

Hazem El -Refaey MD MRCOG,

Consultant in Obstetrics & Gynaecology.

Qualifications:

MBBCh, Cairo University June 1981;
MRCOG, November 1990;
MD with commendation, Aberdeen Univ. November 1994

Career history:

April 1998- March 2002

Senior Lecturer Obstetrics & Gynaecology
Academic Department of Obstetrics and Gynaecology,
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May 1994 - March 1998

Senior Registrar Obstetrics & Gynaecology
University College London Hospitals NHS trust
Honorary Lecturer UCL Medical School

Jan 1992 - May 1994

Registrar and Research Fellow,
Department of Obstetrics & Gynaecology
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SUMMARY OF ACADEMIC ACHIEVEMENTS

During the last decade I developed interest in the therapeutic uses of prostaglandins as a means of myometrial stimulation. Myometrial stimulation is an integral part of Obstetrics and Gynaecology and hence I have led several research projects in the fields of miscarriage, induction of abortion, the management of the third stage of labour, management of post partum haemorrhage and methods of induction labour. I am the first author on a number of publications in the *British Medical Journal*, *Lancet*, *New England Journal of Medicine* and the *British Journal of Obstetrics & Gynaecology*. These publications and pioneering studies have drawn wide scientific interest and a number of leading commentaries have been published about them. My work in the fields of miscarriage and induction of abortion constituted the bulk of my MD thesis which I obtained from the University of Aberdeen with commendation. The gap between research and the implementation of its result is usually large. The results of my studies have been implemented exceptionally quickly in clinical practice.

MISCARRIAGE

Miscarriage is the most common complication of pregnancy and accounts for around 50,000 inpatient admissions in the UK each year. Generally management is a well established routine that has changed little compared to other areas of gynaecological practice. My work in this area was published in the *BMJ* in 1992 and 1993. It has demonstrated for the first time the feasibility of managing miscarriage medically without resort to surgery.

The medical regimens that were developed in the management of miscarriage are now widely applied in many Scottish hospitals. In some, more than 50% of patients with miscarriage resort to the medical approach rather than surgery. An **editorial** in the *BMJ* referred to these studies with the following remark: '*...a medical approach to such a common gynaecological condition has implications for both the health service and patients. It would substantially reduce the surgical workload resulting from miscarriage, thereby freeing time on routine operating list for other cases.*' Editorial. *BMJ* (1993); 306: page 876.

This work has attracted the attention to the possibility of changing and improving the management of such a common problem. I am aware of at least one large study that has been successfully funded to compare expectant, medical and surgical management of miscarriage.

ABORTION

In 1993 and 1994 I investigated methods to improve surgical and medical abortion technology. The observations and findings produced from this research programme generated broad interest and led to a wide change in practice at least in the UK. Recently the Royal College of Obstetricians & Gynaecologists recommended that the

main findings of our research to be implemented in routine clinical practice. They graded the current evidence of our initial findings as Class A evidence (*Induced Abortion, Guideline No 11, July 1997*).

Independently a leading American researcher in the field made similar recommendations in a recent meta analysis which heavily quoted our work (*Grimes: Obs & Gyn: May 1997: 790-795*)

MANAGEMENT OF INTRAUTERINE FETAL DEATH

Intrauterine fetal death is a distressing complication for all involved: patients obstetricians and midwives. Inducing labour in these cases is usually a protracted procedure. I published three randomised trials in *Human Reproduction* and the *British Journal of Obstetrics and Gynaecology* in 1994 and 1995 in which I modified the established prostaglandin regimen to induce evacuation of the uterus in the second and third trimester. This modification led to a considerable reduction in the duration of the procedure. The results were further confirmed upon joining UCH where the regimens became routine practice and the induction to delivery interval was reduced from a median of 18 hours to 8 hours. Whilst the evidence from the published literature is not completely conclusive as yet, our findings were robust enough for the Royal college of Obstetricians and Gynaecologists to refer to its potential (*Induced Abortion, Guideline No 11, July 1997*).

