41 Three-dimensional patient-derived uterine cell culture for evaluating the efficacy of tocolytic combinations

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OBJECTIVE: Despite some improvements in the preterm labor (PTL) treatment, the rates are remaining high. Tocolytic therapies vary in drug class and mechanism of action. Since tocolytics are frequently associated with serious maternal/fetal side effects, using drug combinations could (1) be more efficacious over a single tocolytic, while allowing for (2) dose and, thus, toxicities reduction. Indeed, in cardiovascular, infectious and other disorders, drug combinations are common, yielding safer (lower doses) and more efficient (synergistic action) therapies. However, a recent review (Cochrane 2014) concluded that "It is unclear if a combination of tocolytic drugs for PTL is more advantageous ...". A possible reason for that outcome can be the need for individualization of the doses of tocolytic agents used in combination. Our objective was to design an assay that can shed more light on the efficacy of tocolytic drug combinations for PTL management.

STUDY DESIGN: We developed a new *in vitro* assay, Contractility Bio (CBiO) Assay, that uses magnetic bioprinting/levitation to assemble cells into 3D rings (Fig 1). The bioprinted uterine rings spontaneously contract and the kinetics/ dynamics of this contraction can (1) be assessed by area change using an imaging device; (2) prevented by tocolytics. We have evaluated the effects of tocolytic agent combinations (indomethacin, IND, and nifedipine, NIF) on preventing contraction of uterine cell rings bioprinted from patient derived cells. Uterine tissues were obtained from women undergoing cesarean sections at term (39w) and preterm (34w) gestations. Various combinations of tocolytics were assessed in CBiO assay. Changes in contractility were calculated based on the ring area over time.

RESULTS: (1) There are differences between the response of bioprinted uterine tissues from term and preterm patients (Fig 2); (2) Effects of clinically used tocolytics in preventing the contractions in CBio assay vary; (3) There is a dose range in which drug combinations had synergistic effect in preventing the contractions, as evident from preterm uterine tissue response to a combination of IND 75% and NIF 25%.

CONCLUSION: CBiO assay can serve as a basis for studying the mechanisms by which the use of tocolytics can be personalized to yield safer and more efficient regimens for PTL management.

***Figure 1:** Schematic presentation of the CBiO Assay.*

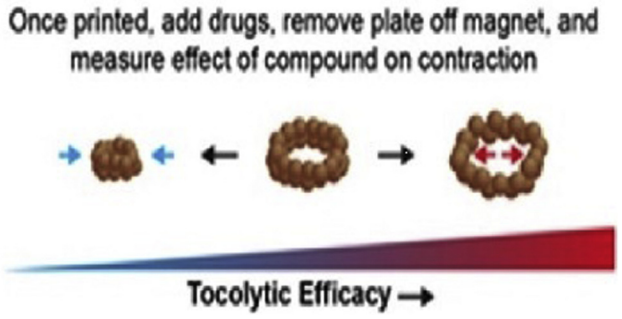

***Figure 2** Changes in response of uterine myometrial cells rings contractility in **CBio assay** in term and preterm patient-derived cells, dosed with various concentrations of 100% indomethacin (IND), 100% nifedipine (NIF), 25% IND and 75% (IND is at 1:4 of the initial dose and NIF is at ¾) and 75% IND and 25% (IND is at ¾ of the initial dose and NIF is at 1/4) solutions. N=8.*