Medical Sciences (CIOMS). ADOC consists of written and oral steps. To document the consent process and prevent falsification, we documented oral steps by audio recording, video recording, and photography (triple media recording [TMR]). We labelled and stored all records. There were five steps to ADOC:

1) We prepared two documents in Spanish describing the study and the planned consent procedure and a form for written consent and submitted these with the study protocol to the relevant legal and ethical authority, the Council of the Paraguayan Institute for Native Indians. The council granted written approval for the study.

2) The study information document and consent form were translated into Guarani with a Guayaki to Spanish (Guayaki is the ancestor language of Guarani) dictionary and a Mbyà-Guarani to Spanish dictionary,[4,5] with the help of an official government-certified Spanish to Guarani translator. Both documents were also translated into English and French for external control and auditing purposes. Furthermore, a back translation from Guarani to French was done for verification purposes.

3) The Guarani, Spanish, French and English versions of the written documents were read aloud and documented by TMR.

4) The study information was read aloud in Guarani to potential participants, about 100 adult Guarani individuals, while being documented by TMR. After the reading, two investigators who could both speak Spanish and Guarani invited and answered questions from the audience, and permanent communication was encouraged.

5) 42 people, 23 men and 19 women (table 2), stepped forward to give their consent to participate in the study. For each of the 42, individual oral consent in his/her natural language was again documented by TMR. Finally, while still recording with TMR, a written form was presented to participants for them to sign in writing or by fingerprint. Eight of the 42 were able to sign by writing.

More than half the potential participants did not come forwards to give consent. We believe that these people were able to exercise their freedom of refusal by not stepping forward, because explicit refusal is not part of Guarani social codes and customs, whereas implicit refusal expressed by silence or inaction is perfectly acceptable.[2] With hindsight, our procedure would have been improved by formally asking all participants to summarise in their own words their understanding of the situation.

Also, parts of the process (eg, document translation, discussion of information with potential participants) were facilitated by several of the researchers being bilingual Guarani and Spanish speaking Paraguayans. However, this factor is not a prerequisite for documented oral consent, provided that the translation procedures are well controlled.

According to UNESCO, an estimated 20·6% of the world population is illiterate. Illiterate people should not be denied the benefits of clinical research or the freedom and protection brought by the World Medical Assembly Declaration of Helsinki. The declaration includes recognition of the needs of economically and medically disadvantaged people (Article 8), and the need for appropriate ethical review committees (Article 13) and well informed consent procedures (Article 20).

	Number	Age (median [years])
Linguistic group		
Mbyà Guarani	37	31·5 (18–66)
Men	20	31·8 (19–63)
Women	17	31·1 (18–66)
Pay Tabytera	5	28·2 (18–46)
Men	3	25·6 (18–35)
Women	2	32·0 (18–46)

Table 2: **Characteristics of participants**

ADOC, or similar standardised procedures designed with the same principles, enables valid informed consent to be obtained from illiterate populations for participation in clinical research, and should be available as an alternative to written and signed consent where needed.

Contributors

O Benitez conceived, planned, designed, and submitted the study, translated and backtranslated in Guarani, Spanish, English, and French, read documents in Spanish by TMR, discussed the study with participants and did medical consultations, individual oral consents, and collected blood samples. D Devaux had the original idea of back translation from Guarani to French, prepared ethical and legal procedures, read documents in French by TMR, did video and audio recording and photography and cryopreserved blood samples. J Dausset had the original idea of audiovisual documentation, and directed and supervised the study. All authors helped to write the report.

Conflict of interest statement

None declared.

