Evaluation of Misoprostol Use in Obstetrics and Gynecology,
Elhassahessa Teaching Hospital, Sudan

BY

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A dissertation

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Dedication

I dedicate this work

To

My Kind mother,
My father soul
My brothers and sisters
And my friends
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First, I thank God for helping me with his care to do this work. I would like to thank my supervisor Dr. Imad Eldin Mohammed Taj Eldin, Head Department of Pharmacology, Faculty of pharmacy, University of Gezira, who acted as a knowledgeable resource for the duration of the study; his support was instrumental in the completion of this thesis. I would like to express my sincere gratitude to my co–supervisor Dr. Abd Elrahman Yousif, for his kindness, unlimited valuable help, constructive suggestions, encouragement and moral support.

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A dissertation Submitted By

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Master of pharmacy (M. Pharm.)

Abstract

Misoprostol is a potent uterotonic agent that is used mainly in obstetrics and gynecology for labour induction, medication abortion and postpartum hemorrhage, this study aimed to evaluate the clinical uses of misoprostol by pregnant women at Department of Obstetrics and Gynecology, Elhassahessa Teaching Hospital, by a retrospective study in which a special designed form was used to collect data from files and records of pregnant women (n=212) who administered misoprostol for different clinical problems, the result of this study showed that misoprostol was commonly indicated to pregnant women for labour induction (n=120; 55.7%) and medication abortion (n=91; 42.9%), but its uses in postpartum hemorrhage was less common (n=3; 1.4%); and the outcomes of viable fetus and stillbirth were (n=103, 85.8%)(n=17, 14.2%) respectively, also the result showed that the uses of misoprostol was not accompanied with serious side effects, so it can be concluded that misoprostol is remarkably effective and relatively safe when used for labour induction and medication abortion, but further studies are needed to assess its use in postpartum hemorrhage.
تقييم استخدام الميزوبروستول في النساء والتوليد في مستشفى الحصاحيصا التعليمي

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(بكالريوس الصيدلة, جامعتى الجزيرة 2001)

ماجستير في الصيدلة (أغسطس 2012)

قسم علم الأدوية، كلية الصيدلة، جامعة الجزيرة

الملخص

الميزوبروستول واحد من المواد الفعالة والقابضة للرحم والتي تستخدم في النساء والتوليد ( في تهيئة الولادة، الإجهاض الطبي، النزف ما بعد الولادة) وقد هدفت هذه الدراسة إلى تقييم الاستخدامات السريرية للبروستيكلاندينات (خاصة الميزوبروستول) في قسم النساء والتوليد في مستشفى الحصاحيصا. وقد تم جمع المعلومات من ملفات وسجلات النساء الحوامل باستخدام استمارة خاصة مصممة بصورة جيدة. وكان عدد النساء الحوامل التي اختارن للدراسة ن = (212) وقد أعطين الميزوبروستول لدواعي مختلفة. وقد كانت النتيجة أن الميزوبروستول يستخدم بصورة شائعة للنساء الحوامل لدواعي: تهيئة الولادة ن = 120 بنسبة (55.7%) وللإجهاض الطبي ن = 91 بنسبة (42.9%) ولكن في النزف ما بعد الولادة كان عدد النساء قليل جداً (3) نساء بنسبة (1.4%) بالمقارنة مع عدد النساء اللائي أعطين الميزوبروستول في حالة تهيئة الولادة والإجهاض الطبي كما وجد أن عدد الأجنة الحية والميتة كانت (103) (17) على التوالي كما وجد أيضاً أن الآثار الجانبية بسيطة وغير خطيرة وعليه نستنتج ان الميزوبروستول فعال وآمن نسبيا عندما استخدم في تهيئة الولادة والإجهاض الطبي ولكن هناك حاجة لدراسات أخرى للتحقق من استخدامه في النزف ما بعد الولادة.
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<td>Prostaglandins</td>
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<tr>
<td>LTs</td>
<td>Leukotrienes</td>
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<tr>
<td>AA</td>
<td>Arachidonic acid</td>
</tr>
<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</td>
</tr>
<tr>
<td>DHA</td>
<td>Docosahexaenoic acid</td>
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<tr>
<td>LCPUFA</td>
<td>Long chain polyunsaturated fatty acids</td>
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<td>PLA2</td>
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<td>Thromboxanes</td>
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<tr>
<td>5-LO</td>
<td>5-lipoxygenase</td>
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<tr>
<td>HETEs</td>
<td>Hydroxyeicosatetraenoic acid</td>
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<tr>
<td>NSAIDs</td>
<td>Non steroidal anti inflammatory drugs</td>
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<tr>
<td>FDA</td>
<td>Food drug administration</td>
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<tr>
<td>WHO</td>
<td>World health organization</td>
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<tr>
<td>LH</td>
<td>luteinizing hormone</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<td>PPH</td>
<td>Postpartum hemorrhage</td>
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CHAPTER ONE

INTRODUCTION
1. Introduction

The first reported in the 1930s, that prostaglandins (PGs) were the most powerful, ubiquitous, diversified, and mysterious biological substances yet discovered. Some 30 years later, they were finally unmasked by the Swedish Medicinal chemists Su¨ne Bergstrom and Bengt Samuelsson, who in 1982 were awarded the Nobel Prize in Physiology with the British pharmacologist John Vane. They isolated, identified, and characterized the prostaglandin family, establishing unsaturated lipids derived from the cell membrane as an unexpected class of highly sensitive bioactive regulators (Zor et al., 2000).

Prostaglandins (PGs), leukotrienes (LTs), and related compounds are called eicosanoids, from the Greek eikosi (“twenty”). Precursor essential fatty acids contain 20 carbons and three, four, or five double bonds 8, 11, 14-eicosatrienoic acid (dihomo-g-linolenic acid), 5, 8, 11, 14-eicosatetraenoic acid (arachidonic acid [AA]; and 5, 8, 11, 14, 17-eicosapentaenoic acid (EPA) (Brunton et al., 2008).

The eicosanoids are oxygenation products of polyunsaturated long chain fatty acids. They are ubiquitous in the animal kingdom and are also found together with their precursor oils in a variety of plants. They constitute a very large family of compounds that are not only highly potent but also display an extraordinarily wide spectrum of biological activity. Because of their biological activity, the eicosanoids, their specific receptor and enzyme inhibitors, and their plant and fish oil precursors have great therapeutic potential. Their short
half-lives-seconds to minutes-make special delivery systems or synthesis of stable analogues mandatory for their clinical use (Trevor *et al.*, 2011).

Arachidonic acid is the most abundant and the most important of the precursors of the eicosanoids, its contain 20-carbon (C20) fatty acid that contains four double bonds beginning at the omega-6 position to yield a 5,8,11,14-eicosatetraenoic acid (designatedC20:4-6) (Trevor *et al.*, 2011).

Arachidonic acid (20:4n-6; AA) and docosahexaenoic acid (22:6n-3; DHA) are two long chain polyunsaturated fatty acids (LCPUFA; ≥2 double bonds, ≥20 carbon) that contribute to normal growth and development during the perinatal period (Park *et al.*, 2011).

**1.1 Synthesis of Prostaglandins:**

All prostaglandins are composed of a cyclopentanone nucleus with two side chains. Primary prostaglandins contain a 15-hydroxyl group with a 13, 14-trans double bond (Figure 1.1).
Figure 1.1: Nomenclature of the prostaglandins (Zreik and Behrman, 2008)
Biosynthesis of arachidonic acid (AA) and docosahexaenoic acid (DHA) from the nutritionally essential linolenic and alpha-linolenic acids occurs through a series of elongation and desaturation reactions catalyzed by a common set of enzymes (Park et al., 2011).

Cell membranes, comprising largely phospholipids, are themselves the major source material for PGs and other biologically reactive eicosanoids (20-carbon unsaturated carboxylic acids) such as leuktriennes (LTs) (Zor et al., 2000). Following an appropriate physiological or pathological stimulus, AA is released from cell membrane phospholipids by one of the many form of phospholipase A2 (PLA2), which is generally regarded as the rate-limiting step in eicosanoids synthesis (Figure1.2)

**Figure 1.2: Release of arachidonic acid by physiological or pathological stimulus**
(Caughey et al., 2005).
There are two major biosynthetic pathways: the cyclooxygenase (COX/PGH synthase) pathway, which synthesizes the PGs and thromboxanes (TXs); and the 5-lipoxygenase (5-LO) pathway, which synthesizes the leukotrienes (LTs), hydroxyeicosatetraenoic acid (HETEs), and lipoxins (Caughey et al., 2005).

