Sir,

In the recent article by Lo et al. (2008) the authors used 2D transvaginal ultrasound to compare the thickness of the endometrial lining (at all stages of the menstrual cycle) between patients with and without Asherman’s syndrome. The subgroups of Asherman’s patients that they focused on were those with adhesions limited to the lower uterine cavity or upper cervix whereas the upper endometrium remained normal (Lo et al., 2008). In addition, they also looked to identify the presence or absence of hematometra in the above patients. Their results demonstrated a significant difference in endometrial thickness (3.9 ± 0.4 mm), as well as a lack of hematometra for this subgroup of Asherman’s patients. They conclude that a lack of cyclical endometrial growth and breakdown occurs even in the patient with supposedly normal upper endometrium and adhesions limited to the lower uterine cavity and upper cervix (Lo et al., 2008) and that ‘normal’ endometrial growth can be effectively ‘turned off’ by the presence of a thin but dense band of adhesions limited to the uterine outflow tract.

Although the authors present theories to explain this finding, the data and resultant conclusions are perplexing. Why should normal endometrium be inhibited by the presence of outflow tract adhesions? Alternatively, we propose that the 2D ultrasound methodology used to evaluate the endometrium and grade the degree of Asherman’s was instead limited in its ability to accurately identify the extent of intrauterine adhesions. In fact, it is possible that the patients whose disease was thought to be limited to the lower uterine segment without involvement of the endometrium, in fact, had disease that extended to the upper endometrium thereby explaining the above results. This is consistent with other studies that have not shown 2D ultrasound to be an accurate tool to assess the extent of intrauterine adhesions (Shalev et al., 2000; Soares et al., 2000). Although the authors state that all patients later went on to have a hysteroscopy, it is not clear if the grade of Asherman’s assigned by transvaginal ultrasound was confirmed on hysteroscopy.

We suggest that routine usage of interactive 3D ultrasound in these patients would allow, through multiplanar reformating, for a more accurate assessment of the uterine cavity while improving diagnostic and prognostic capabilities. The derived images produced by 3D ultrasound are more consistent with the location and extent of lesions the percent of cavity obstructed; correlating more closely with grade of disease.

In a recent study, we evaluated the ability of 3D ultrasound to not only identify the presence of adhesions but also to correctly classify the severity of disease, with respect to percentage of cavity obstructed and lower tract obstruction (Knopman and Copperman, 2007). We demonstrated that 3D ultrasound had higher sensitivity than HSG in correctly assessing the grade of cavity adhesion and differentiating lower tract obstruction from severe cavity disease. We suggest that 3D ultrasound provides a more accurate depiction of the adhesions and extent of cavity damage than other diagnostic modalities (HSG, 2D TVUS) in patients with Asherman’s syndrome, particularly when differentiating severe intrauterine adhesions from lower uterine segment outflow obstruction. As prognosis in Asherman’s patients is based on severity of disease, we propose that 3D ultrasound more accurately assess prognosis.

In addition, as data obtained from the 3D ultrasound correlate more closely with the character and extent of disease, it could be a helpful tool in predicting fertility outcome postoperatively (Knopman and Copperman, 2007). Therefore, although the notion that a normal endometrium can be inhibited by the presence of adjacent adhesions in the uterine outflow tract is intriguing, one must wonder if the authors under-diagnosed the extent of disease as a result of their limited screening modality (2D TVUS) thereby affecting the validity of their results.

References


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Reply: Endometrial thickness measured by ultrasound scan in women with uterine outlet occlusion due to intrauterine or upper cervical adhesions

Sir,

We were interested to read the letter from Drs Knopman and Copperman questioning the ultrasound technique used for
assessing patients in our publication on endometrial thickness in women with Asherman’s syndrome.

We agree that the finding of very thin endometrium in women with upper cervical occlusion is intriguing, but it does appear to be a genuine phenomenon since the same observation has been made by others. Our contribution was to measure endometrial thickness using ultrasound, not assess the ultrasound-determined extent of adhesions, in a carefully assessed group of Asherman’s syndrome patients for the first time.

