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The Use of Angiotensin Converting Enzyme Inhibitors during the First Trimester of Pregnancy

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Abstract

Background: The direct effects of angiotensin converting enzyme inhibitor (ACEI) medications on the fetus are difficult to determine since these medicines are usually administered to women presenting with high-risk pregnancies. The aim of this study was to provide an overview of the dispensing patterns, demographic characteristics and pregnancy outcomes of women dispensed an ACEI during pregnancy.

Methods: Exposed pregnancies were all births in Western Australia, 2002-2005 where the mother was dispensed an ACEI under the Australian Pharmaceutical Benefits Scheme, compared with all other births during the same period.

Result: From 2002 to 2005, there were 96,698 births in Western Australia. At least one form of ACEI was dispensed to 95 pregnant women (0.1%) and a further 677 pregnant women (0.7%) were dispensed an antihypertensive medication that was not an ACEI. Women dispensed an ACEI in the first trimester were more likely to be obese (aOR 33.4; 95% CI: 19.5-57.2), to have gestational diabetes (aOR 2.6; 1.3-5.4), to have a preterm delivery (aOR 2.8; 1.4-5.6), and to have smoked during their pregnancy (aOR 1.9; 1.2-3.0). The children of women dispensed an ACEI were more likely to have a major birth defect (aOR 2.6; 1.3-5.2). The risk of a major uro-genital birth defect (aOR 4.8; 2.0-11.7) was increased.

Conclusion: Although ACEIs are contraindicated, pregnant women continue to be dispensed these medications. This study provides a profile of these women and their pregnancy outcomes. A clear change in the pattern of dispensing ACEIs later in pregnancy was apparent for these women. A greater number of women were dispensed ACEIs during trimester 1, followed by a marked reduction in dispenses in trimester 2 and trimester 3. Although the number of children affected is small, our data suggests that an increased risk of uro-genital defects may arise with maternal ACEI use in the first trimester.

Keywords: Antihypertensive agents; Hypertension; Perinatal outcome; Data linkage; Pharmacoepidemiology; Obesity; Uro-genital defect

Abbreviations: ACEI: Angiotensin Converting Enzyme Inhibitor; AH: Antihypertensive; AOR: Adjusted Odds Ratio; MNS: Midwives' Notification System; PBS: Pharmaceutical Benefits Scheme; WA: Western Australia; WARDA: Western Australian Register of Developmental Anomalies

Introduction

Hypertension is a common complication in pregnancy, with gestational hypertension occurring in approximately 10% of pregnancies and preeclampsia in 2-8% of pregnancies [1-4]. Hypertension in pregnancy is defined by the Society of Obstetric Medicine of Australia and New Zealand as systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg. The Society's guidelines for selecting oral antihypertensive (AH) agents in the management of hypertension are included in the clinical guidelines of the primary tertiary hospital in Western Australia (WA) with treatment generally considered when blood pressure exceeds 150 mmHg systolic or 95 mmHg diastolic on several occasions. The recommended options for first line AH therapy are methyldopa and labetalol. Second line agents are hydralazine, nifedipine and prazosin [5]. The guidelines specify that ACEIs are contraindicated in pregnancy and that their use in the third trimester has been associated with fetal death and neonatal renal failure.

ACEIs are a group of compounds that are commonly used to control hypertension. ACEIs are also used in heart failure and are useful for preserving kidney function in people with diabetes and kidney disease. Captopril, the first ACEI, was reported in 1977 and approved for use in 1981 [6]. The first adverse effects on a fetus were reported in 1981 and these related to exposure during trimesters two and three [7,8]. ACEIs are known to cross the placenta [9-12]. It is now known that when administered mid-late pregnancy, ACEIs can impair fetal development through inducing fetal hypotension, decreasing uterine, umbilical, and renal blood flow [13]. This can induce oligohydramnios, growth reduction, hypocalvaria, hypotension, neonatal renal failure and death [12-15]. Since 1992, the U.S. Food and Drug Administration has required a warning on all ACEIs regarding their fetotoxic effects when used during trimesters two and three [16,17]. The specific features of ACEI

