Title
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Journal
American Journal of Obstetrics and Gynecology, 182(5)

ISSN
0002-9378

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Publication Date
2000-05-01

DOI
10.1016/s0002-9378(00)70188-8

Obstetric emergencies precipitated by malignant brain tumors

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OBJECTIVE: Our goal was to present a case series of pregnancy-associated malignant brain tumors.
STUDY DESIGN: A review was conducted from 1978-1998 at 5 hospitals.
RESULTS: Ten women were diagnosed with a malignant brain tumor during pregnancy (n = 8) or post partum (n = 2). Patients diagnosed antenatally exhibited severe symptoms, manifest between 27 and 32 weeks' gestation. Six were emergently delivered of their infants because of maternal deterioration, and 2 were delivered electively in the early third trimester after documentation of fetal pulmonary maturity. There were 4 maternal deaths and 1 neonatal death; all of the other infants maintained viability.
CONCLUSIONS: Malignant brain tumors rarely occur in pregnancy. In contrast to reports that describe an indolent course, each of the 8 antenatal patients experienced a neurologic crisis. If symptoms are amenable to pharmacologic control, we advocate delivery in the early third trimester after documentation of fetal pulmonary maturity. To minimize temporal lobe or cerebellar herniation in neurologically unstable patients, a consideration should be made for cesarean delivery with the patient under general anesthesia, followed by immediate neurosurgical decompression. (Am J Obstet Gynecol 2000;182:1215-21.)

Key words: Brain tumor, pregnancy, management

In a 1986 population-based epidemiologic study of the German Democratic Republic, Haas et al[1] reported that the number of meningiomas, acoustic neuromas, and primary malignant intracranial neoplasms diagnosed during pregnancy was less than expected when compared with the general population. With the use of tumor registry data from 1961 to 1979, these investigators identified 17 malignant brain tumors and 3 meningiomas among pregnant women. With respect to primary malignant intracranial tumors, the ratio of observed / expected tumors associated with pregnancy was 0.38. In an extensive review of the literature, Roelvink et al[2] of the University of Amsterdam collected 223 cases of pregnancy-related brain tumors from 86 reports and concluded that the relative frequency of tumors of different types in pregnancy was equal to their respective frequencies in age-matched nonpregnant counterparts.

In 1988 Simon[3] postulated that the prevalence of brain tumors in pregnancy may be determined via a simple mathematic exercise in joint probability: the intersection of the probability of being pregnant at any given time with the probability of having a brain tumor at a specific age and sex. Ignoring the impact of the tumor on reproduction (via hormonal, constitutional, and libidinal effects), he calculated that in the United States there are likely to be 89 women each year who are pregnant and have a brain tumor.

The Division of Maternal-Fetal Medicine at the University of California, Irvine was established during the late 1970s. In an effort to better understand this exceedingly rare clinical entity, we have reviewed our entire departmental experience of malignant brain tumors complicating pregnancy.

Material and methods

Patients who had been diagnosed with a malignant brain tumor antenatally or within 6 weeks post partum were identified through 5 local hospital tumor registries. Three of these hospitals had active labor and delivery units during the 1978-1998 study period (numbers 1-3), whereas 2 were built after 1978 (numbers 4 and 5).

1. The University of California, Irvine Medical Center in Orange, California, is a tertiary-care referral center. During the study period, this hospital had 74,264 deliveries.

2. Memorial Medical Center in Long Beach, California, is a tertiary-care referral center. During the study period, this hospital had 99,045 deliveries.

3. Hoag Hospital in Newport Beach, California, is a community hospital. During the study period, this hospital had 63,547 deliveries.

