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PREGNANCY OUTCOME IN PRIMIGRAVID WOMEN ABOVE THE AGE OF 30 YEARS IN SOWETO

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A research report submitted to the Faculty of Health sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Obstetrics and Gynaecology.

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TABLE OF CONTENTS

DECLARATION ……..4

DEDICATION ……..5

ABSTRACT …….6

ACKNOWLEDGEMENTS ……..8

INTRODUCTION …….9

LITERATURE REVIEW …….10

PROBLEM STATEMENT ……....18

OBJECTIVES OF THE STUDY ……19

METHODS ……..20

RESULTS ……23

DISCUSSION ……..30

CONCLUSION ……33

REFERENCES …….34

APPENDICES ……38

LIST OF TABLES AND FIGURES

Page

Tables:

25 Table 1. Antenatal care,maternal weight,blood screening results and HIV status in primigravidas aged 30 years or more(cases;n=76) and controls aged 20 to 24 years(controls;n=76).

26 Table 2.Antepartum pregnancy problems in primigravidas aged 30 years or more (cases;n=76) and primigravid controls aged 20 to 24 years(controls;n=76).

27 Table 3.Problems during labour and delivery in primigravidas aged 30 years or more (cases;n=76) and primigravid controls aged 20 to 24 years(controls;n=76).

28 Fetal outcomes in primigravidas aged 30 years or more(cases;n=77) and primigravid controls aged 20 to 24 years(controls;n=76).

Figures:

24 Figure 1. Age distribution of primigravid controls aged 20 to 24 years(n=76) on the left,and primigravid cases aged 30 years and above(n=76) on the right.

DECLARATION

I,Mashika Abel Ramoba, declare that this research report is my own work.

It is being submitted to the Faculty of Health sciences for the degree of Master of Medicine in Obstetrics and Gynaecology, at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any other degree or examination at this or any other University.

Johannesburg,September 2015

DEDICATION

To my family: especially my wife,for the sacrifices that she made in keeping the family fires burning,whilst I was away,trying to fulfil my academic ambitions.

Thank you Hunadi.

ABSTRACT

BACKGROUND

Delaying the first pregnancy into the thirties is infrequent in low to middle-income South Africans. While primigravidas ≥35 years old are generally considered a high-risk group, it is not known if women aged 30-34 are also at risk for complications and poor pregnancy outcomes.

OBJECTIVE

To determine the frequency of primigravidity at ≥30 years, and to determine thepregnancy risks and outcomes in primigravid women aged ≥30 years, compared to a reference group of primigravidas aged 20-24 years.

METHODS

This was a cross-sectional analytic study of primigravid women resident in Soweto, giving birth to babies weighing ≥500 g at the Soweto maternity services (Chris Hani Baragwanath Hospital and five midwife obstetric units).Pregnancies in women aged ≥30 years were sampled as cases, with those aged 20-24 sampled as controls (reference group).The proportions of primigravidas in the case group and the reference group giving birth at the hospital, as opposed to the midwife obstetric units, were determined before starting the cross-sectional analysis. Because there was no significant difference in hospital birth proportions between the groups, only hospital births were sampled for the study, in a 1:1 ratio of cases to controls. Clinical data werecollected prospectively from hospital case files. The key outcome measures were caesarean section, low birth weight and admission of the newborn baby to the neonatal unit.

RESULTS

Seventy-six primigravidas aged ≥30 years were sampled, with an equal number of controls aged 20-24 years. Antenatal differences included a lower mean gestational age at booking in the cases (17.9 vs. 20.5 weeks; P<0.01), as well as greater maternal weight at booking (86.6 vs. 73.1 kg; P<0.01), and evidence of further progression of HIV disease in terms of mean CD4 cell count (206 vs. 372 cells/mm^3; P<0.01). However, the HIV seroprevalence was not

significantly higher in cases (24.3% vs. 19.7%; P=0.55). Caesarean delivery rates were high in both groups (55.3% vs. 48.7%; P=0.63). There were no significant differences in any other pregnancy outcomes, although there was a trend to lower mean birth weight in cases (2849 vs. 3050 g; P=0.06).

CONCLUSION

Primigravidas of age ≥30 years were not found to be at risk for adverse pregnancy outcomes in this small cross-sectional study. The findings of increased maternal weight and further progression of HIV disease in cases were not unexpected, as these are age-related phenomena. Based on the findings here, it will not be appropriate to assign high risk pregnancy status to primigravidas of age ≥30 years.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Professor E Buchmann, and also Dr K Frank and Professor F Guidozzi, for the contributions they made and for their guidance.

I would also like to thank the staff in the filing department of the Chris Hani Baragwanath Academic hospital for helping me to access the participants' hospital files.

1. INTRODUCTION

Throughout the centuries, maternal age has been an important factor in the survival of mankind. When life expectancy was only into the fourth decade and women had no control over fertility, they had no choice but to bear children as teenagers and young adults. Only recently, with increased life expectancy, delayed marriage and effective birth control, do women have the option of delaying childbearing. As delayed childbearing is becoming increasingly common, it is important to understand the implications of advanced maternal age for both mother and baby.[1,2]

Having a first pregnancy at a relatively advanced maternal age, such as above the age of 30 years, is still unusual in countries such as South Africa. Yet, the deliberate delay of child-bearing is now frequent in high-income countries, where a young woman's education and career may take precedence over plans to have children.[3] Obstetricians in those countries are generally comfortable with clinical care of older primigravidas, who are mostly healthy, well-nourished, self-empowered and have good pregnancy outcomes.[3,4] The same is not true in low and middle-income societies, where older primigravidas have been shown to have significantly poorer pregnancy outcomes than their younger counterparts.[5-8] In such contexts, families and their health providers are understandably concerned when an older woman becomes pregnant for the first time, perhaps after a period of infertility or on a background of chronic ill-health.

