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REVIEW

Sex differences in the cardiovascular effects of GnRH analogues

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Abstract

The integral role of the hypothalamic–pituitary–gonadal axis in reproductive processes makes it a prime therapeutic target. By inhibiting sex steroid synthesis, gonadotropin-releasing hormone (GnRH) analogues are used in the management of cancers, benign neoplasms, infertility and gender dysphoria. However, the wide application of these therapeutics raises concerns regarding the unintended effects upon the cardiovascular system. In males with prostate cancer, GnRH analogues when used as an androgen deprivation therapy appear to increase the risk of cardiovascular disease, which is the leading cause of death in this population. Therefore, due to the utilisation of GnRH analogues across the lifespan and gender spectrum, this relationship merits discussion. Existing data suggest an association between GnRH analogues and major adverse cardiovascular events in males. Conversely, females receiving GnRH analogues for breast cancer treatment appear to be at an increased risk of developing hypertension. In this narrative review, we describe the uses of GnRH analogues in adults, adolescents and children. We discuss whether sex plays a role in the cardiovascular effects of GnRH analogues and explore the significance of sex hormone receptors in the vasculature. We also consider confounding factors such as malignancy, advanced age and infertility.

Keywords: cardiovascular; gonadotropin-releasing hormone; testosterone; oestrogen

Introduction

The gonadotropins, luteinising hormone (LH) and follicle-stimulating hormone (FSH), are integral to male and female reproductive processes, including the menstrual cycle, gamete maturation and pubertal development via the secretion of gonadal sex steroids (oestrogen and testosterone) (Flanagan & Manilall 2017). This is achieved and regulated via the activation of the anterior pituitary gonadotropin-releasing hormone (GnRH) receptors via its decapeptide ligand. Consequently, the GnRH receptor has been identified as a prime therapeutic target in the management of sex steroid sensitive-malignancies, benign neoplasms, infertility and for the cessation of puberty (Fig. 1).

GnRH analogues consist of agonists and antagonists (Fig. 2). GnRH secretion is pulsatile, and therefore initial GnRH receptor stimulation via agonists promotes the secretion of gonadotropins and sex steroids. Chronic activation results in the downregulation of these receptors, subsequently reducing the synthesis of gonadotropins. Conversely, GnRH antagonists directly inhibit the activity of GnRH receptors in the anterior pituitary gland (Shore 2013). GnRH agonists achieve gonadotropin and sex steroid suppression within approximately 1 month, while GnRH antagonists facilitate almost immediate suppression (Williams *et al.* 1986, Klotz *et al.* 2008, Shore 2013).

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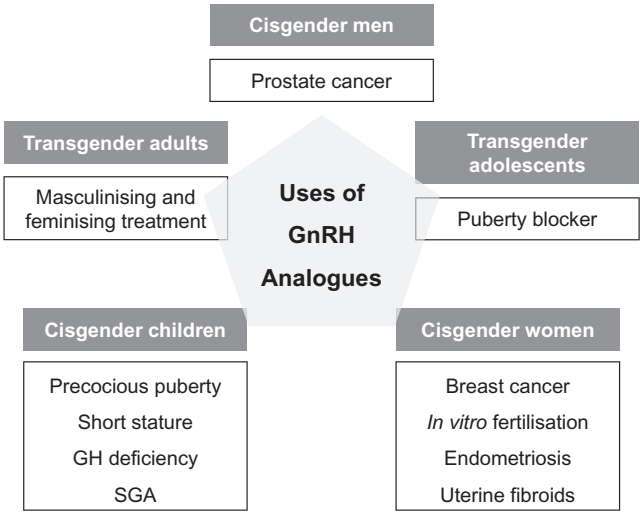

Figure 1

Indications of GnRH analogues. In adults, the GnRH receptor is utilised as a target in the management of malignancies (prostate and breast cancer), benign growths (uterine fibroids and endometriosis), infertility and masculinising and feminising treatment. In children, GnRH analogues are used to suppress puberty for gender dysphoria and to preserve height potential for central precocious puberty, idiopathic short stature, growth hormone (GH) deficiency or small for gestational age (SGA).

