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# Ovarian hormone treatment in adults with Turner syndrome

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**Abstract.** Most women with Turner syndrome (TS) require life-long replacement therapy with oestrogen and progesterone, and we therefore have to consider the optimal strategy for this treatment for 35 years of continuous use. The forms of oestrogen replacement therapy use in young women with TS are usually borrowed from estrogen replacement therapy (ERT) preparations designed for use in postmenopausal women. There have been few attempts at finding an age-appropriate dose of oestrogen for use in young women. There are many end organ responses for exogenous oestrogen that might be used to guide treatment strategies in young women including those in bone, uterus, arterial walls and liver. In this era of caution with ERT brought about by the women's health initiative (WHI) trials in older women, many young women with TS have been advised to reduce the dose of oestrogen replacement or to terminate oestrogen early. This advice may run counter to the concern over quality of life which is already reduced in this group of women. This paper we will consider a selection of target organs for oestrogen for which data are available in women with TS with particular reference to the starting age of oestrogen and possible effects of dose reduction in adult life. Lastly, ovarian androgen secretion is also lost in women with gonadal dysgenesis and some consideration will need to be given to testosterone replacement in the future. © 2006 Published by Elsevier B.V.

*Keywords:* Hormone replacement therapy; Cardiovascular risk; Metabolism; Intima media thickness; Uterus preparation

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## 1. Oestrogen and cardiovascular disease

Women with early onset oestrogen deficiency have an increased risk of cardiovascular disease (CVD), regardless of aetiology. In hypopituitarism, women have twice the risk of

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CVD compared to men and amongst hypopituitary women, those with untreated gonadotrophin deficiency have the greatest risk [1–3]. Women with early menopause have been shown to have an increased cardiovascular mortality which may be due to oestrogen deficiency [4]. In Turner syndrome, the risk of ischaemic heart disease is increased [5] with a seven-fold increase in mortality [6]. Taking these reports together, there appears to be a common theme that oestrogen deficiency in young women is a risk for CVD and that standard replacement regimes fail to reverse this risk.

In postmenopausal women, ERT has been shown to improve some markers of cardiovascular risk, such as lipid profiles [7] and intima media thickness (IMT) [8] and at the same time result in an increase in cardiovascular morbidity in randomised trials [9,10]. A possible explanation for this paradox may be a differential effect of oestrogen at different stages of the atherosclerotic disease process, with beneficial antiatherogenic effects earlier in life but proinflammatory and prothrombotic effects predominating in the older, postmenopausal age group [11–13].

Data on the risks and benefits of oestrogen with respect to cardiac risk factors in young women with TS are few. In studies of women with TS, oestrogen has been shown to induce a reduction in blood pressure and in fasting insulin and glucose concentrations [14–16]. Also, the increase in IMT shown by Ostberg et al. was also evident in women with premature ovarian failure, suggesting that oestrogen deficiency is the mediating factor [17]. Elsheikh et al. showed that arterial stiffness as measured by augmentation index of the arterial pulse wave was improved in women with TS taking when taking oestrogen [16].

In conclusion, ERT appears to improve markers of cardiovascular risk in young women with TS, and it remains to be tested whether these changes are reflected in studies with harder end points.

## **2. Uterus**

The effect of both timing and dose of oestrogen on uterine length in women with TS was noted by Snajderova et al. who found a correlation between the dose of exogenous oestrogen and the uterine length. This study also reported an association between uterine length and the delay of induction of puberty using the parameter of age of artificial menarche [18]. When considering the induction of puberty, it has not been clarified whether the variation in the interval between first exposure to oestrogen and age of artificial menarche is important. It may be that this “window of unopposed oestrogen” is also a crucial factor not only in uterine development but also in breast size. We note that several adult women in the Adult TS Clinic at UCLH have opted for breast augmentation surgery.