In South Africa, national maternity care guidelines recommend that primigravid women aged 35 years or more be referred to hospitals for medically-supervised childbirth, rather than be delivered by midwives at community health centres.[9]There is however concern that primigravidas aged 30 to 34 years are also at risk for poor outcomes. Whether this concern is justified is not clear: not enough is known in South Africa about pregnancy outcomes in primigravidasaged 30 years and above to allow guidelines to be made for their care.

2. LITERATURE REVIEW

2.1: ADVANCED MATERNAL AGE

Advanced maternal age and parity constitutetwo major factors in the outcome of pregnancy andlabour, in both developed and developing countries. Age is considered an important determinant of pregnancy risk, with both upper and lower extremes associated with pregnancy complications and poor outcomes.Pregnancy is defined as 'high-risk' if the possibility of an adverse outcome is higher than in the general population.[10]For the upper extreme, this involves pregnancies in women of 'advanced maternal age', frequently defined as an age of 35 years or more.The elderly primigravida is sometimes believed to have suffered from subfertility and to carry increased risks for adverse pregnancy outcomes.Reduced fertility with increasing maternal age is evidenced by a decline in ovarian oocyte reserve.Also, poor oocyte quality is associated with increased probabilities for fetal aneuploidy and spontaneous abortions. In some countries, such as South Africa, age is a screening criterion for fetal aneuploidy, especially Down's syndrome.[9]While increased risk associated with advanced age is a worldwide phenomenon, it is in low and middle income countries where the poorest associated outcomes are found.

The intention to conceive and the timing of conception are complex issues influenced by many factors. In societies where matrimony and motherhood are still considered a priority lifestyle, it is important to consider the professional and matrimonial background of women postponing marriage. Elderly primigravidity is emerging worldwide as a choice made by women, and should not necessarily be ascribed to subfertility.[10,11]These factors may assist in understanding the potential outcomes of pregnancy at an advanced maternal age. Stillbirth, or late fetal death, is one of the adverse pregnancy outcomes of most concern, but studies on the relation between increased maternal age and stillbirth risk have led to inconsistent conclusions.[12]

Maternal mortality

Two recent South African 'Saving Mothers' reports, on confidential enquiries into maternal deaths from 2002 -2004 and 2005-2007, showed that women over the age of 30 years had disproportionately high maternal mortality rates.Women less than 20 years of age were at greater risk of dying due to complications of hypertension whereas women 35 years or older

were at greater risk of dying of obstetric haemorrhage,ectopic pregnancies,embolism,acute collapse and pre-existing medical disease.[9, 13,14]

Perinatal mortality

Similarly, the seventh 'Saving Babies' report, based on perinatal mortality audit from 2008-2009 in South Africa, found relatively high rates of perinatal death from pregnancies in women of advanced age. The rate of perinatal deaths in the over 34 year-old group was higher than in the 18-34 year-old group,particularly for deaths due to hypertension, although overall the difference was less marked than with the under-18s; 12.8% of perinatal deaths occurred in over 34s, with only 10% of births occurring in this age category.[15]

Age-related medical disorders

The risks of pregnancy at advanced age are well known, and include age-related disorders such as hypertension, diabetes mellitus, venous thromboembolism, obesity and other medical conditions.[16]In a study conducted in Yaounde, Cameroon,the incidence of anaemia,antepartum haemorrhage, hyperemesis gravidarum,malpresentation,intrauterine growth restriction,diabetes mellitus and fibroid uterus were statistically more frequent in elderly primigravidas than in controls.[17]

It is well known that advanced maternal age is associated with gestational diabetes mellitus and hypertensive disorders of pregnancy. Both groups of conditions are partly microvascular disorders. The question has arisen as to what extent advanced maternal age poses a risk factor for adverse pregnancy outcomes in women who do not suffer from pregnancy hypertension or diabetes. It has recently been suggested that advancing age is associated with endothelial dysfunction in both normotensive and essential hypertensive patients, an alteration following on from progressive impairment of the nitric oxide pathway, and resulting in oxidative stress.[20]Endothelial dysfunction could prove to explain poor pregnancy outcomes related to cardiovascular or microvascular events.

Parity-related obstetric risks

Advanced age comes with parity-related risks such as grand multiparity with concerns about intrapartum uterine rupture and postpartum uterine atony; and risks related to previous pregnancy problems such as previous caesarean section. Women who had previously

delivered six or more babies showed higher rates of obstetric haemorrhage, post-term deliveries and intrapartum fetal deaths compared to nulliparous women. A large retrospective study from a rural area in South Africa found that women with high parity,regardless of age, had an odds ratio of 1.8 for fetal death compared with women having a second or third child.[21]

Miscellaneous obstetric risks

Advanced age-related obstetric risks include multiple pregnancy, spontaneous preterm birth, and premature rupture of the membranes, as well as increased risks of intrapartum problems, such as cephalopelvic disproportion,prolonged second stage of labour,fetal distress, primary postpartum haemorrhage, caesarean section and episiotomies, as demonstrated in studies in Cameroon and South Africa.[17,22]

Chromosomal defects

One of the most well-known risks of advanced age is the increased likelihood of giving birth to a baby with chromosomal defects, especially Down's syndrome. Often, a family history of mental retardation, birth defects, or genetic traits is difficult to elicit without a formal genetic counselling or questionaires, nonetheless these areas should be emphasized at the initial history taking.[18]

HIV infection

In southern Africa, the HIV seropositivity rate is highest in pregnant women in their 30s,leading to additional HIV-associated risks. Combined prevention approaches recognise that no single intervention sufficiently addresses HIV and opportunistic infection incidence, and consider the combinations of structural, biomedical and behavioural approaches, which together will probably impact significantly on new transmissions and ultimately survival.[19]

Data on advanced maternal age in South Africa are available from one study done in Soweto at Chris Hani Baragwanath Hospital and its feeder midwife obstetric units (MOUs).[22]The study was done in 1997, before the HIV pandemic had made a significant impact. The study compared women aged ≥35 years with a comparison group aged 20-29 years, the latter being chosen based on their probability of giving birth at the hospital or MOU, to prevent selection bias. The study found higher mean parity (3.9 vs. 1.0), and increased frequencies of previous

caesarean section (13.4% vs. 7.2%), proteinuric hypertension (5.7% vs. 3.2%), diabetes mellitus (0.9% vs 0%), and premature rupture of the membranes (6.9% vs. 2.6%) in the older age group. In terms of outcomes, low birth weight (<2500 g) was more frequent (21.0% vs. 13.4%), as was caesarean section (22.7% vs. 13.1%), although the perinatal mortality rates did not differ significantly.Logistic regression models suggested that age itself was significantly and independently associated with low birth weight and need for caesarean section, along with the complications listed above.

