URINARY TRACT INFECTION AND PRE-ECLAMPSIA IN PREGNANCY: INCIDENCE OF URINARY TRACT INFECTION IN PRE-ECLAMPTIC/ECLAMPTIC PATIENTS AND IN A CONTROL GROUP OF NON-PRE-ECLAMPTIC PATIENTS ADMITTED TO A TERTIARY LEVEL HOSPITAL: A CASE-CONTROL STUDY

THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MMED (OBSTETRICS AND GYNAECOLOGY) OF THE UNIVERSITY OF CAPE TOWN

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For my beloved wife Netsi and my children Mutsa and Tari for their constant encouragement, enormous patience, profound understanding , and deep inspiration

DECLARATION

I, Claitos Chidakwa, do hereby declare that the work contained in this thesis entitled 'Urinary Tract Infection and Pre-eclampsia in Pregnancy: A case-control study of the incidence of urinary tract infection in pre-eclamptic/eclamptic patients and in a control group of non-pre-eclamptic patients' is my original work and any included work done by others has been duly acknowledged.

This study was carried out in the Maternity Centre at Groote Schuur Hospital while working as a registrar in the Department of Obstetrics and Gynaecology at the University of Cape Town in partial fulfilment of the requirements for the degree of MMed (Obstetrics and Gynaecology)

Signed by candidate

Dr Claitos Chidakwa MB CHB

6 October 2009

CERTIFICATE

This is to certify that the study entitled 'Urinary Tract Infection and Pre-eclampsia in Pregnancy: A case-control study of the incidence of urinary tract infection in pre-eclamptic/eclamptic patients and in a control group of non-pre-eclamptic patients' conducted in the Maternity Centre at Groote Schuur Hospital was undertaken by Dr Claitos Chidakwa under our supervision.

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ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
CI	Confidence interval
CRP	C-reactive protein
CSU	Catheter specimen urine
EOPET	Early onset pre-eclampsia
HELLP	Haemolysis,elevated liver enzymes, low platelet count
HIV	Human immunodeficiency virus
IUFD	Intrauterine fetal death
IUGR	Intrauterine growth restriction
LOPET	Late onset pre-eclampsia
MSU	Mid-stream urine
mcs	microscopy culture and sensitivity
NK cell	Natural Killer cell / lymphocyte
OR	Odds Ratio
PET	Pre-eclampsia / eclampsia
PlGF	Placental growth factor
PPROM	Preterm prelabour rupture of membranes
PROM	Prelabour rupture of membranes
sEng	soluble form of Endoglin
sFlt-1	soluble fms-like tyrosine kinase-1
SIRS	Systemic inflammatory response syndrome
SLE	Systemic lupus erythematosus
STBM	Syncytiotrophoblast microparticle
TGF-ß	Transforming growth factor-ß
TNF-a	Tumour necrosis factor-a
UTI	Urinary tract infection
VEGF	Vascular endothelial growth factor

ABSTRACT

Background: Some studies have found a positive association between UTI in pregnancy and the development of PET yet other studies have not found any such association.

Objective: To determine the incidence of UTI in PET patients and thus determine if there is an association between UTI and PET.

Design: Case-control study

Setting: Tertiary level referral Maternity Centre at Groote Schuur Hospital, University of Cape Town, South Africa.

Population: Referred patients at gestation 20 weeks and above. The sample comprised 166 cases (PET) and 257 controls (non-PET).

Methods: Cases and controls were clinically assessed for UTI on admission and their MSU or CSU sent for mcs.

Results: A total of 423 women were recruited into the study made up of 166 cases and 257 controls. A participant with any UTI was significantly less likely to be a case (OR 0.29; 95% CI 0.15-0.59, p=0.001). A one week increase in gestation was associated with a 0.83 times the odds of being a case, compared to a control (95% CI, 0.80-0.87, p<0.001). Parous women had 0.32 times the odds of being a case compared to nulliparous women, this was significant (95% CI 0.18-0.56, p<0.001). Participant's age was not associated with case-control status.

Conclusion: Participants with PET were less likely to have UTI. There was no positive association between UTI and PET. Nulliparity was found to be a risk factor for development of PET in pregnancy. PET was more likely to occur in earlier gestations rather than late in the third trimester. Age seemed not to be a risk factor for PET in this study.

I INTRODUCTION

Pre-eclampsia (PET) occurs in 2-6% of all pregnant women. However, geographic, racial, and socio-economic differences can result in an even higher incidence in some populations (34). It is a major cause of maternal and perinatal mortality and morbidity particularly in poorly resourced countries. In South Africa complications of hypertension, of which PET is the major cause, are the second most common cause of primary obstetric maternal death, after non-pregnancy related infections (62). It is estimated that about 40000 women die each year worldwide as a result of pre-eclampsia/eclampsia (65).

Despite the devastating effects of pre-eclampsia, the precise aetiology of this condition remains largely elusive. In recent years extensive research has been concentrated in this area and as a result a number of hypotheses and theories have emerged. Currently there are two main theories of the pathogenesis of pre-eclampsia (65). Both theories are centred on the placenta as the primary source of the condition. This is also supported by the fact that the only definite treatment of pre-eclampsia is the removal of the placenta.

1 The Two-Stage Model:

In this theory it is postulated that there is relative reduction in placental perfusion as a result of abnormal placentation and/or maternal disease at the microvascular level. This then triggers release of circulating factors that target maternal vascular endothelium causing endothelial dysfunction and consequently the maternal multisystem, multiorgan disorder which characterises this condition. This disorder is called pre-eclampsia. It is also thought that there are maternal factors antedating the index

pregnancy which then determine the patient's increased susceptibility to the disease. One of the factors which is receiving the most attention in this regard is the genetic characteristics of the patient.

