A Review On

"Teratogenic effect of Angiotensin-Converting Enzyme Inhibitors throughout the first, second and third trimester of pregnancy"

In the partial fulfilment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

Submitted To

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This review article, **"Teratogenic effect of Angiotensin-Converting Enzyme Inhibitors throughout the first, second and third trimester of pregnancy,''** has been recognized and approved by the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, for partial completion of the criteria for the Bachelor of Pharmacy (B. Pharm) degree in terms of style and quality.

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In accordance with the Bachelor of Pharmacy (B. Pharm) Degree Requirement, I, hereby humbly declare that I'm conducting this thesis work under the guidance of Aklima Akter, Lecturer (Senior Scale), Department of Pharmacy, Faculty of Allied

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ACKNOWLEDGEMENT

First of all, I would like to express my deep gratitude to the almighty Allah, who is our creator and cares for me to keep me in good health and give me the opportunity to study in this subject, the ability to finish my project work. I would also like to thank my family members for looking out for me and supporting my efforts. Words can't always explain how grateful we are for all the help we've received throughout our lives.

I want to offer my gratitude and humble regards to my research mentor, **Aklima Akter**, Lecturer (Senior Scale), Department of Pharmacy, Daffodil International University, who oversaw my study.

I also want to extend my heartfelt gratitude to **Professor Dr. Muniruddin Ahamed**, Head, Department of Pharmacy, Daffodil International University, for providing me with all the resources I need for this study.

I would also like to express my gratitude to **Professor Dr. Abu Naser Zafar Ullah**, Dean, Faculty of Allied Health Sciences at Daffodil International University, for his ongoing support.

I would like to acknowledge every teacher in the department for their assistance and encouragement. I also want to express my appreciation to everyone who has supported and helped me accomplish my study in some way, whether directly or indirectly.

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Abstract

A compound that prevents a fetus from developing normally is called a teratogen. Teratogens are substances that are known to result in birth abnormalities when consumed while pregnant such as some prescription and over-the-counter pharmaceuticals. Excessive blood pressure is famously treated with ACE inhibitors. However, due to a higher risk of fetal kidney impairment, they are not advised for use by pregnant women.

Over the course of time incidents of fetotoxic consequences have been reported. Among these, renal dysplasia, oligohydramios, anuria, pulmonary hypoplasia, and even infant mortality are the consequences that are most frequently recorded. According to studies, exposure during the final trimester is when the foetotoxic impacts are most frequent. However, because of the grave nature of these health consequences, ACE-inhibitors are not recommended through pregnancy.

This study reviews the academic journals that pointed out the possible fetopathy associated with the use of an ACE inhibitor to treat hypertension during pregnancy. The study of fetotoxic events that happen in all three trimesters of pregnancy as a result of ACE inhibitor exposure is the primary contribution of this work.

Key words: ACE inhibitor (Angiotensin-converting enzyme inhibitors), ACE (Angiotensin converting enzyme), ANG I (Angiotensin I), ANG II (Angiotensin II), RAS (Renin angiotensin-system), AT1 receptor (Angiotensin 1 receptor), AT2 receptor (Angiotensin 2 receptor).

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1 CHAPTER ONE: INTRODUCTION

1.1 Introduction

A compound that disrupts healthy embryonic development and results in congenital defects is characterized as a teratogen. Teratogens include substances including drugs, alcohol, chemicals, and hazardous materials. These substances can potentially raise the chance of stillbirth and premature labor. Around 4% to 5% of congenital conditions are triggered by fetal exposure to teratogens. The impacts of teratogen exposure upon both intellectual and physical growth have been demonstrated by studies. The severity of a teratogen's effect depends on the sort of chemical or drug, how long the expectant mother was exposed, and how many doses she received.

Approximately 6% to 8% of pregnancies are affected with hypertension, which is a reasonably common complication during pregnancy [1]. ACE inhibitors are increasingly often prescribed to patients as first-line medications, yet they're contraindicated during pregnancy because of the risk they pose to the fetus, particularly fetal kidney impairment.

It is generally known that they are problematic to fetuses mostly in the second and third trimesters of gestation. Its use during the first trimester is also linked to an increased risk of serious congenital defects, particularly those affecting the cardiovascular and neurological systems. The following fetal anomalies are frequently reported: renal dyspepsia, hypotension, and pulmonary hypoplasia. Altogether, birth abnormalities are caused in around half of neonates and are associated with exposure to ACE inhibitors.

The FDA has classified ACE inhibitors as pregnancy category C when taken in the 1st trimester of gestation and pregnancy category D when administered in the 2nd and 3rd trimesters [2].

Pregnant women treating hypertension with ACE inhibitors must be informed about the potential risks of these medications throughout the pregnancy and should switch antihypertensive treatment [3].

1.2 Teratogen definition

Teratogens are substances that may be medications, chemicals, or physical agents that is linked to congenital abnormalities and adverse effects on reproduction when introduced to pregnant women. As a teratogenic encounter should indeed consider the agent, dosage, and stage of pregnancy at which the exposure occurs, no teratogenic substance can really be characterized as a teratogen in a strict sense. Also, there is a toxicological dosage response curve for teratogenic substances. This indicates that regardless of which stage of pregnancy the interaction occurs, every teratogen has a borderline concentration below which there is no chance of teratogenesis [4].

1.2.1 Historical Background

Traditionally, fetal abnormalities were thought to be a sign of divine displeasure. Nearly 4,000 years ago, the Tablet of Nineveh written in Babylonia listed 62 malformations.

During the Wars of Religion in the sixteenth and seventeenth centuries, the connection between birth defects and massages from God became a fact.

In the medieval era, it was commonly believed that fetal deformities could not only be a sign from God, but could also because of maternal failings. The Roman naturalist and physician Pliny the Elder (23–79) advised women that they should not look at animals in order to avoid the abnormal development of their developing child [5].

1.2.2 Etymology

The Greek word teratos, which might also mean demon or prodigy, is where the name teratogen originates. It also means every occurrence of horror-related natural phenomena. Lusus naturae which is a Latin term was used in ancient literature to refer to anomalies of various types (freak of nature). Yet, it has a far more specific medical interpretation that refers to any substance, pollutant, or chemical present in the environment that might result in fetal defects when a woman is pregnant.

1.2.3 Scientific Foundations

The eighteenth century saw the beginning of the systematic investigation of embryology, which revealed the actual origins of birth abnormalities and the function of teratogens. The second book of Etienne Geoffroy Saint-Hilaire's Philosophy Anatomique was released in 1822. According to him, prenatal development was interrupted, which led to birth abnormalities. Theorizing that teratogens external agents could be a contributing element in malformations, researcher Camille also claimed that birth abnormalities were caused by insufficient embryonic development.

Dareste's study was carried out by zoologist Charles R. Stockard. In 1973, the Fetal Alcohol Syndrome (FAS) was unexpectedly discovered because to Stockard's study. The teratogenic effects of alcohol on embryonic development were established by American physician Sterling Clarren.

The second half of the 20th century witnessed the discovery of several teratogens. David W. Smith gained notoriety in 1973 for discovering fetal alcohol syndrome) conducted research in the 1960s [6].

1.2.4 Teratogen Group

Teratogens often are categorized into three general categories: chemical, physical and biological teratogens.

- Chemical nature teratogen: Chemical teratogens are a variety of compounds including medications such as several antibiotics, lithium, thalidomide, ACE-inhibitors, warfarin etc. It also includes compounds such as heavy metals (lead, arsenic, mercury). Severe congenital abnormalities are more likely to occur when pregnant women are exposed to organic solvents at workplace [7].

- Physical nature teratogen: Gamma radiation, X-rays and other forms of ionizing radiation are the principal physical nature teratogen.

Ionizing radiation is a potential teratogen for the developing fetus, although it has been discovered that this risk depends on the dosages and the outcomes are related to the stage of pregnancy during exposure [8].

- Biological nature teratogen: Pathogens are thought to be biologically based teratogen. Bacteria and other viruses, such as the HIV virus and the influenza virus, are some of the infectious organisms that cause congenital abnormalities.

In recent times, maternal conditions have also been included in the group of teratogens.

1.2.5 First Human Teratogen

An agent that disrupts the formation of the growing embryo or fetus and results in birth abnormalities is known as a human teratogen. As a result of maternal rubella infection during pregnancy, which resulted in a trio of birth abnormalities in the newborns, the first human teratogen was discovered by ophthalmologist Norman Gregg in 1941. The awareness of the potential teratogenic effects of maternal exposures during pregnancy steadily increased followed the discovery of thalidomide as a serious human hazard. Awareness of in utero exposure to environmental toxins increased as a result of later experimental studies linking exposure to mercury to teratogenic consequences.

1.3 Congenital defect

The structural defects that develop throughout the gestational period are referred to as congenital defects. Reasons might include biological, viral, or chemical substances that interact throughout pregnancy and cause long-term health problems Genetic variables account for 25% of the causes, whilst biological, chemical, physical factors are responsible for 10% of causes of birth defects [9].

1.3.1 Drug-induced congenital defects

About 5% among all pregnancies, birth abnormalities may occur. Drugs are one potential external component that contributes about 1percent of the overall congenital anomalies.

The FDA has created 5 pharmacological groups in 1979 which are A, B, C, D and X risk categories. Medicines classified as class X drugs have a history of teratogenicity. There are around 25 drugs now available that have been shown to have teratogenic effects.

Recognized teratogenic medications include ACE inhibitors, benzodiazepines, lithium, aminoglycoside, valproic acid, carbamazepine, misoprostol, busulfan, NSAIDs, methimazole, penicillamine, retinoids and more [8].

Pregnancy Category	Description
A	Appropriate human studies - no risk
B	Insufficient human studies, but animal research suggests safety **or**: Animal studies show issues but human studies show safety
C	Insufficient human studies, but animal studies show problems **or**: No animal studies, and insufficient human studies
D	Human studies, with/without animal research show fetal risks, but the drug is important to some women to treat their conditions
X	Fetal risks are evident; there are no situations where the risk/benefit justifies use

Figure-1: Pregnancy category of drug

1.4 ACE Inhibitors – An Important Class of Therapeutic Agents

A group of drugs known as ACE inhibitors (angiotensin-converting-enzyme inhibitors) is primarily used to treat heart failure and excessive blood pressure. Other illnesses including scleroderma and migraines may be treated with them.

A Brazilian snake's venom was accidentally found to include a bradykinin-potentiating component with vasodilating capabilities, leading to the development of ACE inhibitors (angiotensin-converting enzyme inhibitors). As it was proven that the peptide combination present in the venom of snake had the capability of inhibiting ACE, the physiological importance of this was confirmed.

