

## ACE inhibitor fetopathy: a case series and survey of opinion amongst New Zealand paediatricians, obstetricians, neonatologists, and nephrologists

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### Abstract

The use of ACE (angiotensin converting enzyme) inhibitors is contraindicated throughout pregnancy due to potential adverse effects to the developing fetus (fetopathy). Despite this, women continue to receive ACE inhibitors both in New Zealand and overseas and large scale epidemiological studies have shown cases of associated harm to infants.

We present three New Zealand infants with potential renal complications following *in utero* ACE inhibitor exposure including hypertension, renal failure and death. We also present data from an email-based survey of experience and opinion from relevant New Zealand specialists on how to best counsel women of child-bearing age regarding ACE inhibitors (quantitative and qualitative data). To our knowledge this is the first data published on this subject in New Zealand.

ACE inhibitor exposure in pregnancy may result in potential renal, cardiac and limb complications for the developing fetus. How best to counsel women regarding ACE inhibitors and pregnancy remains an area for further discussion in New Zealand.

### Cases

Angiotensin converting enzymes (ACE) inhibitors are useful and well tolerated drugs used in the treatment of hypertension.<sup>1</sup> Their use in pregnancy in New Zealand is now contraindicated due to proven adverse fetal effects (fetopathy).<sup>2-6</sup> These effects include malformations following oligohydramnios (lung hypoplasia, ossification and limb defects); direct renal complications (hypertension, renal failure) as well as cardiac and central nervous malformations due to impaired uteroplacental blood flow.<sup>7-9</sup>

Ongoing use of ACE inhibitors during pregnancy has been observed overseas and remains difficult to prevent.<sup>10</sup> Women are often not under specialist care early in their pregnancy and there is a potential lack of clinician awareness of this contraindication.<sup>11</sup> Previously, it was thought that first trimester use of ACE inhibitors was safe, however the large scale cohort study in 2006 by Cooper et al has shown that first trimester exposure is associated with an increased rate of malformations and ACE inhibitors should be avoided throughout pregnancy.<sup>2</sup> Therefore adequate advice and education should be considered prior to pregnancy to avoid this preventable outcome in New Zealand.

We present three New Zealand infants with potential renal complications from in-utero exposure to ACE inhibitors, including hypertension, renal failure and death.

## Infant 1

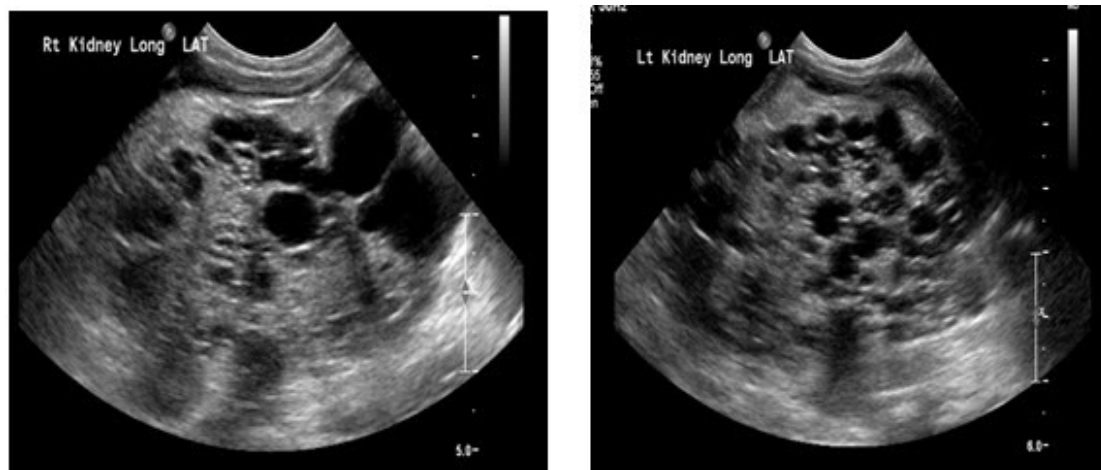
Infant 1 was born to 38-year-old Indian mother, gravida 5 para 1 (2 miscarriages, 1 stillborn at 20 weeks gestation). The pregnancy was complicated by pre-existing hypertension and gestational diabetes (managed with diet control). The mother was taking the ACE inhibitor cilazapril until 17 weeks gestation when the pregnancy was diagnosed. At the 18-week ultrasound scan, bilateral echogenic kidneys were documented, pulmonary hypoplasia and possibility of an absent bladder.