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fetopathy (positional limb deformities, retarded ossification of the skull, hypoplastic lungs) have been described as secondary to oligohydramnios that in turn is secondary to fetal renal dysfunction [18]. These effects were not seen when ACEI use was limited to the first trimester. Animal studies have not suggested that malformations are likely to result from such treatment, [19] and no mechanism by which ACEIs might interfere with embryogenesis is known [20]. A study by Cooper et al. in 2006 reported fetopathy among women dispensed ACEIs during only the first trimester of pregnancy (N=209 children) [21], whereas a much larger study with a more ethnically diverse population did not confirm this [22]. The increased risk of malformations may be more related to the hypertension itself rather than a direct effect of ACEIs [23]. Concerns were also raised as to whether the Cooper study adequately controlled for the confounding effects of maternal diabetes and obesity [24]. Studying medicines at the drug class level is not always useful in investigations of birth defects: the fallacy of "class action" teratogenesis [25]. However the number of pregnancies exposed to an individual generic ACEI is usually too small to report, so most studies have reported analyses at the drug class level of ACEIs.

The Australian pregnancy risk category is D for all ACEIs: "Drugs which have caused are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects." [26].

The direct effects of ACEIs on the fetus are difficult to determine since these medicines are usually administered to women presenting with high-risk pregnancies decreasing uterine, umbilical, and renal [27]. Some studies have not adjusted for co-existing conditions that may potentially confound the risks associated with ACEI use in pregnancy. These conditions include obesity, diabetes, essential hypertension, preeclampsia, maternal age and smoking. The aim of this study was to provide an overview of the dispensing patterns, demographic characteristics and pregnancy outcomes of women dispensed an ACEI during pregnancy, taking into account these potential confounders.

Methods

This was a population-based data linkage study investigating pregnancy events in Western Australia (WA) from 2002 to 2005. A pregnancy event was defined as a hospital admission record in the Hospital Morbidity Data System with a diagnosis code between O00-O99, based upon the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) [28]. De-identified data were provided from the WA Data Linkage System (WADLS), linking the records of women with each pregnancy event to any related records in the Midwives' Notification System (MNS), the Western Australian Register of Developmental Anomalies (WARDA) and the Registry of Births and Deaths. Data related to previous pregnancies for each woman back to 1980 were also extracted. These datasets were linked to each other and to data from the national Pharmaceutical Benefits Scheme (PBS). The linkages and methodology have been described previously [29,30].

The WARDA, the first of its kind in Australia, was established in 1980 and records birth defects (BD) occurring in children born on, or after, January 1, 1980 [31]. For the purposes of the WARDA, a BD is defined as a structural or functional abnormality that is present at conception or occurs before the end of pregnancy and is diagnosed by six years of age [32,33]. The major sources of notification to the WARDA are hospitals and private practitioners, WA Department of Health databases (mortality and hospital morbidity systems), and investigative and treatment centres (cytogenetic, pathology, and genetics services). Most minor defects are excluded unless they are disfiguring or require treatment. Of all cases registered, about 90% have at least one major BD (with or without a minor BD); the remainder have only minor defects. A list of exclusions can be found on the WARDA website [34]. Each individual defect (up to a maximum of 10 defects per case) is coded according to the 5-digit British Paediatric Association (BPA) ICD-9 system [35]. Syndrome diagnoses are coded along with the major individual defects seen in that infant. The WARDA is a comprehensive source of information on BDs in WA with a high level of ascertainment and is used in relevant areas of health service provision, policy development, research, and evaluation.

Potential confounders were identified through the Hospital Morbidity Data System and MNS. The hospital admission data include a principal diagnosis and up to 20 co-morbidities as recorded on the discharge records. The codes are based upon ICD-10-AM [28]. From these codes we determined whether the women were recorded as being obese, had pre-existing diabetes, gestational diabetes, preeclampsia or essential hypertension recorded in any of her hospital admissions during her pregnancy. We used data from the MNS to determine whether the women smoked during their pregnancy, had a previous preterm delivery or previous Caesarean delivery. The medical conditions record women with any of the diagnoses of chronic hypertension, preeclampsia, pre-existing diabetes or gestational diabetes. 'Chronic hypertension' is defined in the MNS as a diastolic blood pressure of at least 90 mmHg recorded on two or more occasions before 20 weeks of pregnancy and not due to any identifiable aetiological factor [36]. 'Preeclampsia' is defined as the development of hypertension with proteinuria, oedema, or both, induced by pregnancy after the 20th week. 'Pre-existing diabetes' refers to Type 1 or Type 2 diabetes antedating pregnancy. 'Gestational diabetes' is abnormal glucose tolerance detected in pregnancy.

