chapter **NINE**

PRABUTI Netherlands Asymptomatic bacteriuria and urinary tract infection in pregnant women with and without diabetes mellitus: a cohort study

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Abstract

BACKGROUND

To compare the prevalence of asymptomatic bacteriuria (ASB) and the incidence of urinary tract infection (UTI) in pregnant women with and without (gestational) diabetes mellitus ((G)DM).

METHODS

We performed a cohort study in five hospitals and two midwifery clinics in the Netherlands. Pregnant women with and without (G)DM were screened for the presence of ASB around 12 and 32 weeks' gestation. Characteristics of participants as well as outcome data were collected from questionnaires and medical records. ASB was defined as the growth of at least 10^5 colony forming units/ml isolated from the urine of a woman without UTI complaints. UTI was considered to be present when a treating physician had diagnosed UTI and prescribed antibiotics.

RESULTS

We studied 202 women with and 272 women without (G)DM. Of all women 31.7% with and 94.9% without and (G)DM provided a week 12 sample. The prevalence of ASB was comparable in women with and without (G)DM (12 weeks' n=322; 4.7% and 2.3%; relative risk (RR) 2.02; 95% confidence interval (CI) 0.52-7.84; 32 weeks' n=422; 3.2% and 3.0%; RR 1.06; 95% CI 0.36-3.09), as was the incidence of UTI (16.8% and 12.9%; RR 1.31; 95% CI 0.85-2.02). Neither ASB nor UTI were associated with preterm birth or babies being small for gestational age.

CONCLUSIONS

In pregnant women with and women without (G)DM, the overall prevalence of ASB was low. Neither ASB nor UTI did differ significantly between the groups. Our data discourage a routine ASB screen and treat policy in pregnant women with (G)DM.

Background

A significant number of bacteriuria cultured from the urine of a woman without symptoms of a urinary tract infection (UTI) is called asymptomatic bacteriuria (ASB).[1,2] In women with a normal pregnancy, the reported prevalence of ASB varies between 2-10% with peaks up to 40%.[2,3]
Associations between ASB and pregnancy complications, including symptomatic UTI and preterm birth, have been found in studies dating back to the sixties and seventies.4 These studies led to the introduction of ASB screening, and subsequent treating (antibiotics) policies for pregnant women all over the world.[5]
A more recent meta-analysis of these studies showed a reduced incidence of pyelonephritis (relative risk (RR) 0.23, 95% confidence interval (CI) 0.13 to 0.41) and low birthweight babies (RR 0.66, 95% CI 0.49 to 0.89) in pregnant women with ASB who were treated with antibiotics compared to those who were not treated with antibiotics. No differences were found in the incidence of preterm delivery.[4]
Causal mechanisms explaining the relation between ASB or UTI and adverse pregnancy outcomes remain unresolved while more recent studies revealed adverse effects on the infant of maternal antibiotic use during pregnancy.[6-9] The expanding knowledge on antenatal care and the changing epidemiology of pregnancy related conditions underscore in our opinion the need for re-evaluation of existing screening policies for ASB in pregnant women.
The prevalence of diabetes mellitus (DM) and gestational diabetes mellitus (GDM), thought to be risk indicators for both ASB and UTI, are increasing.[10,11] In spite of this recent data on the prevalence of ASB, the incidence of UTI and the association of ASB with adverse pregnancy outcomes in pregnant women with and without DM or GDM not distorted by the presence of an ASB screening and treating policy in Western countries are limited.[12-14]
Both limited evidence of the effectiveness of a screen and treat regimen as well as the Dutch restraint use of antibiotics, underlie the lack of a standard screen-and-treat policy for ASB during pregnancy in Dutch perinatal care.[15] This situation provides a unique environment to test the principles behind these policies in Western countries.
The aim of this study was to investigate the prevalence of ASB and incidence of UTI, including causative organisms, in pregnant women with and without DM or GDM. Secondly, we intended to study the associations of ASB and UTI with maternal and neonatal outcomes in the Netherlands.

Material and methods

Study design and participants

We enrolled pregnant women with and without DM or GDM, receiving regular antenatal care in a prospective cohort study. The study was performed from June 2009 to October 2011 at two university medical centres, three non-university hospitals and two midwifery practices.

