MOTHER AND CHILD HEALTH

5.1 Transfer of Therapeutic Drugs from Maternal Circulation to Breast Milk: A Study with Specific Reference to Anti-tuberculosis Drugs

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Duration: 2002 – 2008

Breastfeeding offers innumerable advantages to a growing infant by meeting all its nutritional and immunological requirements. However, it may not be safe in several cases where the mother is on chronic drug therapy and safety of the drug in lactation is not established. Ill health of nursing mothers requiring medical intervention is a common feature in developing countries like India and it has now been established that the drugs present in maternal circulation can be transferred to breast milk and subsequently to the feeding infant. There is information available from previous studies on the apparent effect of many drugs and chemicals on the nurslng. However, the possible long-term effect of these drugs, particularly those that are chronically administered such as the anti-tuberculosis drugs on breastfeeding infant are not clear.

In India tuberculosis (TB) is the most common infectious cause of death among females in the reproductive age necessitating chronic long-term therapy even during critical phases like pregnancy and lactation. A study has therefore been undertaken with the objective to assess i) the transfer potentials of anti-tuberculosis drugs from circulation to breast milk and ii) the factors that may influence their metabolism and transfer to the breast milk. Studies were carried out with regard to the first line drug Isoniazid (INH). Specific aim was to assess the pharmacokinetic pattern of the drug in mother's circulation and its transfer to breast milk and also to determine its milk to plasma ratio.

Nine exclusively breast feeding women on chronic anti-tuberculosis therapy have been studied. Detailed pharmacokinetic analysis was carried out using terminal elimination rate constants and area under the concentration-time (AUC) profile was calculated for both milk and plasma. These results indicate that isoniazid is quickly absorbed and is transferred to milk in a concentration dependent manner. The mean plasma and milk concentration of isoniazid calculated by AUC (0, 24 h) in all the seven patients was found to be 18.4 g/ml (95% CI: 11.2 – 25.6) and 14.4 g/ml (95% CI: 10.5 – 18.3), respectively. The mean M/P ratio of isoniazid calculated by using AUC data was 0.89 (95% CI: 0.7 – 1.1) suggesting that isoniazid has a modest potential to penetrate into breast milk.

Genotyping for NAT2 was carried out by PCR-RFLP and DNA sequencing in 200 subjects, including 140 controls and 60 TB patients. All 9 commonly investigated polymorphisms within the coding sequences of the gene were screened. Fig. 109 shows screening for a T>C polymorphism at position 341 by allele specific PCR. A high degree of polymorphism was seen for SNPs at positions 282, 341, 481, 590 and 803. Allele *6A was found to be predominant in our study population followed by *5B and wild type allele NAT2*4. Based on these genotypes, the population could be classified as fast, intermediate and slow acetylators. In slow acetylators the concentration time profile graph of INH clearly showed a higher concentration of the drug as compared to the fast acetylators.
Fig. 109: Screening for T341C variant in NAT2 gene by allele specific PCR. a: Lanes 1, 5, and 2 - Samples 1 and 2 respectively amplified only by T specific primer - Homozygous wild; Lanes 3, 7, and 4, 8 - Samples 3 and 4 respectively amplified both by T and C specific primers - Heterozygous wild. b: Confirmation of wild type T341C locus by DNA sequencing.

5.2 Magnitude and Determinants of Chronic Obstetric Morbidities in Nasik District in Maharashtra (Funded by UNFPA)

Principal Investigator: Ragini Kulkarni
Co-ordinator: S. L. Chauhan

Duration: 2006-2007

Reproductive morbidities include gynecologic and obstetric morbidities. Chronic obstetric morbidities include obstetric fistula, pelvic organ prolapse, chronic pelvic inflammatory disease and secondary infertility which may occur after abortion or delivery. These morbidities also have serious consequences on woman's domestic, economic and marital relationships. Most of the women suffering from these morbidities do not seek treatment and suffer in silence for years. Available data on obstetric morbidities in India is largely derived from hospital records. In absence of well-designed community-based studies, it is rather difficult to know the true extent of obstetric morbidities in the community. Community based...
prevalence data gives a robust picture of the magnitude of any disease which is essential for setting priorities for planning and resource allocation in the national programme. Considering the need for such information, at the UNFPA’s initiative, The National Institute for Research in Reproductive Health, Mumbai commissioned a study to assess the magnitude and determinants of chronic obstetric morbidities in Nashik district of Maharashtra State.