2 The Continuum Theory:

Normal pregnancy is characterised by an inflammatory response and it is therefore postulated that pre-eclampsia is an exaggerated form of this inflammatory response. The placenta is believed to release excessive amounts of trophoblastic debris when it is hypoperfused, or when it is large as in multiple pregnancy and diabetes, setting into motion this exaggerated systemic inflammatory response syndrome (SIRS). Susceptible women releasing normal amounts of trophoblastic debris can also mount this abnormal SIRS (51). Suggested trophoblastic debris include tumour necrosis factor alpha (TNFa), lipid peroxides, syncytiotrophoblast microfragments(STBMs) and vascular endothelial growth factor (VEGF). Based on the continuum theory it has been hypothesized that infection in pregnancy might be involved in amplifying SIRS and consequently increase the risk of pre-eclampsia. A recent systematic review and meta-analysis has suggested that urinary tract infection in pregnancy increases the risk of pre-eclampsia (11). In this review of seventeen studies involving a total of 7317 pre-eclamptic patients twelve studies reported an association between UTI and increased risk of PET and five studies found no such association. Of note is that thirteen of these studies were carried out in developed countries (Europe, North America and Australia) where the prevalence of PET is much lower than in developing countries such as South Africa. The authors recommend that more studies are required to verify this association. To date we are not aware of any such study that has been conducted and published in Africa. If such an association can be

established conclusively, antibiotics could then play a very crucial role as part of the armamentarium in the fight against this disease. It is on the above background and on the basis of the continuum theory that this case-control study was carried out in an attempt to shed some more light with regards to the relationship between UTI in pregnancy and PET in the South African setting with its high prevalence of PET.

II LITERATURE REVIEW

1 Introduction

Pre-eclampsia/eclampsia (PET) occurs in 2-6% of all pregnant women and is a major cause of maternal and perinatal mortality and morbidity in all societies and especially in poorly resourced countries. It is the commonest cause of iatrogenic prematurity (3, 46). About 5-7% of nulliparous women are affected by this condition (35). However, geographic, racial and socio-economic differences do result in even higher incidence in some populations. In South Africa complications of hypertension, of which PET is the major contributor, are the second most common cause of primary obstetric maternal death after non-pregnancy related infections (62). It is estimated that four million women develop PET worldwide each year and that of these about 40 000 die (35, 65).

There is general consensus that PET arises as a result of abnormal interaction between the trophoblast and decidua, generalized vascular dysfunction, and exaggerated systematic inflammatory response syndrome (SIRS). Why this should occur precisely and why not all women with similar phenotypic characteristics are affected is still unanswered. It is conceivable that this is a multifactorial condition in

which genetic, immunological, environmental, and nutritional factors are involved.

In recent years extensive research has taken place and is still ongoing in an attempt to unravel the precise aetiology of PET. As a result two main hypotheses on the pathogenesis of PET have gained prominence (49, 51). Both hypotheses are centred on the placenta as the primary focus of this condition. This is supported by the fact that the only definite treatment of PET is the removal of the placenta. It is also well known that normal pregnancy is associated with a low-grade systemic inflammatory response (SIRS). The role of this response in PET is under the spotlight and it is now believed that this response is exaggerated in women with PET and is critical in the pathogenesis of this condition.

2 Immunopathology

2.1 Inflammatory or innate immune system:

The inflammatory/innate immune system is believed to play a central role in the pathogenesis of PET. It comprises a number of interacting elements. These include inflammatory leucocytes (granulocytes, macrophages, monocytes, Natural Killer {NK} cells), endothelial cells, platelets, cytokines, chemokines, complement system, coagulation factors, adipocytes and hepatocytes (1, 55).

It is now known that endothelial cells play a key role in the innate immune system. They are involved in presentation of antigens to T lymphocytes, production of pro-inflammatory cytokines, activation of the innate immune system through their receptors and stimulation of

inflammatory leucocytes (19, 55). As already mentioned above normal pregnancy is associated with a low grade inflammatory state. Physiological features of normal pregnancy are in fact components of the acute phase inflammatory response as evidenced by leucocytosis; increased phagocytosis; raised serum levels of cytokines e.g. interleukin-6 and tumour necrosis factor-α (TNF-a); elevated levels of plasma fibrinogen; elevated levels of plasminogen activator inhibitor 1; elevated levels of complement, especially C3; and a raised C-reactive protein (CRP) (55).

3 Hypotheses on the pathogenesis of PET:

Redman and Sargent have postulated two models for the pathogenesis of PET, namely the 2-stage model and the continuum theory.

3.1 The Two-stage Model (Redman, 1991):

In classical PET, which includes PET before 34 weeks or early onset PET (EOPET), it is postulated that the disease occurs in 2 stages. In stage I, which is asymptomatic, there is abnormal placentation and/or maternal microvascular disease leading to reduced placental perfusion, ischaemia and hypoxia. Deficient placentation is probably due to abnormal immune interaction between paternal antigens on the trophoblast and maternal decidual NK lymphocytes (8, 14, 15, 55, 60). Placental ischaemia and hypoxia, accompanied by increased trophoblast apoptosis, then trigger off the release of circulating anti-angiogenic factors from the placental trophoblast and endothelial cells (7, 9, 26, 32, 38). These events lead to further stimulation of the basal SIRS of normal pregnancy which becomes exaggerated. The exaggerated SIRS results in widespread endothelial activation,

damage and dysfunction causing profound disturbances in blood flow, vascular function and arterial blood pressure (19, 47, 58, 70). This is referred to as stage II or the maternal clinical syndrome, characterized by hypertension, proteinuria, eclampsia, HELLP syndrome etc. Hypertension is a direct consequence of widespread vasoconstriction whereas proteinuria results from glomerular endotheliosis and podocyte detachment (7).

One of the two circulating anti-angiogenic factors strongly implicated in the transformation of the disease process from stage I to stage II is the soluble fms-like tyrosine kinase-1 (sFlt-1) which is a receptor for vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) (9, 26, 40). It binds these two growth factors such that even though their total serum levels increase during pregnancy, their free form is drastically reduced in patients with PET. This has a negative impact on placental angiogenesis (32). Studies have shown that levels of sFlt-1 begin to rise during the second part of pregnancy which implies that the processes leading to placental ischaemia and hypoxia will have begun earlier on (7). Some investigators have found out that sFlt-1 levels begin to rise significantly about 5 weeks before the onset of PET (7).

