How to Cite:
El-Gaber Ali, A. E.-N. A., Mohamed, M. H., Khodary, M. M., & Mohamed, A. A.- alal M. (2022). Predictive values of first trimester ultrasound screening for twin-to-twin transfusion syndrome and selective intrauterine growth restriction in monochorionic twin pregnancies. *International Journal of Health Sciences*, *6*(S9), 2786–2794. https://doi.org/10.53730/ijhs.v6nS9.13072

Predictive values of first trimester ultrasound screening for twin-to-twin transfusion syndrome and selective intrauterine growth restriction in monochorionic twin pregnancies

Abd El-Nasar Abd El-Gaber Ali
Professor of Obstetrics and Gynaecology, Faculty of Medicine – South Valley University

Mostafa Hussein Mohamed
Professor of Obstetrics and Gynaecology, Faculty of Medicine – Assuit university

Mostafa Mohamed Khodary
Assistant professor of Obstetrics and Gynaecology, Faculty of Medicine – South Valley University

Altayeb Abd-alal Mostafa Mohamed
Assistant lecturer of Obstetrics and Gynaecology, Faculty of Medicine – South Valley University
Email: eltaib.mostafa89@gmail.com

***Abstract*---**Background: Monochorionic diamniotic (MCDA) twins are at significantly increased risk of perinatal morbidity and mortality due to shared placentation and the presence of inter-twin placental vascular anastomoses. Aim of the work: The main aim of this study was to validate first trimester ultrasound screening for twin-to-twin transfusion syndrome (TTTS) and selective intrauterine growth restriction (sIUGR) in monochorionic twin pregnancies using the triad of nuchal translucency (NT), cord insertion site and inter-twin discordance in fetal size. Summary: We have demonstrated that NT and CRL were significantly higher in TTTS group than sIUGR group. And difference in NT, CRL and cord insertion site was identified as predictive markers for sIUGR and TTTS.

***Keywords*---**monochorionic twin pregnancies, sIUGR, perinatal morbidity.

Introduction

The risk in twin pregnancies is higher than singleton pregnancies with monochorionic twins demonstrating the highest risk. 30% of twins are monochorionic, but they experience 75% of all twin complications. Twin-to-twin transfusion syndrome (TTTS), selective intrauterine growth restriction (sIUGR) and twin anaemia polycythaemia sequence (TAPS) are specific complications to monochorionicity. The most severe is TTTS which usually occurs around 20 weeks gestation and if left untreated it is associated with a perinatal loss rate up to 90%. (Crowther et al, 2001).

Most centers perform US every two weeks to detect these complications. Identifying a high risk of monochorionicity in first trimester would allow more efficient surveillance. Although ultrasonographic features have a reasonable sensitivity and specificity in terms of allocating risk of severe TTTS, such screening is still associated with a significant false positive and false negative rate as the detection rate is only 52%. (Kagan et al, 2007). Till now, we are unable to predict accurately which twins will develop complications or how severe they will be. Several studies are done using different ultrasound soft markers; but none of these characteristics have sufficient efficacy to be used to triage MCDA twin pregnancies ongoing obstetric surveillance (Mogra et al, 2020).

The aim of this study was to validate first trimester ultrasound screening for twin-to-twin transfusion syndrome (TTTS) and selective intrauterine growth restriction (sIUGR) in monochorionic twin pregnancies using the triad of nuchal translucency (NT), cord insertion site and inter-twin discordance in fetal size.

Monochorionic twins

Monochorionic (MC) pregnancies have higher rates of fetal morbidity and mortality when compared to dichorionic (DC) ones. Therefore, the early diagnostic of chorionicity is of great importance. Monochorionic pregnancies have specific complications such as twin to twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin anemia polycythemia sequence (TAPS), and twin reversed arterial perfusion sequence (TRAPS). MC pregnancies have several unique and serious complications that contribute to a perinatal mortality rate of 11% (Mackie et al., 2019).

Monochorionic (MC) twins are identical twins who share one placenta, with vascular anastomoses connecting the circulations of both fetuses. Although the occurrence of MC twin pregnancies is rare (only 0.4% of the general population), associated complications due to a shared placental circulation are frequent and may be very severe (Lopriore et al., 2019).