In 1975, captopril the first Angiotensin - converting enzyme inhibitor that was therapeutically useful was developed [10].

ACE inhibitors have been widely utilized in the treatment of several cardiovascular illnesses since the introduction of the first ACE inhibitor, in 1981 [11].

An enzyme that produces angiotensin II in the body which is a chemical that constricts blood vessels, is inhibited by ACE inhibitors. The kidneys produce more urine when angiotensin II, norepinephrine and aldosterone are present. Reducing their level in the system allows blood vessels to loosen up and expand, which lowers blood pressure as well as kidney pressure. High blood pressure might be a result of this constriction of blood vessels.

They function by causing blood vessels to relax and blood volume to drop, which decreases blood pressure. They also reduce the oxygen requirement for the heart to pump.

Angiotensin-converting enzyme is a key part of the renin-angiotensin system. It transforms the angiotensin I to angiotensin II. It also hydrolyzes bradykinin. And all of this function is blocked by angiotensin-converting enzyme inhibitors (ACE inhibitors). As a result, ACE inhibitors raise levels of the peptide vasodilator bradykinin while reducing the production of the vasoconstrictor angiotensin II.

The ACE inhibitor medications enable higher quantities of bradykinin by blocking the ACE enzyme in the bradykinin system. And by this method they reduce blood pressure [12].

Captopril was the first authorized for clinical use in 1981 in the states. After the approval of captopril, Enalapril (1985), lisinopril (1987) were introduced in market. Benazepril, fosinopril, and ramipril were next authorized for usage in 1991 and finally quinapril in 1992 [10].

Patients who have myocardial infarction, congestive heart failure, or diabetic nephropathy are increasingly using ACE inhibitors. Typically, this classes of drugs are generally tolerated, and severe adverse events are uncommon.

Other hypertension medications are significantly less frequently given than ACE inhibitors. With a much-decreased incidence of cough, angioedema, pancreatitis, and Gastrointestinal bleeding, other antihypertensive drugs showed a significantly superior safety profile than ACE inhibitors [13].

1.4.1 Examples of ACE inhibitors

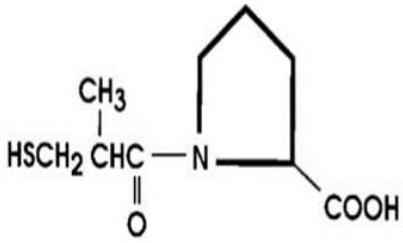
Benazepril, enalapril, ramipril, captopril, zofenopril and lisinopril are examples of commonly prescribed ACE inhibitors.

These drugs are categorized by the chemical composition of the linker including sulfhydryl, carboxyl or phosphinyl. As fosinopril contain phosphinyl group, on the other hand captopril, alacepril and zofenopril all of them contain the sulfhydryl group which gives them unique properties including antioxidative action and a shorter half-life compare to the other group.

Enalapril, lisinopril, benazepril, ramipril contain carboxyl moiety which gave them a higher half-life [14].

Perindopril has shown effectiveness in a variety of indicators of CAD and tends to possess the highest impact on Bradykinin compared to the other ACE inhibitors [15].

In 1981 among the earliest ACE inhibitors that was commercially available in Canada and the US was captopril. It quickly absorbs from the digestive system as having bioavailability of around 75% but Captopril's oral bioavailability is decreased by 25–30% when food is consumed. The majority of the medication is quickly excreted in the urine.



CAPTOPRIL (Mol.Wt. 217.28)

1-(3-Mercapto-2-Methyl-1-Oxopropyl)-L-Proline

Figure-2: Chemical structure of captopril [16].

1.4.2 Efficacy among ACE inhibitors

One analysis of 29 research findings indicate that the least frequency of all-cause fatality was linked to ramipril.

Enalapril had the greatest impact on MAP reduction but had the highest incidence of cough. Furthermore, enalapril was linked to the peak incidence of kidney function impairment, whereas captopril was linked to the lowest.

Lisinopril was the least desirable ACE inhibitor due to a rise in all-cause death rates. Enalapril proved to be the most efficient ACE inhibitor. Enalapril, meanwhile, was also linked with complication including impairment of kidney function, GI tract problems. In terms of lowering both diastolic and systolic pressure trandolapril came out on top [17].

1.4.3 Therapeutic Uses

ACE inhibitors may be administered either alone or in combination with some other antihypertensive medications for the management of hypertension. ACE inhibitors are generally the first-line medication for treating high blood pressure, specifically when patients are also dealing with diabetes. Eventually, they were discovered to be helpful for additional renal and cardiovascular conditions.

ACE inhibitors can be used to treat the following conditions: hypertension, few chronic renal diseases, heart failure, migraine prevention, scleroderma.

For individuals who have diabetes, ACE inhibitors tend to lower their chance of developing diabetic nephropathy.

As for the elderly patients, ACE inhibitors are used with the combination of thiazide diuretics for the management of hypertension. Moreover, systemic sclerosis and chronic kidney failure have also been treated with ACE inhibitors [18].

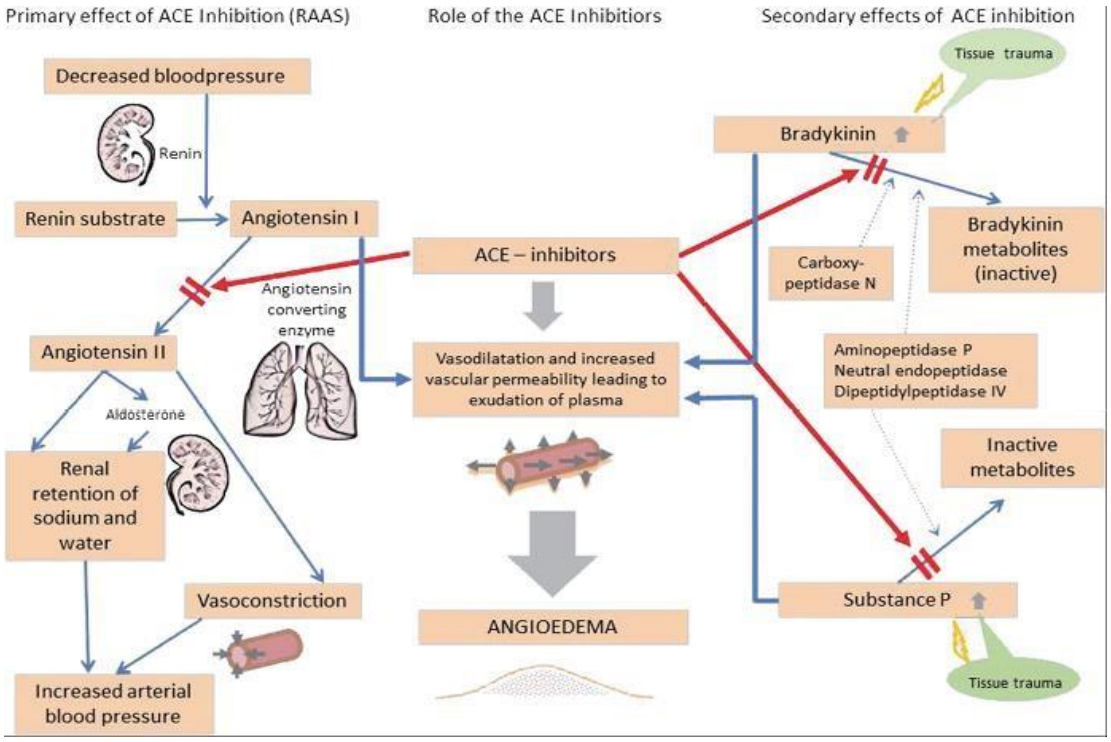


Figure-3: Uses of ACE inhibitor

In addition, ACE inhibitors enhance glucose management, reduce left ventricular mass, and provide some myocardial protection. In healthy or hypertensive individuals without congestive heart failure, ACE inhibitors have no effect on heart rate, pulmonary wedge pressure or in cardiac output. Also, especially compared to beta-blockers, ACE inhibitors have been discovered to help hypertension patients have a higher quality of life. ACE inhibitors decrease microalbuminuria in diabetic patients (both type 1 and type 2), maintain kidney function, and improve insulin sensitivity [16].

As compared to ARBs, a meta-analysis from 2012 that was published demonstrating how effective ACE inhibitors are in lowering the risk of pneumonia. Studies has also shown that individuals who had already experienced a stroke had a 54% lower chance of doing so, those who had heart failure had a 37% lower risk [19].

In cultured endothelium cells, thiol-containing ACE inhibitors are capable of preventing membrane damage brought on by free radicals. Those free radicals might be suppressed by the SH-moiety of this group of drugs [16].

ACE inhibitors, on the other hand, reduce vascular resistance, enhance glucose management, regulate left ventricular mass, and provide some cardiac protection. ACE inhibitors are thought

to have benefits that are independent of their ability to lower blood pressure, including decreased renal disease and decreased insensitivity to insulin. Also, it seems that the SH-moiety present in the ACE inhibitors might stop free radical before they approach the areas of cellular damage [16].

1.4.4 Adverse effects

ACE inhibitors tend to be well tolerated and significant adverse effects are uncommon. With long-term treatment with ACE inhibitors, the most often reported adverse effects are: low blood pressure, skin rash, hyperkalemia, cough, acute kidney failure, skin rash, loss of taste, and in some cases even hepatotoxicity can be seen. But in those cases, the majority of the adverse effects are curable after the use of ACE inhibitors is discontinued [16].

Furthermore, fetal impacts have been reported as a major negative side effects of these class of drugs. An elevated level of bradykinin is also another potential side effect. All ACE inhibitors have the potential to cause kidney issues as a direct result of their mode of action, which leads to a decreased glomerular filtration rate. Hyperkalemia is a common side effect of this drug. The impulse conduction rate in cardiac cells, as well as neurons and muscles, may be slowed down by hyperkalemia. As a result, there is heart dysfunction also neuromuscular effects including muscle weakening, gastrointestinal problems, nausea [20].

Some of the particular negative consequences including:

- Elevated amounts of bradykinin: A dry cough may be a symptom of ACE inhibition induced elevated bradykinin levels. 0.7–35% of patients have been observed to experience ACE-inhibitor-induced cough. The deposition of bronchial bradykinin with the rise in inflammatory mediators including prostaglandin is thought to be the cause of dry cough.

- Hypotension: Another potential symptom of increased bradykinin brought on by ACE inhibitor treatment is low blood pressure. It may be brought on by a combination of the

vasodilating effects of elevated bradykinin levels due to the impact of ACE inhibition and a reduced angiotensin-II level.

