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# MEDIKKA

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# Congenital Anomalies And Prenatal Care

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## ISSUES:

- Metformin Use in Pregnancy: Current Evidence and the Need for Review of Guideline
- Fetal Hydronephrosis: A Review of Current Management Guidelines
- Prenatal Diagnosis of Sickle Cell Disease and Ethical Concerns

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# MEDIKKA

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# Editorial

The 2015 Edition of MEDIKKA journal emerges as the bridge between the previous editions and the gold standard expected of the future editions. Although this is the second publication of the journal after the proscription of the mother association, the University of Nigeria Medical Students' Association (UNMSA), much efforts have been put in place to lunch MEDIKKA into its true place: an International Journal. It has taken a quantum limp to keep with international best practices in scholarly publications. This Edition is seen to have cut down on frivolities and more emphasis now given to the features which portrays the journal as a rich pool of knowledge in all matters related to health. The newly lunched website [www.medikkajournal.us](http://www.medikkajournal.us) has also pedestaled it as a journal with widespread audience across the whole world.

The index theme, *Congenital Anomalies and Prenatal Care* puts a spotlight on issues about birth defects and the current trends in the management of a pregnant woman. In the face of erroneous socio-cultural beliefs, there is a growing need for accurate documentation and sensitization of the public on the incidence, etiological factors and the available preventive and control measures against congenital anomalies in sub-Saharan Africa.

This year marks the terminal point of the Millennium Development Goals (MDGs) and yet maternal mortality rate is still above the 0.25 % target. Birth defects are jointly estimated to account for about 7% of all neonatal deaths worldwide. An effort to discuss these issues is a worthy contribution to the attempted realization of the MDGs 4 and 5.

By way of recognizing the efforts pooled into this publication, the editorial board would like to express a profound gratitude to the Directorate of Research, University of Nigeria College of Medicine under the amiable leadership of Dr U.S.B. Anyaehie. Special thanks to the University of Nigeria College of Medicine Alumni Association (UNNCOMA), North America for the enormous financial support. We are grateful and indeed positively surprised by the warm welcome and overwhelming support of Prof. S. Mgbor, CMD of HANSA Clinics, Enugu. Dr S. O. Ekenze and Dr F. O. Chukwuani in their individual efforts helped greatly by playing the advisory and supervisory roles. We are also grateful to every other organizations and persons who have contributed in various ways to make this edition a success. God bless you all.

**Ahmed Victor Idowu**  
*Editor-in-chief, 2015*

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**Short Communications and Case Reports:** These may be unique case reports, clinical experiences and short reports of original research. (Maximum 1,500).

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# SPECIFIC SSRIS AND BIRTH DEFECTS: BAYESIAN ANALYSIS TO INTERPRET NEW DATA IN THE CONTEXT OF PREVIOUS REPORTS

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## ABSTRACT

**Objective:** To follow up on previously reported associations between periconceptional use of selective serotonin reuptake inhibitors (SSRIs) and specific birth defects using an expanded dataset from the National Birth Defects Prevention Study. **Design:** Bayesian analysis combining results from independent published analyses with data from a multicenter population based case-control study of birth defects. **Setting:** 10 centers in the United States. **Participants:** 17 952 mothers of infants with birth defects and 9857 mothers of infants without birth defects, identified through birth certificates or birth hospitals, with estimated dates of delivery between 1997 and 2009. **Exposures:** Citalopram, escitalopram, fluoxetine, paroxetine, or sertraline use in the month before through the third month of pregnancy. Posterior odds ratio estimates were adjusted to account for maternal race/ethnicity, education, smoking, and prepregnancy obesity. **Main Outcome Measure:** 14 birth defects categories that had associations with SSRIs reported in the literature. **Results:** Sertraline was the most commonly reported SSRI, but none of the five previously reported birth defects associations with sertraline was confirmed. For nine previously reported associations between maternal SSRI use and birth defect in infants, findings were consistent with no association. High posterior odds ratios excluding the null value were observed for five birth defects with paroxetine (anencephaly 3.2, 95% credible interval 1.6 to 6.2; atrial septal defects 1.8, 1.1 to 3.0; right ventricular outflow tract obstruction defects

2.4, 1.4 to 3.9; gastroschisis 2.5, 1.2 to 4.8; and omphalocele 3.5, 1.3 to 8.0) and for two defects with fluoxetine (right ventricular outflow tract obstruction defects 2.0, 1.4 to 3.1 and craniosynostosis 1.9, 1.1 to 3.0). **Conclusions:** These data provide reassuring evidence for some SSRIs but suggest that some birth defects occur 2-3.5 times more frequently among the infants of women treated with paroxetine or fluoxetine early in pregnancy.

## INTRODUCTION

The association between maternal use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), during pregnancy and birth defects in the infants has been the topic of much discussion in recent years. After initial reports of an association between paroxetine and heart defects, the US Food and Drug Administration published an advisory warning of this potential association in December 2005.<sup>1</sup> Recent meta-analyses and systematic reviews combining data from more than 20 epidemiological studies have reached conflicting conclusions and this uncertainty influences perceptions of the safety of antidepressant use in pregnancy.<sup>2,3</sup> In a recent study, 69% of women thought that it was definitely or probably acceptable to take such drugs when not pregnant or breast feeding, but only 33% of women thought that it was definitely or probably acceptable to do so when pregnant.<sup>4</sup> SSRIs are increasingly used by women of reproductive age and during pregnancy, but the inconsistent reports have limited opportunities for clinicians to carefully evaluate the risk compared with benefit of specific SSRIs for a given patient during pregnancy.<sup>5-7</sup>

We reviewed the literature for any reports that assessed the relation between specific SSRIs and one or more of the specific birth defects that are also included in the US National Birth Defects Prevention Study (NBDPS).<sup>28-13</sup> To provide a more robust estimate of the association between individual SSRIs and birth defects, information that is necessary for decision making by patients who are being treated with these drugs and their physicians, we used bayesian methods both to summarize independent findings identified in the literature and to update those findings using the entire set of data from the NBDPS.<sup>14</sup>

## METHODS

**Study Population:** For this analysis we used data from the NBDPS, a population based case-control study of birth defects. The study's methods have been described previously.<sup>15-17</sup> Briefly, cases of birth defects were identified through birth defects surveillance systems in the US states of Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah.

Cases could be live born, stillborn, or induced abortions with one of over 30 major birth defects. The NBDPS excluded cases with known chromosomal or monogenic disorders. Unmatched live born controls from the same geographical region and time period were selected from birth certificates or birth hospital records.

More cases than controls were included overall because the study was designed for the assessment of individual defects, where controls, which were the same for all case groups, outnumbered even the largest case group. Mothers were asked to participate in a telephone inter-view in English or Spanish between six weeks and two years after the estimated date of delivery.

For this analysis we included cases and controls if they were born on or after 1 October 1997 and had an estimated date of delivery on or before 31 December 2009.

Overall participation was 67.4% for cases and 64.8% for controls. A previous NBDPS analysis of the association between SSRI use during pregnancy and birth defects, included in table 1 as Alwan and colleagues, included data from 1997 to 2002.<sup>8</sup>

To avoid double counting, these NBDPS data were excluded from the meta-analyses used to calculate prior odds ratios in the current study, but we used significant findings from the previous analysis along with those of the other studies listed in table 1 to determine which birth defect-SSRI combinations to assess. Because of the strong association between diabetes and birth defects, we excluded case and control mothers who reported pregestational diabetes (type 1 or type 2).<sup>18</sup> We also excluded mothers who reported the use of any of the following known teratogenic treatments: misoprostol, methotrexate, ycophenolate mofetil, thalidomide, or isotretinoin.<sup>19</sup>

## SSRI USE

During the interview for the NBDPS, no specific question addressed depression. Mothers were asked if they had any illnesses other than the ones already discussed (for example, hypertension or diabetes) and whether they took any medication for the illness. Women could report depression here, which would then be followed by a question about any medications taken for the illness.

There were also specific medication related questions: "between three months before conception and [the baby's] date of birth, did you take any of the following medications? Prozac? Paxil? Zoloft? Celexa?" There was no specific question for Lexapro. For this analysis, we considered women exposed if they reported taking citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil), or sertraline (Zoloft) at least once in the period from one month before conception through the third month of pregnancy.

Women who reported taking more than one type of SSRI were only included in the multiple SSRI category. We considered women as unexposed if they did not take any antidepressants in the period from three months before to the end of the pregnancy and did not report any depression, anxiety, bipolar disorder, or obsessive compulsive disorder. Women who did not answer all medication related questions, used SSRIs in a period other than the period of interest, or took antidepressants other than SSRIs (for example, bupropion and venlafaxine) were excluded.

## BIRTH DEFECTS

The NBDPS includes over 30 categories of major birth defects. After ascertainment in population based surveillance systems, the

**Table 1 | Previous studies that assessed use of individual selective serotonin reuptake inhibitors (SSRIs) during early pregnancy in mother and individual birth defects in infant**

Authors	Study design	Controls/ comparison group	Population	Included birth years	SSRIs	Birth defect categories assessed	Included confounders
Alwan et al 2007 <sup>8</sup>	Case-control (subset of current study)	Liveborn infants without major defects	10 sites in USA	1997-2002	Fluoxetine, paroxetine, sertraline	All defects, with at least three exposed	Race/ethnicity, obesity, smoking, income
Louik et al 2007 <sup>11</sup>	Case-control	Non-malformed infants	Boston, Philadelphia, Toronto, San Diego, New York State	1993-2004	Citalopram, fluoxetine, paroxetine, sertraline	All defects	Maternal age, race/ethnicity, education, year of last menstrual period, study center, smoking, alcohol, family history, body mass index, parity, seizures, diabetes, infertility, hypertension, folic acid use
Bakker et al 2010 <sup>9</sup>	Case-control	Fetuses and children with chromosomal or single gene disorder	Population based birth defects registry in Northern Netherlands	1997-2006	Paroxetine	Heart defects categories	Year of birth
Kornum et al 2010 <sup>10</sup>	Cohort	Children of women without SSRI prescription	Northern Denmark	1991-2007	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	Septal heart defects	Smoking, age, birth order, birth year
Reis and Kallen 2010 <sup>13</sup>	Cohort	Children of women without antidepressant use	Sweden	1995-2007	Citalopram, fluoxetine, paroxetine, sertraline	Hypospadias	Year of birth, age, parity, smoking and body mass index
Malm et al 2011 <sup>12</sup>	Cohort	Children of women without SSRI prescription reimbursements	Finland	1996-2006	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	All defects	Age, parity, year of birth, marital status, smoking, other psychiatric medicines, diabetes

diagnostic information was reviewed by clinical geneticists at each site to establish eligibility. Designated individual clinical geneticists reviewed all cases with a particular defect to ensure consistency across sites.<sup>16</sup> Because the primary intent of this analysis was to assess previously reported associations with SSRIs and to determine if those associations were supported by NBDPS data, we included only outcomes with at least one previous report in the peer reviewed literature suggesting a possible association with SSRIs: neural tube defects (international classification of diseases, ninth revision (ICD-9): 740-742.0), anencephaly (ICD-9: 740), all septal defects (ICD-9: 745), ventricular septal defects (ICD-9: 745.4), right ventricular outflow tract obstructions (ICD-9: 746.0-746.1), cleft palate (ICD-9: 749.0), cleft lip with or without cleft palate (ICD-9: 749.2-749.4), esophageal atresia (ICD-9: 750.3), anal atresia (ICD-9: 751.23-751.24), hypospadias (ICD-9: 752.6), any limb reduction defect (ICD-9: 755.2), craniosynostosis (ICD-9: 756.0), gastroschisis (ICD-9: 756.71), and omphalocele (ICD-9: 756.70). Some defects reported in other studies (for example, cystic kidney) could not be evaluated in this analysis because they were not included in NBDPS.<sup>13</sup>

### Development of priors

A bayesian approach requires specification of prior distributions for each of the variables in the model used to estimate the potential association between risk of birth defect and use of SSRIs. These prior distributions are probabilistic summaries of beliefs about the true values of the unknown variables before assessment of new data. The bayesian approach allowed us to incorporate existing information on the association between each SSRI and the birth defect outcome of interest. Prior distributions were developed based on literature review. A systematic review identified six studies published before 2010 that had available specific information on SSRI-birth defect combinations (table 1).<sup>8-13</sup> We created categories of birth defects based on those reports, which corresponded as closely as possible to the NBDPS birth defect categories (table 1).<sup>8-13</sup> The approach used to summarize the information presented in these publications for each of the SSRI-birth defect combinations of interest depended on the number of available studies; to avoid duplication of cases in the current analysis, we did not include the results from the earlier NBDPS analysis.<sup>8</sup> If one published assessment was only available, then the prior distribution for the log of the odds ratio relating the birth defect and use of SSRIs was assumed to be normal, with a mean given by the log odds ratio estimate reported in the study and variance defined using the corresponding reported confidence interval. If two or more studies were identified, we used bayesian meta-analysis methods to summarize the results. The goal of the meta-analysis was to produce an estimate of the log odds ratio relating the specific birth defect and SSRI across studies, taking into account the study specific estimates and their associated sampling errors. The assumed meta-analysis model included a term corresponding to the true underlying log odds ratio relating SSRI use and risk of birth

defects and a collection of random study level effects.<sup>20</sup> All available information was included in developing the meta-analysis based prior estimates, including results indicating no association between risk of birth defects and SSRI use from other published studies. If no information other than the previous NBDPS analysis was identified, then we assumed the log odds ratio relating birth defects and SSRI use to have a non-informative prior distribution, defined using a normal distribution with mean zero and a variance of 1000. Using this non-informative prior places virtually the entire weight in developing the bayesian estimates on the information contained in the full NBDPS data. An alternative approach to this analysis would be to develop estimates of the association between SSRI consumption and risk of birth defects using frequentist methods only focused on the 1997-2009 NBDPS data. These results could be summarized and then included as an additional point in a larger meta-analysis of available information. We chose the bayesian approach for two primary reasons. Firstly, we viewed the collection of information summarized by the meta-analysis as the state of current knowledge concerning potential association between SSRIs and risk of birth defects and the NBDPS data as new information available to update that knowledge. This view is consistent with the bayesian updating paradigm as applied in this analysis. In addition, we believe that only utilizing summary values (for example, estimated odds ratios and their standard errors) from the NBDPS data would be an unnecessary sacrifice of information as opposed to utilizing the individual level data informed by the meta-analysis priors. Bayesian analysis We used a bayesian approach to develop estimates for a logistic regression model relating the log odds of a specific defect and the mother's use of SSRIs (see supplementary appendix 1). In addition to a term reflecting the log odds ratio relating birth defects and use of SSRIs, the model also included confounders selected a priori and obtained through the maternal interview: maternal race/ethnicity (non-Hispanic white versus other), maternal education (0-12 years versus >12 years), obesity (body mass index <30 versus ≥30), and smoking (any smoking versus no smoking from one month before to the end of the first trimester). Although prior probabilities for the variable relating birth defect risk and use of SSRIs were developed, we assumed non-informative priors for the odds ratios associated with maternal race/ethnicity, education, obesity, and smoking in the logistic regression model. Posterior estimates for the model variables were developed using Markov Chain Monte Carlo methods. BUGS was used for the bayesian analyses.<sup>21</sup> The primary results presented here were derived using an analysis based only on NBDPS participants who reported values for all the variables used in the logistic regression model. We also conducted sensitivity analyses focused on assessing the impact of not including participants with missing information, including consideration of a potential association between being

missing and the unknown outcome. This analysis utilized bayesian imputation for missing data both under an assumption that the missing information was missing at random and under plausible assumptions on mechanisms for informative missingness (see supplementary appendix 1).

**Results:**

A total of 38 009 women with births between 1997 and 2009 were interviewed for the NBDPS. We excluded women reporting pre-existing diabetes (n=719), known use of teratogenic drugs (n=65), or depression, anxiety, bipolar disorder, or obsessive compulsive disorder but not reporting any antidepressant use (n=30). And, after excluding defects with no previous reported associations with SSRIs, the final analyses included 17 293 unexposed cases, 659 cases exposed to citalopram, escitalopram, fluoxetine, paroxetine or sertraline, 9559 unexposed controls, and 298 controls that were exposed to one of these SSRIs (figure). Sertraline was the most commonly used SSRI; approximately 40% of control mothers who reported use of an SSRI used sertraline (table 2 ). Although there was some difference in overall SSRI use by state, the distribution of the specific SSRIs was similar across the study sites. There was no difference in the age distribution among SSRI users except for sertraline, which was more often reported among older mothers. Reported use of citalopram and escitalopram started in 2000 and 2002, respectively, and increased over time. Fluoxetine reports decreased over time, but not as much as paroxetine use decreased, and sertraline

use stayed relatively constant. There was no difference in the use of the specific SSRIs before or after 1 December 2006, the date the American College of Obstetricians and Gynecologists published their committee opinion on SSRI use in pregnancy.<sup>22 23</sup>

In a bayesian analysis of the current NBDPS data that takes into account non-NBDPS individual drug-specific birth defect associations previously reported in the literature, no association with maternal use of citalopram or escitalopram monotherapy was found, except for a marginal association between citalopram and neural tube defects (table 3 ). For fluoxetine treatment, associations were seen for ventricular septal defects, right ventricular outflow tract obstruction cardiac defects, and craniosynostosis. Paroxetine had the most previously reported associations, and significant associations were observed for five of the seven defects assessed. Associations between paroxetine and anencephaly, atrial septal defects, and right ventricular outflow tract obstruction cardiac defects found in other studies were confirmed in this independent dataset, and two other associations seen in the previous NBDPS analysis<sup>8</sup> (gastroschisis and omphalocele) were again seen in this analysis. For sertraline, the most commonly used SSRI in our study, the findings for all five defects assessed were not significant. A bayesian analysis using a non-informative prior (that is, assuming there were no previously published studies to help develop an informative prior), and

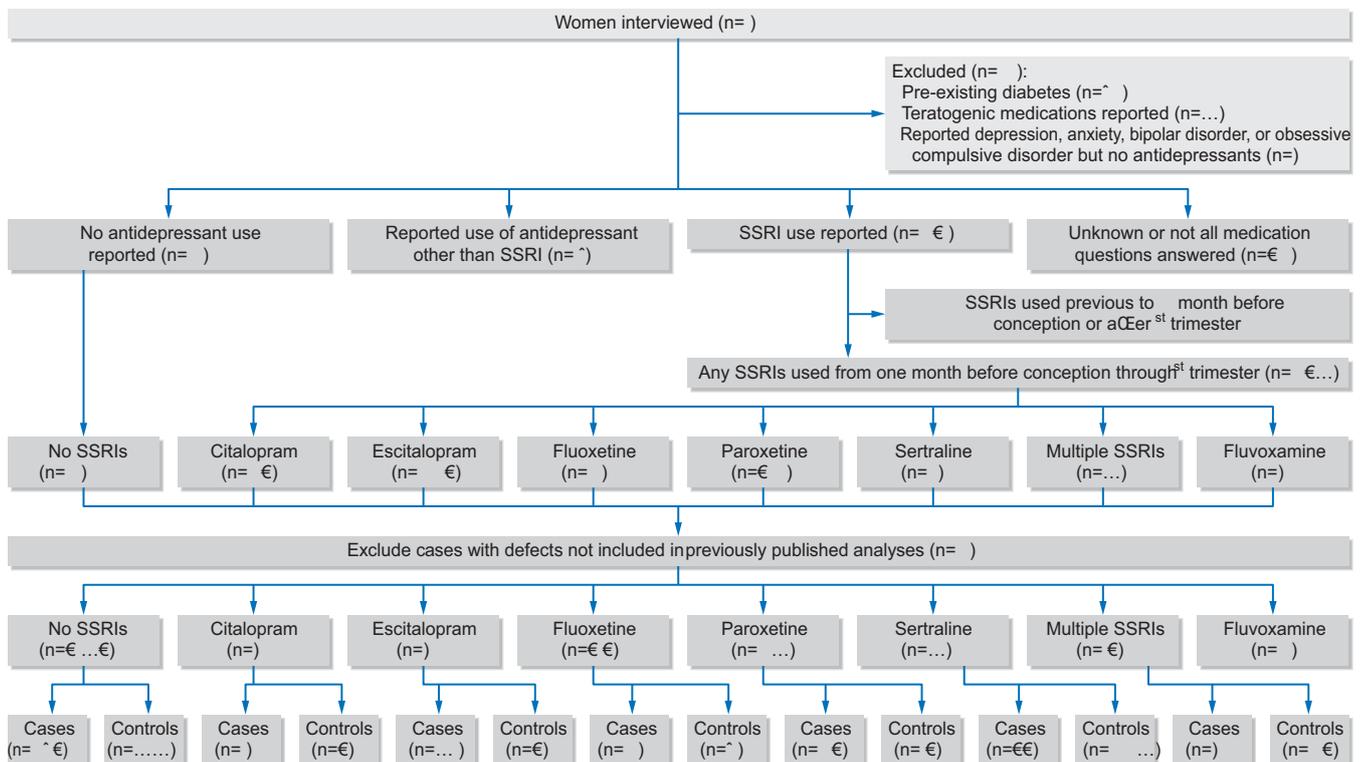


Table 2 | Descriptive statistics of control mothers (n=9857) who reported periconceptional use of selective serotonin reuptake inhibitors (SSRIs), National Birth Defects Prevention Study, 1997-2009

