A Dynamic Model of Circadian Rhythm of Melatonin and the Effect of Night Shifts on Risk of Autism in Late-Stage Pregnancy

Ekin Yurdakul Erkut [(1)*], Kutlu Ulgen [(1)], Yaman Barlas [(2)(3)**]

(1) Department of Chemical Engineering, Bogazici University, 34342, Istanbul, Turkiye.

(2) Department of Industrial Engineering, Acıbadem University, 34638, Istanbul, Turkiye

(3) Department of Industrial Engineering, Bogazici University, 34342, Istanbul, Turkiye

*ekin.yurdakul@std.bogazici.edu.tr, ** yaman.barlas@acibadem.edu.tr

Keywords: circadian, melatonin, malondialdehyde, night shift, fetus, autism, system dynamics, simulation

Funded by Health Institutes of Turkey (TUSEB) Project 2324; The Scientific and Technological Research Council of Turkey (TUBITAK) PhD Scholarship Program 2211/C, Grant Program for Participation in Scientific Meetings Abroad 2224/A; and Acıbadem University

In this study, a simulation model of maternal-fetal circadian rhythm disruption and its impact on autism risk is constructed. This dynamic modeling study examines the effects of circadian disorders resulting from night shifts in the mother on the circadian rhythm of the fetus and the development of autism.

Melatonin is known as a darkness hormone and is even increasingly secreted at night (Rajaratnam et al., 2001). The melatonin hormone is essential to regulate the circadian rhythm, an approximately 24-hour cycle of hormone production affected by light. Melatonin has antioxidant properties that reduce Malondialdehyde levels as an oxidative stress and lipid peroxidation marker (Chakravarty & Rizvi, 2011). During the pregnancy, maternal melatonin levels increase from trimester to trimester, and it helps protect the fetus from oxidative stress and helps the mother regulate circadian rhythm and sleep. Maternal melatonin is transferred to the fetus to synchronize the circadian rhythm, which is essential to arrange it after labor. In the literature, Danish nurses working on the night shift have lower melatonin levels compared to day shift workers, even on their off day, still lower levels, but the difference was more minor (Hansen et al., 2006; Garde et al., 2009). Night shift work during pregnancy disrupts the maternal melatonin circadian rhythm and increases oxidative stress. A study conducted on mothers that has autistic children has lower melatonin levels compared to mothers in the control group (Braam et al., 2018). In addition, in the research conducted by Melke et al., the melatonin levels in the autistic individuals were 50% lower than those in the control group (Melke et al., 2008). The opposite is true for malondialdehyde, with higher levels observed in autistic children (Altun et al., 2018). Increased Malondialdehyde levels and decreased Melatonin levels in the fetus may cause neurodevelopmental disorders and increase the risk of autism in late stages of pregnancy.

In this study, we aimed to model the dynamic effects and causal interactions of disruption of maternal melatonin circadian rhythm (third trimester of pregnancy) due to the night shift and its impact on fetal

melatonin and Malondialdehyde circadian rhythm, and the risk of autism in the fetus.

The stock-flow diagram includes three sectors: maternal-fetal melatonin, maternal-fetal malondialdehyde, and risk of autism, shown in Figure 1. Interactions between maternal and fetal variables, third-trimester values, antioxidant properties of melatonin, and night shift disruption are defined based on the literature. Healthy and disrupted maternal circadian patterns (due to night shift work) are determined and validated, as shown in Figure 2. Different night shift work scenarios, which are tabulated in Table 1, are simulated.