1.1.1 Major Biosynthetic Pathways Cyclooxygenase (COX):

Prostaglandin endoperoxide synthase or COX is abifunctional enzyme that carries out the two first committed steps in the biosynthesis of PGs.

- The oxidation of arachidonic acid to form cyclic endoperoxide PGG2 (cyclooxygenase activity)

- The peroxidation of PGG2 to generate PGH2 peroxides activity.

COX catalyzes two enzymatic activities; namely, the conversion of arachidonic acid to the hydroperoxy- end peroxide PGG2, followed by its subsequent reduction to the labile product PGH2 (Arroyo and Clària, 2003).

PGH2 is the common substrate for number of different cell-specific synthases, which convert PGH2 to the individual PGs or TX, including PGE2, PGI2 (prostacyclin), PGD2, PGF2, and TXA2 (Caughey et al., 2005).

PGH2 is a highly unstable endoperoxide which functions as an intermediate substrate for the tissue-specific synthesis of a variety of prostanoids and thromboxane (TX), depending on the tissue, PGH2 is converted to PGD2 by cytosolicen PGD synthase; whereas PGE2 is formed by membrane-bound enzymes PGE synthase. PGH2 can alternatively be converted to PGF2 by PGF-synthase (Arroyo and Clària, 2003).
Vascular endothelial and smooth muscle cells produce PGI2 or prostacyclin from PGH2 by means of enzyme PGI-synthase. Finally, platelets release TXA2 from the same precursor (PGH2) as the PGs through the action of the thromboxane synthase enzyme, as shown in Figure 1.3.

Both PGI2 and TXA2 have a very short half-life (30s and 3min, respectively) and are rapidly hydrolyzed to the inactive compounds TXB2 and 6-keto-PGF1. In general, PGs and TX are highly potent local mediators that produce an astonishing array of biological effects.

**Figure 1.3: Metabolism of arachidonic acid (AA) to prostaglandin (PG) PGF2, PGI2 (prostacyclin), PGE2, TXA2, and PGD2 by the COX pathway.** PGI2 and TXA2 have very short half-lives (30s) and are converted to the stable but inactive 6-keto PGF1 and TXB2, respectively (Caughey et al., 2005).
There are two forms of COX, COX-1 and COX-2. COX-1 is a primarily constitutive isoform found in most normal cells and tissues, while cytokines and inflammatory mediators that accompany inflammation induce COX-2 production. However, COX-2 also is constitutively expressed in certain areas of kidney and brain, and is induced in endothelial cells by laminar shear forces. Importantly, COX-1, but not COX-2, are expressed as the dominant, constitutive isoform in gastric epithelial cells and are the major source of
cytoprotective prostaglandin formation. Inhibition of COX-1 at this site is thought to account largely for the gastric adverse events that complicate therapy with NSAIDs, thus providing the rationale for the development of NSAIDs specific for inhibition of COX-2 (Brunton et al., 2008). Prostaglandins require the cyclooxygenase (COX) enzymes for their production. The COX enzymes are the rate-limiting enzymes in the conversion of arachidonic acid to PGH2, the precursor to all of the prostaglandins (Cesen-Cummings et al., 2000).

PGH synthase-1 (COX-1) is constitutively expressed, i.e., it is always present. In contrast, PGH synthase-2 (COX-2) is inducible, i.e., its expression varies markedly depending on the stimulus. The two isozymes also differ in function in that COX-1 is widely distributed and has "housekeeping" functions, eg, gastric cytoprotection. Two-fold to four-fold increases occur following humoral stimulation. In contrast, COX-2 is an immediate early response gene product in inflammatory and immune cells, and expression is stimulated ten-fold to eighteen-fold by growth factors, tumor promoters, and cytokines.

The prostaglandins differ from each other in two ways:

- In the substituent’s of the pentane ring (indicated by the last letter, eg, E and F in PGE and PGF)
- In the number of double bonds in the side chains (indicated by the subscript, eg, PGE1, PGE2). (Trevor et al., 2011)
1.1.2 Inhibition of prostaglandins biosynthesis by NSAIDS:

NSAIDs have been prominent analgesic/anti-inflammatory/antipyretic medications since 1898 when aspirin was first marketed. All NSAIDs act as inhibitors of the cyclooxygenase active site of COX isozymes. COX-2-selective drugs were introduced in 1999. Important mechanistic differences in the actions of individual NSAIDs with the COX active site are complex (Simmons, et al., 2004).

The COX pathway is of major clinical importance because it is the major pharmacological target of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin. Inhibition of PG synthesis is considered the primary mechanism responsible for both the therapeutic (anti-inflammatory, analgesic) and the toxic effects of non-steroidal anti inflammatory drugs (NSAIDs).

The clinically significant side effects of NSAIDs include renal impairment, dyspepsia, and upper gastrointestinal bleeding, the latter being particularly associated with inhibition of COX1, by comparison, the anti-inflammatory and analgesic effects are associated with COX-2 inhibition, these observations provided the rationale for fast-track development of selective COX2 inhibitors, which were promoted under the premise that they would have similar anti-inflammatory efficacy to conventional NSAIDs but would have significantly fewer gastrointestinal (GI) side effects (Caughey et al., 2005).

Highly selective COX-2 inhibitors have been relatively successful with regard to their reduced GI toxicity. However, based on the role of COX-2 derived PGs in normal physiology, there exists potentiate for other side effects such as
increased cardiovascular events for at-risk patients and aggravated renal impairment in Patients with reduced renal function (Caughey et al., 2005). Since almost all clinically approved NSAIDs preferentially inhibit COX-1 over COX-2(with the exception of meloxicam and nimesulide), the search for selective inhibitors of the COX-2 isoenzyme considered important. (Noreen, et al., 1998).

The prostaglandin endoperoxide H synthases-1 and 2 (PGHS-1 and PGHS2; also cyclooxygenases-1 and 2, COX-1 and COX-2) catalyze the committed step in prostaglandin synthesis. PGHS-1 and PGHS-2 are of particular interest because they are the major targets of non steroidal anti inflammatory drugs (NSAIDs) including aspirin, ibuprofen, and the new COX-2 inhibitors. Inhibition of the PGHSs with NSAIDs acutely reduces inflammation, pain, and fever, and long-term use of these drugs reduces fatal thrombotic events, as well as the development of colon cancer and Alzheimer’s disease.

Therapeutic doses of aspirin and other NSAIDs reduce prostaglandin biosynthesis by blocking COX, and there is a reasonably good correlation between potency as COX inhibitors and anti-inflammatory activity (Trevor et al., 2011).
1.2 Types of prostaglandins

There are two types of prostaglandins:

1.1.2 Natural prostaglandins

Currently, three classes of prostaglandins are recognized, and these are categorized on:

- The basis of the number of double bonds present within the prostaglandin molecule
- The fatty acid from which they are derived. Thus, prostaglandins of the 1 series have one double bond and are derived from dihomo-γ-linolenic acid, those of the 2 series have two double bonds and are derived from arachidonic acid, and those of the 3 series have three double bonds and are derived from eicosapentaenoic acid (Figure 1.4).
Figure 1.4: Natural prostaglandins (Origins of prostaglandin precursors and formation of endoperoxide and leukotrienes) ((Zreik and Behrman, 2008).
1.2.2 Synthetic prostaglandins

Synthetic prostaglandins are analogues or derivatives of prostaglandins that do not occur naturally in the body. They do not include the product of the chemical synthesis of hormonal PGE. Synthetic prostaglandins are used to induce childbirth (parturition) or abortion, to prevent closure of patent ductus arteriosus in newborns with particular cyanotic heart defects, to prevent and treat peptic ulcers, as a vasodilator in ischemia, in pulmonary hypertension, in treatment of glaucoma, to treat erectile dysfunction and used as an ingredient in eyelash and eyebrow growth beauty products. Synthetic prostaglandins namely are misoprostol, enprostil, rioprostil, arabaprostil, metenoprost, lubiprostone etc (Bharathi, 2010).