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Received for publication September 24, 1999; revised November 23, 1999; accepted December 14, 1999.
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0002-9378/2000 $12.00 + 0 ***6/1/105051***
doi:10.1067/mob.2000.105051

Table I. Neurologic and obstetric emergencies

Case No.	*Presentation*	*Delivery*	*Baby*
1. 22-year-old white woman, gravida 1, para 0 (1981)	28 weeks' gestation: Nausea and vomiting. 40 weeks' gestation: Mental status changes, gait disturbance, and dysphasia	Emergency cesarean at 40 wk; maternal respiratory and cardiac arrest caused by herniation	Birth weight, 4020 g; variable decelerations of fetal heart rate
2. 19-year-old white woman, gravida 1, para 0 (1990)	26 weeks' gestation: Nausea and vomiting, left-sided paralysis, gait disturbance, coma	Emergency cesarean at 28 wk; fetal distress caused by herniation	Birth weight, 935 g; died in neonatal intensive care unit
3. 27-year-old Asian woman, gravida 3, para 1 (1993)	30 weeks' gestation: Mental status changes, urinary incontinence, memory loss, diminished writing ability	Emergency cesarean at 34 wk; midline shift, obstructive hydrocephalus	Birth weight, 2160 g; viable
4. 19-year-old Hispanic woman, gravida 2, para 1 (1995)	26 weeks' gestation: Quadriplegia, respiratory insufficiency, brain death	Emergency cesarean at 27 wk; maternal cardiac and respiratory arrest caused by herniation	Birth weight, 988 g; viable
5. 24-year-old Hispanic woman, gravida 1, para 0 (1997)	27 weeks' gestation: Headache, memory loss. 31 weeks' gestation: Speech impairment, right-sided hemiparesis, obtundation	Emergency cesarean at 32 wk; herniation	Birth weight, 1770 g; viable
6. 37-year-old white woman, gravida 3, para 2 (1997)	28 weeks' gestation: Nausea and vomiting, vertigo	Emergency cesarean at 34 wk; maternal cardiac and respiratory arrest caused by herniation	Birth weight, 2466 g; viable
7. 37-year old Hispanic woman, gravida 6, para 4 (1998)	27 weeks' gestation: Seizure disorder	Elective cesarean at 35 wk	Birth weight, 3360 g; viable
8. 33-year-old white woman, gravida 2, para 1 (1998)	31 weeks' gestation: Personality change, seizure disorder	Elective cesarean at 32 wk	Birth weight, 1814 g; viable

4. Kaiser Permanente Medical Center in Anaheim, California, is a managed care hospital. From 1981 to 1998, this hospital had 52,408 deliveries.

5. Kaiser Foundation Hospital in Riverside, California, is a managed care hospital. From 1989 to 1998, this hospital had 23,381 deliveries.

Names obtained through the tumor registry were cross-referenced with files from the Departments of Pathology and Epidemiology. The labor and delivery birth logbooks from 1978 to 1998 were also carefully examined for all 5 hospitals. Clinical features of each patient were extracted from the medical record. Pathologic material, when available, was reviewed to confirm the diagnosis.

Results

From January 1978 to December 1998, 10 women were diagnosed with a malignant brain tumor antenatally (n = 8) or during the postpartum period (n = 2). The cases were distributed among the 5 regional hospitals where members of the Department of Obstetrics and Gynecology at the University of California, Irvine, cared for patients. Nine of these women were identified through the tumor registry abstracts and the labor and delivery birth logbooks, and one patient was identified in recent months. A total of 312,645 births occurred among the 5 hospitals during the study period. Thus the incidence of malignant brain tumors complicating pregnancy in this population was 3.2×10^{-5}.

Two of the 10 cases were encountered during the postpartum period and consisted of intracranial metastatic gestational choriocarcinoma, occurring in women aged 26 and 21 years. Both had experienced uncomplicated vaginal deliveries at term, followed by persistent vaginal spotting and severe headache; neurologic symptoms were not manifest antenatally in either patient. In each case malignant trophoblastic disease involving the frontal lobe (Fig l, *A*) was treated with aggressive multiagent systemic chemotherapy and whole-brain radiotherapy. One of these patients was first seen in 1979 and died of disease within 4 months; the second patient was first seen in 1981, and a sustained remission was achieved that has lasted for 17 years.

The 8 women with malignant brain tumors diagnosed antenatally each experienced a neurologic crisis during pregnancy (Table I). The median age was 24 years (range, 19-37 years), and parity included 0 (n = 3), 1 (n = 3), and >2 (n = 2).