We agree that the ultrasound methodology for assessment of the extent of intrauterine adhesions may not have been ideal by modern standards, but our transvaginal ultrasound data have been collected over nearly two decades, albeit using the same 2D technique. Like Drs Knopman and Copperman, we now use 3D ultrasound for this assessment. Nevertheless, sonographic imaging was not our sole criterion for the classification of patients into different groupings, including the group in which we were mainly interested, the women who solely had uterine outlet occlusion at the level of the internal os (without any intra-cavitary adhesions). These gradings were determined by careful diagnostic hysteroscopy in all cases (as noted in our publication). Hence, we can refute the statement by Drs Knopman and Copperman that ‘one must wonder if the authors under-diagnosed the extent of disease as a result of their limited screening modality (2D TVUS), thereby affecting the validity of their results’.

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Sperm chromatin structure assay parameters measured after density gradient centrifugation are not predictive of the outcome of ART

Sir,

We read with great interest the article recently published by Bungum et al., in Human Reproduction (Bungum et al., 2008) entitled, ‘Sperm chromatin structure assay parameters measured after density gradient centrifugation are not predictive of the outcome of ART’.

Two years ago I, Alvarez, published a letter to the editor in this journal commenting on the predictive value of the SCSA test in ART. In that article, I pointed out that DNA damage in sperm can affect both mitochondrial and nuclear DNA and that it can be induced by six main mechanisms: (i) apoptosis during the process of spermiogenesis; (ii) DNA strand breaks produced during the remodelling of sperm chromatin during the process of spermiogenesis; (iii) post-testicular DNA fragmentation induced mainly by oxygen radicals, including the hydroxyl radical and nitric oxide, during sperm transport through the seminiferous tubules and epididymis; (iv) DNA fragmentation induced by endogenous endonucleases; (v) DNA damage induced by radio and chemotherapy and (vi) damage induced by environmental toxicants. Of these six mechanisms, the one that appears to play a major role in causing sperm DNA fragmentation is post-testicular damage during sperm transport through the epididymis. This is supported by previous reports that demonstrate that DNA fragmentation is higher in epididymal and ejaculated (Oller et al., 2001; Greco et al., 2005) compared with testicular spermatozoa. More recent reports have confirmed this hypothesis (Suganuma et al., 2005).

In that letter, I also pointed out that, to a first approximation, two types of DNA fragmentation tests can be considered: (i) tests that measure ‘real’ DNA damage, such as TUNEL, ISNT or COMET under neutral pH conditions (n-COMET); and (ii) tests that measure ‘potential’ DNA damage and susceptibility to DNA denaturation, such as the SCSA, DBD-FISH, SCD, Chromomycin A3 or COMET under denaturing conditions. Tests that measure real DNA damage should have a higher predictive value than tests that measure potential DNA damage.

The main question that arises from the report by Bungum et al. is why DNA fragmentation levels in the pellet of the gradient, as measured by the SCSA test, are not predictive of pregnancy outcome, if these are the actual sperm used in ART? One explanation could be that the actual DNA damage that interferes with embryo implantation and/or the development of a viable pregnancy is related to a DNA property that the SCSA test does not measure. As pointed out above, the SCSA test measures ‘susceptibility’ to DNA denaturation. But, in fact, even DNA fragmentation values in neat semen are not predictive of pregnancy outcome after IVF or ICSI according to the present report by Bungum et al. In contrast, the results reported by Borini et al. (2006) and by Duran et al. (2002), cited by Bungum et al. in the present article under discussion, provide strong evidence for the predictive value of DNA fragmentation values in ART in sperm from the gradient pellet, as measured by the TUNEL test. This is even more significant in the report by Duran et al., where the predictive value of TUNEL was applied to IUI cycles, where a limited number of oocytes are available compared with IVF. That is, while in IVF the probability that a mature oocyte be fertilized by a spermatozoon with intact DNA or that a spermatozoon with damaged DNA fertilize an oocyte with a high DNA repair capacity is relatively high, given the high number of oocytes usually obtained after oocyte retrieval, this probability is much lower in IUI where usually 1 to 2 oocytes are available. But, why may TUNEL test values in the gradient pellet be predictive of pregnancy outcome and not SCSA’s? One of the main modes of post-testicular sperm DNA damage is most likely that induced by oxidative stress via the hydroxyl radical resulting in the formation of 8-OH-guanine and 8-OH-2’-deoxyguanosine (8-OHdG) in a first stage followed by double-stranded DNA