Acknowledgments

We thank the Paraguayan Guarani Indian Community for allowing us to do the study; R Benitez, N Cañete, N Benitez, and M T de Parceriza for field research support; and M Bouvier d'Yvoire for redactional help and critical reading of the paper. The study was funded mainly by CEPH (Centre d'Etude du Polymorphisme Humain, Paris, France). The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

1 Joffe S, Cook EF, Cloary D, Clark N, Wuky JC. Quality of informed consent: a new measure of understanding among research subjects. *J Natl Cancer Inst* 2001; **93:** 139–47.
2 Chase Sardi M. El aspecto demográfico-Composicion social y estructura del poder. In: Susnik B, Chase Sardi M, eds. Los indios del Paraguay. Madrid: Mapfre, 1995: 304–23.
3 Shapiro HT, Meslin EM. Ethical issues in the design and conduct of clinical trials in developing countries. *N Engl J Med* 2001; **345:** 139–42.
4 Cadogan L. Diccionario Guayaki-Español. Paris: CNRS-Musée de l'Homme, 1968.
5 Cadogan L. Diccionario Mbyà Guarani-Español. Paris: CNRS-Musée de l'Homme, 1970.

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Parental periconceptional smoking and male: female ratio of newborn infants

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We assessed whether the smoking habits of parents around the time of conception affects the likelihood of the offspring being male or female. We found that the offspring sex ratio (male to female) was lower when either one or both of the parents smoked more than 20 cigarettes per day compared with couples in which neither of the parents smoked. We found the lowest sex ratio among children whose mothers and fathers both smoked more than 20 cigarettes per day (p<0·0001). Parental periconceptional smoking might be a contributing factor to a lower male to female sex ratio of offspring.

Lancet 2002; **359:** 1407–08

The male to female ratio of children has declined significantly during the past few decades as documented by observations from a number of developed countries including Denmark,[1] England, Wales, USA, Canada, the Netherlands, Germany, Sweden, Norway, and Finland. The reason for this reduction is not clear, but it has been suggested that chronic exposure to toxic environmental agents that predominantly affect males

	Non-smoking fathers	Smoking fathers (<19 per day)	Smoking fathers (⩾20 per day)	Total
Non-smoking mothers	1·214, 1975:1627 (1·00; control)	1·032, 577:559 (0·85 [0·74–0·97]) p=0·017	0·984, 2864:2911 (0·81 [0·74–0·88]) p<0·0001	1·063, 5416:5097†
Smoking mothers (<19 per day)	1·059, 54:51 (0·87 [0·59–1·29]) p=0·490	1·026, 40:39 (0·84 [0·55–1·31]) p=0·458	0·951, 214:225 (0·78 [0·64–0·95]) p=0·016	0·978, 308:315
Smoking mothers (⩾20 per day)	0·872, 41:47 (0·72 [0·47–1·10]) p=0·125	0·857, 12:14 (0·71 [0·33–1·51]) p=0·376	0·823, 255:310 (0·68 [0·57–0·81]) p<0·0001	0·830, 308:371†
Total	1·200, 2070:1725*	1·028, 629:612	0·967, 3333:3446*	1·043, 6032:5783

Non-smoking mothers (mean age 33·7 years); smoking mothers <19 (33·4); smoking mothers ⩾20 (33·3); non-smoking fathers (36·0); smoking fathers <19 (35·8); smoking fathers ⩾20 (35·9). Data are presented as sex ratio, male:female (odds ratio [95%CI]). Except where stated the sex ratio of offspring of non-smoking couples served as a control. *p<0·0001 for difference between groups. †p=0·002 for difference between groups.

Parental periconceptional smoking and the offspring sex ratio (male:female)

and the male reproductive system could lead to a lower male to female ratio. After exposure to toxic agents such as dioxin from Seveso[2] and methylmercury from the Minamata Bay disaster[3] the offspring sex ratio declined. Stress could also reduce the sex ratio of newborns as witnessed in connection with the Kobe earthquake, which resulted in an abrupt reduction in sperm motility and a significant decline in the sex ratio 9 months later.[4] Here, we have assessed a possible link between parental periconceptional smoking and the sex ratio of the offspring.

We recorded the sex of 11 815 liveborn infants (all singletons) delivered by 5372 women (mean age 33·6 years [SD 6·2], range 20–49) who attended our clinics for obstetrical and gynaecological assessment from December, 2000, to July, 2001. After obtaining informed consent, each woman was questioned about her and her spouse's daily consumption of cigarettes during the periconceptional period (from 3 months before the last menstruation to when the pregnancy was confirmed). The women and men were each divided into three groups: non-smokers; those who smoked between one and 19 cigarettes per day; those who smoked more than 20 cigarettes per day. The sex ratio was calculated for the children born to mothers and fathers belonging to these groups.