Now that uterine growth charts have been established in puberty, it may be that various oestrogen strategies can be tested prospectively with relatively early outcomes [19]. It may also be that optimisation of uterine growth will improve the lower success rates from ovum donation when comparing women with TS to those with premature ovarian failure. Women with TS who achieve a pregnancy with oocyte donation have a higher risk of miscarriage ranging from 40% to 60% [20–22] compared to 8.7% in other causes of primary ovarian failure [21]. This increased risk for first trimester spontaneous abortion, which has been attributed in part to small uterine size and reduced endometrial receptivity [22], however, data regarding the impact of oestrogen use on pregnancy outcome have been lacking.

### **3. Bone**

The issue of bone integrity in TS will be discussed elsewhere. Suffice it to say that bone is an obvious end organ for the effect of oestrogen. Bone turnover has been shown to be reduced in women with TS taking the potent oestrogen, ethinylestradiol compared to when taking no oestrogen [15]. Oestradiol implants have been shown to be particularly good at improving bone density in this group [23] perhaps by improving compliance and increasing 24-h circulating levels of oestrogen. Improved bone density in TS appears to be associated with longer use of ERT and it is suggested that an early start to oestrogen use is also a determining factor [24].

### **4. Brain and socialisation**

For many years, a policy of delaying the introduction of oestrogen in order to maximise final height for girls with TS has been a systematic policy [25]. Recently, we have become aware that there might be developmental and social consequences of such a policy. Many of the psychological issues that are of concern in TS are sensitive to oestrogen including self-concept, non-verbal processing speed, memory, awareness of poor breast development, bonding and sexual awareness. Firm data in this area have been lacking until recently. In a turning point paper, Carel et al. have shown that the timing of oestrogen in puberty in girls with TS is associated with sexual experience later in life [26]. Those working in adult TS clinics will be familiar with the lonely socially isolated woman with TS and may now ponder on the fact that relationships may have been built with greater strength if puberty was induced at an earlier age.

### **5. Liver**

Women with TS have an increased risk of developing chronic liver disease. Gravholt et al. [5], in an epidemiological study based on hospital registry data looking at the incidence of chronic disease in approximately 600 women with TS, reported a five-fold increased risk of hepatic cirrhosis. Interestingly, the most severe liver disease occurs on women with TS in whom oestrogen replacement has been largely neglected throughout their lives [27].

In a study of 49 women with TS over the age of 35 years, abnormal liver function was found in 80% [28] and it is clear that autoimmunity, viral hepatitis and alcohol are not the cause [15,29]. Women with TS, when receiving cyclical oestrogen and progesterone, have improved liver function compared to when not taking ERT [29]. These studies introduce the possibility that liver dysfunction in TS could be reduced with more assiduous oestrogen replacement perhaps using higher-than-average dose.

### **6. Testosterone**

So far, sex steroid replacement has focussed on oestrogen and progesterone combinations. We also know that women with TS are androgen deficient [30] and from the study of women with ovarian failure or oophorectomy, we could anticipate that women

with TS would benefit from testosterone replacement. A study quantifying such a benefit in women with TS is long overdue with particular reference to Turner specific outcome measures such as bone turnover, sexuality and muscle strength.

## 7. Discussion

In an era when there is a swing of opinion against the use of ERT, we must remember that data from normal asymptomatic women in their eighth decade of life (e.g., the WHI) may not be relevant for young women with TS. Some of the beneficial effects of oestrogen on cardiovascular risk factors may be more important in young women than in these older age groups. It could therefore be argued that following the general trend to a dose reduction of oestrogen post-WHI is not applicable to women with TS below the age of 50.

The issues reviewed above are not intended to be an unqualified promotion of oestrogen use in women with TS, but rather to highlight areas of potential benefit from ERT that must not be overlooked in favour of fashion trends in prescribing. It must be accepted that there is little controlled data for young women with oestrogen deficiency of any aetiology and that this is now a priority area for future research.

There are now increasing instances where we see the benefit of the early introduction of oestrogen for girls with TS. For bone, uterus and sexual function, the early introduction of oestrogen seems to be key and we have yet to discover the optimal age for first exposure. With this in mind, it is paramount that we improve the universally common finding of late diagnosis of TS at ages when the maximal benefit from oestrogen may have passed.

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