Data collection

Women were asked to submit a midstream urine sample during routine prenatal visits around 12 weeks' gestation (range 9 to 20 weeks) and 32 week's gestation (range 27 to 38 weeks). At the same visit participating women were asked to fill out a questionnaire containing questions about their UTI history, current UTI complaints (e.g. burning sensation while urinating), ethnicity, sexual behaviour and antibiotic use. Women were also asked to send urine samples using a dipslide and additional questionnaires by mail when experiencing UTI symptoms. Neither the women nor to the treating physicians were informed on the results of the urine culture.
Demographic and clinical information with respect to diagnosis and treatment of UTI were obtained from questionnaires, hospital records and/or general practitioner (GP) records. Obstetric data were extracted from medical records up to six weeks after delivery.

Exclusion criteria and ethics

Women who did not submit at least one urine for culture, had a positive urine culture in combination with UTI complaints at the time of inclusion, those who had a multiple pregnancy, pre-existing medical conditions with a known association with UTI except for pregnancy and DM or anatomical abnormalities of the urinary tract were excluded. Informed consent was attained. The Ethics committee of the UMCG approved the study and the boards of the other participating hospitals subsequently agreed with execution of the study.

Laboratory

Urine samples were refrigerated between 4-7^{o}C and transported to one of the three participating laboratories for medical microbiology.
Culture plates were examined daily for growth and interpreted as follow:

1. Negative was defined as no growth, growth less than 10^5 colony forming units per millilitre (cfu/mL), growth of non-uropathogens including skin flora or growth of mixed bacterial flora (more than 2 organisms);
2. Positive was defined as the presence of one or two different uropathogens with a growth of at least 10^5 cfu/mL.

Common uropathogens are *Escherichia coli* (*E. coli*), *Proteus mirabilis*, *Klebsiella pneumoniae*, Enterococcus species and *Pseudomonas aeruginosa*. Organisms that are normally found in and around external genitalia and are only rarely associated with infections (including lactobacilli, corynebacteria en coagulase negative staphylococci) were considered non-uropathogens and contaminants.

Definitions

ASB was defined as a positive urine culture (the growth of at least 10^5 cfu/ml of one or two uropathogens) from a woman without complaints of a UTI. UTI was considered to be present when a treating physician had diagnosed urinary tract infection (UTI) and

prescribed antibiotics, as recorded in either a questionnaire or medical record (hospital, midwifery clinic or GP). Both DM (type 1 or type 2) and gestational DM (GDM) were clinical diagnosis made by the treating physicians. Women with DM or GDM during pregnancy were assigned to the diabetes group (from here: (G)DM). Preterm birth was defined as delivery before a gestational age of 37 weeks. Being small for gestational age (SGA) was defined as birth weight below the 10th percentile, appropriate for gestational age (AGA) between the 10th and 90th percentiles and large for gestational age (LGA) above the 90th percentile.[15]

Outcomes

The primary outcome was ASB at 12 and/or 32 weeks' gestation. Secondary outcomes were the incidence of UTI, causative uropathogens, and the association between ASB, UTI and (G)DM. The following maternal and neonatal characteristics were assessed: use of prophylaxis or antibiotics two to four weeks before collection of the study urine samples, gestational age at delivery (categorised as <32, 32-36, 37-39 and ≥40 weeks' gestation), preterm birth (<37 weeks), gender child, SGA, LGA, AGA, admission to neonatal intensive care unit independent of duration, five minute Apgar score less than seven and neonatal antibiotic use within the first six weeks of life.

Statistics

Fisher's exact test and the Mann-Whitney test were used to calculate differences in characteristics of the women and infants born from women with and without (G)DM. Relative risk (RR) and 95% confidence intervals (95% CI) were calculated to estimate differences in binary outcomes. The Mann-Whitney test was used to test differences for continuous outcomes. Regarding missing data for the primary and secondary endpoints complete case analyses per exposure were performed. Data were analysed using SPSS software for Windows, version 21.

