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Mussel RL, De Sa Silva E, Costa AM, Mandarim-De-Lacerda CA (2003). Mast cells in tissue response to dentistry materials: an adhesive resin, a calcium hydroxide and a glass ionomer cement. J. Cell. Mol. Med. 7:171-178.

Booth M, Bundy DA, Albonico P, Chwaya M, Alawi K (1998). Associations among multiple geohelminth infections in school children from Pemba Island. Parasitol. 116: 85-93.0.

Fransiscus RG, Long JC (1991). Variation in human nasal height and breath, Am. J. Phys. Anthropol. 85(4):419-427.

Stanislawski L, Lefeuvre M, Bourd K, Soheili-Majd E, Goldberg M, Perianin A (2003). TEGDMA-induced toxicity in human fibroblasts is associated with early and drastic glutathione depletion with subsequent production of oxygen reactive species. J. Biomed. Res. 66:476-82.

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Full Length Research Paper

Assessment of the pattern of antibiotics use in pediatrics ward of Dessie Referral Hospital, North East Ethiopia

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The main purpose is to assess the prescribing practice of antibiotic in pediatrics ward of DRH, North East Ethiopia. Methods: A hospital-based retrospective cross sectional study was used to assess patient cards for the past 1 year (June 2012- May 2013). Results: About 98 % of pediatrics was prescribed with at least one antibiotic. The most common diagnoses were severe pneumonia (19.6%) and Acute Gastroenteritis (AGE) with some dehydration (10.3%). The most commonly prescribed single antibiotics was crystalline penicillin (33.3%) and multiple antibiotics were ampicillin and gentamicin (62.9%).Accordingly, parenteral route accounted for 377(76%) and with a practice of parenteral to oral shift upon discharge in only 7.9% of cases. The average number of drugs per patient was 1.70±0.93 and antibiotics per patient were 1.457±0.599. More than 61.51% of the patients were exposed to at least two drugs. Conclusion: There is high percentage of antibiotics use in pediatrics ward of DRH and even some of them administered without proper indication. Proper treatment guidelines and policies should be practiced to promote judicious use of antibiotics.

Key words: Antibiotic, pattern, pediatrics, Dessie referral hospital

INTRODUCTION

Antibiotics are drugs taken to kill or inhibit the growth of microorganisms. Antibiotics are strong and effective medicines which are used to treat most different bacterial infections (Woldu et al., 2013). When antibiotics were first introduced, they were strong and efficient treatments for different bacterial infections. Antibiotics saved the lives of numerous people. However, some bacteria change themselves and produce resistance to antibiotics. Consequently, the number of people dying from infectious diseases is mounting up from time to time due to absence of proper treatment. It is evident that the adverse effect of irrational use of antibiotics is more

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serious among children than adults (Abula and Desta, 1999). Misuse/overuse of antibiotics may cause increased adverse effects, resistance to antibiotics, making illnesses more serious, and increasing expenses of health services. In developing countries, antibiotics are prescribed for 44 to 97% of hospitalized patients often unnecessarily or inappropriately (Baktygul, 2011).

Ethiopian hospitals consume about 50% of the National drug budget, which are considered to have high drug budget compared to the population segment using these health facilities. However, very little is known how drugs (particularly antibiotics) are used in hospitals like in other health facilities (Abula and Kedir, 2004).

Information about the utilization of drugs particularly the prescribing pattern of drugs in pediatric wards in Ethiopia is scantly as yet (Abula and Desta, 1999). In developing countries, empirical use of antibiotics is a common practice including Dessie Referral Hospital (DRH). This situation could cause a serious resistance problem unless it is studied periodically in different parts of Ethiopia. Therefore, this situation calls for a need to investigate the pattern of antibiotics use so that we can be in a position to use it for the better. In this regard, infants and children are more exposed to become victims of these disastrous consequences of inappropriate use of antibiotics as these groups of people are frequently caught by various illnesses. Hence, health care professionals, parents and caregivers should know about the judicious use and the negative impact of antibiotics so that they can make informed decisions about it. The outcomes of this study help all concerned bodies to identify the pattern of antibiotic use in DRH Pediatric Ward. Therefore, the study is significant in portraying the actual practice of antibiotic use.

METHODOLOGY

Study area and period

DRH is located in the North East part of Ethiopia, in Dessie town. It is found 401 km away from Addis Ababa, the capital city of Ethiopia towards North East direction. The study was conducted from May to July, 2013.

Study design

A hospital-based retrospective cross sectional study was used to assess patient cards. All patient records were assessed for the past 1 year (June, 2012 to May, 2013). A structured and pre-tested questionnaire was prepared to collect the information.

Sampling technique and sample size determination

From a total of 2951 pediatric patients admitted from June 2012 to May, 2013, the sample size was calculated as 296 by considering 74% proportion (2), confidence interval of 95%, margin of error 5% and adding 10% of samples for those with incomplete cards.

Variables

Antibiotics use was the dependent variable while age, sex, weight, residence of patients, assessment (diagnosis) were the independent variables

Data collection and instruments

In order to collect data, the researcher was used patients' medication records. The data was collected using structured data collection format. After that the collected data was analyzed using SPSS version 16. Interpretation, conclusion and recommendations were drawn afterwards.

Inclusion and exclusion criteria

The inclusion criteria for the study population include all pediatric population admitted to DRH with in this period. The exclusion criteria include those who admitted to the HIV clinic and TB clinic are not included in the study.

Operational definition

Generic drug: The Essential Drug List of Ethiopia is used as a basis to determine drugs as generic or brand name.

Pediatrics: Children having the age of 0 to 14.

RESULTS

From a total of 296 patients whose records fulfilled the inclusion criteria, five medical records were excluded due to incomplete medical records; hence a total of 291 medical records were investigated. Of the total of (n = 291) pediatric patient medical records, almost half of the patients (54.3%) were male and the rest (45.7%) were females. More than half of the pediatric patients (65%) came from areas outside Dessie city and the remaining (35.1%) were within the city. The mean age of pediatric was 3.32 ± 3.876 years and the majority of patients were neonates and infants (44.32%) followed by toddlers (24.47%) as shown in Table 1.

As shown in Table 2, the most common diagnoses were severe pneumonia (19.6%), acute gastroenteritis (AGE) with some dehydration (10.3%) and early onset neonatal sepsis (EONS) (6.2%). Among patients affected by severe pneumonia, the majority of them (57.89%) were infants and neonates followed by toddlers (36.84%) and no adolescent patient were affected by severe pneumonia. In cases of AGE, half of them (50%) were

Table 1. Socio demographic data of patients in pediatric ward of DRH during 2012/2013 Years, Dessie, Ethiopia.

Variable	Frequency (%)
Sex	
Male	158 (54.3)
Female	133 (45.7)
Age	
0-1	119 (40.89)
Toddlers (b/n 1 and 3)	83 (28.52)
Preschool age (3 and 5)	28 (9.6)
School age (5 and 10)	36 (12.37)
Adolescents (10 to 14)	25 (8.5)
Residence	
Dessie Ketema	102 (35.1)
Kombolcha	32 (35.1)
Dessie Zuria	11 (3.8)
Other places*	146 (50.2)

Table 2. The eleven top most diseases of pediatrics (n=291) Pediatric Ward of DRH, during 2012/2013 Years, Dessie, Ethiopia.

