

## Redirection of Cytokine Production Patterns by Dydrogesterone, an Orally-Administered Progestogen

**Authors :** Raj Raghupathy

**Abstract :** Recurrent Spontaneous Miscarriage (RSM) is a common form of pregnancy loss, 50% of which are due to 'unexplained' causes. Evidence exists to suggest that RSM may be caused by immunologic factors such as cytokines which are critical molecules of the immune system, with an impressive array of capabilities. An association appears to exist between Th2-type reactivity (mediated by Th2 or anti-inflammatory cytokines) and normal, successful pregnancy, and between unexplained RSM and Th1 cytokine dominance. If pro-inflammatory cytokines are indeed associated with pregnancy loss, the suppression of these cytokines, and thus the 'redirection' of maternal reactivity, may help prevent cytokine-mediated pregnancy loss. The objective of this study was to explore the possibility of modulating cytokine production using Dydrogesterone (Duphaston®), an orally-administered progestogen. Peripheral blood mononuclear cells from 34 women with a history of at least 3 unexplained recurrent miscarriages were stimulated in vitro with a mitogen (to elicit cytokine production) in the presence and absence of dydrogesterone. Levels of selected pro- and anti-inflammatory cytokines produced by peripheral blood mononuclear cells were measured after exposure to these progestogens. Dydrogesterone down-regulates the production of pro-inflammatory cytokines and up-regulates the production of anti-inflammatory cytokines. The ratios of Th2 to Th1 cytokines are markedly elevated in the presence of dydrogesterone, indicating a shift from potentially harmful maternal Th1 reactivity to a more pregnancy-conducive Th2 profile. We used a progesterone receptor antagonist to show that this cytokine-modulating effect of dydrogesterone is mediated via the progesterone receptor. Dydrogesterone also induces the production of the Progesterone-Induced Blocking Factor (PIBF); lymphocytes exposed to PIBF produce higher levels of Th2 cytokines, affecting a Th1 → Th2 cytokine shift which could be favourable to the success of pregnancy. We conclude that modulation of maternal cytokine production profiles is possible with dydrogesterone which has the merits that it can be administered orally and that it is safe.

**Keywords :** cytokines, dydrogesterone, progesterone, recurrent spontaneous miscarriage

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