

# Modified Silastic implants can deliver stable physiological blood estradiol (E<sub>2</sub>) concentrations in mature mice

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## Introduction

Estradiol has a significant role in male as well as female reproductive physiology. Silastic subdermal implants constitute a convenient and effective depot delivery system for reproductive steroids in rodents to maintain steady-state blood steroid levels proportional to implant length for weeks to months. However, implants filled with E<sub>2</sub> produce markedly supraphysiological blood E<sub>2</sub> concentrations and weight loss that is not satisfactory to study pharmacological or physiological estrogen effects. We therefore developed modified Silastic implants to deliver more physiological E<sub>2</sub> blood levels using cholesterol-diluted E<sub>2</sub> to deliver lower daily doses and maintain physiological blood E<sub>2</sub> concentrations.

## Methods

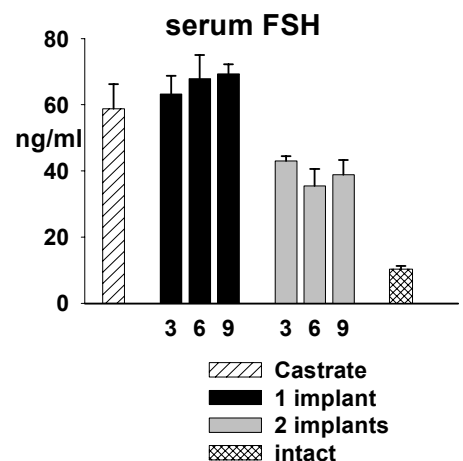
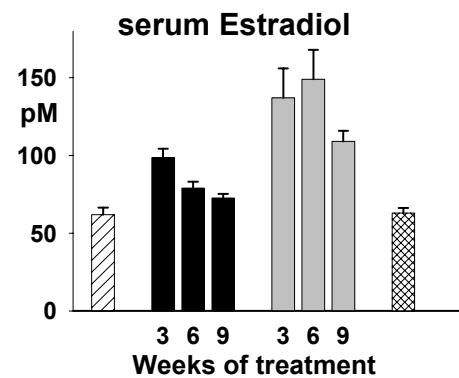
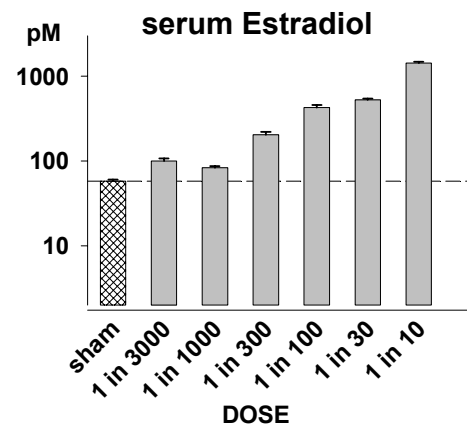
**Expt 1** To establish serum E<sub>2</sub> dose response characteristics, 1cm Silastic implants filled with E<sub>2</sub> recrystallized from ethanol in a range of dilutions with cholesterol (1/3000, 1/1000, 1/300, 1/100, 1/30 & 1/10) were implanted for 2 weeks into mature male mice (n=5-6/group). **Expt 2** To examine the duration of action of the implants, castrate male and female mice were given a physiological dose of E<sub>2</sub> for 3, 6 or 9 weeks when serum E<sub>2</sub>, FSH were measured by delfia assays, and body and reproductive organ weights were collected.

## Results

Serum E<sub>2</sub> showed a dose response relationship with E<sub>2</sub> dose in intact male mice (fig 1). None of the E<sub>2</sub> doses had any effect on body weight. In castrate female mice treated with 2 implants (1/1000 dilution), normal uterine weight and serum E<sub>2</sub> levels were maintained for 9 weeks although FSH levels were suppressed. In castrate male mice, serum E<sub>2</sub> showed a consistent dose response relationship for up to 9 weeks of E<sub>2</sub> treatment (1/1000 dilution) when implanted with 1 or 2 implants, maintaining physiological levels comparable with intact mice (fig 2). As observed in the female group, 2 implants suppressed serum FSH by 50% as compared to castrate levels. However FSH was not suppressed by a lower 1 implant dose (Fig 3).

## Discussion

We conclude that this modified Silastic implant estradiol delivery system can 1) deliver low doses of E<sub>2</sub> that can be easily titrated 2) provide a convenient and practical method to maintain physiological blood E<sub>2</sub> concentrations 3) sustain a stable delivery for prolonged periods in mice without the need for implant replacement.



This study has developed a system for the delivery of low, stable levels of estradiol to experimental mice. This system will enable future investigation of E<sub>2</sub> action on reproductive function and fertility in males, as well as brain, bone, vascular and lipid metabolism in which E<sub>2</sub> also plays a significant role.