

Anaesthesia practice and reproductive outcomes: Facts unveiled

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ABSTRACT

Background and Aims: Anaesthetic practice is associated with a risk of chronic exposure to anaesthetic agents. With the advent of newer inhalational agents and changing anaesthetic practices, the risks for anaesthesiologists with regard to adverse reproductive outcomes is unknown. Hence, a nationwide online survey was conducted to study the anaesthetic practices prevalent in India and their association, if any, with poor reproductive outcomes. **Methods:** The online survey involved 9974 anaesthesiologists. A questionnaire soliciting information regarding anaesthetic practice techniques, reproductive outcomes and perinatal outcomes was designed. All the anaesthesiologists in the ISA National database were mailed a link to the above questionnaire. **Results:** Female anaesthesiologists and spouses of male anaesthesiologists had a higher incidence of first trimester spontaneous abortions than the general population. Female anaesthesiologists when compared with spouses of male anaesthesiologists faced more difficulty with conception ($P = 0.015$). Female anaesthesiologists who worked in the operating room (OR) in their first trimester of gestation had a higher incidence of spontaneous abortions than those who did not work in the OR ($P = 0.05$). Longer hours of general anaesthesia conducted in the first trimester of pregnancy was associated with a higher risk of birth defects in their progeny ($P = 0.05$). **Conclusion:** Spontaneous abortions and birth defects were higher in female anaesthesiologists who worked in the OR in the first trimester of gestation. Both female anaesthesiologists and spouses of male anaesthesiologists had a greater risk for a first trimester miscarriage than the general population.

Key words: Anaesthesia, birth defects, infertility, practices, reproductive outcomes, spontaneous abortions

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/0019-5049.170028

Quick response code



INTRODUCTION

Apprehension about a possible adverse reproductive outcome haunts nearly every anaesthesiologist. Despite an extensive review of literature, it is not clear if the practice of anaesthesia is associated with a higher risk of a poor reproductive outcome than the general population. The introduction of newer inhalational anaesthetic agents and changing anaesthesia practice habits have made it even more imperative to address this question.

Exposure to higher levels of unscavenged nitrous oxide (N_2O) has been associated with less fecundability.^[1] A study on Swedish anaesthesia nurses who had worked in the operating rooms (OR) over a period of 5 years showed a slightly higher

incidence of perinatal deaths, preterm delivery and low birth weight infants compared to the control group and nationwide average.^[2] A meta-analysis of 19 epidemiologic studies published since 1971 yielded an overall relative risk of 1.48 and an absolute risk of 6.24% for spontaneous abortions in women occupationally exposed to anaesthetic agents.^[3]

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How to cite this article: Nagella AB, Ravishankar M, Hemanth Kumar VR. Anaesthesia practice and reproductive outcomes: Facts unveiled. Indian J Anaesth 2015;59:706-14.

Significantly higher rates of spontaneous abortion and of delivering children with congenital abnormalities were reported in a retrospective questionnaire-based study.^[4] All these studies were conducted in the era when N₂O and halothane were predominantly in use. Recently, evidence of genotoxicity and a greater degree of chromosomal damage following exposure to trace anaesthetic agents have been published.^[5-7]

With the introduction of newer inhalational agents and changing anaesthetic practice habits, it was important to study the anaesthetic practices and their association with adverse reproductive outcomes. The diversity of anaesthetic practices in our country further mandates such an evaluation.

METHODS

This study was an internet questionnaire-based analysis. Prior approval was obtained from the Institutional Review Board (2014/64). All enrolled members (male and female) with valid e-mail addresses with the Indian Society of Anaesthesiologists were e-mailed a link to a questionnaire. The questionnaire was primarily designed by the authors of the study. It was subsequently discussed in great detail with a few other faculty members in the Department of Anaesthesiology at the Institute. A pilot survey was then conducted within the department. The questionnaire was 'tested-retested' to avoid ambiguity and duplication of questions and to facilitate the collection of responses relevant to the research question posed. The questionnaire itself was divided into different domains soliciting information pertaining to specific issues that included - anaesthetic practice techniques, reproductive outcomes and perinatal outcomes. A logic design of questioning was applied to end the survey earlier to eliminate irrelevant answers [Figure 1]. Absolute anonymity was maintained both during the response collection and data analysis stages. Duplication of responses was prevented by linking the survey response to the individual's e-mail ID on the survey site, thereby ensuring that not more than one response could be generated from a single e-mail ID. A primary e-mail was mailed to all the members followed by two reminders to non-respondents only in each cycle. An option to opt out of the survey was also provided. History of exposure to radiation, gestational diabetes mellitus, fever with rash, drug intake and family history of congenital defects were elicited. Intake of folate supplements, history of consanguinity in marriage and family history of congenital defects were also asked for [Appendix 1].