Assessment	Frequency (%)
Severe pneumonia	57(19.6)
AGE with some DHN	30(10.3)
EONS	18(6.2)
AGE with severe DHN	14(4.8)
Soft tissue infection	14(4.8)
GI onset sepsis	14(4.8)
URTI	11 (3.8)
AFI	11(3.8)
Pneumonia	10(3.4)
SCAP + HAAD	9(3.1)
Acute appendicitis	8(2.7)
Others*	95(32.64)

Table 3. The Frequency and Percentage of single prescribed antibiotics in pediatric Ward of DRH during 2012/2013 Years, Dessie, Ethiopia.

Individual antibiotic	Frequency (%)
Crystallin penicillin	55 (33.33)
Cefitriaxon	45 (27.27)
Amoxacillin	26 (15.75)
Cotrimoxazole	13 (7.8)
Ampicillin	8 (4.8)
Cloxacillin	6 (3.6)
Cefalexin	5 (3.03)
Augumentin	2 (1.21)
Enhensine	2 (1.21)
Erythromycin syrup	1 (0.60)
CAF	1 (0.60)
Myconazol	1(0.60)
Total	165 (100)

Table 4. The frequency and percentage of multiple antibiotic prescriptions in pediatric Ward of DRH, during 2012/2013 year, Dessie, Ethiopia.

Combined antibiotics	Frequency (%)
Ampicillin + Gentamicin	78 (62.9)
Cloxacillin + Chloramphenicol	9 (7.2)
Ceftriaxon + Gentamicin	6 (4.8)
Cefetriaxon + Metronidazol	4
Cefetriaxon + Cry. penicillin	3
Ampicillin + Chloramphenicol	3
Cloxacillin+Nitrofurazone	2
Cefetriaxon+Doxycycline	2
Cloxacillin+Metronidazol	2
Ampicillin+Gentamicin+Metronidazol	2
Amoxacillin+Ampicillin+Gentamicin	2
Others*	9
Total	124

toddlers followed by infants and neonates (40%). There was no pediatric patient affected by AGE in school age. Soft tissue infection was the most common diagnosis in school age patients.

About 98% of pediatrics was prescribed with at least one antibiotic. The average number of drugs prescribed at a time was 1.71 ± 0.693 whereas average number of antibiotics per patient was 1.457 ± 0.5995. Majority of the patients (58.1%) contain multiple drugs at a time. Among these, patients with one antibiotic (55.3 %) and two antibiotics (39.9%) are common (Figure 1). Accordingly, this study showed that out of the 521 total number of medication prescribed, parenteral route accounted for 76% (Figure 2) and with a practice of parenteral to oral shift upon discharge in only 23 (7.9%) of cases. The most common discharged oral medications include amoxicillin (52%) and cotrimoxazole (26%). Among the total of 521 drugs, the proportion of drugs prescribed in generic name was 96.6%.

Of all prescribed drugs, the most commonly prescribed antibiotics were crystalline penicillin (33.3%), cefetriaxone (27.3%) and amoxicillin (15.8%). The most commonly prescribed multiple antibiotic regimens were ampicillin and gentamicin (62.9%), cloxacillin and chloramphenicol (7.2%), ceftriaxon and gantamicin (4.8%) (Tables 3 and 4). The injections were commonly co-administered with

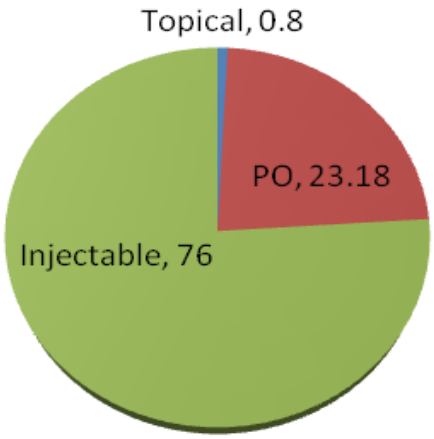

Figure 1. The percent of injectables, POs and topical drugs used by patients in pediatric ward of DRH, during 2012/2013 years, Dessie, Ethiopia.

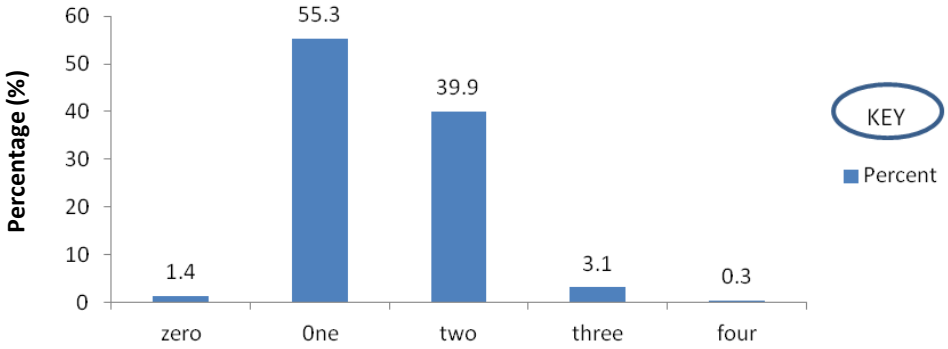

Figure 2. The percentage of antibiotics used by patients in pediatric ward of DRH during 2012/2013 years, Dessie, Ethiopia.

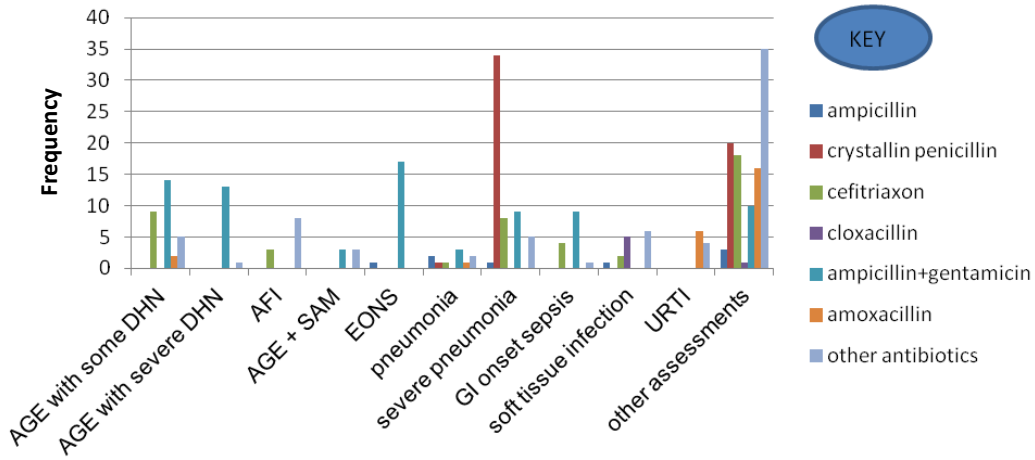

Figure 3. The frequency and percentage of antibiotics and assessments pediatric ward of DRH, during 2012/2013 years, Dessie, Ethiopia.

frequently used combination in DRH and it was used for the treatment of wide variety of diseases like EONS, AGE with dehydration, severe pneumonia and GI onset sepsis. In addition to the mentioned indications, ceftriaxone was recommended in acute febrile illness and soft tissue infection. Cloxacillin was mostly used for the treatment of soft tissue infection in DRH. Amoxicillin was mostly used for the treatment of upper respiratory tract infections (URTI) and in a lesser extent it was used for the treatment of diseases like AGE with some DHN and pneumonia (Figure 3).

DISCUSSION

Antibiotics represent one of the most commonly used drugs in pediatrics ward. Their irrational use leads to a number of consequences in terms of cost, drug interacttions, hospital stay, bacterial resistance and increased medication error (Woldu et al., 2013; Zeleke et al., 2014). According to this study, the most frequent clinical indication was severe pneumonia followed by acute gastroenteritis which is similar to the studies done in Bishoftu (Feleke et al., 2013*),* Jimma (Agalu and Mengistu, 2012) and Nepal (Palikhe, 2004).

