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Aged Gametes and NFP: What Is Currently Known

R. Kambic, R. H. Gray, and J. L. Simpson

Introduction

Since the 1930s, scientists have been interested in the fertilizing life span of gametes (a sperm cell or egg cell) for the purpose of improving livestock (Chang 1975). Studies of this sort advanced the knowledge of sperm banks for breeding animals. In the late 1960s, there was an interest in the application of models of aging gametes to adverse pregnancy outcome (birth defects or spontaneous abortions) in users of periodic abstinence (Lanman 1968, German 1968, Udry 1968, Jongbloet 1969). These studies were put forth around the time of the Roman Catholic controversy on birth control which culminated in the publication of the encyclical Humanae Vitae by Pope Paul VI. Since that time, aging gametes and potential pregnancy problems often have been mentioned as contraindications to natural family planning (NFP) use. In order to more thoroughly investigate these problems, the University of Tennessee and Johns Hopkins University are studying these issues. This paper reviews the literature on the subject and provides background information on these issues which NFP providers should know.

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Lanman (1968) and Simpson (1978) have outlined six ways in which gametes will age in both animals and humans:

1. In females, gametes are arrested early in the first stage of meiosis and remain there until stimulated to develop further. In humans, they may remain from 15 to 45 years until they undergo follicular growth and further development to complete meiosis I and meiosis II.

2. In females, once ovum maturation begins there can be delays prior to ovulation.

3. In females, once ovulation has occurred, there can be a fertilization close to the end of the fertilizable life of the ovum, about 24 hours in the human.

4. In males, the germinal epithelium cells (the cells which produce sperm) are subject to aging over the human life span which is around 70 years.

5. In males, the spermatozoa are subject to pre-ejaculatory aging in the epididymis, and, in humans, the average pre-ejaculatory storage and growth time of sperm is about two months.

6. In males, the spermatozoa are subject to postejaculatory aging in the female reproductive tract until fertilization occurs or the sperm are no longer capable of fertilization. In humans, this is given as three days, but there is evidence, much of it from NFP conception chart review, that it can be much longer.

**Animal Studies: Aging Sperm**

In mammals, data concerning the effects of fertilization of normal ova, by sperm retained for prolonged periods in the male tract prior to ejaculation, suggest potential deleterious effects. Young (1929) found in guinea pigs that the percentage of resorbed or aborted fetuses increased as the age of the sperm increased. Moreover, many fetuses were structurally abnormal. Martin-DeLeon et al. (1973) studied rabbits and found that 8 of 72 blastocysts (11%) resulting from insemination with 7- to 27-day-old sperm, showed chromosomal abnormalities compared to only 1 of 125 (0.8%) in the control group. Martin and Shaver (1972) recovered blastocysts from rabbits inseminated by sperm aged in utero. Thirteen of 134 blastocysts in the group fertilized by
aged sperm were cytogenetically abnormal.

This and other animal data suggest that fertilization by sperm aged either the male or female tract could cause chromosomal abnormalities. Changes known to occur in aging sperm include increased membrane permeability, loss of acrosomal enzymes, decreased Feulgen-stainability without change in DNA content, and redistribution of phospholipids (Simpson 1978). These changes could cause chromosomal abnormalities, but direct relationships have not been proved.

Animal Studies: Aging Ova

Postovulatory aging of ova (delayed fertilization) has been thoroughly investigated in animals. That a time between normalcy and death of unfertilized ova might exist was first recognized by Pfluger in 1882 and, subsequently, investigated by O. Hertwig, R. Hertwig, and later Witschi. Witschi firmly established that delayed fertilization not only leads to decreased fertilizability but also to structurally abnormal embryos.

Studying frogs, Witschi and Laguens (1963) showed that, of 25 embryos that were structurally abnormal as a result of delayed fertilization, 20 (80%) had an abnormal chromosomal complement; all 20 control embryos showed the normal diploid of chromosomes. In mice, Vickers (1969) showed that delayed fertilization slightly but significantly increased the incidence of excess chromosomes.