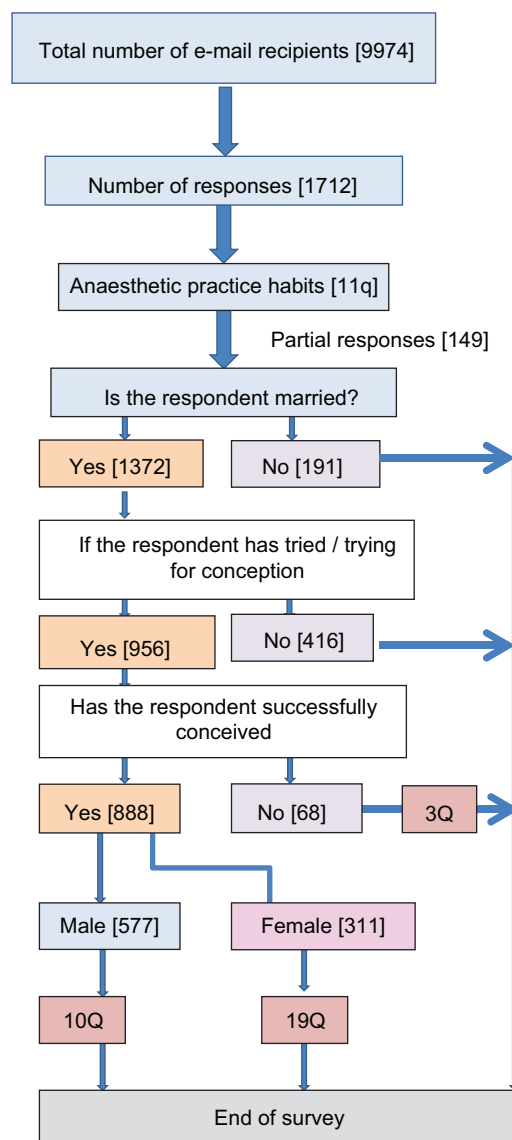


Figure 1: Logic design applied in the conduct of the survey to eliminate irrelevant questions to the respondents

Statistical analysis was performed using Microsoft® Excel (2013), IBM SPSS statistics for Windows version 22. Armonk, NY: IBM Corp. The study population included anaesthesiologists in India. The response rates, anaesthetic practices, the overall outcomes were expressed as percentages. Chi-square test and mid *P* exact test were used for categorical data. Logistic regression and correlations were used to study the association between various anaesthetic practices and reproductive outcomes.

RESULTS

The survey link was e-mailed to 9974 anaesthesiologists from across the country. One thousand seven hundred and twelve responses were obtained; of these, 149 were

partial responses and 1563 respondents completed the survey.

Distribution of respondents with respect to their age and number of years of anaesthetic practice as in Figure 2 suggests a representative sample of the entire anaesthesiologist population in India. Of all the respondents, 90% still use N₂O in their practice. The pattern of usage of inhalational agents [Figure 3] shows isoflurane and sevoflurane to be the commonly used agents in our country. A total of 6.8% respondents used a fresh gas flow <1 L/min routinely and only 15% used a scavenging system for waste anaesthetic gases in their ORs [Figure 4].

Of the 1563 complete responses, 1372 (87.7%) were from married respondents. Of them, 956 (69.67%) respondents were currently trying for conception or had tried for conception in the past. A total of 63.92% (n = 611) of the respondents were males and 36.08% (n = 345) 22 were females [Figure 1]. The various reproductive outcomes looked for in female and spouses of male anaesthesiologists are tabulated in Table 1.

About 60% of female anaesthesiologists had worked in the OR in the first trimester of their pregnancies. Isoflurane and halothane were the commonly used agents in the first trimester of their pregnancies [Figure 5a and 5b]. Female anaesthesiologists, who continued working in the OR in their first trimester of pregnancy had a higher rate of spontaneous abortions (24.68%) as against 11.7% in female anaesthesiologists who had not [Figure 6a]. Of the 67 female anaesthesiologists who used halothane as the most common agent (as against isoflurane and sevoflurane), 9.7% had anomalous pregnancy (P = 0.02).