The major problematic area from this study was high use of antibiotics (98%) which is higher as compared to a report in Jimma hospital (44.9%) by Agalu and Mengistu (2012) and in Arulmoli et al. (2009) (54%). This high percentrage was also reported by Palikh (2004) (93%). Similarly, study done by Bosu et al again showed the variation in average percentage of patients receiving at least one antibiotic, which was 41, 45, 79 and 98% in different health centers. It is not possible to draw any firm conclusion since the patients are not matched socio-economically. The morbidity pattern may also be different. Moreover, around half of patients that came from outside the Dessie city and even the patients living in Dessie need referral to get treatment in Dessie. But one of contributing factors for high use of antibiotics will be the empirical use of antibiotics and use of antibiotics without proper indication like conjestive heart failure, uncomplicated measles, moderate croup which do not require antibiotic treatment.

In this study, most commonly prescribed antibiotics in DRH pediatrics ward are crystalline penicillin and ceftriaxone similar to reports in Gondar, Debretabor (Abula and Desta, 1999) and Nepal (Palikh, 2004). But in these hospitals the second most common drug was chloramphenicol and was the most common drug in Bahirdar hospital (Abula and Desta, 1999) which once a time was widely used. Chloramphenicol nowadays is replaced by other antibiotics like cotrimoxazole and amoxacllin in Jimma (Agalu and Mekonnen, 2012) and third generation cephlosporins like ceftriaxone in Bishoftu (Feleke et al., 2013) and India (Kanish et al., 2014) and cefotaxime in Indonesia (Husni et al., 2004). Chloramphenicol use must be reserved in neonates as it can cause gray baby syndrome at toxic doses (Wardoyo and Tifoid, 2002).

Unlike this study, the most common drugs in pediatrics ward of Iran are amikacin and vancomycin (Mohammadi et al., 2013). This wider variability in commonly prescribed antibiotics might be due to empiric therapy throughout developing countries. In this study, the common practice of crystalline penicillin might be due to high prevalence of severe pneumonia in pediatrics in the area which is best managed by crystalline penicillin as per Ethiopian treatment guideline. The most commonly prescribed combined antibiotic medications were ampicillin and gentamicin (62.9%), whereas in Indonesia, the most common combination of antibiotics are ampicillin and chloramphenicol (Husni et al., 2004). World Health Organization has recommended the use of this type of antibiotics combination in developing countries for empiric therapy and because of this, the ampicilin and gentamicin combination can be used in a wide variety of disease conditions in pediatrics due to the synergistic effect of the combination.

Another problematic area is the high use of injectables. A total of 377 pediatric patients (76%) received injectable antibiotics. One explanation of such high use of injectable antibiotics could be due to social acceptance that intravenous antibiotics are ‘‘stronger’’ than oral antibiotics in treating an infection during hospital stay. Some antibiotics (for example, crystalline penicillin, aminoglycosides) are not mostly available in oral form. Some infections (for example, central nervous system infections) or patients groups (for example, neonates and infants) require parenteral use. Feleke et al. (2013) reported higher administration of parentral antibiotics (81.8%) in bishoftu, Woldu et al. in hawassa (93.6%), Kanish et al(92%) and Sviestina and Mozgis in lativia (64-86%).The finding in this study though relatively good, still should be discouraged and switch to oral medications when there is indication must be practiced because can reduce stay at the hospital, decrease the risk of needle-borne infections like HIV/AIDS and hepatitis and can decrease administration and family-related costs(Rojas and Granados,2006; Lorgelly et al., 2010; Vouloumanou et al., 2008).

According to world health organization (WHO) recommendation, the percentage of drugs prescribed by generic name should be 100%. Prescribing and dispensing of drugs by its generic name avoids confusion between prescribers and dispensers (De Vires et al., 1994).

In our study, we found that the pattern of generic prescribing was 96.6% which is high as compared to other studies conducted in different parts of Ethiopia showed that the use of generic prescription as 70.5% in Bahirdar hospital; 72.6% in Gondar hospital; 84% in Debretabore hospital and 82% in jimma hospital (Abula and Desta, 1999; Agalu and Mekonnen, 2012).

The mean number of drugs prescribed at a time was lower compared to studies conducted in Nepal (Palikh, 2004) and in Hawassa (Woldu et al., 2013) and consistent with the WHO recommendations (WHO, 1993). The mean number of antibiotics prescribed per-prescription was low compared to similar studies conducted in other part of the world (Baktygul et al., 2011; Palikh, 2004) but higher than similar studies conducted in Hawassa (Woldu et al., 2013). The maximum number of antibiotics prescribed at a time was four in DRH, but studies in Nepal shows that 6 to 7 antibiotics prescribed at once. The percentage of multiple antibiotics used in the study area (44.7%) was consistent with other findings in Hawassa (45.3%) (Woldu et al., 2013), but lower than studies conducted in Nepal that is, 79% (Palikh, 2004).
Infants less than one year received anti biotic more frequently was similar with that of the study done in Nepal (Palikh, 2004). This could be due to physician behavior in ordering medication in association with age.

LIMITATION OF THE STUDY

The possible limitation of the study was incomplete patient charts as all necessary information were not recorded: weight, body mass index (BMI), mid upper arm circumference (MUAC), duration of therapy, frequency, etc. Hence the appropriateness of the antibiotics was difficult to determine.

Conclusion

This study gives an overview of the pattern of antibiotic use in the study area. Generally, we can conclude that there was:

1. High percentage of antibiotics use in pediatrics ward of DRH and even some of them administered without proper indication.
2. Crystalline penicillin and ceftriaxone were the most frequently prescribed single antibiotics while ampicillin and gentamicin injection was the most frequently prescribed combined antibiotics.
3. There was good generic prescription but there is still high percentage of injectables.

RECOMMENDATIONS

The high percentage of patients charts involving injectable antibiotics observed in DRH requires rational use of antibiotics and judicious prescribing. We recommend proper interventions that could lead to the reduction in antibiotics overuse which may include:

1. Health education campaigns and professional education for parents and health professionals.
2. The establishment of antibiotic policy with periodic assessment of the sensitivity pattern of pathogenic organisms is recommended.
3. The adoption of an international standard and locally conformable guideline of antibiotic use can help to resolve such problems.
4. The government should recruit clinical pharmacists in the study area which is very important in order to monitor the clinical use of these medications and to tackle associated factors.

Conflict of Interest

The authors report no conflicts of interest.

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Blood pressure lowering and cardio-protective effects of garlic *(Allium sativum)* and ginger *(Zingiber officinale)* extracts in some laboratory animals

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This study evaluated the blood pressure effects and cardio-protective function of ginger and garlic extracts in laboratory animals. Wistar rats of both sexes were assigned into the following groups: Group I: Served as control + distilled water; Group II: 20 mg/kg of garlic; Group III: 40 mg/kg of garlic; Group IV: 20 mg/kg of ginger; Group V: 40 mg/kg of ginger; Group VI: garlic 10 mg and ginger 10 mg/kg; Group VII: garlic 20 mg and ginger 20 mg/kg. Animals were euthanized after four weeks of treatment. Blood samples were collected and serum separated for lipid profile assay. The effect of extracts on perfused rabbit heart was also investigated. Moreover, the effect of extract on blood pressure was tested in anaesthetized cats. The results obtained in the study showed a statistically significant decrease ($p<0.05$) of serum total cholesterol (TC), triglyceride and low density lipoprotein-cholestero (LDL-C) levels at all single and combined doses of the extract when compared with the control group. The extract single and combined doses significantly increased ($p<0.05$) serum high density lipoprotein-cholesterol (HDL-C) level in the treated animals when compared with the control group. The results showed a significantly decreased rate and force of contraction at the combined doses when compared with the baseline line control level ($p<0.05$). The study also revealed that the administration of only garlic at dose of 0.1 and 1 mg/ml produced a significant decrease ($p<0.05$) in the diastolic blood pressure. There was a statistically significant decrease ($p<0.05$) in diastolic blood pressure in all single doses of garlic as well as the combined doses of garlic and ginger extract administered. The result obtained showed that administration of only single doses of ginger produced a significant decrease in $p < 0.05$. Administration of single doses of garlic (0.1 and 1 mg/ml) produced significant reduction ($P < 0.05$) in mean arterial pressure (MAP) when compared with control group. In conclusion, the findings suggest that the extract as well as its combination improved lipid profile and may have a cardio-protective effect.