The other circulating factor gaining recognition in the linkage between stage I and stage II is the soluble form of endoglin (sEng) which is a co-receptor for transforming growth factor-β (TGF-β) types 1 and 3 (24). This impacts negatively on TGF-β angiogenic function and its nitric oxide-dependent vasodilation role (7).
Administration of sEng and sFlt-1 to pregnant rats was accompanied by severe PET and HELLP syndrome in one study (7).

3.2 The Continuum Theory (51):

In non-classical PET, which includes the mild to moderate forms of PET and PET after 34 weeks or late onset PET (LOPET), there is no demonstrable clear evidence of impaired cytotrophoblast invasion or impaired placentation. Hence there is no stage I in this form of PET (54). It is postulated that this form of PET is primarily due to exaggeration of the normal physiological trophoblast apoptosis and exaggerated SIRS which has progressed to a point of decompensation (17, 52, 53). It is suggested that exaggerated SIRS could be due to an infectious insult occurring in pregnancy (34, 59, 66, 71). Urinary tract infection is being singled out as the most likely infection to trigger off such an exaggerated SIRS (6, 11, 25, 34, 41, 63). Therefore in this model PET is seen as an extreme end of a continuum of SIRS of normal pregnancy which has resulted in decompensation of different body systems thus creating the clinical maternal syndrome.

In conditions associated with hyperplacentosis such as diabetes mellitus, molar pregnancy, and multiple pregnancy, the large and/or relatively hypoperfused ischaemic placentas show accelerated trophoblast apoptosis accompanied by increased shedding of trophoblast debris such as syncytiotrophoblast microparticles (STBM's), tumour necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), and lipid peroxidase (9, 23, 27, 51, 54). This debris is believed to amplify SIRS resulting in PET.

Certain medical conditions are accompanied by low-grade systemic inflammation in both men and non-pregnant women (55). These conditions include diabetes mellitus, chronic arterial disease, chronic

hypertension and obesity. If these conditions exist in a pregnant woman, then the normal SIRS of pregnancy is further elevated and it is therefore not surprising that such women are at a higher risk of developing PET.

4. Consequences of placental ischaemia / hypoxia:

The above 2 hypotheses help us to try and make sense of this intriguing condition but the full story is yet to be told. A lot of questions remain unanswered. However, from what we now know it appears that placental ischaemia / hypoxia plays a pivotal role in the pathogenesis of PET, especially in EOPET. It sets into motion a whole cascade of events starting with release of sFlt-1 and sEng which inhibit the angiogenic functions of VEGF, PlGF and TGF-β. There is also release of cytokines e.g. TNF-α and interleukin-6 and trophoblastic debris e.g. STBM's and lipid peroxidase, both leading to SIRS and widespread endothelial activation, damage and dysfunction. This in turn causes systemic vasoconstriction due to raised endothelial production of endothelin, thromboxane, and reactive oxygen radicals; reduced endothelial production of nitric oxide and prostacyclin (natural vasodilators), and increased vascular sensitivity to angiotensin II (which is suppressed in normal pregnancy despite high serum levels of angiotensin II) (32). The end result of all the above events is the multi-system, multi-organ disorder we call PET.

5. Role of maternal infection in the pathogenesis of PET:

Over the years studies have shown that there could be some association between various maternal infections and adverse pregnancy outcomes such as PET, intrauterine growth restriction (IUGR), preterm labour and birth, intrauterine fetal death (IUFD), etc

(2, 20, 21, 39, 61, 63). These infections include UTI, human immunodeficiency virus (HIV) infection, periodontal disease, chlamydia, malaria, bacterial vaginosis and group B streptococcal infections. In their recent systematic review and meta-analysis Conde-Agudelo et al (11) showed that there is an association between PET and UTI, and between PET and periodontal disease in pregnancy. These results give credence to the continuum theory in which the role of an exaggerated SIRS in pregnancy is strongly implicated and that maternal infection most probably plays an important role in amplifying this SIRS.

However, it is difficult to prove a direct causal relationship between PET and maternal infections such as UTI as Karmon and Sheiner (29) have pointed out. von Dadelszen et al (68) have suggested that infection could damage the arterial wall through direct endothelial injury, local inflammation or acute atherosis. Others have demonstrated the role of infections in increasing sFlt-1 levels in nulliparous women and in inhibition of extra-villous trophoblastic invasion thus causing disruption in normal placentation and placental function (4, 31, 44). Interestingly, Faas et al (18) demonstrated features of PET in pregnant rats after infusing them with ultra-low-dose endotoxin. This has not been demonstrated in humans.

Even though one could assume that a relationship does exist between maternal infections such as UTI and PET on the basis of the above, no investigator has been able to give a clear indication as to when exactly such an infection needs to occur during pregnancy in order to cause or influence the development of PET (28).Hence the observation that studies which have taken place so far have been carried out at

varying gestational ages and some even postpartum. This makes comparison and interpretation of results that much more complex. Other problems with most of these studies have been the limited sample sizes, retrospective nature of the larger studies and inadequate control of confounding factors.

III OBJECTIVES

1/ To determine if urinary tract infection (UTI) in pregnancy is associated with pre- eclampsia/eclampsia (PET)

Null Hypothesis: In pregnancy there is no positive association between UTI and PET

2/ To determine if the severity of urinary tract infection is related to the severity of pre-eclampsia/eclampsia

IV METHODOLOGY AND DATA COLLECTION

Basic Design and Description

This is a hospital based quantitative case-control study which was carried out in Groote Schuur Hospital Maternity Centre from 01/03/2009 to 31/08/2009. Groote Schuur Hospital is a tertiary referral teaching hospital attached to the University of Cape Town, South Africa. It caters for the entire metropolitan area of the Western Cape Peninsula. The study protocol was approved by the Ethics and Research Committee of the University of Cape Town. Throughout the

study adherence to the World Medical Association Declaration of Helsinki and Tokyo was observed (74).

Sample size estimation

Assuming a background pre-eclampsia incidence of 6% in the population from which the sample would be drawn, and assuming an increase to10% in association with urinary tract infection, a sample comprising 200 pre-eclamptic/eclamptic patients and 200 controls would need to be recruited, which would give a power of at least 80%, with the two-sided significant level a set at 0.05 and Type II error ß set at 0.2 (36).

