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A Math Research Project Inspired by Twin Motherhood

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Abstract

The phenomenon of twins, triplets, quadruplets, and other higher order multiples has fascinated humans for centuries and has even captured the attention of mathematicians who have sought to model the probabilities of multiple births. However, there has not been extensive research into the phenomenon of polyovulation, which is one of the biological mechanisms that produces multiple births. In this paper, I describe how my own experience becoming a mother to twins led me on a quest to better understand the scientific processes going on inside my own body and motivated me to conduct research on polyovulation frequencies. An overview of the previous mathematical research on multiple births, as well as my own contributions involving polyovulation, is presented. Furthermore, I discuss more generally how motherhood can influence and enrich the research agendas of mathematicians.

1. Introduction

While there are many different forms of motherhood, none of them would be possible without the biological process of ovulation, whether spontaneous or induced, occurring at some point prior. Ovulation may not be a common area of research studied by mathematicians, but I became fascinated with the topic after my own experience becoming a mother to fraternal (or dizygotic) twins. In particular, when my twins were only a few weeks old, I brought them to a math department picnic, where one of my (male) colleagues asked me “Since you have fraternal twins, that means they came from two separate eggs.

Did the two eggs come from the same ovary or from different ovaries?” While this might seem like an unusual question to be asked at a picnic, as an academic the question intrigued me and led me on a quest to find the answer.

As I was researching articles on ovulation, I came across three prevailing theories on ovulation locations:

1. the locations are independent and hence it is equally likely for two eggs to be from the same ovary or from different ovaries,
2. ipsilateral ovulation is favored, where the release of an egg from an ovary has a stimulatory effect, and hence it is more likely for two eggs to be from the same ovary, or
3. contralateral ovulation is favored, where the release of an egg from an ovary has an inhibitory effect, and hence it is more likely for two eggs to be from different ovaries [2].

While there is limited direct evidence to test the three possibilities, the article “Dizygotic Twin Survival in Early Pregnancy” by Tong *et al.*, published in *Nature* [9], was the most relevant source I encountered. In this paper, the authors examined ultrasound scans of women in early pregnancy (5-9 weeks gestation) where the corpus luteum could be identified. The corpus luteum is a temporary endocrine organ, about 2 cm in diameter, that develops where an egg is released from an ovary. Hence, its location can be used to determine from which ovary an egg originated. In the 48 scans where two corpora lutea were present, indicating double ovulation, 23 of the cases had one on each ovary, 12 had both on the left, and 13 had both on the right. This data is consistent with a model where the locations of each egg released are independent and each location is equally likely to be from the left or right ovary.

While I did not have an early ultrasound myself to definitively determine from which ovaries my twins originated (my twins were a surprise at my 21-week ultrasound, by which time the corpora lutea had already decayed), I concluded from my literature review that the best answer to my colleague’s question was that it was equally likely that my fraternal twins came from the same ovary or from different ovaries. Although the initial question had been answered to the highest degree possible based upon existing medical data, it sparked several additional questions that I sought to investigate. In particular, the *Nature* article by Tong *et al.* showed that of the 48 pregnant

women who exhibited double ovulation, only 15 were pregnant with twins and the rest were pregnant with singletons. The roughly 30% probability of a second egg becoming fertilized and implanting is consistent with the well-documented rate at which a single egg results in a successful pregnancy, which led the authors to conclude that each egg is fertilized and implants independently from other eggs [9]. Since I have an older daughter who was born three years prior to my twins, I became curious about whether I had exhibited double ovulation then as well, but with only one child conceived.

As a mathematician who was trained as a probabilist, I was very interested in investigating the probability of double ovulation occurring in the population of fertile women. However, as I continued my literature review into ovulation, I found that while there was a substantial amount known about multiple *birth* frequencies, there was very little known about the frequencies of *polyovulation*, the production of more than one egg during a single menstrual cycle. Hence, I embarked upon a mathematical research project, along with two undergraduate students, to create a novel mathematical model that uses known birth data to estimate polyovulation frequencies. In the next two sections, I present an overview of the previous mathematical research on multiple births, as well as my own contributions involving polyovulation, which is one of the biological mechanisms that produces multiple births.

2. Overview of Mathematical Research on Multiple Births

One of the earliest mathematical contributions to the study of multiple births came at the turn of the 20th century from Wilhelm Weinberg, who used basic probability concepts to estimate the population relative frequencies of identical (monozygotic) versus fraternal (dizygotic) twins ([10], also see [4]). Identical twins originate from the division of a single fertilized egg (zygote), and hence must have the same sex since they have identical DNA. Fraternal twins originate from the fertilization of two distinct eggs, and under the reasonable assumption that the sex of each gender is independent, they are equally likely to be of the same sex or of opposite sex. The prevailing medical practice in Weinberg's era was to classify same-sex twins as either identical or fraternal based upon the number of placentas or close examination of the twins' physical characteristics. However, neither of those methods are reliable indicators of zygosity (the number of eggs from which a set of multiples derived).