The main objective of the study was to assess the magnitude and determinants of defined chronic obstetric morbidities such as obstetric fistula, pelvic organ prolapse, chronic pelvic inflammatory disease and secondary infertility.

**Study design and Methodology:**

This community based–cross-sectional study was conducted between January 2006 and December 2007. Necessary ethical and administrative approvals were obtained from the authorities before initiating the study. Considering the selected rural indicators (percentage of girls married at age less than 18 years, percentage of institutional deliveries, home deliveries and total safe deliveries) of the 33 districts in Maharashtra, Nashik District was at mid-level and hence was selected to represent the population in Maharashtra. For proper representation of the population from the district, stratified, systematic random sampling was done. Six PHC areas (3 each from tribal and non-tribal areas) in Nashik district having a population of 1, 72,903 were selected for the study. The study participants included non-pregnant ever married women with proven fertility (had at least one abortion or live birth or stillbirth) in reproductive age group (15-44 years).

Six focus group discussions were conducted one in each PHC area for understanding the local terminologies for reproductive morbidities and designing the questionnaire. Extensive efforts were made in creating a conducive environment prior to data collection for maximizing women's participation in the study. To achieve a good response rate, close interaction with the government health staff, local stakeholders such as local leaders, mahila mandals etc. was done. Special efforts for community mobilization such as conducting IEC activities in the community, allaying their fears for undergoing examination and involving men in the community were made. Household interviews were conducted among 1560 women and they were encouraged to attend the health facility for clinical examination. Clinical examination was conducted among 1167 women who had volunteered for examination. During camps conducted at the health centers, symptomatic treatment of women was done and they were referred to higher facility for further investigations and management. This resulted in a good response rate of 75 percent among the women in the study.

In-depth interviews of service providers at District hospitals and personnel conducting deliveries such as Dais and ANMs and women suffering from chronic obstetric morbidities were also conducted.

Preliminary findings from three PHC areas have been reported (Annual Report 2006-07, p 181-184).

Majority of the 1560 women respondents were Hindus (94.9%) while 57.6 percent belonged to Scheduled tribes. About half of the respondents (51.4%) were illiterates, 76.8 percent were engaged in unskilled occupation, and majority (70.7%) had per capita income less than Rs. 500. Ninety-five percent of women reported being married before 18 years of age. Among 1560 women, 78 percent used any modern contraceptives i.e 65 percent had undergone tubectomy, 8 percent of their spouses had undergone vasectomy while 3 percent used spacing methods. Seventy-three percent of the women had one or more pregnancies at age less than 21 years. Seventy-two percent deliveries were conducted by Dais, 15 percent by Doctors and 11 percent by ANMs.

Out of 4862 deliveries reported by 1560 women respondents, 490 complications were reported in 462 deliveries, the most common complication being prolonged labour (56.7%). Out of 380 reported abortions, 113 were induced resulting in lower abdominal pain (28.6 %), fever (25.7%) and excessive bleeding (22.8%) as the most common complications.
As seen in Fig.110 the magnitude of symptoms reported to field investigator was comparatively much more as compared to doctor. Out of 1560 women interviewed at household level, 1167 (75%) women volunteered for clinical examination. Among them, 509 women had any reproductive morbidity (373 had gynecological morbidities and 136 had chronic obstetric morbidities). A total of 410 gynecological morbidities were detected in 373 women. Candidiasis was the most prevalent morbidity (8.7%) followed by vaginitis (7.8%).

As seen in Table 8, pelvic organ prolapse was found to be most prevalent, (7.2%) followed by chronic PID (2.6%) and secondary infertility (1.8%). Only one case of vesico-vaginal fistula was detected among the study population during the study. Overall number of reproductive morbidities in 1167 women was found to be 0.4 per woman. Five percent of women had more than one reproductive morbidity. Advancing age, illiteracy, early age at marriage, more number of deliveries, deliveries conducted by unskilled personnel had statistically significant association with pelvic organ prolapse. Only one case of vesico-vaginal fistula was detected in a 28 year old woman, suffering from involuntary passage of urine since last 8 -10 years. The fistula occurred due to obstructed and prolonged labor and lack of transport to health facilities. Her domestic, social and economic activities were severely affected due to fistula. She was operated at District Hospital under the project activity.

Majority of women having symptoms of vaginal discharge, low backache, lower abdominal pain, prolapse and urinary incontinence reported that the presence of their morbidities mainly affected their household work and economic activities. A large percentage
of women (more than 50%) having symptoms of reproductive morbidities did not seek treatment. The predominant reason for not seeking treatment was lack of awareness regarding severity of the problem followed by financial problems. Among those who sought treatment, not much difference was observed between those seeking treatment from private and government doctors.