Power analysis

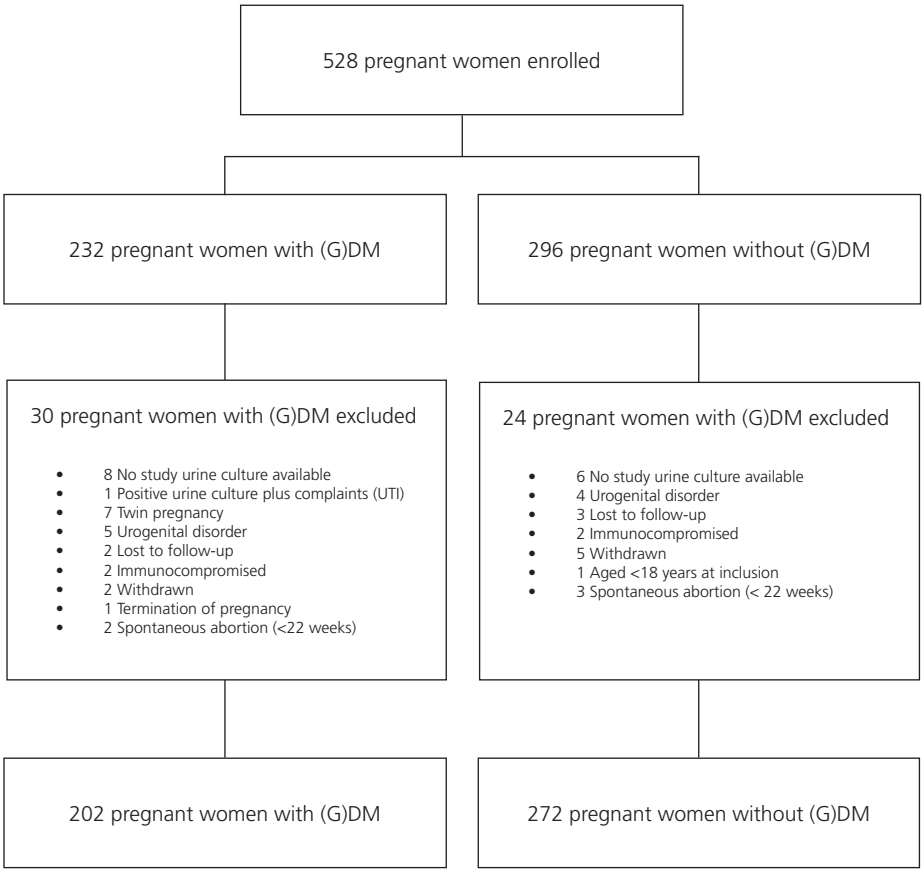
The prevalence of ASB in non-pregnant women with DM has been reported around 26%, versus 6% in women without DM.17 The prevalence of ASB in pregnant women is estimated around 5%, which is similar to that of non-pregnant women. However pregnant women will develop more often a UTI.[3,5,11] To get reliable prevalence figures, we aimed to include 50 pregnant women with (G)DM and ASB therefore we needed to screen at least 200 pregnant women. With two groups of 200 women a difference of at least 12% in the incidence of UTI can be detected between women with and without (G)DM when the proportion pregnant women with a UTI is 10% to 20% (1-ß=0.80, 2-sided =0.05, Fisher's exact test).

Results

Study population & general characteristics

From June 2010 until August 2012 a total of 528 pregnant women participated in the study, of whom 54 women were excluded for final analysis for several reasons including twin pregnancy, structural abnormality of the maternal urinary tract or loss to follow-up (see Figure 1). Leaving 474 pregnant women eligible for analysis; 202 women with and 272 without (G)DM.

Figure 1. Flow-diagram Flowchart inclusion and exclusion women with and without (G)DM



Abbreviations: (G)DM =(gestational) diabetes mellitus; UTI = urinary tract infection

Characteristics of both women with and without (G)DM and infants are presented in Table 1a and 1b. Caucasian women accounted for nearly two third of all women. All women without (G)DM were included through one of the two midwifery clinics and almost all women with (G)DM through both non-university and university hospitals. In more than 50% of both women with and without (G)DM at least one UTI was ever diagnosed during their lifetime.
Women with (G)DM were on average two year older compared to women without (33.4 and 31.2 years, p=<0.001). Of all pregnant women with diabetes, two-third was diagnosed with GDM. The majority of women with (G)DM used insulin. Infants born from women with (G)DM were more often born before 40 weeks' gestation and were more often LGA compared to those born from women without (G)DM.