In Vickers' study (1969), 8 of 309 (2.6%) control blastocysts recovered 3½ days after ovulation were abnormal. Eight of 207 (3.9%) blastocysts recovered from animals mated 5-11 hours after ovulation were abnormal. The finding of fewer abnormalities in the control group was statistically significant. In a second experimental group, 5 of 95 (5.3%) 9½ day to 11½ day fetuses were abnormal.

In guinea pigs, Young and Blandau (1936) observed that the proportions of pregnancies resulting in abortions or embryonic defects increased as the interval between ovulation and insemination increased. Both growth retardation and structural anomalies occurred; however, all liveborn embryos were normal.
Chang (1952) inseminated rabbits at the time ovulation was hormonally induced. In rabbits, about 6 hours are required for capacitation; thus, fertilization occurred 6 hours after ovulation (6-hour delay). Only 51% of ova were fertilized. Only half of the fertilized ova developed into blastocysts, and 12% of the blastocysts were abnormal.

In the rat, Blandau and colleagues (1941, 1952) were the first to show that as the interval between ovulation and fertilization increased (1) litter size decreased and (2) the proportion of pregnancies characterized by fetal resorption or abortion increased. The precise incidences of abnormalities have differed in various studies, perhaps due either to experimental variations or to genetic differences between strains.

Pregnancy Outcome in Humans

The applications of these animal studies to humans is questionable. Gray (1983) points out that, in the species studied, coitus is restricted to the time of estrus or induces ovulation whereas, in humans, intercourse is unrelated to the timing of ovulation. Further, species differ in sperm survival. Simpson (1978) reviewed similar animal data and concluded that: (1) ova retain their capacity for fertilization longer than their capacity for normal development; (2) an excess of chromosomes (polyploidy) is usually the mechanism responsible for the abnormal development associated with delayed fertilization; and (3) gene mutations, although they have not been documented, cannot be excluded. He states that it is reasonable to suggest chromosomal abnormalities as a result of aging human ova or sperm, but less reasonable to suggest more complex genetic disorders.

NFP use has been postulated to offset the sex ratio and increase the frequency of spontaneous abortions and birth defects among users. In order to assess the truth of these statements, it is necessary to look at the baseline sex ratio, frequency of spontaneous abortions, and birth defects in the population. When examining this issue it is important to understand that the level of spontaneous abortions in any population is directly related to the frequency of chromosomally abnormal conceptions in the population.
The distribution of recognized spontaneous abortions peaks around 8 to 12 weeks gestational age or 6 to 10 weeks postovulatory (Roman and Stevenson 1983), and the overall ratio of recognized spontaneous abortions to the total number of pregnancies is from 10% to 20% with older women having higher rates than younger. Roman and Stevenson (1983) review the literature and estimate 40% of pregnancies end in early loss. Simpson and Gray (1986), in a similar review, conclude that unrecognized pregnancy loss is substantial despite difficulties in studying the problem. However, Lanctot (1988) has clinically observed basal body temperature (BBT) pregnancy charts and thinks that the extent of early pregnancy loss is much less. A missed period followed by a continued elevated BBT has been, up to recently, the best initial sign of pregnancy. The majority of the 40% of unrecognized pregnancy loss would have to come in the first four gestational weeks (the first two weeks of true pregnancy) or before the first missed period to go unrecognized in the NFP user population.

In a review article, Bue et al. (1985) noted that estimates of all conceptions lost varied from 24% to more than 60%. The incidence of chromosomal abnormal abortions declined over time from 78% at pregnancy-week 2 to 23% at pregnancy-week 8 to 12. They conclude by saying that “pregnancy wastage represents the main natural means to eliminate the major part (around 99%) of chromosomally abnormal conceptuses.”