The study sample was derived from antenatal patients who where admitted to the maternity centre during this period. These patients were admitted from the maternity centre antenatal clinics or were referrals from secondary level hospitals and clinics in the Western Cape Peninsula area. Recruits were split into two groups: those with PET formed the cases and those without PET but admitted for other obstetric indications formed the controls.

Participants:

Inclusion criteria were patients whose gestation was equal to or above 20 weeks; presence of obstetrician confirmed PET; documented evidence of a negative HIV test within the preceding twelve months. Ineligible women included known epileptics or those with other forms of convulsions not related to PET; those with obstetrician confirmed diabetes mellitus; those with confirmed HIV positive status; febrile women whose fever was not attributable to UTI, e g pneumonia; and

readmissions who had already been admitted into the study on a previous admission.

Matching:

Cases were matched to controls in terms of age and parity. Age was categorised in years as follows: 10-15; 16-20; 21-25; 26-30; 31-35; 36-40; and 41-45. Parity was divided into nulliparity and multiparity.

Definitions of UTI and PET:

In this study any patient who satisfied any one of the following three definitions given below was considered to have UTI: positive urine culture without symptoms and signs of UTI (asymptomatic bacteriuria); positive urine culture with symptoms and/or signs of UTI (cystitis and/or pyelonephritis); and negative urine culture with at least three symptoms and at least two signs of UTI. A culture positive result was defined as bacterial counts in clean catch mid-stream urine (MSU) or catheter specimen urine (CSU) of at least 100 000 colonies per ml. Symptoms of urinary tract infection were defined as follows: frequency, dysuria, fever, nausea/vomiting, abdominal pain, backache, flank pain, and passing blood in urine. Signs of urinary tract infection were defined as follows: suprapubic tenderness, renal angle tenderness, temperature equal to or greater than 37.5°C, and haematuria not associated to bleeding from the genital tract.

PET was defined as a diastolic BP equal to or greater than 90mmHg on any two or more consecutive occasions 4hours or more apart in combination with significant proteinuria i.e. 2+ or more protein on cold test urine sample or 300mg or more protein in a 24h urine collection, at 20 or more weeks gestation in a woman who was

previously normotensive (13). Symptoms of severe PET included headache, epigastric or right upper quadrant pain, and visual disturbances. Eclampsia was defined as the occurrence of one or more convulsions in a PET patient.

There were patients in whom the initial diagnosis of PET was later changed to unclassified hypertension or gestational hypertension after disappearance of significant proteinuria on antibiotic treatment for UTI as defined in this study. Such patients were excluded from the cases and included in the controls. This meant that the investigator followed up the folders of all the recruited cases in order to identify such patients and reassign them appropriately. Patients whose significant proteinuria persisted after such treatment remained in the cases category. Such follow-up was essential in order to solve the problem of interpreting proteinuria in the presence of UTI alone given the fact that proteinuria can occur in both PET and UTI. This also avoided the temptation to set a cut-off level of significant proteinuria that would fall outside the definition used in this study, a definition widely accepted internationally.

Sampling Technique:

Patients being admitted to the maternity centre for various obstetric indications and meeting the inclusion criteria of the study were identified. They were then given a pamphlet explaining the study and its objectives. Written informed consent was obtained by the investigator from those patients voluntarily willing to participate in the study. The patient information pamphlet and consent forms were written in the three major languages in South Africa, i e Xhosa, English and Afrikaans.

A thorough history of UTI symptoms was elicited from every consented patient and an appropriate physical examination conducted. Either a clean catch MSU or CSU was then collected from every participant on admission and sent to the laboratory within one hour. All urine samples were collected before any antibiotic was given. Laboratory urine results were followed up a few days later and recorded on the data capture sheet. A clear record of any clinical symptoms and signs of UTI were documented in the patient's notes and on the data capture sheet. Other parameters which were recorded on the data capture sheet included blood pressure, temperature and cold test proteinuria obtained on admission and four hours later. Protein levels in 24 hour urine collections and number of any convulsions were also recorded.

Statistical methods

Statistical analyses were performed using the software Stata Version 10.0 (Stata Corporation, College Station, Texas, USA). Data coding was facilitated by allocating each patient a "unique identifier" starting at 1001 and counting upwards. The encoded data was then recorded on Excel Spreadsheet. Statistical analyses involved the use of two-sample Wilcoxon rank-sum (Mann-Whitney) test, Pearson's Chi-square test, and Logistic regression analysis. Frequencies, Odds Ratios (OR), p-values, and 95% confidence intervals (CI) were calculated.

V RESULTS

A total of 423 participants were recruited into this study comprising 257 controls and 166 cases. The total number of women recruited slightly exceeded that needed to meet the original sample size calculation.

Table I shows the baseline distribution of diagnoses in the study sample The sample was made up of a total of 423 participants of which 166 (39.24%) were pre-eclamptics (cases) and 257 (60.76%) were non-pre-eclamptics (controls). Time constraints could not permit the recruitment of 200 participants into each arm as originally envisaged. However, application of the power calculations mentioned under section IV on the sample obtained in this study shows that this study is sufficiently powered at more than 99%.

Table I. Baseline distribution of diagnoses

DIAGNOSIS	Controls	Cases	Total
3 x previous stillbirths	1	0	1
CCF / mitral valve disease	1	0	1
Ccervical cancer stage Ib	1	0	1
ELSCS for 1 x previous CS	16	0	16
ELSCS for 2 x previous CS	3	0	3
ELSCS for transverse lie	1	0	1
Hashimoto's thyroiditis	1	0	1
Induction for 1x previous stillbirth	1	0	1
Induction for previous abruption	1	0	1
Induction for 2x previous stilbirths	1	0	1
ITP	1	0	1
IUFD	7	0	7
Twin IUFD	1	0	1
IUGR	1	0	1
PPROM	10	0	10
PPROM / fetal distress	1	0	1
PPROM / twins	1	0	1
PROM	4	0	4
SLE	1	0	1
SLE / oligohydramnios	1	0	1
SLE / renal impairment	2	0	2
Active labour	1	0	1
Anaemia in pregnancy	12	0	12
Asthmatic attack	1	0	1
Blunt abdominal trauma	1	0	1
Breech for CS	4	0	4

