

Review Article

Access this article online	
Quick Response Code:	Website: www.annalsafmed.org
	DOI: 10.4103/1596-3519.91006

On the safety of diagnostic ultrasound in pregnancy: Have we handled the available data correctly?

Shaibu O. Bello^{1,2}, Bissallah A. Ekele³

¹Obstetrics and Gynecology Unit, Karaye Hospital, Sokoto, ²Department of Pharmacology and Toxicology, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, ³Department of Obstetrics and Gynecology, College of Health Sciences, University of Abuja, Abuja, Nigeria

Correspondence to: Dr. Shaibu Oricha Bello, P.O. Box 1522, Sokoto, Nigeria. E-mail: bellooricha@yahoo.com

Abstract

Robust evidence of the bioeffects of ultrasound is available from animal studies but human studies are less convincing. Nevertheless, it is disturbing that the only response to safety issues is a twenty-year old principle known as ALARA (As Low As Reasonably Applicable). Using experience from obstetrics and toxicology, and drawing information mainly from two recent systematic reviews and meta-analysis that extensively covered the subject of ultrasound safety, this review captures the current knowledge of ultrasound bioeffects and suggests that it may be time for an international, multidisciplinary meeting on ultrasound safety to decide how to provide the evidence (available data) to patients and sonographers in a succinct manner.

Keywords: Bioeffects, diagnostic ultrasound, fetal exposure, safety, toxicity

Résumé

Preuve robuste de la bioeffects des ultrasons est disponible à partir d'études animales, mais des études sont moins convaincante. Néanmoins, il est inquiétant que la seule réponse à des questions de sécurité est un principe de vingt - an, appelé ALARA (comme faible comme raisonnablement applicables). À l'aide de l'expérience de l'obstétrique et la toxicologie et de tirer des informations principalement de deux récents examens systématiques et méta-analyse qui couvrait largement le sujet de la sécurité de l'échographie, cette revue capte les connaissances actuelles de l'échographie bioeffects et suggère qu'il peut être temps pour une réunion internationale et multidisciplinaire sur la sécurité des ultrasons de décider comment fournir la preuve (données disponibles) pour les patients et les échographistes de manière succincte.

Mots clés: Bioeffects, échographie diagnostique, exposition du fœtus, sécurité, toxicité

Introduction

In 1955, Ian Donald borrowed an ultrasound equipment to compare the echo patterns of solid tumor versus a lump of normal flesh (steak *ex vivo*) and ended what may be described as the dark ages of medicine.^[1] Over the next 5 decades, ultrasound rapidly developed through the Amplitude-mode

(A-mode), Brightness-mode (B-mode), Grey-scale, and then Colored- mode imaging. In 2011, not only can we visualize living tissues, we can also display them in various colors and flow patterns in real time. The great news is that, it appears, we get away with doing all these with little consequences. However, it may be premature to celebrate ultrasound as a magic bullet of imaging yet because it took 65 years for us to fully realize the dangers of X-ray

irradiation of fetuses.^[2] It also took over 30 years before the discovery of the association between clear cell carcinoma of the vagina in girls and young women who had been exposed to diethyl stilboesterol in-utero.^[3] It is just over 54 years since Ian Donald's experiment and less than 30 years since the widespread and routine diagnostic ultrasound became available. The caution is that the history of medical innovations is replete with what was initially considered harmless turning out to be harmful either because we did not think to test for a particular adverse effect earlier on, or we got them in too many pieces to appreciate the big picture.^[4,5]

Bioeffects of ultrasound

Intuitively, we expect that there will be prices to pay for interrogation of living tissue with high frequency sound waves and, indeed, we have ample evidence of the toxic effects of ultrasound. Bioeffects of ultrasound have been demonstrated *in vitro* and in non-human subjects. Houston *et al.*,^[4] recently presented an excellent review on this topic. Ultrasound has been shown to influence chondrogenic differentiation of mesenchymal stem cells,^[6] enhance hemolysis^[7] and reduce the threshold for membrane damage of phagocytes.^[8] Rao *et al.*,^[9] exposed mice at various gestational ages to diagnostic level ultrasound and showed significant low birth weight although in an earlier study, Brown *et al.*,^[10] demonstrated that exposure of pregnant mice to Doppler and B-mode ultrasound with much higher exposure levels caused only small and transient reduction in weight at 3 weeks with no significant difference at 6 weeks. These different conclusions may suggest that the bioeffects of ultrasound are not linear. Ultrasound-induced lung hemorrhage (UILH) has been consistently demonstrated across four species – rats, mouse, rabbits and pigs, using the same methodology.^[11] More importantly, the threshold of all UILH was within the range of diagnostic ultrasound and the mechanism of injury appeared to be specie and age independent; which increases the transposability of these findings to human fetuses. The possibility of a substantial temperature rise in the brain of fetuses when insonated in utero with diagnostic pulsed ultrasound have been demonstrated in guinea pigs, sheep, and human fetuses,^[12] thus, again, demonstrating specie independent bioeffect.

