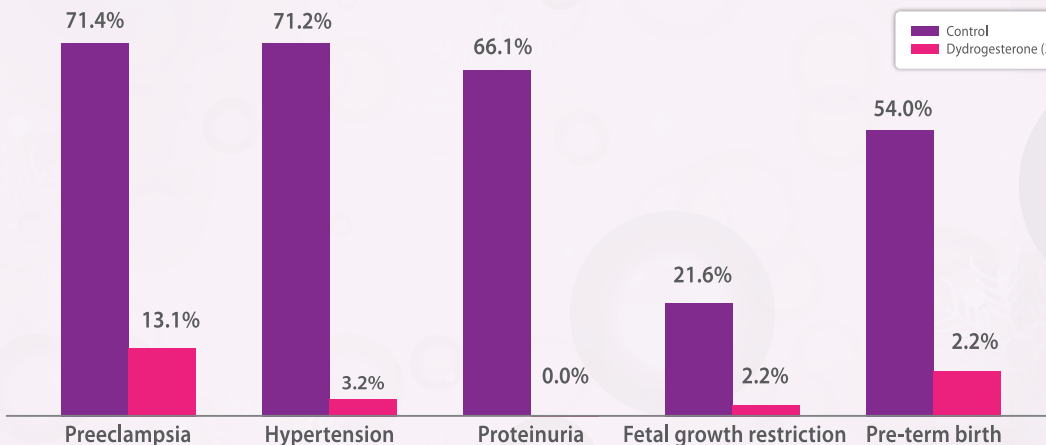


# The role of Dydrogesterone in the prevention of Preeclampsia

- Preeclampsia, with or without severe features, is a disorder of pregnancy associated with new-onset hypertension, usually with accompanying proteinuria, which occurs most often after 20 weeks of gestation.<sup>1</sup>
- This represents a spectrum of hypertensive disease in pregnancy, beginning with gestational hypertension and progressing to develop severe features, ultimately leading to eclampsia and HELLP syndrome.<sup>1</sup>
- This disease encompasses 2% to 8% of pregnancy-related complications, more than 50,000 maternal deaths, and over 500,000 fetal deaths worldwide.<sup>1</sup>
- Early diagnosis and prompt management are essential to prevent maternal and neonatal complications.<sup>1</sup>

## Role of Dydrogesterone in preventing preeclampsia & complications (n=406)<sup>2</sup>



- The use of dydrogesterone (30 mg/d) in early pregnancy with risk factors of preeclampsia (PE) contributed to a statistically significant reduction in the frequency of this complication (13.1% & 71.4%,  $p < .001$ ).
- The frequency of PE in the group of pregnant women without risk factors treated with dydrogesterone was also significantly lower than in the group who were not receiving dydrogesterone (11.6% & 100%,  $p < .001$ ).
- Dydrogesterone significantly reduced gestational complications such as hypertension (3.2% & 71.2%,  $p < .001$ ), proteinuria (0% & 66.18%,  $p < .001$ ), fetal growth retardation (2.2% & 21.58%,  $p < .001$ ), uteroplacental blood flow disorders (3.2% and 21.58%,  $p < .001$ ) & preterm birth (8.6% & 53.95%,  $p < .001$ ).

**Dydrogesterone supplementation, in the early pregnancy (6 to 20 weeks), significantly reduces the incidence of PE in women with high risk pregnancy.**

Ref.: 1. Karrar SA, Martingano DJ, Hong PL. Preeclampsia. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan--2. V Tskhay et al. Gynecol Endocrinol. 2020 Aug.

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# Immunomodulatory mechanisms of Dydrogesterone in pregnancy maintenance

Dydrogesterone, a synthetic retro progestogen, plays a crucial role in supporting pregnancy by modulating the maternal immune system. Its immunomodulatory effects help maintain tolerance to the fetus and prevent immune-mediated pregnancy complications.

## Shift in cytokine profile: Th1 to Th2 dominance<sup>1</sup>

Successful pregnancy is associated with a Th2-dominant immune response. **Dydrogesterone** reduces Th1 cytokines (e.g., IFN- $\gamma$ , TNF- $\alpha$ , IL-2) and enhances Th2 cytokines (e.g., IL-4, IL-10), thereby shifting the immune balance toward a pregnancy-supportive Th2 profile.

## Suppression of inflammatory responses<sup>2</sup>

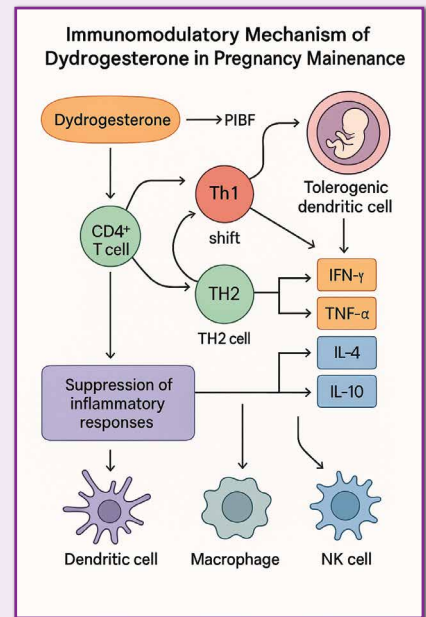
**Dydrogesterone** inhibits the activation of immune cells such as dendritic cells, macrophages & NK cells. It suppresses NF- $\kappa$ B activation, reduce pro-inflammatory cytokines.

## Progesterone-induced blocking factor (PIBF)<sup>2</sup>

**Dydrogesterone** stimulates the production of PIBF, inhibits NK cell cytotoxicity, promotes differentiation of CD4+ T cells into Th2 cells, and reduces fetal rejection.

## Enhancement of tolerogenic dendritic cells and tregs<sup>2</sup>

**Dydrogesterone** promotes the development of tolerogenic dendritic cells, induces regulatory T cells (Tregs). Tregs help maintain immune tolerance at the maternal-fetal interface, supporting pregnancy continuation.



## Dydrogesterone and preeclampsia

### Enhancing trophoblast invasion and spiral artery remodeling

Dydrogesterone supports placental decidualization and vascular remodeling, improves blood flow to the placenta, reducing ischemic damage and oxidative stress

### Endothelial protection

It reduces endothelial dysfunction by lowering levels of endothelin and soluble adhesion molecules, helps maintain vascular integrity and prevents hypertension-related damage.

### Hormonal stabilization

Dydrogesterone stabilizes progesterone levels, prevents the cascade of hormonal imbalance that contributes to vascular and immune disturbances.

**Ref. 1.** Raghupathy, Raj and Szekeres-Bartho, Julia. "Dydrogesterone and the immunology of pregnancy" *Hormone Molecular Biology and Clinical Investigation*, vol. 27, no. 2, 2016, pp. 63-71. <https://doi.org/10.1515/hmbci-2015-0062>; **2.** Raghupathy, R.; Szekeres-Bartho, J. Progesterone: A Unique Hormone with Immunomodulatory Roles in Pregnancy. *Int. J. Mol. Sci.* 2022, 23,1333.



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