Dydrogesterone *versus* Micronized Progesterone

Dydrogesterone *versus* Micronized Progesterone Receptor Selectivity

Biological activity	Dydrogesterone	Progesterone
Progestogenic	+	+
Anti-gonadotropic	–	+
Anti-estrogenic	+	+
Estrogenic	–	–
Androgenic	–	–
Anti-androgenic	±*	±
Glucocorticoid	–	+
Anti-mineralocorticoid	±	+

Dydrogesterone is selective for the progesterone receptor, avoiding other receptor-related side effects[1–4]

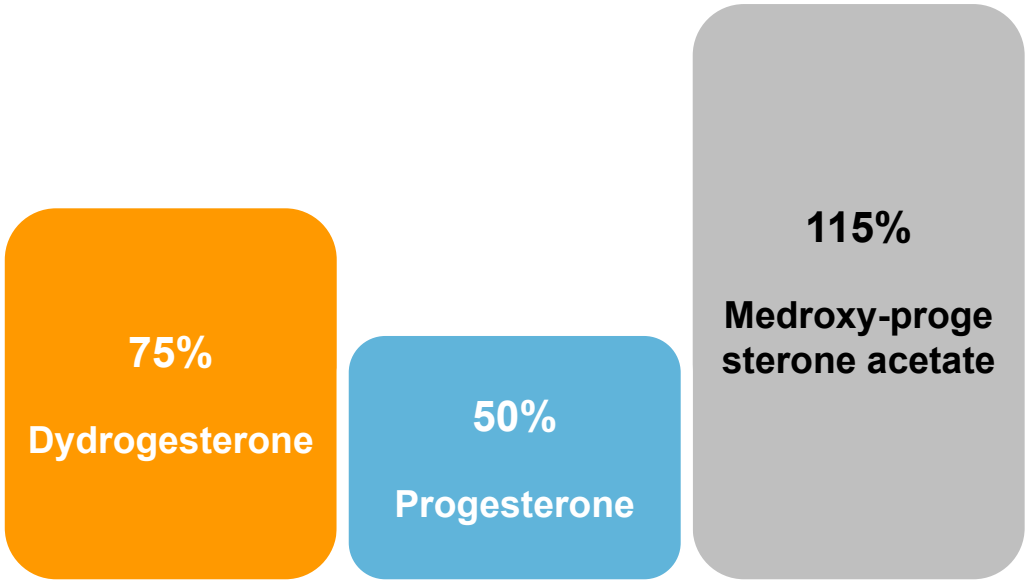
*Dydrogesterone has less pronounced anti-androgenic effects than progesterone; + effective; ± weakly effective; – not effective

1. Schindler AE, et al. Maturitas 2008; 61(1-2):171-180. 2. Schindler AE. Maturitas 2009; 65(Suppl 1):S3-S11. 3. Dydrogesterone CCDS. 23 June 2015. 4. Rižner TL, et al. Steroids 2011; 76(6):607-615.

Dydrogesterone *versus* Micronized Progesterone Receptor Affinity

Dydrogesterone has ~1.5 times better affinity to progesterone receptors than progesterone[1]

Affinity to progesterone receptor[1]