- Hyperkalemia: Changes in psychological condition as well as potentially fatal cardiac dysrhythmias are possible outcomes with ACE inhibitor as it increase the K level or it may not show any symptoms. The speed of impulse generation in the muscle fibers, particularly the cardiac cells, is slowed down by the high potassium concentrations. Cardiac malfunctioning results from this, as do neurological effects such muscle paralysis, loss of sensation, gaseousness, IBS etc. In patients with hyperkalemia should be careful while using ACE inhibitor.

- Angioedema: It develops in 0.1% to 2.2% of patients who are treated with ACE inhibitors. Another theory is that angioedema is a clinical sign of increased bradykinin level caused by ACE inhibitors.

- Renal function decline: Patient treated with ACE inhibitors are seen to have a reduced level of GFR. Reduced renal perfusion, cardiac arrest, polycystic nephropathy, or volume reduction can all be caused by a drop in GFR while being treated with ACE inhibitors. It can also increase the blood creatinine level.

- Hepatotoxic effect: Hardly ever have ACE inhibitors been documented to have hepatotoxicity. It may be the result of anaphylactic reactions, metabolic abnormalities such as bile reduction [20]

1.4.5 Effects of ACE inhibitors in pregnancy

The usage of ACE inhibitors throughout pregnancy have been linked to birth anomalies in women. Birth abnormalities are caused in around half of neonates exposed to ACE inhibitors.

Among the most often documented fetal anomalies are renal dysplasia, hypotension, oligohydramnios, anuria, pulmonary hypoplasia, inadequate ossification of the skull.

According to research on animals, exposure on the final trimester is when the foetotoxic effects are most frequent. And it is recommended for women to refrain from using ACE inhibitors while pregnant because of the foetotoxic effects [21].

Moreover, ACE inhibitors must be avoided during pregnancy, as they are classified as pregnancy category D by The ADEC (Australian Drug Evaluation Committee)

While it is still contradicted whether ACE inhibitors really aren't safe during the early stage of organogenesis. But chronic administration of these medications throughout both second and third trimesters might induce life threatening hypotension, kidney failure or anuria in the fetus [16].

1.4.6 Mechanism of Action

The majority of the physiological effect of ACE inhibitors are thought to be caused by their well-known dipeptidyl peptidase activity being suppressed. ACE inhibitor also shows anti-inflammatory effect and decrease the rate of fibrosis by elevating the level of Ac-SDKA in blood.

Moreover, the effect on kinin B2 receptor agonist were improved by ACE inhibitor. Furthermore, by producing heterodimer ACE inhibitors cause transmembrane protein and B2 kinin receptor interaction [22].

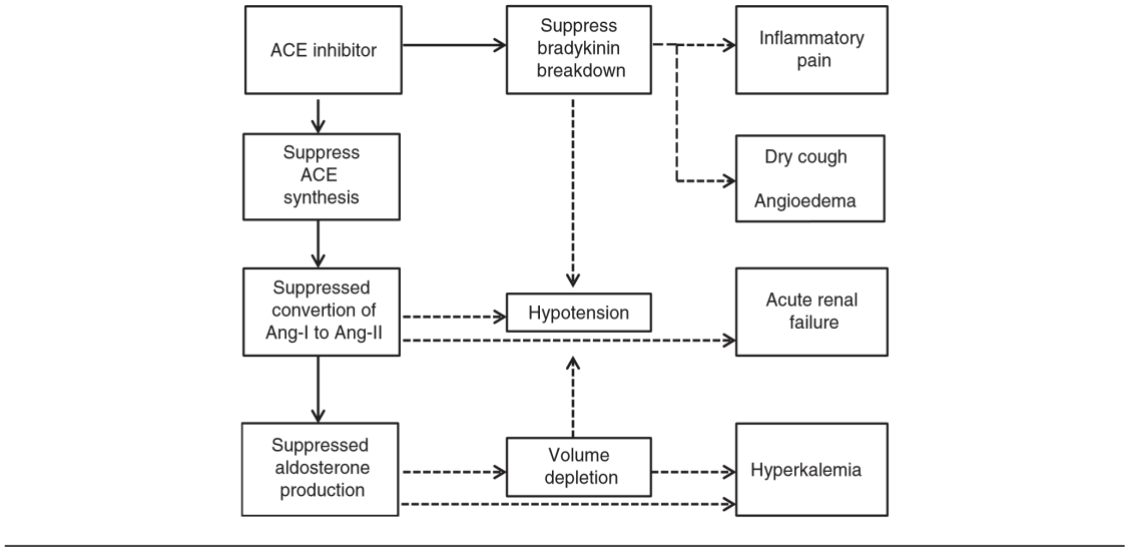


Figure-4: Mechanism of action of ACE inhibitors [20]

Usually ACE inhibitors are known to function in two different mechanisms. Angiotensin I converted into angiotensin II by the angiotensin-converting enzyme. Angiotensin II causes blood vessels to constrict while increasing sodium and water retention, which leads to a rise in blood volume and eventually, higher blood pressure.

Inhibiting ACE prevents the formation of Ang II, a powerful vasoconstrictor, which is how ACE inhibitors work. ACE inhibitors have the ability to inhibit both tissue and plasma angiotensin converting enzyme.

By preventing the breakdown of bradykinin, they also show their therapeutic impact. Bradykinin is a polypeptide that produce both NO and prostacyclin which causes vasodilation [14].

ACE inhibitors boost nitric oxide synthesis by reducing the bradykinin breakdown and limiting the formation of angiotensin II [15].

ACE inhibitors restrict the development of atherosclerosis. ACE inhibitors increase insulin sensitivity. They may also improve glycemic control in diabetic patients. Moreover, ACE inhibitors prevent Ang II from activating peripheral and central sympathetic nerves [14].

The angiotensin I-converting enzyme is effectively and competitively inhibited by the potent and selective medicines known as ACE inhibitors. The main medicinal and therapeutic effects of ACE inhibitors appear to result from reduction of ANG II production. As bradykinin activates prostaglandin production and ACE inhibitors raise the level of bradykinin, bradykinin may help explain some of the therapeutic properties of ACE inhibitors. Moreover, ACE inhibitors block renin's negative feedback that release from kidney.

ACE inhibitors speed up the production of angiotensin I and renin [16].

Tubular potassium ion secretion is decreased as aldosterone secretion is decreased. Aldosterone production is lowered to protect the kidney from various harmful effect. Angiotensin-II level reduction leads the efferent arteriole, to vasodilate. This lowers GFR and systemic arterial flow rate, leading to the prevention of glomerular destruction and protein loss. The decrease in glomerular protein loss help in the improvement in renal function [20].

1.5 The Renin-Angiotensin System

The RAS exerts significant control on blood pressure and salt balance. These processes are managed by combined functions in the kidney, cardiovascular system, and CNS. The RAS regulates a variety of functions, including immunological responses and inflammatory response [23].

It is undeniable and proven that renin-angiotensin system plays a physiologically major role in the control of blood pressure and electrolyte equilibrium. The renin- angiotensin system is a hormonal system that predominantly promotes vasoconstriction, secretion of aldosterone and salt retention to elevate the blood pressure in the arteries. The secretion of the renin from the JG cells into bloodstream leads to the activation of endocrine renin-angiotensin system. Renin works as the rate regulating factor of the RAS in humans by initiating the breakdown of angiotensinogen to produce angiotensin I peptide [24].

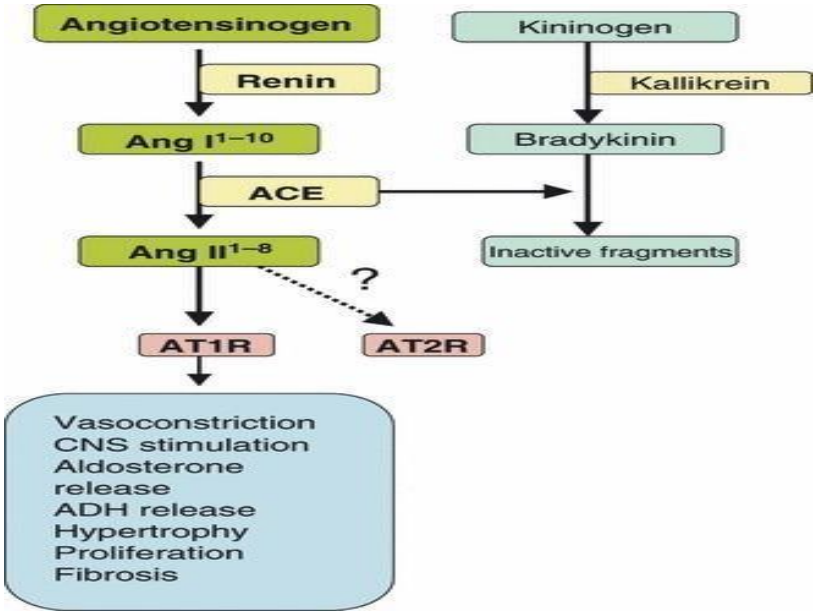


Figure-5: An illustration of the "traditional" circulating RAS [25]

Angiotensinogen act as a precursor in the formation of ANG I by the glycoprotein enzyme renin. angiotensin II, is produced quickly from angiotensin I by ACE. Angiotensin II is a powerful vasoconstrictor that also promotes the adrenal cortex's production of aldosterone while suppressing renin release by causing an increase in salt retention.

It is known that the RAS play a crucial role in the body's natural control of blood pressure and electrolyte balance by the adrenal cortex's production and release of aldosterone. Angiotensin II cause an increase in aldosterone production. Sodium is retained by aldosterone whereas potassium ions are excreted from the kidneys. Bradykinin is also the primary compounds for ACE and inactivate by kinase II. Bradykinin lowers blood pressure if the enzyme does not inactivate it, angiotensin II raises blood pressure [16].

Renin production and release are controlled by several intricate processes. ACE, which is present in significant quantities in the lungs and is specific to endothelial cells, stimulates the formation of ANG-I to ANG-II. The majority of the processes that result in blood pressure increase are facilitated by the interaction of ANG-II to the AT1R. But if the binding occurs to AT2R then it would typically reverse the effects of the AT1R [24].

In the traditional RAS angiotensinogen produce ANG I and ANG II with the help of renin and ACE. The RAS has a complex procedure that has lately been revealed by the discovery of a number of novel peptides, enzymes and receptors [26].

1.5.1 Updated Perspective on RAS

The RAS's clinical significance have increased over time. In most of the tissues and organs there is a local tissue renin-angiotensin system beside the circulating renin-angiotensin system.

Recent research indicates that the RAS also has paracrine and intracrine systems in addition to the endocrine system.

It has been demonstrated that the Ang IV and the Ang III are both physiologically active. The Ang 1-7 which balances out several of Ang II's effects, seems to play a significant role [25].