Yet,in a study conducted in Turkey in 2014,therewas no significant difference between pregnancies of advanced maternal age and low-aged women in terms of preterm birth, delivery method, morbidity, mortality, and chronic diseases such as hypertension and diabetes mellitus. However, the caesarean delivery rate was 40.9% in the control group, suggesting that they constituted a high-risk group on their own. The most common caesarean section indication was fetal distress in women with advanced maternal age, whereas previous caesarean section was found as the most common cause in the control group.[10]

Since there is presently no consensus on the negative impacts of advanced maternal age on pregnancy outcome, with most studies having been retrospective and hospital based,a population-based prospective study that will have a wider scope is advocated.Until this is done, the inconsistencies in findings on this subject will remain.[6]

2.2: PRIMIGRAVIDITY

Being pregnant for the first time is not generally considered an obstetric risk factor. It is standard practice for primigravidas with no pregnancy complications to be managed entirely by midwives during pregnancy and childbirth, as stated in the South African national guidelines for maternity care.[9]

The main concern about primigravidas is that they are obstetrically untested. However, with close vigilance in pregnancy and in labour, complications can be detected and managed at midwifery care level. An example is the normal practice of ‘trial of labour’ for primigravidas, who usually labour less efficiently than multiparas. Their labours are observed closely using a labour graph, with oxytocin augmentation if necessary and effective pain relief, before resorting to caesarean section for dystocia if there is poor labour progress.[23]

2.3: ADVANCED MATERNAL AGE AND PRIMIGRAVIDITY

The 'elderly primigravida' combines the concerns of advanced maternal age, as described above, with those of an obstetrically untested woman. While the risk factors related to high parity and previous pregnancies do not apply, there is an added dimension of 'precious baby', reflecting concern that the first pregnancy in an older woman may be the one and only opportunity to have a child. It has been shown that such women are anxious about their pregnancies.[24]

Elderly primigravidas may come in two forms, the deliberately delayed pregnancy in a healthy woman, or the forcibly delayed pregnancy associated with infertility or chronic ill-health. The deliberately delayed pregnancy is a feature of modern affluent societies, especially in high-income countries. Many women in these societies defer pregnancy to pursue higher education, establish a career, or find the right life partner.[25] Such women enter pregnancies being healthy, self-empowered, and enabled to use high-quality, often private, health care facilities. Pregnancy outcomes are generally good, although age-related complications are frequently encountered. Two studies from the USA, from 1990 and 1995, the most recent that could be found, studied outcomes of elderly primigravidas. This was at a time when the issue of delayed childbearing gained prominence in that country. One study assessed the effect of first pregnancy in women aged 30 years and above in private patients in New York, and could find no significantly increased risk of preterm birth, low birth weight or perinatal mortality, although pregnancy complications and interventions were more frequent with increased age.[3] The other study found increased rates of antenatal (obesity, hypertension, diabetes), intrapartum (malpresentation, caesarean birth) and newborn complications (low birth weight, neonatal unit admission, abnormal karyotypes) in women aged 35 years or more compared with controls aged 25 to 29 years. In a logistic regression model, perinatal mortality was found to be significantly related to fibroid uterus, preterm birth, and chorioamnionitis, but not to maternal age.[4]

Rather similar findings were reported more recently from Saudi Arabia, an emerging high-income country, with the authors summarizing: 'the overall outcome however does not appear grim, as was once believed'.[26]Yet, in a recently published study from Mumbai in India, primigravidas aged 30 to 35 years fared significantly worse than those aged 25 to 29

years. Prolonged labour from both cephalopelvic disproportion and from uterine inertia were more frequent. Induction of labour was also more frequent, with the most frequent reasons for induction being pre-eclampsia, gestational diabetes mellitus and oligohydramnios.[27]

The forcibly delayed pregnancy is more likely to be encountered in poorer countries with high fertility rates. Poverty, disempowerment of women, educational disadvantage, and cultural expectations all militate against delayed childbearing, so that early first-birth is the rule.[28,29] In such societies, delayed pregnancy may result from subfertility due to associated chronic illness such as tuberculosis, HIV infection, pelvic infection, fibroid uterus with anaemia, and malnutrition.[30-32]A pregnancy, if it occurs, may thus be complicated by comorbid underlying illness, in addition to the expected pregnancy problems at advanced age. These effects will likely be compounded by a lack of health care resources in poor countries. Studies from Nigeria, India, Pakistan and Malaysia provide evidence for this in terms of high perinatal mortality rates.[5-8,20,33] There may also be effects on maternal mortality, but no studies on elderly primigravidas have been sufficiently powered to assess this rare but serious outcome.

2.4: THE FREQUENCY OF ELDERLY PRIMIGRAVIDITY

It is difficult to find updated estimates of frequencies of elderly primigravidity. It is certainly uncommon in African populations. A hospital-based study on primigravidas from Nigeria found that primigravidas aged 35 years or more made up 2.0% of all pregnancies. However, this result is likely to be an overestimate because of hospital referral bias. A community-based study of 2101 births from Soweto in the 1990s, designed to minimise referral bias, found 5 births in primigravidas aged35 years above (0.24%) and 23 in primigravidas aged 30 years or more (1.1%)[34] By how much this might have changed in Soweto or South Africa since then is not known.