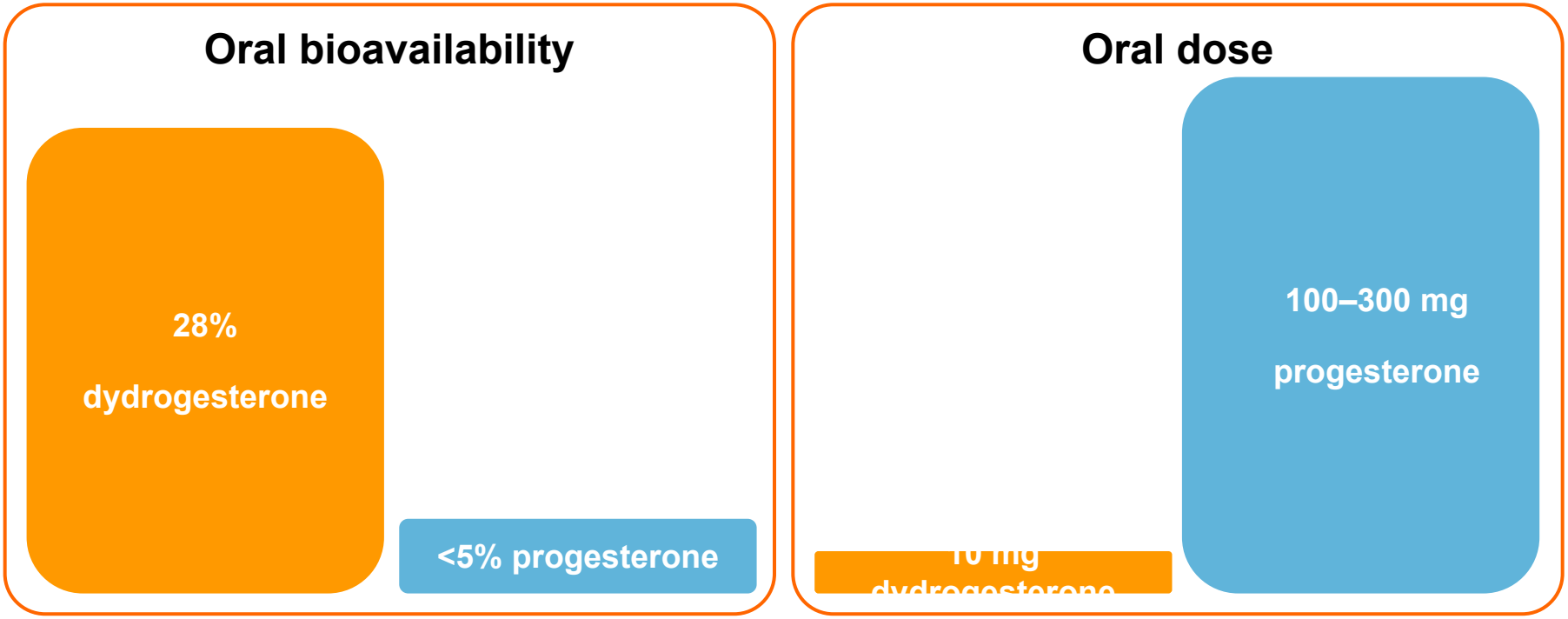


Dihydrodydrogesterone, the main metabolite of dydrogesterone, also has progestogenic activity[1-3]

1. Schindler AE, et al. Maturitas 2008; 61(1-2):171-180.
2. Schindler AE. Maturitas 2009; 65(Suppl 1): S3-S11.
3. Dydrogesterone CCDS. 23 June 2015.

Dydrogesterone *versus* Micronized Progesterone Bioavailability and Oral Administration

Dydrogesterone has ~5.6 times better oral bioavailability than progesterone[1–3]



Dydrogesterone requires a 10–20 times lower oral dose than micronized progesterone,[1–3] providing clear clinical benefits[4–6]

1. Schindler AE, et al. Maturitas 2008; 61(1-2):171-180. 2. Schindler AE. Maturitas 2009; 65(Suppl 1):S3-S11. 3. Stanczyk FZ, et al. Endocr Rev 2013; 34(2):171-208. 4. Patki A, Pawar VC. Gynecol Endocrinol 2007; 23(Suppl 1):68-72. 5. Ganesh A, et al. Fertil Steril 2011; 95(6):1961-1965. 6. Chakravarty BN, et al. J Steroid Biochem Mol Biol 2005; 97(5):416-420.