Variables	No (%) using SSRIs						
	Any SSRIs	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Multiple SSRIs
Total	298 (3.0)	29 (9.7)	26 (8.7)	74 (24.8)	42 (14.1)	115 (38.6)	12 (4.0)
Study site :							
New Jersey	7 (1.2)	0	0	1 (14)	3 (43)	3 (43)	0
Texas	17 (1.4)	1 (6)	1 (6)	3 (18)	2 (12)	9 (53)	1 (6)
California	24 (2.1)	1 (4)	2 (8)	8 (33)	2 (8)	8 (33)	3 (13)
Georgia	23 (2.2)	3 (13)	1 (4)	8 (35)	1 (4)	9 (39)	1 (4)
New York	21 (2.5)	2 (10)	1 (5)	4 (19)	5 (24)	8 (38)	1 (5)
Arkansas	43 (3.5)	3 (7)	4 (9)	11 (26)	2 (5)	20 (47)	3 (7)
North Carolina	28 (3.6)	2 (7)	5 (18)	4 (14)	5 (18)	12 (43)	0
Massachusetts	42 (3.6)	5 (12)	2 (5)	12 (29)	7 (17)	16 (38)	0
Iowa	42 (3.9)	3 (7)	5 (12)	9 (21)	10 (24)	13 (31)	2 (5)
Utah	51 (6.1)	9 (18)	5 (10)	14 (27)	5 (10)	17 (33)	1 (2)
Maternal age (years):							
<20	14 (1.4)	2 (14)	0	4 (29)	3 (21)	5 (36)	0
20-24	55 (2.4)	5 (9)	4 (7)	13 (24)	7 (13)	21 (38)	5 (9)
25-29	81 (3.0)	6 (7)	5 (6)	23 (28)	14 (17)	31 (38)	2 (2)
30-34	100 (4.0)	12 (12)	12 (12)	23 (23)	11 (11)	38 (38)	4 (4)
35-39	41 (3.6)	3 (7)	5 (12)	9 (22)	5 (12)	18 (44)	1 (2)
≥40	5 (3.0)	1 (20)	0	2 (40)	2 (40)	0	0
Maternal race/ethnicity†:							
Hispanic	21 (0.9)	0	1 (5)	8 (38)	3 (14)	8 (38)	1 (5)
Non-Hispanic black	13 (1.2)	1 (8)	0	3 (23)	1 (8)	6 (46)	2 (15)
Other	15 (2.1)	3 (20)	1 (7)	3 (20)	2 (13)	6 (40)	0
Non-Hispanic white	249 (4.4)	25 (10)	24 (10)	60 (24)	36 (14)	95 (38)	9 (4)
Maternal education (years)†:							
0-8	4 (0.8)	0	0	1 (25)	1 (25)	2 (50)	0
9-11	27 (2.4)	2 (7)	0	7 (26)	7 (26)	9 (33)	2 (7)
12	66 (2.8)	3 (5)	6 (9)	21 (32)	9 (14)	24 (36)	3 (5)
13-15	98 (3.8)	13 (13)	9 (9)	19 (19)	16 (16)	37 (38)	4 (4)
≥16	102 (3.3)	11 (11)	11 (11)	25 (25)	9 (9)	43 (42)	3 (3)
Pregpregnancy maternal body mass index (kg <sup>2</sup> /m <sup>2</sup> )†:							
<18.5	8 (1.6)	1 (13)	0	2 (25)	3 (38)	2 (25)	0
18.5-24.9	162 (3.2)	13 (8)	14 (9)	41 (25)	24 (15)	65 (40)	5 (3)
25-29.9	67 (3.1)	11 (16)	5 (7)	18 (27)	5 (7)	23 (34)	5 (7)
≥30	60 (3.7)	4 (7)	7 (12)	12 (20)	10 (17)	25 (42)	2 (3)
Periconceptional maternal smoking:							
No	215 (2.7)	21 (10)	19 (9)	59 (27)	25 (12)	83 (39)	8 (4)
Yes	82 (4.7)	8 (10)	7 (9)	14 (17)	17 (21)	32 (39)	4 (5)
Periconceptional maternal alcohol use:							
No	147 (2.4)	16 (11)	11 (7)	31 (21)	20 (14)	64 (44)	5 (3)
Yes	149 (4.2)	13 (9)	14 (9)	42 (28)	22 (15)	51 (34)	7 (5)
Year of due date:							
1997-99	34 (2.0)	0	0	11 (32)	9 (26)	14 (41)	0
2000-01	36 (2.2)	4 (11)	0	14 (39)	5 (14)	11 (31)	2 (6)
2002-03	43 (2.8)	7 (16)	1 (2)	9 (21)	6 (14)	17 (40)	3 (7)
2004-05	76 (4.5)	2 (3)	8 (11)	18 (24)	14 (18)	31 (41)	3 (4)
2006-07	52 (3.1)	5 (10)	8 (15)	13 (25)	6 (12)	19 (37)	1 (2)
2008-09	57 (3.6)	11 (19)	9 (16)	9 (16)	2 (4)	23 (40)	3 (5)

Sites are statewide for Arkansas, Iowa, and Utah. All other sites are selected regions. Years included: Arkansas 1998-2009, California 1997-2009, Georgia 1997-2009, Iowa 1997-2009, Massachusetts 1997-2009, New Jersey 1998-2003, New York 1997-2002 and 2004-09, North Carolina 2003-09, Texas 1997-2009, and Utah 2003-09.

†Variables were recoded to dichotomous categories for adjusted analyses; non-Hispanic white versus other, 0-12 years education versus >

12 years, body mass index < 30 versus ≥ 30 kg/m<sup>2</sup>.

sensitivity analyses using bayesian methods in which missing data for confounders were replaced with imputed values showed similar results for most associations except for the association between citalopram and neural tube defects. The prior for that association was based on one cohort study, which found a higher odds

ratio, and our logistic regression analysis without considering this prior study showed no association (see supplementary table).

### Discussion:

Using data from the US National Birth Defects Prevention Study (NBDPS), we confirmed previously reported associations between right ventricular outflow tract obstruction cardiac defects

Table 3 Odds ratios and 95% confidence interval, resulting prior odds ratio, and bayesian complete case analysis posterior odds ratio with 95% credible interval, National Birth Defects Prevention Study (NBDPS), 1997-2009

Birth defect by SSRI	Odds ratio (95% CI)		Malm et al <sup>12</sup>	Prior odds ratio (95% CI)	Odds ratio (95% CI): Alwan et al <sup>8</sup>	Posterior odds ratio (95% CrI): NBDPS 1997-2009
	Louik et al <sup>11</sup>	Bakker et al, <sup>9</sup> Kornum et al, <sup>10</sup> Reis and Kaller <sup>3</sup>				
<b>Citalopram:</b>						
Neural tube defects	—	—	2.5 (1.2 to 5.1) (#8)	2.5 (1.2 to 5.1)	—	1.8 (1.0 to 3.0) (#5)
Ventricular septal defects	—	—	1.3 (0.9 to 1.8) (#36)	1.3 (0.9 to 1.8)	—	1.3 (0.9 to 1.8) (#6)
Cleft lip with or without cleft palate	3.2 (0.9 to 11.9) (#4)	—	—	3.2 (0.9 to 11.9)	—	1.4 (0.7 to 2.7) (#6)
Hypospadias	1.9 (0.4 to 8.8) (#4)	1.3 (0.9 to 1.8) (n=38)	—	1.3 (0.6 to 2.5)	—	1.2 (0.7 to 2.0) (#8)
<b>Escitalopram:</b>						
Septal defects	—	4.2 (1.0 to 17.1) (n=3)	1.5 (0.7 to 3.0) (#6)†	1.7 (0.7 to 3.7)	—	1.3 (0.7 to 2.1) (#11)
<b>Fluoxetine:</b>						
Ventricular septal defects	—	—	1.5 (1.0 to 2.2) (#26)	1.5 (1.0 to 2.2)	—	1.4 (1.0 to 1.9) (#16)
RVOTO	1.0 (0.2 to 3.4) (#4)	—	2.7 (0.9 to 8.5) (#3)	1.5 (0.6 to 3.6)	0.9 (0.3 to 2.7) (#4)	2.0 (1.4 to 3.1) (#27)
Esophageal atresia	—	—	—	Non-informative prior	2.4 (0.9 to 6.4) (#5)	1.8 (0.8 to 3.4) (#10)
Craniosynostosis	—	—	—	Non-informative prior	2.8 (1.3 to 6.1) (#10)	1.9 (1.1 to 3.0) (#21)
<b>Paroxetine:</b>						
Anencephaly	Neural tube defect: 3.3 (1.1 to 10.4) (†)	—	—	3.3 (1.1 to 10.4)	5.1 (1.7 to 15.3) (#5)	3.2 (1.6 to 6.2) (#6)
Atrial septal defects	—	5.7 (1.4 to 23.7) (n=3)	1.3 (0.4 to 4.0) (#6)	1.8 (0.7 to 4.5)	—	1.8 (1.1 to 3.0) (#15)
RVOTO	3.3 (1.3 to 8.8) (#6)	—	5.2 (1.6 to 16.3) (#8)	3.9 (1.4 to 10.4)	2.5 (1.0 to 6.0) (#7)	2.4 (1.4 to 3.9) (#16)
Cleft palate	1.5 (0.4 to 5.3) (#3)	—	2.7 (1.0 to 7.1) (#4)	1.7 (0.7 to 4.0)	1.7 (0.6 to 4.8) (#5)	1.3 (0.7 to 2.3) (#10)
Hypospadias	1.0 (0.3 to 3.3) (#3)	2.5 (1.1 to 4.6) (n=9)	—	1.6 (0.6 to 3.4)	0.6 (0.2 to 2.4) (#3)	1.1 (0.6 to 1.9) (#9)
Gastroschisis	—	—	—	Non-informative prior	2.9 (1.0 to 8.4) (#5)	2.5 (1.2 to 4.8) (#13)
Omphalocele	—	—	—	Non-informative prior	8.1 (3.1 to 20.8) (#6)	3.5 (1.3 to 8.0) (#6)
<b>Sertraline:</b>						
Anencephaly	0.8 (0.1 to 6.3) (#1)	—	—	0.8 (0.1 to 6.3)	3.2 (1.1 to 9.3) (#4)	1.2 (0.5 to 2.5) (#7)
Septal defects	2.0 (1.2 to 4.0) (#13)	3.3 (1.5 to 7.5) (n=6)	0.5 (0.2 to 1.3) (#5)†	1.5 (0.6 to 2.9)	0.7 (0.3 to 1.5) (#10)	1.0 (0.8 to 1.4) (#47)
Anal atresia	4.4 (1.2 to 16.4) (#6)	—	—	4.4 (1.2 to 16.4)	0.7 (0.2 to 2.8) (#4)	1.4 (0.8 to 2.3) (#11)
Any limb reduction	3.9 (1.1 to 13.5) (#6)	—	—	3.9 (1.1 to 13.5)	Transverse: 1.2 (0.4 to 4.0) (†)	1.2 (0.7 to 2.0) (#13)
Omphalocele	5.7 (1.6 to 20.7) (#8)	—	—	5.7 (1.6 to 20.7)	1.5 (0.4 to 6.6) (#3)	1.4 (0.7 to 2.8) (#4)

SSRIs: selective serotonin reuptake inhibitor; RVOTO: right ventricular outflow tract obstruction cardiac defects.

Adjusted for maternal race/ethnicity, maternal education, obesity, and smoking.

Priors are only based on studies described in first three columns and exclude Alwan et al. Informative prior was calculated if the only available data were from Alwan et al, but this association was reported in that earlier analysis using a subset of NBDPS data.

†Ventricular septal defect.

in infants and maternal use of fluoxetine<sup>12</sup> or paroxetine<sup>8 11 12</sup> early in pregnancy, and between anencephaly<sup>8 11</sup> or atrial septal defects<sup>9</sup> in infants and maternal use of paroxetine. This analysis also confirmed associations between gastroschisis or omphalocele and paroxetine and between craniosynostosis and fluoxetine that were reported in the analysis of an earlier subset of NBDPS data;<sup>8</sup> however, these still require corroboration in an independent data source. It is reassuring that none of the five previously reported associations between sertraline and birth defects<sup>8 10-12</sup> were confirmed in this analysis, particularly since about 40% of women reporting use of an SSRI in early pregnancy used sertraline. In addition, we did not find support for nine other previously reported associations between maternal SSRI treatment and selected birth defects in the child. Although our analysis strongly supports the validity of the associations that were observed, the increase in the absolute risks, if the associations are causal, is small. The two strongest posterior odds ratios were seen for maternal paroxetine treatment and anencephaly (3.2) or right ventricular outflow tract obstruction cardiac defects (2.4) in the infant. If these associations are causal, the absolute risks in the children of women who are treated with paroxetine early in pregnancy would increase for anencephaly from 2 per 10 000<sup>24</sup> to 7 per 10 000, and for right ventricular outflow tract obstruction cardiac defects from 10 per 10 000<sup>25</sup> to 24 per 10 000. The absolute risks for these birth defects are still low. This analysis confirms the need to assess the association between specific SSRIs and specific birth defects rather than combining an entire drug class or heterogeneous group of birth defects. Although SSRIs are similar pharmacologically, there are chemical differences, and if any of them do have teratogenic activity, it may be completely unrelated to the inhibition of serotonin receptors. SSRIs also differ pharmacokinetically,<sup>26</sup> and this could account for differences in teratogenic activity, whether or not the mechanism involved inhibition of serotonin receptors.<sup>27</sup> Limitations of this study This analysis does not address whether the birth defect associations we observed were caused by maternal SSRI treatment, underlying maternal disease, or some other factor. Since there was no specific question on depression and we cannot identify all participants with untreated depression, there is the possibility of confounding by indication. A recent publication by Furu and colleagues combined data from five Nordic countries.<sup>28</sup> Some overlap occurred between the data included in this recent study and the three Nordic studies we included in our meta-analysis, but this study also included data from Norway and Iceland that is not included in our analyses.<sup>10 12 13</sup> Many of the associations we assessed for septal heart defects and right ventricular outflow tract obstruction cardiac defects showed similar risk estimates in our analysis and the recent study.

One clear different finding is the association reported by Furu and colleagues for anal atresia and sertraline that was also reported by Louik and colleagues but is not evident in the NBDPS data.<sup>11 28</sup> Additional limitations of this analysis need to be acknowledged. Periconceptional exposure was based on maternal self report, with interviews conducted six weeks to 24 months after the expected date of delivery. However, Kwon and colleagues reported good concordance between self report of antidepressants and claims data.<sup>29</sup> We made 21 comparisons between exposure and outcome using five different models, and it is possible that some statistically significant findings occurred owing to the occurrence of false positive associations expected with multiple comparisons.<sup>30</sup> Another limitation is that the small numbers for some of the individual birth defects and some of the specific exposures resulted in unstable estimates. Finally, exposure ascertainment is known to be more complete when women are specifically asked about their use of drugs by name;<sup>31</sup> the interview did not include a specific question about use of escitalopram. Strengths of this study This analysis also has some important strengths. The Bayesian analysis enabled consideration of evidence both for and against an association between use of SSRIs and risk of birth defects from previous epidemiological studies in the analyses and used relatively homogenous and discrete classes of birth defects and SSRI monotherapy. As a result, our study provides strong evidence for the reproducibility and validity of the associations that were observed. The sensitivity assessment showed that missing data were unlikely to have affected the results. The association between SSRIs and heart defects is biologically plausible; Sadler<sup>27</sup> has suggested that the association may be a result of the key role that the neurotransmitter serotonin (5-hydroxytryptamine) plays in embryonic development of the heart. A major advantage of this analysis over some previous reports is the ability to assess individual SSRIs and individual birth defects, while accounting for earlier reported associations. Although the data are self reported, they do represent reported use of the medications and not just filling of the prescription. Approximately 30% of mothers stop taking SSRIs during pregnancy,<sup>32</sup> and this might not be captured if we relied on prescription information or medical records, since prescriptions might have been filled but not taken after the pregnancy was recognized. We have previously used NBDPS data to show that antidepressant prescription patterns have changed over time,<sup>5</sup> making it more challenging to study these associations. Our analyses of a large population based case-control dataset combined with prior odds ratios based on the literature allowed us to show and refine associations between maternal fluoxetine or paroxetine treatment during pregnancy and right ventricular outflow tract obstruction cardiac defects and between maternal use

of paroxetine and anencephaly or atrial septal defects. In contrast, we found no evidence to support 14 other previously reported associations between maternal SSRI use and birth defects. Continued scrutiny of the association between SSRIs and birth defects is warranted, and additional studies of specific SSRI treatments during pregnancy and birth defects are needed to enable women and their healthcare providers to make more informed decisions about treatment. Meanwhile, the current analysis can help guide healthcare providers and women to the safest options for treatment during early pregnancy to minimize the risk of major birth defects, while providing adequate treatment of maternal depression.

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Ethical approval: This study was approved by the institutional review board of the Centers for Disease Control and Prevention and all participating sites.

Data sharing: Previous publications with a subset of this data: Alwan S, Reehuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;356:2684-92 and Alwan S, Reehuis J, Rasmussen SA, et al. Patterns of antidepressant medication use among pregnant women in a United States population. *J Clin Pharmacol* 2011;51:264-70.

Transparency: The leader author (JR) hereby informs that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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**Appendix table:** Odds ratios for associations between selected SSRIs and birth defects using different statistical methods

**Appendix:** statistical methods

# AN ASSESSMENT OF CAUSES AND CHALLENGES OF STREET BEGGING IN ENUGU-NORTH LOCAL GOVERNMENT AREA OF ENUGU STATE; THE BEGGARS PERSPECTIVE

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## ABSTRACT

### Introduction

Begging has been a serious problem confronting many urban areas across the globe. The situation becomes worse when it confronts urban areas of less developed nations. People engaged in begging themselves also recognized begging to be a 'problem'. To them, it's harsh, humiliating, demeaning, degrading and frustrating. Today, their presence in the streets of urban areas of developing countries is recognized to be a serious problem that requires urgent redress.

**Objective:** The main thrust of this research is to assess the causes and challenges of street begging in Enugu-North Local Government Area of Enugu State.

**Materials And Methods:** Convenience Sampling Method was employed in carrying out the research work and researcher-administered questionnaires were used for data collection

**Results:** A total of sixty (60) questionnaires were distributed and simple percentages were used for the analysis of the data. The beggars gave their reasons for begging as follows: poverty (96.6%), medical illness (32.2%), psychiatric illness (6.8%), old age (16.9%), unemployment (69.5%), laziness (11.9%), physical illness (69.5%), peer influence (1.7%), family disintegration (25.4%), drug and alcohol dependencies (3.4%), school dropout and teenage pregnancy (22.0%), natural disaster (5.1%), culture and religion (10.2%), lack of parental education (23.7%), death of parents/relatives (52.5%), easy and profitable business (37.3%) and other reasons (1.7%). Poverty was the commonest reason identified by the beggars as obtained in majority of previous studies, while peer influence accounted for the least reason.

The sampled beggars narrated their challenges as follows: social stigmatization (64.4%), sexual harassment (13.6%), inferiority complex (40.7%), social and economic liabilities (57.6%), being driven from one place to another (42.4%), fear of being captured for sacrifice (15.3), misfortune of being knocked down by passing vehicles (35.6%), molestation by the security officials (27.1%), lack of safe place to sleep (37.3%), unwillingness of people to give alms (22.0%). Exposure to harsh weather was the commonest challenge encountered by most beggars, while sexual harassment accounted for the least challenge.

**Conclusion:** The study has identified that street begging is associated with such causal factors as poverty, unemployment, physical and mental disabilities, death of parents/relatives, homelessness, and family rejection of beggars. Therefore, there is need for more dynamic approach in reducing the incidence of begging in our society.

## INTRODUCTION

Street beggars are individuals or groups, irrespective of age and with or without disabilities, who beg and make a living from the streets by asking people for money, food and clothes as gifts or charity.<sup>1,2</sup> Beggars are called by other names locally. Among the Hausa people, they are called Almajiri, the Ibo people call them Onye-aririo

while Yoruba call them Onibara. Street begging is defined as asking for money without an exchange of service in a public place.<sup>2</sup> Begging can also be defined as a practice whereby a person obtains money, food, shelter or other things from people they encounter by request.<sup>3</sup>

Alms begging has also been regarded as the habit of someone (a beggar) soliciting for favour from others (potential donors) for survival and enrichment.<sup>4</sup> In some other views, begging is regarded as an income supplement necessary for survival at some levels, related to addictive behaviours or the need for food, accommodation, health, and so on. Begging has been variously conceptualized by scholars to reflect different reasons for begging. In the words of Jelili, “to beg” is to simply ask people for money, food, clothes etc as a gift or charity.<sup>5</sup> He conceptualizes begging to involve not only individuals but organizations or countries. In Wikipedia, begging is presented as requesting something in a supplicating manner with the implication that person who is begging will suffer emotional and or physical harm. Like Jelili, Wikipedia also agrees that the term is applicable not only to individuals but to groups. Some scholars use the term mendicancy, vagrancy,<sup>6</sup> panhandling, sponging<sup>7</sup> to reflect means and reasons for begging. While panhandling and sponging are synonymous with street begging, mendicancy and vagrancy connote more than street begging. Mendicancy refers to an act of begging usually associated with religious belief; vagrancy is used to describe the begging activities of jobless, homeless, and wanderers or vagabond.<sup>8</sup> Whatever term used: street begging, panhandling, sponging, mendicancy or vagrancy, it has its root in the general idea of asking people for money, food, clothes etc.

## MATERIALS AND METHODOLOGY

### Study Area

Enugu-North is a Local Government Area of Enugu State, Nigeria, and one of the seventeen (17) local government areas in the state. It is among the three (3) local governments that form the Enugu city. Others are Enugu east and Enugu South local government areas. Its headquarters is located in the heart of Enugu city. It has an area<sup>47</sup> of 106km<sup>2</sup> and a population<sup>48</sup> of 244,852 at the 2006 census.

Just like the other parts of the state, Enugu North Local Government Area is located in the tropical rain forest zone with a derived savannah.<sup>50</sup> Its climate is humid and its humidity is at its highest between the month of March and November, and the mean daily temperature is 26.7°C (80.1°F).<sup>50</sup> As in the rest of the West Africa, the rainy and dry seasons are the main weather periods that recurs in Enugu. Other weather condition affecting the city includes harmattan, a dusty trade wind lasting a few weeks in the months of December and January.<sup>50</sup> The average annual rainfall is around 2,000mm (79 inch),

which arrives intermittently and becomes very heavy during the rainy season.<sup>50</sup>

The main occupation of the people is civil service, with lower percentages of trading and skill work of different kinds.<sup>50</sup> Like most other cities in Nigeria, Enugu city is hot all year round. Social amenities available are electricity, tarred roads, schools, primary, secondary and tertiary health centres, hotels, pipe borne water, though a good number of the people use well water etc.<sup>50</sup>

### Study population

The target population for this study consists of all street-beggars in Enugu-North LGA.