1.3 Prostaglandins Receptors

PG receptors were initially classified on the basis of functional activities of natural and synthetic agonists, and antagonists. PG receptors were classified into the following categories: DP, EP, FP, IP, and TP. The first letter denotes the prostaglandin type, and the letter P stands for “prostanoid.” Later, studies by binding analysis and molecular cloning confirmed the presence of distinct receptor types as well as three or four subtypes of EP (EP1–4). Plasma membrane prostaglandin receptors belong to the super family of G-protein-coupled receptors characterized by seven transmembrane-spanning regions. Intracellular second messengers of prostaglandin receptors include cAMP, protein kinase C, and calcium. At high concentrations, PGE2 and PGF2α interact with the DP receptor; similarly, PGF2α will activate the EP receptor,
whereas PGD2 and PGE2 will interact with the FP receptor at high concentrations. Most tissues contain a mixture of receptors, which appears to be the basis for the often opposite effects of a particular prostaglandin at different doses (Zreik and Behrman, 2008). Prostaglandin PGs act locally near their sites of formation. The diversity of their effects is explained to a large extent by their interaction with a diverse family of distinct receptors.

All eicosanoid receptors are G protein–coupled receptors that interact with Gs, Gi, or GQ to modulate the activities of adenylyl cyclase and phospholipase C (Brunton et al., 2008). Prostaglandins are very potent local hormones that are synthesized rapidly by wide variety of cells in the body. PGs are released into the extracellular space by specific PG transporters. Once released, PGs bind to their cognate receptors, which belong to the G-protein-coupled receptor (GPCR) super family (Zor et al., 2000). The biological actions of PGs are mediated through G-protein-coupled cell surface receptors, which are coupled to specific signal transduction pathways.

Eight subtypes of PG receptors encoded by separate genes are characterized and include the:

- PGI receptor (IP)
- PGF receptor (FP)
- PGD receptor (DP).
The tissue distributions of these receptors are linked to specific functional roles and can be grouped into three categories based on their signal transduction and activities:

- Relaxant receptors (EP2, EP4, IP, and DP): mediate an increase in cAMP and smooth muscle relaxation.
- Contractile receptors (EP1): mediate an increase in intracellular calcium and smooth muscle cell contraction.

1.4 Physiological Activities of Prostaglandins (Figure 1.5):

1.4.1 Bone Metabolism

Bone remodeling depends on maintaining a delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts is mediated by a number of factors, one of which is PGE2. However, the role of PGs in bone metabolism is somewhat contradictory; in that PGE2 can have both anabolic and catabolic Effects (Hyunil, et al., 2006).

1.4.2 Cancer

The involvement of PGs, in particular those arising from COX-2, in the causation and prevention of cancer has been identified recently.

Much of the evidence has come from epidemiological studies that indicate chronic use of aspirin or other NSAIDs can significantly decrease the risk of developing certain cancers (e.g., colorectal cancer). Additionally, aspirin and
NSAIDs can lower the mortality rates and induce tumor regression from colorectal cancer and other forms of cancer (Caughey et al., 2005).

1.4.3 Cardiovascular

The PGs and TX have central role in the regulation of platelet aggregation and vascular tone and as such are particularly important regulators of the cardiovascular system. TXA2 is a potent vasoconstrictor and inducer of platelet aggregation, whilst PGI2 dilates blood vessels and prevents platelet aggregation (Caughey et al., 2005). There are major effects on smooth muscle and platelets where PGE2 and PGI2 have opposite biological properties to those of PGF2 and TXA2. In this regards, PGE2 and PGI2 mainly promote vasorelaxation while PGF2 and TXA2 act as vasoconstrictors, especially on veins. On platelets, TXA2 induces platelet aggregation where as PGI2 strongly inhibits aggregation (Arroyo and Clària, 2003)

1.4.4 Gastrointestinal System

Of the COX isotypes, only COX-1 is constitutively expressed throughout the gastrointestinal (GI) system, where the main PGs produced are PGE2 and PGI2 both have important cytoprotective effects on the GI mucosa, including reducing gastric acid secretion from stomach parietal cells, increasing mucosal blood flow, and stimulating the release of protective mucus (Caughey et al., 2005).

1.4.5 Inflammation

Inflammation is a complex of sequential and partly recursive cellular and biochemical changes in tissue in response to injury or infection, it is a normal
homeostatic process that protects the host against the effects of every day and incident trauma and invasive microorganisms. However, when this process becomes dysregulated unwanted inflammation and tissue destruction arises. Acute inflammation characterized by hyperemia, pain, edema, and leucocyte infiltration (Caughey et al., 2005).

With the discovery of the isoenzyme COX-2, whose production is induced by inflammation mediators, interest in cyclooxygenase inhibitors has grown. The adverse effects observed with traditional non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and indomethacin, are believed to stem from an inhibition of constitutive COX-1 activity, and it is hypothesized that selective COX-2 inhibitors exhibit an improved safety profile.

PGI2 and PGD2 can exert similar effects. These PGs exert their Hyperalgesia effects by increasing sensitivity of pain receptors to peripheral inflammation. PGE2 dilate vessels leads to tissue swelling with both edema and leucocyte infiltration (Caughey et al., 2005).

1.4.6 Renal

Maintenance of normal kidney functions is dependent on PGE2, which regulates vascular tone, blood flow, sodium, and water homeostasis, and renin secretion. PGE2 can reduce sodium and water reabsorption and mediate the release of renin, which in turn can act to regulate blood pressure control.

Under conditions of increased sodium reabsorption, PGE2 can act as a counter-regulatory factor. PGI2 is involved in potassium secretion by stimulating the renin–angiotensins system (Caughey et al., 2005)
Figure 1.5 The different sites of prostaglandins action in human body (http://faculty.ksu.edu.sa/52876/Postgraduate%20lecture/Prostaglandins%20and%20Leukotrienes.pdf)
1.5 Approved of misoprostol

Misoprostol is a synthetic analogue of naturally occurring prostaglandin E1 originally manufactured for the treatment of gastric and duodenal ulcer. It is an effective drug for ripening the cervix and induction of labour. It is less expensive, easy to handle and is stored at room temperature. Although it is not approved by FDA for this indication, the American College of Obstetricians and Gynecologist advocates misoprostol and it is on the WHO essential drug list for labour induction, however, misoprostol is used off-label for a variety of indications in the practice of obstetrics and gynecology, including medication abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage (Majid et al., 2009).

Other agencies await more evidence to its safety including organizations in Britain Canada and Scandinavia. However, generic forms of misoprostol have become available and it is now licensed for labour induction in Egypt and Brazil, and a licensed induction product was expected in UK sometime in 2008 (Majid et al., 2009) as shown in Figure 1.6.

WHO have two guidelines address induction of labour with misoprostol:

- Selected populations such as women with pre-eclampsia and eclampsia and with unfavorable cervix if a caesarean is unsafe.

- Women who have had in-utero fetal death, who have decreasing platelets and spontaneous labour are not imminent (Arroyo and Clària, 2003).
Figure 1.6: World map of misoprostol approval. Produced by Gynuity Health Projects. Reproduced with permission from Gynuity Health Projects. Copyright © 2008. Access at www.gynuity.org.
1.6 Clinical uses of prostaglandins

Several products of the arachidonate series are of current clinical importance. Alprostadil (PGE1) is used for its smooth muscle relaxing, ulcer and in combination with mifepristone for terminating early pregnancies. PGE2 and PGF2 are used in obstetrics.

PGE1 (alprostadil) may be used in the treatment of impotence. Intracavernous injection of PGE1 causes complete or partial erection in impotent patients who do not have disorders of the vascular system or cavernous body damage. The erection lasts for 1–3 hours and is sufficient for sexual intercourse. PGE1 is more effective than papaverine. The agent is available as a sterile powder that is reconstituted with water for injections, (although it has been superseded largely by the use of PDE5 inhibitors, such as sildenafil, tadalafil, and vardenafil (Trevor et al., 2011).

Prostaglandins and thromboxanes have major effects on four types of smooth muscle: airway, gastrointestinal, reproductive, and vascular. Other important targets include platelets and monocytes, kidneys, the central nervous system, autonomic presynaptic nerve terminals, sensory nerve endings, endocrine organs, adipose tissue, and the eye (the effects on the eye may involve smooth muscle). Latanoprost and several similar compounds are topically active PGF2 derivatives used in ophthalmology.

Prostacyclin (PGI2, epoprostenol) is synthesized mainly by the vascular endothelium and is a powerful vasodilator and inhibitor of platelet aggregation (Trevor et al., 2011).
Prostaglandin E2 vaginal pessaries are currently the agents of choice. These are costly and not easily affordable. A more affordable alternative is to use misoprostol for the induction of labour.