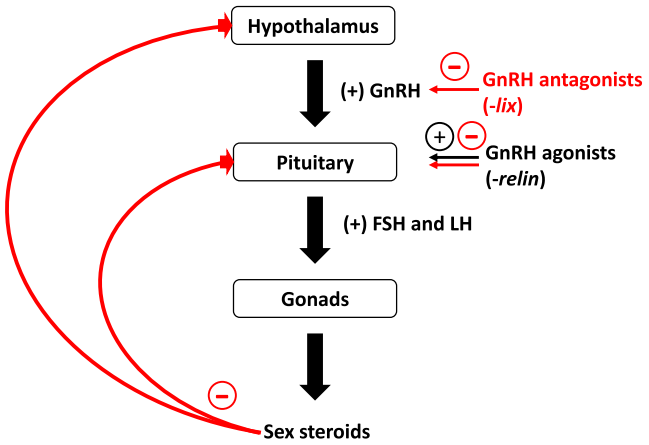

Figure 2

Effects of GnRH analogues on the hypothalamic-pituitary-gonadal axis. GnRH is secreted from hypothalamic neurones and regulates the synthesis of gonadotropins FSH and LH via the anterior pituitary receptors. Gonadotropins, in turn, modulate a multitude of reproductive processes through the action of the gonadal sex steroids and maintenance of negative feedback along this axis. Agonistic GnRH stimulation (-relin) promotes gonadotropin and sex hormone secretion; however, chronic stimulation results in GnRH receptor downregulation and relative hypogonadism. GnRH antagonists (-lix) directly inhibit these receptors thereby suppressing gonadotropin and sex steroid secretion. A full colour version of this figure is available at https://doi.org/10.1530/JOE-23-0309.

Beyond direct effects on reproductive physiology, GnRH suppression may disrupt multiple organ systems following the loss of sex steroid regulation and function. The detrimental influence of gonadal suppression in some aspects of health are well established, such as the relationship between GnRH analogues with bone health and fracture risk (Shahinian *et al.* 2005). However, the effects of these drugs on the cardiovascular system are less well understood. This relationship merits discussion given the diverse utilisation of GnRH analogues across the lifespan and gender spectrum, and high prevalence of cardiovascular mortality among patients receiving GnRH analogues (Sturgeon *et al.* 2019).

In this narrative review, we describe the use of GnRH analogues in adults, adolescents and children. We establish whether sex plays a role in the cardiovascular effects of GnRH analogues and explore the significance of sex hormone receptors in the vasculature.

Cardiovascular outcomes in males

Prostate cancer

GnRH analogues (e.g. abarelix, degarelix, leuprorelin, goserelin) form an integral component of androgen deprivation therapy (ADT) used in the management of localised and metastatic prostate cancer (Cornford *et al.* 2021, Mottet *et al.* 2021), as alternatives to oestrogen and orchidectomy (Levine *et al.* 2010). Testosterone depletion ameliorates androgen receptor activation, thereby preventing the proliferation of prostate cancer cells (Packer & Maitland 2016). GnRH analogues may be combined with direct antiandrogens, such as bicalutamide or abiraterone, which directly inhibit the androgen receptor or androgen synthesis.

Over the past decade we have seen a growing interest in the cardiovascular effects of GnRH agonists. Since 2010, the U.S. Food and Drug Administration has issued warnings regarding the increased risk of myocardial infarction, sudden cardiac death and stroke in this drug class. The decision followed emerging studies demonstrating a link between the use of GnRH agonist and cardiovascular disease in males with prostate cancer (Supplementary Table 1, see section on supplementary materials given at the end of this article) (Keating *et al.* 2006, 2010, Van Hemelrijck *et al.* 2010).

The first of the studies was the Surveillance, Epidemiology and End Results Medicare study published in 2006 (Keating *et al.* 2006). In this population-based analysis of 73,169 males diagnosed with locoregional prostate cancer from 1992 to 1999, males receiving GnRH agonists were at increased risk of ischaemic heart disease (hazard ratio (HR) 1.16, 95% CI 1.10, 1.21), myocardial infarction (HR 1.11, 95% CI 1.01, 1.21) and sudden cardiac death (HR 1.16, 95% CI 1.05, 1.27) compared to those not receiving any form of ADT.