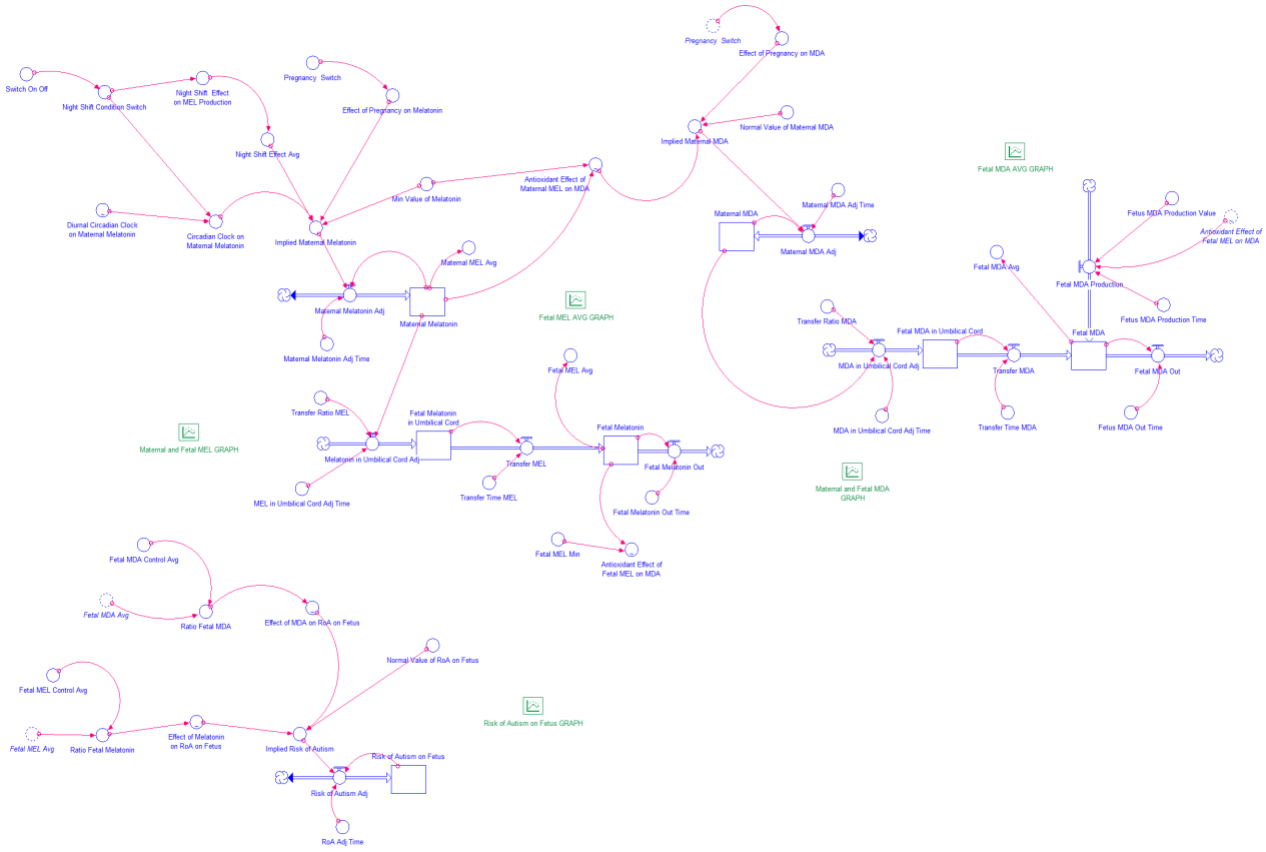


Figure 1. Stock-Flow Diagram of Maternal-Fetal Melatonin, MDA and Risk of Autism Sectors

Table 1. Simulation Experiments

Experiment Number	Night Shift Condition
Experiment Base Run	4 nights of work followed by 3 days off
Experiment 1	5 nights of work followed by 2 days off
Experiment 2	3 nights of work followed by 4 days off
Experiment 3 (Extreme Condition)	2 nights of work followed by 5 days off
Experiment 4	Base experiment quitting the night shift after 1.5 months

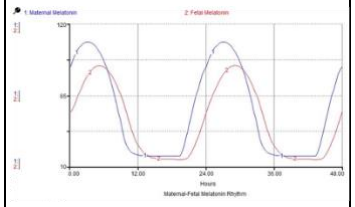
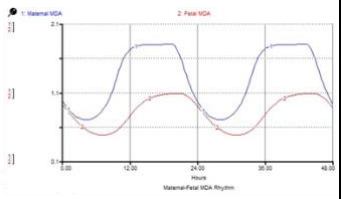
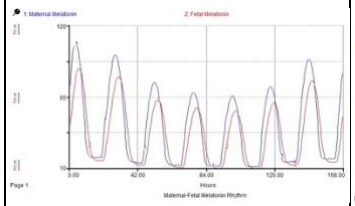
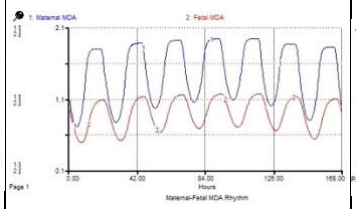
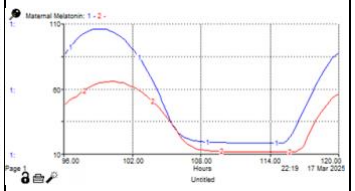
Control Melatonin Levels	Control Malondialdehyde Levels	Base Experiment Melatonin Levels	Base Experiment Malondialdehyde Levels	Melatonin Levels in Shift Workers: Day vs. Night
				

Figure 2. Healthy and Disrupted Maternal Circadian Patterns

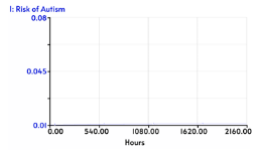
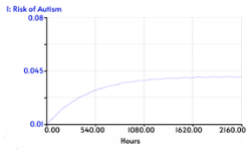
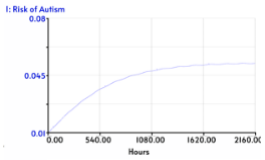
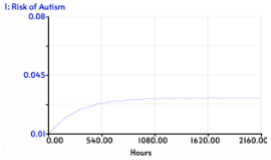
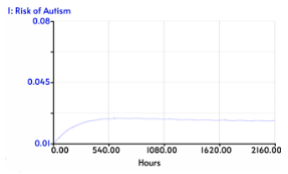
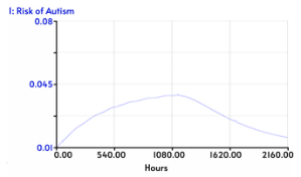
Risk of Autism					
Control	Base	Exp. #1	Exp. #2	Exp. #3 (Extreme Condition)	Exp.#4 (Quitting Night Shift)
					
0.01	0.041	0.052	0.031	0.023	0.015

Figure 3. Risk of Autism Results

This model is an initial simulation study to understand the dynamics of maternal-fetal circadian rhythm and risk of autism that night shift work may cause in the fetus. Night shifts reduce fetal melatonin levels by 22% and increase fetal malondialdehyde by 11%, significantly raising the risk of autism. The risk of autism in the fetus increased as a result of night shifts, and even if the night shift was stopped after a certain period, the risk of autism decreased but did not decrease to the base level as shown in Figure 3. Considering these findings, night-shift related circadian disorders should be examined in more detail, and further clinical studies should be conducted on their impacts on fetal health.

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