2.5: DEFINING ADVANCED MATERNAL AGE FOR A PRIMIGRAVIDA

Given the rarity of elderly primigravidity in sub-Saharan African countries, and the potential complications as discussed earlier, it is worth considering what age constitutes elderly primigravidity in this context. A Nigerian study from the 1980s studied pregnancy complications at different age groups in primigravidas and found significantly increased complication rates from above the age of 25 years, using a reference group of primigravidas aged 20 to 24 years.[35] The authors declared that the term 'elderly primigravida' should be used for any primigravida aged 25 years or more. No other studies from low-income countries have attempted to define the term. For South African public health service users, it seems that 30 years might be an appropriate cut-off for concern in primigravidas, given the findings about over-30s in the Saving Mothers reports.[13,14]

2.6: METHODOLOGY IN STUDIES OF ELDERLY PRIMIGRAVIDAS

The most frequent method of assessing pregnancy risk in older primigravidas is by comparison with younger primigravidas, as done in the analytic observational studies cited above. The studies cited made use of hospital records, and tended to ignore the possibility that a number of births might have occurred out of hospital, in midwife units or at the women's homes. This is especially likely in most African countries, where home births are frequent.[36]In just one example, a study from two Nigerian hospitals in an academic complex found that perinatal mortality rates did not differ between over-35 and younger primigravidas.[8] These hospitals may have been referral points for problem pregnancies. It is quite possible that the comparison group of younger women comprised high-risk pregnancies that had been referred to the teaching hospital, and was not representative of all local primigravidas of that age, resulting in inflated and biased perinatal mortality estimates for the younger age group. It is essential that samples of both over-30s and the comparison groups reflect the whole obstetric population of the community being studied and not just hospital or facility-based pregnancies. This precaution was taken in the Soweto study on advanced maternal age, where the younger comparison group was chosen from both midwife units and

hospital, in an environment where home birth was a rare occurrence, to reflect the proportional usage of those facilities.[22]

To accelerate development of maternity care in developing countries, health care providers need to know the characteristics of the patients and populations they serve, and the risks associated with those characteristics. This applies also to evaluating how maternal age and parity affect pregnancy outcomes. Collecting information on patients can be an expensive and timeconsuming process, even in developed countries. For years, many maternity hospitals and centres in developing countries have had scarce resources to systematically evaluate their services and, therefore, can not determine the most effective means of improving their maternity care services to reduce the number of maternal deaths, stillbirths and neonatal deaths.[37]

3. PROBLEM STATEMENT

In the absence of any evidence for pregnancy risk related to primigravidity at an older age in South Africa,research was needed to define and explain associated risks and poor outcomes.Whether the appropriate age cut-off for high risk should be 30 years,based on the frequency of risk factors and poor outcomes,needed to be determined. The purpose of this study was to evaluate obstetric outcomes in advanced-maternal-age women in a large, contemporary,and unselected urban obstetric population in South Africa.[38]This would inform clinical management guidelines that rely on age and parity as possible risk factors to guide referral and clinical management.

4. OBJECTIVES

4.1: GENERAL OBJECTIVE

In view of the lack of data on the frequency and pregnancy risks associated with elderly primigravidity in South Africa, this study was done to determine the frequency and associations of pregnancy complications and pregnancy outcomes, in primigravidas aged 30 years old and above, to inform future recommendations on guidelines for referral and management of pregnancies in older primigravid women.

4.2: SPECIFIC OBJECTIVES

1. To determine the relative frequency of primigravidity at age 30 years or older in pregnancies that result in births at Soweto provincial health facilities, during one month (July 2011), as a proportion of all births.
2. To describe the frequency of pregnancy complications and outcomes in primigravidas aged 30 years or older at Soweto provincial health facilities, from August to November 2011.
3. To compare the frequency of pregnancy complications and outcomes between primigravidas aged 30 years or olderand those of a primigravid comparison group aged 20 to 24 years.

5. METHODS

5.1: STUDY DESIGN AND SETTING

This was a cross-sectional analytic study, in which pregnancy risks and outcomes were compared between groups of pregnancies based on maternal age differences.

The study was done at Chris Hani Baragwanath Academic Hospital (CHBAH), the referral centre for Soweto, and also for other settlements such as Orange Farm and Lenasia. There are about 2000 births each month at CHBAH, about two-thirds from Soweto. There are five midwife obstetrics units (MOUs) in Soweto: Lillian Ngoyi, Chiawelo, Mofolo, Dobsonville and Zola. The MOUs render level 1 health services, which include antenatal care, normal deliveries and postnatal services. They are staffed by midwives, advanced midwives, and doctors on the same premises. The MOUs each manage between 100 and 200 births each month. CHBAH accepts all referrals from MOUs for conditions that do not allow safe birth at an MOU, as presented in a protocol provided for the MOUs.These units refer problem pregnancies and labours to CHBAH. Home births are a rare occurrence. Currently, the MOU obstetric protocol states that primigravidas aged 35 years or more must be referred to CHBAH for labour and birth. While most referrals are managed in the CHBAH labour ward, seriously ill or very high-risk women are admitted in the CHBAH maternity highcare area.

5.2: STUDY POPULATION AND SAMPLING

First, a count of all births at CHBAH and the five MOUs, by age and primigravidity, was done in June 2011, to meet objective 1. For objectives 2 to 3 the study population was primigravidas, with Soweto addresses, that give birth to infants weighing 500 g or more at birth, at CHBAH from July to October 2011.All primigravidas aged 30 years or more were included (cases) that gave birth on the day before the researcher was available to collect data.