### Study Design

The research design adopted for this study was a descriptive survey design done on September to October 2014.

### Approval and ethical considerations

1. Approval for the study was obtained from the Ethics Committee of UNTH, Enugu.
2. Informed consent was obtained from the street beggars.

### Sample Size Estimation and sampling

The sample size of the beggars was determined using the formula:

$$N = (Z^2pq) \div d^2$$

Where

N = Minimum sample size

Z = 1.96 which corresponds to the 95% confidence level

p = Prevalence of 2% (0.02).<sup>18</sup>

q = 1-P = 0.98

d = precision level 5% (0.05)

$$N = (1.96^2 \times 0.02 \times 0.98) \div 0.05^2 \\ = 30$$

Hence, a sample of at least 30 beggars was determined. For the purpose of this study, twice the calculated minimum sample size was studied {sixty (60) beggars}.

### Sampling method

Convenience sampling method was used due to the nature of the study and people were interviewed as they were seen.

### Inclusion criteria

1. All beggars who were seen in the streets within the study period.
- Beggars who could understand the research questions

and were able to communicate with us.

#### Exclusion criteria

1. The street beggars who refuse to give consent
2. Beggars who as a result of language barrier could not communicate reasonably with the researchers.
3. Beggars who were not on the streets at the time of the study.

#### Data Collection:

Primary and secondary data were utilized in the study. Primary data was collected from the street beggars. The secondary data was collected from various documentary sources such as journal papers, internet materials and other documents relevant for the study.

The study as a whole was drawn from a wide range of data collection instruments so as to meet objectives of the study. These include documentary review, structured researcher- developed questionnaires, and observation techniques. The primary data collection was in the form of structured, self-administered questionnaires with clarification where necessary for literate respondents and researcher-administered questionnaires for the illiterate respondents.

The questionnaires elicited information on social demographic characteristics of the respondents such as age, sex, marital status, tribe, place of residence, educational status, religion, income status etc. Questions covering various aspects of the causes, challenges and solutions of street begging were also included.

#### Data Analysis:

The statistical method used to analyze the data was descriptive. Descriptive statistics was used to obtain frequency counts and percentages of various coded responses. Descriptive analysis was employed for the demographic data, that is, simple frequency counts and

## RESULTS

Sixty (60) questionnaires were distributed and all were retrieved, giving a response rate of 100%.

**Table 4.** Respondent's reasons for Begging

	Frequency(n=60)	Percent of cases
Poverty	57	96.6%
Medical illness	19	32.2%
Psychiatric illness	4	6.8%

percentages and item-by-item analysis was done using mean scores and ranking order. Qualitative and quantitative data were analyzed separately but in interpreting the data collected, quantitative and qualitative data were complementing and supplementing each other. Qualitative data obtained from participant observation was analyzed through themes and content analysis. Subsequently, the responses from the questionnaires were coded, summarized and analyzed using the Statistical Package for Social Sciences (SPSS). Data was presented in tables and charts.

#### Plans for reliability and validity of data

1. All data were collected by us for uniformity and to avoid ambiguity.
2. Street beggars were selected from a very wide variety of public spaces, which ensured a good representation.
3. Only primary information from direct interaction with street beggars was used to ensure that the information was minimally twisted.
4. All questions to the illiterate respondents were strictly administered by the researches. Possible clarifications for the literate respondents were also done only by us. This was to ensure that the respondents got the correct and necessary information required for this research.

#### Limitations of study:

- I. There was language barrier in communicating to beggars who found it difficult to understand our language; however, interpreters were employed to overcome the problem.
- II. Convenience sampling method was used.
- III. Findings were limited to the study area.

The following tables demonstrate the various results obtained from the questionnaires filled by the respondents.

<b>Old age</b>	10	16.9%
<b>Unemployment</b>	41	69.5%
<b>Laziness</b>	7	11.9%
<b>Physical disability</b>	41	69.5%
<b>Peer influence</b>	1	1.7%
<b>Family disintegration</b>	15	25.4%
<b>Drug and alcohol dependencies</b>	2	3.4%
<b>School dropout and Teenage pregnancy</b>	13	22.0%
<b>Natural Disasters</b>	3	5.1%
<b>Culture &amp; Religion</b>	6	10.2%
<b>Lack of parental education</b>	14	23.7%
<b>Death of parents/relatives</b>	31	52.5%
<b>Easy and profitable business</b>	22	37.3%
<b>Others</b>	1	1.7%

\*multiple responses

Poverty was the commonest reason identified by the beggars, while peer influence accounted for the least reason

**Table 5.** Challenges encountered by the Beggars.

	<b>Frequency(n=60)</b>	<b>Percent of cases</b>
<b>Social Stigmatization</b>	38	64.4%
<b>Sexual harassment</b>	8	13.6%
<b>Inferiority complex</b>	24	40.7%
<b>Social and economic liabilities</b>	34	57.6%
<b>Being driven from one location to another</b>	25	42.4%
<b>Exposure to harsh weather</b>	49	83.1%
<b>Fear of being captured for sacrifice</b>	9	15.3%
<b>Misfortune of being knocked down by passing vehicle</b>	21	35.6%
<b>Molestation by the security</b>	16	27.1%
<b>Lack of safe place to sleep</b>	22	37.3%
<b>Unwillingness of people to give alms</b>	13	22.0%

\*multiple response

Exposure to harsh weather was the commonest challenge encountered by most beggars, while sexual harassment accounted for the least reason

**Table 6.** Respondents' solutions to the problem of begging.

	<b>Frequency(n=60)</b>	<b>Percent of cases</b>
<b>Provision of Rehabilitation Centre</b>	36	62.1%
<b>Provision of food for students in Islamic schools</b>	16	27.6%
<b>Issuance of monthly survival allowance</b>	54	93.1%
<b>Establishment of Diverted Giving Scheme</b>	45	77.6%

<b>Bye-laws that prohibit all forms of street begging</b>	25	43.1%
<b>Directives to givers to stop giving</b>	17	29.3%
<b>Establishment of home for the elderly</b>	20	34.5%
<b>Creation of employment</b>	40	69.0%
<b>Establishment of Vocational Centre</b>	46	79.3%
<b>Provision of soft loan</b>	49	84.5%

\*multiple response

Issuance of monthly survival allowance accounted for the major solution to the problem of begging, while provision of food for students in Islamic schools had the least.

## DISCUSSION

A study on the causes and challenges of street begging was carried out in Enugu North LGA using descriptive survey design. The highest concentration of beggars in Enugu State is found in Enugu-North Local Government Area; and in view of this, Enugu-North LGA was chosen as a study area for this research. A total of sixty (60) questionnaires were distributed and all were retrieved as the questionnaires were researcher administered, giving a response rate of 100%. Data were collected by means of an in-depth structured interview. Simple percentages were used for the analysis of the data.

The findings showed that 58% of the sampled beggars were males while 42% were females. This was in consonance with what was obtained in Ogbomoso Nigeria where 62.4% of the sampled beggars were males while 37.6% were females.<sup>42</sup> This may be explained by the fact that males are fundamentally the bread winners in the families. The greatest percentage (30.9%) were within the age group of 31-40 years, followed respectively by age group of above 50 (24.0%), 21-30 year age group (22.0%), and 11-20 year age group (14.0%), while age group 41-50 accounted for the least percentage (9.1%). This might be explained by the fact that in this part of the society, individuals in the age group of 31-40 years form the major portion of the independent population who strive to fend for themselves. Below this age, individuals are normally still catered for by their parents; above the age group, they become increasingly looked after by their children.

Moreover, individuals in the age group of 31-40 year are at the peak of their struggle for success as there are high expectations from them in this period, including marriages and acquisition of houses, cars, and total independence from their parents, etc. This stimulates this age group into involving in more stressful and daring activities which could predispose them to accidental misfortunes that could lead to beggary. Furthermore,

some individuals who have some forms of disability but have resisted the urge to beg may eventually go into beggary in order to fulfill these societal expectations from them at this age group. At 41-50 years, the zeal with which individuals chase wealth wanes and they involve less in risky and stressful adventures. A little percentage of beggars who have not met their expectations by this time give up on the struggle and withdraw from the streets. However, at above 50 years when old age has crept in and people have become increasingly dependent and helpless, a good number of them resort to begging as a means of sustaining their livelihood.

Majority (47.5%) of the sampled beggars were married and living together with their spouses, 33.9% were single, 16.9% were widows/widowers, while 1.7% were divorced. This result conforms to Ogbomoso study where only 18.3% were single.<sup>42</sup> This may prove the fact that family people have greater responsibilities, but may also suggest that unavailability of marital partners is not an important driving force for begging. The largest proportion (55.1%) of the beggars have family size of 1-5, while the least proportion (8.2%) have family members of 11 and above. This implies that large family size does not play any important role in the incidence of beggary. It could also suggest that majority of the beggars have good family planning practice which tends to limit their children to their socio-economic status.

The research findings also showed a decreased prevalence of street begging as the level of formal education increases. It was most pronounced amongst illiterates as 49.2% had informal education, 27.1% had primary education, 20.3% had secondary education, while those with tertiary education accounted for the least with 3.4%. This underscores the importance of formal education both in increasing the earning capabilities and in positive attitudinal change of the individuals towards street begging.

Contrary to the result of most other researches carried out in Nigeria where the greatest proportions of beggars were Hausas, beggars in this study were mostly Ibos (70%). This may be due to the fact that relatively few Hausas are resident in Enugu as compared to the areas of previous surveys. The result may have been affected by the fact that Hausa respondents were not as co-operative as the respondents from other tribes. The social, political and religious unrest at the Northern part of the country at the time of this study may also have affected the result, as many Hausas living in the south may have migrated back to the North for fear of retaliative attack from their hosts. Hausa beggars had the proportion of 26.7% while Yoruba beggars recorded an insignificant proportion of 1.7%, which was the same with the last group 'others' where the only respondent was from Ibibio. The research also revealed that 71.7% of the beggars were Christians as against 26.7% who were Muslims and 1.7% who belonged to the African traditional religion. The preponderance of Christian beggars in Enugu North LGA as opposed to the dominance of Hausas as obtained in many previous surveys may conform to the reasons just mentioned above since majority of Muslims are Hausas.

It was also found that 86.7% of the sampled beggars resided outside their hometown, while 13.3% resided in their hometown. The reasons for their migration included seeking employment (9.8%), seeking medical care (3.9%), accompanied a relative (9.8%), shy to beg at home town (5.9%). However, other reasons (70.6%), virtually all of which included searching for greener pastures, accounted for the major reasons for the beggars' migration outside their hometowns. 55% of the sampled beggars resided in the suburbs, 33.3% in the metropolis, while 11.7% had no specific residential area. Majority of these beggars resided in rented apartments (46.6%), 10.3% in their parents' houses, 8.6% in their friends' houses, 13.8% on the streets, 12.1% in the temples, while only 3.4% resided in apartments owned by them. This corroborates the low socio-economic status amongst the beggars as indicated in most previous researches.

Majority of the beggars (32.1%) received more alms on Mondays and Fridays, while only 3.6% attested to receiving more alms on Thursdays. This may be attributed to sheer chance. 92.3% of them beg from morning to evening, 3.8% beg only in the mornings, while only 1.9% each do so in the evenings only and afternoons only. This shows that majority of the respondents are full time beggars who depend only on alms for survival. 50.7% of the beggars had dependents

with maximum of 20 dependents per beggar, minimum of one dependent per beggar, mean value of 4.34 dependents per beggar, and a range and standard deviation of 19 and 3.447 respectively. This implies that any reliable effort in getting the beggars permanently out of the streets should, as a matter of fact, also put these dependents into consideration.

Majority (39.3%) of the beggars realized between N401 to N800 daily, 25% earned N1 to N400 daily, 19.6% earned N801 to N1,200, while the least proportion (16.1%) earned a daily income of above N1,200. Majority of the beggars (91%) spent their income mainly on food, while only 2% spent it on Alcohol, unlike what obtained in many developed countries where the majority of the beggars' income is spent on alcohol and illicit drugs. This confirms the fact that majority of beggars in Nigeria are low income earners who spend the major proportion of their income on feeding, just for survival.<sup>5</sup>

The study also revealed that 76% of the sampled beggars had physical disability, 22% had mental disability, while 2% had no disability whatsoever. 72.1% of the beggars with disability had their limbs as the most affected organ; 25.6% had eye disability, while 2.3% had other areas affected. This is in keeping with most of previous researches and should serve as an alert to the medical professionals to devise a better and more effective means of preventing and managing physical and mental illnesses in order to prevent the complications of permanent disability.

The beggars gave their reasons for begging as follows: poverty (96.6%), medical illness (32.2%), psychiatric illness (6.8%), old age (16.9%), unemployment (69.5%), laziness (11.9%), physical illness (69.5%), peer influence (1.7%), family disintegration (25.4%), drug and alcohol dependencies (3.4%), school dropout and teenage pregnancy (22.0%), natural disaster (5.1%), culture and religion (10.2%), lack of parental education (23.7%), death of parents/relatives (52.5%), easy and profitable business (37.3%) and other reasons (1.7%). Poverty was the commonest reason identified by the beggars as obtained in majority of previous studies, while peer influence accounted for the least reason.

The sampled beggars narrated their challenges as follows: social stigmatization (64.4%), sexual harassment (13.6%), inferiority complex (40.7%), social and economic liabilities (57.6%), being driven from one place to another (42.4%), fear of being captured for sacrifice (15.3), misfortune of being knocked down by passing vehicles (35.6%), molestation by the security officials (27.1%), lack of safe place to sleep (37.3%),

unwillingness of people to give alms (22.0%). Exposure to harsh weather was the commonest challenge encountered by most beggars, while sexual harassment accounted for the least challenge.

When asked to suggest what could be done to make them stop begging, the beggars gave the following responses: provision of rehabilitation centre (62.1%), provision of food for students in Islamic schools (27.6%), issuance of monthly survival allowance (93.1%), establishment of Diverted Giving Scheme (77.6%), bye-laws that prohibit all forms of street begging (43.1%), directives to givers to stop giving (29.3%), establishment of home for the elderly (34.5%), creation of employment (69.0%), establishment of vocational centre (79.3%), provision of soft loans (84.5%). Issuance of monthly survival allowance accounted for the most frequent suggested solution to the problem of begging, while provision of food for students in Islamic schools accounted for the least.

## CONCLUSION

Based on the findings, the following conclusions were reached. Majority of these beggars had disabilities and they begged on the roads, fuel stations, in the market places, during the heavy traffic, in the bus-stops, in the garages, in the street corners, in front of the churches and mosques and in other public places; majority of them received support/care from family members in addition to living in a safe and secure environment; and most of them aspired for monthly survival allowance and vocations that provide good salary, attractive working conditions and assurance of stable and secure future.

The study also identified that street begging is associated with such causal factors as poverty, unemployment, physical and mental disabilities, death of parents/relatives, homelessness, and family rejection of beggars. It is evident from this work that the researchers are seeking lasting ways of reducing the incidence of begging. Since measures such as zero policing referral interventions have yielded little, a more dynamic approach is necessary. Also, since the research has identified that most of the people who beg were young adults, it implies that the nation is losing the economic contributions of such people, as well as jeopardizing their lives. The solution does not lie with Government alone.

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# AN ASSESSMENT OF THE FACTORS AFFECTING THE RECRUITMENT, DISTRIBUTION AND RETENTION OF HEALTH WORKERS IN ENUGU STATE

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## ABSTRACT

### Introduction

The ever increasing number of health workers, the job opportunities that opportunities that are relatively fixed and unending cry for improvements in health service in Enugu state and Nigeria in general demand a quest into the factors that push and pull health workers around.

### Methods

A cross-sectional survey measured health workers' work experience in the rural areas, satisfaction with, and reasons for undertaking their current work; as well as the possible reasons why they were employed on their current work. Data were also gathered on the impact of government and the private sector on the distribution of health workers.

### Results

The factors that influence the recruitment of health workers were performance in the interview/merit, the individuals relationship with a stakeholder, different types of incentives given to an insider involved in the recruitment process, ethnicity among others. The influence of these factors overlap. Concerning distribution, more than half of the health workers, 56.7% have not worked in any rural area in Enugu. The government owned institutions employ a great majority of the health workers and thus significantly affects their distribution. The factors that influence job satisfaction and by extension job retention are the health workers' preference for jobs that offer academic advancements, good pay, good facilities, good reputation and perhaps less workload.

### Conclusion

The government holds the key to the distribution of health workers and the government owned institutions appear to provide the most conducive working conditions. Corruption however rears its ugly head in the recruitment of health workers. Measures taken to establish government owned health centres and to combat corruption would improve the situation greatly.

## INTRODUCTION

Health professionals (or health workers) study, advise on or provide preventive, curative, rehabilitative and promotional health services based on an extensive body of theoretical and factual knowledge in diagnosis and treatment of disease and other health problems to individuals, families or communities.<sup>1,2,3</sup> Health workers are grouped into key fields of Medical, Midwifery (obstetrics), Nursing, Dentistry, Physical therapy and Allied Health.<sup>1,2,3</sup>

It is an already established fact that the key to effective health services delivery is an adequate health workforce.<sup>4</sup> However, workforce shortages are the most commonly reported staff-related problem in health care, especially in resource-constrained countries.<sup>4</sup>

However it has been claimed that urban areas are also more attractive to healthcare professionals due to the social, cultural and professional advantages of urban work.<sup>4,5,6,8</sup> This seems to agree with the fact that a great number of our healthcare professionals leave the country regularly in search of 'greener pastures'. Nigeria is a major health-staff-exporting nation, accounting for 22% of nurses who emigrated out of Africa between April 2000 and March 2001.<sup>4</sup>

In Nigeria scarce data on the availability, distribution, and trends in human resources for health (HRH) has been a barrier to effective HRH planning. However, it has been established that in the Nigerian public sector there are 13 doctors, 92 nurses/midwives, and 64 community health workers (CHWs) per 100 000 population, an urban Nigerian resident has a 3-fold greater access to doctors and there are twice as many nurses/midwives, compared with a rural resident.<sup>4</sup> By the way this amounts to approximately 169 health workers per 100 000 population (prevalence of 0.169%).

The Nigerian health sector is presently in turmoil, with no less than 5 industrial actions this year alone by various groups of health workers. A majority of the health workforce is employed by the government (at the 3 levels)<sup>7,18</sup> and at the same time, it is widely known that majority of health workers engage in private practice<sup>4</sup>. Definitely these two sets must intersect somewhere, if the intersection is large enough then it could be contributory to the poor health care services rendered in the country (i.e. there could be serious lack of dedication among the health workers).

## METHODOLOGY

### Study Area

The area where this study was conducted is Enugu state. It is located in the south eastern Nigeria, has the following coordinates: 6°30'N 7°30'E / 6.500°N 7.500°E and a total area of 7,161 km<sup>2</sup> (2,765 square miles). As at 2006 it had a population of 3,267,837 with a population density of 460/km<sup>2</sup> (1,200/square miles). The hottest temperatures is about 30.64°C while the coldest is about 15.86°C. Enugu enjoys abundant seasonal rainfall.<sup>17</sup>

Enugu is home to the Igbo tribe of Nigeria but also accommodates a minority of other tribes. Majority of its people are Christians with few adherents of other religions like Islam and African traditional religion. The principal cities in Enugu state are Enugu, Nsukka, Agbani, Awgu, Udi, and Oji-river. There are currently 17 local government areas in Enugu state.<sup>17</sup>

The University of Nigeria Teaching Hospital (UNTH) is located in Enugu State, as is the Enugu State University Teaching Hospital and College of Medicine. In addition to numerous private hospitals and clinics in the state, there are seven District Hospitals at Enugu Urban, Udi, Agbani, Awgu, Ikem, Enugu-Ezike, and Nsukka and at least one health centre or cottage hospital in every one of the seventeen (17) Local Government Areas and thirty-nine (39) Development Centres in the state.<sup>17</sup>

### Study Design

A cross-sectional descriptive study of the factors affecting the recruitment, distribution and retention of health workers in Enugu state.

### Study Population

Health workers who work in Enugu state.

### Inclusion Criteria

1. Medical doctors who work in Enugu state
2. Midwives who work in Enugu state.
3. Nurses who work in Enugu state.
4. Dentists who work in Enugu state.
5. Physiotherapists who work in Enugu state.
6. Radiographers who work in Enugu state.
7. Medical laboratory scientists who work in Enugu state.
8. Allied health workers (e.g. Pharmacists) who work in Enugu state.

### Exclusion Criteria

1. Health workers not registered with their professional bodies.
2. Suspended health workers.
3. Retired health workers.

### Sample Size Determination

The sample size was calculated using the statistical formula:

$$N = \frac{Z^2 P(1 - P)}{D^2}$$

Where N = minimum sample size

Z = standard score at 95% confidence interval which is 1.96

P = prevalence rate from previous studies which is 0.232%

D = margin of error tolerated which is 0.05

Non response will be set at 10%

This yielded a sample size of 237 health workers (rounded off to 250 after taking the 10% non-response into consideration). P refers to the prevalence of health workers in the general population. More recent estimates give a total of 371726 health workers to the entire Nigeria (a population of 160 million) giving a prevalence of 0.232%.<sup>7,18</sup> Eventually (given the limited time and resources) **180 health workers were reached.**

### Sampling Technique

A combination of multistage and convenient sampling techniques was used for this study. The stages were as follows.

1. Three L.G.A.s in Enugu state were selected, one urban and two rural areas, as well as one major federal tertiary health institution.
2. Specific hospitals in the area were selected
  - a. Enugu State University Teaching Hospital and 82 division military hospital in Enugu North L.G.A.
  - b. Jidefor hospital, Mayor hospital, St. Anne's hospital and the District Hospital all in Awgu town of Awgu L.G.A.
  - c. Community Health Centre in Obukpa town of Nsukka L.G.A.
  - d. University of Nigeria Teaching Hospital in Ituku/Ozalla in Awgu and Nkanu L.G.A.s. This hospital does not qualify as a rural hospital since it does not really share the same circumstances as the rural hospitals though it is situated in a rural area. It is a federal government owned institution.
3. In the above locations, various health workers were selected randomly and served the questionnaires according to the researchers' convenience. The quota of each professional cadre was **not** strictly adhered to.