Two subsequent observational studies have shown similar results (Keating *et al.* 2010, Van Hemelrijck *et al.*

2010). Data obtained from the Veterans' Healthcare Administration (Keating *et al.* 2010) demonstrated substantial increases in ischaemic heart disease (HR 1.19, 95% CI 1.10, 1.28), myocardial infarction (HR 1.28, 95% CI 1.08, 1.52), sudden cardiac death (HR 1.35, 95% CI 1.18, 1.54) and stroke (HR 1.22, 95% CI 1.19, 1.36). In addition, a study of the Swedish National Prostate Cancer Register (Van Hemelrijck *et al.* 2010) established an increased risk of cardiac arrhythmia (HR 1.27, 95% CI 1.10, 1.47) and heart failure (HR 1.46, 95% CI 1.28, 1.67) in GnRH agonist users when compared to the general population.

More recently, a Scottish observational study of 20,216 males diagnosed with prostate cancer from January 2009 to December 2015 found significant increases in overall cardiovascular events in those prescribed either GnRH agonists (adjusted HR 1.3, 95% CI 1.2, 1.4) or the GnRH antagonist degarelix (adjusted HR 1.5, 95% CI 1.2, 1.9), which followed a dose–response relationship (Cardwell *et al.* 2020). Importantly, this increase in cardiovascular events was not observed in those utilising bicalutamide monotherapy, which suggests that relative rather than absolute reduction of testosterone concentrations in this cohort may confer a degree of cardio-protection.

Several recent meta-analyses have assessed this relationship. Liang *et al.* (Liang *et al.* 2020) demonstrated that ADT, achieved via anti-androgens, orchiectomy, GnRH agonists, or combined therapy, substantially increased the risk of acute myocardial infarction (relative risk (RR) 1.19, 95% CI 1.02, 1.39). This association was particularly pronounced in those prescribed GnRH agonists, where an increased risk in acute myocardial infarction (RR 1.73, 95% CI 1.05, 2.85) and ischaemic heart disease (RR 2.09, 95% CI 1.02, 4.30) was observed. In a meta-analysis of ten observational studies by Liu *et al.* (Liu *et al.* 2020), an increased risk of stroke was observed with any form of ADT (HR 1.13, 95% CI 1.02, 1.3), which was evident in GnRH agonist users (HR 1.2, 95% CI 1.1, 1.3). Lastly, Zhao *et al.* (Zhao *et al.* 2014) demonstrated an increase in cardiovascular mortality (RR 1.36, 95% CI 1.10, 1.68) in GnRH agonist users.

GnRH agonists do not appear to affect blood pressure in males. In a study by Smith *et al.* (Smith *et al.* 2008), 12-month treatment with leuprorelin did not result in significant blood pressure changes among 26 males with prostate cancer (systolic blood pressure (SBP) −4 mm Hg, diastolic blood pressure (DBP) −1 mm Hg). In this study, androgen antagonist bicalutamide was used to counteract the initial surge in testosterone, though without a control group. Similarly, blood pressure changes did not differ between 16 males treated with goserelin and 15 untreated controls in another study (Dockery *et al.* 2003).

Comparing agonists and antagonists

GnRH antagonists have been developed to circumvent the initial surge in testosterone associated with GnRH agonists (Persson *et al.* 2009). In animal models, GnRH antagonists have demonstrated a favourable safety profile compared to other forms of ADT with respect to reduced atheroma formation and necrosis (Hopmans *et al.* 2014, Knutsson *et al.* 2016), and increased stability of established plaques (Knutsson *et al.* 2016).

Observational studies have thus far been inconclusive (Sciarra *et al.* 2021). George *et al.* reported that users of GnRH antagonists compared with agonists were associated with a higher risk of acute myocardial infarction (HR 1.62, 95% CI 1.11, 2.35) and arrhythmia (HR 1.55, 95% CI 1.11, 2.15) (George *et al.* 2021). Conversely, a Taiwanese observational study involving 666 GnRH antagonist users and 1332 propensity-matched agonist users found a lower risk of major adverse cardiovascular events (MACE) (HR 0.48, 95% CI 0.25, 0.90) and cardiovascular death (HR 0.21, 95% CI 0.06, 0.70) in the antagonist group (Chen *et al.* 2021). Similarly, data from UK general practices showed a lower number of cardiac events among males receiving a GnRH antagonist (RR 0.39, 95% CI 0.19, 0.80), largely driven by a decreased risk of arrhythmia (RR 0.28, 95% CI 0.09, 0.87) (Davey & Kirby 2021).