Anunmatched reference group of primigravidas aged 20 to 24 years was included as a control group for primigravidas aged 30 years or older. The choice of 20 to 24 years was based on the concern that primigravidas aged 25 to 29 years may themselves be ‘elderly’.[35]The reference group women were those that gave birth immediately after the women aged 30 years or more (i.e. the next eligible birth in the delivery book after the case). To prevent

hospital referral bias, sample selection for the younger reference group was predetermined to reflect the proportion of hospital births in the age 20 to 24 group of primigravidas. If, for example, based on the June 2011 count, 80% of primigravidas aged 30 years gave birth at CHBAH (with 20% giving birth in the MOUs), and 60% of the control group gave birth at CHBAH, the ratio of cases to controls would be 80 to 60, or 1.33 to 1. However, if the count provided a ratio of less than 1.2 to 1, or more than 1 to 1.2, then equally sized case and control groups would be chosen, in a 1 to 1 ratio. With a more extreme percentage difference in case to control ratio, hospital controls would be chosen for only a proportion of the cases, or in excess of the number of the number of cases, based on random number use.

Sample size calculations were done for a difference of caesarean section rate of 40% in the cases vs. 20% in the controls, and for an arbitrarily chosen difference of mean birth weight of 2750 g vs. 3000 g, each with standard deviations of 600 g in cases and controls respectively. The ‘sampsi’ function on Stata version 11 software (StataCorp, College Station, Texas, USA)found that for both comparisons, a sample size of 91 cases vs. 91 controls would be needed, assuming a 1:1 ratio of cases to controls, 80% power and a statistical significance threshold (alpha) of 0.05.

5.3: DATA COLLECTION

The primary sourcesfor eligible primigravidas were the birth registers and hospital case files at CHBAH. For each participant, the birth register entry alerted the researcher to find the woman in the postnatal ward and, with the woman’s informed consent, gather data from the hospital case-file. A control woman was similarly found for each case. For newborns admitted to the neonatal unit, a one-week follow-up was made to record neonatal complications or death.

Key outcome variables to be extracted from the case-notes were maternal high care area admission, mode of delivery, birth weight (with low birth weight defined as less than 2500 g), gestational age at delivery, neonatal unit admission, and perinatal death. Key explanatory variables included maternal age, unbooked status, HIV serostatus with CD4 count, hypertension (blood pressure of 140/90 mmHg or greater recorded on at least two occasions four hours apart), gestational diabetes mellitus, gestational age at delivery, and prelabour rupture of the membranes.Postpartum haemorrhage was defined as haemorrhage greater than

500 mL after delivery, requiring blood transfusion.The data extraction tool is attached as Appendix A, and shows all variables that were extracted.

5.4: DATA ANALYSIS

From the data sheet, the data were entered into Excel software, then exported for analysis in Stata software. The data was viewed and cleaned, variable by variable, by running tabulations and summaries.

Descriptive data were summarized using frequencies with percentages, means with standard deviations, and medians with ranges. To investigate the effects of age-group (age 30 years and above vs. age 20 to 24) on obstetric outcome, cross-tabulations and comparisons, comparing the different age groups, were done using Fisher's exact test for categorical variables, and Student's t-test or the Wilcoxon ranksum test, whichever was appropriate. For all calculations, statistical significance was accepted at a P value less than 0.05.

5.5: ETHICS

All participants at CHBAH were informed of the aims and methods of the study, and were reassured that their data would be kept anonymized with no name, initials or hospital number on the data extraction tool. A participant information and consent form was signed by each participant. The study protocol was approved by the University of the Witwatersrand's Human Research Ethics Committee (approval M110604, attached as Appendix B).

6.RESULTS

In the June 2011 count, 69 primigravid Soweto residents aged 30 years or more gave birth, 42 at CHBAH and 27 at the five MOUs in Soweto. It is known from routine data collected at CHBAH and the MOUs that Soweto residents make up 63% of all women who give birth at CHBAH and 95% of womenwho give birth at the MOUs.From the monthly statistics of births at CHBAH and the MOUs, it was thus calculated that the approximate number of births in Soweto was 1829 each month. Given these assumptions, the approximate proportion of primigravidas aged 30 years or more out of all pregnancies was 3.8% (69/1829).

During June 2011, 42 primigravidas aged 30 years or older gave birth at CHBAH, and 27 gave birth at the MOUs, giving a hospital birth proportion of 60.9%. In the same month, the corresponding figures for primigravidas aged 20 to 24 years were276 at hospital and 117 at the MOUs, giving a hospital birth proportion of 70.2%. The difference was 13.2%, with a P value of 0.12. This difference corresponded to a hospital birth case to control ratio of 1 to 1.15, allowing for a 1 to 1 case to control analysis as described above.

In the cross-sectional study, 76 primigravidas aged 30 years or greater were identified at CHBAH.An equal number of primigravid controls aged 20 to 24 years who also gave birth at CHBAH were selected for comparison with the hospital-delivered cases. The age distribution of cases and controls is shown in Figure 1. A majority (n=52; 68.4%) of the cases were aged 30 to 32 years.

All women booked at their antenatal clinics. The mean gestational age at booking (17.9 weeks) was significantly lower in cases than in controls (20.5 weeks; $P<0.01$). Cases weighed significantly more than controls (86.6 kg v. 73.1 kg; $P<0.01$).