### STUDY INSTRUMENTS

The tool for data collection was paper-and-pencil self-administered semi-structural questionnaire administration. The questionnaire comprised questions on demographics and questions to assess the factors affecting the recruitment, distribution and retention of the subjects. A sample of the questionnaire is attached as appendix I.

### DATA COLLECTION METHODS

Paper-and-pencil questionnaires were given to the subjects. Adequate time was given for answering the questions. The questionnaires were retrieved subsequently by the researchers.

### DATA MANAGEMENT

#### Statistical Analyses

Analysis was done electronically using a software programme. This was achieved with SPSS and data was diagrammatically presented. Chi-square test was used to test the significance of the results gotten where necessary.

### ETHICAL CONSIDERATIONS

1. Informed consent: An informed consent was obtained from the subjects.
2. Confidentiality: Information retrieved from respondents was handled with utmost respect and confidentially and for the sole purpose of the study.

### RESULTS

A total of 180 questionnaires were eventually distributed to the health workers, 31 in the rural areas. Most of the workers live and work in the urban area 82.8%. The number of workers decreases with age range, the highest is 42.2% for 20-29 and the lowest 7.2% for 50-59 age range. A greater percent are female, 51.1% while virtually all of them are Christians, 96.7%. Majority are married, 54.4% and almost all of them are Igbo.

#### Professional Cadre Of Enugu Health Workers Used For This Study

Out of the 180 health workers who participated in this study, medical doctors comprised about 36%, more than double the quota of any other group involved in this study. The nurses and the midwives together add up to 31%, the medical lab. Scientists contributed 25%. Among the others include head health attendant, laboratory technologist, medical record officer, medical social worker, pharmacy attendant, pharmacy technician, social worker, student nurse, treatment specialist, etc.

**Table 1: Factors That Affect The Recruitment Of Health Workers In Enugu**

LISTED FACTORS	NUMBER
Performance in the interview/merit	119
The incentives given to an insider	9
Your relationship with a stakeholder	41

The identity of the respondents was not collected for the purpose of anonymity.

### LIMITATIONS OF THIS STUDY

The following are the limitations of this study.

1. Convenience sampling was used to select individual members of the health workforce who participated in the study, quota sampling would have given a better result.
2. The scope of the study was restricted to 3 L.G.A.s, involving more areas would have yielded better results.
3. Only the government owned and the military hospitals from the urban area participated in the study. The private hospitals approached for this study declined participating.
4. The target sample size of 250 was not reached due to time constraints. Exactly 180 questionnaires out of all that was shared were retrieved and used for the project.

and 149 in the urban areas. A few questionnaires were not completely filled, the data provided in such cases were used in the analyses nevertheless.

### DATA ON THE PARTICIPANTS

Your tribe	15
Other suggested reasons*	20

Respondents were allowed to select more than one option, thus the numbers seen here will not add up to 180. Each number represents the proportion of health workers whose recruitment were affected by the corresponding factors. The strongest factor obviously is the performance in the interview since it influenced the recruitment of 119 health workers, followed by the individual's relationship with a stakeholder, influencing the recruitment of 41 health worker. The influence of these factors overlapped in many cases.

#### Health Workers Opinion On The Factors That Influences The Recruitment Of Health Workers In Enugu

Respondents were allowed to select more than one option, thus the numbers seen here will not add up to 180. Each number represents the proportion of health workers who believe that recruitment of health workers in Enugu state is affected by the corresponding factors. The strongest factors in order of decreasing strength are: your relationship with a stakeholder; ethnicity; performance in the interview and the incentives given to an insider. The weakest factors are gender and others (as listed below).

\* includes: bribery and corruption, lobbying, political influences, needs and training, poor salary, unavailability of manpower and supernatural influence

**Table 1: Depiction Of Health Workers Who Have At Any Time In Their Career Worked In Any Of The Rural Areas In Enugu.**

	FREQUENCY	PERCENT
Yes	77	42.8
No	102	56.7
No response	1	0.5
Total	180	100.0

More than half of the participants in this study, 56.7% have not worked in any rural area in Enugu. Not all those who reported to have worked in the rural area are currently working there. Thus the distribution of health workers in Enugu is tilted in favour of the urban areas.

#### **The Factors That Influenced Health Workers to Work In The Rural Area**

Out of a total of 180 persons, a subtotal of 77 persons indicated that they have worked in the rural area; however a subtotal of 81 persons went ahead to give reasons for working in the rural areas. The discrepancy (4 persons) can be due to the single 'no response' in the previous page and 3 persons who might have misunderstood the previous question and answered wrongly.

The highest factor responsible for making people work in the rural areas was 'family' needs and demands. In these cases the family resides in the rural area. Next most important factors are 'transfer' and 'no better option'.

\* includes ambition to reach the grassroots; work with an NGO; charity/humanitarian basis; community outreach; experience; good pay; internship; NYSC posting; personal wish; place of origin; posting; poverty; research work; supervision, volunteer service.

#### **Factors That Deter Health Workers From Working In The Rural Areas**

Despite the fact that only 102 persons denied having ever worked in any rural area in Enugu state, 108 persons went ahead to air their views on factors that deter them from going to work in the rural areas.

40 persons have never thought of going to work in the rural areas; 'poor working conditions' existing in the rural areas is a major deterrent. Majority of the factors listed among the other reasons (see '\*' below) also mirror the poor working conditions and lack of basic amenities in the rural areas.

\* includes unacceptable socio-economic factors e.g. poor electricity, good water supply, accessibility to banks etc.; not opportune, not been posted there; no tertiary centres there for housemanship; I'm still a student; I'm not from Enugu state; I don't have any need for that; and because of future of my kids.

#### **Job Satisfaction Of Health Workers In Enugu**

Out of the 180 respondents who participated in this study, 85% which corresponds to 152 persons admitted being happy or satisfied with their job, while 13% which corresponds to 24 persons admitted not liking their present job. This goes to show that grossly, a majority of health workers in Enugu state are satisfied with their jobs.

#### **Comparing Job Satisfaction In The Rural Area And The Urban Area**

Out of the 31 persons who responded from the rural area, 25 (80.6%) said they were satisfied with their job while in the urban area, 127 (87.6%) respondents said the same about their job. The numerical differences may appear significant but a closer analysis with Pearson Chi-square test shows that the opposite is the case.

#### **CHI-SQUARE TEST**

Null hypothesis: there is no statistically significant difference in job satisfaction between health workers in the rural and urban areas of Enugu state.

Alternate hypothesis: there is a statistically significant difference in job satisfaction between health workers in the rural and urban areas of Enugu state.

	Value	P value
Pearson Chi-square	1.915	0.384
Number of valid cases	180	

With the P value of 0.384 which is greater than the significance level of 0.05, the null hypothesis is accepted and alternate hypothesis rejected. And so there is no statistically significant difference in the job satisfaction of workers in the rural and urban areas of Enugu state.

#### **Factors Influencing Job Satisfaction In Enugu State**

Respondents were allowed to select more than one option, thus the numbers seen here will not add up to 180. Each number represents the proportion of health workers who attributed their job satisfaction to the corresponding factor. The strongest reason for job satisfaction was 'Academic purposes', following it but not so strong 'Good pay'. This goes to show that among health workers job satisfaction is mostly

associated with jobs that offer opportunities for academic advancements. 'Good pay' nevertheless is the second strongest reason for job satisfaction.

### Reasons For No Job Satisfaction

Respondents were allowed to select more than one option, thus the numbers seen here will not add up to 180. Each number represents the proportion of health workers who attributed their lack of job satisfaction to the corresponding factor. The strongest reasons why some health workers are not satisfied with their jobs is 'Poor pay', followed by 'Poor facilities' in the workplace. In the third place is 'heavy workload' while 'No security' and 'No reputation' are fourth and fifth respectively.

\* include: project has ended; it's just voluntary; lack of working materials; logistics; poor amenities; and not just satisfied after the job.

**Table 1: Presents The Reasons For Continuing On The Job Despite The Lack Of Job Satisfaction**

	FREQUENCY	PERCENT
Still searching for a better one	22	12.2
Family	9	5
Pays well	14	7.8
Others*	4	2.2

The reasons above are strong factors for health workers' retaining even when there is no job satisfaction. The highest reason for staying put is that the individual has not found a better job, after that comes the amount of remuneration from the present job. The needs of the family appears to play only a minor role here.

\* Includes: it is compulsory for my training; job security; no way forward for now; and still doing my program.

### The Distribution Of Health Workers According To Their Employers In Both Rural And Urban Areas.

With the P value of 0.001 which is less than the significance level of 0.05, null hypothesis is rejected and alternate hypothesis accepted. And so there is a statistically significant difference in the distribution of government and private workers between the rural and urban areas in Enugu state. While the government employs nearly all the health workers (127 out of 143) in the urban area, the private sector employs most of them (just over twice as much as the government employs) in the rural areas (20 out of 30). Most of those in the rural area are private sector (66.7%) while

in urban area most of them (88.8%) work for the government. More workers in urban area (9.1%) combine both private and government work than those in the rural area (3.3%). It is very glaring that there is a significant twist from the urban areas to the rural areas in the major employers of health workers. This will be corroborated by the Pearson Chi-square test results below.

1 person from the rural area and 6 persons from the urban area did not respond to this question.

### CHI-SQUARE TEST

Null hypothesis: there is no statistically significant difference in the distribution of government and private workers between the rural and urban areas of Enugu state.

Alternate hypothesis: there is a statistically significant difference in the distribution of government and private workers in the rural and urban areas of Enugu state.

	Value	P value
Pearson Chi-Square	89.689	0.001
Number of Valid Cases	173	

### DISCUSSION

180 health workers responded to the questionnaires during the study. Their ages ranged from 20 to 68 years with the highest age frequency falling within the age group of 20 to 29 years making up 32% of the respondents. The lowest age frequency being 68 years which was less than 1% of the respondents. Among the 180 respondents the majorities were the females; the Christians; the married; and the Igbos. In the same pattern as the topic we shall first discuss the findings on **recruitment** of health workers, then we shall discuss the findings on **distribution** of health workers, and finally we shall discuss the findings on **retention** of health workers in Enugu state.

Anticipating that recruitment (as well as distribution and retention) of health workers in Enugu state will be under the influence of multiple factors (even in individual cases), we asked our respondents to select as many options as they saw fit per question.

In Enugu state there are more health workers than can be taken up by the capacity of the employers both government and private, so the factors that come to play here are mainly factors that give one job seeker an edge over the other, not necessarily factors that attract the job seeker to one employer over the other.

The data on recruitment of health workers shows that majority (three quarters) of all the health workers in this study believe that they were employed based on some system of merit (see TABLE 3). When asked about the recruitment of health workers in Enugu state in general, only about one third of the study population still insisted that recruitment of health workers in Enugu state is by merit/performance in the interview. Very few persons would admit the influence of other factors on their recruitment but they all readily agree that these other factors play significant roles generally in the recruitment process in Enugu state. This may be due to the fact that among the factors listed, only the one widely admitted by the individuals is the just means of recruitment, all the others are marred by corruption and other sentiments. One of the factors which scored high in both questions was 'Relationship with a stakeholder'. It was the highest factor thought to be influential in recruitment of health workers in Enugu state. By 'relationship', we mean ties of blood, faith, friendship etc. that generally tend to make the recruitment officers become biased and overlook merit. 41 persons agreed that this played a role in their own recruitment while 88 persons (the highest among all the factors) agreed that it is very significant in the recruitment of health workers in Enugu state.

Very few persons were bold enough to admit that ethnicity and giving of incentives to an insider (15 and 9 respectively), but not so few were the numbers that admitted the significant impact of these two factors (72 and 57 respectively) on recruitment of health workers in Enugu state in general. This significant discrepancy could be due to the obvious criminal and nepotistic nature of these two factors.

The recruitment of health workers has not been studied previously in this manner, from this perspective. Most other studies investigated the factors attracting health workers to the rural and urban areas as has already been mentioned in chapter two. Other factors implicated in recruitment though not very significant are the compulsory NYSC posting, divine intervention and political influences.

Concerning distribution of health workers, out of 180 people interviewed, 42.8% have worked in the rural areas 34% of them gave reasons such as ambition to reach the grassroots; work with an NGO; charity/humanitarian basis; community outreach; experience; good pay; internship; NYSC posting; personal wish; place of origin; posting; poverty; research work; supervision, volunteer service. 23% of them worked in the rural area because of their family. 17% were transferred to the rural areas, 16% could not find better jobs and 10% only worked in the rural areas for autonomy.

56.7% have not worked in a rural areas. 37% of them have never thought of it, 29% cited factors like poor socioeconomic factors, not being opportune, and future for their children as reasons for not working in the rural areas. 18% of health workers interviewed cited poor working conditions, 11% cited accessibility of the rural areas as an impediment while 5% cited security issues

as their reasons.

With regards to distribution of health workers, it is important to note that the employer of the largest number of health workers in Enugu state is the government. Thus it follows that the distribution of health workers will be significantly affected if not entirely decided by the locations of the various government owned and funded health institutions. This has also been noted by previous works and is clearly manifested by the relocation of UNTH to Ituku/Ozalla which caused a shift of a great majority of health workers to that rural area.

Concerning retention of health workers, about 80% of the workers in the rural areas said they like their present job as against their counterparts in the urban areas (87.6%). From our study, the strongest reason for job satisfaction was 'Academic purposes' (33.8%). A lot of the health workers desire to work in an academic environment with more colleagues in their field of interest (also noted by Australian Astor. et al 2005). The second reason, though not so strong (21.1%) is 'Good pay'. This goes to show that among health workers job satisfaction is mostly associated with jobs that offer opportunities for academic advancements over and above 'Good pay'. Strongest among all the other reasons mentioned are 'Good facilities' and 'Reputation' from the job, both being at par (16.1%). This is not surprising as most health workers prefer to work in urban areas because of access to social amenities, training opportunities, better remuneration and general career advancement, better educational opportunities amongst other things<sup>1</sup>. Weakest of all the factors (1.7%) is 'less workload', it is obvious that very few people would be happy with a job simply because it gives them little work to do.

Majority (66.7%) of the participants in the rural areas are solely privately employed as against 2.1% in the urban areas. Health workers often resort to coping strategies, such as adding private practice to their public employment, to overcome unsatisfactory remuneration and working conditions. It is worth notion that from the results in TABLE 11, three times the proportion of health workers in the urban areas as in the rural areas are employed both by the government and the private sector. Some of the health workers (28 out of the 59 persons who answered the question) however do not believe that this might affect significantly the quality of services rendered to both employers. In conclusion, the following factors in order of importance affect health workers retention in Enugu State; academic purposes, good pay, good facilities, reputation, less workload.

## CONCLUSION

The study findings revealed that health workers prefer to work in the urban areas because of the abundance of social amenities, conducive working conditions, career development opportunities, appropriate infrastructure, reputation associated with the job and the good pay that they get. The urban areas also offers more opportunities for health workers to engage in multiple jobs.

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The absence of these same factors deters them from working in the rural areas. In the rural areas, poor remuneration makes job offers there unattractive.

Performance in pre-recruitment interviews, incentives given to an insider, relationship with stake holders and one's ethnicity are the major factors affecting the recruitment of health workers in Enugu.

Our study also showed that adequate incentives/good pay, working conditions, career and research development, provision of the basic social amenities, Governmental interventions like the NYSC program and transfer of workers are the core factors that determine the distribution of health workers between the rural and urban areas.

Concerning retention, majority of individuals working in the rural areas were still on the job because they could not find another job, the implication being that, there would be a huge rural-urban drift if more job opportunities opened up in the urban area. Other major factors were academic purposes, working facilities, work incentives, security and personal reasons.

#### RECOMMENDATIONS

From the results and discussion, it can be seen that the major factor affecting the distribution of health workers mainly revolves around adequate incentives. Others are good roads and transport system, adequate social amenities and a conducive work place. Personal reasons and educational purposes are other factors. Family, administrative transfer and security in the rural areas also contribute.

Appropriate educational adaptation for rural service by structuring the medical educational curriculum to include rural postings/rotation will create more interest to work in the rural areas. Provision of the basic social amenities in rural areas will most likely cause a large reduction in the rural-urban drift. Provision of up-to-date facilities and equipment in the hospitals in the rural areas will most likely cause movement of a lot of professionals to the rural areas. Consolidation of programmes like the on-going National Youth Service Corps is important. NGOs and religious societies should be encouraged to site hospitals in the rural areas as people feel more fulfilled working with such organizations. The issues with security will be alleviated with a general national security improvement. Provision of special security in the hospitals will go a long way to alleviate the fear associated with working in the rural areas. In the area of recruitment, the efforts already underway in the country to combat bribery and corruption need to be intensified, meanwhile it may be better to outsource the organisation and conduction of the screening tests/interviews for employing new health workers. This would go a long way to subvert such factors as ethnicity, relationship with a stakeholder and giving of incentives to an insider.

Government is hereby being encouraged to evenly distribute the health facilities to all rural areas, build

them according to international standards and fund them adequately. This of course would not be enough, a lot of checks and balances need to be put in place to ensure that these facilities are properly and adequately staffed and managed.

The power to implement most of these recommendations lie with the government at the national, state and local government levels.

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## METFORMIN USE IN PREGNANCY: SURVEY OF CURRENT EVIDENCE AND THE NEED FOR REVIEW OF GUIDELINES

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### Abstract

Metformin use in pregnancy has been rather controversial. Much of this controversy has been based on traditional uncertainties regarding its safety and efficacy in pregnancy. We sought to examine the recent scientific evidence in literature, and determine if existing views and recommendations regarding its use in pregnancy are in keeping with current consistently validated understanding.

In our study and selection of literature we were religiously guided by objective judgement of the accuracy and integrity of the information, based on a careful evaluation and discrimination of the relevance and currency of the data, independence and authority of authors, objectivity of study methodology, and the completeness and internal consistency of results or analysis.

Our study of modern evidence shows that the major traditional concerns regarding metformin use in pregnancy are not justified by verified data from both human and animal studies, and that in fact, metformin may have great potential benefit in pregnancy, prompting us to propose that the current guidelines regarding its use be carefully reviewed to reflect the new understanding.

**KEY WORDS:** metformin, pregnancy, evidence, guidelines

### Introduction

Metformin is the most widely prescribed oral antihyperglycaemic drug, with over 50 years history of clinical use. It is the only surviving member of the biguanide group of oral hypoglycaemic agents (1). Metformin is traditionally the first line drug for management of type 2 diabetes mellitus, but interestingly, in the last decade, a growing body of evidence has generated new attention regarding its potential novel applications notably as antitumorigenic and anti-inflammatory agents, among others (1). Moreover, it is being increasingly used on individual discretion by doctors for treatment of gestational diabetes mellitus, type 2 diabetes and polycystic ovarian syndrome in pregnancy (2). Fascinated by recent findings on its spectrum of potential applications, we decided to specifically explore and analyse the substantial body of current knowledge on metformin's utility in pregnancy, and determine the validity of traditional beliefs and positions in this regard in the face of prevailing evidence.

### Pharmacology Of Metformin

From basic pharmacology, metformin is generally believed to exert its anti-diabetic action via suppression of hepatic gluconeogenesis, promoting insulin target cell receptor sensitivity and peripheral utilisation of glucose, and retarding intestinal glucose absorption. However, the exact molecular mechanisms of its pharmacodynamics are still not yet fully understood. Traditionally, it is believed that metformin inhibits complex I of mitochondrial respiratory chain, thus elevating the AMP/ATP ratio and

consequently activating AMP-activated protein kinase (AMPK) (3). Although AMPK activation has been repeatedly demonstrated *in vitro* and *in vivo*, it does not sufficiently explain all metformin effects. Madiraju *et al* proposed and showed that metformin conveys some of its action on glucose homeostasis through inhibiting mitochondrial glycerol-3-phosphate dehydrogenase (mGPD) (4). Besides this, metformin can also directly affect mTOR signalling pathway and protein kinase C and several other enzymes but these are not well understood and their significance are not yet known (5) (6).

Metformin is usually administered orally in two daily doses of maximum of 3 g per day. It is not metabolised, but is excreted unchanged through the kidney, with a half-life of 5-6 hours (7). Maximal plasma concentration is up to 40 µmol/L (8). In pregnancy, metformin clearance increases due to enhanced renal eliminations, so dose may need to be adjusted (greater than 20 % increase) to maintain a therapeutic effect (9). Metformin crosses the placenta; umbilical cord concentrations at the time of delivery are at least half the maternal concentrations and can also exceed them in some cases (10). Even during pregnancy metformin is generally well tolerated with minimal, usually transient, side effects related to the gastrointestinal system (nausea, vomiting, etc), and only very rare incidence of serious adverse effects like lactic acidosis especially in patients with significant renal, hepatic, respiratory or cardiovascular impairment (11).

### Metformin use in pregnancy

Potential therapeutic utilities of metformin in obstetric care include management of type II diabetes mellitus pregnant

subjects, gestational diabetes mellitus patients, polycystic ovarian syndrome patients before, during and after pregnancy, and treatment of pre-gravid obesity which is currently a recognized potent risk factor for poor maternal and fetal gestational and post-gestational outcomes (2).

The major metabolic mechanism underlying diabetes in pregnancy is the consistently rising diabetogenic placental hormones causing a progressive development of insulin resistance and consequent derangement of maternal glucose homeostasis. Thus, given that the primary pathophysiologic mechanism is insulin resistance, it follows therefore, that insulin receptor sensitizers like metformin are most pharmacologically adapted for therapeutic effect (12). However, because metformin crosses the placenta, provoking fetal safety concerns, insulin has been traditionally preferred over it as therapeutic gold standard in gestational diabetes mellitus. This safety concern, as well as questions regarding comparative efficacy, have been premised on a sort of precautionary fear of the unknown, rather than on proven scientific evidence.

Current data have however, firmly established a clinically equivalent safety and efficacy profile of metformin compared to insulin in gestational diabetes management. Several meta-analysis and systematic reviews of randomized control trials and observational studies comparing metformin and insulin treatments in GDM and related obstetric indications concordantly concluded that there is no clinically significant difference in efficacy or safety between metformin and insulin (12-18).

