

**In Vitro and In Vivo Release
of Levonorgestrel from
"Procopper I, II" and "Metraplant"**

Thesis

Submitted in Partial fulfillment for the Degree of M.D
Obstetrics and Gynaecology

By

Nagwa Ibrahim Mohamed

M.B.,B.Ch.,M.Sc. (Obstetrics and Gynaecology)

Under Supervision of

Prof. Dr. Mohamed Ezz EL-Din Aly Azzam

Professor of Obstetrics and Gynaecology
Faculty of Medicine, Ain Shams University

Prof. Dr. Adel Mohamed Gamal EL-Mesery

Professor of Parasitology and Director of M.R.C.
Faculty of Medicine, Ain Shams University

Prof. Dr. Magd EL-Din Magd EL-Din Mohamed

Professor of Obstetrics and Gyneacology
Faculty of Medicine, Ain Shams University

Dr. Mohamed Ahmed EL-Kadi

Lecturer of Obstetrics and Gynaecology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University

2007

Acknowledgement

Acknowledgment

I would like to express my deepest gratitude and appreciation to ***Prof. Dr. Mohamed Ezz El-Din Aly Azzam***, Professor of Obstetrics and Gynaecology, for his great support, assistance and fatherly guidance throughout this work.

I would like also to express my special thanks to ***Prof. Dr. Adel Mohamed Gamal El-Mesery***, Professor of Parasitology and Director of M.R.C., for his kind assistance and advice during all the phases of this work.

Many thanks to ***Prof. Dr. Magd El-Din Magd El-Din Mohamed***, Prof. of Obstetrics and Gynaecology, for his kind guidance and help throughout this work.

Finally, many thanks to ***Dr. Mohamed Ahmed El-Kadi***, Lecturer of Obstetrics and Gynaecology, for his assistance and advice throughout the work.

List of Contents

LIST OF CONTENTS

TITLE	PAGE
Chapter I :	
<i>Introduction and Aim of the Work</i>	1
Chapter II :	
<i>Review of Literature</i>	5
- History of Intrauterine contraceptive devices	5
- History of Hormone releasing LNG IUCD	6
- Pharmacokinetics of LNG IUCD	12
- Mode of Action of LNG IUCD	13
- Physiological Effects of LNG IUCD	16
- Clinical Performance of LNG IUCD	22
- Safety Considerations of LNG IUCD	29
- Non Contraceptive Indications of LNG IUCD	40
- Problems of LNG IUCD	50
Chapter III :	
<i>Patients & Methods</i>	53
- Invitro Study	53
- Invivo Study	55
Chapter IV :	
<i>Results</i>	61
- Invitro Results	61
- Clinical Results	87
Chapter V :	
<i>Discussion</i>	116
Chapter VI :	
<i>Summary</i>	127
<i>References</i>	131
<i>Arabic Summary</i>	

List of Tables

LIST OF TABLES

Table (II-1)	Mean plasma E ₂ and LNG concentrations (Pg/mL) in menstruating and amenorrhoeic women using LNG-IUD	21
Table (II-2)	Cumulative life-table pregnancy rates per 100 users by IUD type compaired study	23
Table (II-3)	Pregnancy rates in different age groups expressed by using pearl rates during five years of use	25
Table (II-4)	Cumulative life-table expulsion rates per 100 users by types of IUDs and study	26
Table (II-5)	Summary of possible non-contraceptive uses of the hormone releasing intra-uterine systems	50
Table (II-6)	Summary of potential problems with hormone releasing intrauterine systems and possible solutions	52
Table (IV-1)	Comparison between the release rate of the LNG from the three types of IUCDs in the 1 st week	61
Table (IV-2)	Comparison between the mean concentration of the release rate of LNG from the three IUCDs during the 2 nd week	68
Table (IV-3)	Comparison between the release rate of LNG from the three types of IUCDs in the 1 st week and 2 nd week	70

Table (IV-4)	Comparison between the mean concentration release rate of LNG from the three IUCDs during the period 1-5 years	76
Table (IV-5)	Comparison between the mean concentration of the LNG release during the 1 st and 2 nd week (short term release) with that after 1y-5y (long term release) in procopper I IUCD	81
Table (IV-6)	Comparison between the mean concentration of the LNG release during the 1 st and 2 nd weeks (short term release) with that after (1y-5y) long term release in procopper II IUCD	83
Table (IV-7)	Comparison between the mean concentration of LNG release during the 1 st and 2 nd week (short term release) with that after 1-5y (long term release) in Metraplant IUCD	85
Table (IV-8)	Comparison between mean age and parity in different groups	87
Table (IV-9)	Comparison between mean concentration of serum level of LNG in ng/ml among three groups at different measuring time	90
Table (IV-10)	Comparison between bleeding index at different measuring time in different groups	105
Table (IV-11)	Comparison between bleeding score at different measuring time in different groups	107
Table (IV-12)	Correlation between serum conc. Versus bleeding index and score in different groups of women using the LNG releasing IUCD	109