Six of these patients were first seen during the latter half of the second trimester (26-28 weeks), and 2 were seen during the early third trimester (30 and 31 weeks) with rapidly escalating neurologic complaints. Intractable nausea and vomiting were most commonly encountered (n = 3), but severe headache, gait disturbance, seizure disorder, urinary incontinence, memory loss, and paralysis were also observed. Magnetic resonance imaging revealed isolated unilateral lesions involving the cerebellum (n = 2), parietal lobe (n = l) and frontal lobe (n = l); multifocal

Tumor	*Site and size of tumor*	*Treatment*	*Outcome*
Anaplastic astrocytoma	Right cerebellum; 5 × 4 cm	—	Maternal death
Anaplastic astrocytoma (recurrent)	Right parietal lobe; 6 × 4 cm	—	Maternal death
Glioblastoma multiforme	Right frontoparietal lobe; 9 × 6.5 × 6 cm	Craniotomy; tumor resection; radiotherapy	Alive with disease and significant neurologic deficit
Anaplastic astrocytoma	Left temporal lobe, corpus callosum, midbrain, cervical and thoracic spinal cord; 6 × 6 cm	—	Maternal death
Glioblastoma multiforme	Left temporal-parietal-occipital lobe; 7 × 6 × 4 cm	Craniotomy; tumor resection	Alive with disease and significant neurologic deficit
Metastatic breast cancer (recurrent)	Left cerebellum; 4 × 4 × 3 cm	Craniotomy; decompression	Maternal death
Glioblastoma multiforme	Right temporal and frontal lobes, corpus callosum; 3.5 × 2 × 3 cm	Craniotomy; tumor resection; radiotherapy	Alive; in remission
Glioblastoma multiforme	Left frontal lobe; 6 × 6 cm	Craniotomy; tumor resection; radiotherapy	Alive; in remission

and extensive disease was present in 5 patients, crossing the corpus callosum in 2 (Fig l, *B*) and extending into the spinal cord in one. Fig 1, *C,* depicts potential symptoms along several topographic regions of the brain.

The mean tumor diameter of the 8 antenatal cases was 5 cm (range, 2-9 cm). Histologic tumor subtypes included glioblastoma multiforme (n = 4), anaplastic astrocytoma (n = 3), and metastatic breast carcinoma (n = l).*

Six of the 8 patients who were seen antenatally were delivered emergently by cesarean delivery between 27 and 40 weeks' gestation because of acute neurologic decompensation (cases 1-6, Table I); of these 6 patients, 2 were delivered within 2 weeks of initial presentation, whereas 4 with pharmacologically amenable neurologic symptoms were delivered 4 to 12 weeks after initial presentation. Fetal distress resulting from progressive maternal acidosis also occurred in 1 case and was demonstrable by fetal heart rate monitoring. Among these 6 women, 5 experienced either cerebellar or temporal lobe herniation with attendant brain stem compression, and 4 died. The 2 surviving mothers have unresectable disease and significant neurologic deficits.

The neonatal outcomes among these 6 cases with emergent delivery included 5 viable infants with birth weights of 988 to 4020 g, each of whom had an uneventful course in the neonatal intensive care unit. The 935-g neonate who had experienced fetal distress had been delivered at 28 weeks' gestation and died during the first week of life of respiratory distress syndrome.

Two patients had neurologic symptoms that were amenable to pharmacologic manipulation during the latter half of the second trimester and did not subsequently experience neurologic deterioration (cases 7 and 8; Table I). They received corticosteroids to enhance fetal lung maturity and aggressive anticonvulsant polypharmacologic therapy. After documentation of fetal pulmonary maturity by amniotic fluid analyses, both women were delivered of their infants electively by cesarean while they were under general anesthesia at 32 and 35 weeks' gestation. Their babies were born with birth weights of 1814 g and 3360 g, and viability was sustained in the neonatal period. The mothers subsequently underwent craniotomy, tumor resection, and postoperative radiation therapy and are currently in remission.

Comment

Each patient in our series with an antenatal malignant brain tumor had severe neurologic signs and symptoms; in 6 instances a catastrophic neurologic event occurred that terminated the pregnancy prematurely. In the context of our cumulative experience, several early reports have described severe symptoms and even maternal death in association with malignant brain tumors.[4-6]

*Estrogen receptor antibodies and progesterone receptor antibodies were obtained from Ventana Medical Systems, Inc (Tucson, Arizona), and immunoperoxidase staining was performed on malignant brain tissues. Estrogen and progesterone receptor proteins were not identified in 7 of the 8 cases for which pathologic material was available (cases 2-8, Table I).