Neutral results have been observed in a study using French health insurance data which found no significant difference in events of myocardial infarction (HR 1.14, 95% CI 0.47, 2.80) and ischaemic stroke (HR 1.25, 95% CI 0.59, 2.66) between agonist and antagonist users (Scailteux *et al.* 2017). A similar study in Germany demonstrated that GnRH agonist users when compared to antagonist users were at a greater risk of developing hypertension (16.40 vs 6.90%) but not cardiovascular disease as a whole (40.26 vs 45.45%) (Hupe *et al.* 2018).

Similarly, clinical trials have not produced conclusive evidence favouring either drug (Sciarra *et al.* 2021). In the first clinical trial with a cardiovascular endpoint (PRONOUNCE), the GnRH antagonist degarelix did not reduce MACE among males with prostate cancer and high cardiovascular risk (HR 1.28, 95% CI 0.59, 2.79) compared to the GnRH agonist leuprorelin (Lopes *et al.* 2021). This trial prematurely ended at 12 months due to recruitment failure, and experienced lower than anticipated cardiovascular events, and therefore was underpowered and could not conclude on cardiovascular risk.

Null results were also observed in an earlier clinical trial by Smith *et al.* (Smith *et al.* 2010) comparing the same drugs (Table 1). Similarly, degarelix did not reduce MACE when compared to the GnRH agonist goserelin in a Chinese study (Sun *et al.* 2020). In contrast, the highly selective GnRH antagonist relugolix significantly reduced cardiovascular events when compared to the GnRH agonist leuprorelin (HR 0.46, 95% CI 0.24, 0.88) (Shore *et al.* 2020).

Pooled data from prostate cancer trials suggested a potential benefit of GnRH antagonists. In a meta-analysis of ten randomised trials, decreases in MACE (RR 0.57, 95% CI 0.39, 0.81) and cardiovascular deaths (RR 0.49, 95% CI 0.25, 0.96) were seen in males receiving

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Table 1 Comparative effects of GnRH analogues in clinical trials.

Study	Population	Drugs	Mean duration	Outcome HR (95% CI)
(Lopes *et al.* 2021) 'PRONOUNCE'	276 antagonist and 269 agonist	Degarelix vs leuprorelin	12 m	MACE 1.28 (0.59, 2.79)
(Smith *et al.* 2010)	416 antagonist and 204 agonist	Degarelix vs leuprorelin	12 m	IHD 0.88, $P > 0.05$
(Sun *et al.* 2020)	142 antagonist and 141 agonist	Degarelix vs goserelin	12 m	MACE 0.73 (0.35, 1.53)
(Shore *et al.* 2020) 'HERO'	622 antagonist and 308 agonist	Relugolix vs leuprorelin	48 w	MACE 0.46 (0.24, 0.88); CV mortality 0.39 (0.14, 1.02)

CV, cardiovascular; HR, hazard ratio; IHD, ischaemic heart disease; MACE, major adverse cardiovascular events.

GnRH antagonists compared to agonists (Cirne *et al.* 2021). The difference in results may reflect baseline cardiovascular risk and study designs. In some of the evidence, the antagonist users had a shorter follow-up (Lopes *et al.* 2021). The tailoring of GnRH antagonist to males with high cardiovascular risk may have nullified the beneficial effects of the drug (George *et al.* 2021).

In summary, there is an increased risk of atherosclerotic cardiovascular disease in males receiving GnRH analogues. The comparative safety of GnRH antagonist over agonist remains uncertain due and may be drug rather than class dependent.

Cardiovascular outcomes in females

Breast cancer

Oestrogen receptors (ERs) are expressed in 60–70% of breast cancers and represent an important component of breast carcinogenesis (Huang *et al.* 2015). In ER-positive breast cancers, oestrogen binding encourages tumour growth and proliferation (Burstein 2020). Consequently, endocrine therapies that disrupt oestrogen signalling are used to ameliorate disease progression. Depending on menopausal status this involves selective ER modulators (tamoxifen); aromatase inhibitors (anastrozole, exemestane and letrozole) that inhibit the conversion of androgens to oestrogen; or GnRH agonists that facilitate ovarian function suppression (OFS) (Bui *et al.* 2020). A Cochrane review of 8 randomised controlled trials showed that GnRH agonists were associated with a ~20% increase in overall and breast cancer-free survival compared to females who did not receive OFS (Bui *et al.* 2020).