In human subjects, several studies have shown an association between in utero insonation of fetuses and delayed speech, dyslexia and non-right-handedness.^[13] These are suggestive of at least subtle neurological effects and are consistent with the results of animal studies described above. A well

designed randomized controlled trial by Newman *et al.*,^[14] revealed a strong association of low birth weight with in utero insonation, also suggesting that animal findings may indeed be extrapolated to humans. Furthermore, the effect on birth weight appears to be stronger after four or more exposures,^[15] suggesting sensitivity to cumulative dosing and dose dependency.

How safe is diagnostic ultrasound in human: Point and counterpoint

The criticism has been that most of the animal studies used machines with higher output in comparison to that used in routine diagnostic equipment and that it is questionable if result of studies in animals can be directly transposed to humans. Furthermore, the recent meta-analysis by Torloni *et al.*,^[16] summarized most of the available data on the safety of ultrasound in humans and concluded that given the available evidence, fetal exposure to diagnostic ultrasonography appears to be safe. The current position, therefore, is that no robust evidence of the toxicity of fetal exposure to ultrasound has been presented. This would be reassuring but most of the primary data used to reach this conclusion were derived from studies that used machines that may be considered obsolete in contemporary ultrasound world of the last ten years. However, the meta-analysis gave a pass-mark to safety precautions in place before 1994.

Meanwhile due to the ease of acquiring ultrasound images, almost any physician that can buy an ultrasound machine becomes an instant sonographer. Also, this apparent safety has been driving technology into producing an increasingly more powerful machine with more imaginative scanning parameters, like 3D, 4D, tissue harmonics, and ultrasound microscopy, even if of unproven clinical utility. Before 1976, the output of ultrasound machines was not regulated.^[4] Again, due to assumed safety, the initial cautious restriction of fetal exposure to 94mW/cm² in 1976 by United State FDA have been updated so that the allowed limits now stand at 720 mW/cm² and 50 mW/cm², respectively^[5] (over 700% increase in allowed fetal exposure). It is, therefore, not surprising that the current safety precaution on ultrasound is a 20-year old principle known as the ALARA (As Low As Reasonably Applicable) principle.^[17] ALARA is based on the use of on screen display of thermal and mechanical indexes which are intended to provide the sonographer on the level of fetal exposure and therefore the risk of bioeffects at all points of the scanning procedure. The sonographer is then expected to self-regulate and use settings that

maximize the benefit of an ultrasound exposure at minimal risk.

Given the narrative above, it may be argued that basic principles of toxicology have not been applied to ultrasound. This is because at optimal performance, toxicology is a science of prediction that seeks to prevent human toxicities by identifying possible (all that could occur), rather than probable (all that are likely to occur, given certain circumstances) toxic effects of stimuli on living tissues. Possible toxic effects are usually identified by super-dosing (usually 10 times higher than the expected exposure level) and the observed effects are then used as readouts for wider explorations of real time clinical situations. For example, if super-doses of ultrasound reveal effects on the brain and lungs, these organs are then focused on for evaluation in clinical audits after exposure to routine doses of ultrasound. Also, because ethics demand that humans are not used as subjects for toxicological studies, *in vitro* studies and studies in non human animal models are robust tools that have been of inarguable utility to toxicologists although they have obvious limitations, especially on the issue of being transposable to human. To partly resolve this, studies are repeated usually in mice, rats, guinea pigs, rabbits, sheep and non human primate. The more species of animal toxic effects are reproduced in, the more the findings may be considered of possible relevance to human exposure. Given these basic principle of toxicology, studies on the adverse effects of ultrasound that may or may not have used super doses of ultrasound exposure and are performed in any animal would be considered valid and usable toxicological data. In the ultrasound world, we appear to be waiting to reach the exposure limit where robust bioeffects have been proven in human whereas the precept of toxicology is that toxic effects of ultrasound in human should not occur. Also, most discussions on the potential toxicity from fetal exposure to ultrasound tend to assume that the exposed fetal population would be of homogenous and equal vulnerability. This may be faulty because experience with noxious stimuli suggests that differences in vulnerability to insult usually exist. The true population distribution of human fetal sensitivity to ultrasound is unknown, but in the science of prediction, it has been shown that when the true distribution is unknown, it is closer to the truth to assume a normal distribution provided that the sample size is large enough (usually = more than 30 to obey the central limit theorem). It is therefore plausible to accept that the sensitivity of fetuses to the toxic effect of diagnostic ultrasound is at least close to a normal distribution. This means that 95% of the population will be expected to fall within two standard deviations from the mean in both directions of a normal curve. In