Chromosomal abnormalities are the principal cause of fetal malformations and account for between 35% and 55% of recognized spontaneous abortions (Roman and Stevenson 1983). Measurement of chromosomal abnormalities is time dependent; more will be seen at conception than during pregnancy, and during pregnancy than at birth. Therefore it is necessary to measure the proportions of chromosomal disorders and malformations among all conceptions, among spontaneous abortions, and among births to estimate population proportions. There are numerous difficulties in definitions, measurement, and analysis with these data. Table 1 provides recent estimates from studies conducted in Japan, England, and elsewhere.
TABLE 1
ESTIMATES OF THE PERCENTAGE OF CHROMOSOME DISORDERS, DOWN'S SYNDROME, AND MAJOR MALFORMATIONS AMONG ALL CONCEPTIONS, AND AMONG ALL BIRTHS; AND THE PERCENTAGE OF THOSE PATHOLOGIES ENDING IN SPONTANEOUS ABORTION

<table>
<thead>
<tr>
<th>PREGNANCY PATHOLOGY</th>
<th>% AMONG ALL CONCEPTIONS</th>
<th>% ENDING IN SPONTANEOUS ABORTIONS</th>
<th>% AMONG ALL BIRTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal Disorders</td>
<td>6.3 - 10</td>
<td>90</td>
<td>0.7</td>
</tr>
<tr>
<td>Down's Syndrome</td>
<td>0.3</td>
<td>65</td>
<td>0.1</td>
</tr>
<tr>
<td>Major Malformations</td>
<td>?</td>
<td>?</td>
<td>3.0</td>
</tr>
</tbody>
</table>


TABLE 2
CAUSES OF PREGNANCY LOSS

FIRST TRIMESTER
- Trisomies
- Polyploidy
- Tetraploidy
- Monosomy X

SECOND AND THIRD TRIMESTERS
- Abnormalities as above
- Recurrent aneuploidy
- Chromosomal translocations & inversions
- Luteal phase deficiency
- Thyroid abnormalities
- Diabetes
- Intrauterine adhesions
- Incomplete mullerian fusion in the mother
- Leiomyomas
- Incompetent cervix
- Infections
- Autoimmune disease
- Shared parental histocompatibility
- Irradiation & neoplastic agents
- Cigarette smoking
- Alcohol
- Toxic chemicals
- Intrauterine device (IUD)
- Trauma
- Psychological factors
Simpson and Carson (1988) reviewed some of the causes of fetal loss (table 2). The effects of some are more well known than others. If one or several of these factors is present in higher than background levels in a study population, it must be considered at the time of data analysis. When studying pregnancy outcome in NFP users it is necessary to consider whether or not NFP users are different from the general population. For example, NFP users may be more inclined to be monogamous and to lead a healthy lifestyle. This would make them less likely to be at risk for adverse pregnancy outcome. Conversely, they may be older than the general population, as some studies have suggested, and this would make them more of a risk for adverse outcome.

**Studies of the Timing of Conception and Pregnancy Outcome**

When examining the literature on aging gametes, the timing of conception, and pregnancy outcome in humans, there are several ways to determine whether or not the gamete is aged (Gray 1983). First there are those studies that associate the use of periodic abstinence or rhythm users with birth outcome. In these studies, no attempt is made to define rhythm or periodic abstinence either as “Ogino-Knaus” or counting of days, that is, 10-10-10 or other technique. Furthermore, individual women are usually not asked about timing of intercourse, for example, whether or not they were abstaining to avoid a pregnancy. For these studies, it is not possible to study the timing of conception with respect to ovulation, but only to look at overall incidence of the good and bad pregnancy outcomes in the study population compared to a control group or the general population. The second kind of study associates pregnancy outcome with an exposure marker but not a marker of ovulation. Here, previous cycle length has been used. When using an exposure marker such as previous cycle length, the results will be diluted by the within- and between-women variation in cycle length (Vollman 1979). Finally, there are studies which use modern natural signs of fertility (such as BBT, cervical mucus, or even hormone assays) to study the relationship between coitus and timing of ovulation. In these studies, insemination can be natural or artificial, and days of coitus or insemination are
known. Gray (1983) points out that even when client records are available with intercourse during the fertile time, it is difficult to determine which act is the one responsible for conception. The potential misclassification here can again dilute the observed effects.