Key words: Garlic, ginger, isolated perfuse heart, total cholesterol, triglyceride, low-density lipoprotein, blood pressure.

INTRODUCTION

Garlic (*Allium sativum*) and ginger (*Zingiber officinale*) are widely consumed spices in food and drink form. Several

studies have been done on these plants separately especially on the heart and blood pressure. But there is no record of their combined effects. However, these plants are often consumed in combined form as food spices. Human and animal studies have substantiated that garlic and ginger lowers serum cholesterol and triglycerides and increases the amount of high-density lipoproteins (HDL) (Brankovic et al., 2011). Garlic is a popular supplement well-perceived as a healthy choice among people looking to increase cardiovascular wellness. Approximately 4% of all cardiovascular disease patients who use herbal supplements take garlic (Hendenreich et al., 2011). Known risk factors for cardio-vascular disease include inflammation, high cholesterol, high homocysteine, high blood pressure, diabetes and vascular dementia (Ginter and Simko, 2010). Garlic reduces cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl-CoA. Garlic has been shown to inhibit low-density lipoproteins (LDL) oxidation, platelet aggregation, arterial plaque formation, decrease homocysteine, lower blood pressure, and improve micro circulation (Lai et al., 2012). *In vitro* studies by Benavides et al. (2007) have confirmed the vasoactive ability of garlic's sulfur compounds whereby red blood cells convert garlic's organic polysulfides into hydrogen sulfide, a known endo-genous cardio-protective vascular cell signaling molecule. In traditional Chinese medicine, ginger is used to improve the flow of body fluids. A Japanese study showed that active constituents in ginger reduced the blood pressure and decreased cardiac workload (Rehman et al., 2011). Several reports, mainly from rat studies, have suggested that ginger exerts many direct and indirect effects on blood pressure and heart rate (Yang et al., 2011). In Guinea pig paired atria, the crude extract exhibited a cardio-depressant activity on the rate and force of spontaneous contractions (Yu et al., 2011). In this study, we compared the blood pressure effects and cardio-protective function of ginger and garlic extracts separately to the combination of both extracts in laboratory animals.

MATERIALS AND METHODS

Management of experimental animals

Strains of albino Wistar rats of both sexes between the ages of 12 and 16 weeks' old and weighing between 150 and 200 g were procured from the Animal House of the Department of Pharmacology Animal House of Ahmadu Bello University, Zaria. The animals were kept in well aerated laboratory cages in the Animal House of the Department of Human Physiology, Ahmadu Bello University, Zaria. They were allowed to acclimatize to the laboratory environment for a period of two weeks before the commencement of the experiment. The rats were given access to standard animal feeds and drinking water a*d libitum* during the acclimatization period.

Collection and preparation of plant extract

The fresh plant of garlic bulbs and dried rhizome ginger were purchased from Samaru market in Zaria, 11° 10' N, 07° 38' E Nigeria. The plant was taken to the herbarium unit of the Department of Biological Sciences where the plant was identified by the taxonomist Mallam Musa Mohammed with the voucher numbers 050913 and 0250913, and was deposited. They were dried under shade and then ground into fine powder using laboratory mortar and pestle. The powder (150 g) of garlic and (208 g) of ginger was macerated in cold water at room temperature for 24 h at light/dark cycle of 12:12 h. This was then filtered using a filter paper (Whatmann size no. 1) and the filtrate was evaporated to dryness on water bath at 40°C to a dry residue of 24 g of garlic and 34 g of ginger. The powder was kept in an air-tight bottle until it was reconstituted for administration.

Experimental design

Thirty five Wistar rats were used. Rats were allocated into 7 groups and treated as follows:

Group 1: Served as control and were administered with 1 ml of distilled water orally.
Group 2: Received 20 mg/kg body weight of garlic orally
Group 3: Received 40 mg/kg body weight of garlic orally
Group 4: Administered with received 20 mg/kg body weight of ginger orally.
Group 5: Received 40 mg/kg body weight of ginger orally.
Group 6: Received garlic 10 mg and ginger 10 mg/kg body weight orally
Group 7: Received garlic 20 mg and ginger 20 mg/kg body weight orally

Collection and preparation of sera samples for lipid profile

Animals were treated with extracts orally as mentioned earlier.
Four weeks after the treatment period, all animals were sacrificed after mild anaesthesia with chloroform. Blood samples were drawn from the heart of each anaesthetized animal from all groups by cardiac puncture. Blood samples (5 ml) were collected in ethylenediaminetetraacetic acid (EDTA) bottles for the determination of haematological parameters. Other blood samples (5 ml) were collected in plain tubes and were allowed to clot, and the serum was separated by centrifugation using Denley BS400 centrifuge (England) at 1,968 × g for 10 minutes. The serum collected was used to determine lipid profile assay.

Determination of lipid profile

Lipid profile was determined spectrophotometrically, using enzymatic colometric assay kits (Randox Laboratories Limited kits, United Kingdom) as the following.

Determination of serum total cholesterol

The serum concentration of total cholesterol was quantified after

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enzymatic hydrolysis and oxidation of the sample as described by Stein (1987). The value of total cholesterol present in the serum was expressed in mg/dl.

Total cholesterol concentration = A sample/A standard × 195.0 mg/dl.

Determination of serum triglyceride

The serum triglyceride concentration was determined after enzymatic hydrolysis of the sample with lipases as described by Tietz (1990). Briefly, 1000 µl of the reagent was added to each of the sample and standard. This was incubated for 10 min at 20 to 25°C after mixing, and the absorbance of the sample (A_{sample}) and standard ($A_{standard}$) were measured against the reagent blank within 30 min at 546 nm. The concentration of triglyceride present in the serum was expressed in mg/dl.

Triglyceride concentration = A sample/A standard > 196.0 mg/dl.

Determination of serum high-density lipoprotein cholesterol

The serum level of HDL-C was measured by the method of Wacnic and Albers (1978). Low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) and chylomicron fractions in the sample were precipitated quantitatively by addition of phosphotungstic acid in the presence of magnesium ions. The mixture was allowed to stand for 10 min at room temperature (37°C), and centrifuged for 10 min at 1,957 × g. The supernatant

represented the HDL-C fraction. The cholesterol concentration in the HDL fraction, which remained in the supernatant, was determined. The value of HDL-C was expressed in mg/dl.

Determination of serum low-density lipoprotein cholesterol

The serum level of LDL-C was measured according to the protocol of Friedewald et al. (1972) using the relationship as follows:

LDL-C = TC-TGL/5 + HDL-C

where LDL-C is low-density lipoprotein cholesterol, TC is total cholesterol, TGL is triglyceride and HDL-c is high-density lipoprotein. The value was expressed in mg/dl.

