

Metformin, a biguanide derivative molecule discovered from *Galega Officinalis* (french lilac) for its hypoglycemia properties. Metformin is a drug used during pregnancy in the treatment of type 2 diabetes and disorders associated with insulin resistance including PCOS (Polycystic ovary syndrome). Few studies have investigated the consequences in gonad after an *in utero* exposure to metformin.

AIM

The aim of the present study was to assess the effects of maternal metformin administration during pregnancy on the fertility of male offspring mice.

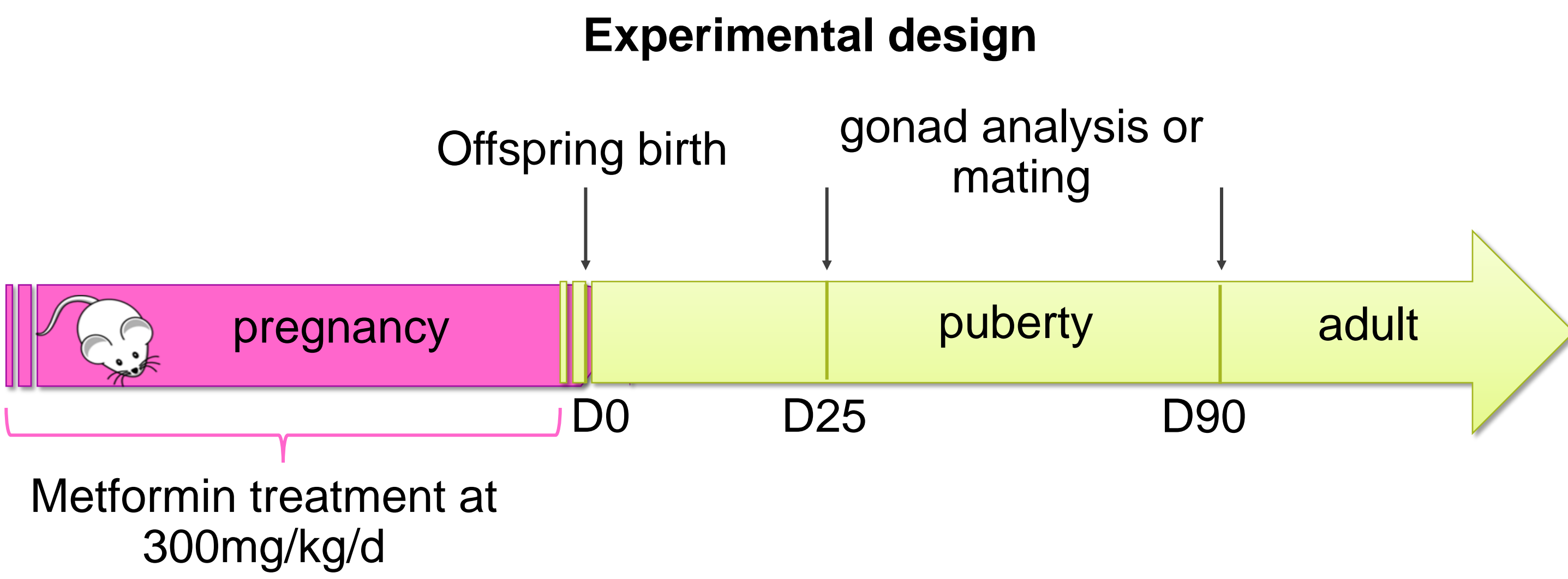


Figure 1: Experimental design Metformin was administered via water at 300mg/kg/d during the entire period of pregnancy. Control mice were provided with untreated water. Fertility analysis was then performed on the male offspring.

