

Review Article

A Review of the Thermal Effects During Pregnancy by Using Ultrasound: Doppler Mode

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ABSTRACT

Doppler ultrasound is used in obstetrics and gynecology fields to serve as the complement mode in the standard prenatal scan. It aids in investigating fetus blood flow in expectant mothers' wombs, usually those who come with pregnancy complications. In the conventional ultrasound beam, the heat produced by attenuation is distributed over the area. However, the Doppler ultrasound beam is focused at only one point. This leads the heat to accumulate at that particular area and hence there is an increase in the temperature. Heat is considered as a teratogen in pregnancy, whereby an increase in the fetal temperature can be fatal to the fetus. Studies have found that Doppler mode is associated with higher acoustic output as compared to the conventional two-dimensional (2D) ultrasound mode. Several studies done on animals have ruled out the evidence of Doppler ultrasound bioeffects. This narrative review only discusses the thermally induced effect of ultrasound by using Doppler mode. This study reviews prior studies with keywords such as Doppler ultrasound, bioeffects, heating effects, rabbit, and pregnancy. Earlier studies noted that the risk of thermal effects increased with the increase of exposure time. However, Doppler ultrasound wave inducing

fetal hyperthermia is not the main reason for causing adverse neonatal outcomes without taking into account other external factors. Therefore, it is essential for the practitioners to adopt and adapt the concept of 'as low as reasonably achievable' (ALARA) to avoid any subtle adverse effects.

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INTRODUCTION

Doppler ultrasound is fast becoming a key instrument in the medical field, especially for prenatal care around the globe and has been used ever since it was introduced. It is known that Doppler ultrasound was used for years in the study of fetus blood flows. It has been used in combination with brightness mode (B-mode) ultrasound during pregnancy check-up, which is usually done to monitor the fetus heart rate and blood flows. Today, together with the advancement in technology, Doppler ultrasound is practiced in most obstetrics and gynecology fields, in which the data are color-coded onto the B-mode images. Despite its usefulness in detecting and monitoring fetus blood circulation in the womb, the usage of Doppler ultrasound itself has a higher thermal index as compared to B-mode ultrasound. It was reported that the use of Doppler imaging may increase the temperature of tissues, thus, when Doppler is used in combination with B-mode ultrasound, the risks of bioeffects tend to be higher. Therefore, the experts have come up with a question whether Doppler ultrasound is safe for pregnant women if used without any diagnostic purposes. The purpose of this paper is to write a review regarding several numbers of studies that revised and discussed the impact of Doppler ultrasound exposure on rabbits. It is expected that this study can give a clear depiction to the public about the potential risk of using Doppler ultrasound without any diagnostic purposes. It is also expected that this review can facilitate the establishment of guidelines on the using of Doppler ultrasound in the future.

The General Theory of Ultrasound and Doppler Mode

Ultrasound is theoretically one of the imaging modalities that uses sound waves propagating through body tissues and produce returning echoes to synthesize gray-scale images (Shung, 2006). Notable advantages of ultrasound are the ability to produce real-time images as well as no association with ionizing radiation exposure (U.S Food and Drug Administration, 2017).

Sound waves are transmitted through a transducer surface into the body tissues where they are attenuated depending on its acoustic impedance, then returning echoes are produced which are also being detected by the transducer. The piezoelectric material is a fundamental component of the transducer which functions by converting electrical energy to mechanical (sound) energy and also to convert the mechanical energy into electrical energy. While resolution and attenuation are directly proportional to the wavelength and frequency of the ultrasound beam, the depth of the beam penetration is inversely proportional. Higher frequency produces better resolution but gives superficial penetration. Conversely, lower

frequency associates with lower resolution but gives deeper beam penetration (Bushberg, Seibert, Leidholdt, & Boone, 2002).

In addition to conventional ultrasound, Doppler mode is occasionally being used during practices. It makes use of the Doppler effect which sometimes is also known as the Doppler shift. Doppler effect is defined as the alteration in frequency of sound wave due to a reflector moving towards or away from an object (Goel, 2015). Doppler ultrasound is used to facilitate monitoring and diagnosing in obstetric fields by taking into account its capability to assess blood movement in both fetal and placental circulation depending on Doppler effect (Mone, McAuliffe, & Ong, 2015).

