RAS BLOCKADE: ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEi) ANGIOTENSIN-II RECEPTOR BLOCKERS (ARB) – PRE-CONCEPTION AND CONTRACEPTIVE ADVICE FOR WOMEN OF CHILD-BEARING AGE

KEY RECOMMENDATIONS

- Women of child-bearing age on, or for consideration of RAS blockade (ACEi or ARB), should have appropriate **pre-conception advice** and **be offered appropriate contraception**.
- **Appropriate contraception is unlikely to be the COCP** (UKMEC3 even with controlled hypertension)
- Pregnant women found to be on an ACEi or ARB should be **switched to an alternative treatment within 48h**.

WHY ARE THESE YOUNG WOMEN ON AN ACEi OR ARB?

ARB and ACEi are commonly used as first-line antihypertensive agents (or in the context of other morbidities such as diabetes with nephropathy or heart failure) including in women of child-bearing age.

ARE ACEi AND ARB DANGEROUS TO THE FOETUS?

YES. Gestational exposure to an ARB (e.g. Losartan, Irbesartan, Valsartan) or an ACEi (e.g. Lisinopril, Ramipril, Penrindopril) comes with a high-risk of neonatal complication including birth defects and poorer long-term prognosis[1].

ARE WE APPROPRIATELY INFORMING THESE WOMEN?

NO. Many women of child-bearing age on ARBs or ACEi are not appropriately counselled and/or on effective contraception. A recent audit of 1,060,844 patients in 3 inner-city London CCGs identified 2651 female patients of child-bearing age on an ACEi/ARB --**pre-conception advice and contraception advice was recorded during the preceding 12 months in only 1.3% and 8.7% of the patients respectively and only 10% of these women were on LARC or oral/transdermal hormonal contraception**[2]! Sadly, this is not improvement on similar finding of over 10 years ago[3].

WHAT SHOULD I DO IF A PREGNANT PATIENT IS FOUND TO BE ON AN ACEi OR ARB?

Pregnant women should **not** be on ACE or ARBs (unless absolutely necessary, after appropriate counselling and with support from secondary care physician). Pregnant women found to the on an ACE or ARB should:

- **Be informed of the potential risk to the unborn child**
- **Be offered support and counselling**
- **Be switched to an alternative treatment within 48h**

WHAT ABOUT NON-PREGNANT WOMEN OF CHILD-BEARING AGE?

Non-pregnant women of childbearing age on, or awaiting, ACEi or ARB treatment should:

- **Be informed of the risk in pregnancy**
- **Have appropriate pre-conception advice**
- **Be advised regarding *appropriate* contraception (see below)**

CURRENT GUIDELINES

Different national and trans-national hypertension management guidelines vary in their advice regarding the use of ACEi and ARB in women of childbearing age –some state this is an absolute contraindication whereas some other suggest it as a possible contraindication for example in the absence of reliable contraception[2]. No guidelines support the use of ACEi/ARBs in pregnancy although some accept there may be rare extreme circumstances where such use is necessary. This information is summarised in the table below.

Region [Guideline]	Women childbearing age	In pregnancy
UK [NICE 2019 Hypertension in adults: diagnosis and management (Draft for consultation]	Refers to NICE 2019 Hypertension in pregnancy: diagnosis and management NICE guideline [NG133]	Refers to MHRA advisory in footnotes
UK [MHRA advisory 2014]		ACE inhibitors and angiotensin II receptor antagonists should not be used at any stage of pregnancy unless absolutely necessary, and only then after the potential risks and benefits have been discussed with the patient.
UK [NICE 2019 Hypertension in pregnancy: diagnosis and management NICE guideline (NG133)]	Discusses pre-conception counselling including **increased risk of congenital abnormalities** and **advice to seek appropriate alternatives** Does **not** discuss contraception	Stop antihypertensive treatment in women taking ACE inhibitors or ARBs if they become pregnant (preferably within 2 working days of notification of pregnancy) and offer alternatives.
EUROPE [2018 ESC/ESH Guidelines for the management of arterial hypertension]	Child bearing age is a **possible contraindication** *without reliable contraception*	Pregnancy is **compelling contra-indication** to ACE and ARB
US [2017 ACC/AHA […] A Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary]	Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol.	Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors.

SUITABLE ALTERNATIVE TREATMENT

NICE guidelines regarding the treatment of various forms of pregnancy-related hypertension have recently been updated[4] but suggested alternatives remain as they have been for a long time: "Consider **labetalol** to treat chronic hypertension in pregnant women. Consider **nifedipine** for women in whom labetalol is not suitable, or **methyldopa** if both labetalol and nifedipine are not suitable". As thiazide or thiazide-like diuretics are also thought to increase the risk of congenital abnormalities, these should be avoided and US guidelines advise against beta-blockers (first line in the UK) as they can induce foetal bradycardia.

Remember that appropriate contraception is unlikely to be a COCP (UKMEC 3 even in controlled hypertension)[5].

As always, appropriate **lifestyle modification (e.g. a low-fat, low-cholesterol diet, regular exercise and smoking cessation) are highly advisable.**

AUDIT SUGGESTIONS

1. Identify women of childbearing age (typically defined as >=15 and <=45 years old) on ACEi or ARBs and **offer pre-conception and contraceptive advice to any women who have not had these**.
2. Audit your practice to identify **pregnant women on ACEi or ARB**s: offer these patient **an urgent review** and **switch them to an alternative antihypertensive within 48 hours.**
3. Consider extending your search to **women on thiazide or thiazide-like diuretics** which may also increase the risk of congenital abnormalities

REFERENCES

1. Bullo, M., Tschumi, S., Bucher, B. S., Bianchetti, M. G. & Simonetti, G. D. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. *Hypertens. (Dallas, Tex. 1979)* **60**, 444–50 (2012).
2. Lovegrove, E., McGettigan, P. & Robson, J. Pregnancy protection and pregnancies in women prescribed angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. *Br. J. Gen. Pract.* **Submitted**, (2019).
3. Martin, U., Foreman, M. A., Travis, J. C., Casson, D. & Coleman, J. J. Use of ACE inhibitors and ARBs in hypertensive women of childbearing age. *J. Clin. Pharm. Ther.* **33**, 507–511 (2008).
4. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management (NICE guideline NG133). (2019). Available at: https://www.nice.org.uk/guidance/ng133. (Accessed: 21st November 2019)
5. FSRH. UKMEC April 2016 (Amended December 2017), Digital Version - Faculty of Sexual and Reproductive Healthcare. (2017). Available at: https://www.fsrh.org/standards-and-guidance/external/ukmec-2016-digital-version/. (Accessed: 3rd September 2019)