Pathophysiology

In monochorionic twin pregnancy, both the fetuses share a single placenta. Monochorionic twin placenta is characterized by anastomoses between artery to artery, vein to vein, and artery to vein and depending upon their number and

type, various complications of varying severity and onset at different times of gestations can occur (Couck & Lewi, 2016).

Because of this fact, MC twins are at a higher risk of antenatal complications (discordance, twin to twin transfusion syndrome, single fetal demise etc.) and perinatal mortality as compared to DC twins. It is proposed by some investigators that once MC twins have achieved lung maturity, it is safer to deliver rather than risk the pregnancy of unexplained intrauterine fetal demise (Dharani, 2020).

Diagnosis

By performing an obstetric ultrasound at a gestational age of 10–14 weeks, monochorionic-diamniotic twins are discerned from dichorionic twins. The presence of a "T-sign" at the inter-twin membrane-placental junction is indicative of monochorionic-diamniotic twins (that is, the junction between the inter-twin membrane and the external rim forms a right angle), whereas dichorionic twins present with a "lambda (λ) sign" (that is, the chorion forms a wedge-shaped protrusion into the inter-twin space, creating a rather curved junction) **(**Peavey & Dotters-Katz, 2021).

The flow direction depends on the types of connection, vessel calibers, and the pulse pressure. TTTS results from an unbalanced chronic perfusion from donor to recipient twin across placental anastomoses. This blood transfer is more likely in those placentas with more AV anastomoses and a lack of superficial balancing AA or VV anastomoses or when these bidirectional anastomoses are unusually small (Toneto, 2018).

Twin-Twin Transfusion Syndrome (TTTS)

Twin-Twin Transfusion Syndrome (TTTS) is a condition that can affect twin gestations that share one placenta. This disorder highlights the importance of determining the chorionicity (number of placentas) and amnionic (number of amniotic sacs) for all twin gestations, which will influence management (Borse & Shanks, 2020).

Clinical manifestations of TTTS

The principal clinical feature in TTTS is hypervolemia in the recipient and hypovolemia in the donor twin that may progress to cardiovascular impairment, hydrops, and fetal death. In the first trimester, diagnosis is difficult, since the amniotic fluid is usually normal in both fetuses. Some sonographic markers such as discordance in nuchal translucency thickness (NT) and abnormalities in ductus venosus (DV) may be early signs of TTTS, but they have a low predictive value **(**Djaafri et al., 2017).

The sonographic manifestations usually may be noted as early as 16 weeks of gestation, but they can appear in the third trimester as well. TTTS manifestations are rare after 28 weeks of gestation (Zaami et al., 2021). Despite the hypervolemia, vascular resistance in the recipient twin is increased. This hypertension is attributed to vasoactive mediators such as endothelin and also a

paradoxically high level of renin. The source of endothelin and renin is probably partly from the placenta and partly from the donor via the vascular communications (Migdal, 2020). These changes in fetal hemodynamics may cause a progressive cardiomyopathy that increases the heart size, reduces the myocardial compliance, and causes atrioventricular valvar regurgitation and abnormal venous Doppler findings (Migdal, 2020).

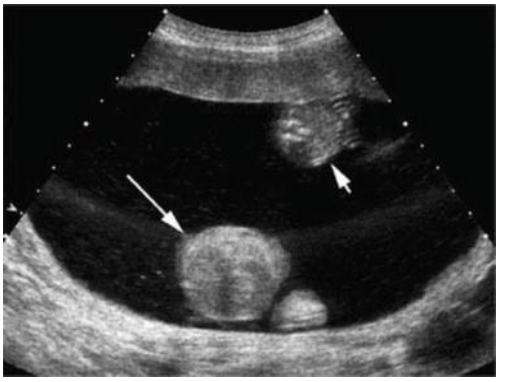

Figure (1): Two fetal abdomens. The smaller one (short arrow) is stuck in the anterior uterine wall and has no amniotic fluid. The bigger fetus (long arrow) has polyhydramnios (Jha et al., 2021).