As a matter of fact, the sound wave that propagates into the body will undergo the process of being scattered, reflected and absorbed into the body as heat (Zaiki & Dom, 2014). Besides its main advantage to provide real time images using non-ionizing radiation, the thermal effect from frequent and higher exposure of Doppler ultrasound may develop some potential risks to be concerned about.

The Thermal Effect of Ultrasound

Ultrasound is replacing the conventional radiography and serves as an essential service offered by most health institutions. While ultrasound provides diagnostic images without ionizing radiation (Ball & Price, 1995), the possibility of adverse effects by using ultrasound cannot be foreseen (Kremkau, 1994). Recently, the matter has been addressed by researchers in many fields.

The mechanism of ultrasound conversion into heat cannot be denied and today has become a part of a primary concern. Theoretically, as the ultrasound waves propagate through tissues, they attenuate and cause the temperature to rise (Kremkau, 1994) as well as cavitation to happen (Abramowicz, 2017). Both effects are termed as bioeffects of ultrasound, where they have been debated by researchers over the years. The American Institute of Ultrasound in Medicine (AIUM) has summarized the above matter in the consensus report on potential bioeffects of diagnostic ultrasound in 2008 (Fowlkes, 2008). The thermal effect occurs when the heat produced by-intense ultrasound exposure gives an undesirable effect on where the ultrasound waves travel to (Bushong, 1993).

In addition, Miller stated that biological effects can only occur if it reaches its threshold and the severity increases with increasing exposure to specific circumstances (Miller, 2008). The risk increases as the technology of ultrasound advanced through the decades. In the same vein, it has been reported that potential cavitation can happen when Doppler is used together with three-dimensional (3D) ultrasound (Pooh et al., 2016). A large and growing body of literature has emphasized that Doppler's acoustic outputs are relatively sufficient to result in apparent biological effects when maximum operating settings are used (Barnett & Maulik, 2001).

This matter leads to numerous studies that attempted to investigate the biological effects of ultrasound. Several studies were conducted to measure the thermal effects of ultrasound (Helmy, Bader, Koch, Tiringner, & Kollmann, 2015; Liang, Zhou, Wells, & Halliwell, 2009). Helmy et al. (2015) expressed their concern on the physical mechanism of Doppler ultrasound, which could harm pregnant women in the early gestational period (Helmy et al., 2015). Through an *in-vitro* study conducted, they found that the temperature of a water bath model significantly increased after being exposed to Doppler ultrasound within one minute. Thus, they concluded that the risk of thermally induced effects by using Doppler ultrasound in early pregnancy period cannot be left out.

Heat As Teratogen for Pregnancy

The fetus also generates heat through metabolism process in the womb but unlike its mother, it cannot dissipate the heat by its own. The fetus is said to have no control over its body thermoregulation. Heat or hyperthermia is known to give effects on pregnant woman. It is proven that elevation of maternal body temperature could give an adverse effect on both the mother and the fetus. In a hyperthermia analysis, a study in 2003 demonstrated that hyperthermia during pregnancy can lead to irreversible damage to the fetus, such as abortion, retardation of growth, developmental defects, and worst of all an embryonic death (Edwards, Saunders, & Shiota, 2003).

In accordance with the previous result, the present study also demonstrated that hyperthermia had affected both maternal and fetal outcomes. A study by Strand, Barnett, and Tong (2011) reviewed that most literature claimed that preterm birth, stillbirth, and low birth weight showed the highest numbers in both extreme seasons; summer and winter. From the literature reviewed by them, some of the authors have speculated that extreme seasons may be a risk factor for poor birth outcomes (Strand et al., 2011). The studies presented thus by far provided evidence in showing that ambient temperature during prenatal exposure taken in place can give an impact on birth consequences.

With respect to hyperthermia, the Intergovernmental Panel on Climate Change (IPCC), in 2007 presented an amount of evidence on how global warming and climate change can give impacts on humans (Rylander, Odland, & Sandanger, 2013). Pregnant women, unborn descendants, and youngsters are considered as high-risk groups in which climate change, especially direct heat exposure, gives severe effect on maternal health as well as the children. Moreover, it is very difficult to get away from complications during pregnancies. Pregnancies are associated with various complications, which may include spontaneous abortion, low birth weight, premature contractions, and neonatal mortality (Goldenberg, Culhane, Iams, & Romero, 2008; Randolph-habecker et al., 2017). Those complications can happen at any stage throughout the gestational periods (Liu et al., 2012).