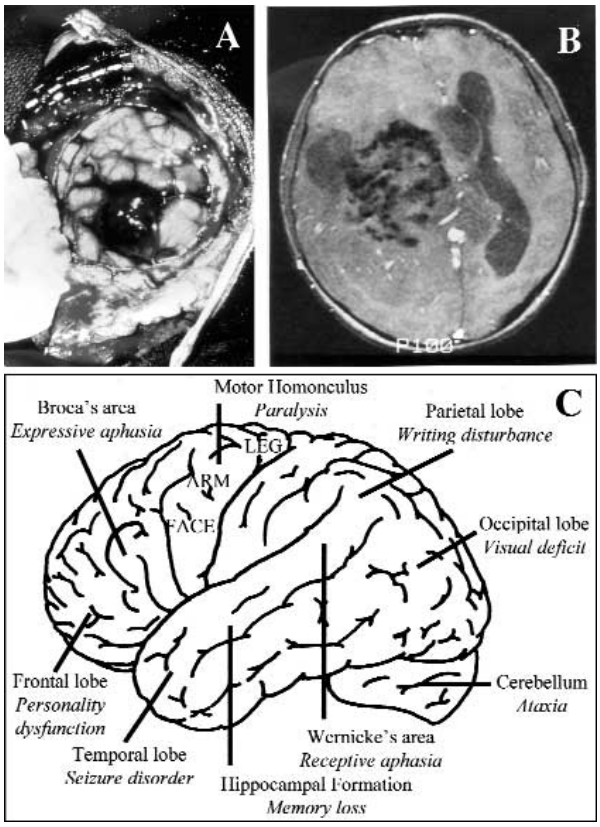

Fig 1. Malignant brain tumors complicating pregnancy. **A,** Postpartum cerebral metastasis of gestational choriocarcinoma at craniotomy. **B,** Magnetic resonance image demonstrating heterogeneous left cerebral tumor and resultant mass effect. **C,** Schematic representation of brain topography depicting lesional regions with corresponding deficits.

In 1961 Barnes and Abbott[7] recorded 4 fatal cases of intracranial brain tumors diagnosed during pregnancy, all of which were malignant. Some of the more contemporary communications have attributed postpartum blindness, sudden maternal death, and massive intracranial hemorrhage to malignant disease.[8-10] Disastrous antenatal outcomes, however, are not the rule; in a 1997 series from Spain, emergent conditions developed in only 1 patient whereas 5 experienced uneventful deliveries followed by postpartum treatment.[11]

Women diagnosed with postpartum malignant brain tumors, specifically, gestational trophoblastic disease, also appear to do poorly. The incidence of choriocarcinoma after a term pregnancy is 1 in 50,000, with brain metastases occuring in 14% to 28% of cases.[12] Whereas cerebral metastases have long been recognized as a poor prognostic factor in gestational trophoblastic disease, it is disconcerting that, among the >50 cases of postterm choriocarcinoma associated with intracranial metastases, only 4 survivors (including 1 from this study) have been recorded in the medical literature.[12-14]

The potentially catastrophic consequences of temporal lobe and cerebellar herniation warrant our being able to triage patients appropriately when they are first seen for medical attention. Of the different malignancies that may arise in pregnancy, brain tumors are unique in that they carry perhaps the greatest potential for maternal death and fetal wastage. A number of theories have been advanced over the years to account for the exacerbation in symptoms that may occur in pregnancies complicated by brain tumors, including immunologic tolerance, steroid hormone–mediated growth,* and hemodynamic instability. Although different brain tumors may be biologically distinct, theoretically, a common pathway to clinical deterioration may be manifest through an intracranial mass effect that is susceptible to exacerbation by hemodynamic changes inherent to pregnancy.

During the preceding half century, several essayists have debated what constitutes optimal management of brain tumors in pregnancy, whether they be malignant or benign.[1-3, 7, 11, 15-20] In 1950 Rand and Andler[16] described 3 women with malignant astrocytomas who died with their babies in utero and suggested that the type of tumor was important. They advocated prompt surgical

*It is beyond the scope of this study to address this theory, because the interpretation of the estrogen and progesterone receptor data is limited by a lack of available pathologic material for all cases and by potential technical limitations of studying archived (10-year-old) tissues.