The findings of the study have been presented in the special session on reproductive morbidities during the Annual Conference of Indian Public Health Association (IPHA) on 8th March 2008. In addition, a dissemination meeting is planned at local and National level in Nashik and Delhi wherein the stakeholders at various levels will be invited to participate.

Recommendations
- Early marriage below 18 years, followed by early and repeated pregnancies has shown a significant association with the reproductive morbidities in the study, hence all round efforts are required to educate the population on delaying marriage and pregnancy, and use of spacing methods of family planning.
- About two-thirds of the deliveries were conducted at home by Dais. Giving institutional care during delivery and post partum care at the health facility could prevent majority of the chronic obstetric morbidities. The scheme of Janani Suraksha Yojana under NRHM takes care of these and should be implemented vigorously.
- The prevalence of pelvic organ prolapse is high (7.2%), hence it needs to be appropriately addressed in the program.
- The study has provided first of its kind community-based prevalence data on chronic obstetric morbidities which has given an insight into the dimensions of disease burden and its pattern. Large-scale surveys such as National Family Health Survey or Rapid household survey in RCH could incorporate questions on common obstetric morbidities to get a country-wide estimate of self-reported morbidities.

5.3 A Study of Psychosocial and Service Dynamics of Illegal Abortion in Rural Areas of India: ICMR Multi-Centric Study

Principal Investigator : Balaiah D
Project Associates : D. D. Naik, Saritha Nair and P Tapase
Duration : 2006 – 2008

Abortion is a sensitive issue impacting crucial aspect of women's health and reproductive rights. Maternal mortality attributable to abortions in India is 12-18 percent and is mostly contributed by illegal abortions nationwide. More so, abortion, willing or unwilling, is invariably a traumatic experience for any women. Even after three decades of legal intervention, women continue to resort to illegal abortion for several reasons, which ultimately drag them mostly to the hands of untrained personnel.

In order to ensure that women who desire termination of unwanted pregnancies have easy access to safe and hygienic facilities, there is need to explore regarding the type of facilities available, whether they are adequately equipped and how well they are utilized. Such information would help strengthen existing MTP services in the country. The proposed study is an attempt to carry out a research in various parts of India and analyze the reasons for illegal abortion from seekers and providers perspectives and related issues. The objectives of the study are to: a) find out the perception and awareness of the community about abortion related issues; b) understand the factors responsible for choosing illegal source of abortion; c) explore the decision making process regarding induced abortion and source; d) study the profile of providers; e) find out the methods used for such abortions and complications faced and remedies sought and; f) carry out a situation analysis of service provisions for induced abortion.

The study is being conducted in seven states i.e. Hariyana, U.P, Rajasthan, Maharrastra,
Tamil Nadu, Orissa and Assam using both qualitative and quantitative methods. Institute has been given the responsibility of carrying out research in Maharashtra. According to the methodology, within each state, two districts i.e., one better performing in RCH and one poor performing will be selected. Within each district, two PHC villages will be selected randomly and within each PHC, two sub-centre villages and two remote villages will be selected by simple random sampling method. In each of these five villages in a PHC area, all women of reproductive age (15-49 years) will be screened for socio-demographic and pregnancy history. In-depth study will be carried out among all those women who had undergone induced abortion. In addition, 50 per cent of the screened women in the village will be studied in detail regarding perception and knowledge issues etc. Further, in each village 50 adult married men will be studied in detail for their awareness and views in relation to induced abortion related issues. In addition to the community, all the providers of induced abortion in these PHC areas including nearby town/district will be studied.

In Maharashtra, two districts were selected for the study i.e. Satara and Ahemadnagar. During April 2007 to March 2008, seven FGDs were held in Umbraj PHC area in the villages; Umraj (1 male and 1 female), Taswade (1 male, 1 female and 1 elderly male) and Korti (1 male and 1 elderly female) of Satara district. From the two PHC areas (Limb and Umraj) from same district, 15 MTP providers were interviewed. Fifty men in each village were interviewed i.e., Talbid, Korti and Taswade.

Chaass and Kolar PHCs were selected from Ahemadnagar district as the study area. In Chaass (PHC village), 543 females and 50 males were interviewed. The two selected sub-centres are Sarola Kasar and Akolner, the remote villages selected were Sonewadi and Ghospuri. In Sarola Kasar (sub-center), 374 females and 50 males were interviewed. In Akolner (sub-center), 217 females and 50 males were interviewed. In Sonewadi (remote village), 179 females and 50 males were interviewed. In Ghospuri (remote village), 189 females and 50 males were interviewed.