Modern studies have in addition to affirming the therapeutic safety and efficacy of metformin compared to insulin, noted some remarkable additional advantages of the drug. For example, *in vivo* animal studies with metformin have demonstrated that exposure of embryogenic pancreas to metformin enhances pancreatic and endocrine progenitors, resulting in higher B-cell function at birth (19). Also, compared to metformin, a number of limitations are associated with insulin therapy in pregnancy. These include: weight gain with associated adverse fetal outcome, significant risk of hypoglycaemia, complexity of regimen and inconveniences associated with administration, relative high cost and uncertainties over intrauterine effects of certain analogues. In contrast, with metformin, there is no associated weight-gain, low risk of hypoglycaemia, low risk of pregnancy associated hypertension, and the regimen is simple, convenient and less expensive (13) (14) (18). This last point is especially relevant in the context of low resource settings, where low socio-economic status and associated grave affordability challenges, poor compliance and follow-up negatively affect the success of insulin therapy.

Metformin administration throughout pregnancy has not been associated with any adverse maternal or fetal outcome. Several independent studies and reports in the last few

decades have failed to document evidence of teratogenic potential. Animal studies of metformin effect on embryogenesis have demonstrated that normal embryogenesis occurs at levels 5 fold higher than the maximum attainable clinical serum levels (40  $\mu\text{mol/L}$ ), with toxicity occurring only at 800  $\mu\text{mol/l}$  which is never attainable *in vivo* (20). The traditionally feared molecular mechanism of possible metformin associated diabetic embryopathy is its *in vitro* antiproliferative property via induction of AMPK signalling. However, current pharmacodynamic studies have clearly, albeit paradoxically, established that *in vivo*, metformin does not stimulate embryo AMPK activity, probably due to lack of its transporters, and thus bear no deleterious potential on embryonic development, as hitherto feared (21). Interestingly, one of us, Umek *et al* have shown experimentally that there is no effect of therapeutic and higher concentrations of metformin (0.03-3 mmol/L) on human muscle progenitor cell proliferation, which is a major step in ontogenetic development of muscle fibres *in utero*; and that AMPK stimulatory activity of metformin occurs only at concentration of 1 mmol/L and higher, and even then, human myoblast proliferation is particularly resistant to its activation, all further reinforcing the evidence that metformin at therapeutic concentrations does not possess *in vivo* embryopathic potential (22). Similarly, there has been no association with fetal distress, intrauterine growth restriction, miscarriage, increased risk of pre-eclampsia/eclampsia, or adverse effects on anthropometric and motor-social development indices in the first 18 months after birth. Metformin is excreted in breast milk, but in clinically insignificant amount with no adverse consequences (e.g. hypoglycaemia) noted in exposed infants (23). While there is limited data on long term follow-up, there is hardly any solidly validated premise according to current evidence to suggest the likelihood of, or justify any grave concern about the possibility of long term adverse outcomes.

Furthermore, new clarifications and expansion of our understanding of the aetiopathogenesis of type II DM and GDM have further reinforced the therapeutic advantage of metformin. For example, several studies have consistently established that inflammatory mediators (TNF-alpha IL-6, CCL2) induce insulin resistance and this is a major pathophysiologic mechanism in the development of type II DM. Obesity/metabolic syndrome in pregnancy are associated with enhanced placental expression of inflammatory biomarkers, and this have been shown to be of pathogenic significance in insulin resistance. In fact, in late pregnancy, maternal TNF-alpha levels have been demonstrated to be of more predictive value in insulin resistance than diabetogenic placental hormones. New pharmacodynamic studies have established that metformin has also a potent anti-inflammatory activity (24). Metformin therapy has been shown to significantly reduce

placental and fetal cytokine levels, thus inhibiting the inflammatory process at the background of metabolic dysfunction.

It is now well known that the maternal metabolic environment of pre-gravid obese women predisposes to a number of adverse ramifications including increased risk of teratogenesis, early pregnancy loss, and long-term effects on the fetus such as developing obesity, metabolic and cardiovascular dysfunction in childhood, adolescence, or later decades. 'Maternal pre-gravid obesity even in women with well-controlled GDM is the strongest risk factor for childhood obesity and metabolic dysfunction'(25). While it is true that majority of these subjects can be satisfactorily managed with lifestyle modification measures, a significant percentage still require pharmacologic intervention and metformin has shown excellent therapeutic benefit in this respect. This is especially significant in the light of the rising obesity epidemic in both developed and developing countries and the changing epidemiology of diabetes with greater prevalence of the type 2 classification in both the general population and in pregnancy.

Apart from obesity and diabetic conditions in pregnancy, the obstetric use of metformin also includes the management of polycystic ovarian syndrome (PCOS). The cardinal diagnostic features of PCOS according to the Revised 2003 Rotterdam Criteria include chronic oligo-/anovulation and consequent infertility, clinical and/or biochemical signs of hyperandrogenism and ultrasonic evidence of polycystic ovarian morphology. The major metabolic defect and endocrinopathy associated with the syndrome include insulin resistance, and compensatory hyperinsulinemia which stimulates ovarian androgen production. Metformin treatment corrects the metabolic derangements (insulin resistance, hyperinsulinemia), reversing the endocrine imbalance and thus either stimulating spontaneous ovulatory cycles or improving response to pharmacologic ovulation induction (20). As already noted above, when continued during pregnancy, there is no evidence of effect on embryogenesis or fetal or maternal complications. On the contrary, metformin therapy has shown excellent efficacy in significantly lowering risks of severe gestational and postpartum complications, including reducing early trimester miscarriage, GDM, macrosomia, preeclampsia/eclampsia (23).

### Conclusion

In the light of all the above considerations, we propose that it is imperative that the current guidelines for metformin use in pregnancy be carefully revised in keeping with the growing body of evidence. Currently, the only FDA approved indication of metformin is treatment of type II diabetes mellitus, and it is listed as a category B drug

(absence of teratogenic evidence based on animal data; human studies are not available, hence not generally acceptable in pregnancy and lactation) (16), even though it is already increasingly used on individual judgement and experience by some doctors for the potential indications discussed above. With current understanding from fairly extensive human studies, we consider that it makes sense to expand the spectrum of formally approved applications of metformin in obstetrics including its use in GDM, PCOS and metabolic syndrome either as monotherapy or with insulin supplementation, in accordingly specified clinical circumstances. We must note here though, that many of the existing studies are relatively small-scale, and thus larger collaborative randomized trials are needed to unequivocally clarify some weakly validated or conflicting data. But while research continues on metformin molecular pharmacodynamic dispositions in pregnancy, long term effects on metabolic phenotype of offspring, with increasing knowledge of epigenetic programming (and consequent clarification of isolated reports of epigenetic changes in mice) (19) (26), it is equally compelling that conventional guidelines be prudently updated to reflect current solidly affirmed evidence regarding therapeutic potential of metformin in pregnancy, to guide and formally harmonize clinical applications.

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## FETAL HYDRONEPHROSIS: CURRENT MANAGEMENT GUIDELINES

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### Introduction

The routine use of antenatal ultrasound has become more prevalent during the past decade and due to this, structural abnormalities in the fetus have been successfully detected antenatally in a greater percentage of pregnancies over the same period. It is estimated that 20% of all antenatally detected structural fetal anomalies are of genitourinary origin and amongst these hydronephrosis has become the most commonly detected antenatal anomaly on fetal ultrasound<sup>(1,2)</sup>

The purpose of this article will be to highlight the assessment and evaluation guidelines for antenatally detected fetal hydronephrosis.

### Definition

The term hydronephrosis refers to dilatation of the renal collecting system. This can be detected antenatally in the fetal kidneys on ultrasound wherein it is referred to as antenatal hydronephrosis.

### Embryology

The collecting system of the permanent kidney develops from the ureteric bud which gives rise to the ureter, renal pelvis, major and minor calyces along with 1-3 million collecting tubules.

### Prenatal Imaging of the Kidney

Fetal kidneys can be visualized by 14<sup>th</sup>-15<sup>th</sup> week of gestation and by the 20<sup>th</sup> week, internal architecture of the kidneys can be assessed making antenatal hydronephrosis detectable by the time of the fetal anomaly scan around the 20<sup>th</sup> week.

### Incidence of Antenatal Hydronephrosis

Structural anomalies of the kidney are estimated to be detected in 1-3% of pregnancies<sup>(3)</sup>

In the U.S hydronephrosis has been detected in 1 out of every 42,000 fetuses (1.4%), making it the most commonly detected fetal anomaly<sup>(4)</sup>

About 50% of these are transient and resolve by 3<sup>rd</sup> trimester<sup>(5)</sup>

Hence it is important to distinguish infants with significant pathology requiring long term follow up or surgery from those with transient hydronephrosis with minimum need for invasive investigation.

### Differential Diagnosis For Antenatal Hydronephrosis

Fetal hydronephrosis is a non-specific finding that can be associated with multiple anomalies of the urinary tract.

The congenital anomalies that may result in hydronephrosis can be categorized as either disorders of urinary reflux or disorders of urinary obstruction.

Disorders of urinary reflux include primary vesico-ureteral reflux, a problem resulting in retrograde flow of urine from an anomalous connection of the ureter to the bladder.

Concerning disorders of urinary obstruction, the usual locations for obstruction include the ureteropelvic junction (UPJ), the uretero-vesical junction (UVJ) and posterior urethra (in males) causing dilatation of all portions proximal to the obstruction

Other congenital anomalies include duplicated urinary system and bladder extrophy, renal tumours and hypospadias as associations.

### Prenatal Evaluation of Antenatal Hydronephrosis

On ultrasound, the antero-posterior diameter of the renal pelvis is used to monitor the degree of hydronephrosis<sup>(6)</sup> Bromley et al studied the use of 1<sup>st</sup> and 2<sup>nd</sup> trimester maternal blood screens to help determine the risk of chromosomal disorders and need for karyotyping in the fetus<sup>(7)</sup>

Gestation at which hydronephrosis is detected and its progress on sequential ultrasound has prognostic value.

Cases with antecedent history of maternal oligohydramnios and persistent hydronephrosis in the 3<sup>rd</sup> trimester show higher rates of postnatal pathology and require follow up after delivery<sup>(8)</sup>

Hence, 3<sup>rd</sup> trimester ultrasound is valuable for identifying fetuses requiring post-natal evaluation and follow up.

### Post-natal Evaluation

Detected case of antenatal hydronephrosis alone is not an indication for early delivery or tertiary care management after delivery .

However, high risk fetuses include the male fetus with severe bilateral hydronephrosis and a distended bladder all pointing to posterior urethral valve. An antecedent history of maternal oligohydramnios and the fetus in which hydronephrosis is one of multiple congenital anomalies are also high risk.

Initial evaluation will begin with physical examination. Findings such as distended urinary bladder, palpable flank mass and respiratory distress are notable findings. Serum urea creatinine levels at birth may serve as baseline for further evaluation.

Further evaluation of high risk cases should begin prior to discharge with appropriate pediatric urology/nephrology consultations.

The timing of uro-radiographic evaluation is dictated by urgency of presentation.

### Conclusion

Antenatal hydronephrosis is a commonly detected anomaly on fetal ultrasonography

Fetuses diagnosed with antenatal hydronephrosis persisting through the 3<sup>rd</sup> trimester should undergo further evaluation in the prenatal and the early postnatal periods.

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# AN OVERVIEW OF IN UTERO DIAGNOSIS

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## Introduction

Congenital anomalies account for 20-25% of perinatal deaths<sup>1</sup>. With the improvement in science and technology, the perinatologist has several approaches for assessing growth and development of the fetus as well as diagnosing many ailments right from the womb using several invasive and non-invasive techniques.<sup>2</sup> Corrective fetal surgeries can even take place in the womb or even get ready to await the deformed child with some neonatal procedures, hence reducing perinatal, neonatal as well as infant mortality.<sup>3</sup> However, (with emphasis on termination of pregnancy as the management of prenatal pathology, this has led to doctors breaking the very oath ("I will give no sort of medicine to any pregnant women, with a view to destroy the child") they swore and killing the very life they swore to protect because of pressure from the society. Today prenatal testing has strayed from this purpose of protecting the health of mother and child. It is used most often to detect anomalies such as trisomy 21, sickle cell disease and the diagnosis frequently results in a decision to maim and kill the child in the womb.<sup>4</sup>

## Types of prenatal Diagnosis

Pre natal diagnosis is classified into invasive and non-invasive types of prenatal diagnosis.

For the non invasive type it includes the following

**Ultrasound** is a non invasive procedure for imaging fetal anatomy. It is harmless to both the mother and the fetus, it can be used to evaluate gestational age, identify twins, fetal position, placental location, fetal growth, development, and movement and any structural birth defects it can assess amniotic fluid volume.<sup>4</sup> The principle underlying the formation of ultrasound images is the same as that of underwater sonar (**s**ound **n**avigation and **r**anging) used by submarines and fishing boats. It relies on the generation of a short burst of sound and the detection of echoes from reflectors in front of it. The same principle applies when we hear our voices reflected

from say, walls, or in tunnels.<sup>5</sup>

**Fetal Visualization Using Fetal Echocardiography:** this can be performed at 15 week of gestation and beyond, when this technique is used with duplex or color flow doppler, it can identify a number of major structural cardiac defects and rhythm disturbances, echocardiography is recommended in cases where cardiac defects is suspected.(ultrasound identification of extra-cardiac malformation, abnormality of another major organ system, suspected genetic disease of fetal chromosome abnormality , exposure to potential teratogenic agents).<sup>6</sup>

**Fetal Visualization Using MRI:** this has greatly enhanced the diagnosis of congenital defects of the Central Nervous System, particularly in assessing the presence or absence of the corpus callosum(difficult to diagnose with ultrasound).<sup>7</sup>

**Fetal Visualization Using Radiography From 10 Weeks Gestation Onward:** This technique is used for the diagnosis of inherited skeletal dysplasias particularly osteochondrodysplasias, in the second and third trimesters<sup>8</sup>. Because of the dangers of predilection of radiation on rapidly dividing cells this technique is rarely used.<sup>9</sup>

**"Screening For Neural Tube Defects Using Maternal Serum Alpha-Fetoprotein (MSAFP):**The developing fetus has 2 major blood proteins, albumin and alpha-fetoprotein (AFP), while adults have only albumin in their blood. The MSAFP level can be used to determine the AFP levels from the fetus. AFP is produced by the yolk sac and later by the liver; it enters the amniotic fluid and then the maternal serum via fetal urine. In the condition of an open NTD (eg, anencephaly, spina bifida) and abdominal wall defects in the fetus, AFP diffuses rapidly from exposed fetal tissues into amniotic fluid, and the MSAFP level rises. However, the MSAFP levels also increase with gestational age, gestational diabetes, twins, pregnancies complicated by bleeding, and in association with intrauterine growth retardation. The MSAFP test has the greatest sensitivity between 16-18 weeks' gestation, but it also can be performed

gestation, but it also can be performed between 15-22 weeks' gestation. A combination of the MSAFP test and ultrasonography detects almost all cases of anencephaly and most cases of spina bifida. Also, a NTD can be distinguished from other fetal defects, such as abdominal wall defects, by the use of an acetylcholinesterase test carried out on amniotic fluid obtained by amniocentesis. If the level of acetylcholinesterase rises along with amniotic fluid AFP, it is suspected as a condition of a NTD".<sup>10</sup>

Low level of MSAFP it indicates the condition of Down syndrome or other chromosomal aneuploidy and failing pregnancies.<sup>11</sup>

Screening for fetal down syndrome the amount of estriol in maternal serum depends of viable fetus, a properly functional placenta and on maternal well being. A low level of estriol is an indication of Down syndrome and adrenal hyperplasia with anencephaly.<sup>12</sup>

Measuring the maternal serum beta-human chorionic gonadotrophin, an increased level may indicate trophoblastic diseases and low levels may indicate abortion or ectopic pregnancy.<sup>13</sup>

Measuring maternal inhibin-A levels can indicate an increased risk for trisomy 21. If it is increased, a high level may also be associated with a risk for preterm delivery.<sup>14</sup>

Other tests include using the free fetal cell nucleic acids from the mother to screen for Down syndrome, trisomy 18, trisomy 13, fetal sex and sex chromosome aneuploidies.

## INVASIVE TECHNIQUES

The common invasive techniques that is done include amniocentesis, chorionic villi sampling as well as cordocentesis.

### Aminocentesis:

This involves the use of probes and needle inserted into the uterus and an approximate 20-30ml of amniotic fluid is drawn.<sup>15</sup>

Most commonly used to obtain fetal cells that can be analyzed for cytogenetic, biochemical, or molecular abnormalities<sup>16</sup>. The fluid is collected at gestational age of around 14 to 20 weeks, it is not done earlier so as give time for fluid development<sup>17</sup>. Risk of pregnancy

loss is 1%.

### Chorionic Villi Sampling (CVS):

Done earlier (between 9.5 and 12.5 weeks of gestation), here 5-20mg of tissue is collected.<sup>16</sup> It may be slightly more risky to the fetus e.g Transcervical chorionic villus sampling carries a significantly higher risk, compared with a 2<sup>nd</sup> trimester amniocentesis, of total pregnancy loss. Cytogenetic, molecular, and some biochemical studies can be performed on CVS samples.<sup>17</sup> "Women who have had CVS should also have maternal serum  $\alpha$ -fetoprotein (MSAFP) screening at 15 to 20 weeks' gestational age to screen for fetal NTDs."<sup>18</sup>

### Cordocentesis:

It is also known as percutaneous umbilical blood sampling (PUBS). Here a fetal blood sampling is obtained. May be used to assess fetal blood disorders, fetal infections, or isoimmunization or may be used for rapid fetal karyotyping. Possible fetal loss is increased around 1-2%.<sup>19</sup>

Other invasive techniques not yet mentioned include fetal visualization by Embryoscopy performed in the first trimester of pregnancy up to 12 weeks gestation, in this technique a rigid endoscope is inserted via the cervix in the space between the amnion and the chorion, under sterile conditions and ultrasound guidance to visualize the embryo for the diagnosis of structural malformations.

Fetoscopy is performed during the 2<sup>nd</sup> trimester. A fine caliber endoscope is inserted into the amniotic cavity through a small maternal abdominal incision under sterile conditions and ultrasound guidance for the visualization of the embryo to detect the presence of subtle structural abnormalities. It is used for fetal blood and tissue sampling. Fetoscopy is associated with a 3-5% risk of miscarriage.<sup>20</sup>

### Fetal tissue sampling - Percutaneous Skin Biopsy

To prenatally diagnose a number of serious skin disorders, such as anhidrotic ectodermal dysplasia, epidermolysis bullosa letalis, epidermolysis bullosa dystrophica, hypohidrotic ectodermal dysplasia, oculocutaneous albinism, and genetic forms of ichthyosis. Percutaneous fetal skin biopsies are taken under ultrasonic guidance between 17-20 weeks' gestation.<sup>21</sup>

Fetal tissue sampling can be done for other organ biopsies, including liver and muscle biopsy.

Fetal liver biopsy is needed to diagnose an inborn error of metabolism, such as ornithine transcarbamylase deficiency,<sup>22</sup> glucose-6-phosphatase deficiency<sup>23</sup>, glycogen storage disease type IA, non-ketotic

hyperglycemia,<sup>24</sup> and carbamoyl-phosphate synthetase deficiency.<sup>25</sup> Fetal liver biopsy also is best performed between 17-20 weeks' gestation under ultrasound guidance.

Fetal muscle biopsy is carried out under ultrasound guidance at about 18 weeks' gestation to analyze the muscle fibers histochemically for prenatal diagnosis of Becker-Duchenne muscular dystrophy.<sup>26</sup>

### Prenatal diagnosis in Nigeria

It was introduced to Nigeria in November 1993 through an initiative of the sickle cell club and the collaboration of the British club. The club organized training course in genetic counseling for 36 counselors in 1986 in collaboration with the World Health Organization<sup>27</sup>. This single effort by the sickle cell club in Lagos culminated in the setting up of a prenatal diagnosis centre in Lagos. Materials from the baby can be obtained for testing in three different ways; 1. Chorionic Villus Sampling 2. Fetal Blood Sampling 3. Amniocentesis. However, most prenatal diagnostic techniques are still rarely done in Nigeria due to lack of facilities, socio-economic factors and ethical considerations.

### Ethical Dilemmas

With the progress in the use of biotechnology in the medical field, new ethical problems also began to arise. This topic would not be effectively dealt with if recourse to its moral and ethical dimension is not sought. Considering that it is a human action and that those involved cannot speak for themselves, hence it is paramount to have at least a glimpse of its ethical dimensions.

*"Every family has to be prepared to welcome a child, even a sick child. The shock of the announcement is harder for those who have never even thought about this possibility and have not decided in their hearts to welcome the child for his or her own sake. Though not in our culture, persons with disabilities are forced to prove that they are happy so as to have the right to live. Nobody can measure someone's degree of happiness. There are plenty of testimonies of persons afflicted with a serious disability who say that they are glad to be alive"*<sup>28</sup>.

A systematic study revealed that 99% of persons with trisomy 21 were happy with their lives, 99% of parents said they loved their child with trisomy 21, and 97% of brothers and sisters ages 9 to 14 said they loved their sibling with trisomy 21.<sup>29</sup> Deciding to have an abortion because of an ailment or malformation in the fetus is judging the value of a human being's life: it is a judgment that because this fetus is afflicted with a

serious ailment, his birth should be prevented and his life has less value than one's own. This does not mean, however that prenatal diagnosis like all diagnostic information is as such immoral. It only takes a bad shape when the aim of diagnosis is to eliminate the fetus in the womb.<sup>30</sup>

### Conclusion

From the foregoing, one can see and appreciate how the giant strides in the development of science has helped to improve the quality of human life. Prenatal diagnosis helps to diagnose, treat and await sick human beings right from the womb. However as we improve in this aspect a lot of sensitivity and due caution has to be in place considering the vulnerability of this fetal populace. We are humans first, before being doctors.