A combined analysis from two clinical trials involving females with breast cancer (SOFT and TEXT) demonstrated that the rates of hypertension were more prevalent in those receiving OFS in combination with tamoxifen (24.6%, 95% CI 21.9, 25.4) or exemestane (24.3%, 95% CI 22.6, 26.1) compared to those receiving tamoxifen alone (18.0%, 95% CI 15.7, 20.5) (Francis *et al.* 2018). All females in TEXT and 91% in SOFT received the GnRH agonist triptorelin as their choice of OFS (Regan *et al.* 2013). The remaining participants received oophorectomy or ovarian irradiation. Importantly, the incidence of cardiovascular outcomes was low in this analysis, potentially because of the short study duration and lack of prespecified endpoints.

In the E5188 trial, the addition of GnRH agonist goserelin to chemotherapy significantly increased the risk of hypertension by 8.1% (Davidson *et al.* 2005). Interestingly, the addition of tamoxifen to chemotherapy and goserelin did not increase the incidence of hypertension (18.8 vs 17.2%), suggesting that ovarian suppression via GnRH analogues alone is sufficient to promote increased blood pressure in females with breast cancer. The lack of data assessing the addition of tamoxifen to chemotherapy precludes any conclusion on whether the effects of GnRH analogues are due to oestrogen deprivation, GnRH modulation or both.

A recent retrospective analysis of 172,850 females with breast cancer demonstrated that those receiving GnRH agonists had a significantly lower risk of developing ischaemic heart disease even after adjustments for age, breast cancer treatment (lumpectomy and radiotherapy) and comorbidities (adjusted HR 0.5, 95% CI 0.39, 0.64) (Chou *et al.* 2022). However, no randomised control trial has been undertaken to assess whether this relationship is causal and therefore significant gaps persist in our understanding of the influence of these therapies on long-term cardiovascular outcomes in this population.

In vitro fertilisation

During *in vitro* fertilisation (IVF) treatment, GnRH analogues are used to reduce gonadotropin synthesis (Li *et al.* 2013). The disruption of the menstrual cycle prevents premature surges of LH, allowing for the uninterrupted development of the follicle and oocyte (Albano *et al.* 1996). Exogenous gonadotropins are subsequently introduced when sufficient endogenous gonadotropin has been suppressed (Manau *et al.* 2002). When compared to human chorionic gonadotropins (HCGs), the use of GnRH agonists to trigger oocyte maturation reduces the risk of ovarian hyperstimulation syndrome, albeit at a lower live birth rate (Youssef *et al.* 2014). Following ovulation, the addition of GnRH agonist to progesterone for luteal phase support may improve

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the chance of a successful implantation (Linden *et al.* 2015).

A case–control study showed that assisted conception with IVF was associated with an increased risk of pre-eclampsia (adjusted odds ratio (OR) 5.3, 95% CI 1.74, 15.89) when compared to those with unassisted pregnancies (Calhoun *et al.* 2011). The findings agree with a previous meta-analysis which showed an increase in pre-eclampsia in mothers following IVF therapy (OR 1.55, 95% CI 1.23, 1.95) (Jackson *et al.* 2004). In addition to demonstrating an increased risk of pre-eclampsia, a cohort study also found an increased risk of gestational hypertension among mothers who received IVF (OR 1.6, 95% CI 1.0, 2.5) (Shevell *et al.* 2005).

The long-term effects of IVF on the cardiovascular system have also been studied. A meta-analysis of 6 observational studies by Dayan *et al.* (Dayan *et al.* 2017) showed no long-term increase in cardiac events (HR 0.91, 95% CI 0.67, 1.25) or stroke (HR 1.25, 95% CI 0.96, 1.63) among females who received fertility therapy. The effects on hypertension remain inconclusive due to significant heterogeneity among the studies included (Udell *et al.* 2013, Westerlund *et al.* 2014, Farland *et al.* 2015). The inclusion of non-IVF-based therapies precludes any firm conclusions on the long-term cardiovascular safety of IVF.

Acute cardiovascular changes among females receiving GnRH antagonist are consistent with normal pregnancy. A recent study demonstrated significant reductions in SBP and DBP in 82 females receiving IVF treatment that consisted of recombinant FSH, the GnRH antagonist cetrorelix and recombinant HCG (SBP −3.0 mm Hg, DBP −2.7 mm Hg) (Akçay & Özdemir 2021).