A systematic review was done by Kuehn and McCormick (2017) on climate change in maternal health demonstrated that extreme heat exposure may affect fetal outcomes (Kuehn & McCormick, 2017). They also stated in their discussion that both extreme and moderate temperature exposures may result in an acute and adverse delayed birth consequences, respectively. Similarly, in 2011, years before the systematic review was done, Sheffield and Landrigan concluded that heat-related health effects include diminished school performance, increased rates of pregnancy complications, and renal effects (Sheffield & Landrigan, 2011). However, the severity of the consequences may vary by the geographical region and socioeconomic status, which later increase health inequalities.

There are several pieces of evidence telling that maternal pyrexia acts as the major determinant of fetal hyperthermia and is associated with the incidence of adverse neonatal outcomes (Trays & Banerjee, 2014). However, they made an argument that the neuronal injury can also be caused by many other factors rather than making hyperthermia as the only causal of event.

Doppler Ultrasound in Pregnancy

Ultrasound is long known as the safest imaging modality as it involves no ionizing radiation and is frequently used in prenatal care for decades. In clinical practices, especially in obstetrics, ultrasound has been crucially used in diagnosing, monitoring, and assessing the fetal progress in the womb and in some cases, ultrasound helps perform the therapeutic intervention in treating fetal anomalies (Schellpfeffer, 2013).

After the invention of ultrasound in the late 1950s, it continued to develop throughout the decades and was commonly applied in screening for pregnant women (Chau, 2002). Today, Doppler ultrasound is commercially applied by private companies and healthcare institutes in prenatal care. Even though traditional ultrasound can give enough information about the fetus well-being in the womb, the advancement of Doppler ultrasound technology, by making use of Doppler effect physics as the result of the motion of blood or direction of the blood flow (Kremkau, 1994), helps practitioners to identify any blood circulation abnormalities of the fetus in a better view.

Currently being practiced, only an expectant mother with high potential complication gets the privilege of using Doppler ultrasound to check on her fetus. As reported, the percentage of stillborn rate could be reduced if Doppler ultrasound is called as a standard practice, instead of the traditional prenatal ultrasound (Hill, 2016). Years before the trend set, the USA today reported that the American Institute of Ultrasound in Medicine (AIUM) notified parents about the possible harms of having an unregulated ultrasound for entertainment purposes (Anonymous, 2004).

Unregulated ultrasound takes a longer time and uses more energy even though there is no confirmed biological effect from the prenatal ultrasound scan was done. The Food

and Drug Administration (FDA) made a statement that concerns the unknown long term effects of tissue heating by frequent visits and prolonged examination time (Diana, 2015). Therefore, the experts stated that ultrasound by using Doppler should only be done on expectant mothers when there is a medical purpose to perform it. However, if it is performed on expectant mothers without any diagnostic purposes, it brings-the question whether it is safe for the fetus or not.

Doppler Ultrasound Bioeffects on Human

Doppler ultrasound is one of the most widely used ultrasound imaging modes and is extensively used for high-risk pregnancies to reduce stillbirths. Although some researches were carried out on its biological effects in humans, scientific understanding is very little. A review conducted by Alfirevic, Stampalija, and Dowswell (2017), showed the possible effects of Doppler ultrasound used in high-risk pregnancies to assess the fetal well-being (Alfirevic et al., 2017). They agreed to the use of Doppler in the obstetric field to reduce the number of fetal death but the fact of Doppler usage resulting in fewer obstetric interventions are yet to be certain.

Previous studies have indicated that routine Doppler ultrasound examination; which was conducted for unselected or low-risk pregnancies cases; gave no benefits to the mother and child. An investigation by Bricker and Neilson (2000) showed that routine Doppler ultrasound resulted neither in increased obstetrics and gynecology interventions nor detectable in both short and long term consequences, such as perinatal mortality and defect neurodevelopment, respectively (Bricker & Neilson, 2000).