Misoprostol is a synthetic prostaglandin E1 analogue that has been marketed in the United States since 1988 as gastric cytoprotective agent. In distinction to prostaglandin E2 preparations (dinoprostone, Prepidil, Cervidil), misoprostol is inexpensive and available in scored tablets that can be broken and inserted vaginally, despite a focused campaign by the manufacturer to curtail its use in obstetric practice (Ferguson et al., 2002).

Misoprostol appears to heal gastric ulcers as effectively as the (H2-receptor antagonists) however, relief of ulcerogenic pain and healing of duodenal ulcers have not been achieved consistently with misoprostol. This drug currently is used primarily for the prevention of ulcers that often occur during long-term treatment with NSAIDs. In this setting, misoprostol appears to be as effective as the proton pump inhibitor (omeprazole).

Other important targets of PGs include the central and peripheral nervous systems, the gastrointestinal tract and the respiratory and reproductive organs, however, the most important physiological action of PGs is their key role in inflammation, thus, in response to an inflammatory, the release of PGs, and more importantly PGE2, constitute a key event in the development of the three cardinal signs of inflammation: vasodilation (erythema), increased vascular permeability (edema) and appearance of pain (hyperalgesia). In addition, PGs also contribute to the amplification of the inflammatory response by enhancing
and prolonging signals produced by pro-inflammatory agents such as bradykinin, histamine and neurokinins (Arroyo and Clària, 2003)

1.6.1 Uses of prostaglandins (misoprostol) in obstetrics and gynecology

PGs play important regulatory roles in three productive processes of ovulation, implantation, and parturition. Just prior to ovulation, there is an increase in PGE2 synthesis by the pre-ovulatory follicle in response to an increase in luteinizing hormone (LH). Induction of COX-2 (by LH) is necessary for this increase in PGE2 synthesis and for the successful rupture of the follicle. After fertilization, PGs (PGE2 and PGI2) play a role in the successful implantation of the embryo and, again, PGE2 production appears to be COX-2 dependent (Caughey et al., 2005).

Also prostaglandins have strong uterotonic properties and are used widely in obstetric and gynecological practice for cervical ripening, together with mifepristone for termination of pregnancy and for induction of labour. Prostaglandin preparations are available in injectable, tablet or gel forms according to their intended use. Prostaglandins agents do not cause hypertension, which enables them to be used in hypertensive patients (Hofmeyr et al., 2007).

Prostaglandins (PG) stimulate contraction of the pregnant uterus and are the final and common mediators of parturition in all species. In women, all intrauterine tissues are capable of producing prostaglandins, but the fetal membranes, the decidua, and the smooth muscle cells of the myometrium are the sources of prostaglandins at term.
The human uterus is composed of 2 basic parts, the fundus and the cervix. The fundus is composed of 2 layers: the myometrium and endometrium. The myometrium, which is predominantly smooth muscle cells, comprises the wall of the uterus and is the thickest layer. The endometrium, which lines the endometrial cavity, undergoes dramatic changes during the menstrual cycle. It changes little during the menstrual cycle and pregnancy until the onset of cervical ripening (Goldberg et al., 2011).

The human cervix consists mainly of extracellular connective tissue; the predominant molecules of this extracellular matrix are type 1 and type 3 collagen, with a small amount of type 4 collagen at the basement membrane (Goldberg et al., 2011). Both PGF2α and PGE2, through their interaction with specific receptors, are known to stimulate myometrial contractility, leading to an increase in intracellular Ca\(^{2+}\). Such a mechanism of prostaglandin-induced uterine hyper-contractility has been implicated in the pathogenesis of primary dysmenorrhea. Elevated levels of PGF2α and PGE2 have been identified in the endometrium and menstrual fluid of women with dysmenorrhea, and antiprostaglandin agents have been shown to result in a marked reduction in pain in these patients (Zreik and Behrman, 2008).

Throughout pregnancy, human myometrial cells undergo several morphological changes. The appearance of a hypertrophied myometrial smooth muscle cell of pregnancy is distinctive, exhibiting increased cellular dense bodies and plaques as well as increased collagen deposition and extracellular matrix. Moreover, under the changing hormonal milieu of pregnancy,
myometrial cells increase the expression of genes for the oxytocin receptor (OTR), as well as increase their ability to produce prostaglandins at parturition and during labor, myometrial smooth muscle cells have a unique phenotype compared to myometrial cells at other stages of pregnancy or during the menstrual cycle (Cesen-Cummings et al., 2000).

The prostaglandins also exert significant uterotonic effects, thus offering a potential synergy in ripening and induction (Ferguson et al., 2002). A complex series of interactions occurs where by various hormones stimulate the chemical reactions critical for cervical ripening, associated with cervical ripening is an increase in the enzyme cyclooxygenase-2, leading to a local increase of prostaglandin E2 (PGE2) in the cervix. The increase in local PGE2 leads to a series of important changes associated with cervical ripening, including the following:

- Dilation of small vessels in the cervix
- Increase in collagen degradation
- Increase in hyaluronic acid
- Increase in chemotaxis for leukocytes, which causes increased collagen degradation (Goldberg et al., 2012).

As the pregnancy progresses, the uterus increases its contractile response, and the contractile effect of oxytocin is potentiated as well. Dinoprostone stimulates the contraction of the uterus throughout pregnancy, also directly affects the collagenase of the cervix, resulting in softening. The vaginal dose enters the maternal circulation, and a small amount is absorbed directly by the
uterus via the cervix and the lymphatic system. Dinoprostone is metabolized in local tissues and on the first pass through the lungs (about 95%). The metabolites are mainly excreted in the urine. The plasma half-life is 2.5–5 minutes (Trevor et al., 2011).

Evidence from both human and animal studies suggests that essential fatty acids of 6 and n-3series play important and modifiable roles in gestational duration. Consumption of preformed n-3long-chain poly unsaturated fatty acids (n-3LCPUFA) has been shown to increase gestational duration and to decrease the incidence of premature birth in human studies (Mark, et al., 2006). Birth weight and gestational age at birth are critical determinants of infant mortality and morbidity, and in the United States, pre-term birth resulting in low birth weight comprises 6–10% of all births (Trevor et al., 2011).

Dinoprostone is available either as a gel (0.5 mg PGE2) or as a controlled-release formulation (10 mg PGE2) that releases PGE2 in vivo at a rate of about 0.3 mg/h over 12 hours. An advantage of the controlled-release formulation is a lower incidence of gastrointestinal side effects (< 1%). A further advantage of this delivery system is that the medication is contained within a vaginal insert that can be retrieved at any time (Trevor et al., 2011).

Recent data implicating a physiological role of prostaglandins in the regulation of gonadotropin-releasing hormone (GnRH) secretion have been published. A number of reports now suggest that prostaglandins, particularly PGE2, exert stimulatory influences on gonadotropin release, an effect that appears to be mediated by an action at the level of the hypothalamus. In addition, PGE1 and
PGE2 appear to be the most potent stimulators of growth hormone release from cultured adenohypophyseal cells. PGB, PGA1, PGA2, PGB2, PGF1, and PGF2 are also active stimulators, but their effects are not seen at physiological doses. In general, prostaglandins appear not to stimulate gonadotropin secretion by a direct action on the pituitary.

Further evidence suggesting that prostaglandins might affect gonadotropin secretion (by acting directly on the hypothalamus) is supplied from studies using prostaglandin synthetase inhibitors, such as indomethacin, which apparently reduce gonadotropin secretion. After the discovery that indomethacin and aspirin (inhibitors of prostaglandin synthesis) could block ovulation, it was suggested that prostaglandins were involved in the ovarian follicular rupture process (Zreik and Behrman, 2008).

Misoprostol has become an important drug in obstetric and gynecologic practice because of its uterotonic and cervical ripening activity and good safety profile. It is useful in the management of medical and surgical abortion, miscarriage, induction of labour and post partum hemorrhage. Compared to other prostaglandin preparations, misoprostol is inexpensive. It does not require parenteral administration or refrigeration and has few systemic side effects. It can help save maternal life by preventing or treating post partum hemorrhage where other safe alternatives do not exist (Majid, et al., 2009).

1.6.1.1 Use of prostaglandins (misoprostol) in facilitation of labour

Definition of normal labour is the spontaneous onset of regular, painful, uterine contractions associated with the effacement and progression
dilatation of the cervix and descent of the presenting part with or without a ‘show’ or ruptured membranes (Warren and Arulkumaran, 2009).

There are many indications for term labour inductions, including post term pregnancy, preeclampsia, diabetes mellitus, oligohydramnios, intrauterine fetal growth restriction, and abnormal ante partum fetal surveillance result (Cheng et al., 2008).