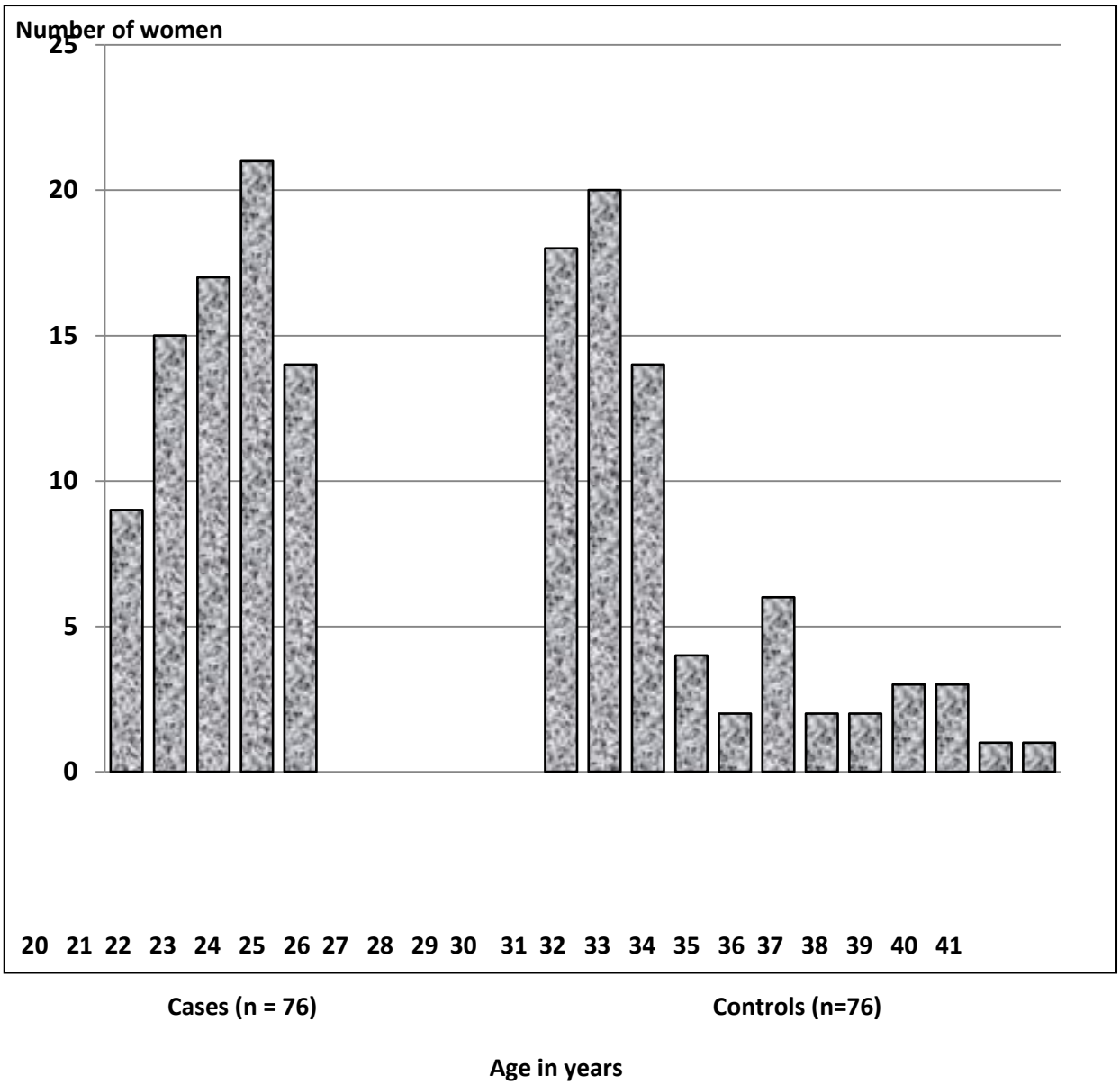

Figure 1. Age distribution of primigravid controls aged 20 to24 years (n=76) on the left, and primigravid cases aged 30 years and above (n=76) on the right.

Mean haemoglobin levels did not differ significantly between the groups, and the frequency of anaemia (haemoglobin <11.0 g/dL) was not significantly different between cases (n=15; 19.7%) and controls (n=22; 29.3%; P=0.19). HIV infection was more frequent in cases, but this was not statistically significant. However, the median CD4 count was significantly lower in cases, with a greater proportion of cases being on highly-active antiretroviral therapy for HIV infection.

Table 1. Antenatal care, maternal weight, blood screening results and HIV status in primigravidas aged 30 years or more (cases; n=76) and primigravid controls aged 20 to 24 years (controls; n=76). Denominators differ in certain rows because of missing information from the antenatal records, or where applicable only to HIV-infected women.

	Cases (n=76)		**Controls (n=76)**		**P value**
	n		**n**		
Booked at antenatal clinic	76	76 (100%)	76	76 (100%)	1.00
Mean gestation at booking ± SD (weeks)	74	17.9 ± 3.1	73	20.5 ± 3.0	<0.01
Mean weight at booking ± SD (kg)	75	86.6 ± 11.8	74	73.1 ± 9.3	<0.01
Mean Hb level at booking ± SD (g/dL)	76	12.1 ± 1.2	75	11.9 ± 1.3	0.24
Syphilis serology positive (RPR); n (%)	73	1 (1.4%)	74	1 (1.4%)	1.00
Rhesus negative blood group; n (%)	74	1 (1.4%)	73	0 (0%)	1.00
HIV positive results; n (%)	74	18 (24.3%)	71	14 (19.7%)	0.55
Median CD4 count (IQR) (cells/mm^3)	18	206 (126-299)	14	372 (184-473)	<0.01
Highly active antiretroviral therapy; n (%)	18	16 (88.9%)	14	6 (42.9%)	<0.01
History of previous tuberculosis	76	2 (2.6%)	76	0	0.50

SD = standard deviation, Hb = haemoglobin; RPR = rapid plasma reagin test; IQR = interquartile range.

The frequencies of antepartum pregnancy problems in the case and control groups are shown in Table 2. No significant differences were found in frequencies of hypertension, gestational diabetes, prelabour rupture of membranes and antenatal hospital admission. Hypertensive disorders are presented as a single group because of inconsistent recording of hypertension severity and proteinuria in the hospital notes. Distinction into pregnancy-induced and pre-eclamptic groups was not possible in a large number of participants.

Table 2. Antepartum pregnancy problems in primigravidas aged 30 years or more (cases; n=76) and primigravid controls aged 20 to 24 years (controls; n=76).