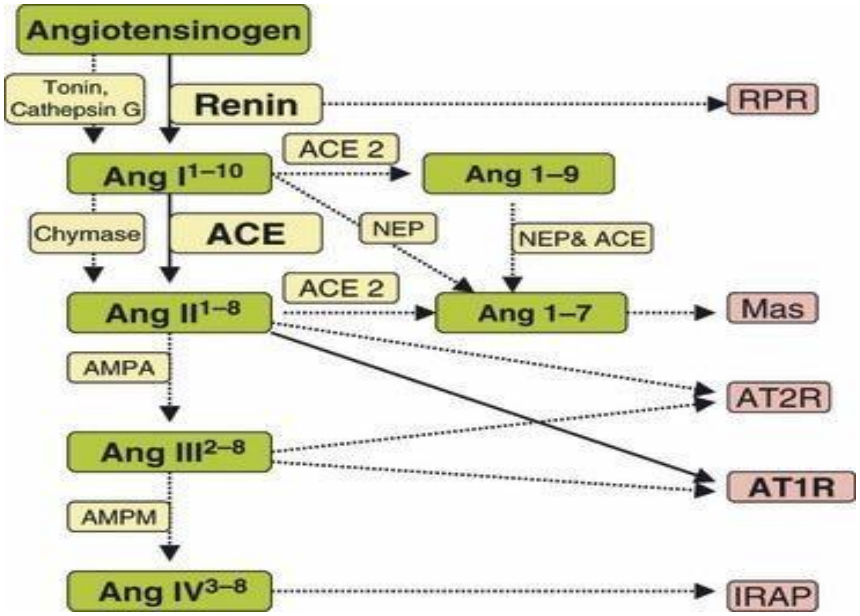


Figure-6: An updated perspective on RAS [25].

Similar in concept to Ang II, Ang III works by activating both AT2 and AT1 receptors. While Ang II is thought to be the primary RAS effector, recent studies show that Ang III may be greater in the case of some activities via AT1 receptors including release of vasopressin.

Many studies imply that Ang IV plays crucial roles in regulating brain function, cardiovascular problem, renal metabolism. Heart fibroblasts, endothelial cells, and smooth-muscle cells in the vascular system all have cell proliferation under its control.it also may has an impact on inflammation.

The recent identification of novel ACE2 highlighted the significance of Ang 1-7. The heptapeptide's vasodilatory effects are caused by ang (1–7)'s binding to the mas' receptors. ACE2 was just recently identified and cloned. The kidney, heart, hypothalamus and aortic wall all have vascular endothelium that is particularly high in ACE2 [25].

1.5.2 Local RAS (Tissue)

There are several tissues, such as the kidneys, heart, CNS that express renin-angiotensin systems locally. According to a recent assessment, local RAS systems were discovered in the majority of the examined tissues and organs. Renal renin is the source of the majority renin present in local renin-angiotensin systems. In case of kidney and heart region, tissue renin angiotensin systems work collaboratively with the circulating RAS. But the brain and adrenal glands are two examples of regions where tissue RAS function separately from the circulating renin-angiotensin system.

Tissue RAS has several local tissues impacts on the cardiovascular system, kidney, CNS including proliferation, development, synthesis of protein etc.

The regulation of brain activities, particularly memory and learning reflexes, seems to involve not only Ang III and Ang II but also Ang IV.

The pathogenesis of the diabetes, hypertension and obesity may involve local RAS. It is often crucial to maintain a good balance among the regulatory and counter-regulating elements of tissue RAS for the organs to function properly [25].

1.5.3 Fetal RAS

The RAS is also present in fetal life from the beginning at six weeks of gestation.

the placenta contains all factors of RAS including renin, ACE. There is evidence that the placental blood circulation is modulated by the placental RAS as well as placental nutrition transfer.

In order to control extra villous cytotrophoblast migration and the regulation of placental angiogenesis, they operate independently of circulatory renin-angiotensin system. Prorenin activation in cells occurs by two methods. The first method is activation by interaction with its receptor. The other is through proteolytic activation by cathepsins.

Moreover, upon activation, it extracts Ang I from angiotensinogen. Angiotensin converting enzyme then transforms Ang I into Ang II. Angiogenesis, rapid multiplication of cell and vasoconstriction are encouraged by Ang II when it interacts with AT1R. The generation of PGF promotes angiogenesis.

When they interact with AT2R, Ang-(1–7) and Ang II counteract the impacts of AT1R activation. Both ACE2 and ACE has the ability to hydrolyze Ang I and Ang II. That leads to the production of Ang-(1-9) and Ang- (1–7). The transformation of Ang II into Ang IV which might lead to hypertrophy, inflammation, and dilatation of vessels.

As a result, interruption of fetal RAS may impact placental blood circulation, which would hinder nutrient supply to the fetus [27].

[28].

Angiotensin II may have a modulatory influence on the prostaglandins that control circulation between fetus and placenta. Placental prostaglandins have a role in the mediation of the vasoconstrictive effects of angiotensin II. Renin is discovered in high quantities in amniotic fluid and is present in the placenta at levels that are particularly high throughout the initial stage of pregnancy. RAS has a crucial part in regulating GFR and in the production of urine and the fetus appears to have a higher level of RAS activity than newborn [16].

1.5.4 RAS in the development of the fetal respiratory system

As early as the first trimester of pregnancy, ACE was found in the placenta, kidneys, and lungs of the developing baby. It has been demonstrated that ACE levels in the tissues and blood rise in the fetus. From earlier days of pregnancy, ACE expression was seen in a rat respiratory system, and it gradually increased.

According to in vitro research, the initial phase of pulmonary morphogenesis has a functioning local RAS. Recent research revealed that fetal rat lungs exhibited all the elements, including ACE, Angiotensinogen, renin, and both AT2 and AT1 receptors. Ang II stimulated lung branching through the AT2 receptor.

In addition to being involved in embryonic lung development, RAS also affects the mechanics of respiration. Angiotensin has been shown to have intriguing impacts on pulmonary mechanics in new research animal studies. In some cases, the plasma content of angiotensin is elevated and enhances bronchoconstriction [29].

Moreover, it has been demonstrated that angiotensin promotes constriction of bronchus in mature guinea pigs as well as bronchial hyper responsiveness [30].

1.6 Hypertension during pregnancy

Hypertension is a common disorder among the pregnant women. According to some studies the frequency of being diagnosis with hypertension during pregnancy varies between 3.0% to 5.0%. They could suffer from both chronic and gestational hypertension and that could lead to severe complications for both mother and the fetus.

Maternal mortality, stroke, and cardiac arrest are among the harms to pregnant women. Moreover, the developing fetus is in danger, and major fetal problems involve fetal growth limitation, prematurity [31].

A rise in the percentage of pregnant women suffering from high blood pressure may be signaled by the growing incidence of obesity. Numerous hypertension conditions are noticeable throughout pregnancy which can cause abnormal autonomic regulation and incorrect release of

vasoactive compounds, which can result in maternal or fetal illness and fatality. The proper identification of these conditions and appropriate treatment are required to have a safe pregnancy and avoid teratogenic effects.

- Chronic hypertension: Around 3% of all pregnant women suffer from chronic hypertension, which is defined as high blood pressure that was diagnosed way before 20 weeks of pregnancy. Many women experience hypertension in the first trimester of pregnancy.
- Gestational hypertension: Around 6% of the pregnant woman suffer from gestational hypertension which occur following twenty weeks of pregnancy without preeclampsia. later about 15% to 45% of them may develop preeclampsia.
- Eclampsia: Preeclampsia is a condition with hypertension (140/90) that develops post 20th week of pregnancy. Preeclampsia can develop at any point throughout pregnancy. About 4% of pregnant woman are affected by the condition, and along with chronic high blood pressure, it can affect approximately 25% of pregnant women [32].

1.6.1 Prenatal antihypertensive treatment

An important step forward in the management of high blood pressure has been the introduction of ACE inhibitors. These drugs have been suggested to be the first-line antihypertensive treatments due to their superior performance and tolerability characteristics over repeated applications Based on how the diastolic blood pressure is determined, how it is categorized, and regional variations throughout pregnancy, hypertension starts just after 20th week and has to be treated in around 15% of women since it increases both maternal and fetal mortality as well as morbidity. [33].

The application of ACE inhibitors represents an important advancement in the management of high blood pressure. ACE inhibitors suppress the generation of a vasoconstrictive peptide and decrease arterial blood pressure by blocking the transformation of ang I into ang II [34].

Though ACE inhibitors are one of the most modern hypertension medications, they cannot be prescribed while pregnant so hypertension treatment in pregnant women is limited to a limited number of medicines [33].

1.7 Ace inhibitor placental transfer

Different ACE inhibitors tend to pass through the placenta differently depending on the medication and the race.

In mice given an oral dosage of 1 mg/kg of ACE inhibitor, it is found that the placental migration of ACE inhibitor occurred in the 1st period of pregnancy mostly on the 19th or 13th day. Enalapril, lisinopril, and captopril do penetrate the placental membrane in medicinally effective concentrations, according to studies in gestationally exposed newborns [16].

In animal studies, it has been proven that ACE inhibitors can penetrate the placental membrane. By using a drug screen test, the transportation of ACE inhibitors through into the fetal tissues is investigated.

Evidently, only a little quantity of the active constituents of enalapril and temocapril cross the placental membrane.

With the help of AUC, capillary gas chromatography, mass spectrometry and other multiple techniques, the values of the transmission, emission, and clearance indicators were determined. Due to the fact that placental membrane seems to possess an ability to act as a binding site for specific kinds of drugs, several drugs can bind with the membrane of placenta. Studies also shows that ACE inhibitors can be metabolized in placental membrane. Because of ACE inhibitors being very hydrophilic, some studies indicate that they can pass to the fetus.

It's fascinating to consider that despite the fact that just 2% to 3% of medications cross the placental membrane to fetus, only approximately 70% of drugs were identified overall in the placental perfusion. It's possible that some of the active chemical was coupled to peptides. A

study shows that after just being introduced to ACE inhibitors in pregnancy, guinea pig newborns had lower concentration of angiotensin II. But nevertheless, in the fetus and infant, a large level of angiotensin II is biologically required to boost arterial pressure in various conditions for the regulation of GFR. It is discovered that ACE inhibitors produce hypotension and electrolyte imbalance in fetus in the rabbit study.

Temocapril's average emission was 35%, while Enalapril's was 39%. The
transfer rate of antipyrine, used as a control sample, was 25.4%. In another study, the temocapril transfer rate ranged from 10.4 to 36.7, while the temocapril transfer rate ranged from 3.2 to 16.4. The differential factor between both the temocapril index and the enalapril is almost 4 times greater which is 0.13 to 0.41. The placental transfers of enalapril was 2.19% and temocapril transmission value was 2.99% [33].