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# NEURAL TUBE DEFECTS AND FOLIC ACID USE IN PREGNANCY

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## INTRODUCTION

Folate (also known as vitamin B<sub>9</sub>) is an essential nutrient required for DNA replication, and as a substrate for a wide range of enzymatic reactions involved in amino acid synthesis and vitamin metabolism.<sup>1</sup>

Through over half a century of research, it has been established that folate has a protective effect on the development of neural tube defects (NTDs).<sup>2</sup> NTDs are a group of conditions in which an opening in the spinal cord or brain remains from early embryological development.<sup>3</sup>

Current evidence, according to the EHO suggests that folic acid supplementation in the periconceptional period, either alone or in combination with other vitamins and minerals, can prevent neural tube defects.<sup>4</sup>

## NEURAL TUBE DEFECTS

### Background

In the 3<sup>rd</sup> week of intrauterine development, also known as gastrulation, specialized cells on the dorsal side of the embryo begin to change shape and form the neural tube.

Normally, the closure of the neural tube occurs around the 30<sup>th</sup> day after fertilization, since the anterior and posterior neuropore closes last, they are the most vulnerable to defect. Inadvertently, a majority of neural tube defects arise in these areas.<sup>5</sup>

Classification of neural tube defects

NTDs can be classified based on embryological considerations and the presence or absence of exposed neural tissue, as open or closed types.

Open NTDs frequently involve the entire CNS (e.g. associated hydrocephalus, chiari II malformation) and are due to failure of primary neurulation.<sup>5</sup>

Closed NTDs are localized and confined to the spine and result from a defect in secondary neurulation. Neural tissue is not exposed and the defect is fully epithelialized, although the skin covering may be dysplastic.

It can also be classified based on:

### Cranial presentation

1. Anencephaly
2. Encephalocele
3. Craniorachischisis totalis

### Spinal presentation

1. Spina bifida aperta (cystica) and occulta
2. Myelomeningocele
3. Meningocele.<sup>5</sup>

## EPIDEMIOLOGICAL CONSIDERATIONS

NTDs are among the most common birth defects. The incidence in developing countries has been reported to be up to four folds higher than in developed countries.<sup>7</sup>

Studies have also shown that birth incidence is higher in white populations than black populations and NTDs also has a female preponderance with anencephaly having a female to male ratio of 3.1. No such difference has been noted in more distal forms of spina bifida.<sup>5</sup>

In 2008, a prospective 5-year study in UMTH, revealed an overall incidence of 43/1000 with a yearly admission rate of between 2.3-8%, the incidence was notably high in mothers booking late and home deliveries.<sup>8</sup>

Another 3-year prospective study at JUTH revealed an incidence of 7/1000 with the commonest defect being meningocele in 45% of cases.<sup>9</sup>

Worldwide, there are more than 300,000 babies born with neural tube defects each year. 10 neural tube defects resulted in 71,000 deaths globally in 2010.<sup>3</sup>

## FOLIC ACID, FOLATE AND FOLIC ACID METABOLISM

Significant differences exist in the nomenclature of folate compounds

Folate also known as vitamin B<sub>9</sub>, is used as a generic name for the group of chemically related structures based on the folic acid structure.<sup>1</sup> It cannot be synthesized by the body *de novo*, and must be obtained either from diet or supplementation.<sup>1</sup>

Dietary folate is a naturally occurring nutrient found in foods such as leafy green vegetables, legumes, egg yolk, liver and fruits.<sup>5</sup>

Folic acid is a synthetic dietary supplement that is present in artificially enriched food and pharmaceutical vitamins. L-methylfolate is the metabolically active form, it is formed from reduced folic acid and it is predominant micronutrient from that circulates in plasma.<sup>1</sup>

### **METABOLISM OF FOLIC ACID**

Folic acid is converted to dihydrofolate (DHF) and then tetrahydrofolate (THF) through enzymatic reduction by the enzyme DHFR. THF is then converted to the biologically active L-methyl folate by MTHFR. L-Methylfolate provides a one-carbon transfer needed for purine/pyrimidine synthesis and regulation of homocysteine metabolism. MTHFR is the hallmark enzyme in the pathway and genetic polymorphism have shown differences in metabolism among individuals. This can lead to the less bioavailability of L-methylfolate.<sup>1</sup>

### **PREVENTION OF NTDs: IMPORTANCE OF FOLIC ACID**

Up to 70% of NTDs have been attributed to folate deficiency during the preconception and conception period.<sup>3</sup>

This shows that optimal folic acid supplementation can lead to prevention of 2/3 of all NTDs. Since the discovery of the link between insufficient folic acid and neural tube defects, governments and health organizations worldwide have made recommendations concerning folic acid supplementation for women intending to become pregnant.<sup>3</sup>

In the US, fortification of grain products with folic acid has been mandatory in the US since January 1998, a rapid increase in RBC folate was noticed immediately among women of childbearing age and a decrease in the prevalence of infants born with NTDs.<sup>11</sup>

### **CURRENT WHO RECOMMENDATIONS**

All women, from the moment they have been trying to conceive until 12 weeks of gestation, should take a folic acid supplement (400mcg folic acid daily).

Women who have had a fetus diagnosed by a neural tube defect or have given birth to a baby with a neural tube defect should:

- Receive information on the risk of recurrence.
- Be advised on the protective effect of periconceptional folic acid supplementation.
- Be offered high dose supplementation (5mg folic acid daily).
- Be advised to increase their food intake of folate.<sup>4</sup>

Current Nigerian effort includes the flour fortification initiative which requires mandatory folic acid fortification of at least one major cereal grain.<sup>11</sup>

In Canada, mandatory fortification of selected foods with folic acid has been shown to reduce the incidence of NTDs by 46%.<sup>12</sup>

Other important uses of folic acid in pregnancy include:

- Prevention of anemia
- Prevention of preterm labour
- Prevention of congenital heart diseases and oral cleft formation.<sup>1</sup>

Epidemiological studies have also shown that pregnancies exposed to folic acid antagonists which includes

- a. DHFR inhibitors (e.g. sulfamethoxazole – trimethoprim)
- b. Anticonvulsants including Phenobarbital, phenytoin, valproate and carbamazepine have a significantly increased risk of developing severe preeclampsia, placenta abruption, fetal growth restriction and fetal death.

### **Risks Of High Dose Folate Supplementation**

The risk of folic acid toxicity is low, because folate is a water soluble vitamin and is regularly removed from the body through urine.<sup>12</sup>

Folate can mask vitamin B12 deficiency (pernicious anaemia) which can also lead to neurological pathologies, care must be taken with susceptible individuals to avoid missing this diagnosis.<sup>1</sup>

Also concerns have been raised about potentially untoward effects of unmetabolized synthetic folic acid with regards to cancer, depression and cognitive impairment. With all these concerns, early data suggests supplementation with L-methylfolate rather than folic acid may mitigate these risks.

### **CONCLUSION**

Periconceptional folic acid supplementation protects significantly against fetal structural anomalies including NTDs.

Lawal et al.<sup>7</sup> illustrated in a study in Ibadan that there is a poor knowledge and poor intake of periconceptional folic acid among women of reproductive age in Nigeria.<sup>7</sup> This highlights the need for a wider implementation of primary preventive strategies

to reduce the incidence of folic acid deficiency and NTDs in pregnancy.

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## DOWN SYNDROME: IS HE REALLY "DOWN"?

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### INTRODUCTION

English physician, John Langdon Down, first characterized Down syndrome as a distinct form of mental retardation in 1862. People suffering from this condition are often referred to as “imbeciles”. Until the middle of the 20th century, the cause of Down syndrome remained unknown. However, with the discovery of karyotype techniques in the 1950s, it became possible to identify abnormalities of chromosomal number or shape. In 1959, Prof. Jerome Lejeune discovered that Down syndrome resulted from an extra chromosome<sup>(1)</sup>. The extra chromosome was subsequently labeled the 21st, and the condition as trisomy 21.

### THE INCIDENCE OF DOWN SYNDROME IN NIGERIA

Studies of Down's syndrome covering a period of 9 years revealed an incidence of 1 in 865 livebirths in a Nigerian hospital. Cytogenetic analysis in 386 patients showed 369 (95.5%) cases to be the result of regular trisomy 21, and translocation trisomy 21 was found in nine (2.5%) patients. Six (1.5%) patients were mosaics and the remaining two (0.5%) cases were classified as miscellaneous. A high incidence of cases among young mothers was recorded, but a search for environmental

factors contributory to non-disjunction in this relatively young age group was unrevealing. The study has shown that Down's syndrome occurs as commonly in Negroes as in other races. Epidemiological studies like this are necessary to heighten the awareness of health planners in communities that have for a long time considered haemoglobinopathies to be the major genetic disorder, in order to prepare the ground for preventive measures<sup>(2)</sup>

### GENETIC ORIGIN OF DOWN SYNDROME

Down syndrome is a chromosomal abnormality characterized by the presence of an extra copy of genetic material on the 21st chromosome, either in whole (trisomy 21) or part (such as due to translocations). The effect of the extra copy vary greatly among individuals, depending on the extent of the extra copy, genetic background, environmental factors, and random chance. Down syndrome occurs in all human populations, and analogous effects have been found in other species such as chimpanzees,<sup>(3)</sup> and mice. The extra chromosomal material can come about in several distinct ways. A normal human karyotype is designated as 46,XX or 46,XY, indicating 46 chromosomes with an XX arrangement for females and 46 chromosomes with an XY arrangement for males.

### Trisomy 21

Trisomy 21(47,XX,+21) is caused by a meiotic non-disjunction event. With non-disjunction, a gamete(i.e a sperm or egg cell) is produced with an extra copy of chromosome 21; the gamete thus has 24 chromosomes. When combined with a normal gamete from the other parent, the embryo now has 47 chromosomes, with 3 copies of chromosome 21. Trisomy is the cause of approximately 95% of observed Down syndromes, with 88% coming from non-disjunction in the maternal gamete and 8%

extra copy of chromosome 21; the gamete thus has 24 chromosomes. When combined with a normal gamete from the other parent, the embryo now has 47 chromosomes, with 3 copies of chromosome 21. Trisomy is the cause of approximately 95% of observed Down syndromes, with 88% coming from non-disjunction in the maternal gamete and 8% coming from non-disjunction in the paternal gamete.

### **Mosaicism**

Trisomy 21 is caused prior to conception, and all cells in the body are affected. However, when some of the cells in the body are normal and other cells have trisomy 21, it is called mosaic Down syndrome(46,XX/47,XX,+21). This mosaicism results from mitotic non-disjunction which can occur in one of the 2 ways: a non-disjunction event during an early cell division in a normal embryo leads to a fraction of the cells with trisomy 21; or a Down syndrome embryo undergoes a non-disjunction and some of the cells in the embryo revert back to the normal chromosomal arrangement. Symptoms in such cases are variable and milder, depending on the proportion of abnormal cells and approximately 1% of Down syndrome patients are mosaics.(4)

### **Robertsonian Translocation**

In about 4% of all cases of Down syndrome, the extra chromosomal material derives from the presence of a Robertsonian translocation of the long arm of chromosome 21 to another acrocentric chromosome,(4) often chromosome 14 (45,XX,t(14;21q)) or itself (called an isochromosome, 45,XX,t(21q;21q)). Translocation Down syndrome is often referred to as familial Down syndrome.

### **Duplication of a Portion of Chromosome 21**

Rarely, a region of chromosome 21 will undergo a duplication event. This will lead to extra copies of some, but not all, of the genes on chromosome 21(46,XX,dup(21q)).(5)If the duplicated region has genes that are responsible for Down syndrome physical and mental characteristics, such individuals will show these characteristics. This cause is very rare and no rate estimates are available.

### **RISK FACTORS**

The chances of having a baby with Down syndrome increases as a woman gets older - from about 1 in 1,550 for a woman who gets pregnant under the age of 20, to about 1 in 25 for a woman who gets pregnant over the age of 45.(4) But most babies with Down syndrome are born to women under age 35 because more younger women have babies.

Parents who have already had a baby with Down syndrome or who have abnormalities in their own chromosome 21 are also at high for having a baby with Down syndrome. No racial predilection is known.

### **HEALTH ASPECTS OF DOWN SYNDROME**

The medical consequences of the extra genetic material in Down syndrome are highly variable and may affect the function of any organ system or bodily process. The most common manifestations of Down syndrome are the characteristic facial features (flat facial profile, oblique palpebral fissure and epicanthic folds), cognitive impairment, congenital heart disease, hearing deficits, short stature, thyroid disorders, and Alzheimer's disease. Other less common serious illnesses include leukemia, immune deficiencies and epilepsy. However, health benefit of Down syndrome include greatly reduced incidence of many common malignancies except leukemia and testicular cancer.(6) Although it is, as yet unclear whether the reduced incidence of various fatal cancers among people with Down syndrome is as a direct result of tumour-suppressor genes on chromosome 21, because of reduced exposure to environmental factors that contribute to cancer risk, or some other as yet unspecified factor.

Down syndrome patients present with a wide variability in individual symptoms due to complex gene and environmental interactions. Prior to birth, it is not possible to predict the symptoms that an individual with Down syndrome will develop. Some problems are present at birth such as certain heart malformations. Others become apparent over time, such as epilepsy. Despite all these problems,

improved medical care has increased the longevity of patients with trisomy 21. Currently, the median age at death is 47 years (up from 25 years in 1983).(4) Fertility amongst both males and females is reduced,(7) with only 3 recorded instances of males with Down syndrome fathering children.(8,9)

## PRENATAL SCREENING AND DIAGNOSIS

There are 2 types of prenatal tests available to detect Down syndrome in the fetus: screening tests and diagnostic tests. Screening tests estimates the risk that a fetus has Down syndrome; diagnostic tests can tell whether the fetus actually has the condition.

### Screening tests:

Screening tests are non-invasive and generally painless. But because they cannot give a definitive answer as to whether a baby has Down syndrome, mostly they are used to help parents decide whether to have more diagnostic tests. Common screening procedures and their principles of operation are discussed below:

**1. Maternal Serum Biochemistry:** This involves measurement of the maternal serum biochemical markers normally performed in the late 1st trimester or early 2nd trimester. 2nd trimester screening (15-22 weeks gestation) involves assaying of 2 main hormones-- $\alpha$ -feto protein (AFP) and human chorionic gonadotrophin (hCG) both of which are of fetal origin. In pregnancies complicated by fetus with Down syndrome, these levels are decreased and increased respectively. Based on maternal age, gestation and variation in hormone levels, an algorithm predicts the individual's risk for Down syndrome pregnancy.(10) 1st trimester screening uses 2 biochemical markers--pregnancy associated plasma protein (PAPP-A), which is lowered in Down syndrome, and  $\beta$ -hCG, which is elevated in addition to maternal age to provide an individual's risk, in a similar fashion to 2nd trimester biochemical screening. Sometimes there may be measurements of various substances in the maternal blood as in the triple screen and quad screen. Screening for trisomy 21 using maternal serum biochemistry is not effective in multiple gestations. This is because the relative contributions from each

twin to each serum marker cannot be isolated.

**2. Nuchal Translucency Testing:** This test, performed between 11 and 14 weeks of pregnancy uses ultrasound to measure the clear space in the folds of tissue behind a developing baby's neck. Babies with Down syndrome and other chromosomal abnormalities tend to accumulate fluid there, making the space appear larger. This measurement, taken together with the mother's age and the baby's gestational age, can be used to calculate the odds that the baby has Down syndrome. Nuchal translucency testing correctly detects Down syndrome about 80% of the time; when performed with a maternal blood test, it may offer greater accuracy.

Even with the best non-invasive screens, the detection rate is 90%-95% and the rate of false positive is 2%-5%. False positives can be caused by undetected multiple fetuses (very rare with ultrasound test), incorrect date of pregnancy or normal variation in proteins.

## CONFIRMATORY TESTS

**1. Amniocentesis:** This test, performed between 16 and 20 weeks of pregnancy, involves the removal of a small amount of amniotic fluid through a needle inserted in the abdomen. The cells can then be analyzed for the presence of chromosomal abnormalities. The lab work can take several weeks but will detect over 99.8% of all numerical chromosomal problems with a very low false positive rate. Amniocentesis carries a small risk of inducing miscarriage which is traditionally quoted as 0.5% but recent studies suggest that it may be considerably smaller.

**2. Chorionic Villus Sampling (CVS):** CVS involves taking a tiny sample of the placenta, also through a needle inserted in the abdomen. The advantage of this test is that it can be performed earlier than amniocentesis, between 8 and 12 weeks. The disadvantage is that it carries a slightly greater risk of miscarriage and other complications.

**. Percutaneous Umbilical Blood Sampling:** Usually performed after 20 weeks, this test uses a needle to retrieve a small sample of blood from the umbilical cord. It carries risks similar to those associated with amniocentesis.

After a baby is born, a diagnosis of Down syndrome can usually be made just by looking at the baby. If the doctor suspects Down syndrome, a karyotype--a blood or tissue sample stained to show chromosomes grouped by size, number and shape- can be performed to verify the diagnosis.

### GETTING HELP

Down syndrome is not a condition that can be cured. However, early intervention can help many people with Down syndrome live productive lives well into adulthood. Experts recommend enrolling children with Down syndrome in early intervention services as soon as possible after the child is born. Physical, occupational, and speech therapists, and early-childhood educators can work with the child to develop motor skills and language, and show the parents how to encourage these skills at home. In Nigeria, the Down Syndrome Association of Nigeria (DSAN) is in the forefront of assisting children with this genetic disorder. DSAN is a non-governmental, not-for-profit association of children with Down syndrome as well as their parents, caregivers, and other interested stakeholders. The association was founded on 4th of December, 2001 by a parent of a child with Down syndrome, Mrs. Rose Mordi, who eventually is the president. The group, supported by well-meaning Nigerians, including the Kanu Heart Foundation, Kiwanis Club International and the immediate past first lady of Lagos State, has been able to bring smiles to the faces of many Nigerian parents with Down syndrome children.

### DOWN SYNDROME AND THE SOCIETY

In most developed countries, since the early 20th century, many people with Down syndrome were housed in institutions or colonies and excluded from the society. However, since the early 1960s, parents and their organizations, educators and other

professionals have generally advocated a policy of inclusion, bringing people with any form of mental or physical disability into the society as much as possible. In many countries, people with Down syndrome are educated in the normal school system; there are increasingly higher-quality opportunities to mix special education with regular education settings.

Despite this change, reduced abilities of people with Down syndrome can pose a challenge to parents and families. Although living with family is preferable to institutionalization for most people, people with Down syndrome often encounter discrimination in the wilder society.

### The Nigerian Perspective

Societal attitude towards parents of people with Down syndrome is totally negative in the Nigerian society. Society defines them by what they do not have rather than what they have; what they cannot do rather than what they can do; they are relegated, denigrated and on the basis of some retrogressive myths and tradition. They are abused physically and sexually. It is against this rather harrowing and ugly backdrop that Down syndrome association of Nigeria evolved with avowed commitment to bridge the gap between children/adults with Down syndrome and the rest of the society through a support system that seeks ultimately to integrate them into the mainstream of the society in which they live.

### CONCLUSION

The Down syndrome patient is a special person with some latent potentials locked up inside of him .All he needs is someone that will nurture him from the cradle all through the dependent stages of human development, with patience and encouragement to him so as to enable him manifest fully his innate abilities. What I actually mean is that if Down syndrome patients are enrolled in special programmes to enhance their adaptive skills and properly integrated into the mainstream of the society, they can grow into adulthood leading a fairly independent existence. They can create a

niche for themselves and be renowned in their chosen field of human endeavour. By this, you will agree with me that the Down syndrome patient is not really down, but if given the necessary support can rise to the challenges in his path. Below are some Down syndrome patients that have made it to the top in their chosen fields of human endeavour:

Bobby Brederlow (German actor)

Chris Burke, actor (*Life Goes On*) and autobiographer

Pascal Duquenne, a Belgian actor who shared the prize for best lead actor with Daniel Auteuil in Festival de Cannes in 1996 for his performance in the movie *The Eighth Day*. King Albert II of Belgium made him Commander in the Order of the Crown in 2004

Stephane Ginnsz, actor (*Duo*) first actor with Down syndrome in the lead part of a motion picture.

Paula Sage, Scottish film actress and Special Olympic athlete (netball). Her role in the 2003 film, *Afterlife* brought her a BAFTA award for best first time performance. *Afterlife* won the Audience Award at The Edinburgh Film Festival 2003. It also won Paula a role as Donna in BBC Scotland's *River City*.

Miguel Tomasin, singer with Argentinian avant-rock band Reynolds.

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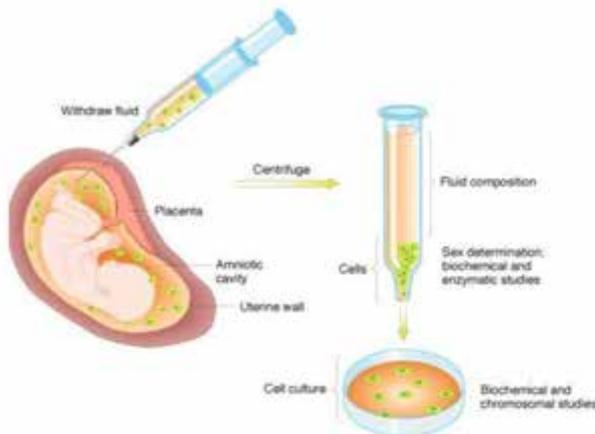
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## PRENATAL DIAGNOSIS OF SICKLE CELL DISEASE AND ETHICAL CONCERNS

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### INTRODUCTION

Sickle Cell Disease (SCD) is a major genetic disease in most countries in Sub-Saharan Africa. In recognition of this, the WHO under the DNC Department, supervise and coordinate interventions relating to the prevention and management of SCD. WHO intend to support Primary prevention (genetic counselling, general public knowledge); Early detection - screening (Prenatal Diagnosis); reduce morbidity ; chemoprophylaxis, vaccines, clinical care of special groups (children, pregnant women); capacity building Human resource; improve quality of life of patients and build partnerships. The disease is a genetic blood disorder that affects the haemoglobin within the red blood cells. The recurrent pain and complications caused by the disease can interfere with many aspects of the patient's life, including education, employment and psychosocial development. The sickle-cell trait is now known to be widespread, reaching its highest prevalence in parts of Africa as well as among people with origins in equatorial Africa, the Mediterranean basin and Saudi Arabia. In Africa, the highest prevalence of sickle-cell trait occurs between latitudes 15° North and 20° South, ranging between 10% and 40% of the population in some areas.