As shown in the table, the sex ratio declined with increasing numbers of cigarettes smoked by mothers and fathers. The sex ratio was 1·214 (1975:1627) in the group in which neither mother nor father smoked, whereas the lowest sex ratio of 0·823 (255:310) was seen in the group in which both mother and father smoked more than 20 cigarettes per day (odds ratio 0·68 [95% CI 0·57–0·81]; p<0·0001). The group in which the mother was a non-smoker and the father smoked more than 20 cigarettes per day also displayed a significant decline in the sex ratio (0·984) compared with the value of non-smoking couples (odds ratio 0·81 [95% CI 0·74–0·88]; p<0·0001). The sex ratio declined significantly among children of fathers who smoked more than 20 cigarettes per day (0·967), irrespective of maternal smoking, compared with that of non-smoking fathers (1·200; p<0·0001). Likewise, the sex ratio declined significantly among children of mothers who smoked more than 20 cigarettes per day (0·830), irrespective of paternal smoking, compared with that of non-smoking mothers (1·063; p=0·002). Thus, cigarette smoking seems to reduce the frequency of male babies, suggesting that parental smoking might be a contributing factor to the observed reduced sex ratio.

The 1958 National Birthday Trust British Perinatal Mortality Survey, which looked specifically at maternal smoking during pregnancy and found no effect on the sex ratio at birth,[5] found the sex ratio among children of non-smoking mothers to be 1·069 (5750:5377). This result was similar to that of smokers (1·076 [2410:2240]). By contrast with these data, periconceptional smoking history and data of paternal smoking were included in the present study, suggesting that smoking reduces the sex ratio around the time of conception, rather than imposing a selective disadvantage on male fetuses during later pregnancy.

In our study the number of fathers who smoked during the periconceptional period was sufficiently large to show that paternal smoking significantly reduced the sex ratio. However, there was only a small number of couples in our study in which the mother smoked but the father did not. The sex ratio among children of such couples seemed low, but overall there was no significant difference in the sex ratio compared with that noted among non-smokers. Further accumulation of birth records from such rare couples is needed to clarify the true effect of maternal smoking on the offspring sex ratio.

The overall sex ratio of our study was 1·043 (6032:5783) and is comparable with the sex ratio in Hyogo Prefecture (1·056 [male to female 27609:26156]) where the study took place, and to that of Japan (1·056 [604769:572900]) in 1999 as a whole. Compared with these values, the sex ratio of 1·214 in non-smoking couples noted in the present study is high. The sex ratio in the human embryonic stage is also high (1·530). However, spontaneous abortions and intrauterine fetal deaths are more common among males than among females and the sex ratio at birth is reported to be around 1·060. We suggest that periconceptional smoking of the parents reduces the frequency of conceiving male children.

Contributors

M Fukuda initiated the study and collected clinical data with help from K Fukuda and T Shimizu. C Yding Andersen and A G Byskov contributed to the analysis and interpretation of the data. All investigators wrote the report and agreed on its final form.

Conflict of interest statement

None declared.

Acknowledgments

We thank Susan Peters and Yayoi Fukuda for their kind assistance in this study.

1 Møller H. Change in male:female ratio among newborn infants in Denmark. *Lancet* 1996; **348:** 828–29.
2 Mocarelli P, Gerthoux PM, Ferrari E, et al. Paternal concentrations of dioxin and sex ratio of offspring. *Lancet* 2000; **355:** 1858–63.
3 Sakamoto M, Nakano A, Akagi H. Declining Minamata male birth ratio associated with increased male fetal death due to heavy methylmercury pollution. *Environ Res* 2001; **87:** 92–97.
4 Fukuda M, Fukuda K, Shimizu T, Møller H. Decline in sex ratio at birth after Kobe earthquake. *Hum Reprod* 1998; **13:** 2321–22.
5 Butler NR, Alberman ED. Perinatal problems. Edinburgh and London: E&S Livingstone, 1969: 339.

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