ACE inhibitor is likely to be excreted by the kidneys eliminated in the fetus. after that it is then absorbed by the amniotic fluid and circulated again. this recirculation of drug could affect the fetal physiology and lengthen the half-life of an unaltered medication in the fetus [16].

1.8 Placental exposure and it’s repercussions

In 1980, there were alarming reports of unusual embryonic loss rates in experimental animals that were given ACE inhibitors throughout pregnancy. The very first incidence of an ACE inhibitor-associated fetal outcome was observed in 1981. Warnings regarding the consumption of ACE inhibitors throughout human gestation were issued in 1985 in response animal studies and an increasing number of pregnancy complications [35].

ACE inhibitors are normally recommended not to use them throughout the 2nd and 3rd trimesters of gestation due to the higher risk of fetal kidney impairment [36].

Since that 50% of conceptions are unintentional, some women will undoubtedly be on Ace inhibitors when they become pregnant.

Most ACE inhibitors likely also pass the placental membrane in significant amounts, as has been confirmed with captopril, lisinopril, and enalapril. Within a fetus, the majority of ACEI is eliminated via the kidneys and may be recirculated through ingested amniotic fluid [37].

Human studies have shown an association between ACE inhibitor usage during the 2nd and 3rd trimesters of gestation and fetal kidney impairment, anhydramnios, oligohydramnios, cranial deformities, contractures of the limbs, and perhaps even deaths.

These problems are thought to be linked to fetal hypotension caused by ACE inhibitors [38]

1.8.1 1ST trimester exposure to ACEI

Fetuses introduced to angiotensin converting enzyme inhibitors throughout the 1st trimester had a higher incidence of congenital abnormalities.

1st trimester ACE inhibitor-exposed pregnancies and the same amount of control pregnancies have been studied, and it has been shown that in two groups, there was no difference in the rate of significant malformations.

Pregnant women without diabetes who were prescribed ACE inhibitors in the first trimester, some of the fetus developed cardiovascular abnormalities.

A research shows that from a group studied newborns who did not have any signs of their mothers having diabetes, among them some newborns were found to have taken ACE inhibitors during the 1st trimester. The major congenital abnormalities risk ratio was a few [31].

On another study among some pregnant women there were only three confirmed incidences of restriction of intrauterine growth [37].

Another study shows that infants with one significant deformity which was renal tubular dysplasia were shown among women who maintained ACE inhibitor through the 14th week mark but there was no sign of renal tubular dysplasia in the babies of mothers who were exposure to ACE inhibitors solely during the 1st trimester [39].

A survey examined the results of pregnant women who used captopril and enalapril. The infants treated with captopril throughout the first trimester, no abnormalities were noted. Women treated in the first trimester with enalapril experienced spontaneous abortions. A stillborn child was delivered after two weeks when enalapril was administered at 24 weeks. When enalapril was started at the time of conception, it resulted in newborns that were too small for their dates. When enalapril was started at the beginning of the pregnancy, that resulted in newborns that were too small for their dates [40].

Among the females that came into contact with ACE inhibitors, a number of spontaneous and therapeutic abortions occurred who were treated just during the 1st trimester. Some intrauterine restrictions on growth were also documented.

In the case of 1st trimester captopril exposure in newborns, some of them suffered significant birth malformations, including hypospadias, polydactyly, limb reduction deformities, and cardiovascular anomalies. According to another analysis, neonates who were introduced to enalapril throughout the 1st trimester suffered severe birth abnormalities, such as polydactyly and cardiovascular diseases. After using lisinopril in the first trimester, polydactyly was seen in some studies [37].

1.8.2 2nd and 3rd trimester exposure to ACEI

Both second and third-trimester exposure to ACEIs appears to be fetotoxic, resulting in fetal hypo calvaria and kidney abnormalities [10]**.**

Use of ACEI throughout the 2nd and 3rd trimesters of pregnancy have been linked to a number of negative outcomes in the exposed fetus, including deadly oligohydramnios, low blood pressure, anuria, and kidney failure in newborns [16].

The exposure to ACEIs throughout the 2nd and 3rd trimesters of gestation has been linked to multiple symptoms of oligohydramnios, fetal hypo calvaria, fetal kidney impairment, and fetal mortality. In 1991, the Federal Drug Agency of the USA identified 29 occurrences of fetal kidney failure linked to ACEI usage [37].

Pregnancies in which the mother was exposed to ACEIs resulted in fatalities including stillbirths and neonatal deaths. According to epidemiologic evidence, exposure to ACEIs throughout the 2nd and 3rd trimesters of gestation is thought to have a significant risk of death [41].

When hypertension and acute renal disease were complicating factors, a moderate dose of captopril was proven to improve maternal hemodynamics. but it is seemed there were no fetal or neonatal complications because of the exposure to a small dose [42].

As these medications may activate the AT2 receptor, which is known to be important in vascular growth and development, it is suggested they be avoided throughout pregnancy or even before conception [43].

1.9 Mechanism involved in fetotoxicity

Although the fetus may experience negative consequences from ACE inhibitor exposure at any point during gestation, late gestation is when these effects are most noticeable [19].

These developmental defects are considered to be caused in part by ACE inhibitors' direct impact on the fetal RAS as well as ischemia brought on by maternal low blood pressure. Another possible reason for fetotoxicity is decreased fetal-placental circulation of blood, and decreased oxygen and nutrition supply toward the fetus [16].

Nevertheless, ANG inhibition during the newborn period might accelerate renal damage caused by congenital UT blockage. Application of ACE inhibitors may decrease the onset of kidney illness in later childhood. The hypotensive effects of these medications are also much more potent in newborns. When using ACE inhibitors in pregnant women or newborns with cardiac or renal illness, it is crucial to comprehend the interconnections of the developing RAS.

Congenital blockage of the urinary system can cause renal damage, which can be made worse by ACE inhibitors in the fetal stage [19].

Unknown pathogenetic pathways produce kidney dysfunction in afflicted fetuses and newborns. There is strong evidence from recently published research that blocking fetal RAS causes the renal perfusion pressure of the fetus to decrease, which causes acute kidney failure

in the newborn Proximal tubule growth disorders are brought on by primary deficiencies in the genes encoding components of tubular development and differentiation. There is growing evidence that the primary cause in humans is hypoperfusion of the developing kidney. Many diseases that cause embryonic kidney hypoperfusion have been linked to lack of proximal tubule maturation and renal tubular mutation [44].

Another study reveals that the lower renal blood flow and fetal hypotension that likely to be the reasons of these abnormalities [10].

1.10 ACE inhibitor-induced fetal defect

Due to possible negative effects on the growing fetus, the administration of ACE inhibitors is prohibited during pregnancy. In prenatal exposure to ACE inhibitors may cause renal problems in neonates, such as high blood pressure, kidney failure, and mortality, according to epidemiological research [45].

Despite being contraindicated during pregnancy due to fetopathy associations like renal dysgenesis, hypo calvaria, oligohydramnios, restriction of intrauterine growth, respiratory hypoplasia, and neonatal anuric kidney failure, ACEI are widely used blood pressure medication [46].

Fetal growth retardation, neonatal anuria, neonatal mortality is among the additional harmful consequences of ACE inhibitors on the fetal development.

Reduced renal performance result in oligohydramnios, which can subsequently cause additional abnormalities such fetal musculoskeletal contractures, anatomical deformities and development of hypoplastic lungs [47].

A number of human and animal fetopathies, including faulty fetal skull development, intrauterine growth restriction, and renal impairment, have been linked to the use of ACE inhibitors [48].

1.10.1 Hypocalvaria

Hypocalvaria, brain lesions, and skull lesions are all seen in the fetotoxic impacts of ACE inhibitors in individuals. The skull membranous bones, hypoplasia, and hypocalvaria are seen with the exposure to ACE inhibitors.

These side effects were linked to captopril, lisinopril, and enalapril. Calvarial bones were discovered in their typical place and form but significantly smaller than usual. In extreme cases, the normally formed brain was practically left exposed by the skull, making it vulnerable to injury during labor and delivery.

It is uncertain what led to the hypocalvaria associated with ACE inhibitor intake. Membranous bones have high vascularity and need high oxygen tension to develop. Because ACE drug exposure is thought to cause fetal hypotension, hypoxic effects that lead to hypocalvaria and poor maturation of the bones of the skull may also occur. Also, angiotensin II suppression may simultaneously block certain growth factors essential for calvarial bone formation [49] [10].

The intrauterine hypotension is to blame for kidney skeletal link brought on by ACE inhibition. Low perfusion of the skull's plate-like skeletal structures can lead to hypocalvaria [50].

1.10.2 Neonatal hypotension

ACEI exposure is thought to cause fetal hypotension, which may have a variety of negative repercussions [16].

As many as 50% of newborns with VlbW show signs of weak myocardial contractility and reduced cardiac output during their initial hours of life, making hypotension a prevalent issue in preterm and post term neonates. In addition to gestational age and disease, ACE inhibitors also play a role in neonatal hypotension [51].

Neonatal hypotension caused by the use of captopril, lisinopril, enalapril during pregnancy. The neonatal hypotension caused by the use of ACEI does not react to dopamine treatment or

volume expansion. That's why this type of hypotension appears to be distinct from the condition in other preterm newborns [52].

1.10.3 Oligohydramnios

The use of captopril or enalapril by the mother has been linked to oligohydramnios in earlier studies [53].

The definition of oligohydramnios is simply amniotic fluid volume that is abnormally low for gestational age. It might indicate a number of fetal, placental, or maternal abnormalities [54].

Oligohydramnios has been linked to poor pregnancy outcomes. Low levels of amniotic fluid can cause fetal growth limitation. Hypoxemia was believed to diminish the flow of blood through the kidneys, which in turn decreased urine production and the amount of amniotic fluid. Low fluid and fetal impairment are connected to each other. Amniotic fluid is crucial for the growth and wellbeing of the fetus.

The physiology of amniotic fluid is a very dynamic system. Amniotic fluid assists in temperature regulation, supports healthy lung and musculoskeletal growth in fetuses, and possesses anti-inflammatory properties and inhibits the growth of bacteria. Oligohydramnios is frequently believed to be related to a number of fetal malformations and burst membranes, which may indicate hypoxia and uteroplacental deficiency [55].

1.10.4 Renal tubular dilatation

RTD is identified by elevated medullary and cortical tissues and mesenchyme, both Bowman's tubule and space enlargement, reduced to nonexistent separation of the convoluted tubules at the proximal end, and fibrosis. The RTD caused by ACE inhibitors shares similarities with abnormalities in other diseases marked by decreased blood circulation in the kidneys.

Fetal low blood pressure and reduced renal perfusion are the main ways that ACE inhibitors interfere with embryonic renal maturation [16].