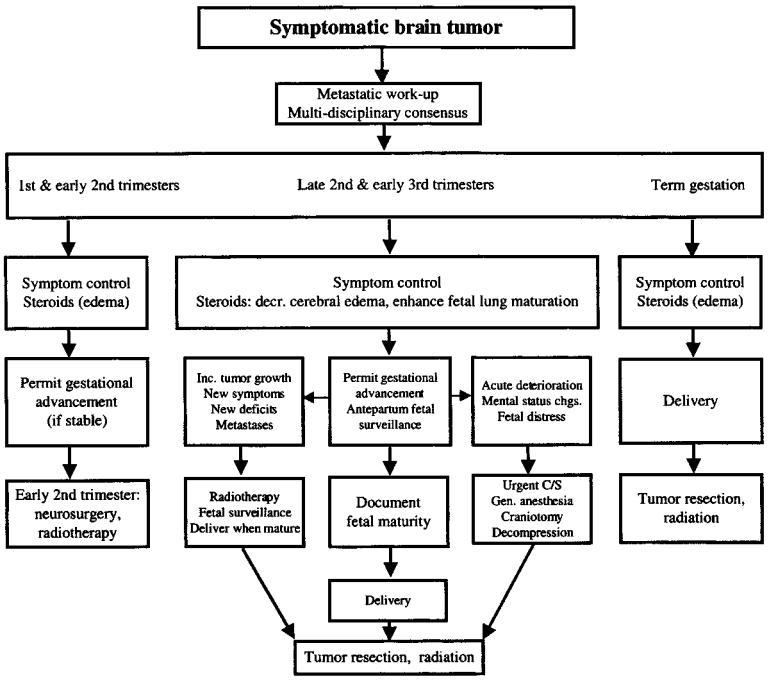

Fig 2. Potential management algorithm for symptomatic brain tumors in pregnancy.

intervention in patients believed to have gliomas (ie, malignant brain tumors). Tarnow[18] combined his own experience with many well-known documented cases from the literature and in 1960 published a very comprehensive review of 97 patients. Two thirds of these survived the pregnancy, delivery, and peurperium. The remaining one third died with either infratentorial lesions or supratentorial malignant tumors. Tarnow concluded that the prognosis of the pregnancy would be favorable provided the tumor was neither malignant nor infratentorial. He advised immediate intracranial surgical intervention and cesarean delivery when there were signs of increasing intracranial pressure. In cases of extreme fetal prematurity he recommended the Torkildsen procedure to facilitate cerebral decompression and permit gestational advancement in utero.

Noting that many of their contemporaries favored a vaginal delivery and advocated interruption of the pregnancy only if the mother's life or vision was in the balance, Kempers and Miller[19] examined the problem at several levels. The authors summarized 16 cases and agreed that, whereas interruption of pregnancy is seldom indicated, it may be required when significant symptoms (eg, seizures) are refractory to medical management because such patients may experience rapid deterioration of their condition. In 4 of their cases the tumors were malignant, and although 3 did not require an interruption in pregnancy, 2 of the mothers died within 1 year of delivery with inoperable tumors. The authors stated that it is distinctly preferable not to perform neurologic surgery during pregnancy because the increased vascularity and potential for hypotension and hypothermia constitute hazards to both the mother and the fetus. Citing the data of Marx et al[21] showing that the cerebrospinal fluid pressure is markedly increased by bearing-down efforts during the second stage of labor (and not by uterine contractions alone), Kempers and Miller[19] advised a shortened second stage of labor with either a low or outlet forceps application. The authors advocated permanent sterilization after delivery or therapeutic abortion in patients with inoperable malignant disease. Finally they concluded that "…the management of pregnancy must be somewhat flexible because of differences in type and location of tumors, difference in symptoms, difference in parity and length of gestation, and differences in the patients' personal wishes."

Fig 2 depicts a potential management algorithm derived through deductive reasoning and from the above-described obstetric heritage. When patients who have neurologic symptoms suggestive of an intracranial lesion are being evaluated, it is important to determine the level of consciousness, the rapidity and type of neurologic deterioration (if present), and the position of the tumor in both the supratentorial and infratentorial areas and possibly even to perform steriotaxic biopsy for accurate determination of the type of tumor (ie, to ascertain malignant histologic features).