Diagnostic criteria and staging

In the past, TTTS was diagnosed at the time of birth based on neonatal criteria that included a growth discordance of 15–20% associated with discordant cord or neonatal hemoglobin concentrations of ≥5 g/dl (Toneto, 2018). In 1992, another study showed that these criteria are present in other conditions such as uteroplacental insufficiency, infection, and malformations and therefore should not be used as diagnostic criteria for TTTS (Toneto, 2018). The screening for TTTS should begin with an early ultrasound in order to confirm the chorionicity. The first trimester scan should be performed to look for morphology abnormalities and discordance in the NT measurement, abnormalities in the DV, and even crown-rump length discordances (Sherer et al., 2021).

The diagnosis is made when discordance in the DVP of the twins is visualized. The DVP of the donor twin should be <2 cm; meanwhile the DVP of the recipient, before 20 weeks, should be >8 cm, and after 20 weeks, it should be >10 cm in the European criteria and > 8 cm in the US criteria. The fetal bladders should also be evaluated since there might be discordance in the size of the fetal bladders (larger in the recipient and smaller in the donor). It is worth reminding that weight discordance is not a diagnostic criterion for TTTS, but it also can be noted in the ultrasound examination (Quintero et al., 1999).

Complications of TTTS

The death of one or both twins is a complication of TTTS, with the survival of one twin ranging from 15% to 70% and survival of both twins hovering around 50%. Cardiac complications can also occur in both the recipient and donor; these

include atrioventricular valve insufficiency, diastolic dysfunction, and pulmonary stenosis or atresia in the recipient, and vascular changes due to increased collagen synthesis and hypertrophy of the vascular media and smooth muscle layers in the donor (Borse & Shanks, 2020). Complications also differ depending upon management. Expectant management carries the complication risk of further stage progression; this risk of progression depends upon the stage at diagnosis as most (75%) of Stage I remain stable or regress without treatment (Borse & Shanks, 2020).

The best treatment for twin-twin transfusion syndrome (TTTS) is fetoscopic laser coagulation of the vascular anastomoses, preferably using the Solomon laser technique (Kanazawa et al., 2021). Greimel et al. show that this surgical intervention is safe and rarely associated with maternal procedure-related complications (Greimel et al., 2019). Importantly, TTTS should not be viewed as a homogeneous disorder and may coexist with selective fetal growth restriction (sFGR) and/or twin anemia-polycythemia sequence (TAPS) (Matias & Blickstein, 2020). In two large TTTS cohorts, Groene et al. and Tollenaar et al. report on the incidence and clinical consequences of these associated complications (Groene et al., 2019) and (Tollenaar et al., 2019).

Management of TTTS

In stage I, it is known that nearly 70% of the pregnancies remain stable or regress, but in 5% of cases of stages I or II, there is fetal death of one or both twins without warning. Besides that, only 30% of pregnancies managed expectantly have double survivors. In the other stages, mortality increases and treatment is necessary (Toneto, 2018). There are several ways to manage TTTS, which include FLPC, amnioreduction, selective reduction, and pregnancy termination. The FLPC is the preferred option because its outcomes are better when compared to serial amnioreduction (Toneto, 2018).

A recent meta-analysis showed that there may be an improved double neonatal survival as well as a decreased donor and recipient fetal demise with the use of the sequential technique, although all the studies are small and underpowered to confirm the hypothesis (Xie et al., 2020).

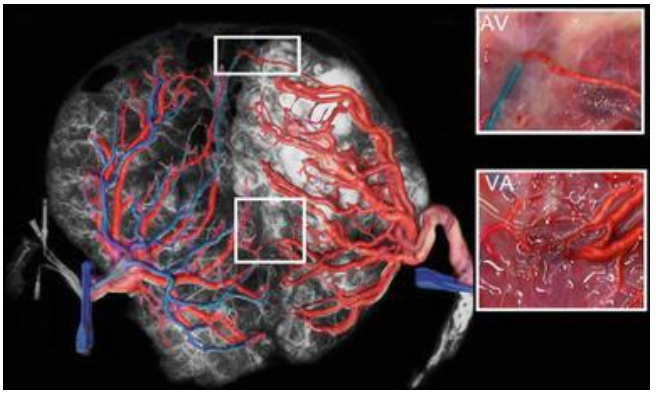

Figure (2): Digitally modified image of placenta with recurrent TTTS with missed AV and VA anastomoses (Toneto, 2018).