The family was counselled prior to delivery that the expected outcome was poor and therefore dialysis would not be offered in New Zealand as discussed with the tertiary paediatric renal service. Infant 1 delivered via ventouse following spontaneous preterm delivery at 35 weeks gestation with shoulder dystocia.

Infant 1 required Neopuff resuscitation taking first gasp at 2 minutes with established respirations at 15 minutes (APGARS 3, 4, 6, 8). The infant was macrosomic with a birthweight of 4130g (far above 97<sup>th</sup> centile) without significant oedema. Infant 1 was admitted to Neonatal Intensive Care with continuous positive pressure (CPAP) respiratory support.

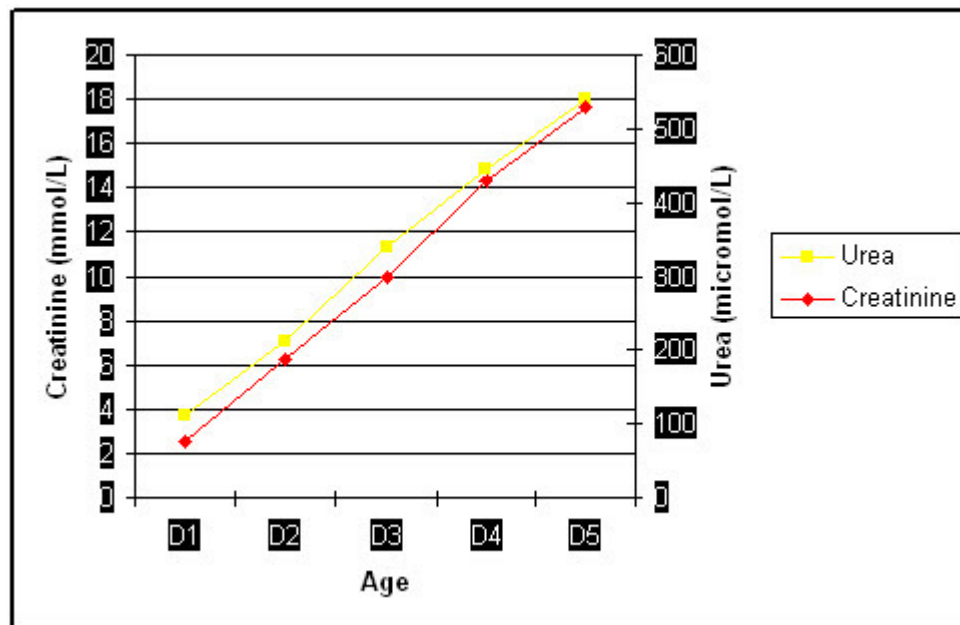
Initial blood gas was consistent with birth asphyxia (pH = 6.99, base excess = -14). Infant 1 remained hypoglycaemic for the first 12 hours despite escalating IV dextrose concentrations. Infant 1 remained anuric for the first 24 hours with initial urea of 5 mmol/L and creatinine of 126 mmol/L (normal maternal biochemistry). Day 2 renal ultrasound scan sited an empty bladder, oedematous kidneys with 'no functional renal tissue' (Figure 1).

**Figure 1. Bilateral multicystic dysplastic kidneys with no renal parenchyma identified**



Ventilation was weaned to oxygen on day 4, but Infant 1 remained anuric with escalating serum urea and creatinine levels (Figure 2). Calcium gluconate and per rectum resonium was used given associated hyperkalaemia.