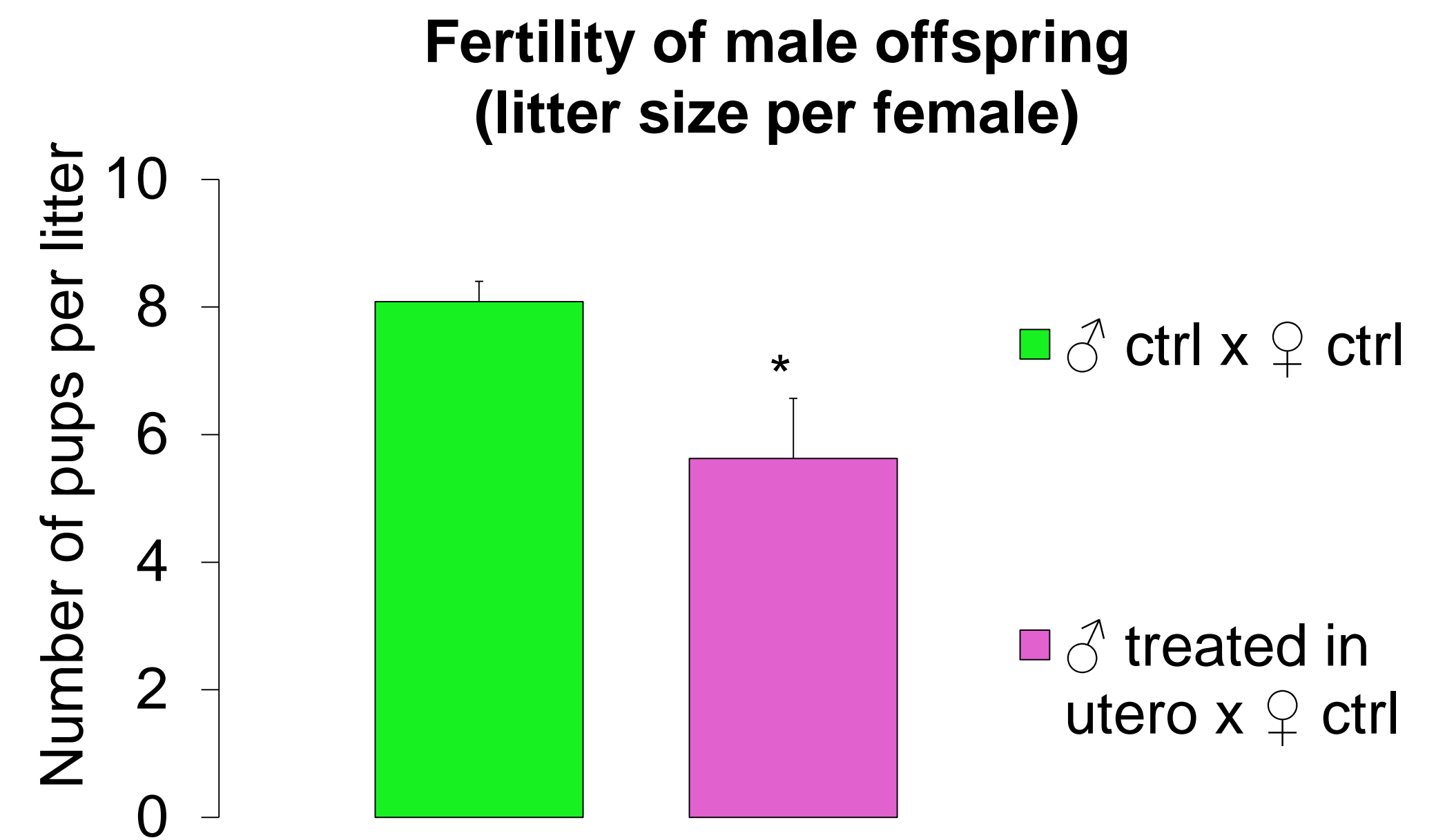


Figure 2: Number of pups per litter from control and *in utero* metformin exposed males. *In utero* exposure to metformin resulted in a 25% reduction in male fertility when mated to untreated females ($P < 0.05$) $n = 8$.