A subsequent randomized trial by Slaghekke et al. compared this new approach called the Solomon technique versus the SFLP and found no difference in the overall survival rates. However, a decrease in recurrent TTTS and TAPS after the procedure was observed in the Solomon group (4 vs. 21%) (Slaghekke et al., 2014)

Acute feto-fetal transfusion by single intrauterine fetal death (sIUFD) and other causes

Acute feto-fetal transfusion in MC twins can occur during pregnancy or during delivery. Regarding delivery, this has been long described in MC twins. It may occur between delivery of one fetus and the other, and it normally carries a good prognosis (Lopriore et al., 2014).

sFGR in MCDA twins

Selective fetal growth restriction (sFGR) refers to growth restriction of one fetus of a monochorionic twin pair. It is a common complication of monochorionic twins that results from discordant placental sharing and is different from the placenta-based growth restriction resulting from deficient uteroplacental perfusion that occurs in dichorionic twins and singletons (Turk et al., 2019).

Early sFGR affects 10% of MCDA twins, with a similar frequency as observed in DC twins. An expert consensus study proposed for the diagnosis an estimated fetal weight (EFW) in one twin <3rd centile as a single criterion, or the presence of at least three of the following: EFW of one twin <10th centile, abdominal circumference of one twin <10th centile, EFW discordance of ≥25%, umbilical artery pulsatility index of the smaller twin >95th centile (Khalil & Liu, 2021). As a whole, both sFGR type II and III are at high risk of very-preterm delivery, IUFD, and neurological sequelae. Type II follows a more “predictable” course, where the small twin progressively deteriorates as shown by Doppler, while type III shows an apparently benign evolution and the smaller twin rarely deteriorates (Micheletti et al., 2021).

Late sFGR may be detected in the third trimester in about 5% of cases of MCDA twins. Late sFGR in MCDA twins is normally a much more benign condition with generally a good prognosis (Sobhani et al., 2021). Selective intrauterine growth restriction happens in 10–25% of MC gestations and it considerably increases perinatal morbidity and mortality (Wixey et al., 2017).

First-trimester Ultrasound in monochorionic twin pregnancies

Identifying a “high risk” cohort of MCDA twins at the time of first-trimester screening would facilitate the appropriate triaging of women for future surveillance. It may, in the future, also be of value in identifying women who would benefit from preventative non-invasive placental separation therapies (Srinivasan et al., 2020). Sebire et al. were the first to describe this finding in a retrospective cohort of 287 monochorionic twins and ascribed a positive likelihood ratio of increased NT (>95th centile) of 3.5 for the subsequent development of TTTS. Findings are similar; 18% (12/65) of fetuses had NT >95th centile and 33% (4/12) of these developed TTTS (Sebire et al., 1997).

The sensitivity and specificity of this screening tool were 44% and 86%, respectively. The positive and negative predictive values were 33% and 90%, respectively, and the positive likelihood ratio was 3.0. Neither the sensitivity nor the negative predictive value was sufficiently strong to make use of first-trimester increased NT as a discriminator for assigning MCDA twin pregnancies into a high or low-risk model of obstetric care and fetal surveillance (He et al., 2017). The data did not establish any association between absence/reversal of the "A" wave of the DV and TTTS; this contrasts to previous reports of a 75% sensitivity and 92% specificity (Mogra et al., 2020).

Although the prevalence of TR is slightly higher in the TTTS group, the numbers are too small to draw any conclusions. Importantly, in 8/9 pregnancies complicated by TTTS, TR was not observed on assessment at approximately 12 weeks' gestation. Although the Quintero staging system identifies haemodynamic changes relatively late in the course of TTTS (associated with stage 3 disease), other groups have shown that significant haemodynamic changes can be demonstrated from earlier time points – if they are actively sought during cardiac evaluation (Mogra et al., 2020). Rychik et al. in a retrospective review of 150 MCDA twins with TTTS found that TR was present in 35% of twins at a mean gestation of 21 weeks (Rychik et al., 2007).

Conclusion

We have demonstrated that NT and CRL were significantly higher in TTTS group than sIUGR group. Also, difference in NT, CRL and cord insertion site was identified as predictive markers for sIUGR and TTTS.