### EPIDEMIOLOGICAL FACTS

In countries such as Cameroon, Republic of Congo, Gabon, Ghana and Nigeria, the prevalence is between

20% and 30% while in some parts of Uganda it is as high as 45%. In countries where the trait prevalence is above 20% the disease affects about 2% of the population. The geographic distribution of the sickle-cell trait is very similar to that of malaria. The sickle cell trait has a partial protective effect against malaria, and this may explain why it has been maintained at such high prevalence levels in tropical Africa. Those who inherit the gene from both parents do not have this protection. In addition, they suffer from severe effects of SCD and many die before they reach reproductive age.

Sickle Cell Anaemia (SCA) is the predominant haemoglobinopathy in Nigeria affecting about 1-3% of the Nigerian population. The disease is associated with a lot of physical, psychosocial, emotional and financial burden and could lead to a disruption of family life. Studies from Nigeria have shown different levels of perception of the disease among family members and caregivers and even among enlightened members of the public. The disease runs a chronic course but it is now curable using gene therapy and bone marrow transplantation. However, these novel means of therapy are not yet widely available in Nigeria hence the importance of preventive measures in these settings.

### PRENATAL DIAGNOSIS OF SICKLE CELL DISEASE

Prenatal diagnosis is the process of testing for fetal anomalies or genetic disorders in-utero (while fetus is still in the womb), to provide expecting parents with information and the opportunity to modify pregnancy management and/or postnatal care.

The availability of prenatal diagnosis (PND) for the disease has opened a window of opportunity for expectant couples to have information about the haemoglobin (Hb) genotype of their unborn child. This gives them the option of termination of the pregnancy in case of positive result and to prepare them psychologically, financially and medically for the arrival of the new child when abortion is not an option. It is interesting to note that many of the respondents in

It is interesting to note that many of the respondents in the studies cited earlier are aware of this possibility even though the test is not widely available in Nigeria (as at the time of the study). Studies from Europe have shown that using prenatal diagnosis (PND) has led to a reduction in the incidence of some genetic disorders like cystic fibrosis and haemoglobinopathies.

### Techniques For Prenatal Diagnosis of Sickle Cell Disease

The type of test that is offered will depend on how many weeks pregnant the woman is. There are three basic types, these are chorionic villus sample (CVS), amniocentesis and fetal blood sampling (FBS). These tests are done in a regional testing Centre or hospital as a day admission and local anesthetic may or may not be used. The sample that is tested is not taken from any part of the baby's body and in all these tests there is a 0.5 - 1% risk of miscarriage as a result of having the procedure done.

- **Chorionic villus sample (CVS):** This test can be done after 10 weeks of pregnancy. A small piece of the placenta (the afterbirth) is taken and sent for testing. The result is usually available within one week.

- **Amniocentesis:** This test can be done from around 14 weeks of pregnancy. A small amount of the liquid around the baby, called amniotic fluid, is taken and sent for testing. The result is usually available within one week. The safety margin in both of these tests ( Chorionic villus sample and amniocentesis) is high, but there is still an increased risk of miscarriage of about 1% as a result of these diagnostic tests. The risk calculation does not take into account the background miscarriage rate which may occur even in women who have not had any procedure done.

- **Fetal blood sample (FBS):** This test can be done around 16 weeks of pregnancy and up to delivery of the baby. A small amount of blood is taken from the cord and sent for testing. This is rarely offered as it has a higher risk of miscarriage than the other diagnostic tests above. The result is usually available in two to four days. The sample for all these tests is not taken from any part of the baby's body.

**Pre-implantation genetic diagnosis (PGD)** is another possible option for couples who do not want to have a child with sickle cell disease yet feel, for whatever reason that they are unable to consider termination of an affected pregnancy. The process

involves removing mature eggs from the woman's ovary. The eggs are then fertilized in the laboratory with sperm obtained from her partner or a sperm donor (if this option is chosen). The developing embryo (egg) is then tested for the genetic condition. If the embryo does not have the condition the fertilized egg is placed in the woman's womb for a pregnancy to become established and continued. This process is often referred to as 'in vitro fertilization (IVF)' or 'test tube baby'. This is still a very new method for couples at risk of having a child with sickle cell disease. Only a few specialist hospitals offer this facility and it is very expensive for a regular Nigerian citizen.

### ETHICAL CONCERNS ON THE PRENATAL DIAGNOSIS OF SICKLE CELL DISEASE

Prenatal testing for genetic conditions generally is associated with a lot of ethical concerns and sickle cell anaemia is not an exception. The aim of this work is to discuss some of these issues especially in the context of a developing country like Nigeria:

The issue of safety of the procedures used for PND is worth mentioning first. Though they are found to be relatively safe, there is still a chance of a miscarriage following chorionic villus sampling and amniocentesis (worse with CVS and usually multi-factorial) and very significant chance of miscarriage with fetal blood sampling.

Abortion of the affected fetus is regarded as a component of PND in most cases. In the case of the fetus having the SS genotype, the ethical question arises whether to have an abortion or to keep the pregnancy. The decision whether to terminate a pregnancy based on a positive result is usually a difficult one that involves religious, psychosocial and cultural considerations. Another reason why the abortion of an affected fetus may not be accepted is because of the risk of complications mainly due to lack of reliable and safe health care practices in Nigeria. Even when abortion is legal in the local context, the question on whether it is right to terminate an innocent life is still a much debated issue. If on the other hand, a decision is made to keep the pregnancy, the next question is whether it is right or not to bring a child with a disease condition that causes so much suffering to the world. Utilitarians would argue that it is more cost effective to abort the affected fetuses as this will reduce on the long run the socio-economic and emotional consequences of the disease. Bringing

up the question of cost-effectiveness and life of patients would be looked at in many developing countries like Nigeria as being cold and inhuman, but the reality of scarcity of resources and rationing of health care resources is there for all to see.

The introduction of pre-implantation genetic diagnosis (PGD) in developed countries would seem to have put the controversial issue of termination of affected pregnancy at rest as only “genetically healthy” embryos will be transferred to the uterus. The practice itself is laden with its’ own ethical dilemmas relating to: the moral status and destruction of embryos, tendencies for eugenic practices (selection of particular traits in the embryo), the possibility of long term complications from the procedure and distributive justice issues.

Opponents of these prenatal or pre-implantation tests would also argue that SCA is now becoming a chronically manageable disease with increase in life expectancy and quality of life of patients hence there is no reason for these investigations.

Some people would argue that using a prenatal diagnosis for SCA would lead to a systematic elimination of the genetic mutation from the population. Could this be called a form of eugenics? The author definitely does not think so as the choice here is not about specific traits that are desired in a child but having a child free of a particular genetic disorder. The right to know is a fundamental right of the couple hence carrying out a PND for SCA actually empowers the couple to plan for the new child (if they decide to keep the pregnancy – if SS genotype) and gives them peace of mind (if AS or AA genotype). This is the autonomous choice of the couple, a right to decide what is acceptable to them. There is also the risk of pressure being put on the couple directly or indirectly by the society to have prenatal diagnosis done because of the availability of the tests (the so called technological imperative). This could lead to affected couples being blamed for not making use of the tests to avoid having children with sickle cell disease.

The scope of genetic counseling offered by health care workers (clinical geneticist, haematologist, nurse or obstetrician) has a lot of ethical implications. Several studies have clearly shown that genetic counseling is considered as one of the best ways of controlling the disease. As usual with

genetic counseling a “non-directive” and “client-centered” form of counseling is preferred. This form of counseling entails disclosure of genetic risk information necessary for the clients to make an informed decision without direct or indirect advice from the counselors. But the question whether it is possible to be absolutely non-directive in counseling is one that is generating a lot of debates among bioethicists and geneticists. How can one ignore his or her own intuition and sense of morality when confronted with challenging situations? Is it possible for a counselor who is a practicing Roman Catholic to be value-neutral when discussing abortion as an option after PND? Counseling for SCA is even more problematic because of the variability in severity of the disease among different patients: while some live fairly crises-free lives for long (50-60yrs), some die during childhood or adolescence. So how do we know which form of the disease the unborn child is going to develop?

Finally, the principle of justice in health care requires that access to PND be fair and equitable. This is definitely not so because of intra-country and inter-country disparity in access to PND; many people requiring prenatal diagnosis for SCA may not have access to it because of lack of the service in their environment or inability to pay for the services. This is particularly common in Nigeria where payment for health care is still mainly “out of pocket”. This problem of access to prenatal diagnosis remains one of the major impediments to the control of SCD in developing countries.

## CONCLUSION

This review article has clearly shown the ethical dimensions of prenatal diagnosis in the setting of a developing country like Nigeria. It is important for health care providers to be conscious of these issues especially when providing service to clients. There is also a need to build capacity in the area of genetic counseling as a means of controlling the spread of sickle cell anaemia. Female education has a lot of role to play. Needless to talk about the overwhelming influences of pastors and other religious leaders in decision making of couples in a very religious country like Nigeria.

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# CONJOINED TWINS: AETIOPATHOGENESIS, DIAGNOSIS AND MANAGEMENT

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## INTRODUCTION

No birth defects have stirred the minds of people with such intensity and amazement as the birth of conjoined twins (Siamese twins). Conjoined twins are identical twins joined in utero. It's a rare phenomenon, the apparent incidence ranges from 1 in 49,000 birth, to 1 in 189,000 birth, with a somewhat higher incidence in South East Asia, Africa and Brazil. Approximately, half are stillborn, and a smaller fraction of pairs born alive have abnormalities incompatible with life. As of date 400 conjoined twins have either still joined or surgically separated in the entire world. The condition is more frequently found among females with a ratio of 3:1.

## AETIOPATHOGENESIS

Two contradicting theories exist to explain the origin of conjoined twins. The older theory is *fission*, where a woman only produces a single egg, which does not fully separate after fertilization. The developing embryo starts to split into identical twins during the first few weeks after conception but stops before the process is completed. The partially separated egg develops into a conjoined fetus.

The second and more generally accepted theory is *fusion* in which a fertilized egg completely separates but stem cells (which search for similar cells) find like stem cells in the other twin and fuse the twins together. Conjoined twins share a single chorion, placenta, and amniotic sac, although these characteristics are not exclusive to

conjoined twins as there are some monozygotic but non conjoined twins that also share these structure in utero.

## Types of Conjoined Twins:

There are like a dozen types of conjoined twins and are typically classified by the point at which their bodies are joined. The most common types of conjoined twins are:

- (i.) **Thoraco-Omphalopagus (28% of cases):** Two bodies fused from the upper chest to the lower chest. These twins usually share a heart and may also share the liver or part of the digestive system.
- (ii.) **Thoracopagus(18.5%):** Two bodies fused from the upper thorax to lower belly. The heart is always involved in these cases.
- (iii.) **Omphalopagus (10%):** Two bodies fused at the lower abdomen. Unlike thoracopagus, the heart is never involved in these cases however, the twin often share liver, digestive system, diaphragm and other organs
- (iv.) **Parasitic Twins(10%):** Twins that are asymmetrically conjoined, resulting in one twin that is small, less formed and dependent on the larger twin for survival.
- (v.) **Craniopagus:** fused skulls, but separate bodies. These twins may be conjoined at the back of the head, the front of the head, or the side of the head but not on the face or the base of the skull.

*Other less common type of conjoined twins include:*

- (vi.) **Cephalopagus:** Two faces on opposite sides of a single conjoined head and the upper portion of the body is fused with the bottom portions are separated. These twins generally cannot survive due to severe malformations of the brain.
- (vii.) **Syncephalus:** One head with a single face but four ears and two bodies.

- (i.) **Cephalothoracopagus:** Bodies fused in the head and thorax. In this type of twins, there are two faces facing in opposite directions, or sometimes a single face and an enlarged skull.
- (ii.) **Xiphopagus:** Two bodies pushed in the xiphoid cartilage, which is approximately from the navel to the lower breast bone. These twins almost never share any vital organs, with the exception of the liver.
- (iii.) **Ischiopagus:** pushed lower half of the 2 bodies, with the spines conjoined end-end at a 180° angle. These twins have four arms, two, three or four legs and typically one external set of genitalia and anus.
- (iv.) **Omphalo-Ischiopagus:** Fused in a similar fashion as ischiopagus twins, but facing each other with a joined abdomen akin to omphalopagus.
- (v.) **Para-Pagus:** Fused side by side with a shared pelvis: Twins that are dithoracic parapagus are fused at the abdomen and pelvis, but not the thorax. Twins that are diprosopic parapagus have one trunk and two faces, twins that are dicephalic parapagus are dicephalic (two heads) and have two (dibrachius), three (tribrachius), or four (tetrabrachius) arms.
- (vi.) **Craniopagus Parasiticus:** like craniopagus but with a second bodiless head attached to the dominant head.
- (vii.) **Pygopagus (Iliopagus):** Two bodies joined at the pelvis.
- (viii.) **Rachipagus:** Twins joined along the dorsal aspect (back) of their bodies with fusion of the vertebral arches and the soft tissue from head to the buttocks.

#### DIAGNOSIS

Conjoined twins can be diagnosed using standard ultrasound as early as the first trimester. More detailed ultrasounds and echo cardiograms can be used about half way through pregnancy to better determine the extent of the twins connection and functioning of their organs. False-positive results can occur before 10th week, however, when identical twins who share an amniotic sac (monoamniotic twins) may appear conjoined. If an ultrasound detects conjoined twins, a magnetic resonance imaging (MRI) scan may be done. It can provide greater detail about where the conjoined twins are connected and which organs they share.

#### MANAGEMENT

Treatment of Siamese twins depends on the unique circumstances of their health, where they are joined, and whether they share organs or other vital structures.

#### Creating A Treatment Plan:

The connection between the twins bodies may range from simple to very complex. Both children may have all the organs and other structures they need, or they may share vital organs, like the heart, or other structures. Their bodies may be able to support both their lives, or it may be hard for one or both to survive because of health problems. So treatment for each twins is unique.

Caesarian section (c-s) is the goal standard for the delivery of conjoined twins, often two to four weeks before the due date.

After birth the joint decision of the parents and the doctor(s) in charge will determine whether separation surgery should be attempted. An emergency separation may be needed if one of the twins dies, develops a life threatening condition or threatens the survival of the other twin. More often, however, separation surgery is an elective procedure done two to four months after birth. Recent advances in prenatal imaging, critical care and anaesthetic care have improved outcomes in separation surgery. The surgical separation of conjoined twins is a delicate and risky procedure, requiring extreme precision and care. Therefore, the decision to separate twins is a serious one. In many cases, the surgery results in the death of one or both of the twins, particularly if they are joined at the head or share a vital organ. This makes the ethics of surgical separation, where the twins can survive if not separated, contentious. Alice Dreger of Northwestern University found the quality of life of twins who remain conjoined to be higher than is commonly supposed.

Mortality rates for twins who undergo separation vary depending on their types of connection and the organs they share. For example, twins joined at the sacrum at the base of the spine have a 68% chance of successful separation, whereas in cases of twins with conjoined hearts at the ventricular level, there are no known survivors. However, advancement in surgical techniques and sophisticated intensive care unit (ICU) have increased the survival rates of separated conjoined twins though success rate is still lower in the developing countries.

In 1987, Ben Carson made medical history by being the first surgeon to successfully separate conjoined twins (the

Binder twins) conjoined at the back of the head (craniopagus twins). The first reported case of successful separation of siamese twins in Nigeria was at Okrika and Port-Harcourt Hospital in 1954 by a British Surgeon, Holgate J. E. assisted by Dr B. J. Ikpeme. Within the period, 1987 to 1991, a team of surgeons, anaesthetists, and nurses at the University of Nigeria Teaching Hospital (UNTH) successfully separated 3 different sets of conjoined twins namely - Pygopagus (joined by the buttocks), Craniopagus (joined by the head) and Ischiopagus (joined by the pelvis). Several other success cases have been reported in various centres in Nigeria.

#### Follow Up Care:

Conjoined twins will need long term follow up visits to check their growth and development whether they stay connected or are separated. Most will need surgeries or other types of treatment for health issues that arise over time.

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## COR TRIARIATUM: A RARE CONGENITAL ANOMALY

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### INTRODUCTION

Cortriatriatum is defined as the division of either the left atrium or right atrium into two chambers due to the presence of an abnormal thin fibromuscular membrane, which can be complete or fenestrated.

Cor triatriatum is an uncommon condition, and its presence is more frequently in the left atrium representing 0.1 to 0.4% of all congenital cardiac malformations. First description of a subdivided left atrium was made by Church in 1868, but the term cor triatriatum was first used in 1905 by Bust. In 1975, Rokitanski described a variant of cor triatriatum involving the right atrium.

It has been reported that atrial septal defect(ASD) or patent foramen ovale(PFO) was present in 70-80% of patients with cor triatriatum. There are two variants of cortriatriatum

- (i.) Cortriatriatum dextrum
- (ii.) Cortriatriatum sinistrum

Cortriatriatum dextrum is when the right atrium is divided while cortriatriatum sinistrum is when the left atrium is divided.

Of the two types, cortriatriatum sinistrum, is the most commonly encountered clinically.

### COR TRIARIATUM DEXTRUM

In cortriatriatum dextrum a separating membrane, originating from the crista terminalis, divides the smooth portion of the right atrium (upper chamber) from its trabeculae portion (lower chamber).

The upper chamber receives blood from both vena cavae and the coronary sinuses, while the lower chamber contains the atrial appendage and the tricuspid valve.

Usually in early cardiac development, two valves (left and right) separate the opening of the sinus venosus in the right side of the common atrium. The left valve will later be incorporated in the septum secundum. The right valve will regress around the 12<sup>th</sup> week and its superior portion will develop into the crista terminalis, while the inferior portion will progress into the eustachian and Thebesian valves. The separating membrane dividing the right atrium results from the complete persistence of the right sinus valve of the embryonic heart. The right sinus valve might persist to a lesser extent, forming a prominent eustachian valve or the Chiari network.

Congenital cardiac malformations most commonly associated with cortriatriatum dextrum include:

Pulmonary valve stenosis or atresia.

Hypoplastic right ventricle

Tricuspid valve stenosis or atresia.

The closest differential diagnosis of cor triatriatum dexter is a right atrial mass.

#### **Clinical Presentation:**

The clinical features of this congenital disorder depends on the degree of right atrial septation and size of the membrane orifice. The severity of the symptoms is proportional to the degree of obstruction produced by the dividing membrane and the association of other heart defects, such as atrial septal defect.

Cyanosis may be present due to the shunting of caval blood into the left atrium through an atrial septal defect.

Right sided congestive heart failure with elevated central venous pressure may be present in cases with intact atrial septum and right ventricular inflow or outflow obstruction.

In the presence of a minor degree of obstruction, patients are asymptomatic and the finding is purely incidental.

#### **COR TRIATRIATUM SINISTRUM**

Cor triatriatum sinistrum is a rare but surgically correctable congenital cardiac anomaly accounting for 0.1 to 0.4% all congenital cardiac anomalies.

It is commoner than cor triatriatum dextrum in occurrence and is associated with other congenital cardiac anomalies in 24% to 80% of cases.

Cor triatriatum sinistrum is characterized by the presence of a fibromuscular membrane that subdivides the left atrium into two chambers. Here the posterior superior chamber receives the pulmonary veins, while the anterior-inferior chamber empties into the mitral valve. This condition have a multitude of anatomical variants. Several theories have been postulated trying to explain the morphogenesis of a subdivided left atrium, but the embryological origin of this condition is still a controversial debate:

#### **The following theories have been put forward**

The Entrapment theory: This states that, during early embryological development, the left atrial ostium of the common pulmonary vein is entrapped by the left horn of the sinus

venosus and prevents it to be incorporated into the left atrium. This theory is thought to be applicable in most cases of the disorder.

The mal-incorporation theory: This postulates an incomplete incorporation of the common pulmonary vein into the left atrium.

There is considerable variety in anatomic forms of cor triatriatum sinistrum, but they can be categorized in 3 basic types; **the diaphragmatic, hourglass and tubular** types. The diaphragmatic type is the most common type. Communication between the upper chamber and the inferior one is possible through a perforation of the dividing membrane which can be presented under several forms: small, large, multiple, central or eccentric.

In 70-80% of the cases, cor triatriatum is associated with congenital cardiac disorders. In 50-60% the commonest associated anomalies Atrial septal defect and patent foramen ovale, others are less common;

Ventricular septal defect

Teratology of fallot

Mitral regurgitation and

Partial anomalous venous return

Coarctation of the aorta.

Persistent patent ductus arteriosus.

A left superior vena cava was described as being more frequent in left triatrial disorder than in other types of congenital cardiac defects.

#### **Clinical Presentation:**

The clinical picture and survival of patients with cor triatriatum sinistrum in adults depends on the degree of obstruction to pulmonary venous flows and the associated intra cardiac defects.

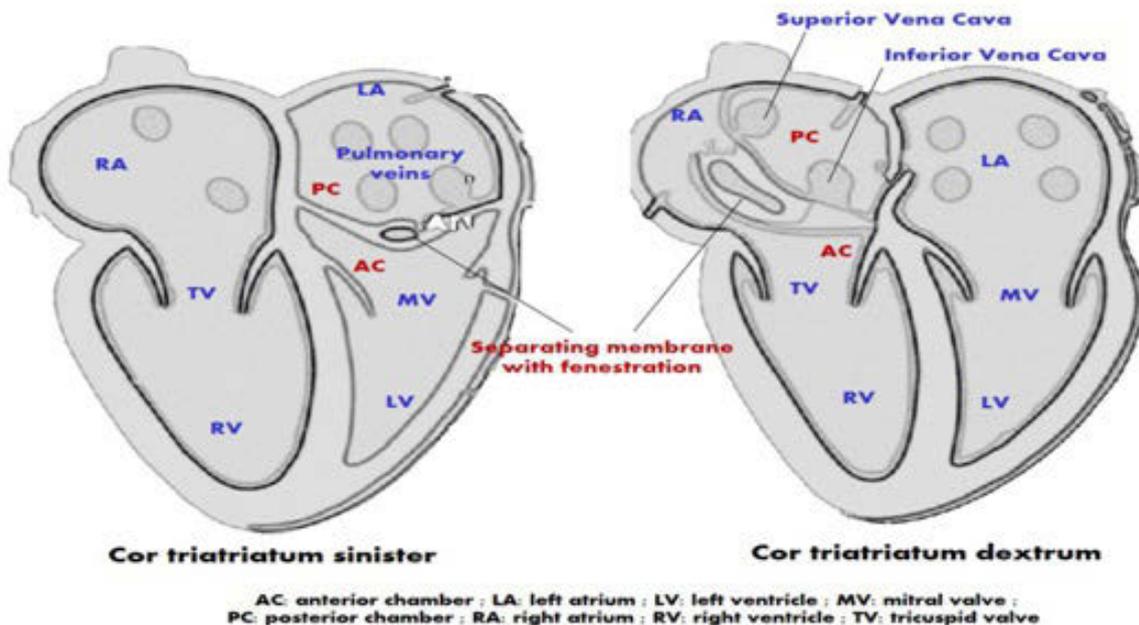
When Atrial Septal Defect (ASD) exists between the left atrial accessory chamber and the right atrium, the patients present to the hospital with symptoms of associated elevated pulmonary venous and arterial pressures, because blood is shunted from left to right. Clinical presentation can range from haemoptysis, syncope, right heart failure atrial flutter or fibrillation. The severity of symptoms is also dependent on the degree of obstruction to blood flow from the superior chamber to the inferior chamber. If the obstruction is complete the patient may present within the first year of life.