**Figure 2. Consistently rising renal biochemistry values following birth**



On day 5 Infant 1 had bloody nasogastric aspirates and prolonged periods of desaturation. Comfort care plans were made, umbilical lines removed and Infant 1 passed away in the presence of family.

## Infant 2

Infant 2 was born to a 43-year-old New Zealand Māori women, G5 P3 (1 previous termination). The women had hypertension noted previously in each of her previous pregnancies and was subsequently diagnosed with a benign pituitary tumour secreting ACTH (Cushing's disease). This was removed and replaced with daily hydrocortisone. The hypertension persisted post resection which was well controlled with the angiotensin II blocker (2<sup>nd</sup> generation ACE inhibitor) candesartan.

The pregnancy was unplanned and unexpected and candesartan continued through the first trimester. The 20 weeks gestation ultrasound scan showed oligohydramnios and candesartan was discontinued. Subsequent ultrasound scans showed recovery in amniotic fluid and a cardiac effusion seen at 22 weeks also resolved. The maternal hypertension was controlled without further medications for the remainder of the pregnancy.

Infant 2 was born following spontaneous rupture of membranes and subsequent induction of labour at 36 weeks. Infant 2 was vigorous at birth, weighed 3275g and did not require resuscitation (APGARS 9, 9, 10). After initial breast feeds, Infant 2 and mother were transferred to a local birthing centre. Within 6 hours respiratory distress was noted and Infant 2 was admitted to Neonatal Intensive Care.

Infant 2 was found to have severe myocardial dysfunction with poorly contractile ventricles seen on echocardiogram. Infant 2 was treated with prostaglandins, dobutamine, nitric oxide, antibiotics and was intubated for 10 days in total. Initial

blood pressures were noted to be surprisingly 'easy to maintain' and as subsequent echocardiograms and overall condition improved, hypertension became evident (with mean arterial pressure recordings above 90 mmHg). This was managed with oral hydralazine at usual dosage.

During the admission, Infant 2 had normal renal ultrasound scans, urea and electrolytes and it was postulated that in- utero hypertension may have caused the initial severe cardiac dysfunction. Infant 2 was discharged from Neonatal Intensive Care on day 15, full suckling feeds on hydralazine with home monitoring of blood pressures.

Renin levels were later found to be elevated (9.3 ng/mL/hour) which is consistent with renovascular malformation *in utero* exposure to angiotension II inhibition<sup>1</sup>. Hydralazine was later changed to Amlodipine with sound growth and developmental progress being made.

### Infant 3

Infant 3 was born to an 18-year-old New Zealand European/Pakeha primip. The mother had a transposition of the great arteries repair at day 10 and pulmonary stenting procedure at age 10 years. From childhood she was treated with the ACE inhibitor quinapril. It is not known whether her parents were counselled regarding pregnancy when this was commenced, however she has no recollection of this being discussed with her directly or before transfer to adult services.

The pregnancy was unplanned and diagnosed at 5 weeks gestation and quinapril was appropriately discontinued. The mother had ongoing urinary tract infections and was on nitrofurantoin as prophylaxis. She was also Group B streptococcus positive at 35 weeks gestation. The pregnancy was noted to have oligohydramnios at the 28 week gestation scan which progressed to anhydramnios. Echogenic kidneys and intrauterine growth restriction was also noted subsequent ultrasound scans. The infant had normal amniocentesis karyotype and TORCH serology. The parents had normal renal ultrasound scans.

Infant 3 delivered following spontaneous labour via forceps assisted vaginal delivery at term. The infant was vigorous (APGARS 7, 9, 9) and symmetrically growth restricted (birthweight = 2005g) with normal male genitalia. The baby received CPAP resuscitation and was intubated for increasing respiratory distress.

Initial chest radiograph revealed a small pneumomediastinum and pneumothorax which resolved without intervention. A single dose of surfactant was given and the infant was extubated on day 2. A widely splayed sagittal suture was noted- a feature consistent with *in utero* ACE exposure.<sup>7,8</sup> Urine output was seen within the first 24 hours however, serum urea and creatinine climbed (peak day 4 = 278 mmol/L).