Determination of effect of extract on perfused rabbit heart

The effects of various doses of the extract on the perfused rabbit heart were recorded after the baseline was established. One dose was given at a time, beginning from a very low dose of 1 mg/ml, then other doses were also tested. Each effect was washed off 2 min before the next. First, the effect of *A. sativum* was studied, and then the effect of *Z. officinale* and finally their combined effects were studied.

Determination of the effect of extract on blood pressure of the cat (*in vivo* studies)

Four cats were used for this study. They were anaesthetized by injection of 40 mg/kg of pento barbbitone sodium (stock concentration 60 mg/ml) intraperitioneally. They were cannulated as the following.

Their carotid arteries and vagus nerve (in the neck) were exposed by dissection. Two short ligatures were placed wider than the carotid arteries and the peripheral one was tied tightly.

1) The carotid artery was temporarily occluded centrally with a clip. A cannula was inserted into the artery, and then connected to a pressure transducer coupled to a recording microdynamometer.
2) Heparin normal saline was injected to prevent clothing.
3) The record of the blood pressure began immediately after the occlusion.
4) The left femoral vein was exposed, tied off with a peripheral ligature.

A 2 ml syringe, containing normal saline for flushing of injected drugs was attached. The various tests drugs were administered beginning from a very low dose of 1 mg/ml to a maximum dose of 10 mg/ml. The effect of different doses of the extract on the blood pressure was recorded. The volume of extract used for each concentration was 0.2, 0.4, 0.8 and 1.0 ml. No additional dose was given until the preparation had fully recovered to the former control level or a new control level. Each effect was flushed by administering 2 ml of 0.9% normal saline. This procedure was done for *A. sativum* and *Z. officinale* separately, and then in combined form.

Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). The data obtained were statistically analyzed using one-way analysis of variance (ANOVA) with Tukey's multiple comparison post hoc tests to determine the level of significance between control and experimental groups. Values of $P < 0.05$ were considered as significant (Duncan et al., 1977).

RESULTS

There was a significant ($P<0.05$) reduction of serum total cholesterol, triglyceride and low-density lipoprotein levels at all single and combined doses of the extract administered to the animals, when compared to the control group. The extract at single and combined doses significantly ($P<0.05$) elevated serum high-density lipoprotein level in the treated animals when compared with the control group (Table 1).

The study assessed the effect of garlic and ginger on blood pressure parameters in cats. The study also revealed that the administration of only garlic at dose of 0.1 and 1 mg/ml produced a significant decrease ($p<0.05$) in the systolic blood pressure when compared with normal control group. On the other hand, there was a statistically significant decrease ($p<0.05$) in diastolic blood pressure in all single doses of garlic as well as the combined doses of garlic and ginger extract administered when compared with the control group. The result obtained also showed that administration of only single doses of ginger produced a significantly reduced ($p<0.05$) pulse pressure when compared with normal control group. In regards to mean arterial blood pressure, administration of single doses of garlic (0.1 and 1 mg/ml) produced a significant reduction in mean arterial pressure when compared with the control group (Table 2).

Table 1. Effects of garlic (*Allium sativum*) and ginger (*Zingiber officinale*) (single and combined) on serum lipid profile in Wistar rats (mg/dl) (n = 5).

Treatment	Serum total cholesterol (mg/dl)	Serum triglyceride (mg/dl)	Serum low- density lipoprotein (mg/dl)	Serum high-density lipoprotein (mg/dl)
Normal + Distilled water	106.97±2.41[a]	86.14±4.15[a]	64.16±4.23[a]	21.57±1.91[a]
Garlic 20 mg/kg body weight	62.49±4.09[b]	48.09±5.96[b]	22.63±2.24[b]	31.64±3.40[b]
Garlic 40 mg/kg body weight	72.64±4.65[b]	49.54±4.31[b]	19.84±1.77[b]	42.89±4.27[b]
Ginger 20mg/kg body weight	59.2.4±4.09[b]	27.66±2.63[b]	11.81±1.13[b]	41.97±3.56[b]
Ginger 40 mg/kg body weight	58.17±5.83[b]	31.24±5.67[b]	15.06±1.44[b]	37.40±3.51[b]
Garlic 10 mg + Ginger 10 mg/kg body weight	51.27±5.29[b]	30.00±6.45[b]	13.49±9.28[b]	31.79±2.54[b]
Garlic 20 mg + Ginger 20 mg/kg body weight	81.86±12.35[b]	27.20±7.16[b]	13.69±2.28[b]	62.73±12.23[b]

[a,b]Values of $P < 0.05$ with different superscript significantly different when compared with control group (Normal + Distilled water).

Table 2. Effects of garlic *(Allium sativum)* and ginger (*Zingiber officinale*) on blood pressure parameters in cats (single and combine).

Dose concentration (mg/ml)	SBP (mm/Hg)	DBP (mm/Hg)	Pulse pressure (mm/Hg)	MABP (mm/Hg)
Normal saline	75.75±0.85[a]	64.3±1.09[a]	11.95±0.82[a]	68.11±0.84
Garlic (0.1)	54.3±1.32[b]	34.5±1.55[b]	19.8±0.25[ns]	41.1±1.46[a]
Garlic (1)	54.0±0.41[b]	35.8±0.48[b]	18.3±0.25[ns]	41.8±0.44[a]
Garlic (10)	55.8±1.12[a]	36.8±0.95[b]	19.0±0.71[ns]	43.1±0.96[ns]
Garlic (20)	59.0±2.48[a]	42.8±0.63[b]	22.8±0.75[ns]	48.8±2.53[ns]
Ginger (0.1)	63.5±2.50[a]	51.5±3.50[a]	12.0±1.00[b]	55.5±3.20[ns]
Ginger (1)	66.2±3.13[a]	56.0±2.97[a]	10.2±0.31[b]	59.4±3.10[ns]
Ginger (10)	56.5±3.52[a]	45.0±4.71[a]	11.5±1.55[b]	48.6±4.45[ns]
Ginger (20)	46.6±0.93[b]	38.8±0.80[b]	7.8±0.73[b]	41.4±0.76[a]
Garlic + Ginger (0.1l)	60.5±0.65[a]	38.8±2.59[b]	21.8±1.88[a]	45.9±1.68[ns]
Garlic + Ginger (1)	59.0±2.48[b]	36.3±2.59[b]	22.75±0.75[ns]	43.8±2.53[ns]
Garlic + Ginger (10)	62.8±1.75[b]	44.5±2.63[b]	18.25±1.11[ns]	50.6±2.32[ns]
Garlic + Ginger (20)	63.5±2.75[b]	43.0±2.79[b]	20.50±0.28[ns]	49.8±2.78[ns]

[a,b]Values of with different superscript are significantly ($P<0.05$) different when compared to control group (Normal saline + distilled water).