Pre-eclampsia is a leading cause of perinatal mortality, and may be associated with future cardiovascular morbidity and mortality (Irgens *et al.* 2001). These observations may be explained by maternal risk factors (older age and obesity) and pregnancy-associated complications (multiple gestation) associated with IVF (Dayan *et al.* 2017). However, due to the small number of studies included and the significant between-study heterogeneity, these results must be interpreted with caution.

Endometriosis and uterine fibroids

Endometriosis is a major cause of chronic pelvic pain among adolescents and adults (Janssen *et al.* 2013). Conversely, uterine fibroids primarily presents with heavy menstrual bleeding (Wegienka *et al.* 2003). The oestrogen-dependent nature of endometrial tissue development (Bulun 2009) allows for the use of GnRH analogues to induce endometrial atrophy, providing pain (Brown *et al.* 2010) and menstrual relief (Schlaff *et al.* 2020). In females eligible for surgery, GnRH agonists are used to down-size uterine fibroids and reduce anaemia, improving postoperative outcomes (Lethaby *et al.* 2017).

An uncontrolled study reported no changes in SBP, DBP and heart rate among 18 females treated with 6 months of the GnRH agonist leuprorelin for endometriosis (Ferreira *et al.* 2010). In the Elaris trials, three cases of hypertension were reported among females receiving the GnRH antagonist elagolix for uterine fibroids (Schlaff *et al.* 2020). None were reported in the placebo group.

Cardiovascular outcomes in transgender adults

In transgender men, GnRH agonists may be prescribed for 6 months prior to the initiation of testosterone to suppress menses (Hembree *et al.* 2017). Likewise, GnRH agonists in combination with oestrogen therapy are used to suppress testosterone synthesis in transgender women (Hembree *et al.* 2017). Current studies involving transgender adults have focused on the cardiovascular effects of gender-affirming hormone therapy (Banks *et al.* 2021) but not of GnRH analogues.

Cardiovascular outcomes in adolescents and children

Puberty blockers

The Endocrine Society recommends the use of GnRH agonists in young transgender people demonstrating persistent gender dysphoria or incongruence following the onset of pubertal physical changes (Hembree *et al.* 2017). GnRH agonists lead to prepubertal levels of sex hormones (Delemarre-Van De Waal & Cohen-Kettenis 2006), preventing further development of unwanted sex characteristics (Claahsen-van der Grinten *et al.* 2021).

GnRH agonists provide the young person time and space to explore their gender identity with the support of Mental Health professionals prior to initiating treatments associated with irreversible changes. Such treatments may include gender-affirming hormone therapy, which has been shown to improve psychosocial function (Chen *et al.* 2023). Through stopping pubertal progression, GnRH agonists alleviates distress and anxiety associated with the appearance of secondary sex characteristics.

The effects of pubertal suppression on blood pressure have been summarised in Table 2. A study of 19 transfeminine adolescents treated with the GnRH agonist triptorelin demonstrated no changes in blood pressure (SBP +0 mm Hg, DBP +0 mm Hg) (Perl *et al.* 2021). However, a larger study reported increases in DBP (+4 mm Hg, 95% CI 1, 7) but not SBP following triptorelin use over a shorter period (Klaver *et al.* 2020). Evidence for transmasculine adolescents are similarly equivocal. A study of 15 transmasculine adolescents receiving triptorelin treatment reported significant increases in DBP (+7 mm Hg) (Perl *et al.* 2020). However, two larger

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Table 2 Blood pressure changes in transgender adolescents receiving GnRH agonist triptorelin for pubertal suppression.

First author	Population	Study design	Mean duration ± SD	Changes in blood pressure (95% CI)
Perl *et al.* 2021	19 TGF	Retrospective	9 ± 6 m	SBP + 0 mm Hg, ns DBP + 0 mm Hg, ns
Klaver *et al.* 2020	71 TGF	Retrospective	2.1 (1.0–2.7) m[a]	SBP + 1 mm Hg (−3, 5), ns DBP + 4 mm Hg (1, 7), $P < 0.005$
	121 TGM	Retrospective	1.0 (0.5–2.9) m[a]	SBP + 2 mm Hg (−1, 4), ns DBP + 1 mm Hg (−1, 3), ns
Perl *et al.* 2020	15 TGM	Retrospective	3 ± 1 m	SBP + 1 mm Hg, ns DBP + 7 mm Hg, $P = 0.009$
Stoffers *et al.* 2019	62 TGM	Prospective	8 (3–39) m[a]	SBP - 6 mm Hg, ns DBP + 4 mm Hg, ns