Forward et al. (2014) analyzed the data of 20 years follow-up of the randomized controlled trial on multiple prenatal ultrasound scans and ocular development (Forward et al., 2014). The study aimed to determine the effect of frequent exposure to several ultrasound modes of ultrasound on ocular development by using previous 20 years cohort study data. They found that frequent exposures to the ultrasound had no significant influence on the ocular development, regardless B-mode or spectral Doppler used. On the other hand, Sheiner et al., (2007) found distinct differences between Doppler and B-mode ultrasound. In her study, she identified that TI reading for Pulsed wave Doppler mode is at the highest followed by color flow Doppler and B-mode. Table 1 below shows the acoustic output during the ultrasound studies adapted from Sheiner et al., (2007).

Then, recent evidence suggested that the use of Doppler ultrasound has given no impact to the fetal outcome. Alfirevic, Stampalija, and Medley (2015) found that there were no group differences seen for the analysis primary outcomes of prenatal death and neonatal morbidity (Alfirevic et al., 2015). Even though there was evidence found for group differences in prenatal death between a single Doppler assessment versus no Doppler, such exposition was unsatisfactory because the outcomes were only based on a single trial.

Table 1

Acoustic Output during the Ultrasound Studies

Mode of ultrasound	Mechanical index (MI)		Thermal index (TI)	
	Mean \pm SD	Range	Mean \pm SD	Range
Pulsed-wave (n = 118)	0.9 \pm 0.2	0.2 – 1.2	1.5 \pm 0.5	0.9 – 2.8
Color Doppler (n = 31)	1.0 \pm 0.1	0.8 – 1.2	0.8 \pm 0.1	0.6 – 1.2
B-mode (n = 190)	1.1 \pm 0.1	0.2 – 1.3	0.3 \pm 0.1	0.1 – 0.7

*Standard deviation (SD)

Note. Adapted from Sheiner et al. (2007)

Therefore, in general, it seems that researchers concluded that the use of Doppler Ultrasound did not give any benefits to both the mother and fetus as the evidence found was not conclusive enough. Even though the bioeffects of Doppler ultrasound were not conclusive enough on humans, some significant can be seen in animal studies.

Animal Studies Conducted on Assessing Doppler Bioeffects

The present studies make several noteworthy contributions towards further investigation on Doppler bioeffects by using an animal model. For a long exposure duration, which is longer than 5 minutes or exceeds 4°C, the threshold temperature elevation for hyperthermia-induced teratogenic effects in trial mammals was estimated to be approximately 1.5°C above core standards (Miller, Nyborg, & Dewey, 2002). However, the finding is yet to be tested on humans, thus the generalizability of the research on this issue seems to be problematic.

So far, the studies of Doppler ultrasound bioeffects being done on humans have shown us a negative conclusion. However, there are significant differences found throughout the animal studies. In 2005, the immediate and long-term effects of color Doppler ultrasound on myocardial cell apoptosis of fetal rate were investigated. Exposures were given in-vivo and the effects were studied for both neonatal and fetal group. They found that there were higher significant differences in the fetal insonification group than in the neonatal insonification group and myocardial apoptosis also showed higher significant differences in the fetal insonification group than I the fetal control group as expected. However, there

were no significant differences found in myocardial apoptosis between the same neonatal insonification group (Jia et al., 2005).

Then, Schneider-Kolsky et al. (2009) had undergone an experiment to assess how ultrasound exposure can affect the learning and memory of chicks (Schneider-Kolsky et al., 2009). B-mode and Doppler ultrasound were exposed to the fetal chicks' brains for several minutes on day 19 of the incubation period. After day 2 post-hatched, they found that significant memory impairment occurred following 4 and 5 minutes of Doppler exposure while no memory impairment was detected for those chicks exposed to B-mode. These findings showed that the prolonged exposure to Doppler ultrasound gave impairment to mammal's cognitive function.

Later in 2011, a study on the effect of pulsed Doppler examination on ductus venosus in rat fetuses had shown positive result where there was a linear correlation between exposure index and apoptotic activities of exposed liver tissues (Pellicer et al., 2011). They found that the longer the pulsed Doppler exposure was given at a time, the higher was the apoptotic index. However, they also found that hours after post-exposure, the cellular damage done was due to the exposure to Doppler disappeared. No significant liver damaged was found despite how long the fetal liver had been exposed.