Renal ultrasound scans showed small dysplastic kidneys with small cortical cysts. Infant 3 commenced suckling feeds within the first week and was discharged on day 9. There was no hypertension during the admission. Oral sodium supplements were required for persistent hyponatraemia and Kindergen (low protein) formula was used to supplement feeds breast feeds. Infant 3 was readmitted to Neonatal Intensive Care for three days for a calcium level of 3.6 which normalized with intravenous pamidronate and fluids.

Following discharge Infant 3 had a normal micturating cystourethrogram. Infant 3's weight remained low (5<sup>th</sup> centile) and nasogastric feeds were commenced. At the age of 8 months a gastrostomy and Tenckhoff catheter was inserted to commence daily dialysis. Weight gains improved further and work up commenced for transplantation as urine output gradually declined.

At the age of 22 months Infant 3 received a deceased donor kidney and has been making satisfactory progress post transplantation.

## Discussion

ACE inhibitor fetopathy is a recognised clinical syndrome consisting of several possible malformations following *in utero* exposure to ACE inhibitors and angiotensin II blockers. These features consist of renal tubular dysplasia, anuria oligohydramnios, growth retardation, hypocalvaria (including widely splayed suture lines) and hypertension.<sup>7,8</sup> These features, as seen in animal models, are thought to be related to fetal hypotension during critical times of fetal development.<sup>9</sup>

Isolating and attributing the outcomes of the infants presented to only ACE inhibitor exposure is not possible and certainly there has been wide phenotypic variation reported following *in utero* ACE inhibitor exposure.<sup>12</sup> Infant 1 was macrosomic and clearly affected by maternal diabetes.

Infant 2's mother was of advanced maternal age and Infant 3's mother was also on Nitrofurantoin (Category B pregnancy drug: probably safe, but concerns<sup>13</sup>) and had multiple infections. Three of the mothers also had hypertension which itself has been linked to complications during labour.<sup>14</sup>

This is also reflective of debate on this subject as safety data regarding the use of ACE inhibitors stemmed from analyses of case reports which are clouded by confounding factors.<sup>15,16</sup> Only recently, following large cohort studies the strength of this contradiction has increased.

The study by Cooper et al (2006) has been the most notable to date, quoting increased risk of malformation rates with risk ratios ranging from 7.2 (central nervous system and cardiovascular) to 9.32 (renal complications) with large confidence intervals given the overall low incidence of these events (less than 1 per thousand live births).<sup>2</sup>

Locally, Medsafe New Zealand currently advises avoidance of ACE inhibitors throughout pregnancy<sup>4-6</sup> and to our knowledge, this is the first report on this subject in New Zealand.

The three infants presented all had renal complications that are consistent with *in utero* ACE inhibitor exposure and therefore are potentially avoidable. Reducing this occurrence in New Zealand infants remains difficult for several reasons which these cases highlight.

Many women may not be aware of pregnancy (and some may not be anticipating this possibility) who are taking ACE inhibitors. Infant 2 and 3's mothers were of advanced in maternal age (38, 43) and pregnancy was not expected. Infant 2 followed from an unplanned pregnancy which is not uncommon in the New Zealand population and has been previously reported at 31%<sup>18</sup> and worldwide at 38% of all live births.<sup>19</sup>

As the indications for ACE inhibitors grow, heightened awareness will be required to avoid inadvertent exposures.

Inadequacy of pregnancy counselling to potential mothers on ACE inhibitors has been observed overseas and will be prevalent to some extent in New Zealand.<sup>11</sup> Lack of clinician awareness, lack of patient awareness and optimal timing of pregnancy counselling are important considerations.

To explore the experience and current opinion of pregnancies potentially affected by ACE inhibitors amongst New Zealand specialists we conducted a brief anonymous, email based survey sent to paediatricians, neonatologists, maternal- fetal medicine obstetricians and nephrologists.