The birth defects reported by the respondents have been classified into various systems as shown in Table 2. The incidence of birth defects in the progeny increased as the number of general anaesthesia (GA) hours conducted per day during pregnancy increased – 3.7% for those conducting <2 h of GA/day, 17.4% with 2–4 h/day and 17.95% with 4–6 h of GA/day (P < 0.05). There was no significant difference between female and spouses of male anaesthesiologists in the occurrence of preterm deliveries and low birth weight in their offspring.

The association between any specific anaesthetic agent and an adverse reproductive outcome was not significant. Similarly, the association between

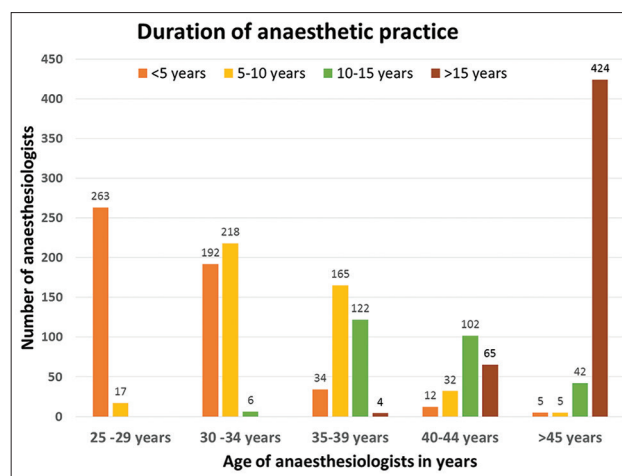


Figure 2: Age distribution and duration of anaesthetic practice pattern of the survey respondents

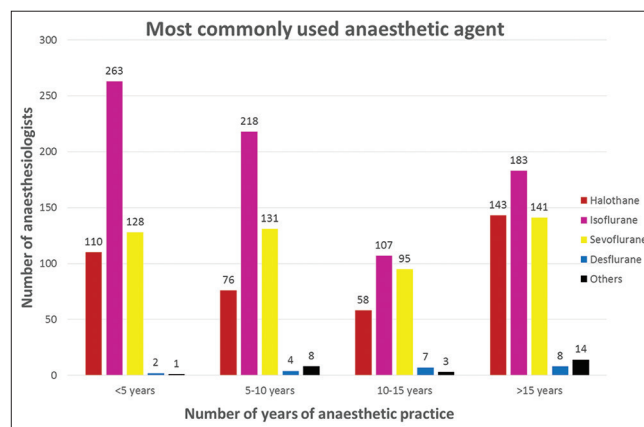


Figure 3: Graphical representation of the extent of usage of different inhalational anaesthetic agents in the survey population

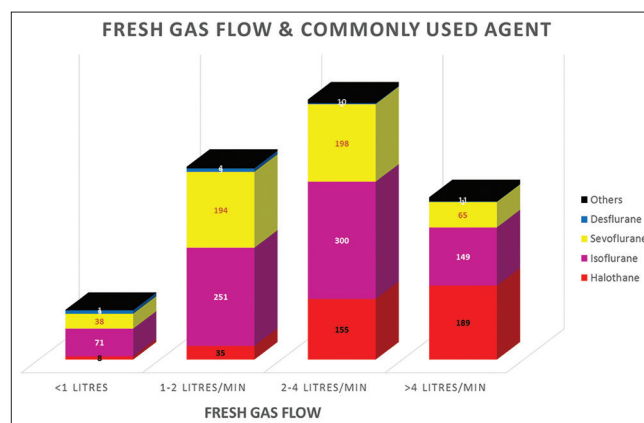


Figure 4: Pattern of fresh gas flow rates used in the study population. The extent of use of various inhalational agents is depicted by the stacked bar graphs

profession and the gender of the first child was not significant (P = 0.19). The number of respondents who used desflurane and scavenging system in their OR was very small to be considered for analysis.