The Australian Bureau of Statistics has released the Socio-Economic Indexes for Areas (SEIFA) based on the information collected in the five-yearly Census of Population and Housing. These indexes are widely used measures of relative socio-economic status and they rank and identify geographic areas that are relatively more, or less, disadvantaged. They provide contextual information about the area in which a person lives derived from analysis of variables including income, education, employment, occupation and housing. The Australian mean is 1000 [37].

In Australia, community prescriptions (i.e. non-public hospital) are dispensed either as private prescriptions or under one of two subsidisation schemes—the PBS and the Repatriation Pharmaceutical Benefits Scheme. All Australians are eligible to receive subsidised rates for prescribed medicines approved under the PBS, with around 80% of prescriptions dispensed in Australia being subsidised. Patients are grouped into two classes: general and concessional. As the general patient copayment rises, the dispensed prices of many of the cheaper medications fall under this level. In such cases the general patient pays the full price and no claim for payment is made under the PBS.

Comparisons were made between women who were dispensed an ACEI during their pregnancy, and all other women who were not dispensed an AH under the PBS. Our first analyses included women dispensed angiotensin receptor blockers. There was one child with a major birth defect (ostium secundum type atrial septal defect). The mother was dispensed an angiotensin receptor blocker in the first trimester only and no ACEIs. This pregnancy is not included in this analysis as the control group is mothers without an AH dispense.

Percentages, univariate odds ratios and 95% confidence intervals (OR; 95% CI) were calculated for each comparison. Stepwise regression

using the SAS procedure, PROC LOGISTIC, was used to adjust odds ratios. T-tests were used to compare means where appropriate.

The WADLS uses the Automatch software package (Matchware Technologies Inc., Kennebunk, ME, USA) with probabilistic matching based upon medical record number, surname, first given name and initial, date of birth, sex and address as the principal matching fields. Missed links have been estimated at 0.11% [38]. The WADLS has been validated previously [38,39] and has been used extensively for health research [40]. All records for this study were also validated internally. For example, sex and dates of birth or death were checked across each source. The researchers received all data in a de-identified form from the WADLS. The datasets were analysed using SAS/STAT software, version 9.3 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). To fulfil the requirements of ethics committees' approvals relating to individual privacy, we have not reported cell sizes with less than five study subjects. This project has approval from the Human Research Ethics Committees of The University of Western Australia and the Department of Health WA.

Results

From 2002 to 2005, there were 96,698 births in WA. At least one ACEI was dispensed to 95 pregnant women (0.1%) and a further 677 pregnant women (0.7%) were dispensed an AH that was not an ACEI. During this period there were 12 generic medicines, including combinations, with 30 forms on the PBS that fell under the category of ACEIs. Of these, 8 generic medicines in 27 forms were dispensed to pregnant women under the PBS. As 20 of the 27 forms were priced below the copayment level for general patients at some time during the study period, the women dispensed an ACEI in this study were primarily concessional patients.

Characteristics of the women and their pregnancies

ACEIs were dispensed during the first trimester to 83 pregnant women with a pregnancy resulting in a birth (84 children), two women with an ectopic pregnancy and 27 women with a termination of pregnancy in a hospital setting. The demographic characteristics of the women with a birth are shown in Table 1. The women who were