Induction of labour is the artificial initiation of labour before its spontaneous onset for the purpose of delivery of the fetoplacental unit (Crane and John, 2001).

A number of observations indirectly implicate the involvement of prostaglandins in parturition. It is known, for example, that the administration of indomethacin or other nonsteroidal anti-inflammatory drugs, such as aspirin, prolongs gestation. Moreover, prostaglandins, particularly PGF2α, are known to be potent stimulators of uterine contractility and induce cyclic contractions of the gravid uterus. Elevated prostaglandin concentrations are associated with the onset of spontaneous labour in humans. Furthermore, the period of time preceding the onset of contractions is characterized by plasma PGF2α levels that are equivalent to those of non pregnant women. Immunization against PGF2α also delays the onset of parturition (Zreik and Behrman, 2008).

In 1997, 18.4% of all live births in the United States were pharmacologically or mechanically induced before the onset of spontaneous labor. Since the initial
description of its synthesis in 1953, synthetic oxytocin has been virtually unchallenged as an induction agent for the viable pregnancy. Its favourable efficacy and safety profiles make it one of the most commonly prescribed drugs in the United States today. However, the success of oxytocin induction is highly dependent on three factors: parity, gestational age, and cervical condition at the time of induction. Of these, only cervical condition presents an option for therapeutic intervention. (Ferguson et al., 2002).

The indication for labour has been increasing in the world. It is known that cervical conditions are directly associated to the success of labor induction. Knowledge of cervix anatomy and physiology during pregnancy and of the different methods for cervical ripening is essential for indicating the best cervical ripening method in a given situation, therefore obtaining the best outcomes following labour induction. This is a challenge for obstetricians where not every method is readily available and accessible, cesarean-sections rates are very high. There are some methods including, breast stimulation, membrane stripping, and the use of relaxin, oxytocin, prostaglandins, hyaluronidase mifepristone, laminaria and Foley catheter (Guilherme et al., 2004).

Labour induction is frequently indicated in a woman with an unfavorable cervix, often resulting in prolonged and difficult labour. Failed inductions requiring cesarean delivery are common in this setting.’ Oxytocin and prostaglandins (PGs) are the agents most frequently used for induction of labor.’ Although oxytocin is widely accepted as a safe and effective initiator of
uterine contractions, its success is dependent on the condition of the cervix at the beginning of induction (Romas et al., 1997).

A variety of cervical ripening agents exist, yet none is ideal. Many have been studied in non–high-risk populations (Ferguson et al., 2002).

There are many different situations in obstetric where there is the need for labour induction in women with unripe cervices. This indication stems from a situation where the continuation of pregnancy may be life-threatening for the mother and/or fetus. Such induction is frequently prolonged, exhausting and very often unsuccessful, resulting in a cesarean section (Aquino and Cecatti, 2003)

Among the pharmacological agents used for labour induction, oxytocin and prostaglandins are the most common. Several studies have shown that continuous intravenous infusion of oxytocin is less efficient, particularly when there are unfavorable cervical conditions, leading frequently to a cesarean section, because of induction failure. In such cases, another pharmacological agent, perhaps a prostaglandin should be used to favour cervical ripening, at least initially (Aquino and Cecatti, 2003)

Among prostaglandins, prostaglandin E1, E2, and F2α have been studied most extensively. Prostaglandins affect cervical stroma by effecting recruitment both of extracellular matrix destructive components and of hyaluronic acid, with which lipophilia increases cervical sub mucosal water content. The prostaglandins also exert significant uterotonic effects, thus offering a potential synergy in ripening and induction. (Ferguson, et al., 2002) Theoretically, PGE2
and PGF2 should be superior to oxytocin for inducing labour in women with Preeclampsia-eclampsia or cardiac and renal diseases because, unlike oxytocin, they have no antidiuretic effect. In addition, PGE2 has natriuretic effects. However, the clinical benefits of these effects have not been documented. In cases of intrauterine fetal death, the prostaglandins alone or with oxytocin seem to cause delivery effectively (Trevor et al., 2011).

Numerous studies have shown that PGE2, PGF2, and their analogues effectively initiate and stimuli labour. However, this is an unlabeled use, there are appear to be no difference in the efficacy of the two drugs when they are administered intravenously, but PGF2 is one tenth as potent as PGE2. These agents and oxytocin have similar success rates and comparable induction-to-delivery intervals. (Trevor et al., 2011)

Misoprostol, is a synthetic E1 methyl analogue prostaglandin, is at present receiving more attention as a cervical modifying agent and labour inductor, as it has the advantages of low cost, stability in relation to temperature, easy handling and storage, and also easy administration (vaginal or endocervical). However, there is still a need to better establish its safety so as to avoid hyper-stimulation syndrome, which could result in undesirable consequences for the newborn (Smith et al., 2000).

Misoprostol has, over the past several years, gained widespread acceptance as both a labour induction and a cervical ripening agent. Such off-label indication has been endorsed by the American College of Obstetricians and Gynecologists and other medical bodies. However, a growing body of anecdotal literature
exists concerning misoprostol-related complications, such as uterine rupture, fetal death, and increased frequencies of meconium passage, neonatal acidemia, and cesarean delivery for fetal distress. These are likely the result of its uterotonic properties, which can be excessive and difficult to reverse (Ferguson et al., 2002).

1.6.1.2 Use of prostaglandins (misoprostol) in abortion

Definitions of successful abortion: some studies define success abortion as complete abortion such that no curettage is required. This definition is similar to the definition used for successful medical abortion (Borgatta and Kapp 2011).

In 2000, the FDA approved medication abortion using 600 mg of oral mifepristone, a progesterone antagonist, with 400 µg of oral misoprostol 48 hours later for pregnancies up to 49 days of gestation (Allen and Brien. 2009).

Termination of pregnancy is one of the most common procedures in gynecological practice. Vacuum aspiration has been used for first trimester termination of pregnancy (Ngail et al., 2000).

Prostaglandins are now used to induce early labour and abortion; indeed, prostaglandin is the drug of choice for accomplishing midtrimester abortions (Zreik and Behrman, 2008).

PGE2 and PGF2 have potent oxytocic actions. The ability of the PGE and PGF prostaglandins and their analogues to terminate pregnancy at any stage by promoting uterine contractions has been adapted to common clinical use.
Many studies worldwide have established that prostaglandins administration efficiently terminates pregnancy. The drugs are used for first- and second-trimester abortion and for priming or ripening the cervix before abortion. These prostaglandins appear to soften the cervix by increasing proteoglycan content and changing the biophysical properties of collagen.

Antiprogestins (eg, mifepristone) have been combined with an oral oxytocic prostaglandin (eg, Misoprostol) to produce early abortion (Trevor et al., 2011).

A combination of mifepristone followed by a prostaglandin analogue is the preferred non-surgical method for inducing abortion in the second trimester when mifepristone is not available, as is the situation in many countries, abortion can also be induced safely with prostaglandin analogues, such as misoprostol alone, a large variety of different regimens have been described in the literature, and no commonly approved guide-lines on misoprostol use were available (Hertzen et al., 2009).

Medical abortion with a combination of mifepristone and Misoprostol is safe and effective alternative to Suction & Evacuation (Sonali, et al 2010). The main advantage of medical abortion is that it allows women to avoid the risks of surgery and anesthesia

PGF2 is available for clinical gynecological use, this drug, carboprost tromethamine (15-methyl-PGF2). Carboprost is used to induce second-trimester abortions and is usually administered as a single 2.5 mg intra-amniotic injection. The abortion is normally completed in less than 20 hour (Trevor et al., 2011). The most serious adverse effects of this route of
administration involve cardiovascular collapse. Most of the reported cases have been diagnosed as anaphylactic shock, but others may have been due to the drug escaping into the circulation and causing severe pulmonary hypertension. In pregnant anesthetized women, PGF2, 300 g/min intravenously, doubles pulmonary resistance and increases the work of the right side of the heart threefold. Thus, only minimal amounts of the 40 mg intra-amniotic dose need to reach the circulation to cause cardiovascular effects. This problem may be avoided by instilling the drug under ultrasonic guidance.

Intramuscular injection of carboprost tromethamine can also be used to induce abortion. Unlike the one-time intrauterine instillation of dinoprost, carboprost is given repeatedly up to the total dose of 2.6 mg normally required to cause abortion. Intra-amniotic administration has close to a 100% success rate, with fewer and less severe adverse effects than intravenous administration (Trevor et al., 2011).