On the other hand, in spite of much new knowledge about the Doppler effects, several other studies have also been done to investigate the heating effects of prenatal ultrasound without using the Doppler mode. In 2013, a study of fluctuations in hematological analysis and fetal weight were statistically found to be different in the newborn of *Oryctolagus cuniculus* after being exposed to traditional prenatal ultrasound (Ahmad Zaiki, Md Dom, Abdul Razak, & Hassan, 2013; Zaiki & Dom, 2014). In 2016, Zaiki and Dom later also found in their study that the heating effect during prenatal scanning interfered with the fetal neuro-development (Zaiki & Dom, 2016).

DISCUSSION

As some practitioners agreed that the development of ultrasound over the years did give benefits to humans, especially in the obstetrics and gynecology, the drawbacks of having ultrasound unnecessarily still existed. In reviewing the literature, most researchers concluded that there are long term effects that might affect the well-being of fetus, specifically. It is hypothesized that the longer ultrasound exposure time is given, the risks of having adverse effects also increase significantly. Regardless of which mode of ultrasound used, the risk of bioeffects still increases with the increase of the exposure period. It is possible, therefore, that the safety of using Doppler ultrasound without any prior concern during pregnancy may come into question.

Another important finding is that some authors have speculated that the acoustic energy produced by particular ultrasound mode is also one the potential causes of ultrasound

bioeffects. 3D ultrasound is said to be as safe as B-mode because it scans the whole volume without repeatedly being exposed on the fetal point, while four dimensional (4D) ultrasound will have the same effect as both if the exposure to 4D ultrasound is limited within 30 minutes (Pooh et al., 2016). Doppler ultrasound, which is mainly used to evaluate blood flow of the fetus in the womb of the mother can generate acoustic energy higher than other modes. This result may be explained by the fact that Doppler ultrasound uses pulse wave to generate images. Unlike conventional 2D mode ultrasound, the transducer or probe is kept stationary at a specific point. The ultrasound beam is focused on that specific region only, thus, it eventually alters the fetal exposure in terms of dwelling times as the beam is not scanned (Miller, 2008).

We can see that as we compare between modes, the spatial peak temporal average intensity (I_{SPTA}) for B-mode, motion (M) mode and Doppler are significantly increased where temporal averaged intensity can reach maximum $10\text{W}/\text{cm}^2$ (Abramowicz, 2017). The FDA put the exposure limit to $720\text{ m W}/\text{cm}^2$ for all applications, except for eye scanning after the former regulation was revised in 1992. The exposure towards ultrasound energy beyond the threshold limit might not be considered as safe anymore. Besides that, the development of scanners and transducers after 1993 may increase the possibility of tissues being exposed to higher intensities, thus, increases the risk of higher bioeffects occurrences (Deane & Lees, 2000). The practitioners need to observe the exposure of ultrasound so that it does not exceed the threshold limit.

As FDA has highlighted the threshold value of ultrasound exposure, here is where the output display standard (ODS) takes its role. Thermal index (TI) and mechanical index (MI) are two main components displayed on the screen. TI is essential in estimating the maximum tissue temperature rise for a given exposure, while MI is known as an indicator for the non-thermal phenomenon to occur. Even though TI cannot measure the actual temperature in the tissue (Abramowicz, 2017), it is important for the practitioners to follow the guidelines given as higher TI can be associated with a higher temperature rise. Miller mentioned in his paper that a slight elevation of temperature of less than $(1 - 1.5)^\circ\text{C}$ above normal body temperature is not expected to give any harm because the elevation is still within the normal variation of body temperature (Miller, 2008). It must be made clear that TI only represents a ratio of instantaneous power to the theoretical power needed to raise the tissue temperature by 1°C . However, when Doppler is in use, the temperature might increase more than when conventional ultrasound was used.