	ACE N=83		non-AH N=95,926		
	N	%	N	%	
Mothers	83		95,926		
Children	84		97,553		
	Mean	Median	Mean	Median	Pr> |t|
Maternal age, y	33.4	34	29.9	30	<0.0001
height, cm	166.2	166	164.6	165	0.0664
GA, wk	36.7	37	38.6	39	<0.0001
SEIFA[1]	957.1	953	997.8	1,009	<0.0001
	N	%	N	%	OR (95% CI)
Caucasian	66	79.5%	81,469	84.9%	0.69 (0.40-1.17)
Parity>1	62	74.7%	66,822	69.7%	1.29 (0.78-2.11)
Smoked during pregnancy	23	27.7%	16,400	17.1%	1.86 (1.15-3.01)
Previous pregnancy characteristics					
Previous preterm delivery	14	22.6%	5,475	8.2%	3.27 (1.80-5.93)
Previous Caesarean	20	32.3%	13,100	19.6%	1.95 (1.15-3.33)
Complications of pregnancy					
Pre-eclampsia	21	25.3%	4,134	4.3%	7.52 (4.58-12.35)
Gestational diabetes	8	9.6%	3,741	3.9%	2.63 (1.27-5.45)
Other complications of pregnancy	35	42.2%	18,598	19.4%	3.03 (1.96-4.69)
Medical conditions					
Essential hypertension	37	44.6%	783	0.8%	97.74 (63.04-151.53)
Pre-existing diabetes	12	14.5%	523	0.5%	30.83 (16.62-57.18)
Asthma	10	12.0%	10,112	10.5%	1.16 (0.60-2.25)
Obese	17	20.5%	734	0.8%	33.40 (19.51-57.21)
Other medical condition	29	34.9%	17,148	17.9%	2.47 (1.57-3.88)
Delivery characteristics					
Obstetrician attended	34	41.0%	39,303	41.0%	1.00 (0.65-1.55)
General anaesthetic during delivery	4	4.8%	1,950	2.0%	2.44 (0.89-6.67)
Preterm delivery, adjusted[2]	25	30.1%	7,754	8.1%	2.79 (1.38-5.63)
Caesarean, adjusted[3]	43	51.8%	30,737	32.0%	1.77 (0.93-3.37)
Complications of labour and delivery					
Fetal distress	20	24.1%	13,151	13.7%	2.00 (1.21-3.31)
PPH ≥ 500 ml, adjusted[4]	20	24.1%	8,739	9.1%	1.55 (0.88-2.73)
Failure to progress<3 cm	6	7.2%	2,413	2.5%	3.02 (1.31-6.94)
Other complications of lanour	35	42.2%	24,403	25.4%	2.14 (1.38-3.30)

[1]Population mean=1000
[2]Adjusted for maternal age, plurality, smoked during pregnancy, previous preterm birth, greatest SEIFA disadvantage, parity, co-morbidities (obesity, pre-existing diabetes, or diabetes mellitus in pregnancy)
[3]Adjusted for previous Caesarean delivery in women with parity >1
[4]Adjusted for Caesarean delivery, preeclampsia, plurality, co-morbidities (obesity, pre-existing diabetes, or diabetes mellitus in pregnancy)

Table 1: Demographic characteristics of the women dispensed an ACEI during trimester 1, birth events.

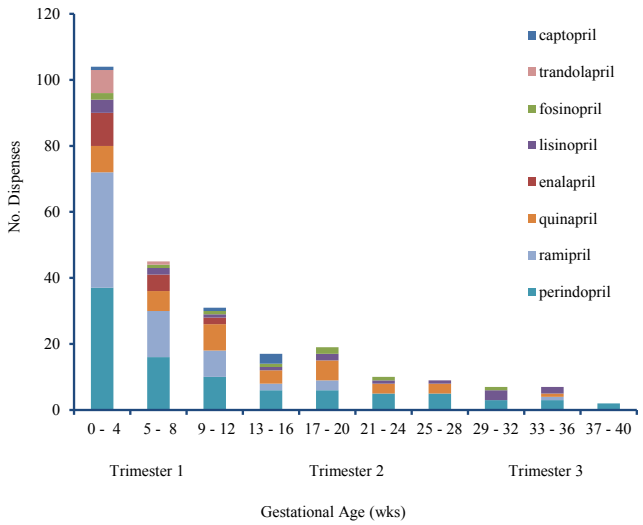
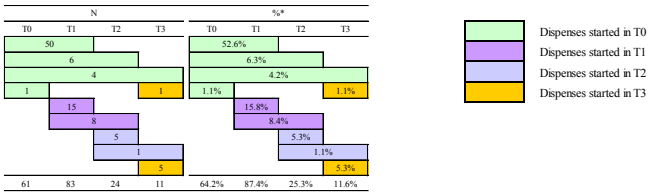


Figure 1: Number of women dispensed each ACEI during each trimester of pregnancy.



T0: 3 months before pregnancy, T1: first trimester, T2: second trimester, T3: third trimester

*Percentages are the proportion of all birth events dispensed an ACEI within each trimester.

Figure 2: Dispensing patterns of ACEIs during each trimester of pregnancy.