Dydrogesterone *versus* Vaginal Micronized Progesterone Absorption and Plasma Levels

Dydrogesterone[1]

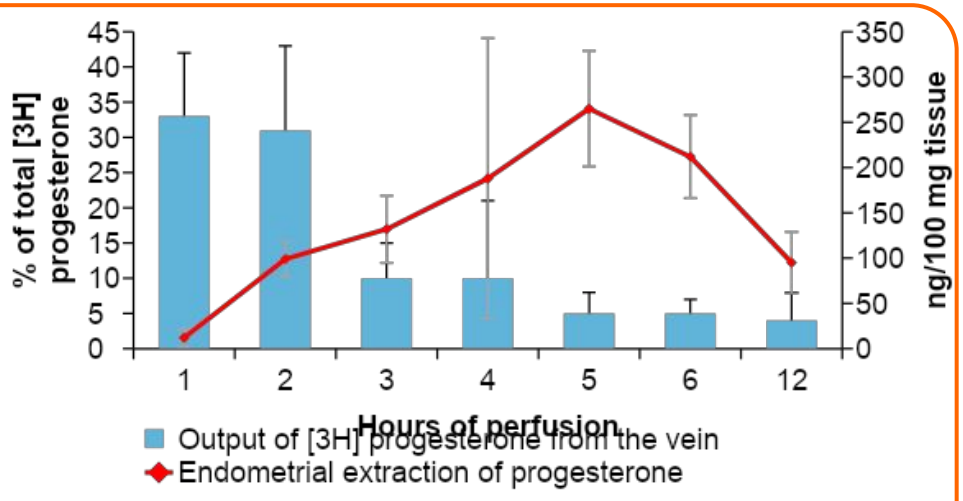
- Has **quick-effect onset** (rapidly absorbed, reaching maximal levels between 30 minutes and 2.5 hours after administration)
- Has a **long, stable effect** (mean terminal half-life is 5–7 hours)

Vaginal progesterone[2]

Progesterone diffuses through the entire uterus by 4–5 hours, and then decreases concentration after 5 hours

Venous blood outflow from the uterus was highest in the first 2 hours

Vaginal route permits targeted drug delivery for a short period of time



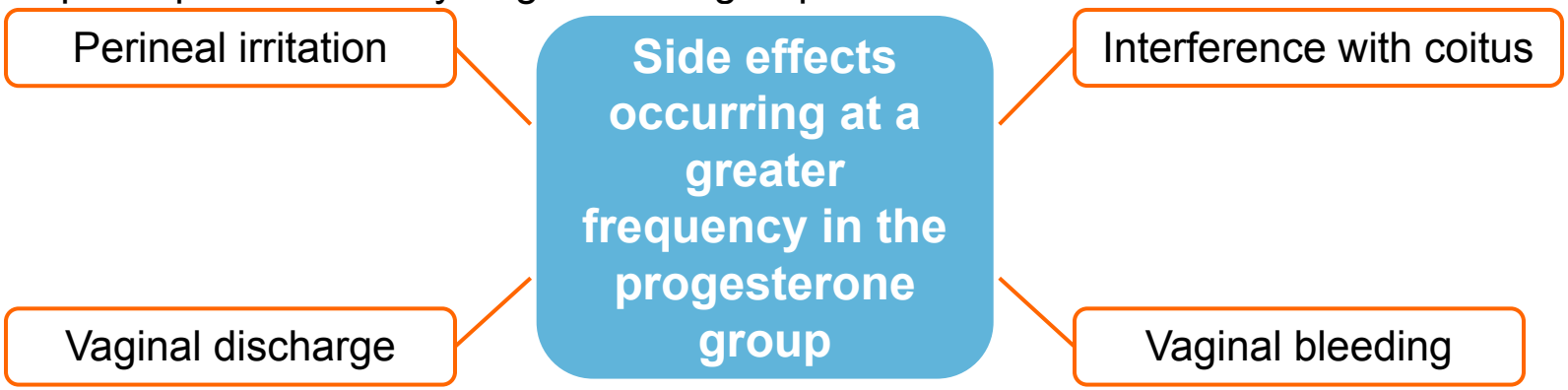
Adapted from Bulletti C, et al. Hum Reprod 1997; 12(5):1073-1079

Dydrogesterone reaches peak absorption levels more rapidly than vaginal progesterone, and these levels are maintained for a longer duration[1,2]

