the endometrial lining was measured. After "unfreezing" the picture, the sonographer made sure that the uterus was still within the same sonographic position as it was before the picture was frozen. The probe was then moved slowly to ensure measuring only the remaining part of the endometrial cavity (**Figure 2**).

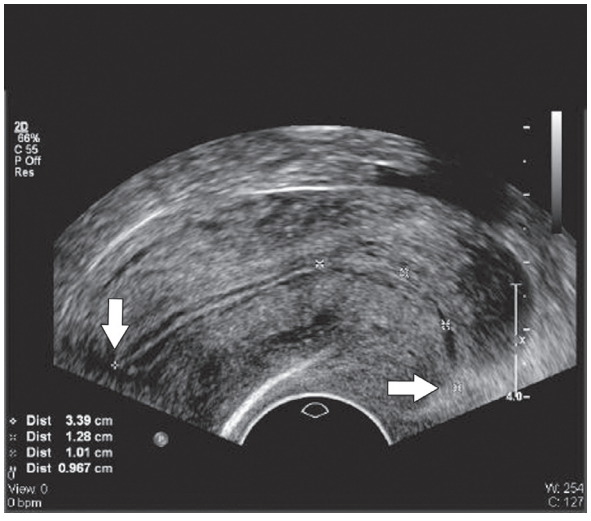

Figure 1 - Trans-vaginal scan measurement of the uterine depth in a single-frame format. The uterine depth measurement was carried out by summing multiple smaller measurements extending from the upper end of the endometrial cavity to the external cervical os.

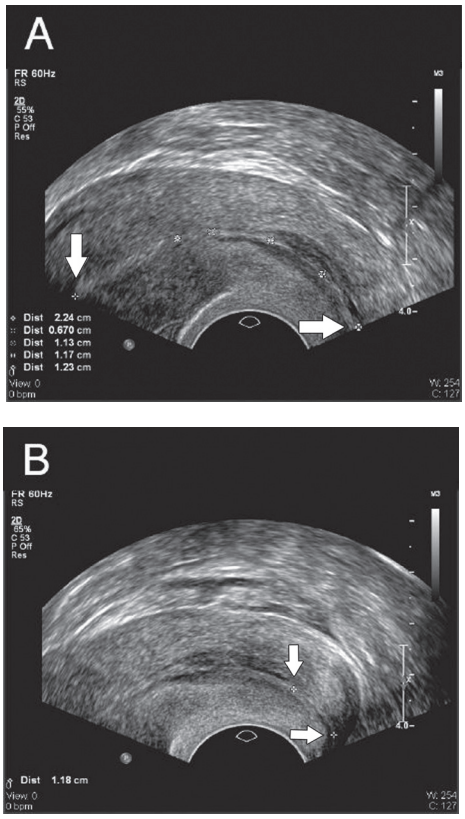

Figure 2 - Trans-vaginal scan measurement of the uterine depth in a 2-frame format. The uterine depth measurement was carried out by summing multiple smaller measurements extending from the upper end of the endometrial cavity to the lowest part of the endometrial cavity that can be seen in frame A) and adding this to the measurement of the endometrial cavity obtained in frame B), which extends from the lowest part of the cavity seen in frame A to the external cervical os

The clinician performing the UTT was then allowed into the room, and was kept blinded to the measurement carried out by the sonographer. In the same dorsal lithotomy position, a bivalve speculum was used to visualize the cervix. A soft distal-end catheter was used to navigate the cervical canal into the uterine cavity until its tip reached and touched only the uterine fundus. This was carried out under U/S guidance, with the aid of the same sonographer, using a 3.5 MHz trans-abdominal probe, and the same U/S machine. Once the uterine fundus was reached, a sponge forceps was used to grasp and mark the catheter just at the level of the external cervical os. The catheter was then gently pulled out, and the part that was inside the uterine cavity (from the sponge forceps mark to the tip of the catheter) was measured and recorded by the same clinician, using a paper measuring tape.

All measurements were carried out on cycle day 2, 3, or 4 in the month preceding the ovarian stimulation cycle. This was the same day when antral follicle count (AFC) was carried out. Since our usual practice was to carry out UTT measurement for all patients undergoing IVF treatment on the same day at which AFC calculation was carried out by TVS, no special consent to measure the UD using TVS was required. Both TVS and UTT measurements were tested for normality using Kolmogorov-Smirnov test. Because the data was not normally distributed, we compared median measurements using the non-parametric Wilcoxcon signed rank test. Chi-Square was used for categorical variables. Statistical significance was considered at $p<0.05$.