Table 1: Various reproductive outcomes among female and spouses of male anaesthesiologists			
Reproductive outcomes	Spouses of male anaesthesiologists n=611 (%)	Female anaesthesiologists n=345 (%)	P
Difficulty in conception	34 (5.56)	34 (9.855)	0.015*
Took more than one year to conceive	Not collected	59	-
Assisted conception	Not collected	10	-
Spontaneous first trimester abortion	110 (18.00)	69 (20)	0.49
Anomalous pregnancies (electively terminated)	9 (1.47)	16 (4.64)	0.0048*
Birth defects	49 (8.02)	27 (7.83)	0.92
Preterm deliveries	64 (10.47)	46 (13.33)	0.19
Low birth weight	88 (14.40)	66 (19.13)	0.059

P value less than 0.05 was considered significant

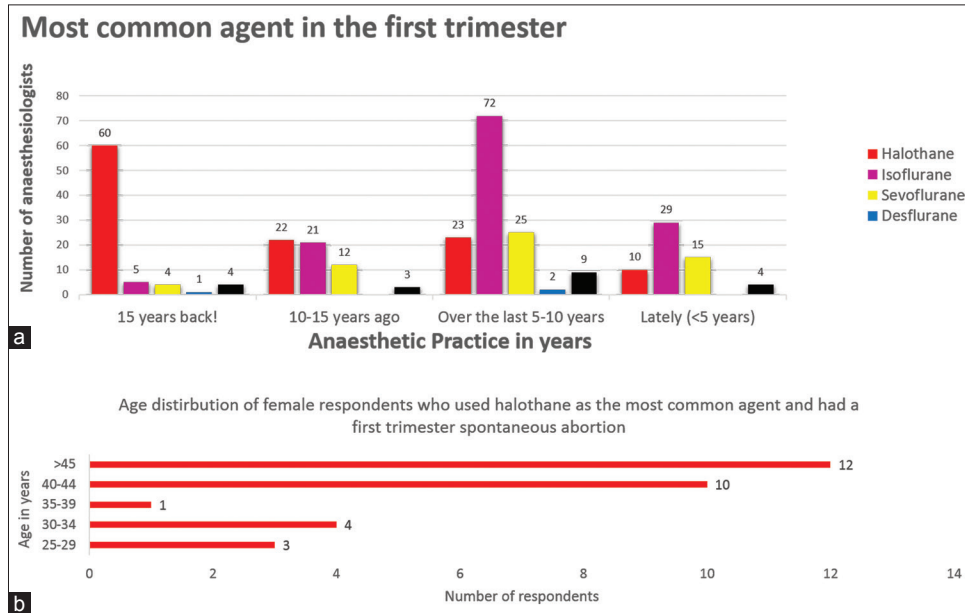


Figure 5 : (a) Graphical representation of the extent of usage of different inhalational anaesthetic agents among female anaesthesiologists in the first trimester of their pregnancies; (b) inset is the age distribution of the female anaesthesiologists who used halothane the most and had a first trimester spontaneous abortion

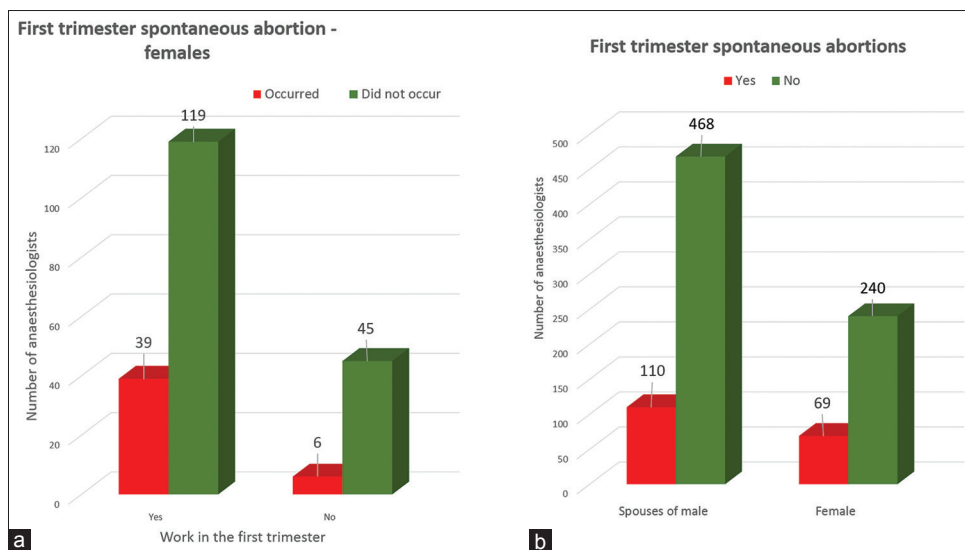


Figure 6: Spontaneous abortions. (a) Incidence of spontaneous abortions among female anaesthesiologists who worked in the first trimester of their pregnancies; (b) incidence of spontaneous abortions among female and spouses of male anaesthesiologists