Seminiferous tubule diameter at 25 dpp (days post partum)

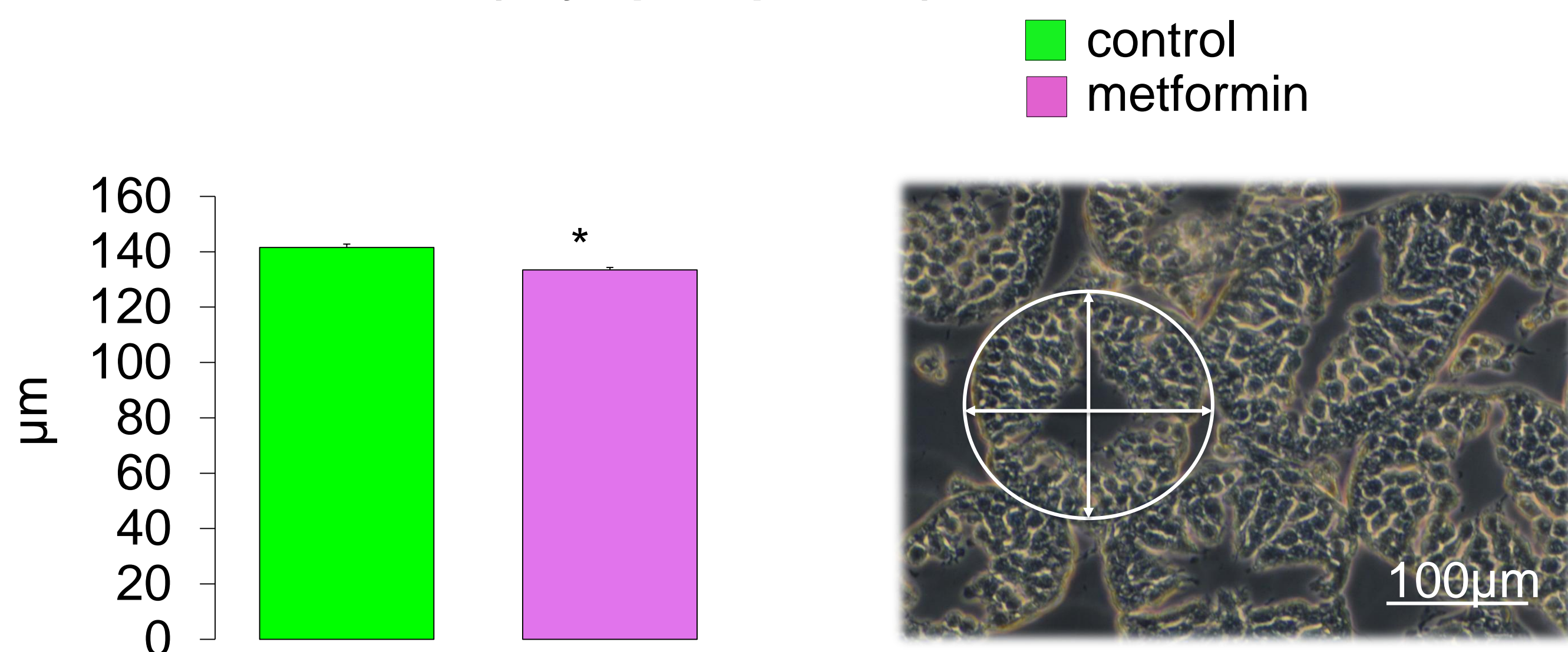


Figure 3: Metformin exposed males had a reduction in seminiferous tubule diameter ($P < 0.05$) $n = 225$ tubules