[a]Presented as median (interquartile range).
DBP, diastolic blood pressure; ns, not significant; SBP, systolic blood pressure; TGF, transfeminine adolescent (natal male); TGM, transmasculine adolescent (natal female).

studies did not find any changes in blood pressure after triptorelin use in transmasculine adolescents (Stoffers *et al.* 2019, Klaver *et al.* 2020).

Transgender adolescents may have different baseline blood pressures compared to their cisgender counterparts. In a cross-sectional study of 78 transgender adolescents prior to receiving puberty blockers or gender-affirming hormone therapy, the transgender cohort had increased SBP and DBP compared to their cisgender peers of the same natal sex (Millington *et al.* 2020). Although the authors have acknowledged that variations in blood pressure measurement between the two cohorts may explain the differences, the findings raise questions on the validity of comparing transgender individuals to members of the same natal sex (Connelly *et al.* 2019).

None of the blood pressure changes in any of the studies met the age- and sex-dependent criteria for hypertension. Evidence supporting increases in blood pressure with pubertal suppression is largely limited to uncontrolled retrospective studies (Klaver *et al.* 2020, Perl *et al.* 2020) with prospective studies being conducted (Millington *et al.* 2020).

Improving height potential

Long-acting GnRH agonists are used to preserve height potential in children with rapidly progressive forms of central precocious puberty (CPP) (Eugster 2019). An observation period of 6 months may be necessary in female adolescents prior to Tanner stage B2 to exclude forms of CPP which do not respond to treatment (Carel *et al.* 2009). Girls under the age of 8 derive the most benefit from treatment (Bertelloni *et al.* 2017). In addition, GnRH agonists may be used alongside growth hormone (GH) to improve height in children with idiopathic short stature (Cohen *et al.* 2008), GH deficiency (GH Research Society 2000) or those born with small for gestational age (Lem *et al.* 2012).

The infrequent use of GnRH agonists to improve height potential may explain the paucity of evidence surrounding their cardiovascular effects. To date, only three cases of hypertension have been reported in children treated for CPP (Calcaterra *et al.* 2013, Siomou *et al.* 2014, Palma *et al.* 2020).

Discussion

We have described the clinical uses of GnRH analogues (Fig. 1) and their reported cardiovascular effects (Table 3). Data from observational studies suggest that GnRH agonists increase the risk of ischaemic heart disease (Liang *et al.* 2020) and stroke (Liu *et al.* 2020) among adult males. No changes in blood pressure were recorded (Dockery *et al.* 2003, Smith *et al.* 2008). Comparisons between GnRH antagonists and agonists remain inconclusive.

In females treated with breast cancer, clinical trials have established the link between GnRH agonists and the development of hypertension (Regan *et al.* 2013, Francis *et al.* 2018), an effect that remains uncertain among females treated with uterine fibroids (Schlaff *et al.* 2020) or endometriosis (Ferreira *et al.* 2010). Similar associations have been observed between GnRH analogue-based IVF therapy with pre-eclampsia (Jackson *et al.* 2004, Calhoun *et al.* 2011) and gestational hypertension (Shevell *et al.* 2005) but not stroke (Dayan

Table 3 Effects of GnRH agonists on cardiovascular disease.

Condition	Male	Female	Strength of evidence
Ischaemic heart disease	↑	↓	B–C
Stroke/TIA	↑	↔	B–B
Hypertension	↔	↑	C–A

↑ indicates an increase in risk; ↓ indicates an decrease in risk; ↔ indicates no difference in risk. A: evidence derived from more than 1 randomised controlled trials; B: evidence derived from a single randomised controlled trial or more than 1 observational studies; C: evidence derived from a single observational study.
TIA, transient ischaemic attack.