## **Survey**

### **Aims**

To gather the opinion both quantitatively and qualitatively on the use of ACE inhibitors during pregnancy by relevant hospital-based specialists in New Zealand (paediatricians, neonatologists, maternal- fetal medicine obstetricians and nephrologists).

### **Methods**

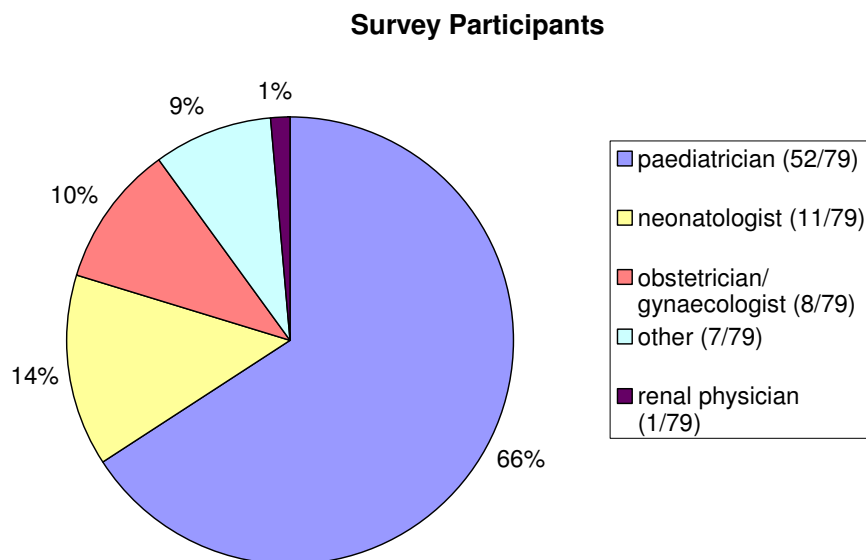
We constructed a brief (<1 minute completion time) email-based survey with a short introductory statement on the subject.<sup>20</sup> The email was sent via the paediatric society web server, perinatal society webserver and to maternal fetal medicine and nephrology colleagues in New Zealand.

### **Results**

#### **Q1 identifying survey participants**

The majority of the responses were from paediatricians (52/79 responses, 65%) with the remainder of the responses made up from neonatologists (11), obstetricians (8) and other physicians including nephrologists (8) (Figure 3).

**Figure 3. Survey participants**



**Q 2,3—Do you have experience with a pregnancy which has had ACE inhibitor exposure? What was the outcome/s?**

Twenty-seven responses stated they had experience with a pregnancy which had antenatal ACE inhibitor exposure. Of this, 14 out of 27 (52%) responses stated that the neonate was affected as a result of ACE exposure, with 3 out of 27 (11%) resulting in fetal/ neonatal demise.