Jongbloet (1970, 1975, 1978) has published a number of articles on the relationship between rhythm users and pregnancy outcome. He interviewed parents of 127 mentally retarded children regarding the birth spacing of their children. Among rhythm users who experienced an unplanned pregnancy, the percent of abnormal children was 57.1%, and, among those who planned pregnancy, only 11.8% had an abnormal child. In another survey of 211 Roman Catholic couples, 23% of rhythm “failures” had abnormal progeny and 7% of planned pregnancies were abnormal. Jongbloet (1975) has reported a seasonal variation in the birth of 529 Down’s syndrome patients and attempts to link the season of birth with aging gametes. Gray (1983) has characterized these studies of Jongbloet as “scientifically unsound.” In Jongbloet’s study of retardation on 49 children, 18 had retardation of postnatal origin. Moreover, information on the type of birth-spacing was subject to recall bias. Gray states “there is a strong likelihood of recall bias since parents with abnormal children may search for a cause of the abnormality.” Boue (1975) and Ferguson-Smith (1984) found no temporal or geographic trends in their data on chromosomal abnormalities.

**Birth Defects**

In a retrospective study of 135 conceptions to BBT users, Marshall (1968) observed 5 (6.2%) birth defects in 81 women for whom results could be assessed. This is not an unusual rate. Marshall collected the results by a mailed self-reported questionnaire, and 54 (40%) of the pregnancies could not be studied. Kuhr (1977) did not find an association between neural tube defects and rhythm users in a case-control study. The frequency of rhythm use among the 119 cases was 6.7% and among controls 10.1%. Oescheli (1976) reported 5.14% of birth defects among 779 rhythm users and 4.73% among 2,718 women who conceived while not using contraceptives. Among rhythm users, 5.1% of the infants had a low birth
weight and, among noncontraceptors, 7.2% had a low birth weight. Oescheli did not adjust for age, and rhythm users are often older than the average population.

Boue et al. (1975) examined 31 cases of polyploidy (extra sets of chromosomes) compared with 43 normal cases for which they had BBT curves to estimate the timing of ovulation. The average day of ovulation of cases of polyploidy was cycle day 17 compared with 14.9 for normal cases. The longer average follicular phase is evidence for overripe ova in the polyploids. Further, in 24 cases, they estimated the probable conception intercourse and related it to ovulation by the BBT curve. Where the probable conception intercourse was two or more days from ovulation, the frequency of anomalies increased to 79% from about 25%. The authors do not present their criteria for evaluating BBT, whether nadir or rise was used, and they do not present their criteria for determining the probable conception intercourse. Their evidence for an association between pregnancy outcome and timing of conception is mixed.

Bracken and Vita (1983) conducted a case-control study on the association between birth defects and nonhormonal contraceptives. There were 1,427 cases and 3,001 controls identified from five hospitals. Cases were medically-confirmed birth defects and controls were healthy infants born in the same period. Women were interviewed about family planning use (including the rhythm method) before conception, at the time of conception, and during pregnancy. Of the nine methods studied, rhythm was used most commonly at the time of conception by about 4% of cases and controls, partially reflecting its effectiveness. Rhythm use was not associated with an increased risk for birth defects in general, but there was an indication of risk for certain groups of defects. Women delivering children with chromosomal anomalies or major cardiac anomalies were twice as likely to have used rhythm as controls, but this was not statistically significant. There was a significantly increased risk for cleft lip and palate (2.91) and congenital hydrocele (4.64) among NFP users, but the authors say that these conditions are unrelated to each other, and it is difficult to think of a mechanism for aged ova to cause these defects. Bracken
and Vita go on to say that these results were most likely caused by chance, which can occur when doing multiple statistical comparisons. The authors adjusted their data on rhythm use for marital status, age, religion, race, and education, and their estimate of overall lack of risk to rhythm users did not change.