In Kolar (PHC village), 540 females and 50 males were interviewed. The two selected sub-centres are Pathare and Babhaleshwar, the remote villages selected were Hanumantgaon and Tisgaonwadi. In Pathare (sub-center), 368 females and 50 males were interviewed. In Babhaleshwar (sub-center), 350 females and 50 males were interviewed. In Hanumantgaon (remote village), 179 females and 50 males were interviewed. In Tisgaonwadi (remote village), 179 females and 50 males were interviewed. Eleven Focus Group Discussions (FGDs) with male groups and another 11 FGDs with female groups were held in 10 villages from both the PHCs in Ahemadnagar district. Coding and data entry has been carried out for both the districts i.e. Satara and Ahemadnagar. Data verification is in progress.

5.4 Mechanisms for Relations of Domestic Violence to Poor Maternal and Infant Health (Funded under the Indo-US Program on Maternal and Child Health and Human Development Research (MCHDR) Programme)

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<td>Saritha Nair and D.D. Naik</td>
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<tr>
<td>Collaboration</td>
<td>Population Council, India Harvard School of Public Health, Boston University School of Public Health, U.S.A.</td>
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<td>Duration</td>
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India continues to have the greatest number of infant deaths and second greatest number of maternal deaths of any nation in the world. Among Indian women of childbearing age, fifty per cent report some type of spousal or in-law violence in their lifetime. Considerable amount of such victimization occurs during pregnancy. Violence during maternity results in
adverse maternal and child health outcomes. Evidence clearly documents the link between partner violence and poor maternal and child health outcomes in India and other countries. Nevertheless, research clarifying the mechanisms underlying these associations is urgently needed to develop better interventions to address these concerns.

The purpose of the study are to: (1) assess experiences of violence to the recent mothers from husbands and other family members around the time of pregnancy; (2) determine proximal mechanisms for the relations of pregnancy complications and poor maternal and infant health to domestic violence; (3) develop program recommendations based on these findings for culturally-informed family and clinic-based interventions to reduce the likelihood of husband and family violence against low-income child-bearing Indian women living in urban slum communities.

The research will employ a descriptive, cross-sectional, retrospective research, utilizing a mix of qualitative and quantitative methods. The first year of the research will particularly focus on in-depth qualitative data collection from women, for an approximate total of 40 in-depth interviews; and 4 focus group discussions (2 each) from mother-in-laws and men. Also, the first year will involve analysis of qualitative data, the development and administration of survey instruments for women. The second year will involve analysis of both qualitative and quantitative data and translation of the data into preparing a module to deal with issues concerning domestic violence in the clinic, and health messages for women in the community.

The data generated by this project will be utilized for national dissemination to policy makers, for development of culture-sensitive curriculum to train local and national health care providers on assessing and addressing domestic violence within the framework of maternal and child health services, and for the community health education to improve of women's health in the three study communities and in other urban poor communities in India.

Tools for in-depth interviews were prepared. Collaborators from United States visited the institute in the month of March, 2008. In addition to discussion on the project, they conducted training of the staff on ethical issues and qualitative data collection. Also inputs were provided on documentation of information collected. Site visits were carried out. The research team had interaction with Urban Health Centre (UHC) staff and discussed ways to facilitate data collection at the UHC. Pilot interviews were conducted to test the in-depth interview guideline. In-depth interviews are in progress.

5.5 Elucidating the Role of Progesterone on Cervical Ripening in Pregnant Rats (Funded by the Department of Science and Technology)

Principal investigator : Lalita Savardekar
Project Associates : Vijaya Raghavan, Pervin K. Meherji, Tarala Nandedkar, Deepashree Mankar and R. B. Kadam
Duration : 2007 - 2010

Cervical ripening, softening and dilation of the cervix is a slow process throughout pregnancy and gets augmented preceding labor. It is a complex process with substantial remodeling of extra cellular matrix. Disturbances in this process result in major clinical problems such as, dysfunctional and protracted labor due to insufficient cervical softening and premature delivery due to premature cervical ripening with early onset of labor. The study plans to establish the sequence of cellular and molecular events and correlate the expression of steroid receptors with cytokines (IL-1β, IL-8, MMPs -1,-2, -9,-13, TIMP-1, -2) in the cervical ripening process and to investigate the influence of progesterone supplementation on cervical ripening in pregnant rats.