References

Borse V, Shanks AL (2021). Twin-To-Twin Transfusion Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563133/

Couck, I, Lewi, L. (2016). The placenta in twin-to-twin transfusion syndrome and twin anemia polycythemia sequence. *Twin Research and Human Genetics*, *19*(3), 184-190.

Crowther C. Multiple pregnancy (2001). In: James D, Steer P, Weiner C, Gonik B, editors. High risk pregnancy. 2nd ed. London: WB Saunders; 2001. p. 129-51

Dharani, R. (2020). *Study of Fetomaternal Outcome in Twin Pregnancy* (Doctoral dissertation, Chengalpattu Medical College and Hospital, Chengalpattu).

Djaafri, F, Stirnemann, J, Mediouni, I, Colmant, C, Ville, Y. (2017, December). Twin–twin transfusion syndrome–what we have learned from clinical trials. In *Seminars in Fetal and Neonatal Medicine* (Vol. 22, No. 6, pp. 367-375). WB Saunders.

Greimel, P, Zenz, A, Csapó, B, Haeusler, M, Lang, U, Klaritsch, P. (2019). Maternal complications and hemodynamic changes following intrauterine interventions for twin-to-twin transfusion syndrome in monochorionic diamniotic twin pregnancies. *Journal of clinical medicine*, *8*(5), 605.

Groene, S. G, Tollenaar, L, Oepkes, D, Lopriore, E, van Klink, J. (2019). The Impact of Selective Fetal Growth Restriction or Birth Weight Discordance on

Long-Term Neurodevelopment in Monochorionic Twins: A Systematic Literature Review. *Journal of clinical medicine*, *8*(7), 944. https://doi.org/10.3390/jcm8070944

He, H, Tan, C, Wu, J, Dai, N, Hu, W, Zhang, Y, et al. (2017). Accuracy of ASGE high-risk criteria in evaluation of patients with suspected common bile duct stones. *Gastrointestinal endoscopy*, *86*(3), 525-532.

Jha, P, Feldstein, V. A, Revzin, M. V, Katz, D. S, Moshiri, M. (2021). Role of Imaging in Obstetric Interventions: Criteria, Considerations, and Complications. *RadioGraphics*, 200163.

Kagan KO, Gazzoni A, Sepulveda-Gonzalez G, Sotiriadis A, Nicolaides KH (2007). Discordance in nuchal translucency thickness in prediction of severe twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol; 29(5):527-32.

Kanazawa, S, Ozawa, K, Muromoto, J, Sugibayashi, R, Wada, Y, Wada, S, et al. (2021). Risk Profiling of the Solomon Technique versus Selective Technique of Fetoscopic Laser Surgery for Twin–Twin Transfusion Syndrome. *Twin Research and Human Genetics*, *24*(1), 42-48.

Khalil, A, Townsend, R, Reed, K, Lopriore, E. (2021). A call to action: long-term neurodevelopment in monochorionic twins. *Ultrasound Obstet Gynecol*.

Lopriore E, Ortibus E, Acosta-Rojas R, Le Cessie S, Middeldorp JM, Oepkes D, et al. (2009). Risk factors for neurodevelopment impairment in twin-twin transfusion syndrome treated with fetoscopic laser surgery. Obstetrics and Gynecology; 113(2 Pt 1):361-366. DOI: 10.1097/AOG.0b013e318195873e

Lopriore, E, Lewi, L, Khalil, A. (2019). Monochorionic twins: a delicate balance.

Mackie, F. L, Rigby, A, Morris, R. K, Kilby, M. D. (2019). Prognosis of the co-twin following spontaneous single intrauterine fetal death in twin pregnancies: a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, *126*(5), 569-578.

Matias, A, Blickstein, I. (Eds.). (2020). *Developmental and Fetal Origins of Differences in Monozygotic Twins: From Genetics to Environmental Factors*. Academic Press.

Micheletti, T, Eixarch, E, Bennasar, M, Martinez, J. M, Gratacos, E. (2021). Complications of Monochorionic Diamniotic Twins: Stepwise Approach for Early Identification, Differential Diagnosis, and Clinical Management. *Maternal-Fetal Medicine*, *3*(1), 42-52.