this two-tailed system, 2.5% of fetal population will be super tolerant and another 2.5% will be hypersensitive to ultrasound waves. This translates to millions of fetuses at risk considering the current scale of the use of diagnostic ultrasound. In these vulnerable (supersensitive) fetuses, routine power outputs may induce bio-effects that may only occur at output range 10-100 times higher in the general population.

How may we present the available information to the pregnant woman and how might we reply a woman who simply seeks to know if exposing her fetus to diagnostic ultrasound is safe? It may be argued that the ALARA principle is an inadequate safety precaution. In a recent study, Houston *et al.*,^[18] found that only 10.9% of residents and 22.7% of fellows use output display standards during ultrasound examinations and up to 39% freely use Doppler ultrasound at all stages of pregnancy. Even when used, the indexes may be misinterpreted by sonographers to be actual thermal or mechanical stresses while they are only estimators of risks based on assumed simple physical models. The indexes probably underestimate the in-situ acoustic and thermal stress and may not be applicable to obstetric scans. Furthermore, the self-regulatory component of the ALARA principle suggests paternalism and benevolent good will (though this is probably not the intention of the vast of ultrasonographers) because it excludes pregnant women from real time risk evaluation. Also, should adverse effect attributable to ultrasound occur in an index exposure, it is practically unverifiable that ALARA was adhered to during the procedure. Traditionally, obstetric risks are handled differently. The obstetrician acts as an informed counsel that continuously engages the pregnant woman in risk benefit estimations presents clear options and supports the woman in her choice. It may, therefore, be more useful to determine and rate the risk of harm to the fetus using simple, clear indicators and update such indicators continuously during exposure.

Beyond ALARA

Ultrasound exposure may be rated into safety categories. The details of the safety categories may need to be worked out by a multidisciplinary committee and may involve the use of the Delphi protocol (a formal consensus process). Current modalities, like grey scale, continuous wave Doppler, pulse wave Doppler, Power Doppler, tissue harmonics, 3D and 4D, are sufficiently different in all parameters that may induce toxicities as to be categorized separately. Even within each type of ultrasound modality, varying ranges of on screen power output, mechanical or thermal indexes may

be sufficiently different in risk to be separately re-categorized. Safety categories have been used for drugs (e.g. United States FDA pregnancy letter categories; A, B, C, D, and X or that of Germany; Gr1-Gr11). Although this has been heavily criticized, the aim of categorizing ultrasound exposure will be simply to succinctly present available safety data in animals and humans, and unlike drug, not to predict clinical outcome. The clinical importance of this shorthand is that clear and indeed accurate information is presented to clinicians and pregnant women who may then together negotiate the limits of overall output category for a given examination. Using appropriate software, the negotiated limit may then be pre-specified into the ultrasound machine before the scanning procedure. In-built output restriction monitors may then control the setting options available for the index scan.

It is probably time for the World Health Organization or the appropriate agency to convene a meeting of experts to discuss the safety of ultrasound, determine how available data should be utilized and improve future research and data collection techniques. In the era of 3D and 4D, it is easy for the lay public and even routine providers^[19] of ultrasound to view ultrasound in the same category as television and probably consider safety cautions as scare mongering that are not worthy of serious consideration.^[20]

Conclusion

Diagnostic ultrasound has increased the level of our interaction with the growing fetus. Obvious toxic effects have not been proven in human fetuses but have been documented in various non human models. It may be important to avail both providers and users of diagnostic ultrasound with rating tools that may be used to succinctly convey the level of risk for specific exposures. This is probably more meaningful than simple on the screen display of safety indexes that then assumes benevolent goodwill by the sonographer.