	Cases (n=76)	**Controls (n=76)**	**P value**
Hypertensive disorder of pregnancy; n (%)	13 (17.1%)	8 (11.5%)	0.35
Gestational diabetes mellitus; n (%)	1 (1.3%)	1 (1.3%)	1.0
Prelabour rupture of membranes; n (%)	9 (11.8%)	4 (5.3%)	0.25
Antenatal admission; n (%)	15 (19.7%)	12 (15.8%)	0.67

SD = standard deviation

There were no statistically significant differences between cases and controls in terms of labour and delivery, although there was a trend to delivery at earlier gestational age in cases (Table 3). Among the cases, 18 women (23.7%) gave birth at less than 37 weeks, compared with 10 women (13.2%) among the controls (P=0.14). The most frequent indications for induction of labour were prelabour rupture of membranes (n=4) and post-term pregnancy (n=3) in the cases, and post-term pregnancy (n=3), prelabour rupture of the membranes (n=2) and intrauterine death (n=2) in the controls. The most frequent reasons for caesarean section were fetal distress (n=29) and poor progress in labour (n=4) in the cases, and fetal distress (n=23) and poor progress in labour (n=3) in the controls. Where a combined indication of

fetal distress and poor progress in labour was stated as the reason for caesarean section, fetal distress was taken as the main reason for caesarean section.

Fetal outcomes are shown in Table 4. There were 77 babies in both groups, with one twin pregnancy in each. There was a trend to a lower mean birth weight in cases (2849 g) than in controls (3050 g; P = 0.06), with no significant difference in low birth weight rate. There were no significant differences in frequencies of stillbirth, low Apgar score, neonatal death, and neonatal unit admission.

Table 3. Problems during labour and delivery in primigravidas aged 30 years or more (cases; n=76) and primigravid controls aged 20 to 24 years (controls; n=76).

	Cases (n=76)	**Controls (n=76)**	**P value**
Mean gestational age at delivery ± SD (weeks)	37.6± 3.3	38.4 ± 2.6	0.11
Induction of labour; n (%)	10 (13.2%)	9 (11.8%)	1.0
Augmentation of labour with oxytocin; n (%)	11 (14.5%)	14 (18.4%)	0.67
Breech presentation; n (%)	0	2 (2.6%)	0.50
Transfer from MOU to hospital in labour; n (%)	3 (3.9%)	2 (2.6%)	1.0
Caesarean delivery; n (%)	42 (55.3%)	37 (48.7%)	0.63
Assisted vaginal delivery; n (%)	0	1 (1.3%)	1.0
Postpartum haemorrhage; n (%)	2 (2.6%)	3 (3.9%)	1.0

SD = standard deviation; MOU = midwife obstetric unit

Table 4. Fetal outcome in primigravidas aged 30 years or more (cases; n=77) and primigravid controls aged 20 to 24 years (controls; n=77).

	Cases (n=77)	**Controls (n=77)**	**P value**
Mean birth weight ± SD (g)	2849 ± 705	3050 ± 598	0.06
Low birth weight (<2500 g); n (%)	16 (20.8%)	14 (18.2%	0.84
Stillbirth; n (%)	2 (2.6%)	2 (2.6%)	1.0
Apgar score less than 7 at 5 minutes; n (%)*	6 (7.8%)	6 (7.8%)	1.0
Neonatal unit admission; n (%)*	17 (22.1%)	11 (14.3%)	0.50
Early neonatal death (less than 7 days); n (%)	2 (2.6%)	1 (1.3%)	1.0

SD = standard deviation; *denominator is number of live births (n=74 in both groups)

The circumstances of the perinatal deaths are described as follows. Among the cases, there were two stillbirths and two early neonatal deaths. These were: 1) a 30 year old woman who had booked for antenatal care and presented with intrauterine fetal death and spontaneous rupture of membranes at about 35 weeks of gestation, and went on to deliver a macerated stillborn baby weighing 2935 g; 2) a 33 year old woman with pregnancy-induced hypertension, who delivered a macerated stillborn at 26 weeks gestational age weighing 800g; 3) a 33 year old woman, who booked at 16 weeks of gestation and delivered an infant at 38 weeks with low Apgar scores and a birth weight of 2825g; the baby died on the following day due to complications related to hypoxic ischaemic encephalopathy; and 4) a 30 year old woman,HIV infected with proteinuric hypertension,admitted with prelabour rupture of membranes at 24 weeks gestational, who delivered a few hours later; the baby died as a result of complications related to extreme prematurity.

In the control group, there were two stillbirths and one early neonatal death. These were: 1) a 20 year old woman, who booked at 17 weeks of gestation, who was admitted with prelabour rupture of membranes and delivered a macerated stillborn baby weighing 2205 g; 2) a 24 year old woman, booked at 19 weeks,admitted with prelabour rupture of membranes and intrauterine death at 29 weeks, and delivered a macerated stillborn baby weighing 1109g; and 3) a 20 year old woman, booked at 19 weeks' gestational age, admitted with prelabour rupture of membranes at 35 weeks; following attempts at induction of labour, a caesarean section was done for fetal distress and the baby, weighing 2215g died later in the neonatal unit from complications related to hypoxic ischaemic encephalopathy.

7.DISCUSSION

The proportion of primigravidas at age 30 years or more out of all births in Soweto was measured at approximately 3.8%, greater than the 1.1% reported from the Soweto study in 1995.[34]This may reflect changing demographics and fertility choices in women in Soweto, in line with worldwide trends of delayed childbearing, as discussed earlier.[10]

This study was able to describe pregnancy characteristics and outcomes in primigravid women of age 30 years or older, after taking into account hospital referral bias. The women who gave birth at MOUs were not recorded in this study, but it was known from the July count that approximately equal proportions of both case and control groups would have given birth at Soweto MOUs. Because of the MOU referral protocols, none of the women who gave birth at MOUs would have had hypertension, preterm labour at less than 34 weeks of gestation, postpartum haemorrhage requiring blood transfusion, oxytocin induction or augmentation of labour, or caesarean section.

The 100% rate of booking for antenatal care was a welcome finding, suggesting good health-seeking behaviour patterns in primigravid women in this small sample. The mean gestational age at booking was significantly lower in cases(17.9 weeks) than in controls(20.5 weeks). Although reasons for this difference were not sought in this study, it is possible that older primigravidasput more value on their pregnancies carrying so-called ‘precious babies’, or were of higher socio-economic status, as reflected by delaying their first pregnancies. Therefore, this finding was not surprising.