Potential bioeffects of ultrasound are crucial in pregnancy. As discussed earlier in this part, the acoustic energy is greater when Doppler mode is in used compared to other ultrasound modes. It is agreed that the thermally induced effect is more obvious by using Doppler (Barnett & Maulik, 2001). In pregnancy, the first 12 weeks of gestation period is the most crucial period because the growing fetus is very sensitive to any external

influences. Medications, exposure to X-ray, infectious diseases, and hyperthermia are categorized as teratogenic agents that can harm the fetus (Abramowicz, 2010). The heat produced by ultrasound wave is also considered as a teratogen in pregnancy. Most animal studies done had concluded that heat produced by ultrasound; mainly Doppler ultrasound, gave substantial effects to the growing fetus.

The second and third trimesters of pregnancy also cannot be left out from having potential thermally induced effects from ultrasound waves. Theoretically, in the mechanism of heat absorption, the bone absorbs heat better than tissue. This is because the bone has higher attenuation coefficient as compared to other tissues, thus greater absorption occurs. As noted by Barnett and Maulik (2001), the risk of inducing thermal effects is higher in the last two trimesters; second and third trimesters (Barnett & Maulik, 2001). This is because during these periods, bones are already formed and thus, interception of fetal bone and ultrasound beam can lead to a temperature increase in the fetal brain. This view is supported by Maeda and Kurjak, (2012) who wrote that different tissues absorbed, attenuated, and perfused differently.

Decreased birth weight, neurological impairment as well as decreased cognitive functions and altered cellular proliferation are the examples of the consequences of exposure towards both conventional and Doppler ultrasounds for a given time. Contrary to the expectations, studies did not find a significant difference between Doppler ultrasound and its bioeffects on humans. This matter opens abundant rooms for further progress in determining Doppler ultrasound bioeffects on humans. Although the current study is based on animal studies and has yet to find evidence on humans, the findings can serve as the evidence that there are roughly bioeffects of Doppler ultrasound.

However, the generalizability of these results is subjected to certain limitations. The whole-body temperature of an expectant mother (animal study) can also be elevated, not only because of the acoustic energy heat-generated but also due to other hyperthermia-induced external factors. Generally, developmental impairment in animal models is seen when the maternal core temperature increases above normal of approximately 2 °C for an extended period of time, (2-2.5)°C for 0.5-1 hour or $\geq 4^{\circ}\text{C}$ for 15 minutes (Ziskin & Morrissey, 2011). An increase in the mother's core body temperature can increase the fetal temperature. Apart from that, the inability of a fetus to remove its own heat can also lead to an increased fetal temperature in the womb. Therefore, it is void to conclude that the heat produced by ultrasound is the main reason for fetal hyperthermia without taking into account other external factors. These findings also open a new door for researchers to dig out more unknown risk associates with ultrasound.

CONCLUSION AND RECOMMENDATION

The study of bioeffects of ultrasound is still limited only on animal studies and the significance of the result is yet to be implemented. This is mainly caused by the differences between animals and human features, either physiology or anatomy. For example, even though the mammals such as rabbits, rat, and sometimes monkeys are the nearest animals mimicking humans, there are still existing gaps that need to be filled.

Therefore, in general, it seems that the heat produced by the acoustic energy from Doppler ultrasound wave can induce thermal bioeffects. Thermally induced effects can be fatal for the fetus, especially in the first trimester of pregnancy. Intense Doppler exposure throughout pregnancy period should also be avoided by all means. Since the application of ALARA principle can be found in radiology with respect to reducing radiation risk, this concept can also be directed towards reducing heat effects in ultrasound. AIUM has released their official statement in which the ALARA principle should observe the controls adjustment and transducer dwell periods which could affect the ultrasound acoustic output (American Institute for Ultrasound in Medicine, 2014). Therefore, health practitioners should always practice 'as low as reasonably achievable' (ALARA) concept and minimize the use of Doppler ultrasound in pregnancy while maintaining the diagnostic quality. This view has been also recommended by FDA (U.S Food and Drug Administration, 2017).

This review has thrown up many questions in need of further investigation. As was mentioned in the literature, the lack of evidence on the Doppler bioeffects on humans clearly showed that further research and investigation are needed. This is due to the fact that a significant difference is found in many animal studies. Even though it is known to be challenging to implement the results of animal studies onto humans, the bioeffects of Doppler ultrasound cannot be taken for granted. If the debate of ultrasound safety is to be moved forward, a better understanding of Doppler ultrasound bioeffects needs to be developed.

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