Harlap et al. (1985) studied 33,551 abortions and births among women in northern California from 1975-1977. An unplanned pregnancy was assumed to have occurred if a woman was using a method the first day of the cycle in which conception occurred and continued to use it past that date. There were 338 rhythm “unplanned” pregnancies and 2 cases of Down’s syndrome. When this was compared with all other nonrhythm births, there was a crude elevated risk of 4.59. This study shows an association between rhythm users and Down’s syndrome. It did not define the kind of rhythm used, and it did not adjust for potentially confounding variables although the data was available to do so. Since rhythm users are often older women, the Down’s syndrome cases could be age related.

France et al. (1984), discussed in detail later, reported 7% spontaneous abortions in 57 NFP planned pregnancies. No timing effects were seen. From 1979 to 1986, Roetzer (1988) collected pregnancy outcome data on 617 NFP pregnancies with outcome known in 611 (99%). There were five major malformations (0.8%). There was no evidence that these were related to the timing of conception, with the five pregnancies being the result of intercourse on or just before the peak day.

Spontaneous Abortion

Marshall (1968) reported a spontaneous abortion rate of 14.8%, not elevated from the expected. Guerrero and Rojas (1975) retrospectively studied 965 pregnancies using BBT as a marker. They established strict guidelines for the most likely conception intercourse. The overall probability of spontaneous abortion was 7.8%, not elevated above the expected. However, they found a trend toward a higher proportion of abortions as the distance increased from the BBT shift to the most likely conception intercourse. They concluded that aging of sperm in the female genital tract is asso-
ciliated with an increase of spontaneous abortions. Roetzer (1988), studying the Sympto-Thermal Method, reported 51 spontaneous abortions among the 611 pregnancies of known outcome (8.3%), with a higher proportion of abortions per pregnancy in the optimally fertile time (8.7%) versus the less fertile time (6.4%).

The World Health Organization (WHO), in a prospective, five-country study of the Ovulation Method (1984), reported that, of the 163 pregnancies with outcome known, there were 16 spontaneous abortions (9.8%) and 2 congenital malformations (1.2%). WHO took care to identify the most likely day of conception. There was a significant relation of spontaneous abortion rate to age. WHO did not find evidence of a time relationship between the most likely day of conception and either spontaneous abortion or congenital malformation.

Gray et al. (1985) combined data on NFP users from Guerrero and Rojas (1975), WHO (1984), and a new study of 102 NFP related pregnancies from Chile. When using the WHO classification of conception within ±2 days of the ovulation marker and ±3 or more days from the ovulation marker, all three studies showed an excess of spontaneous abortions further from the marker. When combining the data sets, the odds ratio for spontaneous abortion in conceptions ±3 or more days versus ± days from the marker was 2.2 and significant. In none of the three studies was the overall proportion of spontaneous abortions higher than among women using no family planning. Gray et al. concluded that the risk of spontaneous abortions among NFP users is distributed between periods of lower and higher risk.

Sex Ratio

Guerrero (1974) studied 1,318 pregnancies from five countries. BBT charts were used for an analysis of the relationship between sex ratio and time of insemination. The male proportion of significantly higher the greater the distance between the responsible intercourse and the BBT rise. Guerrero suggests that his results are due to the differences in survival or fertilizing capacity of the X- and Y-bearing sperm.

Harlap (1979) reports on 3,658 births to Orthodox Jewish wom-
en in Jerusalem who have a prescribed time in the menstrual cycle to resume intercourse. The expected date of ovulation was calculated from estimates of previous cycle lengths. Harlap found an excess of male births when intercourse occurred further from the presumed day of ovulation. This effect held for all age, ethnic, and educational classes. Because there is no direct marker of ovulation, the results may be diluted. Further, Harlap (1979) shows a much stronger sex-selection effect postovulatory, and Guerrero (1974) shows a much stronger sex-selection effect preovulatory. This may be due to the less accurate estimation of ovulation used by Harlap.

