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Melatonin Doesn't Just Make You Sleepy: The Connection Between Melatonin and IVF Success

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The Connection Between Melatonin and IVF Success

Getting pregnant poses a challenge for many; couples who struggle with infertility, people in same-sex relationships, and individuals who choose to get pregnant without a partner, must all look for an alternative to conceiving a child through coitus. In vitro fertilization (IVF) provides a different way for people to get pregnant. It is when mature eggs are harvested, inseminated and then implanted into a uterus. According to the World Health Organization (WHO), infertility affects 15% of reproductive age couples around the world (Infertility). Thankfully, IVF has been a successful option for assisted reproductive technology (ART) pregnancies since 1978 and has improved significantly since then (Eskew and Jungheim). However, even with IVF and its developments, infertility still proves to be a roadblock to many pregnancies. Oftentimes, during IVF, incubators and the handling of oocytes expose the embryos to higher oxygen concentrations, which are associated with higher imbalances of 'reactive oxygen species' (ROS). (Fernando and Rombauts) Though a vital component of biological functions, a plethora of ROS with fewer antioxidants can result in cellular damage known as 'oxidative stress.' As recent studies have shown, oxidative stress acts as a contributing factor of infertility (and as a result, unsuccessful IVF treatment) because it negatively impacts the quality of the embryos and oocytes through harming cells and tissues (Fernando and Rombauts).

Oxidative stress has been found to "cause toxic effects on oocyte maturation and is considered one of the causes of poor oocyte quality." (Hu et al.). It has also been found that when ROS levels are misregulated, "meiotic progression and early embryonic divisions are defective," both vital functions for a successful fertilization (Petrova et al.). Because "reproductive outcomes

depend directly on the quality of oocytes," (Vitale et al.), and higher amounts of oxidative stress worsen oocyte quality, oxidative stress contributes to infertility. In summary, as stated in a study observing Melatonin and Female Reproduction,"Although the etiology of infertility is complex and not fully clarified, a recurring aspect appears to be excessive production of reactive oxygen species in the follicular fluid" (Olcese). In regard to IVF specifically, the process exposes oocytes to higher oxygen concentrations, therefore the risk of oxidative stress is high and thus can hold an impact on the success of an IVF pregnancy. The problem is identified, oxidative stress. The question is now raised to find a solution, how can oxidative stress be reduced in order to improve the quality of oocytes and thus, the success of IVF pregnancy?

A solution to (reducing oxidative stress in oocytes) currently under investigation is the supplementation of melatonin (a neuro-hormone primarily produced and secreted from the pineal gland) throughout infertility treatment. Rationale behind this research is that melatonin, as an antioxidant, has oxygen scavenging abilities. It can be used to combat ROS (a key component of oxidative stress) through giving reactive oxygen species an electron in order to stabilize them (Understanding Antioxidants). More antioxidants must be introduced into the system in order to return the cells to a "redox balance*" (Vitale et al.), melatonin, in this case, acts as a stabilizer. Recent studies show that melatonin has "been shown to exhibit unique oxygen scavenging

abilities," different from those of classical antioxidants (Fernando and Rombauts). Some of its unique qualities include binding sites within the nucleus, and it being amphiphilic (it can go through cell membranes easily). Melatonin is also a "suicidal terminal antioxidant," meaning it does not promote oxidation at any point because it is an electron-rich molecule, unlike other antioxidants which need to undergo redox cycling (Fernando and Rombauts; Tan et al.).

Melatonin's unique qualities continue with its ability to scavenge more than one molecule per melatonin molecule, this quality makes it a powerful antioxidant and contributes to its strength in oxygen scavenging (Tan et al). Melatonin has also been found to, "enhance the activity of other endogenous antioxidants including glutathione peroxidase and superoxide dismutase"** (Fernando and Rombauts). In addition to the speculation of melatonin's effect on oxidative stress levels, a systematic review and meta analysis done in regards to melatonin supplementation on oxidative stress parameters concluded that, "Melatonin intake was shown to have a significant impact on improving Oxidative stress parameters." (Morvaridzadeh et al.). Melatonin's distinctive traits suggest and prove that it is a highly efficient antioxidant in terms of oxygen scavenging, which is a vital component to reducing oxidative stress, a direct link to determining the success of infertility treatment.

Considering melatonin's unique oxygen scavenging abilities, researchers are led to investigate the link of melatonin supplementation with the success of IVF and reproduction. In relation to the reproductive system, "Melatonin receptors have been demonstrated in a variety of cell types in the female reproductive tract uterus… Hence, one should consider all of these [reproductive] cells to be potential targets for melatonin action." (Olcese). A meta-analysis of

randomized trials regarding the supplementation of melatonin during ART found that melatonin treatment, "significantly increased the clinical pregnancy rate," along with the amount of oocytes collected, matured oocytes, and good quality embryos (Hu et al.). Among clinical studies done surveying the oral supplementation of melatonin throughout the IVF phase of ovarian stimulation, with a 3 mg daily dose of melatonin (during specific times of women's cycles), found a statistically significant increase in rates of good embryos, fertilization, and MII oocyte

counts. The rate of good embryos in the melatonin cycle was as high as 65%, as opposed to before melatonin supplementation, when it was just 27%. Additionally, the fertilization rate increased from 20.2% prior to melatonin supplementation to 50% after. This may potentially be related to the fact that there were also higher MII oocyte counts (mature oocytes), going from 4.4 to 9 after melatonin supplementation (Fernando and Rombauts). The results from this study show the positive correlation between melatonin supplementation and not only oocyte health, but also more successful fertilization in general. In light of that, a trial studying melatonin's impact on IVF pregnancies from implantation to birth deduced that "Overall, both experimental and clinical studies support the positive effects of melatonin on oocyte quality and embryo implantation, and patients with subfertility or infertility may benefit from melatonin supplementation." (Carlomango et al.)

In conclusion, all of the studies and research conducted in relation to melatonin and fertility indicate a positive connection between melatonin and higher rates of fertilization in IVF pregnancies. As discussed, oxidative stress harms oocyte health and is directly linked to lower fertility rates. To further the challenge of infertility, IVF, though a proven successful ART,

exposes oocytes to higher oxygen concentration, thus increasing ROS in the cells and in turn, oxidative stress. As a result of melatonin's unique oxygen scavenging abilities, it is able to stabilize the free radicals (ROS) and therefore reduce oxidative stress within the cells. As meta-analysis, and exploratory and clinical studies have shown, a dose of 3 mg of melatonin daily, during specific phases of IVF treatment, is directly associated with higher quality oocytes, higher embryo G1 transfer rates, and higher fertilization rates. This is likely due to melatonin's lowering of oxidative stress in oocytes and thus improvement of oocyte health and quality.

Melatonin has the potential to contribute to the solving of certain challenges of infertility in general and more specifically, could play a key role in making IVF more effective.

*The cellular redox environment is a balance between the production of reactive oxygen species (ROS), reactive nitrogen species (RNS), and their removal by antioxidant enzymes and small-molecular-weight antioxidants. (Sarsour et al.)

**Enzymes found in living cells that catalyze specific chemical reactions. They contribute to the breaking down of excessive oxygen molecules in cells.

Resources

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