VASA positive-cells per seminiferous tubule at 25 dpp

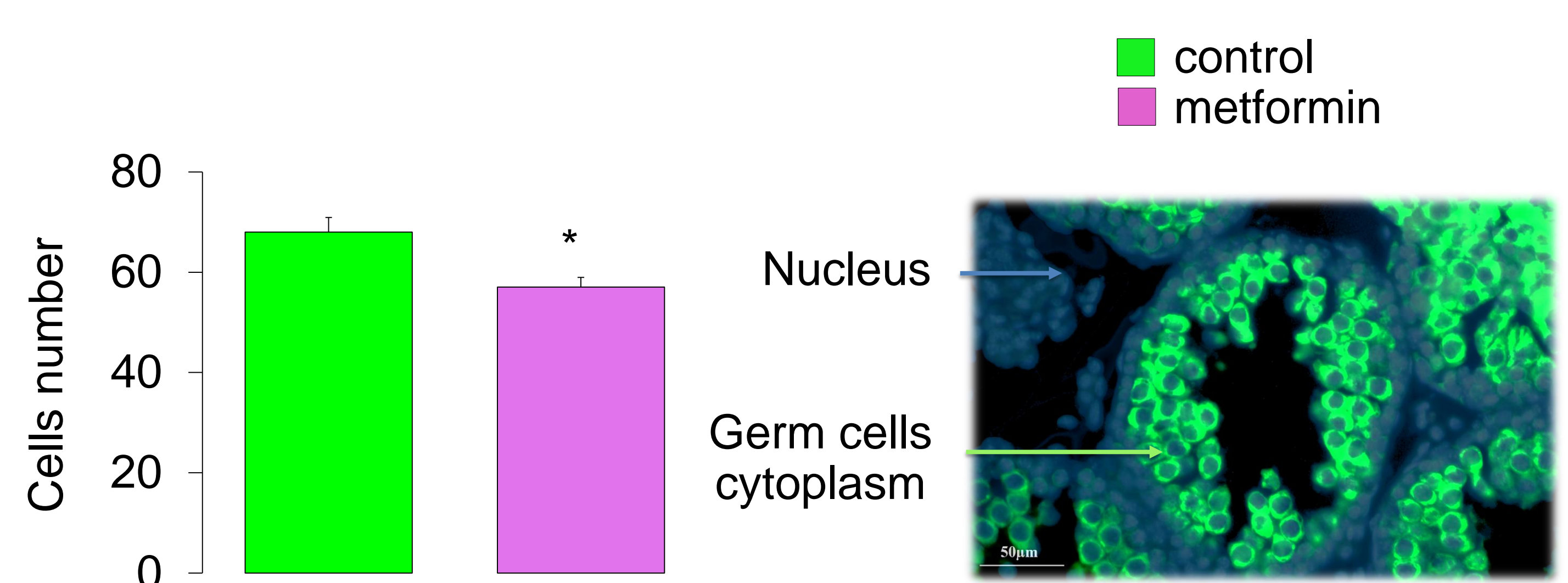


Figure 4: Metformin exposed males had a reduction in germ cell number per seminiferous tubule ($P < 0.05$) $n = 40$ tubules

