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Editorial

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It is Time to Evaluate Human Chorionic Gonadotropin for the Treatment of Preterm Births

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Births between 20th to 37th completed gestational weeks are considered preterm. More births occur during late (34-36 weeks) than in early (before 34 weeks) preterm period. Preterm births account for more infant deaths than any other cause. The prematurely born infants have breathing problems, feeding difficulties, cerebral palsy, developmental delays, vision problems and hearing impairment. These complications are generally more severe in early than in late preterm born infants. Preterm infants require medical care in neonatal intensive care units for several weeks after birth. The surviving infants are at a greater risk for early death and life-long neurological and cognitive difficulties. All this medical care costs billions of US healthcare dollars. In addition, parents go through considerable amount of guilt and emotional trauma.

The incidence of preterm births is about 9% in US and higher in third world countries. Despite the basic science and clinical research advances to better understand and control preterm births, the rates are increasing. The current therapies include β-androgenic agonists, calcium channel blockers, non-steroidal anti-inflammatory compounds, nitric oxide donors, oxytocin antagonists, etc. Among them Magnesium sulfate ($MgSO_4$) is a popular first line therapy. Most of these drugs are only used for about 24-48 hours, so that the patients can be treated with corticosteroids to promote fetal lung maturity. The infants with relatively mature lungs have better survival chances. There is a clear unmet need to improve upon the current therapies to better control and treat preterm births.

The paradigm shift on human chorionic gonadotropin (hCG) actions revealed that it can act on human myometrium.[1] It contains hCG/luteinizing hormone receptors and their activation results in an inhibition of contractions.[1-5] These findings are consistent with the notion that hCG promotes myometrial quiescence, which is a prerequisite for pregnancy initiation and continuation.[5] The quiescence declines as pregnancy advances, which permits myometrial stimulants to dominate so that they can facilitate normal labor progression.[5] The maintenance of myometrial quiescence by hCG suggests, that it could be used for suppression of prematurely activated myometrial contractions, that are responsible for preterm births.[5,6] In fact, hCG has been shown to be effective in preventing preterm birth in a mouse model.[7]

There are now five clinical studies testing hCG in the treatment of preterm births.[8-12] Four of them were on women with active labor and the fifth was on women with a previous history of preterm births.[8-12] The studies on women with active labor were compared with $MgSO_4$ treatment.[8-11] The results showed that while hCG was equally effective, it did not have the side effects of $MgSO_4$.[8-11] In the prophylactic study, hCG was found to be equally effective as vaginal micronized progesterone tablets with a better compliance rate than progesterone.[12]

Despite this encouraging data, there are no large scale clinical trials with hCG, like those conducted with 17-hydroxy-progesterone caproate (17-OHP-C) and progesterone.[13,14] The US Food and Drug Administration approved 17-OHP-C use in women with previous his-

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tory of at least one preterm birth with singleton pregnancies. It is effective, but it is not known how it works. For example, 17-OHP-C does not inhibit myometrial contractions, it is only a week binder to PR-A and PR-B and is not converted to progesterone in the body.[15] Finally, it is not cheap and the potential side effects have not yet been completely resolved. In contrast, hCG is an inhibitor of myometrial contractions, antagonizes the oxytocin actions and the mechanisms of action are rather fairly well defined.[2-4,16] It has minor side effects that do not generally require medical attention. In addition, it is cheap and can be made even cheaper by scaling up the production of recombinant hormone. In third world countries, where access to medical care is minimal to non-existent in rural areas, inexpensive therapies, that have a minimal or no maternal or fetal side effects, are easy to adopt.

A large multicenter, randomized, double-blind clinical trials on women with active labor and those with a previous history of preterm births are needed for hCG on a comparable scale to the ones done with 17-OHP-C and progesterone. These trials require the support of governmental and non-governmental organizations, which are dedicated to improving maternal, neonatal and child health, which is heavily impacted by preterm births. Should hCG be proven useful, it is possible to develop long acting analogs, synthetic mimetics, lozenges, delivery by nanoparticles, improving intravenous infusion conditions, combination therapies to increase the treatment effectiveness, etc. As any therapy, hCG treatment may not work in every single patient. Finally, hCG therapy may not be a panacea, but it is likely to become an important part of an obstetricians tool box to treat preterm births.

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