DISCUSSION

Diseases mainly affecting the heart or blood vessels are primarily termed as cardiovascular diseases (CVDs). Today, CVDs constitute one of the major causes of mortality and have become a major health hazard all over the world since they account for more than 30% of the global deaths every year (American Heart Association medical/scientific statement, 1994; Thomas, 2011). Hyperlipidaemia is an important risk factor of coronary artery diseases which often lead to myocardial infarction and heart failure (NCEP, 1993; Ghotto et al., 2005). The present study investigated the cardio-protective activity of garlic and ginger extract and their combination in laboratory animals. Management of plasma cholesterol levels continues to be a cardinal issue in cardiovascular disease prevention, as hypercholesterolemia plays a crucial role in pathogenesis of atherosclerosis and related heart diseases (Ginte and Simko, 2011). The results showed that there was a statistically significant ($P<0.05$) decrease of serum total cholesterol concentration in the animals administered both single and combined doses of aqueous garlic and ginger extract when compared with the control group. Allicin has been proposed as the active compound produced by garlic which is responsible for its hypocholesterolemic effect (Ginte and Simko, 2011). Garlic and ginger have been reported to modify lipid metabolism by inhibiting cellular cholesterol biosynthesis, increasing bile acid biosynthesis to eliminate cholesterol from the body and increasing fecal cholesterol excretion, therefore, cholesterol synthesis is reduced by up to 75% (Singh and Poter, 2006; Matsuda et al., 2009). The cholesterol lowering effects of garlic has also been attributed not only to its organosulfur constituents but also to a

variety of steroidal saponins present in garlic extract (Ramaa et al., 2006). There was also significantly decreased serum triglyceride and low density lipoprotein levels at all single and combined doses of the aqueous garlic and ginger administered to animals when compared with the control group. However, the extract at single and combined doses significantly elevated ($p<0.05$) serum high density lipoprotein level in the treated animals when compared with the control group. These findings are in agreement with Ali et al. (2000) who suggested that administration of garlic to rats is effective in decreasing total cholesterol and triglycerides significantly. The mechanism for triglycerides lowering effect of garlic is not well understood. However, Yeh and Yeh (1994) demonstrated that the rate of acetate incorporation into fatty acid was reduced in hepatic cell culture treated with garlic extract. Thus, the triglycerides lowering effect of garlic may somehow be due to the inhibition of fatty acids synthesis. Elshater et al. (2009) revealed that post treatment with ginger extract for 6 weeks to diabetic rats produced significant reduction in the levels of plasma cholesterol, triglycerides and LDL-cholesterol and significant elevation in the HDL-cholesterol when compared with diabetic group. In another study, Alizadeh et al. (2008) investigated the effect of 45 days ginger capsules on the lipid levels in patients with hyperlipidemia and indicated that ginger has a significant lipid lowering effect when compared with placebo. The reduction in LDL-c level by garlic may be due to allicin, an active compound produced by garlic which reduces the production and release of LDL-c by the liver and promote LDL receptors activity in the liver cells, which helps the liver to clear the circulating LDL-c (Holzgartner et al., 1992). Brousseau et al. (2004) reported that the increase in HDL-c level is usually attributed to allicin, which significantly altered the distribution of cholesterol among HDL and LDL subclasses. Hyperlipidemia is the underlying pathophysiology of the number one killer, atherosclerotic coronary artery heart disease (Elrokh et al., 2010). The present study also revealed that administration of the extract especially at the combined doses produced a reduction on the rate and force of contraction when compared with the baseline line control level. The interaction between the extract and the standard drug (adrenaline) revealed that the extract completely blocked the action of adrenaline when co-administered, hence reducing both the rate and force of contraction. This suggests that the extracts may be acting via β_1-adrenergic receptor located on the myocardium. The blockade of β_1 receptors has been shown to cause negative inotropic and chronotropic effect which in turn bring about decrease in cardiac work and cardiac output (Katzung, 2007). These effects are useful in the treatment of cardiac infarction, cardiac arrhythmias and angina pectoris. Recent *in vitro* studies by Benavides et al. (2007) have confirmed the vasoactive ability of garlic's sulfur compounds whereby red blood cells convert garlic's organic polysulphides into hydrogen sulfide, a known endogenous cardio-protective vascular cell signaling molecule. Ghayur and Gilani (2005) reported that the crude extract of ginger induced a dose-dependent decrease in the arterial blood pressure of anesthetized rats and in guinea pig paired atria, the crude extract exhibited a cardio-depressant activity on the rate and force of spontaneous contractions. The study also revealed that the administration of only garlic at dose concentration of 0.1 and 1 mg/ml produced a significant decrease ($p<0.05$) in the systolic blood pressure when compared with normal control group. Similarly, there was a statistically significant decrease ($p<0.05$) diastolic blood pressure in all single doses of garlic as well as the combined doses of garlic and ginger extract administered when compared with the control group. The result obtained also showed that administration of only single doses of ginger produced a significant decrease ($p<0.05$) pulse pressure and mean arterial blood pressure when compared with the normal control group. Nitric oxide (NO) is an important mediator of blood pressure (BP) homeostasis. It has been reported that pharmacologically reducing the bioavailability of NO can lead to hypertension in normal rats (Ribeiro et al., 1992). In our present study, garlic may appear to exert blood pressure reducing activity by modulating the activity of several mechanisms that are vital in blood pressure homeostasis, which include the prostaglandin system (Al-Qattan et al., 2003), rennin-angiotensin system (Sharifi et al., 2003), and renal tubular transport mechanisms (Al-Qattan et al., 2003). Another possible mechanism by which garlic might reduce blood pressure is the direct and indirect vasodilatory actions of NO (Kim-Park and Ku, 2000; Gouvea et al., 2003). Garlic was reported to contain arginine and enhance the synthesis of NO (Kim et al., 2001).

Conclusion

Conclusively, the findings suggest that the extract as well as its combination improves lipid profile in the animals and the cardio-protective effect of garlic and ginger was alongside its negative ionotropic and chronotropic effect.

Conflict of interest

The authors of this research work declare that there is no conflict of interest concerning the publication of this manuscript.

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Pregnancy in renal transplant recipients

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Fertility is considerably affected in chronic renal insufficiency and periodic hemodialysis, and it is improved by renal transplantation. Transplanted patients recover from their renal failure state, and pregnancy occurred in 2% renal graft recipients who were fit to procreate. The aim of this study was to bring back the cases of pregnancies carried out in our renal patients who had transplantation surgery and to specify the possible complications of the foetus before and after the childbirth. It is a retrospective study with records of 20 years period (1986 to 2006) of 10 pregnancies which occurred in 7 renal transplant recipients in our Charles Nicole hospital department. Mean patient age was 33.8 years (29 to 43 years). Mean time between transplantation and the onset of pregnancy was 6.5 years (1 to 18 years). Before pregnancy, hypertension was observed in 1 case and proteinuria in other case. All our patients had creatininemia <1.50 mg/dl. Immunosuppressive treatment associated steroids and azathioprin in 3 cases, steroids and ciclosporin A in 2 cases and steroids, ciclosporin A and azathioprin in 2 cases. One patient developed diabetes. Maternal complications were rare, essentially hypertension in 2 cases, proteinuria in 1 case, ascension of creatininemia in 2 cases and hepatic cholestase in 2 cases. Prematurity was observed in 2 cases; it was related to premature rupture of membranous in 1 case and uterine contractions in cesarean patient in other case. The mean neonatal weight was 2950 g (2100 to 3500 g) with 4 small gestational age (< 2800 g). It was noted in 1 case of newborn, down's syndrome in a pregnant women who was 37 years. After a mean follow up of 7.4 years follow-up, mean cretininemia was 1.80 mg /dl (0.74-5.53 mg /dl). One patient showed chronic rejection. Immunosuppressive treatment seemed without adverse effects on fetus. The only case of chromosome abnormality appeared in a pregnant women who was more than 35 years old. The course of pregnancy after renal transplantation is generally uncomplicated without increased risk of graft loses. However, a normal arterial pressure, a stable renal function and absence of proteinuria were requested before allowing a pregnancy.

Key words: Renal transplantation, pregnancy.