Sperm head deformities at 90 dpp

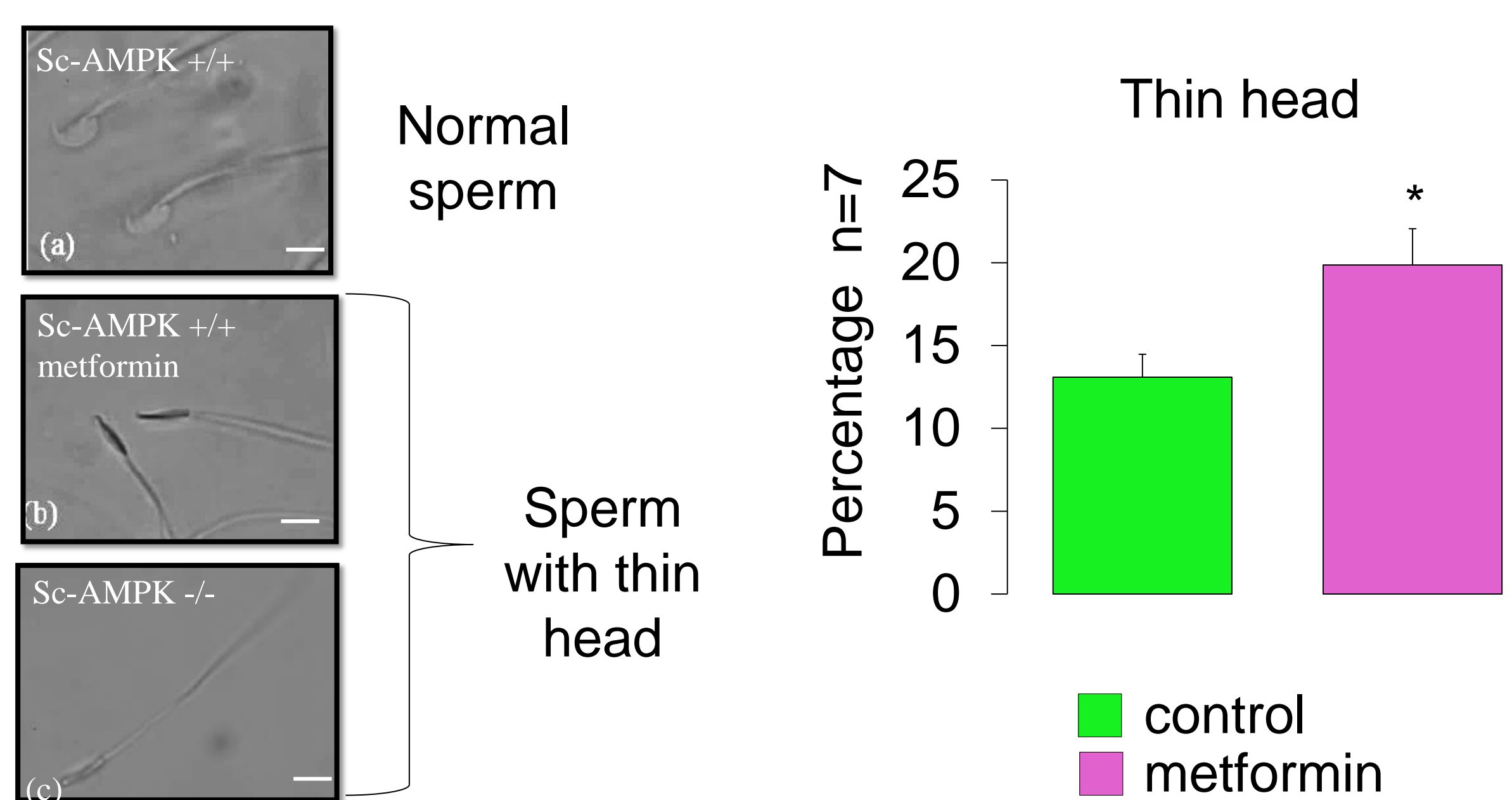