THE MANAGEMENT OF THE THIRD STAGE OF LABOUR

In 1995 and 1996 I started developing a new method to manage the third stage of labour. Such management has not changed for the last half a century. The world wide mortality associated with bleeding during the third stage of labour is responsible for more than 200,000 maternal deaths every year. There is therefore a need for an effective oral medication which could be used to curtail this problem. The *Essential Drugs Task Force of the WHO* admitted that the search for such an agent has been largely unsuccessful over the last 5 decades (*Hogerzeil, H.V et al (1993) Stability of injectable oxytocics in tropical climates World Health Organisation, Geneva*)

I have investigated the use of the oral prostaglandin E1 analogue, misoprostol, in the management of the third stage of labour in more than 1400 patients so far. This new approach seemed promising and we have published in the *Lancet* and the *British Journal of Obstetric and Gynaecology* our initial results and have just completed a randomised study. I believe that the results of this work could have world wide implications.

Since post partum haemorrhage is a leading cause of maternal death globally, I decided to contact the WHO, rather than seeking funding for a local British study. In 1996 I visited the WHO Safe Motherhood Program steering group in Geneva and presented our initial results. Without delay, they adopted our project and on the basis of our findings they have succeeded in securing funding from the World Bank of more than one million dollars to conduct a multinational study in 10 countries involving 20,000 patients. I sit on the steering Committee of this large study.

The development of misoprostol as an agent to manage the third stage of labour has fired the enthusiasm of several research groups around the world : I am now aware that the Asian and Oceanic Federation of Obstetric & Gynaecology is planning their own multicentre study in south East Asia. Another two large studies are now underway in South Africa and the United States.

PROSTAGLANDINS

The effects of prostaglandins on the cervix, myometrium and blood pressure has been at the centre of my research activities over the last 5 years. Basic scientific and physiological studies on the myometrium and cervix were essential in guiding me to the changes required in treatment regimens and dosages to achieve the required clinical effects. They were also necessary to provide evidence before pursuing larger clinical trials. The value of these studies are specially highlighted in research in the third stage of labour where basic physiological studies provided indisputable proof that encouraged me to pursue clinical studies. Throughout the last 6 years I have:

-Examined histochemical and microscopic changes induced in the human cervix by prostaglandins on the cervix (*Lancet 1994*).

- Looked at blood pressure changes in response to different prostaglandin dosages in early pregnancy (*BJOG 1994*).

- Looked at different methods of manipulating myometrial contractility in the early pregnant uterus by antiprogesterones and prostaglandins and compared the oral to the vaginal route (*FIGO proceedings : Zurich 1996 : In press*).

-Assessed postpartum uterine contractility in response to oxytocin, Syntometrine and different prostaglandins. Different routes of administration were also examined (*work done in conjunction with Professor Arulkumarun in Singapore: now submitted to BJOG*)

- We are currently investigating the use of misoprostol for the induction of labour.

These studies involved co-operation with teams outside obstetric departments: scientists, physicians and medical physicists. In many of these studies I have attempted to adopt the expertise and methodology used in other disciplines to further our research programmes. This exercise proved beneficial and was a great learning opportunity for me.

M.D THESIS

The projects which were organised in Aberdeen constitute the basis of my MD thesis, which was submitted to the University of Aberdeen in June 1994. In November 1994, I passed my MD oral examination and was awarded an MD degree with

commendation. The thesis is entitled 'The Role of Misoprostol in Evacuation of The Pregnant Human Uterus'.

Peer Reviewed Publications:

1. Khan RU, El-Refaey H, Sharma S, Sooranna D, Stafford M. Oral, rectal, and vaginal pharmacokinetics of misoprostol. *Obstet Gynecol*. 2004 May;103(5 Pt 1):866-70.
2. Khan RU, El-Refaey H. Pharmacokinetics and adverse-effect profile of rectally administered misoprostol in the third stage of labor. ***Obstet Gynecol***. 2003 May;101(5 Pt 1):968-74.
3. Lokugamage AU, Forsyth SF, Sullivan KR, **El Refaey H**, Rodeck CH. Randomized trial in multiparous patients: investigating a single vs. two-dose regimen of intravaginal misoprostol for induction of labor. ***Acta Obstet Gynecol Scand***. 2003 Feb;82(2):138-42.
4. Lokugamage AU, Forsyth SF, Sullivan KR, **El Refaey H**, Rodeck CH. Dinoprostone versus misoprostol: a randomized study of nulliparous women undergoing induction of labor. ***Acta Obstet Gynecol Scand***. 2003 Feb;82(2):133-7.
5. Lokugamage AU, Paine M, Bassaw-Balroop K, Sullivan KR, **Refaey HE**, Rodeck CH. Active management of the third stage at caesarean section: a randomised controlled trial of misoprostol versus syntocinon. ***Aust N Z J Obstet Gynaecol Suppl***. 2001 Nov;41(4):411-4.
6. Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L, Abdel-Aleem H, Cheng L, Hofmeyr G, Lumbiganon P, Unger C, Prendiville W, Pinol A, Elbourne D, **El-Refaey H**, Schulz K. (2001) WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. ***Lancet***. 2001 Sep 1;358(9283):689-95.
7. Lokugamage AU, Sullivan KR, Niculescu I, Tigere P, Onyangunga F, **El-Refaey HE**, Moodley J, Rodeck CH. (2001) A randomized study comparing rectally administered misoprostol versus Syntometrine combined with an oxytocin infusion for the cessation of primary post partum hemorrhage. ***Acta Obstet Gynecol Scand***. Sep;80(9):835-9.
8. Chong YS, Chua S, **El-Refaey H**, Choo WL, Chanrachakul B, Tai BC, Rodeck C, Arulkumaran S. Postpartum intrauterine pressure studies of the uterotonic effect of oral misoprostol and intramuscular syntometrine. ***BJOG***. 2001 Jan;108(1):41-7
9. Le Roux PA, Pahal GS, Hoffman L, Nooh R, **El-Refaey H**, Rodeck CH. (2001) Second trimester termination of pregnancy for fetal anomaly or death: comparing mifepristone/misoprostol to gemeprost. ***Eur J Obstet Gynecol Reprod Biol***. Mar;95(1):52-54.
10. **El-Refaey H**, Nooh R, O'Brien P, Abdalla M, Geary M, Walder J, Rodeck C. (2000) The misoprostol third stage of labour study: a randomised controlled comparison between orally administered misoprostol and standard management. ***BJOG*** Sep;107(9):1104-10.
11. O'Brien, **El-Refaey** et al (1998) Rectally administered Misoprostol for treatment of post-partum haemorrhage unresponsive to oxytocin and ergometrine; a descriptive study. *Obstet Gynaecol* 92 (2) 212 – 4

12. **El-Refaey H.**, O'Brien P., Morafa W., Walder J., Rodeck C. (1997) Use of oral Misoprostol for the prevention of post-partum haemorrhage. *Br J Obs Gyn*, **104**, 336-339

13. **El-Refaey H.**, O'Brien P., Morafa W., Walder J., Rodeck C. (1996) Misoprostol for third stage of labour. *Lancet*, **347**, 1257.

14. **El-Refaey H.**, Rajasekar, D., Abdalla, M., Calder, L., Templeton, A. (1995) Early induction of abortion with mifepristone (RU 486) and misoprostol: a randomised comparison between the oral and vaginal administration of misoprostol. *N Engl J Med* **332**, 983-987.

15. **El-Refaey H.** & Templeton, A. (1995) Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: a randomised comparison between two misoprostol regimens. *Hum Reprod* **10**, 475-478.

16. Hinshaw, K., **El-Refaey H.**, Rispen, R. & Templeton, A. (1995) Mid-trimester termination of pregnancy for fetal abnormality - advantages of a new regimen using mifepristone in combination with misoprostol. *Br J Obs Gyn* **102**, 559-560.

17. Penney, G. C., Mckessock, L., Rispen, R., **El-Refaey H.**, Templeton, A. (1995) An effective, low cost regimen for early medical abortion. *The British Journal of Family Planning* **21**, 5-6.

18. **El-Refaey H.**, Calder, L., Wheatly, D., & Templeton, A (1994). Cervical priming with misoprostol: a clinical and histochemical study. *Lancet* **343**, 1207 - 9.