dispensed at least one ACEI during pregnancy were significantly older (mean 33.4 v 29.9 years, *p*-value<0.0001), had a lower measure of mean socio-economic status (*p*-value<0.0001) and were more likely to have smoked during their pregnancy (1.9; 1.2-3.0). These women's pregnancies were more likely to be complicated by preeclampsia (7.5; 4.6-12.4) and pre-existing diabetes was more likely to be present (30.8; 16.6-57.2). They were more likely to have had a previous preterm delivery (3.3; 1.8-5.9) and a previous Caesarean delivery (2.0; 1.2-3.3). The delivery was more likely to be a Caesarean section (2.3; 1.5-3.5) and, after adjusting for a previous Caesarean delivery in women with parity >1, the risk was still greater, although not significantly (1.8; 0.9-3.4). The children were more likely to be delivered prematurely (4.9; 3.1-7.8). When the risk of preterm birth was adjusted for known confounders for preterm delivery - plurality, smoked during pregnancy, maternal age, previous preterm birth, greatest SEIFA disadvantage, parity, co-morbidities recorded on the birth admission (obesity, type 2 diabetes mellitus, or diabetes mellitus in pregnancy) - the risk was still increased (2.8; 1.4-5.6). The exposed women were more likely to experience a primary postpartum haemorrhage of ≥ 500 ml (3.2; 1.9-5.2). This risk was adjusted for Caesarean delivery, preeclampsia, plurality, and co-morbidities recorded on the birth admission (obesity, type 2 diabetes mellitus, or diabetes mellitus in pregnancy) and the risk remained elevated but no longer statistically significant (1.6; 0.9-2.7).

ACEIs dispensed

Overall, 8 different ACEIs were dispensed at some time in pregnancy (Figure 1). The most commonly dispensed medicine was perindopril, which was dispensed to 46.3% (N=44) of the women in the ACEI group. Ramipril was dispensed to 23.2% (N=22).

Dispensing patterns

There were 68.4% of the women (N=65/95) dispensed an ACEI in the first trimester but discontinued the medicine for the remainder of their pregnancy (Figure 2). A further 55 women were dispensed an ACEI in the three months before their pregnancy but were not dispensed the medicine during their pregnancy and so were not included in the ACEI group. There were 11 women dispensed an ACEI in trimester two or three but not during the first. There were 4.2% (N=4) of the women dispensed an ACEI in each trimester and these women had all been dispensed an ACEI during the pre-conception period as well. We also investigated the mix of ACEIs and other AH agents dispensed to each woman during her pregnancy. There were 38 women dispensed another AH agent that was not an ACEI.

The women dispensed an ACEI during their pregnancy were also dispensed other medicines (N=71, 74.7%). The leading five ATC conditions for which other medicines were prescribed are listed in Table 2. Whilst the category of medicine dispensed to the most ACEI women was 'antibacterials for systemic use' (3.6; 2.3-5.5), the most likely medicines dispensed (compared with women not dispensed an AH agent) were for 'drugs used in diabetes' (37.9; 23.0-62.4) and 'lipid modifying agents' (176.0; 84.5-366.8).

Characteristics of the children and their birth admission

There were 84 children resulting from 83 pregnancies with a mother dispensed an ACEI during the first trimester of her pregnancy. These children were more likely to have a lower birth weight (2966 g cf. 3331 g; p-value <.0001), have a shorter birth length (48 cm cf. 50 cm; *p*-value<0.0001), and an increased risk of a major birth defect (aOR 2.6; 1.3-5.2): Table 3.

There were 10 children born with a major birth defect to mothers dispensed an ACEI during the first trimester. Eight of these children were male. There were six children with a uro-genital defect (aOR 4.8; 2.0-11.7). One of these six mothers continued with perindopril into her second trimester and another continued with quinapril through to her third trimester. The most common defect was '752.5 undescended testicle' with an increased (adjusted) risk of 11.5 (3.8-34.8) times the rate seen in the male children of mothers not dispensed an AH agent. Three quarters of these male children were born preterm. After adjusting for maternal age and other possible confounders, an increased risk of a chromosomal defect (aOR 14.8; 3.6-59.8) remained.

The most common morbidities recorded on the infant's birth admissions were 'P59 Neonatal jaundice' (32.1% v 7.8%) and 'P22 Respiratory distress of newborn' (29.8% v 7.3%): Table 4. The increased risks of these being seen in the ACEI children compared with the non-AH children were aOR 2.7; 1.5-4.7 and aOR 3.1; 1.7-5.5, respectively.