Table 1a. Characteristics of pregnant women with and without (G)DM

	With (G)DM N=202		Without (G)DM N=272		P-value[a]
Age (years)	33.4±5.3		31.2±4.8		<0.001
Ethnicity					
• Caucasian	130	65.7%	182	74.0%	
• Asian	15	7.6%	8	3.3%	<0.001
• Aboriginal	24	12.1%	45	18.3%	
• Other or mixed	29	14.6%	11	4.5%	
Lifetime no of UTIs					
• Never	76	38.8%	101	38.0%	
• 1 or 2 times	68	34.7%	96	36.1%	0.447
• 3, 4 or 5 times	24	12.2%	42	15.8%	
• >6 times	28	14.3%	27	10.2%	
Multipara	129	64.2%	124	45.8%	<0.001
Centre (inclusion)					
• University hospital	94	46.5%			
• Non-university hospital	104	51.5%			NA
• Midwife clinic	4	2.0%	272	100%	
Type of DM					
• Type 1	44	21.9%	NA	NA	NA
• Type 2	22	10.9%			
• GDM	135	67.2%			
Treatment diabetes					
Insulin	140	71.4%	NA	NA	NA
Oral hypoglycemics	10	5.1%			

For both women with and without DM the maximum number of missing values for any characteristic was 7 except for ethnicity with a maximum number of missing values of 26. Abbreviations: UTI= urinary tract infection; (G)DM= (gestational) diabetes mellitus; NA = not applicable. [a] P-value calculated either with Fisher's exact test or Mann-Whitney test. Figures are numbers and percentages; or mean and standard deviation.

Table 1b. Characteristics of infants born from women with and without (G)DM

	With (G)DM N=202		Without (G)DM N=272		P-value[a]
Perinatal mortality (< 22 weeks)	0	0%	2	0.7%	0.510
Gender					
• Male	113	55.9%	134	49.3%	0.164
• Female	89	44.1%	138	50.7%	
Weight and gestational age					
• SGA	5	2.5%	20	7.4%	<0.001
• AGA	126	62.4%	198	73.1%	
• LGA	71	35.1%	53	19.6%	
Pregnancy duration					
• < 32 weeks	1	0.5%	2	0.7%	
• 32-37 weeks	24	11.9%	10	3.7%	<0.001
• 37-40 weeks	163	80.7%	124	45.6%	
• > 40 weeks	14	6.9%	136	50.0%	
Apgar at 5 minutes <7	10	5.0%	10	3.7%	0.499
Admission to NICU	6	3.1%	10	3.8%	0.799
Antibiotic use <6 weeks	20	10.6%	23	8.5%	0.521

For both women with and without DM the maximum number of missing values for any characteristic was 14. Abbreviations: (G)DM = (gestational) diabetes mellitus; SGA = small for gestational age; AGA= appropriate for gestational age; LGA= large for gestational age; NICU = neonatal intensive care unit. [a] P-value calculated using the Fisher's exact test or Mann-Whitney test. Figures are numbers and percentages; or mean and standard deviation.

ASB and UTI

Since most women with GDM were diagnosed after 20 weeks' gestation only 64 (31.7%) women with DM collected a week 12 urine sample compared to 258 (94.9%) women without DM. Sixteen percent of all women who collected a week 12 urine sample (n=322) did not collect a second urine sample around week 32.

The overall prevalence of ASB was 2.8% (9/322) at week 12 and 3.1% (13/422) at week 32. No differences were found between women with and women without (G)DM at week 12 (n=322; 3 (4.7%) and 6 (2.3%); RR 2.02; 95% CI 0.52-7.84) and week 32 (n=422; 6 (3.2%) and 7 (3.0%); RR 1.06; 95% CI 0.36-3.09). *E. coli* was the most common causative organism of ASB at 12 (66.7%) and 32 weeks' gestation (38.5%). Of all women who collected a week 12 urine sample 4.0% (13/322) and of all women who collected a week 32 sample 2.1% (9/422) were known to have used antibiotics in the four weeks prior to the day of urine collection.

The overall incidence of UTI was 14.6% (69/474). No differences were found between women with and women without (G)DM (34 (16.8%) and 35 (12.9%); RR 1.31; 95% CI 0.85-2.02).