List of Figures

LIST OF FIGURES

Fig. (II-1)	The levonorgestrel-releasing IUD	10
Fig. (II-2)	Metraplant IUCD	10
Fig. (II-3)	Procopper IUCD	11
Fig. (II-4)	Insertion instructions of Mirena IUD	39
Fig. (IV-1)	Mean concentration of release rate from the three IUDs types during 1 st week	62
Fig. (IV-2)	Release pattern of LNG during the days of the 1 st week from the three IUCDs	63
Fig. (IV-3)	Release profile of levonorgestrel (LNG) using HPLC (Standard Curve)	64
Fig. (IV-4)	Release profile of LNG from Metraplant IUCD in invitro medium during 1 st week using HPLC	65
Fig. (IV-5)	Release profile of LNG from Procopper II IUCD in invitro medium during 1 st week using HPLC	66
Fig. (IV-6)	Release profile of LNG from Procopper I IUCD in invitro medium during 1 st week using HPLC	67
Fig. (IV-7)	Mean concentration of LNG release from the three IUCDs during the 2 nd week	69
Fig. (IV-8)	Release pattern of the LNG during the days of the 2 nd week from the three IUCDs	71

Fig. (IV-9)	Pattern of release rate of LNG from the three IUCDs during the days of 1 st and 2 nd week	72
Fig. (IV-10)	Release profile of LNG from Metraplant IUCD in invitro medium during 2 nd week using HPLC	73
Fig. (IV-11)	Release profile of LNG from Procopper II IUCD in invitro medium during 2 nd week using HPLC	74
Fig. (IV-12)	Release profile of LNG from Procopper I IUCD in invitro medium during 2 nd week using HPLC	75
Fig. (IV-13)	Release pattern of LNG during the period 1-5 y	77
Fig. (IV-14)	Release profile of LNG from Metraplant IUCD in invitro medium during 1-5 y using HPLC	78
Fig. (IV-15)	Release profile of LNG from Procopper II IUCD in invitro medium during 1-5 y using HPLC	79
Fig. (IV-16)	Release profile of LNG from Procopper I IUCD in invitro medium during 1-5 y using HPLC	80
Fig. (IV-17)	Mean concentration of the LNG release during the 1 st and 2 nd week (short term release) with that after 1y-5y (long term release) in procopper I IUCD	82

Fig. (IV-18)	Mean concentration of the LNG release during the 1 st and 2 nd weeks (short term release) with that after (1y-5y) long term release in procopper II IUCD	84
Fig. (IV-19)	Mean concentration of LNG release during the 1 st and 2 nd week (short term release) with that after 1-5y (long term release) in Metraplant IUCD	86
Fig. (IV-20)	Mean age in the different groups	88
Fig. (IV-21)	Mean parity in different groups	89
Fig. (IV-22)	Mean serum concentration of the three groups of women wearing the LNG IUCDs at different time of sampling	91
Fig. (IV-23)	Mean serum concentration in the three groups of women wearing the LNG releasing IUCDs at different time of smapling	92
Fig. (IV-24)	Release profile of LNG from serum sample taken from woman using Metraplant IUCD after 1 month	93
Fig. (IV-25)	Release profile of LNG from serum sample taken from woman using Metraplant IUCD after 3 month	94
Fig. (IV-26)	Release profile of LNG from serum sample taken from woman using Metraplant IUCD after 6 month	95

Fig. (IV-27)	Release profile of LNG from serum sample taken from woman using Metraplant IUCD after 1 year	96
Fig. (IV-28)	Release profile of LNG from serum sample taken from woman using Procopper II IUCD after 1 month	97
Fig. (IV-29)	Release profile of LNG from serum sample taken from woman using Procopper II IUCD after 3 month	98
Fig. (IV-30)	Release profile of LNG from serum sample taken from woman using Procopper II IUCD after 6 month	99
Fig. (IV-31)	Release profile of LNG from serum sample taken from woman using Procopper II IUCD after 1 year	100
Fig. (IV-32)	Release profile of LNG from serum sample taken from woman using Procopper I IUCD after 3 month	102
Fig. (IV-33)	Release profile of LNG from serum sample taken from woman using Procopper I IUCD after 6 month	103
Fig. (IV-34)	Release profile of LNG from serum sample taken from woman using Procopper I IUCD after 1 year	104
Fig. (IV-35)	Comparison between bleeding index at different measuring time in different groups	106

Fig. (IV-36)	Bleeding score at different measuring time in different groups	108
Fig. (IV-37)	Scatter diagram showing the relation between concentration and bleeding index ..	110
Fig. (IV-38)	Scatter diagram showing the relation between conc. and bleeding score	111
Fig. (IV-39)	Scatter diagram showing the relation between conc. and bleeding index	112
Fig. (IV-40)	Scatter diagram showing the relation between conc. and bleeding score	113
Fig. (IV-41)	Scatter diagram showing the relation between conc. and bleeding index	114
Fig. (IV-42)	Scatter diagram showing the relation between conc. and bleeding score	115

List of Abbreviations