1.6.1.3 Use of prostaglandins (misoprostol) in post partum hemorrhage

By definition, postpartum hemorrhage (PPH) refers to a blood loss of more than 500 ml (or 1000 ml during a caesarean section, after the delivery of the fetus. However, this is an ‘arbitrary’ value, as patients with a low Body Mass Index (BMI) may have a low blood volume (70 ml/kg) (Warren and Arulkumaran, 2009).
Postpartum hemorrhage is excessive bleeding after childbirth is one of the leading causes of maternal mortality in the developed world (Ford et al., 2007).

Active management of third stage of labour is very important in reducing the blood loss and prostaglandins are known to have good therapeutic role in the management of postpartum haemorrhage (Mustafa et al., 2007).

Postpartum haemorrhage (PPH) is a major cause of morbidity and mortality during childbirth, especially in low- and middle-income countries. Traditionally, oxytocin and ergot preparations have been used as uterotonic agents for PPH prophylaxis mostly as part of active management of the third stage of labour. These agents, although effective in decreasing the blood loss, have the disadvantage of instability in tropical climates and also require syringes and trained personnel for administration. Another disadvantage, mainly related to ergot preparations, is the relatively high incidence of side-effects such as nausea, vomiting and increase in blood pressure. Prostaglandins have been mainly used for intractable PPH as a last resort when other measures fail (Hofmeyr et al., 2007).

The prostaglandins alone or with oxytocin seem to cause delivery effectively. In some cases of postpartum bleeding, 15-methyl-PGF2 will successfully control hemorrhage when oxytocin and methylergonovine fail to do this. (Trevor et al., 2011).

Misoprostol, an E1 prostaglandin analogue, is apotent uterotonic agent whose usefulness is increasingly recognized in obstetric and gynecological practice, including in the control of PPH (Prata et al., 2006).
Misoprostol can be administered orally, rectally, vaginally, or sublingually without syringes or intravenous equipment, and it is inexpensive, easy to store and stable at room temperature. Studies comparing the results of prophylactic use of misoprostol for the reduction of blood loss with conventional uterotonics have concluded that misoprostol had a positive effect. Although some studies have found that conventional uterotonics were superior to misoprostol, none has rejected using misoprostol when injectable uterotonics are not available or cannot be properly used (Prata et al., 2006).

1.6.2.4 Use of prostaglandins (misoprostol) in dysmenorrheal

Primary dysmenorrhea is attributable to increased endometrial synthesis of PGE2 and PGF2 during menstruation, with contractions of the uterus that lead to ischemic pain. NSAIDs successfully inhibit the formation of these prostaglandins and so relieve dysmenorrhea in 75–85% of cases. Some of these drugs are available over the counter. Aspirin is also effective in dysmenorrhea, but because it has low potency and is quickly hydrolyzed, large doses and frequent administration are necessary. In addition, the acetylation of platelet COX, causing irreversible inhibition of platelet TXA2 synthesis, may have an adverse effect on the amount of menstrual bleeding (Trevor et al., 2011).

1.7 Adverse Effects of Prostaglandins

The adverse effects of the prostaglandins are moderate, with a slightly higher incidence of nausea, vomiting, and diarrhea than that produced by oxytocin. PGF2 has more gastrointestinal toxicity than PGE2. Neither drug has significant maternal cardiovascular toxicity in the recommended doses
In fact, PGE2 must be infused at a rate about 20 times faster than that used for induction of labour to decrease blood pressure and increase heart rate. PGF2 is a bronchoconstrictor and should be used with caution in persons with asthma; however, neither asthma attacks nor bronchoconstriction have been observed during the induction of labor. Although both PGE2 and PGF2 pass the fetoplacental barrier, fetal toxicity is uncommon. (Trevor et al., 2011)

The effects of oral PGE2 administration (0.5–1.5 mg/h) have been compared with those of intravenous oxytocin and oral demoxytocin, an oxytocin derivative, in the induction of labour. Oral PGE2 is superior to the oral oxytocin derivative and in most studies is as efficient as intravenous oxytocin. However, the only available form of PGE2 in the USA at present is dinoprostone for vaginal administration, and by this route of administration the drug is slightly less effective than oxytocin. Vaginal PGE2 is also used to soften the cervix before inducing labor. Oral PGF2 causes too much gastrointestinal toxicity to be useful by this route (Trevor et al., 2011).
1.8 Rationale

Traditionally, oxytocin has been used for a long time for induction of labour, but its use is sometimes accompanied with many side effects. Misoprostol is a synthetic prostaglandin $E_1$ analogue that is used off-label for a variety of indications in the practice of obstetrics and gynecology, including medication abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage. Due to its wide-ranging applications in reproductive health, misoprostol is on the World Health Organization Model List of Essential Medicines. This study was selected and designed to evaluate the clinical problems of obstetrics and gynecology in which misoprostol can be used, especially problems of labour induction, medication abortion and postpartum hemorrhage and how to overcome these problems by the used one of the prostaglandins analogues, misoprostol.

1.9 Objectives

1.1.9 General Objectives

The main objective of this study is to evaluate the clinical uses of the prostaglandin analogue, misoprostol in obstetrics and gynecology at Elhassahessa Teaching Hospital.

1.2.9 Specific Objectives

- Assessment of the use of different doses of misoprostol in labour induction, medication abortion, and postpartum hemorrhage.
- Determination of the side effects of the use of misoprostol in obstetrics and gynecology.
CHAPTER TOW

MATERIAL AND METHODS
2. Materials and Methodology

2.1 Methods

2.1.1 Study Area

This study has been conducted at Department of Obstetrics and Gynecology, Elhassahessa Teaching Hospital, Central Sudan, during the period of January up to April 2012. Elhassahessa Teaching Hospital is a governmental hospital contains different departments. The Department of Obstetrics and Gynecology provides obstetrics and gynecological services to a great number of patients in Elhassahessa City and surrounding villages in Gezira State.

2.1.2 Study population

The present study was designed mainly to evaluate the clinical uses of the prostaglandin analogue (misoprostol) in obstetrics and gynecological problems in particular induction of labour, medication abortion and treatment of postpartum hemorrhage.

The study population composed of 221 files of pregnant women. They were selected according to the type of case (clinical condition) in which misoprostol was indicated for induction of labour, medication abortion and treatment of postpartum hemorrhage. The pregnant women who received other type of uterotonics rather than misoprostol, those delivered normally without induction, women who delivered by elective caesarean section and those treated for abortion without the use of misoprostol (e.g. evacuation) were excluded from this study.
Ethical approval for this study has been obtained from the Ethical Committee of Elhassahessa Teaching Hospital and from the Ethical Committee of The Department of Obstetrics and Gynecology.

2.1.3 Study Design

This was a retrospective study, used to collect data from a group of specified pregnant women at Elhassahessa Teaching Hospital, Department of Obstetrics and Gynecology, between the period of January to April 2012.

Especial forms were designed to collect the data from files and records of 212 pregnant women who came voluntary to Department of Obstetrics and Gynecology and treated with different doses of misoprostol for induction of labour, medication abortion and treatment of postpartum hemorrhage. The pregnant women had been followed up to evaluate their treatment with different doses of misoprostol by a number of specialists in Obstetrics and Gynecology in the Department of Obstetrics and Gynecology.

The special designed form composed of different questions about the age of pregnant women, the type of case for which misoprostol was used (either labour induction, medication abortion or postpartum hemorrhage) the dose of misoprostol, the different route of administration (orally, vaginally, sublingual, orally plus vaginally, sublingual plus vaginally. It also contains the type of outcomes in the case of labour induction (live baby or stillbirth) and in case of abortion the type of outcomes (complete abortion or partial abortion) after used of misoprostol. There were also questions about the exposure of pregnant women to operation section after use of misoprostol in case of labour induction.
(cesarean section) or medication abortion (evacuation). The side effects after use of misoprostol (pyrexia, bleeding, placenta retention and pain) and an induction interval for delivery (1-4, 4-24, and more than 24 hours) were also included in this form.

2.2 Material
Misoprostol 200 (Mesotac) tablets (Sigma Tau, Sudan)

2.3 Statistical analysis:
Data were analyzed using statistical program for social sciences (SPSS) version 17. The t-test of significance was used to compare numerical values, and the Chi-square test was used to compare percentages. A $P$ values less than or equal to 0.05 were considered as statistically significant.