Table 2. Prevalence of ASB and incidence of UTI in women with and women without (G)DM[a]

Week 12	With (G)DM		Without (G)DM		RR (95% CI) or P-value †
Number of samples	N=64		N=258		
Gestational age	13.8±2.0		13.3±1.6		0.020
ASB	3	4.7%	6	2.3%	2.02 (0.52-7.84)
Uropathogens cultured					
• *E. coli*	2	66.7%	4	66.7%	-
• GBS	0	-	0	-	
• Others or mixed	1	33.3%	2	33.3%	
Week 32	**With (G)DM**		**Without (G)DM**		**RR (95% CI) or P-value †**
Number of samples	N=64		N=258		
Gestational age	32.7±2.0		32.6±1.7		0.020
ASB	6	3.2%	7	3.0%	1.06 (0.36-3.09)
Uropathogens cultured					
• *E. coli*	1	16.7%	4	57.1%	-
• GBS	1	16.7%	0	-	
• Others or mixed	4	66.7%	3	42.9%	
UTI data					
Number of women with a week 12 and/or 32 sample	With (G)DM N=64		Without (G)DM N=258		RR (95% CI)
≥1 UTI diagnosed	34	16.8%	35	12.9%	1.31 (0.85-2.02)

Abbreviations: (G)DM =(gestational) diabetes mellitus; ASB = asymptomatic bacteriuria; UTI = urinary tract infection; GBS = Group B *Streptococcus*; RR = relative risk; 95% CI = 95% confidence intervals. [a] Figures are numbers and percentages; or mean and standard deviation. [b] RR and 95% CI for binary variables, p-values calculated with Mann-Whitney test for continuous variables.

Similar results were found when repeating the analysis only including women with GDM compared with women without DM (data not shown).

In two women ASB was diagnosed in both the week 12 and week 32 urine sample. In four (20.0%) out of the 20 women with ASB at 12 and/or 32 weeks' gestation a UTI was diagnosed by the treating physician during pregnancy. In three women the UTI was already diagnosed and treated with antibiotics before ASB was diagnosed in the urine sample collected for this study.

We received 16 urine samples (urine dipslides) by post of 15 women suffering from UTI symptoms. Four of these 16 (25%) were positive, confirming the diagnosis.

In women with a history of one or more UTIs during her life (n=285) compared to those without a history of UTI (n=177) a lower prevalence of ASB (6 (2.1%) and 13 (7.3%); RR 0.29; 95% CI 0.11-0.74) and higher incidence of UTI (56 (19.6%) and 12 (6.8%); RR 2.90; 95% CI 1.60-5.25) was found. Detailed information concerning ASB and UTI is provided in Table 2.

Pregnancy outcomes in women with ASB or UTI

No differences were found in adverse pregnancy or neonatal outcomes between pregnant women with (20) and without ASB (454) including preterm birth (10.0% and 7.7% RR 1.30 95% CI 0.34 to 5.02) and SGA (5.0% and 5.3%; RR 0.91 95%; CI 0.13 to 6.36). Neither were there differences between women with (n=69) and women without at least one UTI during pregnancy (n=405) with respect to preterm birth (8.7% and 7.7% RR 1.14 95% CI 0.49 to 2.62) and SGA (7.2% and 4.9%; RR 1.49; 95% CI 0.58 to 3.83).

Discussion

The overall prevalence of ASB found in Dutch women was low in both the first (around 12 weeks' gestation) and third trimester of pregnancy (around 32 weeks' gestation). The results of our study support the recommendation of the current Dutch guidelines not to screen and treat for ASB in pregnant women.[15] Since the found prevalence of ASB and incidence of UTI was not increased in pregnant women with (G)DM, we discourage a targeted ASB screen and treat policy in those women. Also, no associations were found between women with ASB or UTI and adverse pregnancy outcomes including preterm birth and SGA.

The strengths of this study are the prospective design and the completeness of follow-up till six weeks after delivery. Therefore this study provides essential up-to-date background information for ASB screening and treatment policies in pregnant women with and without DM or GDM. A limitation is that only a limited number of women with (G)DM collected a week 12 urine sample, thus generating a lack of precision in the estimate of prevalences. The largest part of women with diabetes (nearly 2/3) had GDM and GDM is often diagnosed in the second trimester. However, including only women with GDM and not women with DM in the analyses did not change the results.