INTRODUCTION

Women with end-stage chronic renal failure have low fertility and high-risk pregnancies (Fuchs et al., 2007). Kidney transplantation in most cases restores fertility for these women (Audra and Laville 1996; Ville et al.,

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1992). 14 000 births in the whole world were reported in organ transplant recipients (Mc Kay and Josephson 2006). The first pregnancy after organ transplantation was recorded in 1963 in a woman who had received a kidney allograft (Audra and et Laville 1996) and since it was successful pregnancies were reported in 2% of kidney transplant recipients of childbearing age (First et al., 1995; Davison 2006). However, pregnancy in kidney transplant recipients is not without risks (Fuchs et al., 2007; Ben Youssef et al., 2006). The course of the pregnancy is favorable by respecting the recommendations such as the European recommendations of good practices IV (Fuchs et al., 2007; O" Bas aran et al., 2004). The objective of our study, was to study the course of pregnancy after kidney transplantation and to assess the impact of the pregnancy on the fetus and on the kidney graft.

METHODOLOGY

Patients

This is the retrospective study of the medical histories of 312 kidney transplant recipients whose operations were performed between 1986 and 2006 in our hospital. Kidney transplant recipients received likely a living related graft in 241 cases, a non related graft in 17 cases and a cadaveric graft in 54 cases. Among the107 kidney transplantation in females, 10 spontaneous pregnancies occurred in 7 kidney transplant recipients. We had contra-indicated pregnancy during the first 2 years after kidney transplantation.

Experimental

Patients were reviewed in terms of the reason for kidney failure, type of dialysis (hemodialysis or peritoneal dialysis), length of pretransplant dialysis and age at kidney transplantation. For donors, these demographics included age, sex, blood group, type of donor (deceased or living), and relationship to the recipient. For each patient, transplantation-pregnancy interval, age at diagnosis of pregnancy, immunosuppressive regimen, and function of the kidney at the time of diagnosis of pregnancy circumstances of discovery of the pregnancy and its complications were reviewed. Arterial pressure and labour values were all evaluated. Graft function and mortality rate were also reviewed. The infants' general health and follow-up were examined closely. The mode of delivery (natural childbirth or cesarean section), the baby's weight, length, head circumference, Apgar score and labor values were all evaluated. Low-birth-weight is defined by weight between 1500 and 2500 g and very low-birth-weight by weight between 1000 to 1500 g at birth. Premature babies are delivered between gestational weeks 29 and 37. We also inquired about growth, laboratory tests, and the last measured height and weight.

RESULTS

The mean age at kidney transplantation was 28.5 years (25 to 35 years). Causes of the end stage renal stage were interstitial in 3 cases (nephronophtis in 1 case), glomerular in 2 cases (IgA nephropathy in 1 case and membranous nephropathy in 1 case) and unknown in 2 cases. Kidney transplant recipients received a living related graft in 5 cases and a cadaveric graft in 2 cases. Immunososuppressive regimen associated steroids and azathioprine with or without ciclosporine. A patient presented a microscopic hematuria and a graft dysfunction explained by the recurrence of Ig A nephropathy on the kidney graft. Hypertension was observed in 2 cases, proteinuria in 2 cases under 1 g/24 h, anemia in 1 case and post transplantation diabetes in 1 case. The mean serum creatininemia before pregnancy was at 1.03 mg /dl (0.81- 1.47 mg /dl). No case of acute rejection of the graft was observed before diagnosis of pregnancy. Patients had regular menstrual cycles and were not under contraception. (Table 1) Circumstances of discovery of the pregnancy were delay by the menstruations in all the cases. The mean interval from transplantation to pregnancy was 6.5 years (1 to 18 years) and it was higher than 2 years in 70% of the cases. The mean age at diagnosis of pregnancy was 33.8 years (29 to 43 years). No modification of immunosuppressive regimen was noted during pregnancy.

The mean creatininemia during pregnancy was constant at 1.04 mg /dl (0.77 to 1.88 mg /dl) with the creatininemia higher than 1.5 mg /dl in 2 cases. Pregnancy complications included new-onset proteinuria in 1 case in the third trimester and the onset of hypertension without proteinuria in 1 case. The hypertension was associated with proteinuria in 3 cases. Graft dysfunction during pregnancy was observed in 2 cases, hepatic cholestasis in 2 cases and hyperuricemia in 4 cases. No peripartum maternal deaths were reported (Table 2).

Fetal complications were premature in 3 cases caused by a premature rupture of the membranes in 1 case, uterine contractions on cicatricial uterus in 1 case and preeclampsia in the third case. Mean weight at birth was 2950 g (2100 to 3500 g) with 4 cases of low-birth-weight. A patient presented an allograft dysfunction caused by an infection of the amniotic liquid. Postpartum was without complications in all the cases. Only one patient was lost to follow-up after the childbirth. Six patients were followed. After a mean follow-up of 7.4 years (2 to 14 years) after childbirth, blood pressure was normal in 3 patients and hypertension was observed in 3 patients. No acute rejection was noted. Renal function remained stable in 9 cases. A puncture biopsy of the graft practiced in the patient having creatininemia at 5.53 mg /dl showed chronic allograft dysfunction and chronic ciclosporine toxicity with tubulointerstitial and vascular lesions.

Concerning the 3 patients who had 2 pregnancies, after a follow-up respectively of 4, 6 and 14 years, hypertension was noted in 2 cases, creatininemia was respectively at 1.12; 1.40 and 1.06 mg /dl and proteinuria was observed in 1 case. One death was observed 8 years after the childbirth secondary to colic cancer. Growth was normal for 9 children. Only one baby had down syndrome whose mother was 36 years old (Table 3).

Table 1. Clinical exam and biology before pregnancy.

NI	Age at KT (year)	Donor age (years)	Ttt IS	BP cmHg	Treatment	Creat (mg /dl)	Gly (mmol/l)	Uric acid (µmol/l)	Hb (g/dl)	Hepatic biology	24 h- Proteinuria (g)
NIC/PBR: nephronophthisis	28	Mother (47)	CS- AZT	11/7	0	0.98	5.8	264	13.2	Nl	0
				12/8	0	0.94	5	317	12.6	Nl	0
NIC/RVU	28	Mother (57)	CS- AZT-CicloA	12/8	0	1.36	4.8	435	9.5	Nl	0
NGC/PBR: IgA nephropathy	25	Deceased	CS-AZT	11/6	0	1.47	5.7	393	12.2	Nl	0.5
				12/8	metoprolol	1.39	5	378	12.2	Nl	0.8
NIC	23	Mother (44)	CS-CicloA	11.5/7	0	0.91	5.2	309	14.2	Nl	0
				9/6	0	0.81	5	300	13.5	cytolysis	0
NC/PBR inconclusive	31	deceased	CS-CicloA	13/9	metoprolol	0.84	4.4	205	13.5	Nl	0
NGC/PBR:GEM	35	Brother (30)	CS-AZT-CicloA	11/6	0	0.81	5.8 (diabetes)	334	12.6	Nl	0
NC	30	Brother (30)	CS-AZT	12/8	0	0.80	5	300	12	Nl	0

AZT: azathioprin, BP: blood pressure, Cs : steroids, CicloA: ciclosporine, Creat: creatininemia, Gly: glycemia, Hb: haemoglobin, K T : kidney transplantation, Nl: normal, Prot/24h: 24-hours proteinuria.

Table 2. Clinical exam and biology during pregnancy.