References

1. Donald I, MacVicar J, Brown TG. Investigation of abdominal masses by pulsed ultrasound. *Lancet* 1958;1:1188-95.
2. O'Dowd MJ, Philipp EE. *The History of Obstetrics and Gynaecology*. 2nd ed. New York: Informa Health Care; 2000.
3. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N Engl J Med* 1971;284:878-81.

4. Houston LE, Odibo AO, Macones GA. The safety of obstetrical ultrasound: A review. *Prenat Diagn* 2009;29:1204-12.
5. Bello SO. How we may be missing some harmful effects of ultrasound--a hypothesis. *Med Hypotheses* 2006;67:765-7.
6. Cui JH, Park K, Park SR, Min BH. Effects of low-intensity ultrasound on chondrogenic differentiation of mesenchymal stem cells embedded in polyglycolic acid: An *in vivo* study. *Tissue Eng* 2006;12:75-82.
7. Chen WS, Brayman AA, Matula TJ, Crum LA. Inertial cavitation dose and hemolysis produced *in vitro* with or without Optison. *Ultrasound Med Biol* 2003;29:725-37.
8. Miller DL, Dou C. Membrane damage thresholds for 1- to 10-MHz pulsed ultrasound exposure of phagocytic cells loaded with contrast agent gas bodies *in vitro*. *Ultrasound Med Biol* 2004;30:973-7.
9. Rao S, Ovchinnikov N, McRae A. Gestational stage sensitivity to ultrasound effect on postnatal growth and development of mice. *Birth Defects Res A Clin Mol Teratol* 2006;76:602-8.
10. Brown AS, Reid AD, Leamen L, Cucevic V, Foster FS. Biological effects of high-frequency ultrasound exposure during mouse organogenesis. *Ultrasound Med Biol* 2004;30:1223-32.
11. O'Brien WD Jr, Simpson DG, Frizzell LA, Zachary JF. Superthreshold behavior and threshold estimation of ultrasound-induced lung hemorrhage in adult rats: Role of beamwidth. *IEEE Trans Ultrason Ferroelectr Freq Control* 2001;48:1695-705.
12. O'Brien WD Jr, Yang Y, Simpson DG, Frizzell LA, Miller RJ, Blue JP Jr, et al. Threshold estimation of ultrasound-induced lung hemorrhage in adult rabbits, and comparison of thresholds in mice, rats, rabbits and pigs. *Ultrasound Med Biol* 2006;32:1793-804.
13. Abramowicz JS, Barnett SB, Duck FA, Edmonds PD, Hynynen KH, Ziskin MC. Fetal thermal effects of diagnostic ultrasound. *J Ultrasound Med* 2008;27:541-59.
14. Barnett SB, Vella GJ, Horder MM. Validation of the thermal index for ultrasound-induced heating of the fetal brain. In: *Proceedings of the 43rd Annual AIUM*.
15. Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI. Effects of frequent ultrasound during pregnancy: A randomized controlled trial. *Lancet* 1993;342:887-91.
16. Torloni MR, Vedmedovska N, Merialdi M, Betrán AP, Allen T, González R, et al; ISUOG-WHO Fetal Growth Study Group. Safety of ultrasonography in pregnancy: WHO systematic review of the literature and meta-analysis. *Ultrasound Obstet Gynecol* 2009;33:599-608.
17. Ziskin MC. Update on the safety of ultrasound in obstetrics. *Semin Roentgenol* 1990;25:294-8.
18. Houston LE, Allsworth J, Macones GA. Ultrasound Is Safe . . . Right?: Resident and maternal-fetal medicine fellow knowledge regarding obstetric ultrasound safety. *J Ultrasound Med* 2011;30:21-7.
19. Sheiner E, Shoham-Vardi I, Abramowicz JS. What do clinical users know regarding safety of ultrasound during pregnancy? *J Ultrasound Med* 2007;26:319-25.
20. Salvesen KA, Lees C. Ultrasound is not unsound, but safety is an issue. *Ultrasound Obstet Gynecol* 2009;33:502-5.

Cite this article as: Bello SO, Ekele BA. On the safety of diagnostic ultrasound in pregnancy: Have we handled the available data correctly?. *Ann Afr Med* 2012;11:1-4.

Source of Support: Nil, **Conflict of Interest:** None declared.