Table 2: Count of different birth defects in the progeny as reported by the respondents

System affected	Number of responses
Urogenital and renal anomalies	17
Cardiac anomalies	13
Autism and other similar disorders	12
Orofacial, ear and eye anomalies	5
Musculoskeletal and limb defects	4
Neural tube defects	3
Gastrointestinal anomalies	2
Rare syndromic anomalies not listed above	2

DISCUSSION

The average prevalence of 'infertility' in this study was 7.1%; this was in concordance with the WHO estimate of the overall prevalence of primary infertility for India (3.9–16.8%).^[8] The difference in the proportion of women and men who had difficulty in conception was statistically significant ($P = 0.015$). However, in this study, 29.85% of female anaesthesiologist respondents had faced difficulty with conception - either in the form of inability to conceive at all, time to conception being >1 year (17.1%) or the requirement for assisted conception therapies (2.89%). This is in congruence with the findings published by Rowland *et al.*, which showed lower fecundability and longer time to conception in dental assistants exposed to high levels of N₂O at work.^[1]

We found that the incidence of spontaneous abortions in the spouses of male anaesthesiologists was 18/100 pregnancies and 20/100 pregnancies in female anaesthesiologists (average - 18.72%) which is higher than the Indian national average 4.5/100 pregnancies (according to the National Family Health Survey) [Figure 6b].^[9] This is in concordance with a previous meta-analysis that also established higher rates of spontaneous abortions in anaesthesiologists.^[3] Importantly, we found that female anaesthesiologists who worked in the OR in the first trimester of pregnancy had higher rates of spontaneous abortion than those who had not. Total of 22 of 30 female anaesthesiologists who had predominantly used halothane in their first trimester and had a first-trimester spontaneous abortion were above 40 years of age [Figure 5b]. This probably can suggest that in the days of extensive use of halothane, the risk of spontaneous abortion was higher.

As per the WHO, 1 in 33 infants are born with birth defects.^[10] The global survey on birth defects by the March of Dimes Foundation has reported the

incidence of birth defects in India to be 64.3 per 1000 live births.^[11] The reported prevalence of birth defects provided by Birth Defects Registry of India in 2010 was 84.2/10,000, much lower than estimated prevalence of at least 2%. The low prevalence is probably due to poor data collection and registration.^[12] Due to the paucity of proper nationwide data, it is difficult to make meaningful comparisons with the data generated in this survey. In the current survey, we collected data about major and minor birth defects. Our survey showed that 7.82% of female anaesthesiologists and 8.02% of spouses of male anaesthesiologists had delivered children with birth defects (major or minor). We found that female anaesthesiologists who conducted longer duration of GA in a day in their first trimester had a higher incidence of birth defects in their progeny ($P = 0.05$).

We solicited information about the history of anomalous pregnancies that were electively terminated separately as they would not have been reported as either spontaneous abortions or live births with birth defects. Of the 25 electively terminated anomalous pregnancies, one case each of Down's syndrome (trisomy 21), Patau's (trisomy 13) and trisomy 16 were reported. Karyotype was normal in three pregnancies, and one report was still awaited. The karyotyping details of the other 18 fetuses were not available. Female anaesthesiologists who used halothane more commonly in their practice showed a higher incidence of anomalous fetuses than those who rarely used halothane ($P = 0.02$). An *in vitro* study on the genotoxicity of halothane in human peripheral blood lymphocytes has shown increased DNA damage.^[13]

Review of literature suggests that chronic exposure to anaesthetic agents has been linked with various deleterious effects on the human biology.^[5-7] Personnel with chronic exposure to anaesthetic agents were found to have a greater degree of chromatid breaks/gaps, micronucleus frequency and sister chromatid exchanges. Rozgaj *et al.* found that there was a higher rate of chromosomal damage in personnel exposed to anaesthetic agents when tested with micronucleus test.^[5] Chinelato and Froes studied the chromosomal aberrations in peripheral blood lymphocytes and suggested that anaesthesiologists may be at a higher risk of genotoxicity.^[6] They suggested an improvement in the OR working conditions. Chandrasekhar *et al.* evaluated the possible genotoxic effects of waste anaesthetic gases by performing a chromosomal aberrations analysis and comet assay

in peripheral blood lymphocytes and micronucleus test on buccal epithelial cells in 45 OR personnel. The results showed a statistically significant increase in DNA damage in the exposed group.^[7]