1.10.5 Decreased Renal Blood Flow

Severe impairment of embryonic renal function has been linked to ACEI medications the most frequently. These kidney abnormalities might be brought on by ACE inhibitors lowered fetal blood flow to the renal system.

ACE inhibitors alter the blood circulation to the fetal kidneys. There is evidence from animal studies that ACEI causes fetal hypotension, perhaps as a result of a lower angiotensin and an elevated bradykinin level. Reduced fetal renal blood flow ultimately results in reduced GFR [56].

1.10.6 Pulmonary hypoplasia

Lung hypoplasia that is clinically serious might result from developmental disruptions.

The formation of the lung required the successive maturation of several cell structures with sufficient surface area, volume, and extensibility to permit effective gaseous exchange throughout the lung with blood cells [57].

Oligohydramnios from weeks 16 to 22 of pregnancy may result in deadly pulmonic hypoplasia [58].

Depending on when the fluid is lost, initial pulmonary fluid loss causes substantial lung hypoplasia, or anatomical immaturity. The elimination of lung fluid halted lung expansion. It occurs in conjunction with some other illness, such as congenital diaphragmatic hernia or renal agenesis, musculoskeletal chest issues, diseases that hinder fetal respiratory movements, or premature membrane fracture and amniotic fluid loss during the first trimester.

They contribute to a decrease in embryonic lung development. fewer branches develop because of the loss of fetal respiratory tract fluid and because the size of the lungs is reduced [57].

1.10.7 Renal Impairment

Decreased kidney perfusion has been proposed as the potential reason for long-term renal impairment after exposure to ACEI [2].

By decreasing blood flow to the kidneys, ACEI seems to have an effect on the fetal kidney. Uterine blood flow can be decreased by ACE inhibitors. Reduced neonatal renal blood flow ultimately results in a reduced glomerular filtration rate. Inadequate glomerular filtration could serve as the main cause of irregular tubular growth. The efferent arteriole can get constricted by ACEI. Regulation of glomerular filtration in the embryonic kidney depends on efferent arteriolar constriction. Hence, glomerular filtration would decrease if this constriction were lost as a result of ACE inhibition. Renal impairment results from a reduction in glomerular filtration.

There is an absence of functional proximal tubules in the kidneys of ACEI-exposed fetuses. A decrease in distal tubules is the outcome of increasing mesenchymal tissue. Reduced renal perfusion may possibly be the cause of this dysfunction [56].

When ACE inhibitors are administered to the mother, the fetus is more likely to suffer from renal impairment because of the elevated levels of renin-angiotensin. The efferent arteriole is largely constricted by angiotensin. ACE inhibitors reduce glomerular filtration rate, filtration fraction, and renal vascular resistance. Acute renal failure may result from a sudden decline in glomerular filtration [59].

There are fewer glomerular lobules, fewer tubules, poorly defined corticomedullary junctions, and more medullary mesenchymal cells are seen. That leads to oligohydramnios and renal impairment in the neonates. ACEI-induced non-immune hydrops is also seen. That could be the result of renal failure coupled with fluid overload [60].

1.10.8 Neonatal anuria

Since ACEI can penetrate the human placenta, using them while pregnant has been linked to fetal harm. Fetal growth limitation, hypocalvaria, fetal hypoplasia, and renal failure without urine production are all symptoms of fetopathy.

ACE inhibition slows glomerular development since angiotensin II is also renal growth factor. The ability to pass the placenta and harm the fetus was the reason for the patient's severe kidney

failure with neonatal anuria. ACE-I reduced the rate of glomerular filtration, induced hypotension resulting neonatal anuria [61].

1.10.9 Intrauterine growth restriction

The increased placental-fetus vascular resistance in gestation can cause intrauterine growth restriction. In one case, measurements revealed that limb lengths were abnormally short as the mother was taking ACEI. Hence, it seems to indicate that intrauterine growth restriction would be a characteristic of ACEI fetopathy [10].

Defects in the ossification of the skull and bone deformities have been reported. In addition, there have been cases of in utero mortality, patent ductus arteriosus, limb rigidity, and respiratory distress syndrome (RDS) [50].

1.11 Alternatives to ACE inhibitors during pregnancy

Methyldopa, which functions as a false neurotransmitter, is used as a first-line treatment for hypertension during pregnancy.

Labetalol (non-selective ß-blocker), Nifedipine (calcium channel blocker), Hydrochlorothiazide (diuretic), and Hydralazine (direct vasodilator) Selective beta-blockers include Metoprolol are used as a second-line agent.

Direct vasodilators include diazoxide and Nitroprusside, labetalol, hydralazine, and, Nifedipine is used as an emergency medication for hypertension [32].

2 CHAPTER TWO: PURPOSE OF THE STUDY

In between 6 and 8 percent of pregnancies, hypertension is a problem. Also, because ACEI is a first-line treatment for hypertension, there is a higher possibility of using this medicine throughout pregnancy, which could lead to congenital malformations because ACEI has teratogenic effects. The purposes in conducting this study were as follows:

- The primary objective of this study is to find a rational correlation between the time of intake of the drug (trimester) and the possible outcomes.
- To gain a thorough understanding of the major congenital malformations following maternal exposure to ACE inhibitors.

3 CHAPTER THREE: LITERATURE REVIEW

Data are currently inadequate for identifying if ACE inhibitors have a specific pattern of fetotoxicity when it comes to 1st trimester exposure. For a precise estimate of the teratogenic risk following first-trimester administration, there are not currently enough reported instances. Some authors have stated that major malformations are not uncommon, although this does not always mean that exposure during the first trimester does not pose a teratogenic risk. According to some authors, there are alternative options for treating hypertension, so it is best to avoid this medication even though the possibility of a teratogenic effect is not very common. Regarding the late pregnancy exposure, ACEIs throughout the 2nd and 3rd trimesters of pregnancy pose strong evidence to make sure that they are very fetotoxic, and none of the authors suggested providing this medication during this time period. The primary area of disagreement among the authors is that while some of them agree that exposure to ACEI early in pregnancy should be classified as a teratogen because it may have harmful effects, some authors don't support that because there is no specific mechanism or controlled studies to support their claim. However, all scholars agreed women of reproductive age should consider using alternative antihypertensive drugs rather than ACE inhibitors.

4 CHAPTER FOUR: METHODOLOGY

4.1 Materials collection and data analysis procedure

To collect published studies in renowned journals and organizations, I've done a brief search and collected studies from web search engines including Google Scholar and PubMed, publishers including Elsevier and Springer, and journals including The Lancet, The BMJ, and JAMA. For collecting materials, I've done thorough web search from February 2023 to April 2023 using the terms teratogen, angiotensin converting enzyme inhibitors, mechanism of action, angiotensin I, ANG II, renin-angiotensin-system, fetal RAS, maternal hypertension, congenital defect, ACE inhibitors - adverse effect, therapeutic effect, local RAS, fetus, fetotoxic mechanism, fetal renal impairment. This study was completed by collecting the results of a thorough literature search, choosing relevant research, and summarizing the results of the studies that were found. After reviewing about 64 of the literature studies, all the precise, effective, and appropriate data were selected and analyzed.

5 CHAPTER FIVE: RESULT & DISCUSSION

5.1 Fetotoxicity in animals

Studies have revealed some significant ACE inhibitor-induced fetotoxic effects observed in animal models. Animals are administered ACE inhibitors during all three trimesters to determine which trimester has the most impact on the fetus.

5.1.1 Captopril-induced fetal toxicity

Both rabbits and sheep given captopril throughout the 2nd and 3rd trimesters exhibit fetal morbidity and death. In the rabbit model, hypotension and decreased blood flow were also demonstrated [16] [34].

During late pregnancy, maternal sheep were treated with captopril and showed hypotension [34].

Captopril causes prenatal growth retardation in the rat model; however, there are no fetal malformations. To generate high mortality, captopril has to be administered daily throughout pregnancy [16].

5.1.2 Enalapril-induced fetal toxicity

Enalapril treatment in the baboon model causes fetal mortality and intrauterine developmental retardation. In the fetus, ACE activity was similarly observed to be lowered.

Enalapril results in intrauterine growth retardation and an inadequate ossification of the skull in a rat model. Enalapril also causes nephrotoxicity in rabbits when given in the first trimester, and it causes 100% of fetal deaths when given in the second and third trimesters [16].

5.2 Fetotoxicity in human

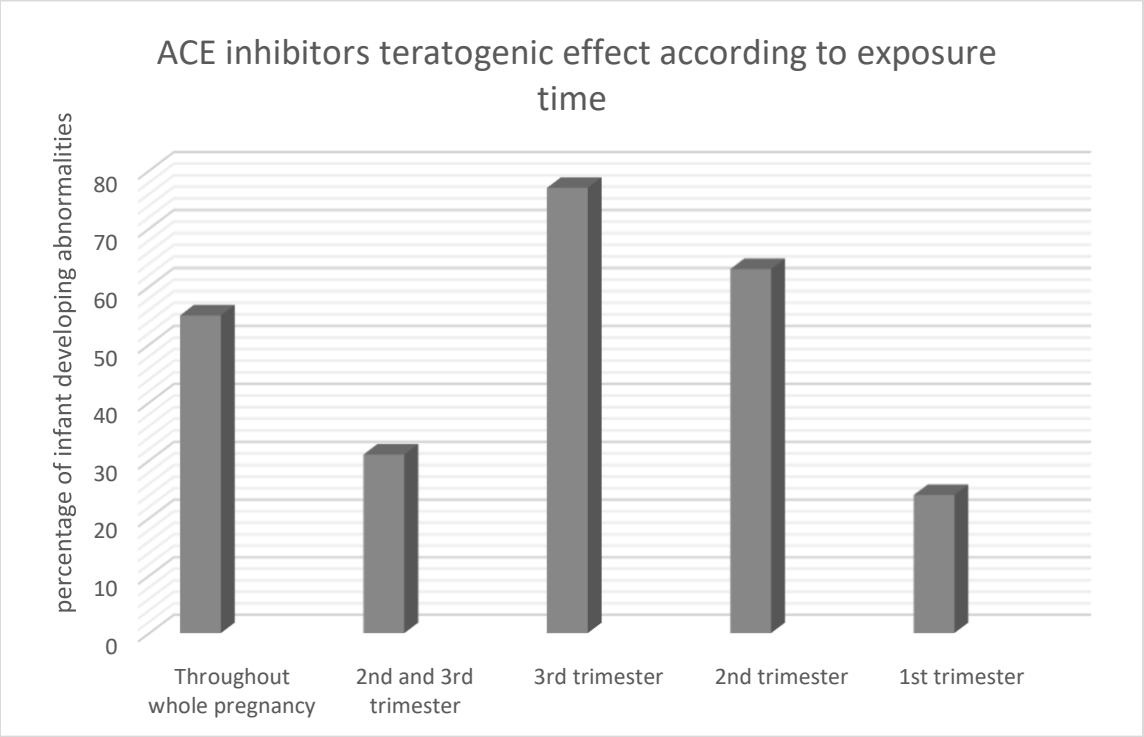
When used during pregnancy, ACE inhibitors have adverse effects on the growth of the fetus. And they seem to be contraindicated throughout all three trimesters of pregnancy. Studies have found that different drugs show different types of congenital anomalies.