Shiono et al. (1982), using the same data as Harlap (1985), studied the sex ratio in 33,205 pregnancies. The overall proportion of males was 0.517, which is similar to the U.S. as a whole (0.515). The proportion of males among the 335 rhythm failures was 0.567, higher than the other methods but not significantly.

France and his colleagues (1984) reported on a prospective study of 185 couples using NFP to plan pregnancy. The couples were instructed on how to observe and chart BBT and cervical mucus and were instructed to have only one act of intercourse during the fertile phase of the cycle. There were 57 pregnancies of which 52 went to term. There were 4 spontaneous abortions (7.0%). For 19 pregnancies, there was more than one act of intercourse during the fertile period, and those 19 pregnancies were excluded. Of the 33 pregnancies studied, there were 22 males (66.6%). Using the mucus peak as an indicator of ovulation, 75% of the male infants were found to have been conceived with sperm surviving 2 or more days compared with 45% of the females. This was a significant difference. Using the BBT and luteinizing hormone (LH) as an indicator of ovulation showed similar but not significant differences.

WHO (1984) did not find a difference in sex ratio by cycle day of the most likely conception intercourse. Perez et al. (1985), studying 114 mucus method pregnancies in Chile, found an excess of females (proportion male 0.37) on the days of highest fertility and an excess of males (proportion male 0.76) on days of reduced fertility. Combining data from WHO (1984), Shiono et al. (1982),
France et al. (1984), and the Chilean data showed that NFP users had a significant excess of male births. Perez et al. (1985) attributed this excess of male births to conception intercourse away from the time of highest fertility and the avoidance of intercourse around the time of highest fertility by NFP users. Roetzer (1988) reports a male proportion of 0.54 but does not give information about timing of intercourse and sex ratio.

**Discussion**

From the evidence presented, it appears that there is a clear relationship between the sex ratio and timing of conception. Guerrero (1974), Harlap et al. (1979), France et al. (1984), and Perez et al. (1985) all show that the further away from the days of highest fertility that intercourse occurs, the more likely a male child is to be conceived. Of the other investigators cited, only WHO (1984) looked for a timing effect and found none. Both Shiono (1982) and Roetzer (1988) found an elevated proportion of male births among NFP users (table 3).

<table>
<thead>
<tr>
<th>STUDIES OF SEX RATIO AND NFP USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBJECTS</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Guerrero (1974)</td>
</tr>
<tr>
<td>Harlap (1979)</td>
</tr>
<tr>
<td>Shiono et al. (1982)</td>
</tr>
<tr>
<td>France et al. (1984)</td>
</tr>
<tr>
<td>WHO (1984)</td>
</tr>
<tr>
<td>Perez et al. (1985)</td>
</tr>
</tbody>
</table>

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Guerrero and Rojas (1975) and Gray et al. (1985) provide evidence for a timing effect on spontaneous abortion, with significant statistical effects, but their results are contradicted by WHO (1984), Marshall (1968), France et al. (1984), and Roetzer (1988) (table 4).

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>EXPOSURE CRITERIA</th>
<th>SPONTANEOUS ABORTIONS</th>
<th>TIMING EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall (1968)</td>
<td>81</td>
<td>BBT</td>
<td>14.8% No timing effect</td>
</tr>
<tr>
<td>Guerrero &amp; Rojas</td>
<td>965</td>
<td>BBT</td>
<td>7.8% Risk increases with distance from ovulation</td>
</tr>
<tr>
<td>(1975)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France et al. (1984)</td>
<td>57</td>
<td>Mucus</td>
<td>7.0% No timing effect</td>
</tr>
<tr>
<td>WHO (1984)</td>
<td>163</td>
<td>Mucus</td>
<td>9.8% No timing effect</td>
</tr>
<tr>
<td>Gray et al. (1985)</td>
<td>1,178</td>
<td>NFP</td>
<td>7.9% Risk increases with distance from ovulation</td>
</tr>
<tr>
<td>Roetzer (1988)</td>
<td>611</td>
<td>Sympto-Thermal</td>
<td>8.3% Risk decreases with distance from ovulation</td>
</tr>
</tbody>
</table>