Migdal, K. U. (2020). *The Impact of Dietary Sodium on Cerebral Blood Flow Regulation*. University of Delaware.

Mogra, R, Saaid, R, Tooher, J, Pedersen, L, Kesby, G, Hyett, J. (2020). Prospective validation of first-trimester ultrasound characteristics as predictive tools for twin-twin transfusion syndrome and selective intrauterine growth restriction in monochorionic diamniotic twin pregnancies. Fetal diagnosis and therapy, 47(4), 321-327.

Peavey, M. C, Dotters-Katz, S. K. (2021). *Ultrasound of Mouse Fetal Development and Human Correlates*. CRC Press.

Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kurger M (1999). Staging of twin-twin transfusion syndrome. J Perinatol; 19: 550-555

Rychik, J, Tian, Z, Bebbington, M, Xu, F, McCann, M, Mann, S, et al. (2007). The twin-twin transfusion syndrome: spectrum of cardiovascular abnormality and development of a cardiovascular score to assess severity of disease. *American journal of obstetrics and gynecology*, *197*(4), 392.e1–392.e3928. https://doi.org/10.1016/j.ajog.2007.06.055

Sebire NJ, D'Ercole C, Hughes K, Carvalho M, Nicolaides KH (1997). Increased nuchal translucency thickness at 10-14 weeks of gestation as a predictor of severe twin-to-twin transfusion syndrome. Ultrasound Obstet Gynecol; 10 (2):86-9.

Sherer, D. M, Al-Haddad, S, Cheng, R, Dalloul, M. (2021). Current Perspectives of Prenatal Sonography of Umbilical Cord Morphology. *International Journal of Women's Health*, *13*, 939-971.

Slaghekke F, Lopriore E, Lewi L, Middeldorp JM, Van Zwet EW, Weingertner AS, et al (2004). Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: An open-label randomised controlled trial. Lancet; 383(9935):2144-2151. DOI: 10.1016/j.ajog.2007.06.009

Sobhani, N. C, Sparks, T. N, Gosnell, K. A, Rand, L, Gonzalez, J. M, Feldstein, V. A. (2021). Outcomes of Monochorionic, Diamniotic Twin Pregnancies with Prenatally Diagnosed Intertwin Weight Discordance. *American Journal of Perinatology*, *38*(07), 649-656.

Srinivasan, S, Treacy, R, Herrero, T, Olsen, R, Leonardo, T. R, Zhang, X, et al. (2020). Discovery and verification of extracellular miRNA biomarkers for non-invasive prediction of pre-eclampsia in asymptomatic women. *Cell Reports Medicine*, *1*(2), 100013.

Tollenaar, L, Slaghekke, F, van Klink, J, Groene, S. G, Middeldorp, J. M, Haak, M. C, et al. (2019). Twin-Twin Transfusion Syndrome with Anemia-Polycythemia: Prevalence, Characteristics, and Outcome. *Journal of clinical medicine*, *8*(8), 1129. https://doi.org/10.3390/jcm8081129

Toneto, B. R. (2018). Complications in Monochorionic Pregnancies. In *Multiple Pregnancy-New Challenges*. IntechOpen.

Turk, E. A, Stout, J. N, Ha, C, Luo, J, Gagoski, B, Yetisir, F, et al. (2019). Placental MRI: developing accurate quantitative measures of oxygenation. *Topics in magnetic resonance imaging: TMRI*, *28*(5), 285.

Wixey, J. A, Chand, K. K, Colditz, P. B, Bjorkman, S. T. (2017). Neuroinflammation in intrauterine growth restriction. *Placenta*, *54*, 117-124.

Xie, J, Cheng, Z, Wu, T, Wei, Y, & Wang, X. (2020). Protocol: Microwave ablation versus radiofrequency ablation for the treatment of severe complicated monochorionic pregnancies in China: protocol for a pilot randomised controlled trial. *BMJ Open*, *10*(8).

Zaami, S, Masselli, G, Brunelli, R, Taschini, G, Caprasecca, S, Marinelli, E. (2021). Twin-to-Twin Transfusion Syndrome: Diagnostic Imaging and Its Role in Staving Off Malpractice Charges and Litigation. *Diagnostics*, *11*(3), 445.