Breech in preterm labour	1	0	1
Cardiac disease	1	0	1
Cervical incompetence	1	0	1
Chronic hypertension	25	0	25
Cystitis	6	0	6
Eclampsia - 5 convulsions	0	1	1
Eclampsia -1 convulsions	0	1	1
Eclampsia -2 convulsions	0	2	2
Elevated liver enzyme	1	0	1
Fetal anomaly	2	0	2
Fetal anomaly (47XXY)	1	0	1
Fetal anomaly-anencep	1	0	1
Gestational hypertension	22	0	22
Gestational proteinuria	1	0	1
Headache	1	0	1
Hyperemesis gravidarum	1	0	1
Hypothyroidism	1	0	1
Imminent eclampsia	0	2	2
Impaired glucose tolerance	1	0	1
Latent labour	9	0	9
Latent labour / triplets	1	0	1
Limb body wall defect	1	0	1
Macrosomia for CS	5	0	5
Mitral vulve disease	1	0	1
Myasthenia gravis	1	0	1
Obstrucive perineal warts	1	0	1
Oligohydramnios	6	0	6
Placenta praevia grde I	1	0	1
Placenta praevia grade III	7	0	7
Placenta praevia grade IV	5	0	5
Placenta praevia IV/	1	0	1
Post dates	6	0	6
Pre-eclampsia	0	134	134
Pre-eclampsia / CIN I	0	1	1
Pre-eclampsia - HELLP syndrome	0	6	6
Pre-eclampsia / IUFD	0	1	1
Pre-eclampsia - abruption	0	1	1
Pre-eclampsia - chronic hypertension	0	13	13
Pre-eclampsia / postdates	0	2	2
Prolonged pregnancy	30	0	30
Protein C deficiency	1	0	1
Pyelonephritis	4	0	4
Pyelonephritis - cystitis	1	0	1
Recurrent pregnancy loll	1	0	1
Recurrent pyelonephritis	2	0	2
Rhesus iso-immunisation	3	0	3
Rheumatic heart disease	1	0	1
Severe IUGR	3	0	3
Sickle cell anaemia	1	0	1
Social ELSCS	1	0	1
Threatened preterm labour	7	0	7
Trisomy 18 for medical termination	1	0	1
Unclassified antepartum haemorrhage	8	0	8
Unclassified hypertension	4	0	4
Unstable lie	1	0	1
Ventricular septal defect	1	0	1
Total	257	166	423

Starting out from the null hypothesis that the median age, the median gestation, and the median parity of controls were equal to those of cases, application of the two-sample Wilcoxon rank-sum (Mann-Whitney) test revealed significant differences, as shown in Table II:

Table II. Medians of Age, Gestation, and Parity of Controls versus Cases

	Controls	Cases	p-value
Median Age(yrs)	28	26	0.065
Median Gestation(wks)	38	31	<0.001
Median Parity	1	0	<0.001

Table III shows the distribution of parity between controls and cases.

Table III. Distribution of parity between controls and cases

PARITY	CONTROLS	CASES
	(%)	(%)
Nulliparous	83	85
	(32.30)	(51.20)
Multiparous	174	81
	(67.70)	(48.80)
TOTAL	257	166

Application of Pearson's Chi-square test with one degree of freedom revealed that cases were significantly more likely to be nulliparous compared to controls.

In this study 9.6% of cases had UTI compared to 17.3% in controls (Table IVb). The overall incidence of UTI in this study sample was 14.3%. The most common type of UTI as defined in this study in both groups was asymptomatic bacteriuria making up 8.4% of all UTI's in cases and 9.4% of all UTI's in controls. Cystitis and/or pyelonephritis occurred in 1.2% of cases as compared to 5.1% in controls. UTI's based on signs and symptoms only were absent in cases and were only 2.75% in controls (Table IVa).

Table IVa. Distribution of UTIs among cases and controls.

UTI BASIS	CONTROLS (%)	CASES (%)	TOTAL (%)
No UTI	211 (82.75)	150 (90.36)	361 (85.75)
Culture only	24 (9.41)	14 (8.43)	38 (9.03)
Signs/symptoms only	7 (2.75)	0 (0.00)	7 (1.66)
Culture/signs/symptoms	13 (5.10)	2 (1.20)	15 (3.56)
TOTAL	255	166	421

Table IVb: Binary distribution of UTIs among cases and controls (any UTI vs no UTI).

ANY UTI	CONTROLS (%)	CASES (%)	TOTAL (%)
0	211 (82.75)	150 (90.36)	361 (85.75)
1	44 (17.25)	16 (9.64)	60 (14.25)
TOTAL	255	166	421

Table V shows that among all forms of PET, UTI occurred in 7.8% of mild to moderate PET; in 0.6% of imminent eclampsia; in 0% of eclampsia; and in 1.2% of HELLP syndrome.

Table V. Frequency of UTI according to Severity of PET

Severity of PET	No. of UTI's	Total No. of PET	Frequency of UTI
Pre-eclampsia	13	166	13/166 = 0.078
Imminent PET	1	166	1/166 = 0.006
Eclampsia	0	166	0/166 = 0.000
HELLP	2	166	2/166 = 0.012

A logistic regression model was used to compare the association between any form of UTI as defined in this study versus the absence of UTI, and the case-control status of participants, adjusted for age, gestation and parity category (Table VI).

Table VI. Results of Logistic regression analysis

Case-Control	Odds Ratio	[95% Conf. Interval]
Any UTI	0.2949747	0.1469614 - 0.5920608
Age (yrs)	1.0208930	0.9777476 - 1.0659410
Gestation (wks)	0.8338981	0.7971072 - 0.8723872
Parity	0.3191147	0.1834110 - i0.5552242

The following conclusions can be drawn from Table VI:

Participants with any UTI were significantly less likely to be a case (odds ratio, 0.29; 95% confidence interval, 0.15-0.59, p=0.001).

Participant age was not associated with case-control status.