…
2.4 The special designed form for study

University of Gezira/Faculty of pharmacy

1. Serial No.

2. Age

   ( ) 20-25 ( ) 25-30 ( ) 30-45

3. Type of case

   ( ) Labor induction ( ) medication abortion ( ) postpartum hemorrhage

4. Prostaglandins used

   ( ) Misoprostol ( ) Dinoprostone ( ) other

5. The route of administration:

   ( ) Orally ( ) IV ( ) IM ( ) vaginal (pessaries) ( ) cervix gel

6. The dose of misoprostol:

   ( ) 50mcg ( ) 100mcg ( ) 200mcg ( ) other

7. In case of labor induction (the type of outcome):

   ( ) Live baby ( ) stillbirth

8. In case of abortion (the type of outcome):

   ( ) Complete abortion ( ) partial abortion

9. Exposure of pregnant women to operation section after used prostaglandin (misoprostol): ( ) Yes ( ) no

10. Side effect after used of prostaglandins:

    ( ) diarrhea ( ) vomiting ( ) bleeding ( ) pain ( ) hypotension

11. Induction interval for delivery (after used one of misoprostol)

    ( ) 1-4 hour ( ) 4-24 hour ( ) more than 24 hour

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CHAPTER THREE

RESULTS AND DISSUCTION
3. Results and Discussion

3.1 The use of misoprostol in relation to age

The use of the prostaglandin analogue (misoprostol) in different age groups of pregnant women, showed that 91 (42.92%), 80 (37.74%) and 41 (19.34%) patients were used misoprostol in the age groups of 18-25, 26-33 and 34-41 respectively (Table 3.1 and Figure 3.1). This finding indicated that misoprostol can be used in different age groups of the pregnant women according to the type of case and clinical condition.

As shown in Table 3.1 and Figure 3.1, the majority of the pregnant women (n=171) who used misoprostol were among the age group of 18-33, which is the reproductive age of women in which all cases (labour induction, medical abortion or postpartum hemorrhage) can occur.

Table 3.1: Age distribution of pregnant women (n= 212)

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-25</td>
<td>91</td>
<td>42.92</td>
</tr>
<tr>
<td>26-33</td>
<td>80</td>
<td>37.74</td>
</tr>
<tr>
<td>34-41</td>
<td>41</td>
<td>19.34</td>
</tr>
<tr>
<td>Total</td>
<td>212</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure 3.1 Age distribution of pregnant women (n= 212)

3.2. Type of case (clinical condition)

Regarding to the clinical condition (type of case) in which misoprostol was used, the obtained results revealed that 118 (55.7%) of the pregnant women used misoprostol for labour induction, while 91 (42.9) of them administered it for medication abortion and only 3 (1.4%) pregnant women used it in treatment of postpartum hemorrhage.

According to this study, it was evident that misoprostol is mainly used for labour induction and/or medication abortion purposes (n=209; 98.6%) while a few number of pregnant women (n=3; 1.4%) used it in treatment of postpartum hemorrhage. These results agreed with that reported by Memon and Sikandar (2007) who stated that misoprostol has been found to be safe when used for induction of labour in resource constrained hospital settings in developing countries where basic clinical tools for monitoring may be used.
Also the obtained findings concerning labour induction matched the results of Majid, et al., (2009) who reported that induction of labour is a common procedure on the labour ward, and it is performed for a variety of conditions, some being relevant to maternal health while in others the fetal health and well being after birth is the main consideration. With an unripe cervix, induction of labour may be difficult and unsuccessful, thus use of agents to ripen the cervix prior to conventional methods of induction is the standard practice. Prostaglandin (E1) is most frequently used for ripening the cervix and induction of labour.

Regarding to the treatment of postpartum hemorrhage (PPH) using misoprostol, this study found that only three pregnant women used it in this purpose. That means misoprostol is rarely used in treatment of PPH and this agreed with that mentioned by Elhassan (2008) who reported that currently is insufficient evidence to support the routine use of misoprostol to prevent postpartum hemorrhage when oxytocin or ergometrine is available.

**Table 3.2: Type of case in which misoprostol is used:**

<table>
<thead>
<tr>
<th>Type of case</th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labour induction</td>
<td>118</td>
<td>55.7</td>
</tr>
<tr>
<td>Medication Abortion</td>
<td>91</td>
<td>42.9</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>212</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Figure 3.2 Type of case in which misoprostol used

3.3. Route of administration of misoprostol:

The routes of administration by which misoprostol was used were shown in Table 3.3 and Figure 3.3. It was found that, intravaginal route was the main route of administration by which misoprostol was administered to pregnant women (n=125; 59%), while 77 (36.3%) pregnant women, given misoprostol intravaginally and sublingually. A few number of pregnant women (n=6; 2.8%) received misoprostol orally and only one woman (n=1; 0.5%) administered it sublingually.

It was evident that the intravaginal route of administration was safe and effective, especially for labor induction and this on line with that mentioned by Abbasi et al., (2008) and Majid et al., (2009) who reported that the use of misoprostol per vaginal was useful and helpful for labour induction in
unfavorable cervix, and also misoprostol appeared to be more effective than conventional methods of cervical ripening and labour induction. On the other hand Japir and Smeet (2009) found that intravaginal and oral application of misoprostol was equally effective in achieving cervical dilatation.

When the sublingual route of administration was compared to intravaginal route alone or intravaginal plus sublingual, it was found that the sublingual route was less effective than the other two routes, although Shah et al., (2010) found that sublingual and intravaginal misoprostol were both equally effective for the medical management of missed miscarriage although their overall effectiveness is low within the first 24 hours.

In this study, the oral route of administration appeared to be not commonly used and less effective than intravaginal route. Borgatta and Nathalie (2011) mentioned that vaginal administration was associated with shorter induction times compared to oral administration.

**Table 3.3: Route of administration of misoprostol**

<table>
<thead>
<tr>
<th>Type of route</th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orally</td>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>Vaginal</td>
<td>125</td>
<td>59</td>
</tr>
<tr>
<td>Sublingual</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Orally + vaginally</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>Sublingual + vaginally</td>
<td>77</td>
<td>36.3</td>
</tr>
<tr>
<td>Total</td>
<td>212</td>
<td>100</td>
</tr>
</tbody>
</table>
3.4. Outcomes of using misoprostol for labor induction

To evaluate the outcomes of misoprostol use in case of labor induction, there are two types of outcomes, live baby and still birth. The obtained results showed that the number of the live babies were 103 (48.6%), stillbirth 17 (8%) and the missing were 92 (43.4%) that means the majority were live babies (Table 3.4 and Figure 3.4).

These findings agreed with the studies of Majid et al., (2009) and Allen and Brien (2009) in which they found that there was no peri-natal death after use of, misoprostol which has also been shown to be effective for induction of labor with a viable fetus.
Table 3.4: Outcomes of using misoprostol for labor induction

<table>
<thead>
<tr>
<th>Type of outcome</th>
<th>Frequency</th>
<th>Percent (%)</th>
<th>Valid percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valid Live baby</td>
<td>103</td>
<td>48.6</td>
<td>85.8</td>
</tr>
<tr>
<td>Valid Still baby</td>
<td>17</td>
<td>8</td>
<td>14.2</td>
</tr>
<tr>
<td>Valid total</td>
<td>120</td>
<td>56.6</td>
<td>100</td>
</tr>
<tr>
<td>Missing</td>
<td>92</td>
<td>43.4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>212</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3.4: Outcomes of using misoprostol for labor induction
3.5 Exposure of pregnant women to operation section after use of misoprostol

As shown in Table 3.5 and Figure 3.5 number of pregnant women exposure to caesarian section after use of misoprostol were 98 (46.2%), while the rest (n=114; 53.8%) did not. This indicated that, when misoprostol was used for medication abortion and/or labour induction the rate of caesarian section was declined. These results agreed with that reported by Cheng et al., (2008) who mentioned that, there was a significant lowering in cesarean section delivery rates in the women who received the misoprostol regimen.

Table 3.5: Exposure of pregnant women to operation section after use of misoprostol

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>98</td>
<td>46.2</td>
</tr>
<tr>
<td>no</td>
<td>114</td>
<td>53.8</td>
</tr>
<tr>
<td>total</td>
<td>212</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure 3.5: Exposure of pregnant women to operation section after use of misoprostol

3.6 Different doses of misoprostol used for different cases

Misoprostol which is used in this was vaginal tablet 200mg. Table 3.6 and Figure 3.6 showed that the most commonly used dose of misoprostol was 50 mg (quarter of the tablet) followed by 800 mg, which were used by 96 (45.3%) and 73 (34.4%) respectively. Also Table 3.6 and Figure 3.6 demonstrated other doses ranging between 100 mg and more than 800 mg used by different pregnant women.