Table-1: Birth defects caused by a particular ACE inhibitor (early pregnancy)

Drug	**Exposure period**	**Congenital abnormality**
Captopril	1st trimester	There are no obvious serious congenital defects.
Enalapril	1st trimester	There are spontaneous abortions.
Lisinopril	1st trimester	Around 13.3% of the newborns included in the research had significant birth abnormalities, such as intrauterine growth restriction and neonatal hypotension.

5.2.1 Relationship between the rate of birth defects and the drug's intake period (trimester)

According to the exposure period, ACE inhibitors have distinct fetopathy effects, as per 118 well-documented studies. This is due to the fact that the fetal RAS performs differently depending on the stage of fetal development.



From the data above, it is clear that during 3rd trimester, ACE inhibitors are most contraindicated [62].

5.2.2 Early pregnancy fetotoxic effects

According to several earlier investigations, women who were exposed to ACEI in the first trimester of pregnancy did not have any malformations among their liveborn neonates. Just 2.71% of babies are born with serious congenital malformations, according to research. Also, it was demonstrated that there wasn't any particular deformity pattern [16].

In a cohort study of 29,507 babies exposed to ACE inhibitors in the first trimester, it was reported that many malformations were present, including CNS malformation, GIT malformation, musculoskeletal defects like upper limb defects, urological defects like fetal renal impairment, cardiovascular defects like pulmonic stenosis, and atrial septal defects [62].

Another study asserts that newborns of women who were exposed to ACE inhibitors in some way during the early stages of their childbearing days suffered from a number of congenital malformations, including phocomelia, heart defects, respiratory failure, and renal impairment [34].

It is evident from recent cohort studies and a number of case reports that with the exposure to ACEI, there were various congenital abnormalities, such as some heart deformities and skull ossification. The research additionally demonstrates that while fetal RAS inhibition damages fetal organ development, fetal renal development is not susceptible to ACEI in early pregnancy [31].

5.2.3 Late pregnancy fetotoxic effects

The idea that ACE inhibitors are fetotoxic in the second and third trimesters has been widely accepted since very early on. A very high (10%–20%) morbidity rate was observed. This medication has been linked to a number of fetal defects, such as oligohydramnios, anuria, kidney failure, neonatal hypotension, hypocalvaria, and, in rare extreme cases, death of the fetus [16].

Table-2: Birth defects caused by a particular ACE inhibitor (late pregnancy)

Drug	Exposure period	Congenital abnormality
Enalapril	2nd & 3rd trimester	Pulmonary hypoplasia and intrauterine growth restriction, which affect 10% of the investigated newborns, are the main effects.
Captopril	2nd & 3rd trimester	Hypocalvaria and fetus renal impairment are the major defect that were seen.

According to a recent study, 10% of reported pregnancies resulted in neonatal hypotension, while 14% of newborns had pulmonary hypoplasia. Particularly, captopril is associated with fetal renal impairment and hypotension [34].

Table-3: ACE inhibitor induced congenital anomalies throughout late pregnancy

Total cases 118 (%)	Abnormality
23%	Fetal kidney impairment
19%	Oligohydramnios
18%	Fetal death
20%	Anuria
15%	Intrauterine growth retardation
17%	Neonatal hypotension
8%	hypocalvaria
14%	Pulmonary distress syndrome
4%	CNS abnormalities
8%	Muscular deformation
5%	Pulmonary hypoplasia

the effects are more severe if given during the third trimester of pregnancy rather than only 1st or 2nd trimester [62].

5.3 Discussion

Hypertension, a moderately frequent problem during pregnancy, affects a lot of pregnancies. The first-line treatment for hypertension is ACE inhibitor, which is frequently provided to women, although it has negative effects. From the beginning of pregnancy, ACE inhibitors have been discovered to be contraindicated; however, it is unclear if this applies to the first trimester of pregnancy.

They unquestionably induce serious congenital abnormalities in the second and third trimesters. Nevertheless, the precise mechanism is still unknown. The fetal and tissue RAs, which are important factors in fetus development, are thought to be interfered with by ACE inhibitors, which are thought to cause fetopathy.

Particularly in the case of renal development, the fetal RAS and Ang II play a crucial role in fetal growth. The fact that RAS is not fully developed during the early stages of fetal development may be the cause of the lack of fetotoxic effects during the first trimester. Nevertheless, when the fetal RAS begins to grow, ACEI prevents the conversion of ANG I to ANG II, which unquestionably hinders the fetal RAS and causes fetotoxicity to occur in the last trimester of pregnancy.

Regarding fetotoxicity in the first trimester, animal research demonstrates that ACE inhibitors unquestionably have teratogenic effects in the first trimester. Nevertheless, it appears that various animals affected by ACE inhibitors have distinct malformations, making it inappropriate to draw the inference that humans would be similarly impacted. There isn't much evidence to support the claim that maternal hypotension and other complications during the first trimester of pregnancy cause fetal complications.

It is debatable whether exposure to ACE-inhibiting medications throughout the initial trimester of pregnancy causes serious, persistent congenital abnormalities because the studies are not confident in their outcomes. Nevertheless, whether used for a long or short period of time, ACE inhibitors have a significant fetotoxic impact in the second and third trimesters.

6 CHAPTER SIX: CONCLUSION

ACE inhibitors are first-line medications for the management of hypertension, and they are well tolerated by the patient. but when it comes to prescribing them or using them irrationally, patients and physicians should be aware of their adverse effects when administered during pregnancy. It is commonly known that they should not be used during the second and third trimesters of pregnancy, and numerous studies contend that they are just as dangerous during the first trimester. Moreover, evidence of ACEI-induced congenital abnormalities is available from both human and animal models. However, the findings of those studies are inconsistent, and there is currently no definite mechanism that may account for the teratogenicity of ACEI in the first trimester. Overall, since negative effects are being discovered, it is important to raise awareness regarding ACEI medication exposure during pregnancy. Also, it should be suggested that non-pregnant women with hypertension on ACE inhibitors switch to a different antihypertensive therapy. In order to prevent complications and to have precise knowledge, further control studies concerning its impact and mechanism are very needed.

7 References

[1] M. A. Zamorski and L. A. Green, "NHBPEP report on high blood pressure in pregnancy: a summary for family physicians," *American Family Physician,* vol. 64, no. 2, pp. 263274, 2001.

[2] T. L. L. &. A. H. Saar, "Reversible Fetal Renal Impairment following Angiotensin Receptor Blocking Treatment during Third Trimester of Pregnancy: Case Report and Review of the Literature," *Case reports in obstetrics and gynecology,* vol. 2016, 2016.

[3] G. Y. e. a. Lip, "Angiotensin-converting-enzyme inhibitors in early pregnancy," *Lancet (London, England),* vol. 350, no. 9089, p. 1446–1447, 1997.

[4] R. L. Brent, "The cause and prevention of human birth defects: What have we learned in the past 50 years?," *Congenital Anomalies,* vol. 41, pp. 3-21, 2001.

[5] R. Betterton, "Promising Monster: Pregnant Bodies, Artistic Subjectivity, and Maternal Imagination," *Hypatia ,* pp. 80-100, 2006.

[6] S. D. U. C. S. P. Jones KL, "PATTERN OF MALFORMATION IN OFFSPRING OF CHRONIC ALCOHOLIC MOTHERS," *The Lancet,* pp. 1 (7815): 1267-1271, 9 june 1973.

[7] K.-M. G. M. K. B. M. K. D. K. G. Khattak S, "Pregnancy Outcome Following Gestational Exposure to Organic Solvents: A Prospective Controlled Study," *JAMA,* vol. 281, pp. 1106-1109, 1999.

[8] E. D. G. G. S. A. C. A. C. F. S. R. B. M. C. M. De Santis, "Ionizing radiations in pregnancy and teratogenesis: A review of literature," *Reproductive Toxicology,* vol. 20, no. 3, pp. 323-329, 2005.

[9] G. S. B. C. A. F. C. L. D. S. Marco De Santis, "Risk of drug-induced congenital defects," *European journal of obstetrics, gynecology, and reproductive biology,* vol. 117, no. 1, pp. 10-19, 2004.

[10] B. M. Jr, "Teratogen Update: Angiotensin-Converting Enzyme Inhibitors," *Teratology,* vol. 50, no. 6, pp. 399-409, 1994.

[11] F. H. B. S. B. C. &. R. S. F. Messerli, "Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use?," *Journal of the American College of Cardiology,* vol. 71, no. 13, p. 1474–1482, 2018.

[12] J. B. Byrd, C. V. S. Ram and E. V. Lerma, "Pharmacologic treatment of hypertension", Elsevier, 2019, pp. 477-482.

[13] R. S. M. A. K. H. M. S. M. J. S. S. D. J. P. N. R. C. G. M. D. Y. S. C. R. P. B. &. H. G. Chen, "Comparative First-Line Effectiveness and Safety of ACE (AngiotensinConverting Enzyme) Inhibitors and Angiotensin Receptor Blockers: A Multinational Cohort Study.," *Hypertension,* vol. 78, no. 3, pp. 591-603, 2021.

[14] S. Shibata and T. Fujita, ""Renin Angiotensin Aldosterone System Blockers"," in *Hypertension: A Companion to Braunwald's Heart Disease*, Elsevier, 2018, pp. 230-241.

[15] A. A. .. J. T. .. M.-L. N. Trung, "A Review of the Role of Bradykinin and Nitric Oxidein the Cardioprotective Action of Angiotensin-Converting Enzyme Inhibitors: Focus on Perindopril," *Cardiology and Therapy,* vol. 8, no. 2, pp. 179-191, 2019.

[16] H. Buttar, "An overview of the influence of ACE inhibitors on fetal-placental circulation and perinatal development.," *Molecular and Cellular Biochemistry,* Vols. 176 :61-71, 1997.

[17] W. Z. H. G. J. Z. X. Z. L. L. C. &. Z. L. Sun, "Comparison of the Efficacy and Safety of Different ACE Inhibitors in Patients With Chronic Heart Failure: A PRISMA-Compliant Network Meta-Analysis," *Medicine,* vol. 95(6), 2016.