Participant gestation was significantly associated with case-control status, with a 1-week increase in gestation associated with a 0.83 times the odds of being a case, compared to a control (95% CI, 0.80-0.87, $p<0.001$).

Parous women had 0.32 times the odds of being a case compared to nulliparous women, this was significant (95% CI 0.18-0.56, $p<0.001$). Therefore this regression model indicates that UTIs were inversely associated with being a case; age was not associated with being a case; increasing gestation was inversely associated with being a case; and parity was inversely associated with being a case.

VI DISCUSSION

This case-control study was primarily looking at any possible positive association between UTI in pregnancy and PET. The design of the study was not meant to investigate any causal relationship between UTI and PET. Some investigators have found a positive association whilst others have not (11). In the continuum theory it is postulated that some cases of PET could actually be exaggerated forms of the SIRS of normal pregnancy which results in decompensation triggered off by an infectious insult. Why UTI in particular should be the major infection involved in this process has yet to be explained.

In this study 9.6% of pre-eclamptics had UTI compared to 17.3% in non-pre-eclamptics. The overall incidence of UTI in this study sample was 14.3%. Delzell and Lefevre (16) state that in pregnant women the incidence of UTI can be as high as 8%. The higher incidence in this study could be explained by the fact that participants were a highly selected group referred for tertiary level care and therefore might not be

representative of all pregnant women in general. The most common type of UTI as defined in this study in both groups was asymptomatic bacteriuria, making up 8.4% of UTI's in cases and 9.4% of UTI's in controls. These figures for asymptomatic bacteriuria in pregnancy are close to the prevalence of 10 percent cited in other literature (16). Cystitis and/or pyelonephritis occurred in 1.2% of cases as compared to 5.1% in controls. Again these figures are at slight variance with those quoted in other literature where cystitis is reported to occur in 1.3% and pyelonephritis in 2% of pregnant women (22, 24). This difference could also be a reflection of the tertiary level nature of participants in this study. UTI's based on signs and symptoms only were rare, being absent in cases and making only 2.75% of UTI's in controls.

The primary outcome of this study does not lend support to the hypothesis that UTI is positively associated with PET. The study in fact showed the opposite, which is that patients who had UTI as defined in this study were unlikely to be pre-eclamptic. This finding, however, is in accord with five of the studies which were included in the recent systematic review and meta-analysis by Conde-Agudelo *et al.* 2008, in which a negative association was found. These five studies evaluated the moment of exposure to UTI at the time of the first antenatal visit whereas in this study participants were evaluated for exposure at the time they presented for admission into the maternity centre at any gestation from 20 weeks and above. With such a different approach to the moment of exposure evaluation as in this study one would have expected a different outcome. It therefore seems that the gestation at which the evaluation of exposure to UTI had little bearing on the final primary outcome. The moments of exposure evaluation in the other twelve studies which showed a positive association between UTI and PET in the above-

mentioned systematic review and meta-analysis varied from the first antenatal visit to the time of delivery.

It is important to understand that the continuum theory on which this study is based does not indicate at what point in time during pregnancy the infectious insult needs to occur in order to cause PET. This obviously makes comparison and interpretation of the various studies conducted so far in this area difficult.

It is generally accepted that eclampsia and HELLP syndrome represent the most extreme and severest forms of PET (3). As a secondary outcome this study showed that the greater the severity of PET the smaller the frequency of UTI. This seems to corroborate the primary outcome of this study which showed that patients who had UTI as defined in this study were unlikely to be pre-eclamptic.

This study also confirmed the already known fact that nulliparity is a risk factor for development of PET in pregnancy. Although it is known that women below 20 years of age and those above 40 years of age are at a higher risk of PET this study could not confirm this (46). It is difficult to explain this study finding.

As discussed in the literature review section, it appears that there are different forms of PET with attendant different pathophysiological and aetiological processes (42). EOPET is associated with abnormal placentation whereas there are other forms where abnormal placentation is not demonstrable and in these cases PET is believed to occur mainly due to exaggeration of SIRS of normal pregnancy as a result of infection (55). Therefore the outcome of studies such as this one is also influenced

by the number of participants with the different types of PET included in the study, knowledge of which would be crucial in excluding cases of PET where infection is not a determinant. However, up to now no published study has looked into this.

South Africa is believed to have more people with HIV/AIDS than any other country globally. The latest HIV data collected at antenatal clinics in this country suggest that HIV prevalence in pregnant women stood at 28% in 2007 (72). Therefore HIV positive patients form a large percentage of patients admitted to the maternity centre at GSH. Such patients were excluded from this study mainly because there is no clear consensus yet on the influence of HIV infection on PET. Some studies suggest a possible protective effect of the virus from PET whilst others have found no such effect (30, 37). This is a significantly large number of participants to have been excluded from the study and this could have affected the outcome either way.

Another group of participants excluded from this study were those with diabetes mellitus. They also form a large percentage of women admitted to the maternity centre. The reason they were excluded is that glycosuria in diabetics and the depressed immune status during pregnancy seem to increase the incidence of UTI in these women although some studies dispute this (10, 12). Including diabetics would possibly have had a confounding effect on the outcome. On the other hand diabetes mellitus in pregnancy is known to be associated with increased risk of PET. Thus exclusion of these women could actually also be confounding and affect the outcome.

One of the strengths of this study is the adequate sample size which was sufficiently powered to allow for meaningful analysis of data. The other strength of this study is that it was conducted at a tertiary institution where all severe cases of PET are referred from the entire metropolitan area of the Western Cape Peninsula. The third strength of this study lies in the strict application of and adherence to internationally accepted definitions of UTI and PET.

As expected with most studies, this case-control study had a number of limitations. Firstly, exposure (UTI) and possible outcome (PET) were measured at the same time and this means causality cannot be determined. Secondly, the design of the study did not permit follow-up of participants to determine if controls who had confirmed UTI went on to develop PET later in the pregnancy. Such a follow-up would obviously influence the outcome of the study.