Another finding that was not surprising was in the mean maternal weight at booking, which was statistically significant and considerably higher in the older primigravidas (86.6kg vs. 73.1 kg). Weight gain is part of the aging process in young to middle age, associated with increasing risks of hypertension and diabetes mellitus. However, the study was not sufficiently powered to determine any differences between the older and younger primigravidas with respect to hypertension and diabetes. A lack of detail in hospital files combined with late booking in a large proportion of women made it impossible to classify hypertensive disorders to distinguish pregnancy-induced from chronic disease. Even pre-eclampsia was difficult to confirm in a large number of files. Therefore, not much comment can be made about the trend to increased rates of hypertension in the cases, except that the

difference was not surprising in view of previous evidence of age-related risks in pregnancy in Soweto and elsewhere.[20,22]

Another expected finding was that HIV seropositivity was more frequent in cases, although the difference was not statistically significant. HIV seropositivity rates in antenatal surveillance in South Africa have been found to increase consistently from teenagers to women in their forties. In this study, the rates of 24.3% and 19.7% in cases and controls respectively were lower than the 2010 Gauteng Province averages in government antenatal clinics (39.1% and 24.4% respectively in the applicable age groups).[18] One may speculate that these differences are related to primigravidity, which could be associated with reduced exposure to unsafe sex and use of contraception including condoms. In women who were HIV infected, the median CD4 count in cases was significantly lower than in the controls. Also, significantly more of the cases were on highly active antiretroviral therapy. Again, these findings are not surprising given that older women are more likely to have been HIV-infected for longer, and therefore would be at more advanced stages in their illnesses.

Prelabour rupture of the membranes(PROM) was non-significantly more frequent in the older primigravidas. The previous study from Soweto showed a significant positive association between age of 35 or more, and prelabour rupture of the membranes. It was notable that a number of perinatal deaths in this study were related to prelabour rupture of membranes, but the numbers were too small in absolute terms to draw any conclusions.Overall, despite trends to increased rates of hypertension and PROM, there was no increased likelihood of hospital admission, or induction of labour, or augmentation of labour among the cases. There was a high rate of caesarean section, at around 50%, in both cases and controls, even after taking into account that these were hospital-referred women with higher than usual probability of needing caesarean section. However, the sample size was small and a 50% caesarean section rate for 76 women will have a 95% confidence interval from 38% to 62%, so no firm conclusions should be made on the caesarean section rates.There was no difference in caesarean section rate between cases and controls.

The mean gestational age at delivery and the mean birth weight showed non-significant trends towards earlier gestation at delivery and lower birth weight in the older primigravidas. No differences could however be discerned in low birth weight, neonatal morbidity or mortality, or stillbirth rates. As is discussed further below, the low sample size does not allow any conclusion regarding these differences or lack thereof.

7.1: LIMITATIONS

A limitation of this study was its lack of power to identify any differences in uncommon but important outcomes such as perinatal death or severe morbidity in the women. The necessary sample size (n=91 each in the case and control group) was not attained because there was no longer any time for data collection after October 2011, with the researcher transferred to another hospital in accordance with the demands of his registrar rotation.

A further limitation was the inability to obtain detailed data on births at the clinics. Not only is one restricted to only birth register data, but it was also impossible to obtain prospective data from the clinics without breaching the ethical rules expected from the University of the Witwatersrand's Human Research Ethics Committee. This body requires that all prospective research on individual patients, including record reviews, must include the patient's informed consent. This was clearly not possible as the researcher could not be in contact with all participant woman at the five MOUs. Instead, the calculation of the proportions of hospital births in the 30 and above and the 20 to 24 age groups allowed some adjustment for hospital referral bias which however turned out not to be an issue because the proportions were similar.

Another limitation of this study is that it can make no statements about primigravidas aged 35 years or more, since there were not enough of such women in the study for any meaningful analysis. In any case, this study was not designed to interrogate the age cut-off of 35 years and older. It could also be argued that the issue of women over 30 years should have been investigated by excluding women over 35 of age, who would have been at greater risk of complications. In view of the eventual finding of no significant differences, such an exclusion would most likely not have altered the results.

8.CONCLUSION

This study showed no significant differences in morbidity and pregnancy outcomes between primigravidas aged 30 years old or more and a younger control group, other than the expected differences in weight and HIV seroprevalence. There was a suggestion, based on earlier antenatal booking combined with a 100% antenatal booking rate, that older primigravidas may take better care of themselves than other pregnant women in terms of health-seeking behaviour.

One can conclude that there is no evidence from these data to suggest that primigravidity at age 30 and above is of serious concern in terms of risks for common morbidities. The disorders found to be more frequent (HIV infection, overweight, and a trend to hypertension) are amenable to screening at antenatal clinic. No changes in current local protocols can be suggested based on the data. Primigravidas over 35 years of age should however remain a high risk group as is the current protocol.

A large body of literature exists, describing the impact of advanced maternal age on maternal and fetal outcomes. As the proportion of advanced-age primigravidas continues to grow, obstetric providers will benefit from further up-to-date outcome data from research, to enhance preconceptual and antenatal counselling in these women.[37]

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Appendix A. Data sheet

| | | |

Admission to neonatal unit		Early neonatal death	
Cause of SB/ENND:..			
PPH needing blood transfusion		Admission to ICU		Maternal death	
Notes:			

Appendix B: Human research ethics committee clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Abel Ramoba

CLEARANCE CERTIFICATE	**M110604**
PROJECT	Pregnancy Outcome in Primrgravid Women Above the Age of 30 Years in Soweto
INVESTIGATORS	Dr Abel Ramoba.
DEPARTMENT	Department of Obstetrics & Gynaecology
DATE CONSIDERED	24/06/2011
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 24/06/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof E Buchmann

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

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