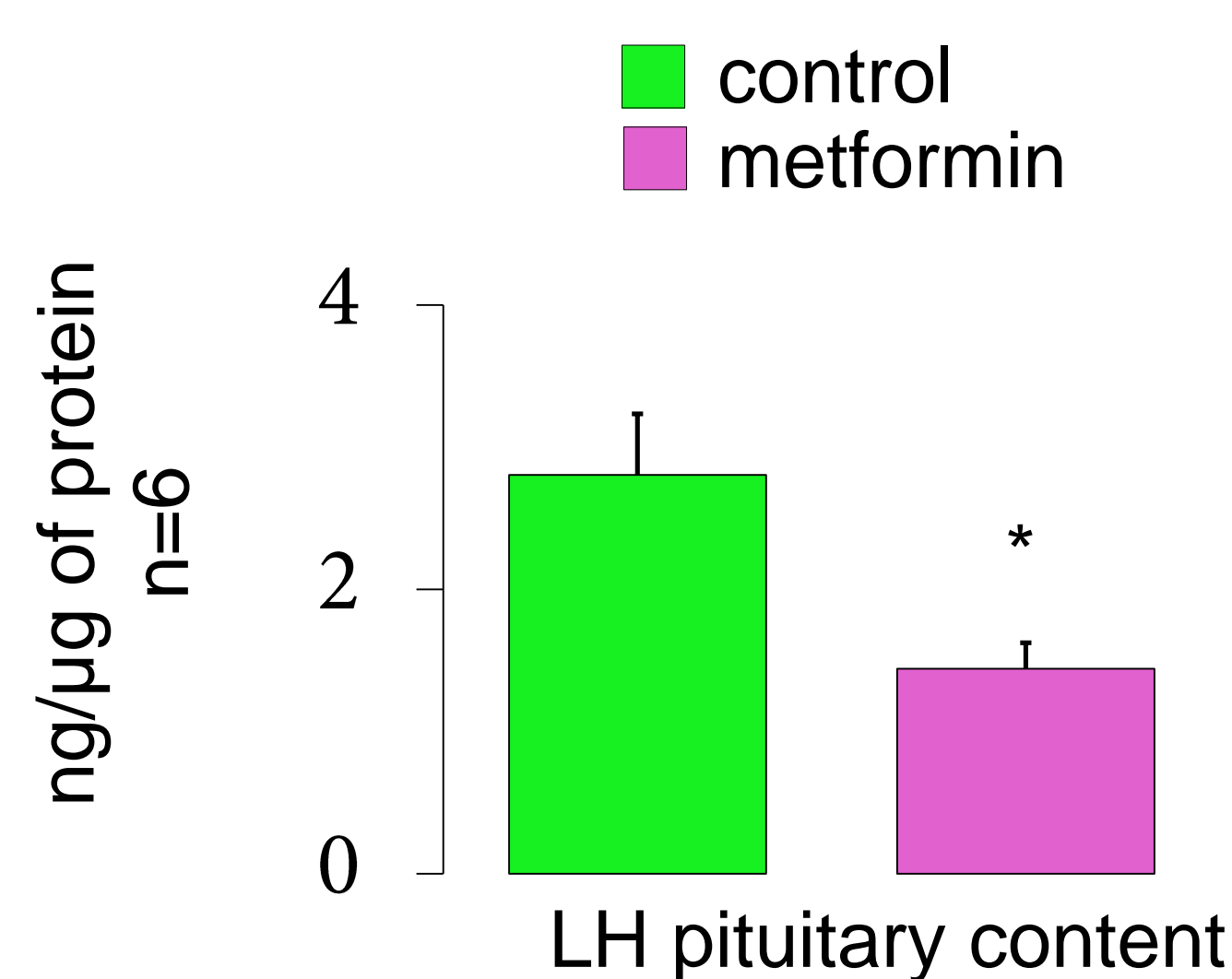