The exact mechanism by which anaesthetic agents induce genetic damage is not clearly understood. N₂O oxidises and inactivates the methionine synthase activity, and, therefore, affects the DNA synthesis. This may disrupt any biological activity requiring rapid mitosis like folliculogenesis and early development of the conceptus.^[1] There is established evidence about halothane, isoflurane, sevoflurane and desflurane causing DNA damage.^[13-16] Therefore, it could be hypothesised that chronic exposure to these agents can induce genetic damage and increase the risk of an untoward reproductive outcome.

Overall, 13.3% of female anaesthesiologists and 10.47% of spouses of male anaesthesiologists had preterm deliveries, the average being 11.51%. This is not different from the incidence of preterm deliveries in lower income countries reported by the WHO (12%).^[17] A study by Heinonen *et al.* in Finland compared the reproductive outcomes in female doctors and their teachers. In their study, the reported incidence of preterm deliveries was 4.8% among female doctors.^[18] In comparison, the incidence of preterm deliveries was higher in this survey. However, the study population was from Finland making the comparability questionable.

The WHO reported incidence of low birth weight for lesser developed countries ranges from 5% to 33% with an average of 17%.^[19] A south Indian study by Rekha *et al.* reported an incidence of 23.01% when measured by conventional weighing methods.^[20] Specifically when looked at the doctor population, the Heinonen *et al.* study reported an incidence of 3.9% low birth weight in 331 female doctors from Finland included in their study.^[18] In our survey, 19.13% of female anaesthesiologists and 14.4% of male anaesthesiologists had low birth weight new-borns, with an average of 16.12%. Data from Indian doctors not exposed to anaesthetic agents is lacking and thus a good comparison is difficult.

This survey showed that there was no increased likelihood of the first child being female. The male to female offspring ratio was 0.94. The sex ratio for Indian population according to the population census

2011 is 1.4 i.e, 940 female births to 1000 male births.^[21] The difference was not statistically significant *P* value being 0.14. Our survey results contradict the findings of Gupta *et al.* study that showed a first born sex ratio skewed towards being a female offspring.^[22]

Though our study found a significant correlation between some factors and adverse reproductive outcomes, a clear cut association was lacking. The validity of a survey as a representative snapshot of data mainly depends on the response rate. Although, this survey had a statistically adequate response rate, it is noteworthy that there were fewer female respondents than male (of the 1563 complete responses which were considered for analysis, only 345 were female respondents). We also need comparative data from a control population who are of almost the same age as anaesthesiologists during conception and face similar stress at work. To get more robust results, we recommend recruitment of more respondents by hand-out questionnaires and also by inclusion of other personnel such as OR nurses and technicians who have similar exposure to anaesthetic agents and gases. We also recommend similar studies in comparison with the general population for a better contrast.

CONCLUSION

The rate of occurrence of spontaneous abortions and birth defects were higher in female anaesthesiologists who worked in the OR during the first trimester of their gestation when compared to those who had not. Both female anaesthesiologists and spouses of male anaesthesiologists seemed to be at a greater risk for a first trimester miscarriage than the general population. Paucity of similar data from other groups of Indian doctors prevents us from performing a robust comparison of data between the groups to suggest a clear cut association between anaesthetic practices and adverse reproductive outcomes.

Acknowledgements

We thank Dr. Venkatesh Madhugiri, Associate Professor, Department of Neurosurgery, JIPMER for the immense help provided with data analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Model of questionnaire that was mailed to the respondents

As a parent, having a child with a birth defect, be it major or minor, is a traumatic experience. Congenital anomalies affect an estimated 1 in 33 infants and result in approximately 3.2 million birthrelated disabilities every year. As anaesthesiologists, we are the small minority of 'physicians' who are exposed to low concentration of anaesthetic vapours / agents on a daily basis. The impact of this exposure on the reproductive health of anaesthesiologists as well as on their children has not been quantified in India. This study is an effort to quantify the risk we are at, as anaesthesiologists in India.