Results. Sixty-six patients were included in this study. The median (and 95% confidence interval) UD measurement using TVS method was 6.9 cm (5.0-12.5) and UTT was 7 cm (5.9-13.5). A statistically significant difference between the 2 modalities of UD measurements was found ($p<0.0001$). When uterine depth measurements using TVS was performed, 57/66 patients, had their measurements carried out in a single frame, while 9 patients had their measurements carried out by 2 frames. After excluding the latter 9 patients, the median (and 95% confidence interval) UD measurement using TVS method was 6.7 cm (5.0-7.9) and UTT was 7 cm (5.9-9.5). The difference in measurements between the 2 modalities remained to be statistically significant ($p=0.003$).

Out of the 66 patients, 15 (22.7%) had a difference of >1 cm between the 2 measurement modalities (group B). Compared to patients with a difference of ≤1 cm between the 2 measurement modalities (group A), 93.3% of patients in group B (n=14/15) and only 9.8% of patients in group A (n=5/51) had a UD of ≥8 cm, when measured by UTT. A Chi-square test confirmed statistical significance ($p<0.0001$). Between groups A and B, group B had a significantly longer uterine cavity when measured by UTT, and a trend towards a statistically significant longer uterine cavity when measured by TVS (**Table 1**). By excluding patients who had their UD measurement performed by 2 frames while using TVS (n=9), the percentage of patients that had a difference of >1 cm between the 2 measurement modalities (group B) was 21% (n=12/57), which is comparable to the percentage, when all patients were included. The TVS measurements generally underestimated UD when compared with UTT. Out of

Table 1 - Comparison of UD measurements between group B (difference >1cm) and group A (difference ≤1cm), using TVS and UTT.

UD (cm)	Group B*	Group A*	*P*-value
TVS	7 (6.8 - 8)	6.7 (6.5 - 7.2)	0.055
UTT	8.5 (8.2 - 9.2)	7 (6.8 - 7.5)	<0.0001

*Median and 95% confidence interval, UD - uterine depth, TVS - trans-vaginal ultrasound, UTT - ultrasound-guided trial transfer

the 66 patients, 55 (83.3%) had UD that is shorter on TVS compared with UTT. The same was true when we looked at group B alone, as out of the 15 patients in this group, 14 (93.3%) had UD shorter on TVS compared with UTT.

Discussion. Although it would have been of great clinical importance to find no significant difference between the 2 modalities of UD measurements; in order to justify the replacement of the invasive UTT measurement with the non-invasive TVS measurement, our study did not show such equivalence. The UTT measurement has always been the gold standard method to measure UD for patients undergoing IVF treatment after publications from Pope et al[6] and Shamonki et al.[11,12] Although this is an invasive technique, it has several advantages, one of which is the prediction of potential technical difficulties that may occur during ET. If a technical difficulty was encountered during UTT measurement that was carried out before the start of ovarian stimulation, whether this was due to the position or orientation of the uterus, or stenosis of the internal cervical os for example; one may consider performing an UTT before conducting ET, by placing the outer ET catheter within the endometrial cavity before loading the embryo(s) into the inner ET catheter. This maneuver will minimize the exposure time of the embryo(s) to the out-of-incubator environment; before placing them successfully within the endometrial cavity, which has been shown to affect embryo quality and blastulation rate.[13] Although our study agrees with the general conclusion of Pope et al[6] and Shamonki et al[11,12] that UTT should be the gold standard technique to measure UD, there are major differences between our study and those previous studies. Pope et al[6] performed a retrospective study in which they compared "blind" trial ET (MOCK transfer) performed one month prior to UG-ET, and they found that UD measurement by abdominal U/S differed from UD by MOCK transfer, by at least 1 cm in >30% of cases.[6] They used a Tomcat catheter for the "blind" MOCK transfer, which is a tapered catheter (thinner at the tip and gradually widens towards its base), and they argued that the wider base may have stuck at the external cervical os giving a "false" impression of resistance before reaching the uterine fundus; thus, underestimating the cavity length of a "longer" uterus, especially since the MOCK transfer was carried out "blindly" (not under U/S guidance). Additionally, those catheters are semi-rigid compared to the actual ET catheters (soft catheters), and this may also lead to UD underestimation, if the semi-rigid tip of the MOCK catheter was impacted against any part of the uterine cavity along its length, especially in a uterus that does not have a uniform axis. They also argued that UD measurement may differ before and after ovarian stimulation, as some researchers demonstrated a positive correlation between estradiol exposure and uterine size.[14,15]