Figure 5: Similar phenotype where found between males Sc-AMPK +/+ exposed to metformin *in utero* & Sc-AMPK -/- and males exposed to metformin *in utero* had more sperm with a thin head ($P < 0.05$) $n = 7$ males

LH pituitary concentration at 90 dpp



Fat weight at 90 dpp

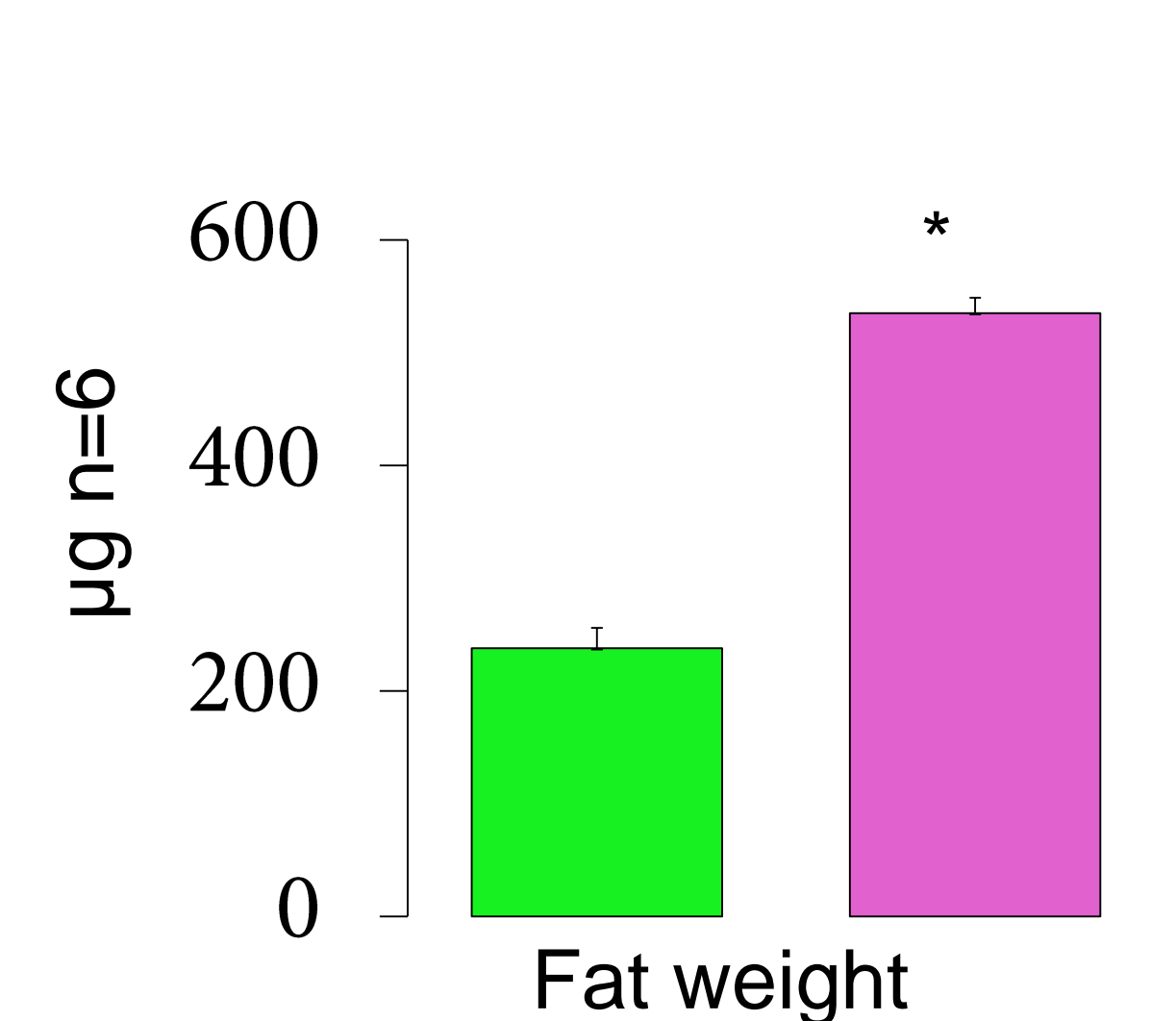


Figure 6: *In utero* exposed males had lower LH concentrations in the pituitary. Exposed adult males presented with significantly more visceral adipose tissue ($P < 0.05$) $n = 6$ males

Conclusion

In utero, metformin exposure has consequences on the fertility of male offspring, mainly by affecting testis development, seminiferous tubules diameter, germ cells number & the quality of sperm. Together these results complete Tartarin et al 2012 data which shown a negative effect on ability of fetal murine and human testis explants to secrete testosterone after metformin exposure and complete the *in vitro* results from Bertoldo et al., 2014 which have demonstrated a direct effect of metformin on spermatozoa.