1. Dydrogesterone CCDS. 23 June 2015.
2. Bulletti C, et al. Hum Reprod 1997; 12(5):1073-1079.

Dydrogesterone *versus* Vaginal Micronized Progesterone Safety and Tolerability

- Both oral and vaginal micronized progesterone are metabolized by the liver[1,2]
  - Progesterone is associated with a risk of cholestasis in pregnancy, therefore it is only licensed in the UK for use up to Week 12 of gestation in ART/IVF and only by the vaginal route
- It is estimated that more than 10 million pregnancies have been exposed to dydrogesterone. So far, there have been no indications of a harmful effect of dydrogesterone use during pregnancy[3,4]
- A randomized controlled trial in 853 infertile women compared the efficacy and tolerability of 20 mg/day oral dydrogesterone and 90 mg 8% vaginal progesterone gel used for luteal support. Numerically more local side effects occurred in the progesterone group compared to the dydrogesterone group[5]



ART, assisted reproductive technology; IVF, *in vitro* fertilization

1. Utrogestan 200 mg oral capsules. SPC UK. October 2013. 2. Utrogestan 200 mg vaginal capsules. SPC UK. October 2013. 3. Queisser-Luft A. Early Hum Dev 2009; 85(6):375-377. 4. Dydrogesterone CCDS. 23 June 2015. 5. Tomic V, et al. Eur J Obstet Gynecol Reprod Biol 2015; 186:49-53.

Dydrogesterone *versus* Vaginal Micronized Progesterone Preference and Acceptability

- In studies that compared oral *versus* vaginal formulations of non-progestin drugs, women prefer to use oral formulations than vaginal ones[1,2]
- Application of vaginal tablets requires a private, clean room; whereas tablets can be taken orally, anywhere

A comparative study between dydrogesterone and vaginal micronized progesterone for luteal support[3]

Vaginal discharge or irritation	Dydrogesterone group: 0%	Progesterone group: 10.5%
Satisfaction with tolerability of treatment	Dydrogesterone group: ~95%	Progesterone group: ~73%
	Statistically significant difference ($p<0.05$)	

1. Arvidsson C, et al. Eur J Obstet Gynecol Reprod Biol 2005; 123(1):87-91.
2. Bingham JS. Br J Vener Dis 1984; 60(3):175-177.
3. Chakravarty BN, et al. J Steroid Biochem Mol Biol 2005; 97(5):416-420.

Conclusions

Dydrogesterone

- Is produced from a natural source[1] like other progestogens
- Is very similar to progesterone, but has enhanced oral bioavailability[2,3]
- Is highly selective and has a high affinity for progesterone receptors[2,3]
- Is metabolized into compounds that are either progestogenic or inactive[2,3]
- Has a fast onset of action and long, stable effect[4]
- Is well tolerated and has a favorable safety profile in all approved indications, including pregnancy[4–9]

Note: the effectiveness and safety records of dydrogesterone are based on the body of evidence for treatment of threatened[5,6,10,11] and recurrent miscarriage[7]

1. University of Maryland Medical Center. Complementary and Alternative Medicine Guide. Wild yam. http://umm.edu/health/medical/altmed/herb/wild-yam. 2. Schindler AE, et al. Maturitas 2009; 65(Suppl 1):S3-S11. 3. Schindler AE, et al. Maturitas 2008; 61(1-2):171-180. 4. Dydrogesterone CCDS. 23 June 2015. 5. El-Zibdeh MY, Yousef LT. Maturitas 2009; 65(Suppl 1):S43-S46. 6. Pandian RU. Maturitas 2009; 65(Suppl 1):S47-S50. 7. El-Zibdeh MY. J Steroid Biochem Mol Biol 2005; 97(5):431-434. 8. Dutta DK. Asian J Obstet Gynae Pract 2001; 5(2):3-5; 9. Queisser-Luft A. Early Hum Dev 2009; 85(6):375-377. 10. Omar MH, et al. J Steroid Biochem Mol Biol 2005; 97(5):421-425. 11. Carp H. Gynecol Endocrinol 2012; 28(12):983-990.