**Q4. When is the best time to counsel women on ACE inhibitors?—**

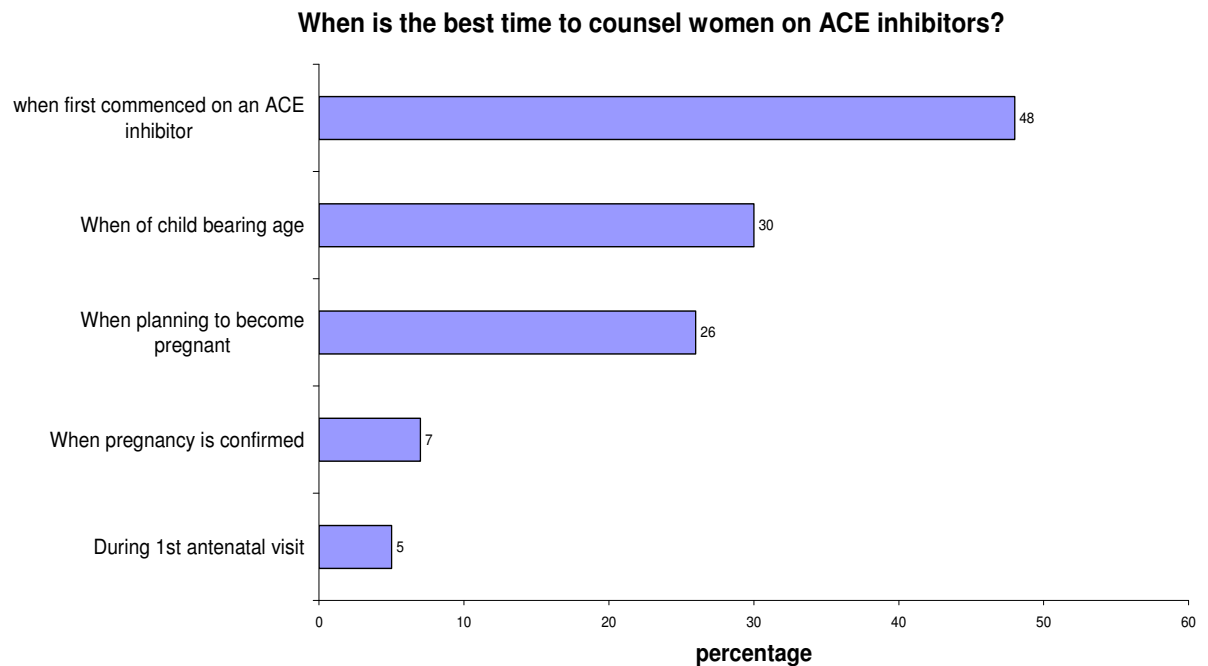
Nearly half of all responses indicated that at the time an ACE inhibitor is first commenced is the best time to counsel regarding pregnancy. In addition two responses commented that all of these times are appropriate (Figure 4).

**Q5. Who is best placed to counsel women on ACE inhibitors?**

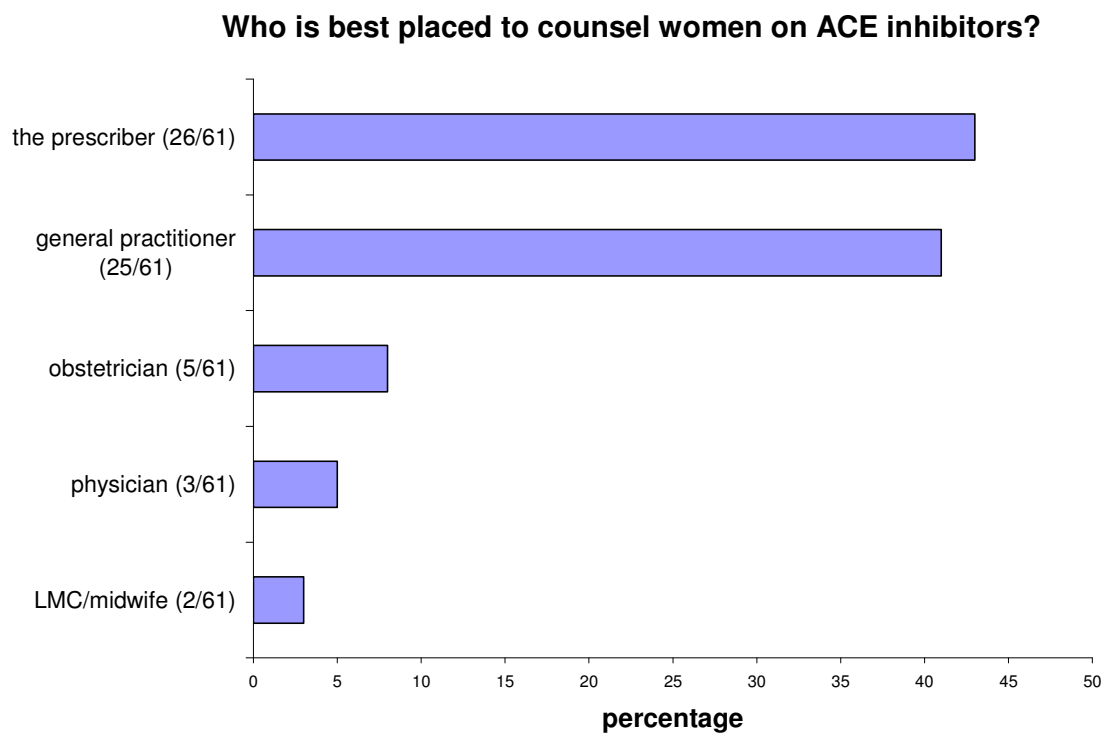
Most responses either suggested the prescribing practitioner (26/ 72, 36%) or the general practitioner (25/72, 35%) (Figure 5). A small number of responses suggested that the LMC/ midwife would be best placed to do this (2 responses).



