NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Can We Risk It Again?

Genetics and Recurrent Pregnancy Loss

by
Melanie E. Peffer
Health Professions Residential Academic Program
University of Colorado Boulder

Part I – Scott and Celeste

Scott and Celeste met in college through marching band. During long bus rides to away football games, Scott and Celeste often played a game where they would list as many favorite names for future children as they could. Scott loved "Max" for a boy, but Celeste's favorite was "Chris." After seven years of dating, they married. After enjoying the early years of their marriage and getting settled into their careers, Scott and Celeste decided to start trying to get pregnant. A year later they welcomed a baby girl, Mariposa, into their lives.

When Mariposa was a few years old, Scott and Celeste decided it was time to add to their family. Little did they know that having another child would be a far bumpier ride. When Celeste found out she was pregnant again, the parents were overjoyed. Then eight weeks later, Celeste passed blood. Her midwife ordered an ultrasound to check on the developing baby and the parents received the heartbreaking news that the baby had passed away. Celeste had miscarried.

Question

1. Approximately 25% of pregnancies end in miscarriage. What is the medical definition of a miscarriage? In your answer, differentiate between a chemical pregnancy, ectopic pregnancy, missed miscarriage, and molar pregnancy.

Part II – Trying Again

After waiting a few months to physically and emotionally recover from the miscarriage, Scott and Celeste decided to try again to get pregnant. Several months later, Celeste was pregnant.

Given that Celeste had a previous miscarriage, her midwife, Debra, sent in orders for regular ultrasounds to monitor the baby's development. Celeste and Scott attended each ultrasound with a mix of excitement and fear. They craved the reassurance of seeing their baby grow but were afraid of receiving bad news of a miscarriage. Debra was concerned but hopeful as the baby grew until the ninth week of pregnancy. At the nine week checkup there was no additional growth and no heartbeat. Celeste had miscarried, again.

Although miscarriages caused by chromosomal abnormalities are very common, it is uncommon to have back-to-back or recurrent miscarriages. Recurrent miscarriages are defined as having two or more miscarriages in a row. Often there is an underlying biological reason why a couple will have recurrent miscarriages. Debra referred Celeste and Scott to see a fertility specialist, Dr. Valery.

Questions

1. Miscarriages are often the result of chromosomal abnormalities in the fetus. Hypothesize below what kinds of chromosomal abnormalities could cause miscarriage.

2. Name three different non-genetic causes of miscarriage.

3. Since Scott and Celeste have a living child, Mariposa, could there be a genetic reason for the recurrent miscarriages? Why or why not?

Part III – Testing

During the initial consultation, Dr. Valery explained that there are a wide variety of reasons why a couple may face recurrent miscarriage. Genetic reasons include everything from unhealthy gametes (eggs or sperm) to chromosomal rearrangements, like translocations or inversions. Celeste could also have a congenital uterine malformation, meaning her uterus did not form correctly during her development. Their living child, Mariposa, may have implanted in an area of the uterus with good blood flow, whereas the other embryos did not. Endocrine changes in Celeste such as thyroid problems or hormonal imbalance could also explain the miscarriages. Yet another possibility was that Celeste had an undiagnosed autoimmune or blood clotting condition (thrombophilia). Consequently, her miscarriages could be caused either by her immune system attacking the developing embryo or from micro clots affecting the uterus, resulting in decreased blood flow in the embryo. Dr. Valery laid out a clear plan for testing for both Scott and Celeste, and informed them that they would re-group once the testing was complete.

A few weeks after the testing was complete the phone rang; it was Dr. Valery. "We found something," she said. "Scott has a condition called balanced translocation, which occurs when part of one chromosome breaks off and reattaches to another chromosome."

"A what?" asked Scott. "I've always been perfectly healthy; how could there be something wrong with my chromosomes?"