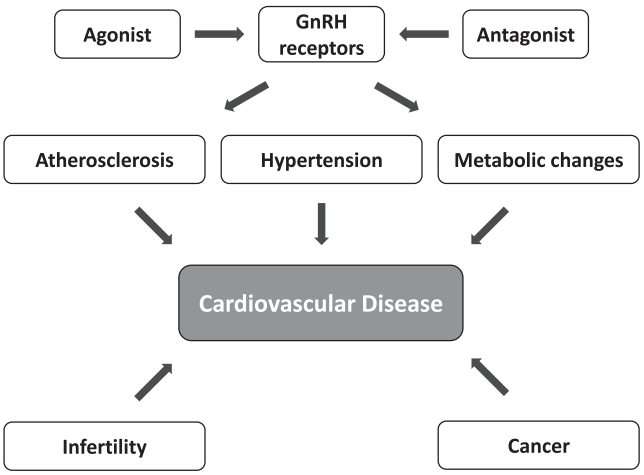

Figure 3

Possible explanations for sex differences in cardiovascular effects. GnRH analogues may contribute to cardiovascular disease via three main processes – atherosclerosis, hypertension and adverse metabolic changes. Infertility and cancer are major confounding factors among users of GnRH analogues.

et al. 2017). Conversely, females with breast cancer receiving GnRH agonists are shown to have a lower risk of developing ischaemic heart disease (Chou *et al.* 2022).

The transgender population faces lifelong disparities in healthcare, largely driven by biological and psychosocial factors (Streed *et al.* 2021). These disparities manifest as a higher incidence of myocardial infarction among transgender populations (Alzahrani *et al.* 2019). Whether this reflects differences in clinical risk factors remains uncertain, and may be a consequence of behavioural risk factors, such as smoking (Kcomt *et al.* 2020) and lack of physical activity (Gilani *et al.* 2021). However, the long-term cardiovascular effects of puberty blockers in transgender adolescents remain uncertain.

Patients receiving GnRH analogues have a higher baseline cardiovascular risk, which may be confounded by comorbidities, including malignancy and infertility (Fig. 3). In view of this, observational studies involving males with prostate cancer (Keating *et al.* 2006, 2010, Van Hemelrijck *et al.* 2010) and infertility (Jackson *et al.* 2004, Shevell *et al.* 2005, Calhoun *et al.* 2011) have adjusted for baseline demographics and comorbidities. However, these analyses may have left out confounders that were not identified or recorded. Conversely, the increase in cardiovascular events may reflect improved overall survival among cancer patients treated with endocrine therapy (Francis *et al.* 2018). In addition, several cancer therapies lead to direct and indirect cardiovascular toxicity (Crocetto *et al.* 2023), highlighting the need to evaluate the cardiovascular safety of such treatment.

Furthermore, the metabolic effects of GnRH agonists are well established. GnRH agonists led to a shift in body composition from lean mass to fat mass (Smith *et al.* 2006, 2008, Mueller *et al.* 2011), hyperinsulinaemia (Dockery *et al.* 2003), reduced insulin sensitivity (Smith *et al.* 2006) and diabetes mellitus (Keating *et al.* 2010). In contrast to GnRH agonists, oral antiandrogens were not associated with an increased risk of diabetes amongst males with prostate cancer (Keating *et al.* 2010), suggesting a role of GnRH signal disruption in the development of diabetes.

In male mice models, GnRH agonists led to the destabilisation of established atherosclerotic plaques, a process likely caused by T cell-mediated inflammation (Knutsson *et al.* 2016). The activation of GnRH receptors present on T cells (Chen *et al.* 1999) may stimulate their pro-inflammatory activity (Tanriverdi *et al.* 2005). The lack of such a response in mice treated with GnRH antagonists suggests that the cardiovascular effects of GnRH agonist are largely driven by the initial surge of gonadotropins and testosterone (Knutsson *et al.* 2016). While GnRH and FSH receptors are known to be expressed within the vasculature (Chegini *et al.* 1996, Stilley & Segaloff 2018), their function and effects on cardiovascular disease remain unknown.

In conclusion, although GnRH analogues share a common mechanism, their wide application and interaction with sex alters cardiovascular risk via multitude of mechanisms. Uncertainty remains whether the effects are due to gonadotropin antagonism, a consequence of hypogonadism, or a combination of both factors. Clinical context with respect to cardiovascular risk should be considered to provide disease monitoring and initiate early intervention (Levine *et al.* 2010). Raised baseline cardiovascular risk should be a consideration but not an absolute contraindication. Further research is required to understand the role of GnRH and its downstream effectors in cardiovascular health and disease.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/JOE-23-0309.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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