### MANAGEMENT OF CORTRIARIATUM

Before any investigation is carried out a high index of suspicion must be made and proper history taking and physical examination carried out. The findings of physical examination are directly related to the severity of the pulmonary obstruction.

Symptomatic children usually have mild tachypnea. On palpation a right ventricular impulse is detected at the

inferior portion of the left sternal border. There is accentuated pulmonary component of S2. There may be no murmur, or a low frequency systolic ejection murmur at the mid third of the left sternal border. When an ASD is present there is a fixed splitting of S2 and the systolic ejection murmur is louder.



### PRENATAL DIAGNOSIS

Echocardiography is probably the only feasible modality for the detection of cor triatriatum in the prenatal period.

Almost all of the reported cases were accompanied by other cardiac or extracardiac abnormalities, including ASD, Teratology of Fallot. Another prenatal diagnostic modality that can be attempted is ultrasonography.

### INVESTIGATIONS

Echocardiography and ECG form the main stay of investigations but other modalities can be combined to give a better picture of the diagnosis.

The following modalities can be used:

**Echocardiography:** which is the most used method for identification of cor triatriatum. It is key in establishing the diagnosis, assessing haemodynamic repercussions and detecting associated defects.

Transthoracic two-dimensional echocardiography may be supplemented by transesophageal imaging where further evaluation is necessary.

Although cross-sectional echocardiography with Doppler has been shown to be of great value in diagnosis of patients with cor triatriatum; particularly the sinister variant; biplanar Trans oesophageal Echocardiogram (TEE) provides a more complete and detailed data of the anatomy of cor triatriatum.

**Electrocardiographic** changes are nonspecific, but can be employed and may show right atrial enlargement, right axis deviation and right ventricular hypertrophy depending on the variant of the triatrial disorder.

CT and MRI scans can be used to give better anatomical detail of the structural abnormalities.

### TREATMENT

The treatment of this condition can be medical or surgical.

However, the definitive treatment is primarily surgical and involves a right atrial, transeptal approach to the common pulmonary chamber and excision of the left atrial membrane (Atriotomy) in cases where the left atrium is involved (Sinister).

Only two reports of balloon catheter dilation were noted. The mortality associated with surgical correction depends on the patient's pre-operative state, in several studies the mortality rate was 14-16%. In the case of neonates in need of inotropic and ventilatory support, mortality rate can be as high as 25-40%. In clinically stable adults it is low. Generally, long term prognosis after surgical correction is good. Medical treatment with Anti failure regime (Digoxin) and high ceiling diuretics when in cardiac failure may help stabilize the patient while surgery is awaited.

Note that some cases may be asymptomatic and may not pose any immediate risk to the patient. Such cases require careful monitoring once the incidental diagnosis is made.

The diagnosis of Cor triatriatum in a neonate calls for a more thorough search for other congenital anomalies.

### CONCLUSION

Cor triatriatum is a rare congenital anomaly. Surgical correction offers good and long term results.

In a resource poor country, high index of suspicion, early diagnosis and timely referral are warranted so as to avert death.

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## THE POSTERIOR URETHRAL VALVES

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### INTRODUCTION

Posterior urethral valves (PUV) are membranes that lie along the posterior part of the male urethra just distal to the verumontanum (of the posterior urethra) causing obstruction to urinary flow. PUV have been estimated to occur in 1 in 5000-8000 live male births. It is among the commonest congenital anomalies in males and it is the commonest cause of obstruction uropathy in male children.

### BRIEF EMBRYOLOGY OF THE URETHRA

The development of the urethra occur between the fourth and seventh week of intrauterine life (IUL) from the lower two-third of urogenital sinus. During the fourth to seventh week of development, the cloaca develops into the urogenital sinus anteriorly and anal canal posteriorly. The urorectal septum (a mesodermal layer) then lies between the two parts with the tip of the septum forming perineal body which completely separates the two parts of the cloaca.

The urogenital sinus has three portions:

1. The upper and largest part
2. The pelvic part
3. The phallic part or definitive urogenital sinus

The upper part develops to form urinary bladder, while the pelvic and phallic parts form the various parts of the urethra. Pelvic part forms the prostatic and membranous parts of the urethra. The development of the phallic part of the urogenital sinus differs greatly between the two sexes; in males it forms the penile urethra. The epithelium of the urethra (in both sexes) originates from the endoderm; the surrounding connective and smooth muscle tissue is derived from visceral mesoderm.

### DEVELOPMENT OF THE POSTERIOR URETHRAL VALVE

This is a developmental anomaly along the posterior part of the urethra. It occurs when one of the epithelial membrane thicken in the form of a crescentic paper-thin valves which arise from the verumontanum and extend

downwards and laterally to the sidewalls of the urethra at the apex of the prostate. Retrograde instrumentation through the urethra can be done without difficulty due to the structure and position of the posterior urethral valve. But during micturition, the valve cusps come together and cause obstruction to the outflow of urine. The urinary flow obstruction results in stasis of urine in the urethra proximal to the obstruction and this leads to dilatation of the prostatic urethra and distension of the bladder. If uncorrected, the distended bladder becomes hypertrophied, trabeculated, sacculated and diverticular formation and even cause vesico-ureteric reflux resulting in hydronephrosis and even renal failure. Urinary tract infection can also occur from the stasis of the urinary flow and this can lead to ascending spread of the infection to the kidneys causing pyelonephritis.

### CLINICAL FEATURES OF POSTERIOR URETHRAL VALVE

The following features and symptoms are associated with the presence of posterior urethral valve:

1. Voiding symptoms of lower urinary tracts
2. Urinary retention and dribbling of urine (these may be the presenting complain)
3. Urinary tract infection
4. Failure to thrive
5. Abdominal distension
6. Vomiting
7. Cachexia

The failure to thrive and vomiting may be due to uraemia which follows renal failure.

### DIAGNOSIS

The diagnosis can be made in antenatal care with ultrasonography which demonstrates bilateral hydronephrosis above a distended bladder. Postnatal diagnosis lies on the tripod of: good history taking, physical examination and investigations.

**History Taking:**

The onset of symptoms are very much important as well as their associations. These symptoms most often present early in the first few days or months of life. The symptoms listed above should also be explored.

**Physical Examination should include:**

General examination

Abdominal examination: the abdomen is often distended due to the distended urinary bladder and hydronephrotic kidneys and tortuous dilated ureters.

Digital Rectal Examination: this reveals distended ureter bulging into the rectum.

**INVESTIGATIONS**

These include:

- Voiding cytourethrography/expression cystogram after filling the bladder with contrast medium: this shows the dilated prostatic urethra above the point of obstruction.
- Abdomino-pelvic ultrasonograph: this may reveal hydronephrosis and hydroureters.
- Serum electrolytes, urea and creatinine: can help determine renal function.
- Urinalysis: may reveal urinary tract infection.

**MANAGEMENT**

The management should begin as soon as the diagnosis is made so as to rescue the kidneys from deteriorating into failure (if it has not failed).

Initial management is by catheterization to relieve the back pressure and to allow the effects of renal failure to improve.

Infection is treated with antibiotics while azotaemia and dehydration are corrected. The valves are resected or destroyed via suprapubic cystostomy, perineal urethrotomy or transurethral.

In patients whose ureteric musculature has decompensated, a temporary loop may be performed to aid drainage of urine from hydroureters after or before excision of the valves if necessary.

There should be continued supportive treatment of the dilated urinary tract, the recurrent urinary infection and uraemia.

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## THE CHALLENGES OF TRANSLATIONAL RESEARCH IN NIGERIA

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Our knowledge of human biology and many diseases has remain largely incomplete. It is not surprising then that translating such partial knowledge into disease treatment has often failed to ameliorate the diseases<sup>1</sup>. Currently, the goal is to investigate the patient in a comprehensive manner and there are many new approaches including whole genome sequences, another field that has been receiving increasing attention in the last few years and there are promising results for some diseases which, otherwise, have defied cure with drug treatment. In addition basic researchers today have access to species of animals in which many disease models that mimic human diseases have been developed. This has made possible a tremendous amount of information emerging from basic research. It is important, therefore, that the medical research community should continue to translate our still incomplete understanding of human biology into human treatments to remedy human diseases.

### WHAT IS TRANSLATIONAL RESEARCH?

To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at “the bench” with basic research - in which scientists study disease at a molecular or cellular level - then progress to the clinical level, or the patient's “bedside.” Since Translational research is a new and rapidly evolving domain, it is difficult at this point to give it a precise definition. As such, the definition is bound to evolve over time. Suffice to say that Translational research is a way of thinking about and conducting life sciences research to accelerate healthcare outcomes. Today's translational research is generally defined as the investigation that transforms scientific discoveries arising in the laboratory, clinic, or population into new clinical tools and applications that reduce disease incidence, morbidity and mortality<sup>1</sup>.

With its focus on removing barriers to multi-disciplinary collaboration, translational research has the potential to drive the advancement of molecular-based medicine. By enabling physicians and pharmacologists to leverage systems biology technologies, translational research can enable early detection of cancer and other diseases, increase efficiency in drug development, improve drug efficacy and enable personalized medicine. The possibilities of using biomarkers to predict, detect, and monitor disease make personalized medicine tangible.

Translational Research is the foundation of Translational medicine “the process which leads from evidence based medicine to sustainable solutions for public health problems”<sup>2</sup>. To attain the goal and promise of translational research to improve the health of the populace would depend on developing interdisciplinary broad-based teams of scientists and scholars to link basic scientific discoveries with the arena of clinical investigation, and translating the results of clinical trials into changes in clinical practice. It has three phases<sup>2</sup>.

### Phase One Research

Phase 1 Translational Research is the initial research process usually laboratory based or involving clinical investigations. It explores needs, develops potential treatments in basic laboratory research, and tests safety and efficacy, principally in randomised clinical trials. The concept arose from research into pharmacotherapy and formed the initial basis for evidence-based practice and clinical guidelines, now incorporated into Translational Medicine<sup>2</sup>. In the case of drug discovery and development translational research typically refers to the translation of laboratory-based research into real therapies for real patients. This is often called the “bench to bedside” definition.

### Phase Two Research

Phase 2 Translational Research examines how findings from clinical science, shown to be efficacious and safe treatments established in phase 1 translational research, function when they are applied in routine practice<sup>3</sup>. The Wikipedia succinctly has this to say with regards to phase two translational research. "It thus addresses development and application of new technologies in a patient driven environment - where the emphasis is on real patients in real-life situations, where demographic factors and competing priorities modify clinical decisions, and treatment responses. Phase 2 Translational Research thus informs guidelines about needs, acceptability, effectiveness, and cost efficiency in ecological settings and policies to promote uptake for optimal management and resource use"<sup>4</sup>. By this approach, investigators are not only concerned with the bench to bedside translation of basic research findings. It is also important to explore the behavioral responses of patients to interventions as well as evaluate the health economics of treatment in order to gain insights into compliance and willingness of patients to pay<sup>5</sup>.

### Phase Three Research

Phase 3 Translational Research adds the necessary information to convert treatments and prevention strategies, shown to be effective and cost-effective in Phase 2 Translational Research, into sustainable solutions.<sup>2</sup>

### CHALLENGES TO TRANSLATIONAL RESEARCH

Growing barriers between clinical and basic research, along with the ever increasing complexities involved in conducting clinical research, are making it more difficult to translate new knowledge to the clinic and back again to the bench. These challenges are limiting professional interest in the field and hampering the clinical research enterprise at a time when it should be expanding. Only when clinicians, researchers and the various operational staff can work together effectively, will the movement of scientific discoveries accelerate into the clinic and clinical findings more rapidly fuel research directions.

This is particularly so in parts of developing nations including Nigeria where the thought of incorporating basic research findings into clinical practice does not seem to exist. This is understandable for numerous reasons:

1. Basic laboratory investigators in Nigeria are for the most part concerned with the very primary aspects of research such as pharmacodynamic effects of natural

products on various organs and tissues of animal models. The characterization of the natural product to elucidate its molecular structure usually is done in laboratories overseas even though we have well over forty chemistry departments in the country. Sadly, this is happening at a time when the world research community is agog with cell biology research and gene therapies, and that also includes some developing nations like India, China, Argentina, South-Africa, etc.

2. Clinical investigators seem to take interest largely in epidemiological surveys and case report studies. Interest in population studies spanning over many years seems to be lacking among the clinicians. There is no doubt that the medical practice of the physician would be enhanced if he in addition does some basic research in the areas of his specialization. A cardiologist, for instance, can do MRI of pigs to understand certain things about an agent and the heart.
3. It is almost inconceivable to have the scientists and the clinicians come together on a meaningful scientific project. When they do there is usually some beneficial outcome. A case in point is the coming together of both clinicians (Fellows) and scientists (Ph.Ds) in the Department of Pharmacology and Therapeutics of our College of Medicine to develop an effective antiretroviral drug which at the present is undergoing the phase two translational research<sup>6</sup>. Both Ph.Ds and Fellows could be employed together in clinical departments as is the custom in some leading universities overseas.
4. The Nigerian universities lack necessary research equipments for high tech studies which is the norm in the universities of the west and many emerging nations. The problem of epileptic power supply is a big handicap too for even with necessary equipments research cannot make any headway without constant electricity. Isolated cardiac myocytes for culture in the incubator would die almost as soon as power to the incubator is severed.
5. Researches in Nigeria are hardly funded.

### RECOMMENDATIONS

There is a lot to be done to ensure that our basic and clinical researchers take their proper place among the world research community.

There is a need for interdisciplinary and multidisciplinary approach to research in the country.

1. The Federal Ministry of Education should through the National Universities Commission (NUC) set up a body comprising provosts of Nigerian Colleges of Medical Sciences and Heads of research institutes charged with development of the framework for the new discipline of clinical and translational science.
2. The consortium will have as members, individuals with Ph.Ds and professional fellows of medical bodies who have proved their worth through publications in international peer-reviewed scientific journals. Nigeria Academy of Science may prove useful in this regard.
3. The intent will be to link a number of institutions together in a coordinated fashion in order to facilitate and energize the discipline of clinical and translational science. They will assist institutions to forge a uniquely transformative, novel, and integrative academic home for Clinical and Translational Science that has the consolidated resources to: 1) captivate, advance, and nurture a cadre of well-trained multi- and inter-disciplinary investigators and research teams; 2) create an incubator for innovative research tools and information technologies; and 3) synergize multi-disciplinary and inter-disciplinary clinical and translational research and researchers to catalyze the application of new knowledge and techniques to clinical practice at the front lines of patient care.
4. The members of the consortium are expected to serve as a magnet that concentrates basic, translational, and clinical investigators, community clinicians, clinical practices, networks, professional societies, and industry to facilitate the development of new professional interactions, programs, and research projects.
5. Some Nigerian universities can be encouraged to start innovative advanced degree programs such as MD/Ph.D in Biomedical Engineering and other areas for exceptional students with a first class in any of the biological sciences and a good master's degree.
6. The basic equipments for meaningful research should be provided in the universities including uninterrupted power supply and the government as a matter of priority should set up grant awarding bodies to fund good proposals written by researchers, akin to NIH in the United States. This way the investigator shall be able to purchase other equipments relevant to his research interest. Private sector should also be

encouraged to come on board especially when it comes to translating laboratory findings into clinical applications otherwise promising ideas for novel therapeutic interventions may encounter roadblocks in bench-to-bedside testing. Where private sector capacity is limited or not available, public resources can bridge the gap between discovery and clinical testing so that more efficient translation of promising discoveries may take place.

## CONCLUSION

The world research community is ever progressing with cut-edge researches such as whole genome sequences, gene expression profiles, proteomic analysis for entire genome changes, state of art imaging systems, and stem cell biology. We need to tread with the rest of the community and be part of translational medicine. Nigeria has some of the world's best brain and if government provides the enabling environment as the politician would say there is no doubt that we would be part of it. For now the challenges are enormous.

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## MEDICAL QUOTES

Compiled By the Editorial Board

1. Beware of the men that call you "Doc." They rarely pay their bills.  
-Pratt J. H.
2. To serve the art of medicine as it should be served, one must love his fellow man.  
-*The Evolution of Internal Medicine In Modern Medicine: Its Theory and Its Practice. Philadelphia: Lea Brothers, 1907:34.*
3. The practice of medicine is an art, not a trade; a calling, not a business; a calling in which your heart will be exercised equally with your head.  
-*The Master-word in Medicine, in Aequanimitas, 368.*
4. The art of the practice of medicine is to be learned only by experience; 'tis not an inheritance; it cannot be revealed. Learn to see, learn to hear, learn to feel, learn to smell, and know that by practice alone can you become expert.  
-*Thayer W. S. Osler the Teacher, in Osler and Other Papers, 1.*
5. Live a simple and a temperate life, that you may give all your powers to your profession. Medicine is a jealous mistress; she will be satisfied with no less.  
-*Thayer W. S. Osler the Teacher, in Osler and Other Papers, 4.*
6. One cannot practice medicine alone and practice it early and late, as so many of us have to do, and hope to escape the malign influences of a routine life. The incessant concentration of thought upon one subject, however interesting, tethers a man's mind in a narrow field. The practitioner needs culture as well as learning.  
-*Chauvinism In Medicine, In Aequanimitas, 285*
7. To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions.  
-*Chauvinism In Medicine, In Aequanimitas, 267*
8. Once gain the confidence of a patient and inspire him with hope, and the battle is half won.  
-*The Reserves of Life. St. Mary's Hospital Gaz 1907;13:95-8.*
9. Some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of the physician.  
- *Hippocrates*
10. The motto of each of you as you undertake the examination and treatment of a case should be "put yourself in his place." Realize, so far as you can, the mental state of the patient, enter into his feelings ...scan gently his faults. The kindly word, the cheerful greeting, the sympathetic look.  
-*Penfield W. Neurology in Canada and The Osler Centennial. Can Med Assoc J. 1949;61:69-73.*
11. Our work is an incessant collection of evidence, weighing of evidence, and judging upon the evidence, and we have to learn early to make large allowances for our own frailty, and still larger for the weaknesses, often involuntary, of our patients.  
-*The Evolution of Internal Medicine. In Modern Medicine: Its Theory and Practice. Philadelphia: Lea Brothers, 1907:31.*
12. The physician needs a clear head and a kind heart; his work is arduous and complex, requiring the exercise of the very highest faculties of the mind, while constantly appealing to the emotions and finer feelings.  
-*Teaching and Thinking, In Aequanimitas, 126.*
13. The average physician wastes fifty to sixty per cent of his time in going from place to place or in the repetition of uninstructional details of practice.  
-*Gwyn n. The Early Life of Sir William Osler.*
14. In his character as a physician a man has a threefold relation: with the public, with the profession and with

## MEDICAL QUOTES

himself. Not one of us in all, only a few of us in some of these diverse relations, live up to our full capacity.

-*Dr. Johnston As a Physician. Washington Med Ann 1902;1:158-61.*

15. At times, and in degrees differing with our temperaments, there come upon us bouts of depression, when we feel that the battle has been lost, and that to fight longer is not worth the effort, periods when, amid the weariness, the fever and the fret of daily practice, things have gone against us; we have been misunderstood by patients, our motives have been wrongly interpreted, and smitten perhaps in the house of our friends, the worries of heart to which we doctors are so subject make us feel bitterly the uncertainties of medicine as a profession, and at times make us despair of its future.

-*Elisha Bartlett, In An Alabama Student, 137-8.*

16. And from the standpoint of medicine as an art for the prevention and cure of disease, the man who translates the hieroglyphics of science into the plain language of healing is certainly the more useful.

-*Teacher and Student, In Aequanimitas, 30.*

17. A man cannot become a competent surgeon without a full knowledge of human anatomy and physiology, and the physician without physiology and chemistry flounders along in an aimless fashion, never able to gain any accurate conception of disease, practicing a sort of popgun pharmacy, hitting now the malady and again the patient, he himself not knowing which.

-*Teaching And Thinking, In Aequanimitas, 121*

18. Let it be also an ambition to add your mite [contribution] to the store of medical knowledge. Everyone can do something; and the routine of general practice affords many cases worth reporting or commenting upon.

-*Valedictory Address to The Graduates In Medicine and Surgery, McGill University. Can Med Surg J. 1874-75;3:433-42.*

19. Some people think that doctors and nurses can put scrambled eggs back into the shell.

-*Dorothy Canfield Fisher*

20. We work by wit and not by witchcraft, and while these patients have our most tender care, and we must do what is best for the relief of their sufferings, we should not bring the art of medicine into disrepute by quack-like promises to heal.

-*Cushing H. The life of William Osler, vol. 2, 179.*

21. The great secret of doctors, known only to their wives, but still hidden from the public, is that most things get better by themselves; most things, in fact, are better in the morning.

-*Lewis Thomas, NY Times Magazine*

22. To combine in due measure the altruistic, the scientific and the business side of our work is not an easy task. In the three great professions, the lawyer has to consider only his head and pocket, the parson the head and the heart, while with us the head, heart, and pocket are all engaged.

-*Remarks On Organization In The Profession. Brit med j 1911;1:237-9.*

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