Pregnant women who are seen at term may safely undergo radiographic assessment. Patients in whom a brain tumor is discovered should receive corticosteroids to diminish cerebral edema (if present), and delivery should be accomplished expeditiously. In the presence of a mass

effect cesarean delivery with the patient under general anesthesia may be preferable, because elimination of both the second stage of labor and epidural placement would theoretically decrease the risk for brain stem herniation. Because there have been no studies that have directly addressed this hypothesis, these issues remain unclear. Clearly, induction of labor is not feasible in neurologically unstable patients who have impending herniation; vaginal delivery, however, may be permissible for the subset of clinically stable patients. A craniotomy with neurologic surgery may be performed at the time of delivery or in the postpartum period. Depending on the operative findings, whole-brain radiotherapy may also be indicated and should be administered with appropriate pelvic shielding so as not to result in premature ovarian failure and the attendant risks of accelerated cardiovascular disease, osteoporosis, and sterility.

At the other end of the gestational spectrum, some patients may have neurologic symptoms suggestive of a brain tumor during the first and early second trimesters. These patients should be at less risk for chronically increased intracranial pressure if hemodynamic alterations are a significant contributing factor to neurologic decompensation. Whereas anticonvulsant medications exhibit cumulative teratogenicity during the first trimester, obviously, they should not be withheld if indicated. In addition, because the fetus is remote from viability and the risks of intracranial hemorrhage are not as great, neurologic surgery may be considered during this period. Radiotherapy, radiosurgery, and image-guided surgery during gestations beyond the first trimester may also be an option.

During the latter half of the second trimester (when maternal intravascular volume peaks) and in the early third trimester, many patients may first come to medical attention. This places the clinician in a conundrum, because the fetus may be either (or both) previable or extremely premature. Tight pharmacologic control of symptoms should be attempted (eg, anticonvulsants, antiemetics, and the like), and admission to the hospital may be advisable. Interventional radiologic procedures to contain small intracranial hemorrhages may be required. Corticosteroids to control cerebral edema and accelerate fetal lung maturation should also be administered. If symptoms worsen, new deficits manifest, or there is evidence of increased tumor growth or metastases, radiotherapy during pregnancy may be contemplated with a calculation of radiation scatter to the fetus by phantom measurements.[22] If acute clinical deterioration or impending herniation manifests, to avoid fetal wastage, expeditious delivery of the baby should be accomplished by cesarean with the patient under general anesthesia, followed by cerebral decompression and tumor resection.

Should women whose symptoms are controlled be permitted to carry the pregnancy to term? It must be emphasized that, unless radiotherapy has been administered, a stable neurologic status only suggests that the symptoms of a neoplasm have been masked. In cases in which treatment was not given, complete tumor resection was not possible in 4 of our survivors. Other cases in the literature, previously discussed, confirm this observation. In the nonpregnant population, although there is a lack of evidence that early treatment of malignant gliomas significantly improves survival rates, certainly, the increased morbidity associated with expansive tumor growth that even terminally ill patients would have to endure must be considered. Therefore in an effort to optimize the mother's opportunity for optimal surgical cytoreduction of resectable tumors and postoperative radiotherapy for radiosensitive lesions, once fetal pulmonary maturity is demonstrable, we advocate delivery of stable patients who are seen in the early third trimester.

Perhaps the most important consideration is the conduct of the pregnancy in neurologically stable women who are seen in the latter half of the second trimester. Given the previously described concerns regarding expansive tumor growth that may be associated with treatment delays (eg, subsequent paralysis from spinal cord involvement), should delivery be contemplated even in the absence of fetal pulmonary maturity (for example, at 28 weeks' gestation)? The modern neonatal intensive care units and recombinant surfactant may provide a survival benefit for neonates electively delivered at such gestational ages. Clearly, a multidisciplinary approach is required, and patients and their families must be counseled extensively to be able to fully participate in these types of management decisions.

We acknowledge Rosa Maria Ballestero, the hospital unit service coordinator of the Labor and Delivery Unit of the University of California, Irvine, for all of her hard work and assistance in obtaining the total number of deliveries at the different hospitals during the 20-year study period.

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