**Figure 4. When is the best time to counsel women on ACE inhibitors?**



**Figure 5. Who is best placed to counsel women on ACE inhibitors**





In addition, three responses were thankful in alerting this to their attention as they were not aware of this potential problem in pregnancy. Similar comments also stated that the use of ACE inhibitors in pregnancy is underappreciated.

## Discussion

The survey was limited by its nature and is by no means a useful estimation of the true frequency of fetuses affected by ACE inhibitors in New Zealand. The denominator was unknown and due to its anonymous nature, there is also the possibility to have duplication of cases experienced by respondents. In New Zealand PHARMAC reports well over a million ACE inhibitor prescriptions are filled per year with an unknown, but potentially large number, to women of child bearing ages.<sup>21</sup>

The opinions of how best to deal with this potential problem in pregnancy highlights several issues such as prescriber responsibility, timely pregnancy counselling and clinician practice scope.

The general practitioner or prescriber was thought to be the most appropriate person placed to counsel women by the majority of our survey responses. The difficulty in keeping up to date of current best practice is an ongoing challenge for clinicians, not helped by previous safety claims in the first trimester.<sup>11</sup>

A smaller group responded that the obstetrician or midwife (8/72, 11%) are better placed to do so. The potential pitfalls of this approach are highlighted by the cases presented in that the pregnancy may not be diagnosed for several weeks to months. Another wider issue also exists of assigning (or assuming) responsibility by other healthcare colleagues. This is most particularly pertinent in the care of pregnant women where the sharing of care may take place between LMC, GPs and hospital specialists.

The best time to counsel women remains another difficult area. Women may have been commenced on ACE inhibitors years prior (such as infant 3's mother) and pregnancy counselling may not be appropriate, ideal or long lasting. Although 35% (26/74) of responses suggested the best time would be at the time of planning a pregnancy, in many situations the pregnancy may be unplanned<sup>18</sup>.

Furthermore, 12/74 stated the best time would be once pregnancy was confirmed or at the first antenatal visit. This may reflect a slightly differing knowledge base of pregnancy that our responders, primarily paediatricians, have towards pregnancy. This was reinforced by the three comments received thanking our study for raising awareness of this issue as they were previously unaware.

Our results suggest there is a range of opinion amongst our survey participants reflecting differing experience and awareness. Heightened awareness by all health care professionals involved in the use of ACE inhibitors is a good basis to reduce this avoidable occurrence.

As the indications for ACE inhibitors grow, the challenges discussed will continue to evolve. Although we only surveyed consultant specialists in our survey, similar questions and opinions will be equally valuable and valid from LMCs, GPs, pharmacists and legislators.

## Conclusion

In New Zealand we present three infants with potential renal complications from *in utero* exposure to angiotensin converting enzyme (ACE) inhibitors, including hypertension, renal failure and death. ACE inhibitors remain contraindicated throughout pregnancy and to our knowledge this is the first data published on this subject in New Zealand.

How best to counsel women regarding ACE inhibitors and pregnancy remains an area for further discussion in New Zealand. From a paediatric point of view we need to take into account that a drug may be started at an early age and remember to counsel appropriately once the patient reaches an appropriate age.

**Competing interests:** None known.

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