Thirdly, within the confines of this study no attempt was made to find out if a participant had had UTI at an earlier gestation in the index pregnancy, and if so , if any antibiotic treatment was given and what the outcome of such treatment was. In the same vein, a history of use of antibiotics for any other infection was not solicited for the purposes of this study. It is conceivable that for participants who had asymptomatic bacteriuria at an earlier gestation in their pregnancy the use of an antibiotic for other concurrent infections could have cleared the UTI by the time they were recruited into the study. However, so far no study has shown what effect treatment of UTI during pregnancy has on subsequent development of PET if any.

Fourthly, the role of other infections that might have occurred prior to or at the time of recruitment into this study was not considered. Based on the postulates of the continuum theory, any infectious inflammatory process has the potential to trigger off an exaggerated SIRS and subsequently result in PET.

The importance of this study lies in its contribution to the ongoing debate in the quest to understand the aetiology of pre-eclampsia and the possible pathogenetic mechanisms involved in this devastating condition. The outcome of this study also raises the issue that perhaps the reported positive association between UTI and PET could be spurious or confounding and that perhaps it is erroneous to concentrate only on one infection as a possible inflammatory trigger in the pathogenesis of some forms of PET. There is need to investigate further the contribution of other infections in pregnancy. The results of this study call for a more holistic approach in the search for infectious triggers of exaggerated SIRS and decompensation into PET.

There is need for studies that will address the question of causality. Such studies could be in the form of large multicentred prospective and randomised trials with the same moments of exposure evaluation set early in the first trimester and follow-up of each participant until one week postpartum since PET can occur up to that point. More and larger studies need to be conducted looking into the possible influence of other common infections and medical conditions such as HIV infection and diabetes mellitus on PET and UTI. These conditions affect a large proportion of pregnant women worldwide and their possible impact on outcomes of studies such as this one needs to be accounted for. Other

studies are required to investigate the effect of treating UTI in pregnancy on PET.

Finally, in their analyses it is perhaps also very important for researchers to know what form of PET each participant had since not all forms of PET are influenced by infectious insults to the same extent as explained earlier on. One way would be to take placental bed biopsies in every participant post delivery looking for any changes in decidual and intramyometrial spiral artery structure thus confirming the presence or absence of abnormal placentation and facilitating categorisation into EOPET, LOPET and other forms of PET.

VII CONCLUSION

The major finding of this study was that patients who had UTI as defined in the study were unlikely to be pre-eclamptic. It was also shown that the greater the severity of PET the smaller the frequency of UTI. Therefore no positive association between UTI and PET was found in this study.

The study did, however, confirm that that nulliparity was a risk factor for development of PET in pregnancy. The other finding is that PET was more likely to occur in earlier gestations rather than late in the third trimester. Age seemed not to be a risk factor for PET in this study.

There were a number of limitations associated with this study. Firstly, the fact that exposure (UTI) and possible outcome (PET) were measured at the same time meant that causality cannot be determined. Secondly, there was no follow-up of participants to determine if controls who had confirmed UTI went on to develop PET later in the pregnancy. Such a

follow-up would obviously influence the outcome of the study. Thirdly, possible previous episodes of UTI in index pregnancy and their treatment was not taken into consideration. Fourthly, the role of other infections that might have occurred prior to or at the time of recruitment into this study was not considered.

This study also raises a number of important issues. To begin with, in order to answer the question of causality large multicentred and randomised studies are needed. Such studies should have the same moments of evaluation of exposure to UTI, preferably early in the first trimester, and the participants followed up for the same period postpartum. Secondly, such studies should also be designed in such a way that participants can be stratified according to the type of PET they had. Other studies should look at the effect of treating UTI in pregnancy on PET. Above all the relationship between PET and other infections and conditions occurring in pregnancy should continue to be rigorously investigated. Lastly, there is a need for studies to be carried out at less selective levels of care, e.g. at primary health care level, as the tertiary care patients are highly selected and are prone to bias.

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IX APPENDICES

DATA CAPTURE SHEET:

A Date:

B Study Number:

C Age: Gestation Gravidity: Parity: Miscarriage: Ectopic:

Reason for admission/Diagnosis:
Documented negative HIV status within last 12 months: YES/NO
MSU / CSU sent to lab within 1hr of collection: YES/NO
Number of convulsions:
Where any of the following symptoms present?

a) frequency: YES/NO
b) dysuria: YES/NO
c) fever: YES/NO
d) nausea/vomiting: YES/NO
e) abdominal pain: YES/NO
f) passing blood in urine: YES/NO

Where any of the following signs present?

i) suprapubic pain: YES/NO
ii) renal angle tenderness: YES/NO
iii) temperature =37,5°C: YES/NO
iv) haematuria: YES/NO

D MSU / CSU result:

E BP (mmHg) on admission: BP (mmHg) after 4hrs:
Urine cold test on admission: Urine cold test after 4hrs:
Temperature (°C) on admission: Temperature (°C) after 4hrs:

F 24 hour urine protein in g/24h:

UTI/PET STUDY CONSENT FORM

Date:

I , would like to participate in the above study. I do understand the importance of the study to pregnant women. I also understand that there will be no financial cost or financial benefit to me arising from this study.

Name of patient/parent/guardian giving consent:

Signature of patient/parent/guardian giving consent:

Name of Doctor or Nurse taking consent:

Signature of Doctor or Nurse taking consent:

TOESTEMMING VIR UTI/PET NAVORSING

Datum:

Ek , sal baie graag wil deelneem aan bogenoemde navorsing. Ek is bewus van die belange van die navorsing vir swanger vrouens. Ek is ook bewus daarvan dat daar geen finansiele koste of finansiele vergoeding vir my sal plaasvind deur hierdie navorsing nie.

Naam van patient/ouer/voog wat toestemming gee:

Handtekening van pasient/ouer/voog wat toestemming gee:

Naam van dokter of verpleegster wat die toestemming neem:

Handtekening van dokter of verpleegster wat die toestemming neem:

UTI/PET STUDY IPHEPHA LEMVUME

Umhla:

Mna u , ndingathanda ukuba yinxenye yaloluphando. Ndiyaqonda ukubaluleka kwaloluphando komama abakhulelweyo. Ndiyaqonda ukuba soze ndibhatale okanye ndibhatalwe.