19. **El-Refaey H.** & Templeton, A. (1994) Early abortion induced by a combination of mifepristone and oral misoprostol: A comparison between two dose regimens of misoprostol and of their effect on blood pressure. *Br J Obs Gyn* **101**, 792 - 6.

20. **El-Refaey H.** & Templeton, A (1994) Early pregnancy termination induced by a combination of oral mifepristone and misoprostol administered vaginally. *Contraception* **49**, 111 - 114

21. **El-Refaey H.**, Hinshaw, K. & Templeton, A. (1993) The abortifacient effect of misoprostol in the second trimester. A randomised comparison with gemeprost in patients pre-treated with mifepristone (RU486). *Hum Reprod* **8**, 1744 - 6.

22. Henshaw, R., Cooper, K., **El Refaey H.**, Smith, N. & Templeton, A. (1993) The medical management of miscarriage: non surgical uterine evacuation of incomplete and inevitable spontaneous abortion. *Br Med J* **306**, 894 - 5.

23. **El-Refaey H.**, Hinshaw, K., Henshaw, R., Smith, N. & Templeton, A. (1992) Medical management of missed abortion and anembryonic pregnancy. *Br Med J* **305**, 1399.

Reviews and chapters in Textbooks

1. **El-Refaey H.**, Rodeck C. Post-partum haemorrhage: definitions, medical and surgical management. A time for change. *Br Med Bull*. 2003;67:205-17.

2. Lokugamage AU, **Refaey HE**, Rodeck CH.: Misoprostol and pregnancy: ever-increasing indications of effective usage. *Curr Opin Obstet Gynecol*. 2003 Dec;15(6):513-8.

3. Sharma S, **El-Refaey H.** Prostaglandins in the prevention and management of postpartum haemorrhage **Best Pract Res Clin Obstet Gynaecol.** 2003 Oct;17(5):811-23.
4. Sunita Sharma and **Hazem El-Refaey** Postnatal Problems: Post Partum Haemorrhage. **Evidence based Obstetrics :.A companion volume to High risk pregnancy.** edited by David James, Kassam Mohamed, Peter Stone, Wim Van Wijngaarden, Lyndon Hill. and others Elsevier Science 2002 Chapter 48.1
5. Sunita Sharma and **Hazem El-Refaey** Postnatal Problems: Other Problems of the third stage. **Evidence based Obstetrics :.A companion volume to High risk pregnancy.** edited by David James, Kassam Mohamed, Peter Stone, Wim Van Wijngaarden, Lyndon Hill. and others Elsevier Science 2002 Chapter 48.2
6. Rehan Khan and **Hazem El -Refaey** Post Partum Haemorrhage and third stage of labour. **Obstetrics and Gynaecology Clinical and basic science** edited by Murdo elder Imperia;l college press and World Scientific www.icpress.co.uk 2001 Chapter
7. Eric Jauniaux , Kaminopeters, P, **Hazem El Refaey,** : *Early Pregnancy Loss in Fetal medicine: Basic science and clinical practice* (2000) , ed Charles Rodeck & Martin Whittle (Chapter)
8. **El-Refaey, H** Termination of pregnancy: methods, safety and recent developments. **in Foetal medicine: Basic science and clinical practice** (2000) , ed C. H. Rodeck & M. Whittle (Chapter)
9. **El Refaey H** Kingdom J *Postpartum Haemorrhage : aetiology diagnosis and therapeutic strategies: in Oxford textbook of critical care.* (1999) ,ed Webb A, Shapiro M, Singer M and Suter, P. , (Chapter)
10. O'Brien P **El Refaey H.** (March 1997:27-32): The Management of the third stage of labour using misoprostol in low risk women **Contemporaray Obstetrics and Gynaecology,** (Review)
11. **El-Refaey H,** Jauniaux E: *Methods of induction of labour in Current opinion in Obstetrics and Gynecology* 1997, 9:375-378 , (Review)
12. **El-Refaey H.** (1995) Misoprostol: esoteric uterotonicity revealed or the place of misoprostol in the evacuation of the human pregnant uterus. **Fertility Control Reviews** 4, 19-21. , (Review)