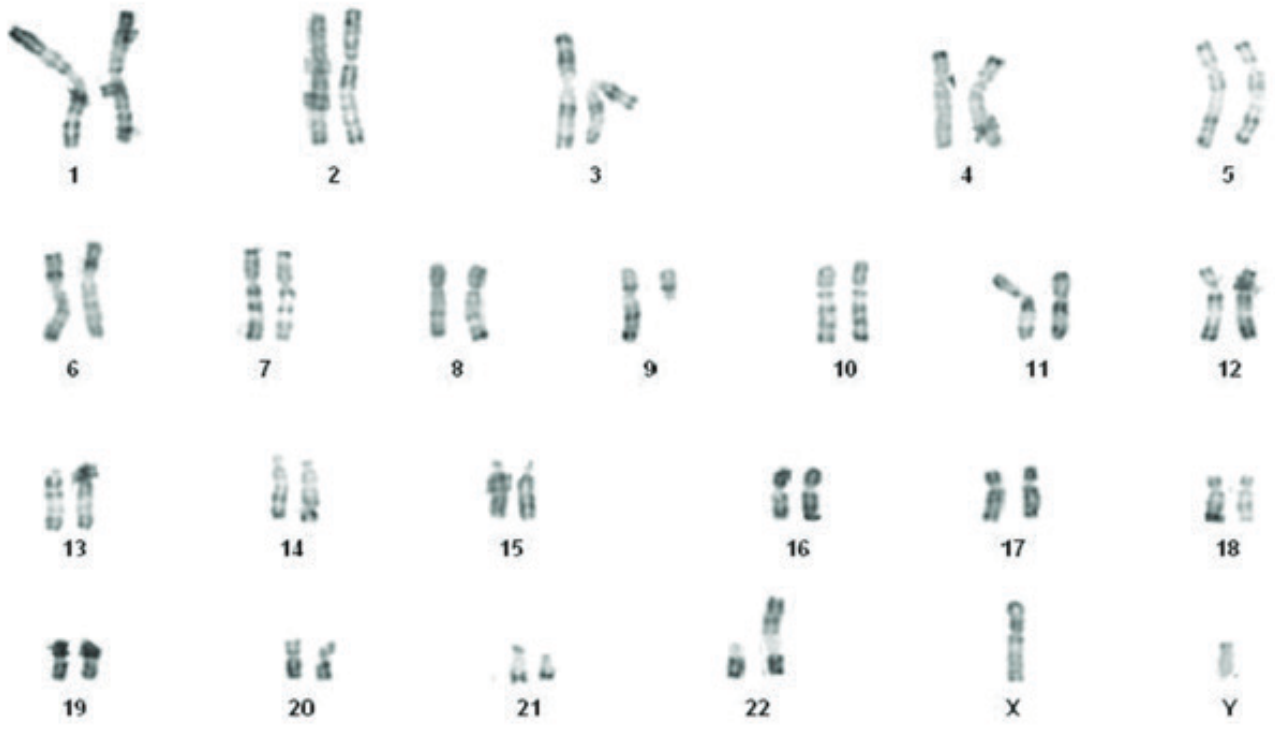

Figure 1. Karyotype. Adapted and used with permission from Fig. 5 in: Hammami, W., Kilani, O., Khelifa, M. B., Ayed, W., Bouzouita, A., Zhioua, F., ... & Amouri, A. (2015). Genetic diagnosis in non-obstructive azoospermic Tunisian men. *Austin J Reprod Med Infertil* 2(2), 1012.

Questions

1. Scott's karyotype resembled the one displayed in Figure 1 above. Between which two chromosomes did a balanced translocation occur? How do you know?

2. If Scott has a balanced translocation, why is it possible that he has lived a healthy life and was unaware of it until now?

3. How could a balanced translocation lead to a miscarriage?

4. Draw the possible gametes Scott can produce. You only need to represent the translocated chromosomes in your drawing. (*Hint:* start by drawing out the four possible arrangements of the translocated chromosomes in meiosis I.)

5. Based on your drawing, what percentage of Scott's gametes would be viable (e.g., have the correct gene dosage)?

6. Is it possible for Scott and Celeste to produce a healthy child that has the same balanced translocation? Why or why not?

Part IV – What Next?

"Well, now what are we going to do?" asked Celeste as she glanced at Mariposa's picture on her phone. She had always been grateful for her healthy energetic toddler, but now felt doubly so.

Dr. Valery said, "With no medical intervention, the chances of having another miscarriage are doubled."

Scott then chimed in, "We can't understate the emotional trauma these consecutive miscarriages have had on us. I'm not willing to risk another miscarriage unless we can do something about it. What options do we have?"

"Well," said Dr. Valery, "If you don't want to leave things up to chance, there are some assisted reproductive technologies available. Since Celeste's chromosomes are normal, we could look at artificial insemination with donor sperm. We could also do *in vitro* fertilization (IVF), which is when we combine sperm and egg outside the body; then we can screen for embryos with Scott's normal chromosomes using preimplantation genetic diagnosis (PGD) before transferring a genetically healthy embryo into Celeste.

After weighing the options, Scott and Celeste decided to proceed with PGD and IVF. Ten months later, they welcomed another healthy baby girl, Felicity, to their family.

Questions

1. Many health insurance companies will not pay for the kind of testing Scott and Celeste received until after two (and sometimes three, depending on the policy) miscarriages. Miscarriages are biologically the loss of an embryo or fetus, but emotionally represent the loss of a baby, and all that baby would have been. What are some of the physical and emotional tolls of miscarriage?

2. Dr. Valery ordered several tests to determine the cause of Celeste's and Scott's losses. These tests are not considered standard of care for pre-pregnancy planning. What tests do you think should or should not be offered to couples planning a pregnancy? What would you include and why?

3. Scott and Celeste decided to pursue PGD and IVF rather than artificial insemination. How much do these therapies cost for couples? What does this tell you about social inequities in medicine?

4. Reflect on this case. How did this story exemplify how we see content in genetics or other biology classes as part of our daily lives?

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This case study is written in memory of all the babies gone too soon, and especially for my little ones: Debra, Mariposa, and Celeste. My hope is that this case study, inspired by my losses, will catalyze meaningful educational experiences for our next generation of medical providers and scientists, ultimately lead to meaningful change in preventing pregnancy loss, care for bereaved parents, and offer accessible medical solutions for all.

I would like to thank my genetics colleagues at University of Colorado Boulder (Drs. Jessica Gorski, Jennifer Knight, Christy Fillman, and Maureen Bjerke) for feedback on this case study. I would also like to thank my Spring 2022 cohort of genetics students for piloting the case study and providing valuable feedback.