We respect your privacy. We do not wish to know any details pertaining to your identity. Please do spend 5 minutes of your valuable time to answer this brief questionnaire.

This survey has been approved by the Institutional Ethics Committee of Mahatma Gandhi Medical College and Research Institute, Pondicherry. This questionnaire is being sent only to Anaesthesiologists in INDIA. You can also help us by giving valid email addresses of your friends to the contact address given at the end. We hope that the data thus generated could throw some light on the risks and lead to safer anaesthetic practice in India.

Thanking you in anticipation for your participation in this study.

-
1. For how many years have you been in anaesthetic practice?
 2. In a typical day, what is the average number of cases you anaesthetise?
 3. Of these, what is the average number of cases under GA?
 4. What is the average number of hours of general anaesthesia you perform in a day?*
 5. Which breathing system do you routinely use?*
 6. Does your general anaesthetic technique include Nitrous oxide?*
 7. Kindly rank the below inhalational anaesthetic agents in the order of most common to least commonly used in your anaesthetic practice*
 8. What fresh gas flow rates do you routinely use in your anaesthetic practice?*
 9. Does your hospital have a scavenging system for waste gases?*
 10. What is your age?*
 11. Are you married ?*
-
12. Is the marriage consanguineous?
 13. Have you / your spouse ever tried for conception of pregnancy?*
-
14. Have you / your spouse ever conceived? *
 15. If infertility was a concern, were there any established medical reasons for failure of conception?
 16. What is your gender? *
 17. If you choose to, kindly express your comments about the probable medical cause/diagnosis for infertility
-
18. How many children do you have?*
 19. What is your child's gender?
 20. What is your gender?*
-
21. After deciding to have a child, how long did you have to try to get pregnant?*
 22. What is the age when you had first conceived?*
 23. Have you opted for medical termination for *unplanned pregnancy*?

24. Did you have any first trimester spontaneous abortions?*
25. Have you opted for medical termination of pregnancies for suspected chromosomal anomalies, genetic defects or malformations in the foetus?*
26. Did you take any folic acid supplements *prior to/during* the first trimester of your pregnancy?
27. Were any of these risk factors present during your pregnancy? (choose all that apply)
28. Did you work in the operation theatre in the first trimester of your pregnancy?*
29. What is the average number of hours of general anaesthesia you performed in a day during first trimester of your pregnancy?*
30. Was any karyotype analysis of the fetus done after the termination of pregnancy?
31. Which breathing system did you use during that time?*
32. Did your general anaesthetic technique included Nitrous oxide?*
33. Kindly rank the below inhalational anaesthetic agents in the order of most common to least commonly used during your pregnancy*
34. Were any of your children delivered preterm?
35. Were they of appropriate body weight at birth?
36. Have any of your children had any birth related defects? Kindly include both the minor as well as major defects*

-
37. Did your wife have any spontaneous first trimester abortion?*
 38. Have you opted for medical termination for *unplanned pregnancy*?
 39. Were any of these risk factors present during your spouse's pregnancy? (choose all those that apply)
 40. Have you and your wife opted for medical termination of any of your pregnancies for chromosomal anomalies, major congenital defects?*
 41. Was any karyotype analysis of the products of conception done after the abortion or termination of pregnancy?
 42. Were any of your children delivered preterm?
 43. Were your children of appropriate birth weight?
 44. Have any of your children had any birth related defects? Kindly include both the minor as well as major defects*
 45. Kindly choose the anomaly present from the following dropdown menu. (choose all those that apply)
 46. Feel free to express your comments pertaining to your pregnancy, risk factors and anaesthetic exposure
 47. Kindly provide us the contact email address of your anaesthesia colleagues

* - compulsory/mandatory question

Announcement

ISA Announcement: Membership and Updation

The ISA Membership Application form is to be filled and submitted online. A print out of the same with signatures and requisite fee is to be sent by surface mail. Copies of registration & degree / bonafide certificates are to be submitted online.

Membership fee (from 1st April 2015) of Rs. 7,500/- is to be paid by Online Transfer or DD, favouring "INDIAN SOCIETY OF ANAESTHESIOLOGISTS", S.B. A/c No.30641669810 (IFSC:SBIN0006715), payable at SBI, Kasaragod Branch.

Member Updation, City / State Branch updations are also to be done online only.