While DNA testing is now available, there is limited data on genetic classification of twins, and thus, Weinberg's Differential Rule is still a useful method for estimating relative frequencies of identical versus fraternal twins.

To illustrate how Weinberg's Differential Rule works, consider a population with a sets of same-sex twins and b sets of opposite-sex twins. All of the opposite-sex twins must be fraternal, and since fraternal twins are equally likely to be of the same sex or of opposite sex, we would estimate that b of the same-sex twins sets are also fraternal. The difference $a - b$ is then the estimate of the number of identical twin sets. This leads to an estimate that in the population, $\frac{2b}{a+b}$ of the twins are fraternal and $\frac{a-b}{a+b}$ of the twins are identical. While the rate of identical twinning is fairly constant across the globe, the rate of fraternal twinning varies substantially, and hence, the relative frequencies vary between countries. Applying Weinberg's Differential Rule to U.S. birth data results in an estimate that approximately 62% of spontaneous twins are fraternal and 38% are identical [7].

In regards to estimating the frequency of multiple births among all births, one of the first mathematical models, called Hellin's Law, was developed in 1895, around the same time as Weinberg's Differential Rule ([5], also see [3]). Hellin's Law states that the ratio of twin births to all births is equal to the ratio of triplet births to twin births, as well as to the ratio of quadruplet births to triplet births. Hence, if x is the frequency of twin births among all births, then the frequency of triplet births among all births is x^2 and the frequency of quadruplet births among all births is x^3 . While there is no clear biological justification for Hellin's Law, Hellin estimated x to be $1/89$ and his law has been found to be a relatively good fit for birth data.

In 1957, Bulmer, building upon earlier work by Hellin [5] and Jenkins and Gwin [6], provided an estimate of the zygosity type relative frequencies of triplets and quadruplets. The zygosity analysis for higher order multiples is more complex than that for twins since, for example, a set of mixed-sex triplets could be dizygotic (one pair of identical siblings, plus one fraternal sibling) or trizygotic (three fraternal siblings). Bulmer's work contained one of the first mathematical models of polyovulation. Namely, Bulmer assumed that at least one egg is always ovulated and that the number of additional eggs released follows a Poisson distribution [3]. Hence, if R is the number of extra eggs released, Bulmer's model proposed:

$$P(R = r) = \frac{e^{-\mu} \mu^r}{r!},$$

where μ is the average number of extra eggs released. Since μ is unknown, but small, Bulmer further simplified the model to be:

$$P(R = r) = \frac{x_2^r}{r!},$$

where x_2 is the frequency of dizygotic twins in the population and can be computed from combining Hellin's Law and Weinberg's Differential Rule to obtain $x_2 = \frac{2b}{a+b}x$. Bulmer modeled polyovulation and the division of zygotes, the two distinct biological mechanisms that give rise to multiples, as independent processes, with the number of divisions following a Yule process where each zygote has a constant probability of dividing that is independent of the number of divisions that have already occurred.

In 1960, Gordon Allen provided an alternate estimate of the zygoty type relative frequencies of triplets and quadruplets through an extension of Weinberg's Differential Rule, rather than by assuming particular forms for the probability distributions of the number of eggs ovulated and the number of divisions of fertilized eggs [1]. Letting p_k be the probability of having k extra eggs ovulated and q_k be the probability that a zygote undergoes a k th division, Allen computed the probabilities for each zygoty type in terms of the p_k 's and q_k 's. For example, trizygotic triplets would have probability p_2 since two additional eggs are released, dizygotic triplets would have probability $2p_1q_1$ since one additional egg is released, and then one of the two fertilized eggs undergoes a primary division, and monozygotic triplets would have probability $2q_1q_2$ since the one fertilized egg undergoes a primary division and then one of the two offspring undergoes a secondary division.

Note that these formulas are simplifications since, for example, the full formula for the case of trizygotic triplets would need to account for the probability that none of the three fertilized eggs divide. However, since the probabilities of division and polyovulation are fairly low, complements of division and polyovulation probabilities were omitted.