Interval KT/P (years)	BP cmHg	Treatment	Creat mg /dl	Gly mmol/l	Uric acid µmol/l	Hb g/dl	Hepatic biology	24h- Proteinuria (g)
1	10.5/8	0	0.83	5.5	273	9.8	Nl	0
3	11.5/7	0	0.77	5	274	10	Nl	0
2	12/8	Acebutolol	1.60	5	532	7.5	Nl	0
12	11/6	0	1.88	5.5	525	12	Nl	1.5
18	13/9	metoprolol	1.40	5	458	12.2	Nl	0.9
7	12/8	0	0.75	5	291	10.8	cholestasis	0
10	12/8	0	0.75	5	300	10.4	cholestasis	
4	11/8	Acébutolol	0.94	5 (diabetes)	300	8.7	Nl	0.8
2	12/8	0	0.76	5.5	501	12	cholestasis	0
6	12/8	0	0.80	5	300	11	Nl	0

BP: blood pressure, Creat: creatininemia, Gly: glycemia, Hb: haemoglobin, K T : kidney transplantation, Nl: normal, P:pregnancy, Prot/24h: 24-hours proteinuria.

Table 3. Complications in fetuses or neonates and kidney recipients mothers.

Follow-up (years)	Fœtus	Mother
14	-	HBP
12	-	
4	Preterm delivery-	Cesarean section
11	-	Cesarean section -HBP-prot =0,5g/24h
5	-	
7	-	RAS
4	Preterm delivery	
8	-	ARF (amniotic infection) – cesarean section HBP-CGD-prot =0,6g/24h death
2	Preterm delivery-	Cesarean section
Lost to follow-up	Down's syndrome	-

ARF: acute renal failure, CGD: chronic graft dysfunction, HBP : High blood pressure.

DISCUSSION

In this study, 6.5% of childbearing age women experienced pregnancy, an incidence that was lower than what was recently reported (49). Since successful pregnancies were reported in 2% of kidney transplant recipients (First et al., 1995; Davison 2006). All pregnancies occurred after 1 year post transplantation; creatininemia was lower than 150 µmol/l in all cases, normal blood pressure under treatment in 2 cases and a proteinuria under 1 g/24 h in 2 cases.

The maternal complications during the pregnancy were gravidic arterial hypertension in 3 cases, proteinuria in 3 cases, hepatic cholestasis in 2 cases and hyperuricemia in 4 cases. A patient presented an acute renal failure due to amniotic liquid infection. The fetus complications were premature in 3 cases and a fetal hypotrophy in 4 cases. One case of Down's syndrome whose mother was 36 years old is noted. Kidney transplantation improved the fertility in chronic failure patients (Fuchs et al., 2007). Several registers studied the course of these pregnancies (Coscia et al., 2007; Sibanda et al., 2004).

These pregnancies were rare, occurring in 97% of cases after the first year of kidney transplantation (Levidiotis et al., 2009). All our patients carried out a pregnancy test after the first year of renal transplantation. The mean age at the time of these patients were 29±5 years comparable with that of our patients (Levidiotis et al., 2009). Multiple pregnancies are rarer (Nicovani et al., 2009). Pregnancy must be planned since risk factors increase to 75% of the maternal and/or fetal complications (Davison 2006; Davison 1995; Fitoussi et al., 1990 ; Ross 2006).

The risk factors are a short interval between kidney transplantation and pregnancy lower than 2 years, a pre conceptional controlled hypertension, a creatininemia > 1.50 mg/dl and a proteinuria. Immunosuppressive treatment must be adapted (Rizzoni et al., 1992; Armenti et al., 1995; Armenti et al., 2008; Framarino et al., 2007). Prematurity in these patients are more frequent in our study than in other literatures in general population (30 to 92% versus 12.5%) (Framarino et al., 2007; Armenti et al., 1994; Muirhead et al., 1992; Davison et al., 1976; Blowey and Warady 2007; Rudolph et al., 1979). Prenatal steroid therapy is indicated in some cases to reach fetal pulmonary maturation (Hibbard 2007). In our series, a prematurity was observed in 2 cases. The fetal hypertrophy is more frequent than in the general population (8 to 45 % versus 5%) particularly when creatininemia is > 1.50 mg/dl, there is an hypertension (Davison et al., 1976; Framarino di Malatétaita et al., 1993; Nojima et al., 1996) during treatment by ciclosporine compared to the azathioprine (Haugen et al., 1994; Pickrell et al., 1988; Williams et al., 1988). In our series, the fetal hypertrophy was observed in 4 cases in spite of a creatininemia lower than 1.50 mg /dl in our patients. Opportunist infections are life threating to the fetus (Hibbard 2007).

The teratogenicity risk of the immunosuppressive drugs is possible with important doses except mycophenolate mofetil taken during the pre-conceptional period responsible for cranio-facial and cardiovascular malformations (Haugen et al., 1994; Pickrell et al., 1988; Williams et al., 1988; Anderka et al., 2009; Dei Malatétaita et al., 2009). It is then recommended to plan a pregnancy if doses of corticoids are lower than 15mg/j, ciclosporine lower than 15 mg/j and azathioprine lower than 2 mg/kg/j (3). It is also recommended to stop the mycophenolate mofetil and to replace it by the azathioprine 2 months before conception. In our series, the only case of chromosomal aberration appeared with the waning of a late pregnancy. We have not noted any case of neonatal mortality which is more important in literature than that in general population (1 to 39% versus 0.68%) (Blowey and Warady, 2007). After birth, the psychomotor development of the children is normal

(Nicovani et al., 2009).

The maternal complications are mainly hypertensive in 38 to 56% aggravated by steroids and ciclosporine (Armenti et al., 1994; Haugen et al., 1994; Pickrell et al., 1988; Williams et al., 1988; Bererhi et al., 1997). These patients can be treated by beta blocker, alpha-methyl dopamine, hydralazine or calcium blocker (Carosella 2009). Hypertension is responsible for pre eclampsia in 20 to 30% of cases in these patients (Levidiotis et al., 2009; Davison, 1995 ; Rizzoni et al., 1992; Armenti et al., 1994; Rudolph et al., 1979). In our study, a gravidic hypertension was observed in 3 cases, accompanied by a rise of the creatininemia in 1 case, a proteinuria in 2 cases and a hyperuricemia in 2 cases. Disturbances of the hepatic enzymes during pregnancy are frequent and due to multiple causes (Nicovani et al., 2009; Rahman and Wendon, 2002; Pereira et al., 1997). Infections particularly urinary tract infections are frequent in these patients (Bouattar et al., 2009; Caplan et al., 1970; Chaouat et al., 1989; Hamid 1986). Gestational diabetes occurs in 1 to 11% of cases in these patients (Levidiotis et al., 2009; Gutiarrez et al., 2009). Vaginal is proposed in 1st intention in these patients (Penn et al., 1980). Acute rejection is similar or even lower than in general population (Armenti et al., 1994; Davison 1995 ; Framarino di Malatétaita et al., 1993; Tanabe et al., 1997; Moritz 2002), in the absence of risk factors, which can explained anti-HLA antibodies made during and after the pregnancy (Cornella et al., 2009). We did not observe any case of acute rejection in our study. The incidence of the chronic graft dysfunction of the graft is also similar to the general population of the renal persons receiving a transplant when the creatininemia is lower than 150 µmol/l (First et al., 1995; Rizzoni et al., 1992; Nojima et al., 1996; Thompson 2003). In our study, we observed only one case of chronic graft dysfunction explained by ciclosporine toxicity.

Conclusion

Pregnancy in kidney recipient's patients is at high risk of fetal complications. It is reasonable to wait at least a period of 1 year after kidney transplantation to program a pregnancy, to have a normal blood pressure, a stable renal function (creatininemia < 1,50 mg /dl), absence of proteinuria and adapted immunosuppressive treatment. A multidisciplinary collaboration between nephrologist's transplants, gynecologists and podiatrists is mandatory.

Conflict of Interest

The authors report no conflicts of interest.

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