Studies of the relationship of rhythm or NFP use and birth outcome are not as clear. Jongbloet's work, often cited, is weak and unscientific; therefore it should be disregarded. Oescheli (1976), Harlap et al. (1985), Bone et al. (1975), and Bracken and Vita (1983) show some effects in large population-based surveys. These studies have problems with misclassification bias, do not adjust in every case for confounding variables, and have difficulty showing timing effects. Marshall (1988), WHO (1984), Kuhr (1979), and Roetzer (1988) did not show an association of birth defects with NFP (table 5).

**Current Johns Hopkins/Tennessee Study**

In order to study these questions, a three-year prospective study of NFP users is under way at the University of Tennessee
and the Johns Hopkins University. Using collaborating NFP centers in South America, the USA, and Italy, the study is designed to examine the questions of timing of conception and sex ratio, spontaneous abortion, birth defects, and chromosomal abnormalities.

The study is a prospective one in order to eliminate the possibility of recall bias when examining cases of adverse pregnancy outcome. In fact, in this study, the investigators will often have the pregnancy chart before the birth occurs. The cohort design will also eliminate problems in case finding. All clients of the participating centers will be followed for the duration of the study and pregnancies will be registered as they occur. If the follow-up is done as expected, no pregnancy in the cohort should be missed. The investigators have taken care to account for other causes of pregnancy loss mentioned in table 2. Detailed histories of all regis-
trants are taken, including smoking habits, alcohol use, prior pregnancy histories, drug exposure, medical history, and family genetic history. An edited sample of the clinical intake form is shown in figure 1.

The exposure groups are conceptions among NFP users, including method failures, user failures, and planned pregnancies. A planned pregnancy is where the user's intention was to become pregnant, and intercourse occurred during the fertile time; a user-related pregnancy is when the user's intention was to avoid pregnancy, and intercourse occurred during the fertile time; and a method failure is where the user wants to avoid pregnancy, and intercourse occurs outside of the fertile time. Method and user failures are more likely to be associated with aged gametes. It is estimated that 20% of pregnancy charts will be difficult to classify, and these will be a residual group reflecting ambiguous conceptions. Only charts showing NFP symptoms and/or BBT and acts of intercourse will be acceptable as measures of exposure. The timing of conception will be based on independent chart review by a panel of NFP experts. The NFP reviewers will not know the pregnancy outcome at the time of the chart review. As far as possible, the days of conception will be estimated, and the data will be analyzed by the interval between the most likely day of conception intercourse and estimated day of ovulation.

Results to Date

In order to accurately assess timing of conception using NFP charts and without further hormonal measurements, one of our first tasks was to address the reliability of the mucus and BBT as estimators of ovulation. Only one previous study has been done on this (Bauman 1981), however, the reviewers were not NFP experts (see Kamlic 1982).

We asked four NFP experts to examine 28 NFP pregnancy charts to determine the BBT rise, the mucus peak, and two most likely days of conception. The reviewers were able to agree on the most probable day of conception in 96.4% of the cases, the mucus peak in 74.1% of the cases, and the interval between the most probable conception intercourse and mucus peak in over
70% of the cases. There was poor agreement (38.5%) on the first day of the BBT rise (Kambic and Gray 1988). The authors conclude that the mucus peak is a more valid indirect measure of ovulation because it is subject to less interobserver variation.