Allen then matched the expected sex ratios of triplets and quadruplets to known ratios from birth data in order to estimate the polyovulation and division probabilities. The results yielded an estimated ratio of monozygotic

to dizygotic to trizygotic triplets of approximately 1:2:1, and a corresponding ratio of zygosity types for quadruplets of approximately 2:6:5:4. The high relative frequency of dizygotic quadruplets is unsurprising due to the fact that this type includes two distinct subtypes: two identical pairs or three identical siblings with one fraternal sibling.

What both Bulmer and Allen failed to take into account is the fact that not every egg that is ovulated is actually fertilized and successfully implanted into the uterus of the mother. Hence, both Bulmer and Allen's estimates of polyovulation frequencies were significant underestimates of the true probabilities. Moreover, neither Bulmer nor Allen took into account the timing of division, which can significantly affect the outcome of the pregnancy. Divisions that occur fairly early, 1-3 days after fertilization, result in offspring with separate placentas, which then by the work Tong *et al.* [9], we would assume would implant independently. Divisions that occur later result in a shared placenta, which would imply that either all the resulting offspring successfully implant or none do. Moreover, divisions that occur after implantation (around day 8), result in not only a shared placenta, but also a shared amniotic sac, which carries a very high risk of miscarriage [4].

3. A Math Research Project on Polyovulation

During the summer of 2015, I collaborated with two undergraduate students, Kaylyn Banaszak and Anna Kaniewski, to create a more complex mathematical model of polyovulation. Both students were rising junior mathematics and secondary education double majors participating in Valparaiso University's Mathematics and Science Education Enrollment and Development (MSEED) program. Funded by the National Science Foundation, the MSEED program is an initiative with the goal of better training future math and science high school teachers by providing them with in-depth research experiences in their content areas.

Our polyovulation model built upon Allen's work, adding the complexity of the fertilization, timing of division, and implantation processes, as well as miscarriage probabilities that depended upon the number of shared placentas and shared amniotic sacs. In particular, by considering the various biological processes that eggs undergo in order to result in live births, we modeled the probability of $B_{k,z,c,a}$, the event that a pregnancy results in k live births,

with the offspring possessing zygosity z , chorionicity (number of placentas) c , and amnionicity (number of amniotic sacs) a , in terms of ovulation probabilities. We then estimated the overall probability of k live births,

$$P(B_k) = \sum_{z=1}^k \sum_{c=z}^k \sum_{a=c}^k P(B_{k,z,c,a}),$$

using the same birth data used by Allen. Allen's data was from the 1950s before the introduction of artificial reproductive technologies, and hence, a better reflection of spontaneous polyovulation than more recent birth data.

Using the birth probabilities and linear algebra techniques, we were able to solve for the desired polyovulation probabilities. We estimated that double ovulation occurs approximately 3.5% of the time in the population of fertile women in the U.S., with triple ovulation and quadruple ovulation occurring approximately 0.05% and 0.004% of the time, respectively [7]. Future work related to our polyovulation research could involve adding further complexity to the model to more fully represent the true underlying biological processes, as well as performing sensitivity analysis on the various literature estimates for the parameters used in the model. Moreover, our polyovulation estimates are of population-wide frequencies, but it would be interesting to investigate the conditional probability of polyovulation for women, such as myself, who have a known history of polyovulation. While we estimated that double ovulation occurs approximately 3.5% of the time in the U.S. population of fertile women, it may be that women with a history of twins exhibit double ovulation more frequently.

4. Other Mathematical Research Motivated by Motherhood

While the demands of motherhood, with its sleep deprivation, hormonal changes, and unending time commitments, can often impede the research agendas of mathematicians and other academics, I believe that motherhood can also be a source to enrich one's scholarly life. As my own experience illustrates, motherhood may spark new research projects in the field of mathematical biology. It is well-documented that having a personal connection to a topic can increase motivation [8], which in turn can help scholars persevere with research despite the demands of motherhood.

For example, a mother of a child with cancer, or some other illness or disease, may be motivated to seek out how she can contribute to that subfield of research.

In addition to mathematical biology research, motherhood may also spark an interest in pursuing scholarship on the teaching and learning of mathematics. I found it fascinating to observe my children advance from simply reciting their numbers from 1-10 to understanding how the names of the numbers correspond to a physical number of objects. Now that my older daughter is in elementary school, I have a vested interest in how mathematical concepts are taught and the types of experiential learning activities used in the classroom. There is a wide array of opportunities for mothers to partake in math education research.

Beyond applied research that has a specific topical connection to motherhood, the experience of motherhood can also reawaken a love for the pursuit of knowledge for its own sake. As we watch our children grow and explore the world around them with a mixture of curiosity and wonder, we can be reminded of the simple joy of learning. This reminder can reignite the spark to engage in research, whether it be applied or abstract, as we pursue the pure beauty of mathematics.

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