Discussion

The direct effects of ACEIs on the fetus are difficult to determine since these medicines are usually administered to women presenting with high-risk pregnancies [27]. The women in our study who were dispensed an ACEI were different in many ways from the reference group of non-AH women. These women were older, more likely to

	ACE N=95		non-AH N=95,926		OR 95% CI
	N	%	N	%	
J01 Antibacterials for systemic use	**31**	**32.6%**	**11,509**	**12.0%**	**3.55 (2.31-5.46)**
cephalexin	15	15.8%	3,969	4.1%	4.34 (2.50-7.55)
amoxycillin	14	14.7%	5,740	6.0%	2.72 (1.54-4.79)
N02 Analgesics	**28**	**29.5%**	**4,188**	**4.4%**	**9.15 (5.88-14.24)**
codeine phosphate with paracetamol	19	20.0%	2,491	2.6%	9.38 (5.66-15.53)
paracetamol	14	14.7%	1,694	1.8%	9.61 (5.44-16.99)
A10 Drugs used in diabetics	**20**	**21.1%**	**670**	**0.7%**	**37.91 (23.02-62.45)**
metformin hydrochloride	13	13.7%	107	0.1%	141.97 (76.75-262.61)
insulin isophane (N.P.H)	9	9.5%	431	0.4%	23.19 (11.59-46.37)
insulin aspart	7	7.4%	220	0.2%	34.60 (15.85-75.56)
insulin neutral	6	6.3%	197	0.2%	32.76 (14.16-75.76)
C10 Lipid modifying agents	**9**	**9.5%**	**57**	**0.1%**	**176.01 (84.47-366.76)**
atorvastatin calcium	8	8.4%	38	0.0%	232.03 (105.21-511.71)
R03 Drugs for obstructive airway diseases	**14**	**14.7%**	**5,053**	**5.3%**	**3.11 (1.76-6.15)**
salbutamol sulfate	11	11.6%	2,320	2.4%	5.28 (2.81-9.92)
A03 Drugs for functional gastrointestinal disordres	**11**	**11.6%**	**3,686**	**3.8%**	**3.28 (1.75-6.15)**
metoclopramide hydrochloride	11	11.6%	3,662	3.8%	3.30 (1.76-6.19)
A02 Drugs for acid related disorders	**16**	**16.8%**	**2,639**	**2.8%**	**7.16 (4.18-12.27)**
ranitidine hydrochloride	11	11.6%	1,493	1.6%	8.28 (4.41-15.56)
N06 Psychoanaleptics	**15**	**15.8%**	**4,609**	**4.8%**	**3.71 (2.14-6.45)**
paroxetine hydrochloride	5	5.3%	676	0.7%	7.83 (3.17-19.33)

Table 2: Other medicines dispensed to women with an ACEI dispensed during pregnancy, by ATC conditions and generic name.

Demographics	**N**	**%**	**N**	**%**	**OR (95% CI)**
Mothers	83		95,926		
All Children	84		97,533		
Males	50	59.5	49,999	51.3	1.40 (0.90-2.16)
Birth weight <2500 g[1]	21	21.9	6,996	7.2	1.86 (0.79-4.37)
Birth length ≤ 50 cm [2]	56	58.3	55,751	57.2	0.70 (0.36-1.35)
Preterm[3]	26	27.4	8,749	9.1	3.26 (1.65-6.45)
		Mean		Mean	t-test
Birth weight, g		2,965.7		3,330.6	<0001
Birth length, cm		48.1		49.8	<0001
APGAR		8.8		9.0	0.0533
POBW[4]		0.990		0.996	0.7116
Major birth defects	N	%	N	%	adj OR (95% CI)[5]
Any major birth defect	10	11.9	3,950	4.0	2.58 (1.27-5.24)
745-747 CARDIOVASCULAR DEFECTS	**<5**	**1.2**	**691**	**7.1**	**0.82 (0.11-6.33)**
746 Other congenital abnormalities of heart	<5	1.2	249	0.3	2.42 (0.32-18.36)
7464 Congenital insufficiency of aortic valve	<5	1.2	42	0.0	16.77 (1.65-170.03)
747 Other congenital abnormalities of circulatory system	<5	1.2	246	0.3	2.19 (0.29-16.53)
7471 Coarctation of aorta	<5	1.2	58	0.1	10.89 (1.02-116.00)
752-753 URO-GENITAL DEFECTS	**6**	**7.1**	**1,346**	**1.4**	**4.82 (1.98-11.70)**
752 Congenital anomaly of urinary system	<5	6.0	846	0.9	6.77 (2.70-16.96)
7525 Undescended testicle (males only)	<5	4.8	373	0.4	11.49 (3.79-34.84)
7526 Hypospadias and epispadias (males only)	<5	1.2	358	0.4	3.00 (0.41-21.79)
753 Congenital anomaly of urinary system	<5	1.2	532	0.5	1.40 (0.18-10.71)
7532 Obstructive defects of renal pelvis and ureter	<5	1.2	228	0.2	4.38 (0.60-31.81)
758 CHROMOSOMAL DEFECTS	**<5**	**3.6**	**222**	**0.2**	**14.76 (3.64-59.77)**
7580 Down Syndrome	<5	2.4	114	0.1	9.56 (2.20-41.63)
7585 Other total trisomy syndromes	<5	1.2	29	0.0	15.41 (1.19-199.64)