In two years, after all the data are gathered, we expect to be able to give clear answers to the questions of the relationship between NFP use, aging gametes, and problems with birth defects and spontaneous abortions. This information will add to the knowledge of NFP and be of assistance in answering questions from both the public and biomedical communities.
IDENTIFYING INFORMATION
1. Form B
2. Center Number
3. Patient ID

GENERAL INFORMATION
(Answer each of the following about the baby's mother and father, if known)
4. Mother's date of birth
   m d y
5. Birthdate of baby's father
   m d y
6. Mother's prepregnancy weight in kgs
7. Predominant race:
   1. White, not of hispanic origin
   2. White, of hispanic origin
   3. Black, not of hispanic origin
   4. Black, of hispanic origin
   5. American Indian or Alaskan native
   6. Oriental
   7. Asian Indian
   8. Other Asian or Pacific Islander
   9. South American Indian
8. Employment:
   1. Never been employed
   2. Employed in the past
   3. Currently working
9. Usual occupational category:
   Homemaker
   1. Professional & technical workers
   2. Managers and administrators (except farm)
   3. Sales or clerical workers

Fig. 1. English language draft of the Clinical Intake Form, edited for inclusion here, for the University of Tennessee/Johns Hopkins University Pregnancy Outcome Study.
4. Craftsmen
5. Machine operators (except transport)
6. Transport equipment operators
7. Laborers (except farm)
8. Farm workers or managers
9. Private household worker
10. Student

10. Does the mother smoke?
   1. Never smoked
   2. Used to smoke but stopped
   3. Currently smokes occasionally
   4. Currently smokes daily

A. How many times was she smoking per day just before she became pregnant?
B. How many times did she smoke per day since she became pregnant?

11. A. In the last six months, has she drunk any beer, wine, or liquor?
    1 No 2 Yes
    B. If she consumes less than one drink per week, check here and skip to question 12.
    2 Yes

C. How many days per week does she (did she) usually drink?
   1. Before pregnancy (days/week)
   2. During pregnancy (days/week)

D. How many drinks does she (did she) usually take at any one time?
   1. Before pregnancy (# of drinks)
   2. During pregnancy (# of drinks)

E. What is (was) the maximum number of drinks that she took at any one time?
   1. Before pregnancy (# of drinks)
   2. During Pregnancy (# of drinks)

MEDICAL HISTORY OF MOTHER

12. Does she have any chronic medical problems or serious illness?
    1 No 2 Yes
    If yes, specify

Fig. 1. (Cont.)
13. A. Was she taking any medications or drugs when she became pregnant (including recreational drugs), or since she became pregnant excluding vitamins and iron)?
   1 No 2 Yes
   If yes, list below

B. Has she taken seizure medication?
   1. No
   2. Yes, with the 4 months before LMP
   List drugs taken

14. A. Has she had any infection or illness during this pregnancy?
   1 No 2 Yes

B. If yes, type of infection:
   1. urinary tract
      14B1
   2. vaginal infection
      14B2
   3. gonorrhea
      14B3
   4. other pelvic infections
      14B4
   5. Other, specify__________
      14B5

PAST PREGNANCIES
(Complete the following information for each pregnancy, including miscarriages and stillborns. Begin at first Pregnancy.)

15. Starting with the first time she was pregnant, how many previous pregnancies did she have, including miscarriages and stillborns?
   A. Pregnancy Number
      15A
   B. Year pregnancy ended
      15B
   C. Length of pregnancy wks
      (normal length = 40 wks)
      15C
   D. Was it a multiple pregnancy?
      No ( ) 1 Yes ( ) 2
   E. Pregnancy outcome
      (check one)
      Livebirth
      ( ) 1
      Miscarriage
      ( ) 2
      Stillbirth (>8 wks)
      ( ) 3
      Tubal pregnancy
      ( ) 4
      Loss for other reason
      ( ) 5
   F. Pregnancy complications (Check all that apply)
      Delivery>3 wks early
      ( ) 1

Fig. 1. (Cont.)
Premature rupture of membranes (months) (2)
Vaginal bleed (months) (3)
Abruptio placenta (4)
Premature Labor (5)
Preeclampsia (6)
Hypertension (7)
Diabetes (8)
Other (9)
G. Newborn weight: gms /__/__/__/__
H. New Born Sex 15H
I. Was this father different from the current father? 15I
J. Was this child born with abnormalities? 15J
16. Do any of the mother's relatives have a birth defect? 16
17. Do any of the father's relatives have a birth defect? 17
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