To achieve the objectives, the study will be conducted in animal model, Rat- Holtzmann strain. For the second objective, animals will be
supplemented with 2.5 mg of progesterone in olive oil, intramuscular, from Day 18 of pregnancy until Day 22 of pregnancy. Animals (10 in each group) will be sacrificed on days 14, 17, 18, 19, 20, 21, 22 and post partum for the control group and on days 18, 19, 20, 21, 22, 23 and post partum for the study group (progesterone treated).

Eighty animals have been sacrificed and cervical tissue has been processed for H&E and IHC. Preliminary findings are presented herewith. Histology (haematoxylin and eosin) revealed increasing secretory activity in the ectocervical squamous epithelium with advancement of pregnancy. This secretory activity however was not evident in post partum cervix as part of the secretory epithelium was denuded. Disorganized collagen with stromal edema is evident in late term pregnancy. Among the infiltrating cells, eosinophils predominate. A precipitous increase in the number of infiltrating cells was seen on Day 18 of pregnancy. This could be attributed to the changes in the steroid hormonal status. The blood vessels, majority of which are seen in the subepithelial region increase in number and diameter with advancing pregnancy and appeared collapsed in postpartum cervix. On day 2 postpartum the reorganization of cervical tissue architecture was observed. Changes were more evident in the ectocervical region in comparison to the endocervical region. Immunohistochemistry protocols for progesterone receptor A/B, interleukin-1β and matrix metalloproteinase 9 in cervical sections are been standardized.

The study will give us a better understanding of the cervical ripening process (as reflected by the cytokines, MMPs, hyaluronic acid) with respect to the local hormonal milieu. It will also shed some light into the role of peripheral levels of progesterone in pregnancy and its impact on cervical ripening. Since supplementation of progesterone is one of the treatment modalities for preterm labor, the study may give us some insights into the effect of progesterone at the level of cervix, and thereby the process of cervical ripening and thus labor.

5.6 Comparison of two doses and two routes of administration of Misoprostol after pre-treatment with Mifepristone for early pregnancy termination (WHO Funded Project A35148)

Principal investigator : Lalita Savardekar
Project Collaborators : Y. S. Nandanwar, Lokmanya Tilak Municipal and General Hospital, Sion, Mumbai
S.V. Parulekar, Seth G.S. Medical College and K.E.M. Hospital, Parel, Mumbai
H. Pai, Pregnancy Advise and Care Centre, Dadar, Mumbai

Duration : 2006 - 2008

In India, Mifepristone with misoprostol (oral route) is approved by the Government of India for termination of pregnancy with less than 49 days of gestation. Misoprostol is used orally, vaginally or sublingually. The main objective of the present randomized trial is to compare four misoprostol regimens when administered either sublingually or vaginally 24 hours after 200 mg of mifepristone, among women with a gestational age of up to 63 days. The four regimens will be compared in respect of the following main outcomes: (i) their efficacy to induce complete abortion; (ii) induction-to-abortion interval, when possible; (iii) the occurrence of side effects; and (iv) women's perceptions.

The design of the study will be placebo-controlled, single blind, randomized, stratified by centre and by the length of gestation: ≤49 days; 50-56 days; 57-63 days. A total of 188 women with pregnancies of < 63 days from last menses (verified by ultrasound) were recruited for the study. Side effects were recorded at hourly intervals up to 3 hours after misoprostol administration and women were followed up at 15 day and 42-day post mifepristone. The study was conducted at Lokmanya Tilak Municipal and
Enrollment of women has been completed and of which 186 women have completed 15-day follow-up. Efficacy of treatment as assessed at follow-up was as follows: Continuing live pregnancy in 3 (1.6%) subjects, incomplete abortion in 2 (1.6%) subjects, lost to follow-up in 2 (1.7%) subjects and in 178 (95.7%) subjects abortion was complete. Women gave history of expulsion of products of conception (POC) on Day 2 (n=141; 75%), Day 3 (n=7; 3.7%), Day 4 (n=6; 3.2%), Day 5 (n=4; 2.1%), Day 6 (n=2; 1.0%), Day 7 (n=1; 0.5%), Day 8 (n=1; 0.5%), Day 12 (n=1; 0.5%), not known (n=20; 10.6%). Of the three women who had live pregnancy, 2 gave history of passage of POCs, thus reflecting that the history of passage of POCs could be misleading in some women. All the women preferred to have the tablets in the clinic under supervision, perceived medical abortion as an easy method and were satisfied with the method; except the three women who had to undergo surgical abortion because of failure of medical method.