[1]Adjusted for gestational age, birth length, smoked during pregnancy, SEIFA, multiple birth, maternal age
[2]Adjusted for gestational age, birth weight, smoked during pregnancy, SEIFA, multiple birth, maternal age
[3]Adjusted for birth weight, birth length, smoked during pregnancy, SEIFA, multiple birth, maternal age
[4]Population mean=1000
[5]Adjusted for gestational age, smoked during pregnancy, SEIFA, multiple birth, maternal age, parity, ethnicity, marital status, pre-existng diabetes, preeclampsia, essential hypertension, obesity, gestational diabetes

Table 3: Characteristics of children born to women dispensed an ACEI during trimester 1.

			Non-AH N=97,533		Adj OR (95% CI)*
	N	%	N	%	
P59 Neonatal jaundice from other and unspecified causes	27	32.1%	7578	7.8%	2.66 (1.51-4.67)
P22 Respiratory distress of newborn	25	29.8%	7074	7.3%	3.09 (1.74-5.50)
P07Disorders related to short gestation and low birth weight, not elsewhere classified	22	26.2%	7112	7.3%	1.15 (0.52-2.54)
Z03 Medical observation and evaluation for suspected diseases and conditions	21	25.0%	10779	11.1%	1.12 (0.62-2.00)
P28 Other respiratory conditions originating in the perinatal period	15	17.9%	3731	3.8%	2.72 (1.38-5.34)
P70 Transitory disorders of carbohydrate metabolism specific to fetus and newborn	13	15.5%	2427	2.5%	1.59 (0.73-3.45)
Z29 Need for other prophylactic measures	13	15.5%	5152	5.3%	1.23 (0.60-2.54)
P92 Feeding problems of newborn	10	11.9%	7020	7.2%	0.64 (0.29-1.41)
P05 Slow fetal growth and fetal malnutrition	7	8.3%	2118	2.2%	1.91 (0.83-4.43)
P29 Cardiovascular disorders originating in the perinatal period	7	8.3%	1482	1.5%	1.64 (0.62-4.33)

*Adjusted for maternal age, smoked in pregnancy, GA, parity, ethnicity, marital status, SEIFA and co-morbidities (obesity, preeclampsia, essential hypertension, type 2 diabetes mellitus, or diabetes mellitus in pregnancy), recorded at birth admission

Table 4: Leading 10 co-morbidities recorded on the children's birth admission summary.

smoke during their pregnancy, to be obese and to have pre-existing diabetes. They were more likely to have already had at least one previous preterm delivery and more likely to have a previous Caesarean delivery. Their delivery was more likely to be preterm. When we reviewed the other medicines dispensed during pregnancy, the women were also more likely to be dispensed medicines for other medical conditions such as depression, diabetes and elevated cholesterol. Renal disease and hypertension are well recognised complications of diabetes [41] and in our study the women in the ACEI group were 37.9 times more likely to be dispensed a medicine for use in diabetes.

A major strength of this study is the ascertainment of birth defects. The WARDA is a comprehensive source of information on BDs in WA with a high level of ascertainment and is used in relevant areas of health service provision, policy development, research, and evaluation. We restricted the analyses to major defects. Although the number detected was small, we found an increased risk in uro-genital defects with first trimester exposure. We did not find an increased risk of cardiac defects. The increased risk of a chromosomal defect remained after adjusting for maternal age.

Although most of the male infants with undescended testis were born preterm, the WARDA only registers cases of undescended testis that have been treated with surgery. It is believed normal testicular descent occurs in two phases: the first phase (transabdominal) between gestational weeks 8 and 17 and the second phase (inguino–scrotal) between weeks 26 and 35 [42,43]. Thus, testicular descent may be vulnerable to adverse lifestyle and environmental factors throughout pregnancy [44]. Although an increased risk in undescended testis in infants born to mothers with diabetes and gestational diabetes have been reported [45,46], the increased risk in our study remained after we adjusted for both of these factors. We cannot determine whether exposure in the first trimester was the critical time for two of these cases, who were both also exposed in trimester two and one in trimester three.