This study is a prospective one, in which we measured UD by TVS and UTT sequentially on the same day. Although this should eliminate the potential effect of the "blindness" nature of their MOCK transfer, and also the potential effect of estradiol on UD, we found a significant difference in UD measurements between TVS and UTT. Furthermore, we found the difference to be more common in "longer" uterae; as Pope et al[6] noted; however, a difference of ≥1 cm between the 2 UD measurement modalities was found in ≈23% of our cases compared with 30% of their cases. This may or may not be significantly different, but it suggests that TVS is more accurate than blind MOCK; however, this can also be explained by the fact that all our UTT were carried out by a single doctor, while their MOCK transfers were carried out by multiple practitioners. We used a uniform catheter width (not tapered) that also has a semi-soft distal part that eliminate the potential effect of the tapered and the semi-rigid nature of the MOCK catheter used in Pope et al's[6] study; however, the type and characteristics of the catheter we used in our study had no effect on our outcome, since all our measurements were carried out by U/S or under U/S guidance.

Shamonki et al's[11] initial study had a different objective. They wanted to assess the importance of UG-ET; therefore, they measured the UD using a "blind" MOCK transfer 1-6 months prior to the ovarian stimulation cycle and again on the day of ET using UTT. They used a tapered semi-rigid catheter (Cook Obs/Gyn, Spencer, IN, USA), and found a difference of ≥1 cm between the "blind" MOCK measurement and measurement obtained by UTT in approximately 30% of their cases. This difference was also more common in patients with longer uterae. They used the same

arguments of the potential effect of the semi-rigid and the tapered nature of catheter that was used for their "blind" MOCK transfer, and the potential effect of estrogen on changing the uterine size. They concluded that UG-ET maybe beneficial for some patients; however, they suggested the need for larger randomized studies before they confirm if UG-ET should be used for all patients.[11]

In their following study, Shamonki et al[11] wanted to assess if UTT is more accurate than "blind" MOCK, in order to determine if UTT carried out prior to starting the ovarian stimulation cycle, can be utilized as an alternative to UG-ET. In other words, they wanted to determine the characteristics of patients that can lead to inaccurate "blind" MOCK transfer. In a prospective manner, all patients in their study had a "blind" MOCK transfer by a single physician (compared to multiple physicians in their first study) a month or more, prior to ovarian stimulation and after the physician performing the MOCK transfer believed he reached the uterine fundus, another physician did an abdominal U/S and measured the distance (if any) from the top of the uterine cavity to the tip of the catheter and labeled this as the difference in length (DL). They found a DL of ≥1 cm in ≈14% of their patients. Again, the same semi-rigid tapered catheter (Cook Obs/Gyn, Spencer, IN, USA) was used.[12]

The variations from our study were noticeable; however, the percentages of patients who had ≥1 cm difference in UD measurement were both lower than Shamonki et al's[11] first study (23% in our study, 14% in Shamonki et al's[12] second study, 30% in Shamonki et al's[11] first study). This can be explained by the fact that in our study as well as Shamonki et al's[12] second study, a single physician was involved, compared with multiple physicians in Shamonki et al's[11] first study.

Despite the presence of a statistically significant difference between the 2 modalities used in our study for UD measurement, one may argue that 0.25 cm difference of the median may not be clinically significant, especially knowing that the best location for ET has ranged in different studies from 1.5-2 cm from the uterine fundus.[5-8] Additionally, some researchers[16,17] have demonstrated that the best location for ET is the center of the uterine cavity, and that the relative site of embryo deposition is more important than the actual distance from the fundus.[16,17]

Repeating our study with a larger sample size, or involving different personnel and/or equipment, may lead to a clinically significant difference (≥0.5cm). Someone may logically argue that measuring UD by TVS in 2 frames (as is the case for larger uterae) may not be as accurate as measuring it in one frame (as is the case for small and average size uterae), and this could have led to our finding of a significant difference between the 2 modalities of UD measurement under investigation (TVS and TTC); however, the difference remained significant even after excluding patients who had their UD measurement carried out by 2 frames. Additionally, TVS tended to underestimate UD measurement in most cases, whether they had larger uterae or not.

Study limitations. The present study has limitations including the small sample size; however, one of its greatest strengths is that all TVS were performed by the same sonographer using the same U/S machine, and that all UTT measurements were carried out by the same clinician using the same catheter. This should eliminate the potential effect of inter-observer variation and variability from the use of different equipment. Another strength of our study is the fact that the clinician performing the UTT was blinded to the measurements obtained by the sonographer; however, it is important to note that we only looked at a surrogate outcome (UD measurement) and not the actual important outcome; pregnancy rate (PR).

Larger sample-size studies involving different personnel and equipment are needed before we can draw a rigid conclusion from our study. Looking at the most important outcome (PR) is also important, before adopting the outcome of this study into clinical practice.

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Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.