The prevalence of ASB in both women with (4.7% week 12 and 3.2% week 32) and without (G)DM (2.3% week 12 and 3.0% week 32) found in our study was lower than expected, especially in pregnant women with DM. Other studies reported ASB prevalences between 4.0%-18% in pregnant women with and 4.6%-8.2% without DM and/or GDM.[12-14] Rizk *et al*. found comparable prevalences in pregnant with and without GDM using a similar definition of ASB as we did.[14] Golan *et al*. provided a limited definition of ASB and did not describe how mixed growth was handled.[12] The retrospective design, which is often accompanied by reporting bias and exclusion of women with mixed cultures, may explain the higher ASB prevalence found by Alvarez and colleague.[13]

As our study, these previous studies did not find significant associations between ASB or symptomatic UTI and preterm birth or SGA, albeit all women with ASB in these previous studies received antibiotic treatment.[12-14] ASB screening and treatment programmes were introduced in order to prevent adverse pregnancy outcomes.[5] Recent studies have shown that maternal antibiotic use during pregnancy can be associated with adverse effects for the infant.[7-9] These data warn caution for a low threshold to use antibiotics in pregnancy.

UTI is known to be one of the most common diagnoses during pregnancy.[18,19] The incidence of UTI during pregnancy in our study (14.6%) is comparable or higher than the incidence in pregnant women reported in earlier studies and increased in comparison to the incidence reported in non-pregnant women.[18,20,21] A weakness of our study is that UTI diagnoses were made by treating physicians and were mostly not confirmed by objective laboratory measurements. Treating physicians may be biased in diagnosing UTIs by common knowledge of increased incidence during pregnancy. This may lead to over-diagnosing UTI and an overestimated incidence in our study. This may also explain why a history of UTI was associated was increased incidence of UTI during pregnancy but a decreased prevalence of ASB. UTI history may decrease the threshold to report symptoms or diagnose and treat a new infection. Still, a history of UTI might be a more important risk factor for UTI during pregnancy than ASB. This is in line with a recent study by Cai *et al.* in young women, which even suggested that ASB may have a protective role and prevent (recurrent) UTI.[22]

Analyses of data obtained by our questionnaires showed that UTI like symptoms such as frequency and lower abdominal pain are common in pregnant women. These pregnancy-associated complaints can be mistaken for UTI symptoms. Currently most pregnant women receive antibiotic treatment for symptoms mimicking UTI without a confirmative urine culture thus generating overtreatment possibly leading to overtreatment. Symptoms alone may therefore not be sensitive enough to diagnose UTI in pregnant women. This is illustrated by our finding that only 25% of the women with symptoms of a UTI who sent a dipslide had a positive urine culture result.

The common used criterion of growth of at least 10^5 cfu/mL of one or two microorganisms implies that the diagnosis of ASB is straightforward. However for symptomatic UTI, lower colony counts ($\geq 10^3$ cfu/mL) sufficient proof of infection. The clinical relevance of asymptomatic lower colony count group B *Streptococcus* (GBS) bacteriuria is investigated.[23] In an earlier study we showed that urine samples of pregnant women are often contaminated with skin flora (>80%) possibly resulting in mixed growth (>2 microorganisms).24 Interpretation of mixed growth or low colony count is difficult for both clinical practice and research purposes and is possibly resulting in under- or over-diagnoses (and treatment) of ASB. To properly investigate the need for an ASB screening and treatment programme a clear definition of ASB and reproducible diagnostic method is insurmountable.

Before a screen policy is implemented several criteria must be met. The problem (prevalence of ASB) and consequences (poor pregnancy and neonatal outcomes) need to be substantial, the disease requires to be well defined, a specific and sensitive test to identify those at risk and an adequate strategy to prevent this risk should be present.[25] Most importantly, our study showed that the prevalence of ASB is low in both women with and without (G)DM and that ASB is not associated with poor pregnancy and neonatal outcomes. Moreover our questionnaire data and urine culture results revealed once again that diagnosing and defining ASB is complicated. Finally recent literature described that antibiotic treatment, the proposed strategy to prevent possible adverse effects of ASB, may have consequences for both the mother and the infant itself.

In summary, in pregnant women with and women without (G)DM, the overall prevalence of ASB was low. Neither ASB nor UTI did differ significantly between the groups. Our data discourage a routine screen and treat policy in pregnant women with (G)DM.

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NAME/
NOMBRE
DATE/
FECHA
TIME/
HORA
NUMBER/
NUMERO
TEST/
ANALISIS
After use may contain hazardous material,
Puede contener material peligroso despues
de ser usado.
120
100 ML

part FIVE

conclusion