[18] S. Bangalore, R. Fakheri, S. Wandel, B. Toklu, J. Wandel and F. Messerli, ""Renin angiotensin system inhibitors for patients with stable coronary artery disease without heart failure: systematic review and meta-analysis of randomized trials"," vol. 356, 19 January 2017.

[19] D. A. J. V.-C. A. &. C. J. Caldeira, "Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis.," vol. 345, 2012.

[20] G. S. &. G. Navis, "Safety of ACE inhibitor therapies in patients with chronic kidney disease," *Expert Opinion on Drug Safety,* vol. 13, no. 10, pp. 1383-1395, 2014.

[21] A. M. C. S. J. T. E. A. D. &. P. J. S. Sørensen, "Teratogenic effects of ACE-inhibitors and angiotensin II receptor antagonists," *Ugeskrift for laeger,* vol. 160, no. 10, pp. 14601464, 1998.

[22] O. A. Carretero, "Novel mechanism of action of ACE and its inhibitors," *American Journal of Physiology-Heart and Circulatory Physiology,* vol. 289, no. 5, 2005.

[23] M. A. C. S. D. G. S. B. M. M. &. C. T. M. Sparks, "Classical Renin-Angiotensin system in kidney physiology," *Comprehensive Physiology,* vol. 4, pp. 1201-1228, 2014.

[24] P. G. J. G. J. L. &. S. C. D. Nakagawa, "The Renin-Angiotensin System in the Central Nervous System and Its Role in Blood Pressure Regulation," *Current hypertension reports,* vol. 22, 2020.

[25] F. a. S. O. Fyhrquist, "Renin-angiotensin system revisited," *Journal of Internal Medicine,* vol. 264, no. 3, pp. 224-236, 2008.

[26] M. A. C. S. D. G. S. B. M. M. &. C. T. M. Sparks, "Classical Renin-Angiotensin system in kidney physiology," *Comprehensive Physiology,* vol. 4, no. 3, pp. 1201-1228, 2014.

[27] S. J. L. E. R. E. S. J. M. P. &. P. K. G. Delforce, "Dysregulation of the placental reninangiotensin system in human fetal growth restriction," *Reproduction,* vol. 158, no. 3, pp. 237-245, 2019.

[28] N. W. G. S. S. D. S. M. M. R. A. &. S. K. R. Morrell, "Developmental regulation of angiotensin converting enzyme and angiotensin type 1 receptor in the rat pulmonary circulation," *American journal of respiratory cell and molecular biology,* vol. 14, no. 6, 1996.

[29] U. B. Gandhi C, "Roles of the Angiotensin System in Neonatal Lung Injury and Disease," *JSM Atheroscler,* vol. 1, no. 3, 2016.

[30] K. M. S. F. M. T. H. K. T. &. N. S. Watanabe, "Importance of the angiotensin type 1 receptor in angiotensin II-induced bronchoconstriction and bronchial hyperresponsiveness in the guinea pig," *Experimental lung research,* vol. 30, no. 3, pp. 207-221, 2004.

[31] A. W. A. &. K. G. Al-Maawali, "Taking angiotensin-converting enzyme inhibitors during pregnancy: is it safe?," *Canadian family physician Medecin de famille canadien,* vol. 58, no. 1, pp. 49-51, 2012.

[32] L. L. T. J. D. B. Scott R. Yoder, "Hypertension in Pregnancy and Women of Childbearing Age," *The American Journal of Medicine,* vol. 122, no. 10, pp. 890-895, 2009.

[33] C. E. B. S. P. E. E. E. E. R. W. Klaus Reisenberger, "Placental passage of angiotensinconverting enzyme inhibitors," *American Journal of Obstetrics and Gynecology,* vol. 174, no. 5, pp. 1450-1455, 1996.

[34] A. Quan, "Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists," vol. 82, no. 1, pp. 23-28, 2006.

[35] P. G. Pryde, A. B. Sedman, C. E. Nugent and M. J. Barr, "Angiotensin-converting enzyme inhibitor fetopathy," *Journal of the American Society of Nephrology : JASN,* vol. 3, no. 9, pp. 1575-1582, 1993.

[36] J. G. V. M. J. &. K. G. Ray, "Taking ACE inhibitors during early pregnancy: is it safe?," *Canadian family physician Medecin de famille canadien,* vol. 53, no. 9, p. 1439–1440, 2007.

[37] S. &. K. G. Ratnapalan, "Taking ACE inhibitors during pregnancy. Is it safe?," *Canadian family physician Medecin de famille canadien,* vol. 48, p. 1047–1049, 2002.

[38] C. Schaefer, "Angiotensin II-Receptor-Antagonists: Further Evidence of Fetotoxicity but Not Teratogenicity," *Birth Defects Research,* vol. 67, pp. 591-594, 2003.

[39] Centers for Disease Control and Prevention (CDC), "Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy-United States, Canada, and Israel, 1987-1995," *MMWR. Morbidity and mortality weekly report,* vol. 46, no. 11, p. 240–242, 1997.

[40] C. P. P. F. T. C. &. B. M. J. Kreft-Jais, "Angiotensin-converting enzyme inhibitors during pregnancy: a survey of 22 patients given captopril and nine given enalapril," *British journal of obstetrics and gynaecology,* vol. 95, no. 4, p. 420–422, 1988.

[41] M. K. M. J. V. F. &. V. A. F. A. Hanssens, "Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy," *Obstetrics and gynecology,* vol. 78, no. 1, p. 128–135, 1991.

[42] T. R. C. D. B. D. C. D. C. B. D. A. &. S. B. Easterling, "Low-dose, short-acting, angiotensin-converting enzyme inhibitors as rescue therapy in pregnancy," *Obstetrics and gynecology,* vol. 96, no. 6, p. 956–961, 2000.

[43] L. G. B. M. B. D. Chung NA, "Angiotensin-II-receptor inhibitors in pregnancy," *Lancet,* vol. 357, p. 1620–1621, 2001.

[44] K. M. S. G. N. T. Laube GF, "Angiotensin-converting enzyme inhibitor fetopathy: longterm outcome," *Arch Dis Child Fetal Neonatal Ed,* vol. 92, no. 5, p. F402–F403, 2007.

[45] K. T. Deva M, "ACE inhibitor fetopathy: a case series and survey of opinion amongst New Zealand paediatricians, obstetricians, neonatologists, and nephrologists," *The New Zealand medical journal,* vol. 125, no. 1361, p. 51–61, 7 September 2012.

[46] S. S. R. G. C. &. C. A. J. Neves, "Fetopatia pelo uso de inibidores da enzima de conversão da angiotensina [Fetopathy associated with exposure to angiotensin converting enzyme inhibitors]," *Acta medica portuguesa,* vol. 23, no. 4, p. 697–700, 2010.

[47] B. M. Jr, "Teratogen update: angiotensin-converting enzyme inhibitors," *Teratology,* vol. 50, no. 6, pp. 399-409, 1994.

[48] R. d. C. L. R. V. d. A. A. J. M.-A. P. R. D. A. G. J. Emerson Luiz Botelho Lourenço, "Fetopathies associated with exposure to angiotensin converting enzyme inhibitor from Tropaeolum majus L.," *Drug and Chemical Toxicology,* vol. 40, no. 3, pp. 281-285, 2017.

[49] C. M. J. Barr M Jr, "ACE inhibitor fetopathy and hypocalvaria: the kidney-skull connection," *Teratology,* vol. 44, no. 5, pp. 485-495, 1991 .

[50] J. S.-K. J. M. C. Soohyun Ri, "Hypocalvaria of Newborn Infant: Intrauterine Exposure to an Angiotensin Receptor Blocker," *Perinatology ,* vol. 28, no. 3, 2017.

[51] K. BT, "Management of Neonatal Hypotension," *Neonatal network,* vol. 36, no. 1, p. 40–47, 2017.

[52] J. M. Mastrobattista, "Angiotensin converting enzyme inhibitors in pregnancy," *Seminars in Perinatology,* vol. 21, no. 2, pp. 124-134, 1997.

[53] C. J. K. L. P. J. B. K. S. S. &. W. J. Cunniff, "Oligohydramnios sequence and renal tubular malformation associated with maternal enalapril use," *American journal of obstetrics and gynecology,* vol. 162, no. 1, p. 187–189, 1990.

[54] R. L. &. S. A. L. Skovgaard, "Oligohydramnios. Literature review and case study," *Journal of nurse-midwifery,* vol. 38, no. 4, p. 208–215, 1993.

[55] M. B. Munn, "Management of oligohydramnios in pregnancy," *Obstetrics and gynecology clinics of North America,* vol. 38, no. 2, pp. 387-95, 2011.

[56] R. A. J. K. L. M. A. B. M. J. &. B. K. Martin, "Effect of ACE inhibition on the fetal kidney: decreased renal blood flow," *Teratology,* vol. 46, no. 4, p. 317–321, 1992.

[57] C. M. Cotten, "Pulmonary hypoplasia," *Seminars in fetal & neonatal medicine,* vol. 22, no. 4, pp. 250-255, 2017.

[58] W. J. W. Laudy J. A. M., "The fetal lung 2: pulmonary hypoplasia," *Ultrasound in Obstetrics and Gynecology,* vol. 16, no. 5, p. 482–494, 2000.

[59] B. J. M. R. S. A. Lumbers ER, "The effects of a converting enzyme inhibitor (captopril) and angiotensin II on fetal renal function," *British journal of pharmacology,* vol. 110, no. 2, p. 821–827, 1993.

[60] K. P. D. S. N. A. Murki S, "Fatal neonatal renal failure due to maternal enalapril ingestion.," *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,*, vol. 17, no. 3, p. 235–237, 2005.

[61] S. D. F. P. C. C. M. M. D. G. P. I. Lavoratti G, "Neonatal anuria by ACE inhibitors during pregnancy," *Nephron,* vol. 76, no. 2, p. 235–236, 1997.

[62] W. O. H.-D. S. A. P. G. D. J. A. D. S. G. P. S. H. K. &. R. W. A. Cooper, "Major congenital malformations after first-trimester exposure to ACE inhibitors," *The New England journal of medicine,* vol. 354, no. 23, p. 2443–2451, 2006.

[63] M. Bullo, S. Tschumi, B. S. Bucher, M. G. Bianchetti and G. D. Simonetti, "Pregnancy Outcome Following Exposure to Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Antagonists A Systematic Review," *Hypertension,* vol. 60, no. 2, pp. 444-450, 2012.

[64] R. L. Chevalier, "Mechanisms of fetal and neonatal renal impairment by pharmacologic inhibition of angiotensin," *Current medicinal chemistry* , vol. 19, no. 27, p. 4572–4580, 2012.