Igama lesigulana/lomzali/lomnakekeli onika imvume:

I-signature yesigulana/yomzali/yomnakekeli onika imvume:

Igama likagqirha okanye likamongikazi othatha imvume:

I-signature kagqirha okanye kamongikazi othatha imvume:

UTI/PET STUDY: Patient Information Leaflet

Dear Madam

Pregnant women can suffer from high blood pressure accompanied by loss of protein in their urine. This condition is referred to as pre-eclampsia (PET). The condition can lead to poor fetal growth, premature separation of the afterbirth with resultant bleeding and fetal compromise, all of which can lead to the demise of the fetus. The pregnant woman can also become very sick, developing fits, stroke, liver and kidney failure, and severe shortness of breath due to water logging in the lungs. Doctors are therefore forced to deliver these premature babies in order to save their lives and that of their mothers without guaranteed success. Why this condition occurs is still largely unclear although a huge amount of research is being undertaken the world over to try and answer this important question and thus hopefully prevent this condition from occurring or give better treatment to affected pregnant women.

Some studies have suggested that urinary tract infection (UTI) in pregnancy might be associated with the development of PET. Our study is looking into this possible association by investigating interested women for possible UTI and PET during their pregnancy. On admission to GSH Maternity Centre we will ask the women to give us a sample of their urine which we will send to the laboratory to be checked for urinary tract infection. They will also have their blood pressures and temperature recorded. In the event that we discover urine infection or pre-eclampsia the woman will be given the full appropriate treatment and care. All the women participating in the study have the right to withdraw from the study at any point in time and are assured that they will still receive the full obstetric care they require.

If you are interested in joining this study we will ask you to give us consent by signing a consent form which will be made available to you.

Thank you

UTI/PET NAVORSING: Pasient Informasie Bladsy

Geagte Dame

Swanger vrouens kan lei aan hoë bloeddruk wat gepaard gaan met die verlies van proteine in die urine. Hierdie toestand word verwys na pre-eclampsia (PET). Die toestand kan lei tot swak fetale groei, skeiding van die nageboorte met resultate bloeding en fetale komproie, al van wat kan lei to die dood van die fetus. Die swanger vrou kan ook baie siek word, die ontwikkelling van epileptise siekte, beroerte, lewer en nier vervalling , en hewige kortasemheid as gevolg van water op die longe. Dokters is daarom gevorseer om die babas te lewer ten opsigte die lewens van die babas en hul moeders sonder sukses te waarborg. Die rede waarom hierdie toestand gebeur is nog baie onduidelik alhowel 'n groot aantal navorsing geonderneem word die hele wereld deur om te probeer en te beantwoord die belangrike vraag en dus hoopvol te vermy dat hierdie toestand nie herhaal word nie of beter behandeling vir die geaffekteerde swanger vrouens te gee.

Sommige studies her voorgestem dat urinary tract infection (UTI) in swangerskap mag geassosieer word met die ontwikkeling van PET. Ons studie kyk na moontlike assosiasie van moontlike geintreseerde vrouens vir moontlike UTI en PET gedurende hul swangeskap. Op toelating tot GSH Kraamafdeling vra ons die vrouens om vir ons 'n uriene monster te gee wat ons na die labratorium toe stuur om getoets te word vir urinary tract infection. Hul bloeddruk en tempratuur word ook aangeteken. In die geval dat uriene infeksie of pre-eclapmsia ontdek work sal die vrouens 'n volle toepaslike behandeling en sorg gegee word.

As u belangstel om aan hierdie navorsing deelteneem, vra ons u om toestemming te gee deur die toestemmings vorm te teken wat beskikbaar sal wees vir u.

Baie dankie

UTI/PET STUDY: Inkcazelo yesigulana

Nkosikazi

Abafazi abakhulelweyo bangaba ne-blood pressure ephakamileyo ehambelana nomchamo one-protein. Lesisimo sibizwa i-pre-eclampsia (PET). Lesisimo singabangela ukuba umntwana angakhuli kakuhle, ukopha nokungaphephi komntwana, konke lokhu kungabangela ukufa komntwana. Nomama okhulelwe angagula kakhulu, axhuzule, abethwe yi-stroke, isibindi nezintso singasebenzi, imiphunga ibe namanzi bese angakwazi ukuphefumla. Oogqirha bayanyanzeleka ukuba babelekisa labomama ngaphambi kwexesha. Asazi ukuba lesisimo sibangelwa yintoni kodwa kukho uphando olunintsi emhlabeni wonke jikelele ozama ukuphendula lombuzo futhi siyethemba ukuba sizakwazi ukufumana indlela yokunqanda lesisimo no kusinyanga kangcono.

Olunye uphando luthi mhlawumbe ukuba nokusulela komchamo umithi kungabangela i-PET . Uphando lwethu lufuna ukuphendula lombuzo ngokuxilonga omama abakhulelweyo (ngemvume yabo) sijonge ukuba banakho ukusulela komchamo ne-PET. Ngenkathi omama befika e GSH Maternity Centre, sizawucela umchamo ozokuya e-laboratory lapho uzawuxilongwela ukusulela. I-blood pressure ne-temperature zizawubhalwa phansi. Umama onokusulela komchamo okanye I-PET, uzawufumana amayeza aphinde anakekelwe.

Umangabe ufuna ukusinceda ngaloluphando, sicela usinikeze imvumo ngokusayina iphepha lemvumo esizawukunika lona.

Siyabulela

UNIVERSITY OF CAPE TOWN

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Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
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29 January 2009

REC REF: 472/2008

Dr C Chidakwa
Obstetrics & Gynaecology

Dear Dr Chidakwa

PROJECT TITLE: URINARY TRACT INFECTION AND PRE-ECLAMPSIA.IN PREGNANCY: A STUDY OF THE INCIDENCE OF URINARY TRACT INFEC TION IN PRE-ECLAMPTIC/ECLAMPTIC PATIENTS AND IN CONTROL GROUP OF NON-PRE ECLAMPTIC PATIENTS ADMITTED TO GROOTE SCHUUR HOSPITAL MATERNITY CENTRE,UNIVERSITY OF CAPE TOWN

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 31st January 2010.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
lemjedi

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.