We also reviewed the women's hospital records relating to the birth admission to determine co-morbidities recorded in those records. The women were significantly more likely to have Type 2 diabetes or gestational diabetes, to be obese, and although the numbers were small, more likely to suffer from depression. Maternal obesity is a known risk factor for adverse pregnancy outcomes [47-51] and our study highlighted the co-occurrence of obesity, diabetes and hypertension.

It is clear that no singular data source can provide the full morbidity profile for these women. When we investigated the mothers' hospital admissions at delivery, we found these records provided a further 4.1% reported comorbidity relating to hypertension not reported in the midwives' records. The inclusion of midwives' records, hospital admission records, and medicine dispensing records provide a rich resource. The analyses of health administrative data, reported at the time of the event, can provide a morbidity profile of pregnant women without the selection and recall biases that can arise with case-control studies which rely on maternal interview some months after delivery.

The PBS dataset includes only medicines dispensed under subsidy. This was around 88% of all AH prescriptions in Western Australia, so the number of pregnant women identified as treated with ACEIs in this cohort will be under-estimated and more likely to be concessional patients.

As we have data linkage records for all of the women's previous pregnancies delivered in WA since 1980, we were able to investigate the risk of a preterm birth and adjust for known factors related to an increased risk of preterm delivery: smoking during pregnancy, lower socio-economic status, co-morbidities recorded on the birth admission (obesity, type 2 diabetes mellitus, or diabetes mellitus in pregnancy), maternal age, parity, and previous preterm birth. We found there was still an increased risk of preterm delivery in women dispensed an ACEI during their pregnancy (2.8; 1.4-5.6). We also investigated the risk of a primary postpartum haemorrhage of ≥ 500 ml after adjusting for Caesarean delivery, preeclampsia, plurality, and co-morbidities recorded on the birth admission (obesity, type 2 diabetes mellitus, or diabetes mellitus in pregnancy) and found there was still an increased risk, although not statistically significant (1.6; 0.9-2.7). This may be associated with the medications, the underlying disease, or a combination of the two.

There are several methodological limitations in the current study. We have no way of determining whether the women consumed the medication as prescribed. Another limitation is that not all the ACEIs are subsidised under the PBS, so these results don't provide complete ascertainment. This would mean that women not captured under the PBS scheme as being dispensed an ACEI would be in the non-AH group and therefore our risk estimates are more likely to be biased towards the null. We have no information on the severity of hypertension nor diabetes and whether they were well-controlled during pregnancy.

A clear change in the pattern of dispensing ACEIs later in pregnancy was apparent for these women. A greater number of women were dispensed ACEIs during the first trimester, and there was a marked reduction in dispenses in the second and third trimester. This

large decrease is probably due to practitioners changing or ceasing prescribing ACEIs once the pregnancy was recognised due to concerns of the possible fetopathy of ACEIs in mid to late pregnancy.

Conclusion

The aim of this study was to show the dispensing patterns of ACEIs to women during pregnancy, the demographic characteristics of these women and their pregnancies. There are striking differences between the demographic characteristics for women who were prescribed an ACEI and those women who were not. Thus any study that attempts to demonstrate a relationship between ACEIs and fetal outcome must take into account the characteristics of the women rather than attributing differences in fetal outcome to the ACEI alone. The most recent statistics from the PBS show that perindopril is ranked 5th in the most frequently dispensed generic items [52]. In Australia, all ACEIs are classified as category D for use in pregnancy. As around 50% of pregnancies are unplanned in Western Australia [53], medical practitioners caring for women of child-bearing age should discuss the risks and benefits of using ACEIs with their patients. The study adds to the limited data available in relation to first trimester exposure to ACEIs. Our data suggests that an increased risk of uro-genital defects may arise with maternal ACEI use in the first trimester.

Acknowledgement

This project has approval from the Human Research Ethics Committee of The University of Western Australia (ref #RA/4/1/1390) and was performed under the auspices of the WA Cross Jurisdictional Data Linkage Project covered by a Memorandum of Understanding between the Western Australia Department of Health and the Australian Government Department of Health and Ageing. The person-based linkage was covered by approvals from the two agencies' ethics and confidentiality committees. Before the event-based data linkage was undertaken, approval was also obtained from the Confidentiality of Health Information Committee (approval #200534) and permission to use the required data was obtained from the relevant data custodians. Carol Bower was funded by a National Health and Medical Research Fellowship (#634341).

Competing Interests

There are no competing interests to declare.

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