For labor induction the quarter of the tablet (50 mg) was first administered to pregnant women, when delivery did occur another dose was given (100mg) after four hours. If there was no response another dose was repeated after four hours until delivery took place.
In this study 96 (45.3%) pregnant women delivered after quarter of misoprostol tablet (50 mg), 15 (7.1%) after half of the tablet (100 mg), 7 (3.3%) after one tablet of misoprostol. That means misoprostol was very effective for labour induction when small doses were used. This agreed with that reported by Majid et al., (2009) who found that most women delivered with a single insertion of quarter of misoprostol tablet (50mg), while few others given a second dose.

The second dose (100mg) was only given in case of no improvement in uterine contraction. This second dose was only given in case of no improvement in bishop score or non-establishment of regular uterine contractions and was not given before 6 hours of the first dose. The subsequent dose of misoprostol was withheld in the presence of at least 3 regular uterine contractions in 10 minutes, active phase of labour (Abbasi et al., 2008).

The doses of 800mg were used mainly in cases of medication abortion; although surgical abortion is safe when done properly some women choose medication abortion, especially those at younger age.
### Table 3.6: Different doses of misoprostol used for different cases

<table>
<thead>
<tr>
<th>Dose of misoprostol</th>
<th>Frequency</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50mg</td>
<td>96</td>
<td>45.3</td>
</tr>
<tr>
<td>100mg</td>
<td>15</td>
<td>7.1</td>
</tr>
<tr>
<td>200mg</td>
<td>7</td>
<td>3.3</td>
</tr>
<tr>
<td>400mg</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>600mg</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>800mg</td>
<td>73</td>
<td>34.4</td>
</tr>
<tr>
<td>50+100mg</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>50+200mg</td>
<td>6</td>
<td>3.8</td>
</tr>
<tr>
<td>More than 800mg</td>
<td>8</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>212</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

![Figure 3.6: Different doses of misoprostol used for different cases](image-url)
3.7: Side effect of misoprostol use

The use of misoprostol by pregnant women resulted in different side effects as shown in Table 3.7 and Figure 3.7, in which two women (0.9%) suffered from vomiting, one (0.5%) affected by diarrhea, 44 (20.8%) experienced hypotension, and 48 (22.6%) women suffered from pain, while 112 (52.8%) of the pregnant women did not show any side effects. Surprisingly two pregnant women (0.9%) experience hypotension and pain at the same time and 3 (1.4%) suffered from bleeding.

The use of misoprostol was found to cause vomiting and diarrhea and this agreed with that mentioned by Abbasi et al., (2009) who reported that the used of misoprostol was less frequency cause vomiting and diarrhea compared with other side effects.

The hypotension and pain as side effects of misoprostol use were occasionally occur (Sonali et al., 2010) and pain associated with use of misoprostol sometimes requiring analgesic. This study revealed that majority of pregnant women did not experience any side effect, indicating that misoprostol is quite safe and effective and can be used in different problems of obstetrics and gynecology. The obtained results agreed with that reported by Majid (2009) who found misoprostol vaginal insert was safe and effective drug for induction of labour in term, parous women.
Table 3.7: Side effect of misoprostol use

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Number of female</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vomiting</td>
<td>2</td>
<td>.9</td>
</tr>
<tr>
<td>diarrhea</td>
<td>1</td>
<td>.5</td>
</tr>
<tr>
<td>hypotension</td>
<td>44</td>
<td>20.8</td>
</tr>
<tr>
<td>pain</td>
<td>48</td>
<td>22.6</td>
</tr>
<tr>
<td>No side effect</td>
<td>112</td>
<td>52.8</td>
</tr>
<tr>
<td>Hypotension + pain</td>
<td>2</td>
<td>.9</td>
</tr>
<tr>
<td>bleeding</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>total</td>
<td>212</td>
<td>100</td>
</tr>
</tbody>
</table>
3.8: Induction interval for delivery after use of misoprostol

The induction interval for delivery is a time from induction of labour until pregnant women delivered. As shown in Figure 3.8 and Table 3.8 the number of pregnant women who delivered vaginally after use of misoprostol (to produce labour induction) and did not require cesarean section operation were 80 (37.7%) pregnant women. The remaining female patients (n=132; 63.3%), had been either delivered after labour induction and subjected to cesarean section or aborted.

Therefore to find out the induction interval for delivery, those pregnant women (n=80) who delivered vaginally were concerned. Out of those eighty pregnant women, there were 9 (11.2%), 55 (68.8%) and 16 (20%) women, their induction...
interval for delivery were 1-4, 4-24 and more than 24 hours respectively. These results indicated the majority of pregnant women, their rate of induction interval for delivery when misoprostol was used were between 4-24 hours. The obtained results were on line with that reported by Abbasi et al., (2009) who found that vaginal misoprostol appeared to be fairly safe and effective for cervical ripening in the third trimester, and it has an increased rate of vaginal delivery within 24 hours without significant difference in caesarean section rate and fetal outcomes. Moreover it can be used in circumstances where extensive monitoring techniques are not available but close observation and vigilance is mandatory. They also agreed with that mentioned by Majid et al., (2009) who found that induction to delivery time ranged between 5 hours to 16 hours.

**Table 3.8: Induction interval for delivery after use of misoprostol**

<table>
<thead>
<tr>
<th>Induction interval</th>
<th>frequency</th>
<th>Percent%</th>
<th>Valid percent%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 hours</td>
<td>9</td>
<td>4.2</td>
<td>11.3</td>
</tr>
<tr>
<td>4-24 hours</td>
<td>55</td>
<td>25.9</td>
<td>68.8</td>
</tr>
<tr>
<td>More than 24 hours</td>
<td>16</td>
<td>7.5</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>37.7</td>
<td>100</td>
</tr>
<tr>
<td>Missing</td>
<td>132</td>
<td>62.3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>212</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
3.9. Cross tabulation between type of cases and exposure of pregnant women to operation section after use of misoprostol

When the different types of cases after use of misoprostol and exposure of pregnant women to caesarian section were crossed tabulated, there were 40 (40.8%) pregnant women in case of labour induction were exposed to caesarian section while 78 (68.8%) women were not. Regarding the other case of medication abortion there were 57 (58.2%) pregnant women were exposure to caesarian section, while 34 (29.8 %) pregnant women were not. But in case of postpartum hemorrhage only 1(1%) pregnant woman was exposed to section, while 2 (1.8) were not. This indicated that misoprostol was more effective for
labour induction compared to its use for medication abortion or postpartum hemorrhage.

**Table 3.9: Cross tabulation between type of cases and exposure of pregnant women to operation section after use of misoprostol**

<table>
<thead>
<tr>
<th>Type of cases</th>
<th>Exposed pregnant women to operation section after use misoprostol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Labour induction</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>40.8%</td>
</tr>
<tr>
<td>Abortion</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>58.2%</td>
</tr>
<tr>
<td>Post partum hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Total</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

P-value = 0.00
Conclusion

- At Elhassahessa Teaching Hospital, Department of Obstetrics and Gynecology, the type of prostaglandins that most commonly used was misoprostol, because it is available, affordable and stable at room temperature.

- Misoprostol was the most commonly agent used for labour induction and medication abortion rather than postpartum hemorrhage.

- The common route of administration of misoprostol among different types of cases was intravaginal route for labour induction and intravaginal plus sublingual route for abortion and postpartum hemorrhage.

- In case of labor induction after use misoprostol by pregnant women there were two types of outcomes, live baby (n=103; 85.8%) and stillbirth (n=17; 14.2%).

- For the different cases, there were different doses of misoprostol have been used for labour induction (50mg), medication abortion (800mg) and post partum hemorrhage (800mg).

- The induction interval for delivery for most of the pregnant women was ranging between 4 to 24 hours.
Recommendation

- Misoprostol is very effective agent for labour induction; therefore it can be administered to pregnant women when there is an unripe cervix.

- The use of misoprostol was accompanied with different side effects such as vomiting and hypotension, thus some precautions are required to avoid such side effects.

- Although misoprostol can be used in treatment of postpartum hemorrhage, but further studies are recommended.

- A clear protocol or guidelines are crucially needed to determine the different doses of misoprostol in cases of labour induction, medication abortion and postpartum hemorrhage.
CHAPTER FOUR

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